Vascular Health and Risk Management

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ORIGINAL RESEARCH

Elevated Lp(a) Levels Correlate with Severe and Multiple Coronary Artery Stenotic Lesions

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Backgrounds and Aims: The role of Lipoprotein(a) (Lp(a)) in increasing the risk of cardiovascular diseases is reported in several populations. The aim of this study is to investigate the correlation of high Lp(a) levels with the degree of coronary artery stenosis.

Methods: Two hundred and sixty-eight patients were enrolled for this study. Patients who underwent coronary artery angiography and who had Lp(a) measurements available were included in this study. Binomial logistic regressions were applied to investigate the association between Lp(a) and stenosis in the four major coronary arteries. The effect of LDL and HDL Cholesterol on modulating the association of Lp(a) with coronary artery disease (CAD) was also evaluated. Multinomial regression analysis was applied to assess the association of Lp(a) with the different degrees of stenosis in the four major coronary arteries.

Results: Our analyses showed that Lp(a) is a risk factor for CAD and this risk is significantly apparent in patients with HDL-cholesterol ≥35 mg/dL and in non-obese patients. A large proportion of the study patients with elevated Lp(a) levels had CAD even when exhibiting high HDL serum levels. Increased HDL with low Lp(a) serum levels were the least correlated with stenosis. A significantly higher levels of Lp(a) were found in patients with >50% stenosis in at least two major coronary vessels arguing for pronounced and multiple stenotic lesions. Finally, the derived variant (rs1084651) of the *LPA* gene was significantly associated with CAD.

Conclusion: Our study highlights the importance of Lp(a) levels as an independent biological marker of severe and multiple coronary artery stenosis.

Keywords: lipoprotein(a), cardiovascular diseases, stenosis

Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally. According to the WHO, almost 20 million people died from CVD in 2020 with 85% of the cases blamed on coronary artery disease (CAD) and stroke. Together, these two latter manifestations account for about 70% of the total deaths in the United States alone.[1] Recently, there has been a major focus on the identification of tractable risk factors for CAD and their interactions with classical risk factors involved in the onset and progression of these pathologies. These efforts are geared towards the development of effective prevention of first and recurrent episodes of cardiovascular events.[2–4]

The National Heart Lung and Blood Institute (NHLBI) report in 2018 estimated that 1.4 billion people worldwide have Lp(a) levels ≥ 50mg/dL, with a prevalence of 10–30% and even higher in patients with atherosclerotic

Received: 31 October 2022
Accepted: 21 December 2022
Published: 19 January 2023

cardiovascular disease (ASVCD), calcific aortic valve disease (CAVD) or chronic kidney disease.[5] Lp(a) concentration distributions vary with populations.[6] High concentrations of Lp(a) have been long linked to increased risk of development of ischemic CVD and especially coronary heart disease and atherosclerosis.[7–10] In 2016, the Canadian guidelines recommended the screening for Lp(a) levels in people at risk of CVD.[8]

In Korea, measuring Lp(a) in a group of patients with CAD undergoing coronary angiography helped stratifying these patients into different categories of risk for CVD: those with higher levels of this biomarker were at a significantly increased risk of major adverse cardiovascular events.[11]

In vitro and in vivo studies have implicated the role of Lp(a) in atherosclerosis, foam cell formation, plaque inflammation, and instability while some identified the Lp(a) antigen in arterial lesions.[12–14] Human Lp(a) is an unusual serum lipoprotein characterized by the presence of a unique plasminogen-like glycoprotein apolipoprotein(a) (apo(a)) covalently linked to apolipoprotein B-100 (apoB100) by disulfide bridges.[15] Apo(a) is readily released from the lipoprotein particle by mild reductive cleavage with disulfide reducing agents.[16] The reduced lipoprotein, free of apo(a), is virtually identical to LDL-C in its physicochemical properties and its cellular uptake by the LDL receptor in cultured human fibroblasts.[17] Although LDL-C and Lp(a) are structurally similar, the two lipoproteins appear to be under separate metabolic control and differ in function. Lp(a) is the preferential lipoprotein carrier for oxidized phospholipids, a proinflammatory and proartherogenic biomarker.[5,18]

The clinical cut-off value for Lp(a) is population-specific.[19] Despite the dynamics of Lp(a) with lipids along with its role in CVDs, studies of population-specific associations of Lp(a) levels and CAD are sparse or lacking. The aim of this study is to investigate the association of elevated Lp(a) levels with CAD in a study population of Lebanese patients. It also evaluates the correlation of different confounding factors and comorbidities with Lp(a) levels.

