# Lp(a), ApoB and ApoB/ApoA1 Ratio as Potential Serum Markers for Predicting Early-Onset Acute Coronary Syndrome

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**ABSTRACT**

**BACKGROUND**
Prevalence of coronary artery disease is higher in elderly population (>60 years) however, it is increasingly seen in younger population due to change in lifestyle. Lipoprotein a [Lp(a)], Apolipoprotein B (ApoB) and Apolipoprotein A1 are among the emerging markers for acute coronary syndrome (ACS). Routine lipid profile does not incorporate these markers and cardiovascular diseases (CVD) in young individuals who show marked derangement in their blood biochemical profile. In this study we assessed Lp(a), ApoB, ApoA1 and ApoB/ApoA1 ratio in non-elderly individuals and compared it with routine lipid profile.

**METHODS**
This is a cross-sectional study comprising of 75 cases and 69 controls between 15-55 years of age from whom morning fasting blood samples were collected and analysed for lipid profile, Lp(a), ApoB, ApoA1 and ApoB/ApoA1 ratio.

**RESULTS**
We found that all the parameters in routine lipid profile as well as Lp(a), ApoB and ApoB/ApoA1 were significantly elevated in cases compared to controls. However, the risk of developing early onset acute coronary syndrome is high in the presence of non-routine markers like Lp(a) [Odds Ratio (OR)=11.71], ApoB (OR=11.70) and ApoB/ApoA1 (OR=11.74).

**CONCLUSIONS**
This study suggests that complementing the traditional lipid profile with ApoB, ApoB/ApoA1 and Lp(a) would be favourable additions for predicting early onset ACS.

**KEYWORDS**
Acute Coronary Syndrome (ACS), Lipoprotein a [Lp(a)], Apolipoprotein B (ApoB), ApoB/ApoA1 Ratio, Lipid Profile

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## BACKGROUND

Cardiovascular disorders are the leading causes for death worldwide. Nearly 17.9 million people died in 2016 due to CVD alone which comprises 31% of total deaths.[1] More than three quarter of premature deaths from non-communicable diseases occur in the middle- and low-income countries.[1] Majority of the CVD deaths are related to coronary artery disease and cerebrovascular accidents (CVA). This necessitates the need for intensified health check-up and newer diagnostic modalities for early detection of the disease.

Lipid profile is an effective, universal and accessible laboratory parameter for measuring and screening the risk for CVD. It is routinely complemented to diagnostic imaging modalities like coronary angiography which enables measuring the extend of coronary artery obstruction. Metabolic syndrome is a common premorbid condition occurring prior to coronary artery disease (CAD) which is diagnosed clinically based on the presence of abdominal obesity, hypertriglyceridemia, reduced HDL, hyperglycaemia and hypertension. Identifying this condition early necessitates routine laboratory screening of lipid profile.[2] Lipid profile consists of a battery of investigations that routinely measure serum total cholesterol (TC), triglycerides, LDL-C (low density lipoprotein, bad cholesterol), HDL-C (high density cholesterol, good cholesterol) and VLDL (Very low-density lipoprotein). Computerized tomography angiography (CTA) show that the presence of non-calcified plaques (NCP) are significantly associated with elevated levels of non-HDL particles like LDL, HDL and TC.[3]

Anti-atherogenic molecule HDL which functions as reverse cholesterol transporter is a lipoprotein that structurally consist apolipoprotein A1. Apolipoprotein A1 component of HDL facilitates the reverse cholesterol transport via ABC (adenosine triphosphate binding cassette) A1 mediated cellular cholesterol efflux.[4] It also enhances the maturation of HDL particles by regulating the activity of lecithin cholesteryl acyl transferase (LCAT). Apolipoprotein B is the structural component of VLDL, intermediate density lipoprotein (IDL) and LDL which favours atherogenic deposition of cholesterol into peripheral tissues including vascular subendothelial region leading to development of plaques.[5] Another patient compliant feature is that apolipoprotein measurement does not require fasting sample. The ratio of ApoB/ApoA1 in larger studies like Apolipoprotein Related Mortality Risk (AMORIS) and INTERHEART, have unambiguously shown that it predicts CAD mortality better than isolated lipid profile.[6,7]

Lipoprotein a, also known as Lp(a), for the past few decades has been implicated as a marker associated with increased risk of premature or early onset cardiovascular disorders.[8] Lp(a) has prothrombotic effect as it functionally resembles plasminogen or plasmin but does not carry fibrinolytic activity thereby incapacitating spontaneous recanalization of occluded blood vessel. Lp(a) is rich in cholesterol and accelerates atherosclerotic changes similar to high LDL-C.

