RESEARCH ARTICLE

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Serum Lipoprotein(a) as a Marker of Severity of Coronary Artery Disease in Aortic Valve Sclerosis Patients

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Abstract

Background and Aim: Aortic valve sclerosis (AVS) and severity of coronary artery disease (CAD) share common risk factors, but not all patients have the same severity of coronary lesions. Lipoprotein(a) [Lp(a)] is a significant, causal, and non-modifiable indicator of valvular outcomes and CAD in the general population. This study aimed to evaluate the correlation between serum Lp(a) level and CAD severity in individuals with AVS.

Materials and Methods: This cross-sectional study was conducted in 100 individuals with an established diagnosis of AVS who had chest pain and/or dyspnea and were provisionally diagnosed with CAD. Participants were subdivided into two groups: the normal-level group (n=42), with a cut-off serum Lp(a) level of 30 mg/dL. High level group (n=58): high-risky Lp(a) level.

Results: A significant correlation was observed between the number of diseased epicardial coronary arteries and high Lp(a) levels [51.73% vs. 4.77% for 3-vessel disease, and 3.45% vs. 66.66% for one-vessel disease, in the high and normal Lp(a) groups, respectively] ($P < 0.001$). SYNTAX score had been elevated (35.07±6.08) in those with elevated Lp(a) level contrasted to reduced Lp(a) (14.76±4.5 SD) ($P < 0.001$).

Conclusion: Elevated serum Lp(a) was significantly associated with greater coronary lesion severity and higher SYNTAX scores among patients with AVS.

Keywords: Lipoprotein(a), aortic valve, lipid marker, coronary artery disease.

INTRODUCTION

Aortic valve sclerosis (AVS) is characterized by focal or diffuse aortic valve thickening without significant hemodynamic obstruction.[1,2] Despite its lack of effect on aortic valve function and subsequent benign classification, multiple studies in the last several years have linked AVS to an escalated risk of cardiovascular (CV) death in the general population and at-risk subsets.[3]

There is an initial stage of AVS pathophysiology that includes lipid infiltration, inflammation, and oxidation, and a subsequent stage that includes calcification and fibrosis of the aortic cusps.[4] Bicuspid aortic valve is the primary etiology of AVS in persons aged 70 years or younger and results in a more intense progression of AVS.[5]

No medical therapy existed to lessen the manifestations or to halt or slow the AVS progression.[6] Currently, surgery or transcatheter AV replacement is the only technique known

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to improve survival rates. Half of all patients exhibiting AVS symptoms will die over the next 12 to 18 months unless surgical intervention is attempted.[7]

In recent years, there has been growing interest in lipoprotein(a) [Lp(a)] as an important, largely genetically determined, and relatively non-modifiable biomarker associated with valvular outcomes and coronary artery disease (CAD)s in the general population.[8,9]

Lp(a) is a cholesterol-dense particle comprising the large glycoprotein apolipoprotein (a) [apo(a)], which is covalently linked to apolipoprotein B-100 by a single disulfide bond. The genetic background is the primary determinant of circulating serum Lp(a) levels, mediated by the *LPA* gene that encodes apo(a).[10] Apo(a) has a protease-like domain, a kringle V domain, and a kringle IV repeat domain (KIV), all of which share a high degree of sequence similarity with plasminogen. A strong inverse association existed between Lp(a) concentration in plasma and the number of KIV2 repeats, which are responsible for the substantial size variation in apo(a) isoforms. The apo(a) sequence only contains one repeat of KIV2.[11]

The pathophysiological mechanism of Lp(a) activity remains under investigation. Lp(a) has been suggested to transport cholesterol to the leaflets of the valves, thus promoting the microcrystals formation, that could lead to calcification.[12] Elevated inflammation and oxidative stress are prevalent pathophysiological contributors to vascular endothelial dysfunction and to the earliest phases of valvular osteogenesis. Lp(a) is additionally the principal carrier of oxidized phospholipids, that cause these conditions.[13]

Numerous researchers have proposed that Lp(a) might serve as an independent risk factor for cardiovascular system (CVS) illness[14,15] and have noted a favorable correlation between serum Lp(a) levels and both the severity and frequency of CV disease.[16]

Consequently, we aimed to ascertain the relationship between serum Lp(a) levels and the degree and complexity of coronary lesions as assessed by the SYNTAX score in individuals with AVS.