Materials and Methods

Study Subjects and Data Collection

A total of 268 Lebanese patients were included in this study. These patients were part of a larger and comprehensive investigation on coronary artery disease, the FGENTCARD Consortium which became part of the CARDIoGRAMplusC4D (http://www.cardiogramplusc4d.org/). For the current study, patients who underwent coronary artery angiography and who had Lp(a) serum level measurements available were included. 20 mL of blood was collected after 12 hours fasting. For DNA extraction, blood was collected on EDTA-containing tubes. For biochemical and serological testing, plasma and serum were collected on gel separator tubes. All subjects received a brief description of the study; they were informed that their participation was voluntary and were assured of the anonymity of their participation. Patients who agreed to participate gave their informed consent before enrollment in the study. The Institutional Review Board (IRB) of the Lebanese American University gave approval for the study protocol. All protocols were performed according to the Helsinki Declaration of 1975. After signing the informed consent, patients responded to a questionnaire about their medical history and traditional CAD risk factors, administered by a trained health worker. Additional clinical information was obtained from patients' medical charts.

Family history (Fx) of CAD was considered positive when a sibling, parent, or first-degree relative had a coronary event before the age of 55. The age of CAD onset was defined as the age of the patient when he/she was diagnosed with CAD by cardiac catheterization. Patients were considered hypertensive if they were being treated with antihypertensive medications or diagnosed by their clinician as indicated in their medical chart. Patients were reported as diabetic if they were being treated with blood glucose lowering medication or diagnosed by their clinician as indicated in their medical chart. Patients were considered to have hyperlipidemia if they were treated with medication to treat dyslipidemia or diagnosed by their clinician as indicated in their medical chart. HDL-C and LDL-C were measured on COBAS INTEGRA 400 Plus using fasting blood samples collected from patients. The particle enhanced Lp(a) immunoturbidimetric assay from Roche was used on a COBAS c501 chemistry analyzer according to the manufacturer protocol. The height and weight of each patient were measured by the interviewers using well-calibrated scales and Body Mass Index (BMI) was calculated as per standard measurements. Additional data were retrieved from medical charts (laboratory tests, prescribed medications, and presence of other diseases and conditions). Angiography was performed to visualize

the major coronary arteries: the left main coronary artery (LMCA), the left anterior descending artery (LAD), the right coronary artery (RCA), and the left circumflex coronary artery (Cx). The resulting angiograms were reviewed by two cardiologists who estimated the extent of coronary lesions visually upon comparison of the diameter of the studied artery to a proximal arterial segment that was assumed normal. This examination resulted in the classification of each of the four main arteries into two categories: controls were subjects with ≤50% stenosis in any of the 4 coronary arteries and cases were patients with >50% stenosis in any of the 4 coronary arteries. For multinomial regression analysis, patients with ≤50% stenosis were considered controls; patients with >50% stenosis in one vessel were considered CAD category 1; patients with >50% stenosis in 2 vessels were considered CAD category 2; and patients with >50% stenosis in more than 2 vessels were considered CAD category 3.

Statistical Analysis

In this cross-sectional study, all data collected on the enrolled participants were electronically recorded, and their analysis was processed by the R package (R version 4.1.2). Three Lp(a) categories were used in this analyses: 1) 80th percentile according to the 2016 European Atherosclerosis Society (EAS) guidelines,[20] 2) a cut-off of 50 mg/dL as recommended by the 2010 European guidelines[21], and 3) a cut-off of 30 mg/dL; the clinically relevant value adopted by most US clinical laboratories.[22] The absolute cut-offs of 30 and 50 mg/dL represent the 43rd percentile and the 67th percentile in our study, respectively. Obese individuals were defined as people with BMI ≥30 Kg/m^2. Older patients were defined as patients aged ≥65. High HDL was defined as HDL ≥ 35 mg/dL, and high LDL was defined as LDL ≥ 100 mg/dL. Continuous variables such as age, BMI, total-cholesterol, HDL-C, LDL-C, C-reactive protein (CRP), triglycerides, fasting blood sugar (FBS), and homocysteine were stratified by each category and dependence was tested with Two Sample *t*-test. Categorical variables (older age, gender, diabetes, hypertension, obesity, high LDL, high HDL, Fx CAD, statin intake, CAD, CAD category, and smoking) were compared between the Lp(a) categories using the X^2 test. Pearson product-moment correlation coefficient between Lp(a) levels and HDL levels was calculated.

Generalized linear model (GLM) binomial logistic regression was computed in R to study the association of High Lp(a) [(Lp(a)≥30, Lp(a)≥50 and Lp(a)≥80th percentile)] and CAD risk factors. In addition, binomial logistic regression model was applied with CAD (>50% lesion) as an outcome variable and high Lp(a) [(≥30 mg/dL, ≥50mg/dL and ≥80th percentile)] as a predictor variable. We subdivided patients according to LDL concentration and HDL concentration: High LDL group (LDL ≥ 100 mg/dL), Low LDL group (LDL < 100 mg/dL), High HDL group (HDL ≥ 35 mg/dL) and Low HDL group (HDL < 35 mg/dL). We also subdivided the patients according to gender and obesity: obese group (BMI ≥ 30 Kg/m^2) and non-obese group (BMI < 30 Kg/m^2).