In this study we analysed the association between ApoB, ApoB/ApoA1 ratio, Lp(a) and acute coronary syndrome (ACS) based in a tertiary health care center which incorporates subjects from northern districts of Kerala state, India. Kerala has high incidence, prevalence and mortality related to CAD both in young and old adults. This necessitates the need for newer laboratory parameter to efficiently screen and predict the occurrence early in this population.

## METHODS

Ethical clearance from the Institutional Ethics Committee was obtained. Cases were defined as subjects who presented to the casualty with first attack of chest pain. Chest pain due to ACS encompasses both acute myocardial infarction (ST or non-ST elevation) as well as unstable angina. Their inclusion criteria consisted of subjects within the age group of 15-55 years in both sexes presenting with first attack of ACS and not on any lipid lowering drugs. Alongside subjects with hyperglycaemia, hypertension and smoking history were also included as cases. Controls on the other side were apparently healthy age matched subjects between 15-55 years and not on any drugs. Subjects with hyperglycaemia, hypertension and smoking history were excluded from the control group. Hyperglycaemia was considered beyond fasting blood sugar level of 100 mg/dl and hypertension beyond 140/90 mmHg.[9,10] The methodology was designed as a comparative cross-sectional study consisting of 75 cases and 69 control who presented to the Emergency Department.

ApoB, ApoA1, Lp(a), Lipid profile and glucose levels was measured in fasting serum sample using ERBA EM360 fully automated clinical chemistry analyser. ApoA1 and ApoB levels were measured using turbidimetry assay technique (immunoturbidimetry) as per manufacturers protocol (ERBA Mannheim).[11] Their serum levels were subsequently applied to derive ApoB/ApoA1 ratio. Lp(a) was quantitated similarly by immunoturbidimetry.[12]

Total cholesterol (TC) estimated by enzymatic method (Cholesterol oxidase) as per manufacturers protocol (ERBA Mannheim). HDL-C was estimated using an AutoZyme HDL-Cholesterol Precipitating Reagent as per manufacturers instruction (ERBA Mannheim).[13] Their values were subsequently applied to derive TC/HDL ratio. Triglycerides levels were measured using GPO-POD (Glycerol phosphate oxidase-peroxidase) method (ERBA Mannheim).[14] VLDL was estimated based on the serum triglyceride level as per the equation: Triglycerides (mg/dl)/5, as recommended by NCEP (national cholesterol education program). LDL-C was estimated as per the empirical equation of Friedwald and colleagues: [LDL cholesterol] = [Total cholesterol] - [HDL cholesterol] + [Triacylglycerol]/5.[15] Blood glucose was measured using glucose oxidase-peroxidase (GOD-POD) method as per manufacturers instruction (ERBA Mannheim). Statistical analysis of sociodemographic and biochemical parameters between the cases and controls were done using SPSS software program version 15. The quantitative

variables were analysed using Student's unpaired 't' test and qualitative variables using Pearson's Chi square test.

## RESULTS

### Sociodemographic Characteristics

Significant proportion of cases had hypertension with elevated mean systolic and diastolic blood pressure, diabetes mellitus (DM), body mass index (BMI) and waist circumference as compared to control. Physical inactivity was observed 13% and 12% in cases and control which was statistically insignificant and comparable in both groups. (Table 1)