METHODS

Design and Population

This cross-sectional study was conducted on 100 participants with an established diagnosis of AVS who had chest pain and/or dyspnea and were provisionally diagnosed as CAD.

The study was conducted following approval by the Local Research Ethics Committee of the Faculty of Medicine, Sohag University, in accordance with the Declaration of Helsinki (approval no: Soh-Med-24-09-5PD, date: 11.09.2024). Verbal informed consent was obtained from all participants. ClinicalTrials registration was not required for this study.

Eligibility Criteria

Exclusion criteria were aortic stenosis, previous aortic valve prosthesis, chronic kidney failure, untreated hypothyroidism, pregnancy, and regular use of systemic immunosuppressive or anti-inflammatory medications, including chronic corticosteroids, disease-modifying antirheumatic drugs, biologic immunosuppressive agents, or long-term non-steroidal anti-inflammatory drugs for more than four weeks before enrollment.

Grouping

Participants were subdivided into two groups: the normal-level group (n=42), with a cut-off of serum Lp(a) level of 30 mg/dL. High level group (n=58): high-risky Lp(a) level.[17]

Clinical Evaluation and Baseline Data Collection

All of them had been exposed to comprehensive taking of history, clinical examinations, laboratory tests [blood sugar, kidney function tests (creatinine and blood urea nitrogen), full blood picture and lipid profile] and radiological investigations.

Assessments

Detailed echocardiography was performed to evaluate aortic valve structure and function, and to assess ejection fraction and segmental wall motion abnormalities.

Age, sex, the most prevalent risk factors for CV disease such as hypertension, dyslipidemia, diabetes mellitus (DM) and smoking in addition to the clinical justification for coronary angiography were all noted for each patient.

Coronary angiography was performed at a rate of 12.5 frames per second; digital angiographic images were captured using an angiography system (Philips Harvey IL 60426, USA, 2000).

Detailed analysis of coronary lesions by two observers was done to assess: [the diseased coronary arteries number, the severity of epicardial coronary lesions (significant lesions if >70%) and SYNTAX scoring for complexity of coronary lesions of each patient (low score (<22), moderate (22-33) and high score (≥34)].[18]

A venous blood sample was obtained from each patient during a scheduled follow-up visit approximately one month (4 weeks) after hospital discharge to measure serum Lp(a) levels. The samples were centrifuged for 10 minutes at 2-8 °C; the serum was then divided into aliquots and stored at -20 °C. The human

Lp(a) kit (Biotang Inc., HU9148) was used to determine the Lp(a) levels. We utilized the enzyme-linked immunosorbent assay.

No participants initiated PCSK9 inhibitors or underwent major changes in lipid-lowering therapy during this interval. As Lp(a) concentrations are predominantly genetically determined and relatively stable over time, major short-term fluctuations were considered unlikely.

Sample Size Calculation

Sample size was calculated using G*Power 3.1.9.2 (Universität Kiel, Germany). We conducted a pilot study (5 cases in each group) and found that the incidence of significant coronary lesions according to Lp(a) level was 40% in participants with normal Lp(a) levels and 70% in those with high Lp(a) levels. The sample size was based on the following considerations: an α error of 0.05, 80% power, and the addition of sixteen instances to account for dropout. Therefore, we recruited 100 cases for this study.

Statistical Analysis

Data were analyzed using STATA version 14.2 (Stata Statistical Software: Release 14.2 College Station, TX: StataCorp LP.). Quantitative data were expressed as mean and standard deviation (SD) and analyzed using the Student's t-test. Qualitative data were reported as numbers and percentages and analyzed using the chi-square test. Graphs were produced using Excel or STATA. Univariate regression was used to estimate the relationship between a dependent variable and one independent variable. Multivariate regression was also used to estimate the relationship between a dependent variable and multiple independent variables. A two-tailed *P*-value ≤0.05 will be considered statistically significant.

RESULTS

The mean age of the subjects in our research was 60.76 years with SD ±5.39 years, and 68% of them were males. We assessed the conventional CV risk factors and discovered their overlap. Among patients, 54% had dyslipidemia and 56% had arterial hypertension. DM also represented 56% of our population. Fifty percent of the patients were smokers. The mean low-density lipoprotein (LDL) of the subjects in our research was 116.9 mg/dL with SD ±32.35 mg/dL. Forty percent of the study population had a high SYNTAX score, 18% had an intermediate score, and 42% had a low score. The mean Lp(a) concentration was 39.8 mg/dL; 58% of patients had high blood levels of Lp(a) (>30 mg/dL), with a mean of 55.68 mg/dL, and 42% had low blood levels of Lp(a), with a mean of 16.68 mg/dL Table 1.