Multinomial logistic regression model predicting CAD category 1, 2 or 3 was computed in R using multinom function. Lowess spline curve was plotted using GraphPad Prism 9 for the relationship between CAD categories and Lp(a) levels.

SNPs (Single Nucleotide Polymorphisms) genotyping was performed using the Illumina Human610-Quad BeadChip and the Illumina Human660W-Quad BeadChip (552,510 overlapping SNPs). The BeadChip array included 13 SNPs in the *LPA* gene region. Association analyses between CAD and Lp(a) SNPs were performed using PLINK 1.9 (www.cog-genomics.org/plink/1.9/). The Hardy-Weinberg equilibrium (HWE) was tested with X^2 test.

Results

Lp(a) was measured in 268 subjects. The distribution was skewed to the right with a median of 33.7 mg/dL and an interquartile range (IQR) of 44.775 (Q3 = 63.375 and Q1 = 18) and a mean of 45.13 mg/dL ± 38.64 (standard deviation (SD)) (Supplementary Figure 1).

CAD Associations with Lp(a) and HDL Levels

Lp(a) was correlated positively and significantly with CAD (stenosis>50%), HDL-cholesterol and BMI (Table 1). HDL was found significantly more elevated in patients with Lp(a) ≥30 mg/dL when compared with those with Lp(a) <30 mg/dL (45.928 ± 13.507 vs 41.862 ± 9.607, P = 0.006) (Table 2). In addition the regression models showed that diabetes and Fx CAD were positively associated with Lp(a) ≥30 with OR = 7.78 (P = 0.04) and OR = 1.95 (P = 0.04), respectively

Table 1 Regression Between Lp(a) and CAD Risk Factor

	Total Cholesterol	HDL	LDL	BMI	Age	CAD	Hyper tension	Diabetes	Male	Obesity	Smoking	Older Age	High HDL	High LDL
Coefficient	0.05	0.52	0.04	−1.1	0.26	13.65	6.8	10.068	−2.6	−4.9	−7.7	2.4	6.38	−4.12
***P*-value**	0.25	**0.006**	**0.4**	**0.03**	0.16	**0.006**	0.14	0.06	0.60	0.3	0.14	0.6	0.28	0.44

Notes: CAD: patients with > 50% stenosis. Obesity: BMI ≥30 Kg/m^2. High HDL: HDL ≥ 35 mg/dL. Low HDL: HDL<35 mg/dL. High LDL: LDL ≥ 100 mg/dL. Low LDL: LDL<100 mg/dL. Older age: patients aged ≥ 65. Statistically significant values (P-value<0.05) are emphasized in bold.
Abbreviation: Lp(a), Lipoprotein(a).

(Figure 1). Using the Lp(a) ≥ 80th percentile as a cut-off, only HDL was found significantly more prevalent (Table 2). In addition, among the three Lp(a) categories, only Lp(a) ≥30 mg/dL was found significantly associated with CAD (stenosis >50%) and with CAD category (P = 0.002) (Supplementary Table 1). Lp(a) at the 80th percentile was found to be significantly correlated with statin intake (P = 0.025).

The correlation plot between Lp(a) and HDL-C levels (Supplementary Figure 2A) showed a significant positive correlation with Pearson's r = 0.18 and P = 0.004. In addition, more than half of CAD patients (51.67%) have HDL-C ≥35 mg/dL and Lp(a) ≥30 mg/dL (Supplementary Figure 2B). When comparing the levels of Lp(a) in patients with HDL ≥35 mg/dL, 93 CAD patients were in the category of Lp(a)≥ 30 mg/dL vs 54 in the Lp(a) <30 category indicating that high HDL levels (≥ 35 mg/dL) and low Lp(a) levels (<30 mg/dL) were the least associated with CAD (Supplementary Figure 2D).