### Parameters Analysed

In the study we biochemically estimated the following parameters; ApoB (mg/dl), ApoA1 (mg/dl), total cholesterol (mg/dl), triglycerides (mg/dl), HDL-C (mg/dl), LDL-C (mg/dl) and FBS (mg/dl). Subsequently, ApoB/ApoA1 and TC/HDL-C ratio were calculated and compared. All the parameters except ApoA1 and HDL-C were significantly higher ($p<0.05$) in cases compared to controls. ApoA1 and HDL-C levels were significantly lower in cases compared to control. Accordingly, we also found that ApoB/ApoA1 and TC/HDL-C ratio were higher in the patients compared to apparently healthy subjects. The odds ratio for ApoB/ApoA1 and TC/HDL-C was significantly higher in cases compared to control group asserting that the odds of developing ACS increases with elevated ratio. (Table 2)

| Parameter | Cases | Controls | p |
|---|---|---|---|
| **Age (Years)** | | | |
| Mean age | 49.28 | 51.26 | 0.012 |
| **Sex** | | | |
| Males | 59 (78.7%) | 59 (86.7%) | 0.055 |
| Females | 16 (21.3%) | 10 (13.3%) | |
| **Occupation** | | | |
| Unemployed | 2 (2.7%) | 2 (2.8%) | 1.000 |
| Household work | 4 (5.3%) | 4 (5.9%) | |
| Unskilled | 48 (64%) | 48 (69.6%) | |
| Skilled | 17 (22.7%) | 13 (18.9%) | |
| Business | 4 (5.3%) | 2 (2.8%) | |
| **Blood Pressure** | | | |
| Mean systolic | 148.77±29.47 | 114.15±5.81 | <0.05 |
| Mean diastolic | 95.57±13.13 | 77.11±4.1 | |
| BMI ($Kg/m^2$) | 24.41±2.49 | 20.23±2.26 | <0.05 |
| **Waist Circumference (cm)** | 92.73±5.98 | 85.69±4.54 | <0.05 |
| **Family History** | | | |
| Hypertension | 54 (72%) | 16 (23%) | <0.05 |
| Diabetes mellitus | 48 (64%) | 29 (32%) | |
| Physical Inactivity | 10 (13%) | 9 (12%) | 1.000 |

***Table 1. Sociodemographic Characteristics of the Study Population (Cases and Controls)***

| Parameters | Cases | Controls | Odds Ratio | p |
|---|---|---|---|---|
| ApoB (mg/dl) | 188.16±39.5 | 89.28±35.37 | 11.70 | <0.05 |
| ApoA1 (mg/dl) | 104.41±32.13 | 186.27±47.18 | 5.12 | <0.05 |
| ApoB/ApoA1 | 2.01±0.79 | 0.52±0.38 | 11.74 | <0.05 |
| Lp(a) (mg/dl) | 31.03+9.15 | 20.61+8.42 | 11.71 | <0.05 |
| Total cholesterol (mg/dl) | 222.30±52.56 | 173.14±25.96 | 5.95 | <0.05 |
| Triglycerides (mg/dl) | 183.37±61.2 | 148.11±41.82 | 1.67 | <0.05 |
| HDL-C (mg/dl) | 35.47±8.42 | 40.80±6.91 | 4.96 | <0.05 |
| LDL-C (mg/dl) | 140.23±46.28 | 104.49±14.04 | 7.90 | <0.05 |
| TC/HDL-C | 6.43±1.87 | 4.53±2.49 | 11.95 | <0.05 |
| FBS (mg/dl) | 123.93±39.86 | 93.11±5.46 | 9.51 | <0.05 |

***Table 2. Parameters Analysed in the Study Population (Cases and Controls)***

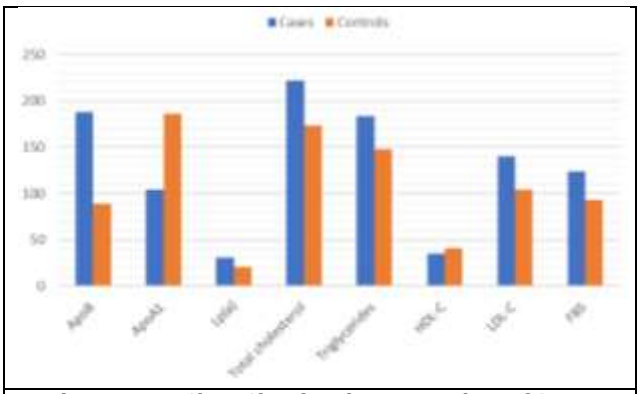


***Figure 1. Bar Chart Showing the Mean Values of Serum Analytical Parameters in Cases and Controls. p Value is Significant ($p<0.05$) for All the Analysed Variables***