Patients with high levels of LP(a) had significantly higher rates of smoking (75.86% vs. 14.29%), hypertension (89.66% vs. 9.52%), DM (86.21% vs. 14.29%), and dyslipidemia (89.66% vs. 4.76%), a higher prevalence of a high SYNTAX score (68.97% vs. 0%), a higher proportion of males (75.86% vs. 57.14%), and higher mean age (63.83 vs. 56.52 years) and higher LDL (139.79 vs. 85.29 mg/dL) than patients with normal levels of LP(a) ($P < 0.05$) Table 2.

Hypertension and DM were more common in patients with significant lesions than in patients without significant lesions, but the difference was not statistically significant Table 3.

Additionally, we found that high serum Lp(a) levels showed a significant direct relationship with the number of diseased coronary arteries ($P < 0.001$), with 51.73% in three-vessel disease versus 3.45% in single-vessel disease. A significant increase in serum Lp(a) levels ($P < 0.001$) was associated with the severity of coronary lesions, with severe lesions accounting for 75.88% of individuals in the high Lp(a) group versus 24.12% with non-severe lesions in that group Table 4.

In univariate regression analysis, age, sex, smoking, hypertension, LDL, and Lp(a) were independent predictors of a high syntax score ($P < 0.05$). In multivariate regression analysis, LDL and Lp(a)were independent predictors of high syntax score ($P = 0.001$), while age, sex, smoking, and hypertension were not Table 5.

SYNTAX score had been significantly greater in the group with high Lp(a) level (35.07±6.08) than normal Lp(a) group (14.76±4.5) ($P < 0.001$) Figure 1.

Table 1. Demographic data and cardiovascular risk factors distribution of the studied population

		n=100
Age (years)		60.76±5.39
Sex	**Female**	32 (32.0%)
	Male	68 (68.0%)
Risk factors	**Smoking**	50 (50.0%)
	Hypertension	56 (56.0%)
	DM	56 (56.0%)
Lipid profile	**Normal**	46 (46.0%)
	High (dyslipidemia)	54 (54.0%)
LDL (mg/dL)		116.9±32.35
SYNTAX score	**Intermediate**	18 (18%)
	Low	42 (42%)
	High	40 (40.0%)
Lp(a)	**Normal level**	42 (42.0%)
	High level	58 (58.0%)

Data are presented as mean ± SD or frequency (%)

DM: Diabetes mellitus, LDL: Low-density lipoprotein, Lp(a): Lipoprotein(a), SD: Standard deviation

Table 2. Relation between demographic data and cardiovascular risk factors and Lp(a)

		Lp(a)		*P*-value
		Normal level (n=42)	High level (n=58)	
Age (years)		56.52±2.51	63.83±4.77	<0.001*
Sex	Female	18 (42.86%)	14 (24.14%)	0.048*
	Male	24 (57.14%)	44 (75.86%)	
Risk factors	Smoking	6 (14.29%)	44 (75.86%)	<0.001*
	Hypertension	4 (9.52%)	52 (89.66%)	<0.001*
	DM	6 (14.29%)	50 (86.21%)	<0.001*
Lipid profile	Normal	40 (95.24%)	6 (10.34%)	<0.001*
	High (dyslipidemia)	2 (4.76%)	52 (89.66%)	
LDL (mg/dL)		85.29±12.8	139.79±20.75	<0.001*
SYNTAX score	Intermediate	6 (14.29%)	12 (20.69%)	<0.001*
	Low	36 (85.71%)	6 (10.34%)	
	High	0 (0%)	40 (68.97%)	

Data are presented as mean ± SD or frequency (%)

DM: Diabetes mellitus, LDL: Low-density lipoprotein, Lp(a): Lipoprotein(a), SD: Standard deviation, *: Significant as $P < 0.05$

Table 3. Relation of angiographic significance of coronary lesions to conventional risk factors

		Non-significant lesions	Significant lesions	*P*-value
Hypertension	Yes	22 (39.28%)	34 (60.72%)	0.284
	No	22 (50%)	22 (50%)	
DM	Yes	28 (40%)	42 (60%)	0.218
	No	16 (53.33%)	14 (46.67%)	

Data are presented as frequency (%)

DM: Diabetes mellitus

Table 4. Comparison of the number of diseased epicardial vessels and angiographic significance of coronary lesions in relation to Lp(a) level