Logistic regression analyses were applied with CAD cases (>50% lesion) as an outcome variable and high Lp(a)≥30 mg/dL as predictor variable (Supplementary Figure 3). High Lp(a) was found positively and significantly associated with CAD (OR = 2.27; P = 0.002) even after adjustment for age and sex (OR = 2.52, P = 0.002). The association between high Lp(a) and CAD was stronger in patients with high HDL (OR = 2.87, P = 0.001) and in the non-obese patients (OR = 3.15, P = 0.004), after adjustment for age and sex. Among patients with high LDL, the OR was 2.41 (P = 0.01), and among younger patients the OR was 2.44 (P = 0.014). Among males, the association decreased to OR = 1.04 (P = 0.01) however, among females the association between CAD and high Lp(a) was not significant. The association between CAD and Lp(a) ≥50 and Lp(a) ≥80th percentile was also tested (Supplementary Figure 3). CAD was only significantly associated with Lp(a) ≥50 or Lp(a) ≥80th after adjustment for age and sex (OR = 2.29, P = 0.004). In addition, among patients with high HDL and low LDL, and among non-obese, male and younger patients, the association between CAD and Lp(a) ≥50 and Lp(a) ≥80th percentile was only significant after adjustment for age and sex. In these two Lp(a) categories, the association between CAD and high Lp(a) was stronger among patients with high HDL and non-obese patients.

Lp(a) Levels and Number of Vessels with Stenotic Lesions

The distribution of patients according to their Lp(a) levels and stenosis is shown in Supplementary Figure 4. Lp(a) levels were significantly more elevated in patients with >50% stenosis than in subjects with ≤50% stenosis in the LAD (53.1 ± 3.43 vs 36.1 ± 3.01 mg/dL, P = 0.0002) and in the left circumflex coronary artery (53.7 ± 4.15 vs 40 ± 2.78 mg/dL, P = 0.004).

Results of the regression analysis with stenosis in the 4 major coronary arteries as an outcome variable and high Lp(a) [(Lp(a)≥30, Lp(a)≥50 and Lp(a)≥80th percentile)] as predictor variable are shown in Supplementary Table 2. Lp(a)≥30 was significantly associated with the presence of more than 50% stenosis in the LAD (P = 0.03; OR = 1.89), the RCA (P = 0.01, OR = 2.14) and the circumflex (P = 0.02; OR = 2.07). Lp(a)≥50 and Lp(a)≥80th percentile were found significantly associated with stenosis in two arteries, the RCA and the circumflex.

A Lowess curve illustrating the relationship between the number of vessels with >50% lesion and Lp(a) levels is shown in Supplementary Figure 5. The shape of the association of the number of stenosed vessels with Lp(a) levels was positive and broadly linear. The regression coefficients of the association between CAD category (defined as the number of vessels with >50% lesion) and Lp(a) levels (Supplementary Table 3) showed significant and positive associations

Table 2 Clinical and Biochemical Features of the Study Population by Lp(a) Categories

	Lp(a)<30	Lp(a)≥30	P	Lp(a)<50	Lp(a)≥50	P	Lp(a)<80th Percentile	Lp(a)≥ 80th Percentile	P
	N= 116 (43%)	N= 152 (57%)		N= 180 (67%)	N= 88 (33%)		N= 214 (80%)	N= 54 (20%)	
Age	58.897 ± 11.173	59.197 ± 11.703	0.832	58.767 ± 11.040	59.682 ± 12.308	0.54	58.421 ± 11.402	61.630 ± 11.419	0.066
BMI (Kg/m^2)	29.437 ± 4.602	28.525 ± 4.024	0.089	29.267 ± 4.413	28.186 ± 3.978	0.059	29.083 ± 4.394	28.264 ± 3.869	0.223
Total cholesterol (mg/dL)	197.147 ± 44.064	206.184 ± 49.643	0.122	198.400 ± 46.112	210.193 ± 49.360	0.056	202.131 ± 48.151	202.833 ± 44.915	0.923
LDL cholesterol (mg/dL)	118.191 ± 33.356	125.987 ± 42.453	0.105	119.944 ± 38.300	128.091 ± 39.817	0.108	122.662 ± 39.652	122.500 ± 36.246	0.978
HDL cholesterol (mg/dL)	41.862 ± 9.607	45.928 ± 13.507	**0.006**	43.244 ± 11.886	46.057 ± 12.453	0.074	43.397 ± 11.560	47.222 ± 13.841	**0.038**
CRP (mg/L)	8.060 ± 11.811	10.999 ± 16.355	0.104	8.258 ± 11.886	12.754 ± 18.758	**0.018**	8.976 ± 13.141	12.681 ± 19.212	0.096
Homocysteine (μmol/L)	13.679 ± 6.537	12.967 ± 5.901	0.351	13.222 ± 5.896	13.383 ± 6.765	0.841	13.427 ± 6.610	12.674 ± 4.060	0.425
Triglyceride (mg/dL)	197.931 ± 122.163	195.250 ± 129.272	0.863	195.622 ± 123.664	198.023 ± 131.411	0.884	201.799 ± 132.602	175.056 ± 93.572	0.164
FBS (mg/dL)	111.422 ± 35.532	119.539 ± 48.070	0.128	115.383 ± 41.153	117.341 ± 47.352	0.728	117.883 ± 45.111	108.667 ± 34.018	0.162