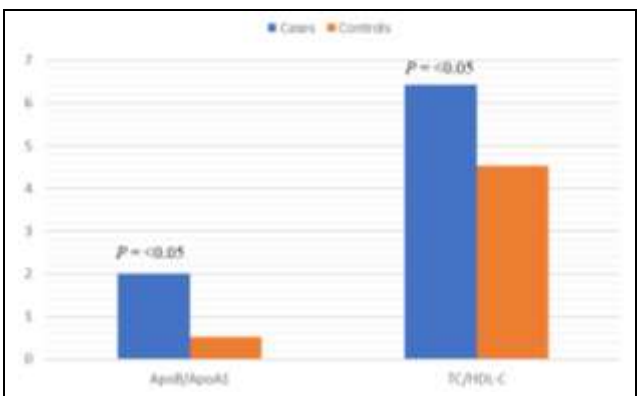


***Figure 2. Bar Chart Comparing the Mean ApoB/ApoA1 Ratio and TC/HDL-C Ratio Between Cases and Controls***

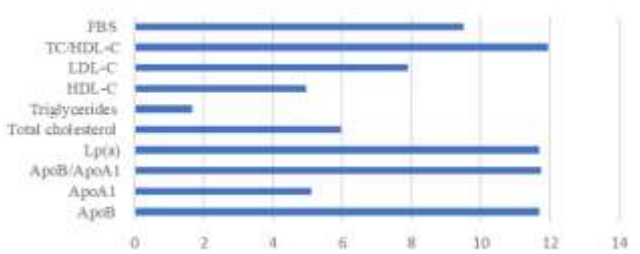


***Figure 3. Odds Ratio of the Laboratory Parameters. It Signifies the Odds of Having AMI in the Presence of Altered Biochemical Parameters***

## DISCUSSION

Senior citizenship or elderly status is attained beyond 60 years of age, following which an individual is at an increased risk of developing cardiovascular diseases.[16] In this study, we evaluated patients presenting with ACS at a relatively younger age (<60 years). Our study uniquely determines the importance of measuring non-routine serum markers like Lp(a) and ApoB/ApoA1 for screening individuals at increased risk for ACS.

ApoB is the principle protein component (apolipoprotein) present in LDL particles. In association with other apolipoproteins it is also found in VLDL and IDL.[17] For long period it was considered that elevation in LDL-C is a definitive risk factor for CVD but in the past decade mounting evidence point out that ApoB, rather than LDL-C has greater implications in development of CVD.[18] Specific

polymorphisms in ApoB gene also results in increased incidence of coronary artery disease (CAD) and myocardial infarction.[19] Walldius et al. in the AMORIS study concluded that high ApoB, ApoB/ApoA1 as well as low ApoA1 are better predictors of cardiovascular mortality than routine lipid assays.[6] Sniderman et al. reported an increased risk of myocardial infarction (MI) in younger age group attributed to elevated ApoB levels.[20] However, they also noted that ApoA1 and HDL significantly increased with age at a constant rate and did not show any variation between different age groups. ApoA1 or Apolipoprotein A1 is the principle protein present in HDL particle.[21] HDL-C is an essential component in the NCEP ATPIII criteria for determining the presence of metabolic syndrome which subsequently increases the risk for developing CVD.[22] Based on coronary angiographic findings, Noma et al. reported HDL-C and Apo-A1 are suitable markers in discriminating the diseased and normal subjects.[23] The ratio of ApoB and ApoA1 (ApoB/ApoA1) represents an equilibrium between pro-atherogenic and anti-atherogenic factors. Rasouli et al. reported high ApoB, ApoB/ApoA1 and Lp(a) in patients suffering from CAD as compared to controls. Also, the INTERHEART study on a global scale found ApoB/ApoA1 ratio as an essential marker associated with MI.[7] Their findings suggest that ApoB/ApoA1 ratio can be the best predictor for future CAD risk as compared to other markers.[24] Nayak et al. found an increase in ApoB and ApoB/ApoA1 as well as decrease in ApoA1 in hypertensive subjects which together are high risk factors for future CVDs.[25] In our study we found elevated Apo B (188.16±39.5 mg/dl) and ApoB/ApoA1 (2.01±0.79) in patients presenting with ACS. We could also infer that the odds of developing ACS were higher in the presence of raised serum ApoB (OR=11.70) and ApoB/ApoA1 ratio (OR=11.74) (Figure 1 & Figure 2). We also found that only TC/HDL-C (OR=11.95) in routine lipid profile is as effective as ApoB/ApoA1 for predicting early onset ACS. Even though we found that the odds of developing ACS increase with low ApoA1 (OR=5.12) but in comparison to raised ApoB and ApoB/ApoA1, it is of lesser concern.