	Lp(a) *levels		*P*-value
	Normal level (n=42)	High level (n=58)	
Number of diseased epicardial vessels			
One vessel	28 (66.66%)	2 (3.45%)	<0.001*
Two vessels	12 (28.57%)	26 (44.82%)	
Three vessels	2 (4.77%)	30 (51.73%)	
Angiographic significance of coronary lesions			
Non-significant	30 (71.42%)	14 (24.12%)	<0.001*
Significant	12 (28.58%)	44 (75.88%)	

Data are presented as frequency (%)

Lp(a): Lipoprotein(a), *: Significant $P < 0.05$

DISCUSSION

Serum Lp(a) is a separate macromolecular lipoprotein characterized by significant homology and particular antigenicity, having an essential impact in the onset and progression of atherosclerosis and thrombosis by disrupting the lipid metabolism and fibrinolytic system, which is peculiar for Lp(a) other than alternative apolipoproteins.[19]

To our knowledge, our study is one of the few studies to use SYNTAX scores to assess the correlation between the severity of coronary lesions and Lp(a) in AVS patients.

Clinical factors correlated with aortic sclerosis including age, male gender, hypertension, smoking, diabetes, elevated serum Lp(a) levels and low-density lipoprotein.[20]

The Lp(a) concentrations varies significantly across various populations and it is mainly determined by hereditary factors.[21] However, its individual concentration remains relatively stable and is not influenced by the use of statins, patients' age, gender, diet, environment, smoking habit or lipid metabolism.[22]

AVS and the severity of CAD share common risk factors, but not all patients have coronary lesions of the same severity. Previous investigators did not clearly establish this relationship.

The present study is designed to identify the correlation between serum Lp(a) levels and the extent of CAD and the severity of coronary lesions in individuals with AVS.

A previous, similar study examined the impact of elevated Lp(a) levels on CAD. Maranhão et al.[23] proposed that Lp(a) might serve as an independent risk factor for CVS illness, whereas Nordestgaard et al.[22] noted a positive relationship between serum Lp(a) levels and both the incidence and severity of CV illness.

This outcome was comparable to the findings of Lima et al.,[24] Maher et al.,[25] Utermann,[26] and other prior research, which indicated that blood levels of Lp(a) gradually escalate in accordance with the severity of coronary atheromatosis.

Rajasekhar et al.,[27] noted that serum Lp(a) levels had been considerably elevated in triple vascular disease compared to single vessel disease, corroborating findings from earlier research.

Conversely, Schwartzman et al.[28] observed no significant variation in plasma Lp(a) levels across different CAD categories based on the number of affected arteries or angiographic disease severity, findings that were comparable to those of other researchers.[29] The discrepancy between their findings and ours may be explained by differences in study population and assessment methods. Our cohort specifically included patients with AVS, a condition that shares inflammatory, lipid-

Table 5. Univariate and multivariate logistic regression analyses of factors associated with high SYNTAX score

	Univariate			Multivariate		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (years)	1.591	1.35: 1.87	**<0.001***	1.1442	0.891: 1.47	0.292
Sex (female)	0.375	0.148: 0.951	**0.039***	0.405	0.039: 4.16	0.447
Smoking	15.58	5.51: 44.07	**<0.001***	3.15	0.664: 14.96	0.149
Hypertension	44.33	9.64: 203.79	**<0.001***	0.544	0.043: 6.93	0.639
DM	1.72	---	0.997	---	---	---
LDL (mg/dL)	1.089	1.06: 1.12	**<0.001***	1.086	1.038: 1.136	**0.001***
Lp(a)	1.277	1.134: 1.438	**0.001***	1.249	1.099: 1.421	**0.001***

CI: Confidence interval, DM: Diabetes mellitus, LDL: Low-density lipoprotein, OR: Odds ratio, LP(a): Lipoprotein(a), *: Significant $P < 0.05$