Notes: Data are mean values followed by ± standard deviation. The *p*-value (P) is generated using Two Sample *t*-test. P-value is significant if P-value < 0.05. Statistically significant values (P<0.05) are emphasized in bold.
Abbreviations: CRP, C-Reactive Protein; Lp(a), Lipoprotein(a); Fx CAD, family history of coronary artery disease; FBS, fasting blood sugar.

https://doi.org/10.2147/VHRM.S394134 DovePress

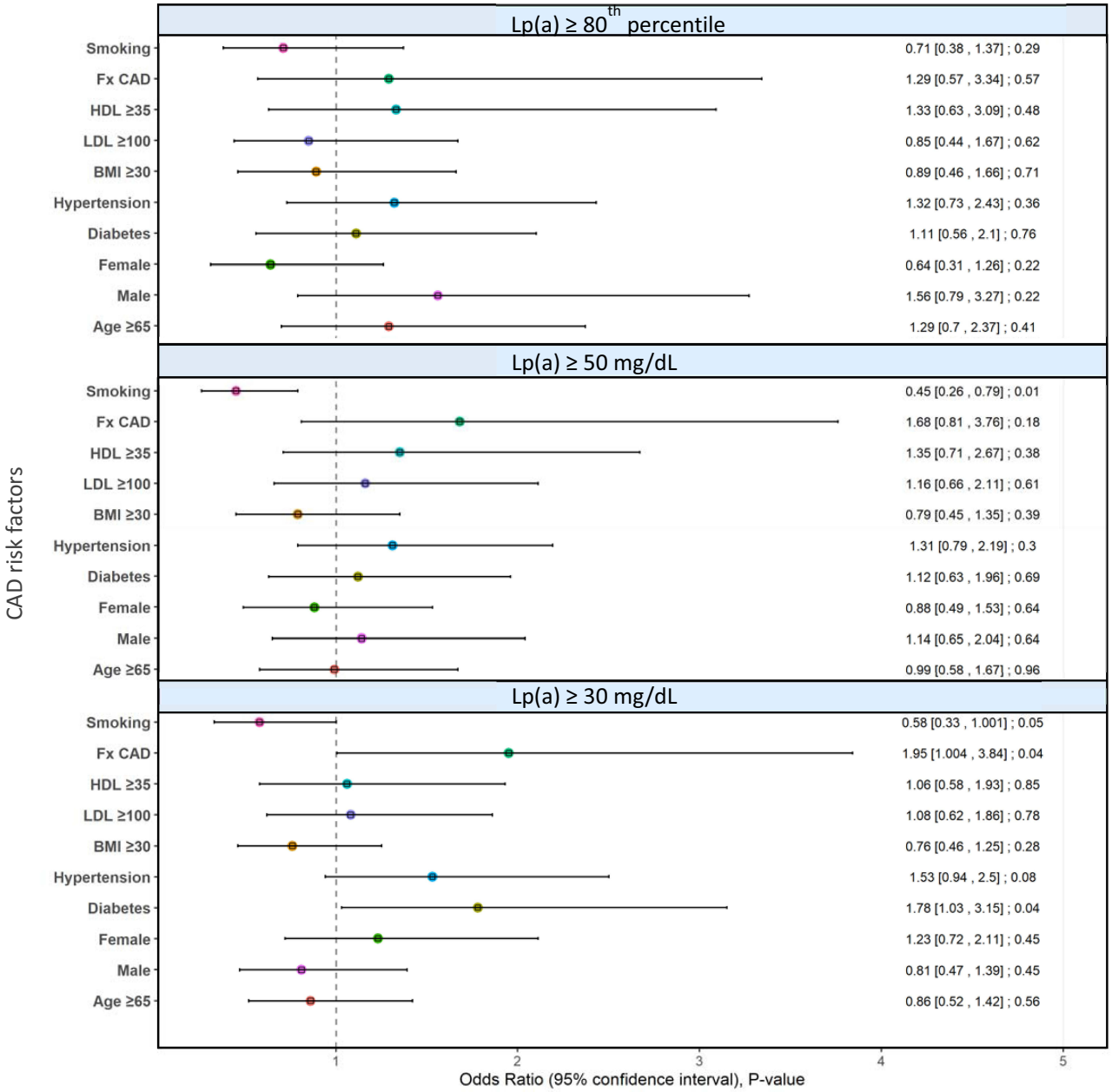

Figure 1 Binomial logistic regression analysis between the different categories of Lp(a) and CVD risk factors. The squares indicate odds ratios for high Lp(a), and the horizontal lines indicate 95% confidence intervals (CI). Obesity: BMI ≥30 Kg/m^2. Older age: patients aged ≥65. High HDL: HDL ≥ 35 mg/dL. High LDL: LDL ≥ 100 mg/dL.

between Lp(a) levels and stenosis in 2 vessels and in 3 to 4 vessels. The odds ratios for multinomial logistic regression using CAD category as an outcome variable and High Lp(a) (three categories) as predictor are shown in Figure 2. Only Lp(a) ≥30 mg/dL was a significant predictor of >50% stenosis in 2 vessels (CAD category 2: OR = 3.57, P = 0.001) and in 3 to 4 vessels (CAD category 3: OR = 2.7, P = 0.005).