Lp(a) measurement is recommended for individuals at high risk for premature CVD, family history of premature CVD or elevated Lp(a), familial hypercholesteremia, recurrent CVD and persons at high risk for developing fatal coronary heart disease as per UK and US guidelines.[8] It is necessary to retain the serum levels of Lp(a) below 50 mg/dl which is less than 80$^{th}$ percentile, for considerably reducing the risk for CVD. Beyond this concentration it is considered as a significant risk factor for CVD in the European population.[26] FOURIER trial had shown that evolocumab, a PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitor, reduced Lp(a) levels and significantly reduced the risk for developing CVD.[27] In Indian population, Singh et al. reported elevated Lp(a) in subjects presenting with CVD (measured 4 weeks post-myocardial infarction) especially in females compared to males.[28] They also observed higher levels in subjects having family history of T2DM and hypertension. In south Indian population, Rajasekhar et al. found that Lp(a) levels >25 mg/dl positively correlated with multi-vessel coronary artery disease.[29] Surprisingly large population-based cohort studies in western population (Norfolk) have shown a reciprocal association between Lp(a) and type 2 diabetes mellitus (T2DM). Even raised Lp(a) due to genetic polymorphisms show no association with occurrence of T2DM.[30] Similarly, Arsenault et al. observed low levels of Lp(a) in T2DM subjects.[31] This suggest that the causal association between Lp(a) and T2DM are limited to strong ethnic boundaries which needs further evaluation. In our study we found that subjects with high Lp(a) have an increased risk of developing early onset ACS. In the patient group, 48% subjects were having diabetes mellitus (DM) and elevated FBS (OR=9.51), which was significantly associated with ACS. However, in our study we find the probability of elevated Lp(a) with an OR of 11.71 (Fig. 3), as significant risk factor for early manifestation of ACS than FBS alone. The patient group also had subjects with hypertension and elevated mean BMI (body mass index). Nasri in a cross-sectional study reported elevated blood pressure (both systolic and diastolic) to have positive association with elevated Lp(a).[32] Chan et al. identified elevated Lp(a), hypertension and poor renal function in patients with familial hypercholesteremia as distinct risk factor for developing CAD.[33] Donatelli et al. found elevated Lp(a) in obese individuals with or without DM and strikingly Berk et al. found that weight reduction by dietary modifications result in elevation of mean Lp(a) that could possibly subjugate the beneficial effect of weight loss.[34,35] However, Lp(a) and ApoB along with homocysteine, pro-inflammatory markers and pro-thrombotic factors are considered as emerging cardiometabolic risk factors as per updated NCEP ATPIII guidelines (National Cholesterol Education Program Adult Treatment Panel-III).[36] Our study in concert with other supportive evidence suggest that implementation of screening for Lp(a) in routine clinical practice is necessary for early identification of individual who are at high risk for developing early onset ACS.

## CONCLUSIONS

Early onset ACS is a multifactorial condition with high morbidity and mortality. Lipid transporting molecules like Lp(a), ApoA1 and ApoB are potential biochemical markers for predicting ACS at younger age. We found a significant increase in ApoB, ApoB/ApoA1 and Lp(a) in ACS subjects (<55 years of age). This study suggests that complementing the traditional lipid profile with ApoB, ApoB/ApoA1 and Lp(a) would be favourable additions for predicting early onset ACS.

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