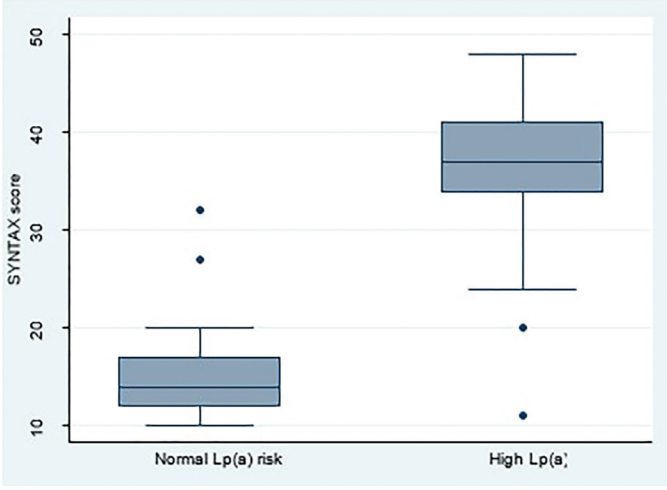

Figure 1. Comparison of mean serum lipoprotein(a) [Lp(a)] levels according to SYNTAX score categories, demonstrating significantly higher levels among patients with greater coronary lesion complexity

mediated, and calcific pathways with CAD. In addition, we assessed coronary disease complexity using the SYNTAX score rather than relying solely on traditional vessel counts, allowing a more detailed evaluation of lesion burden, anatomical complexity, and overall angiographic severity.

Although conventional CV risk factors are established determinants of CAD severity, our findings demonstrate marked differences in coronary lesion burden and the SYNTAX score across Lp(a) levels. However, interpretation of these findings requires caution because the elevated Lp(a) group was older and had higher LDL levels and a higher prevalence of smoking, hypertension, DM, and dyslipidemia. To address this potential confounding, multivariate logistic regression was performed; Lp(a) remained independently associated with a high SYNTAX score after adjustment for relevant covariates. Nevertheless, residual confounding cannot be excluded, and causality cannot be inferred from the present observational design.

The present investigation revealed a significant increase in the frequency and severity of coronary atherosclerosis, as identified by CA, among individuals with elevated blood levels of Lp(a) over 30 mg/dl compared with individuals with normal levels.

Coronary angiography demonstrated a significant increase in the number of affected coronary arteries in individuals with elevated Lp(a) levels compared with those with normal Lp(a) levels.

The SYNTAX score, the most recent and reliable angiographic tool for quantifying the severity and complexity of CAD and predicting outcomes of coronary interventions depending on anatomical complexity, was employed in our current study to mitigate bias and enhance decision-making. It was substantially elevated in individuals with high Lp(a) levels contrasted to those with normal levels of Lp(a), with cut-off values of 22 for mild risk and 34 for high-risk scores.[30,31]

Study Limitations

Some limitations should be acknowledged. First, the sample size was relatively small, and the study was conducted at a single center, which may limit external validity. Second, baseline characteristics were not homogeneous between study groups: patients with elevated Lp(a) levels were older and had higher LDL levels and a higher prevalence of smoking, hypertension, DM, and dyslipidemia. Although multivariate regression analysis was performed to adjust for potential confounders, residual confounding cannot be completely excluded. Third, selection bias may have occurred because the study included symptomatic AVS patients referred for coronary angiography, thereby limiting generalizability to asymptomatic populations. Fourth, the Lp(a) measurement was performed approximately one month after discharge, which may have introduced variability, although no major changes in lipid-lowering therapy occurred and Lp(a) levels are generally stable over time. Finally, the absence of longitudinal clinical outcomes precludes assessment of prognostic implications. Therefore, larger prospective multicenter studies with longitudinal follow-up are warranted.

CONCLUSION

Elevated serum Lp(a) levels were independently associated with greater CAD severity and higher SYNTAX scores among individuals with AVS. By applying the SYNTAX score to this AVS population, the present study highlights the potential clinical value of Lp(a) as a marker of angiographic disease burden and of coronary lesion complexity. Larger multicenter longitudinal studies are warranted to validate these findings.

Ethics

Ethics Committee Approval: The study was conducted following approval by the Local Research Ethics Committee of the Faculty of Medicine, Sohag University, in accordance with the Declaration of Helsinki (approval no: Soh-Med-24-09-5PD, date: 11.09.2024).

Informed Consent: Verbal informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.A., S.M.T., S.P.A., A.I.B., Concept: R.S.A., S.M.T., S.P.A., A.I.B., Design: R.S.A., S.M.T., S.P.A., A.I.B., Data Collection or Processing: R.S.A., S.M.T., S.P.A., A.I.B., Analysis or Interpretation: R.S.A., S.M.T., S.P.A., A.I.B., Literature Search: R.S.A., S.M.T., S.P.A., A.I.B., Writing: R.S.A., S.M.T., S.P.A., A.I.B.

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