Associations of *LPA* Variants with CAD

Results from PLINK association analysis for the 13 SNPs in the *LPA* gene investigated in the CAD population are shown in Table 3. Only one SNP, rs1084651 (G>A), displays nominal significance (P =0.04) for association with CAD (OR = 3.18). The frequency of the derived allele rs1084651*A in CAD cases is 0.07 and the allelic frequencies were in agreement with the HWE (P >0.05).

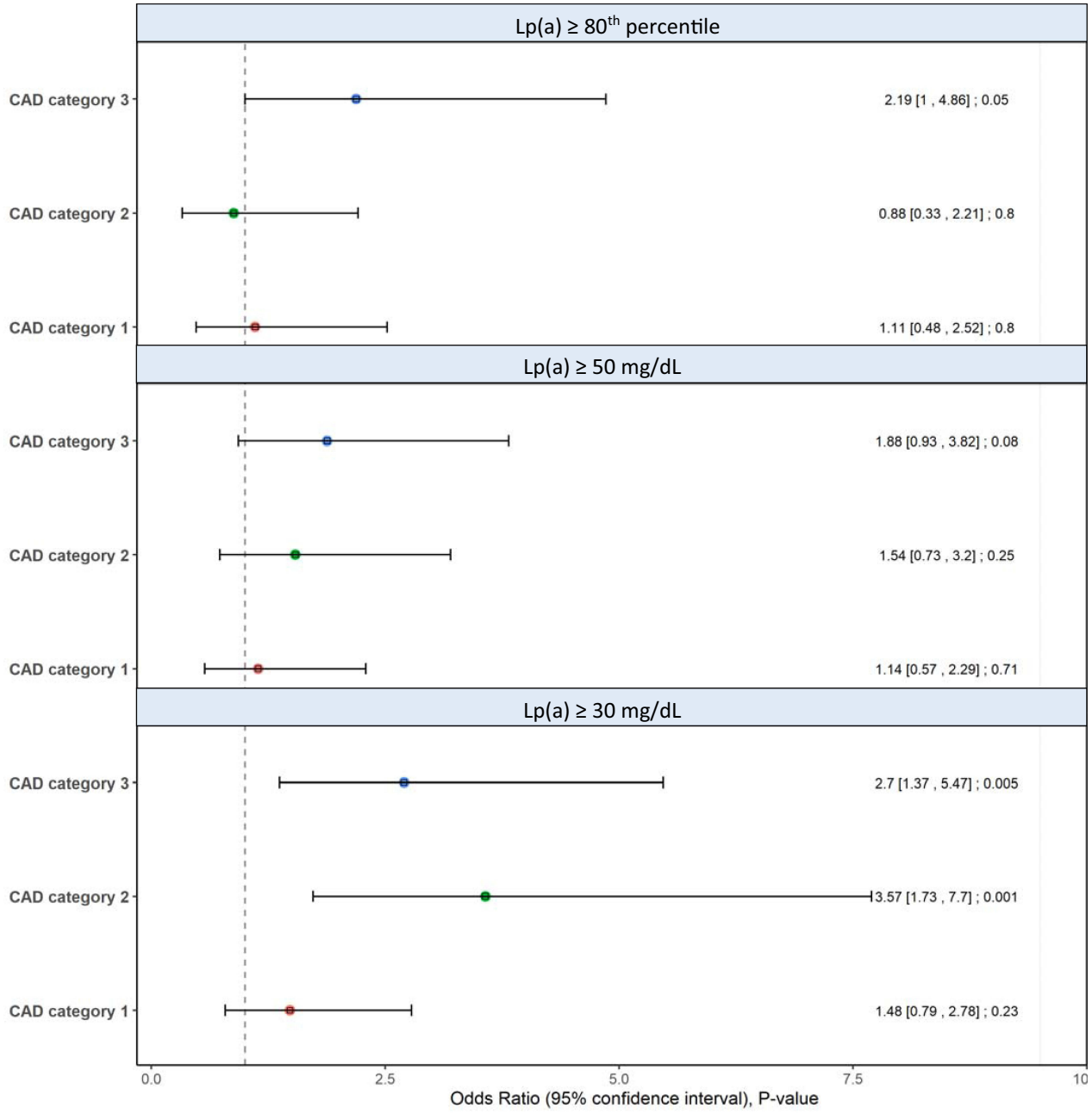

Figure 2 Multinomial logistic regression analysis between CAD category (number of vessels with >50% stenosis) and Lp(a) ≥30 mg/dL, Lp(a) ≥50 mg/dL and Lp(a) ≥80th percentile. CAD category 1: patients with >50% stenosis in one vessel; CAD category 2: patients with >50% stenosis in 2 vessels; and CAD category 3: patients with >50% stenosis in 3 or 4 vessels. Values are odds ratio (95% Confidence Interval).

Discussion

The Lp(a) distribution varies broadly according to ethnicity,[23] and presents a broad and skewed distribution to the right (toward higher Lp(a) values), which is largely controlled by genetic variants in the *LPA* gene on 6q27. The clinical cut-off of Lp(a) may be determined by ethnicity-based differences in the Lp(a) distribution pattern. Despite the demonstrated dynamic interaction between Lp(a) and its impact on CAD, guidelines that indicate clinically relevant levels of Lp(a) have not yet been established. The 2016 European Atherosclerosis Society (EAS) guidelines used the 80th percentile of Lp(a), the 2010 European guidelines used 50 mg/dL, and most US clinical laboratories use 30 mg/dL as clinical relevant cut-offs. Given these variable guidelines and the lack of international consensus on a common clinically relevant Lp(a) level cut-off value, we tested all three suggested Lp(a) cut offs in our cross-sectional study. Our study confirms the strong

Table 3 Association of SNPs in *LPA* with Risk of Coronary Artery Disease

SNP	Chromosome	Position	Gene	A1	A1 Frequency	A2	OR	*P*-value
rs6919346	6	160,880,349	*LPA*	T	0.16	C	1.10	0.4
rs7449650	6	160,957,114	*LPA*	T	0.46	G	1.06	0.4
rs11751605	6	160,963,230	*LPA*	C	0.02	T	1.37	0.3
rs7761293	6	160,970,963	*LPA*	A	0.40	G	0.98	0.7
rs6415084	6	160,980,330	*LPA*	C	0.50	T	1.15	0.4
rs9365171	6	160,981,736	*LPA*	A	0.45	C	0.86	0.07
rs6923877	6	160,916,787	*LPA*	G	0.44	A	0.87	0.1
rs3798221	6	160,918,138	*LPA*	T	0.33	G	0.96	0.6
rs9355296	6	160,937,983	*LPA*	A	0.07	G	0.80	0.1
rs13202636	6	161,029,728	*LPA*	C	0.21	T	1.02	0.8
rs10945682	6	161,069,941	*LPA*	A	0.32	G	0.93	0.3
rs783149	6	161,088,918	*LPA*	A	0.20	C	1.09	0.4
rs1084651	6	161,089,817	*LPA*	A	0.07	G	3.18	0.04
rs1358754	6	161,090,520	*LPA*	A	0.09	C	0.81	0.5

Abbreviations: SNP, Single Nucleotide Polymorphisms; A1, minor allele; A2, major allele; OR, odd ratio.

correlation between Lp(a) levels and severe coronary artery stenosis, and shows that the risk of stenosis is present even at low levels of Lp(a).

Reports on Lp(a) levels and their correlation with cholesterol in the settings of CAD remain conflicted. Lipoproteins are complex particles consisting of a central core containing triglycerides and cholesterol esters surrounded by free cholesterol, apolipoproteins, and phospholipids. These components facilitate lipoprotein formation and function.[24] Low-density lipoprotein cholesterol (LDL-C) is implicated in lesion formation and growth, while high-density lipoprotein cholesterol (HDL-C) exerts a protective role against atherosclerosis.[25,26] Recent studies showed that vascular disease recurrence in patients with high levels of Lp(a) (≥50 mg/dL) is attenuated only at very low LDL-C (<55 mg/dL) but not when LDL levels ≥70 mg/dL.[27,28] Kinetic studies suggest a preferential accumulation of Lp(a) particles in vessel walls which may increase the artherogenic potential of Lp(a) cholesterol over LDL-C. High levels of Lp(a) are highly correlated with rapid progression of coronary atherosclerosis, a strong predictor of adverse outcome. Patients with high Lp(a) levels develop high risk unstable plaques with complex morphology which are prone to rupture. Further studies showed a correlation between CAD, elevated plasma levels of Lp(a), and LDL-C levels < 100 mg/dL.[29,30] Our findings are consistent with these recent studies, suggesting that at low LDL levels the impact of Lp(a) maybe rather more apparent than pronounced.

High Lp(a) levels were also correlated with CAD and HDL irrespective of the HDL concentration which is paradoxically supposed to yield a protective effect against CAD.[31,32] Our data showed that even in the presence of high HDL serum levels (≥35 mg/dL), high levels of Lp(a) (≥30 mg/dL) yielded increased number of patients with CAD, thus dampening the protective effect exerted by HDL on artery stenosis. Observational studies have demonstrated that HDL can be converted to a dysfunctional form in the presence of conditions associated with systemic and vascular inflammation and therefore the anti-atherosclerotic effects of normally functioning HDL can be frequently impaired.[33,34] We specifically established that higher levels of Lp(a) are significantly associated with multiple lesions as well as stenosis percentage (>50%) which suggests that Lp(a) is a marker for severe and multiple lesions. Even though Lp(a) measurements in people at risk of CAD are recommended,[35] this has not yet gained recognition by practicing physicians. While some results might propose an effective treatment for high Lp(a) levels such as PCSK9 inhibitors,[36,37] additional investigations are warranted to translate into mainstream therapies. Current therapies involving the use of specific antisense oligos targeting Lp(a)[38] remain with undetermined efficiency in reducing CAD.

High Lp(a) is positively associated with stenosis in the RAD and the circumflex which show a clear tendency towards an increased risk of stenosis with increasing Lp(a) levels, even when the Lp(a) ≥30 mg/dL was considered. In addition, only Lp(a) ≥30 increases the risk of stenosis in the LAD. The non-significant correlation between the elevated levels of Lp(a) and stenosis of the LMCA (>50% stenosis) could be due to the following: first, the limited number of patients in

this category (mainly due to low survival rate of patients with occlusion of LMCA) since stenosis of LMCA is the highest-risk subset of ischemia,[39] and similar studies reported this limitation[40] and second, the difference in the diameter of the LMCA (relatively wider) in comparison with the other coronary arteries. Given that LMCA is the widest coronary artery in diameter,[41,42] CAD stenosis is inversely proportional to the diameter of the individual coronary artery.[43,44]

The role of Lp(a) in the development and progression of atherosclerotic plaques has been well established in humans.[45,46] Several landmark studies provided evidence that Lp(a) is a causal factor in the atherothrombotic process.[47] The risk of Lp(a) on CAD stenosis is not limited to the ability of this molecule to promote atherogenesis in the coronary arteries, but it extends to its role in thrombosis.[45] Lp(a) inhibits endothelial cell plasmin activity which in turn inhibits TGB-beta in the aortic wall and serum concomitantly promoting the proliferation of vascular smooth muscle cells, the hallmark of atherosclerosis.[48,49]

In genome wide association studies of case–control cohorts, the *LPA* locus on chromosome 6 (6q26-q27) had the strongest association with coronary heart disease[50], with several SNPs in the *LPA* locus reaching genome wide significance for the presence of aortic-valve calcification, a finding which was repeated across multiple ethnic groups. In our study, rs1084651, a SNP in an intron of the *LPA* gene, was found strongly associated with CAD. This SNP has been previously found associated with elevated total cholesterol and HDL-C.[51]

The ability of Lp(a) to escape lipid lowering drugs poses a great risk for individuals predisposed to hyperlipidemic profile. In fact, in the absence of an effective therapy to reduce Lp(a), the solely recommended approach remains apheresis of Lp(a)[52] in view to reduce the risk of cardiovascular disease. However, apheresis is expensive and is unavailable in most countries. Recently, results from several clinical trials using siRNA have yielded drugs with effective Lp(a)-lowering abilities however, their therapeutic impact on CAD is yet to be fully elucidated.[53,54]

In conclusion, we established herein a robust correlation between Lp(a) levels and CAD and determined Lp(a) as a primary marker for severe stenosis and multiple stenotic lesions. Our study underscores the necessity to evaluate Lp(a) levels in blood at an early age among patients with high-risk conditions as a prophylactic approach to reduce Lp(a)-mediated risk of CAD, and assess the clinical benefits of novel and potent lipoprotein lowering therapies.

Given the cross-sectional study-design, the cut-off threshold values for Lp(a) used should be interpreted with caution as they do not necessarily demonstrate clinical significance. Hence, the need to investigate Lp(a) levels and CAD risk in multiple populations to determine appropriate clinical relevance for each population as demonstrated here. Further, additional data and a larger study population is required to fully elucidate this interaction and to determine whether the high Lp(a) levels negate the beneficial effect of HDL-C. Concerted efforts to understand Lp(a) pathophysiology, the biochemical triggers associated with increased Lp(a) levels, and its relationship and dynamic with HDL-C is warranted. One of the study limitations is the relatively small number of patients on whom Lp(a) values are available. As with every cross-sectional retrospective study, limited access to prospective data presents many challenges. To mitigate that problem, we selected three different Lp(a) values to better evaluate its clinical importance in discriminating its impact on CAD.

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.

Disclosure

The authors report no conflicts of interest in this work.

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