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Original Article

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Unravelling the Role of Apolipoprotein-B, Lipoprotein(a), and Homocysteine in Myocardial Infarction: A Tertiary Hospital Case-Control Analysis

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ABSTRACT

OBJECTIVE Cardiovascular disease (CVD) causes approximately 17.9 million deaths globally each year, making it one of the leading causes of mortality. Around 15.00-20.00% of cardiovascular events occur without the presence of traditional risk factors. Some less commonly detected risk factors in CVD patients include hyperhomocysteinemia, metabolic syndrome, lipoprotein(a) (Lp(a)), apolipoprotein B (Apo-B), and elevated procoagulant levels. High levels of homocysteine (Hcy), Lp(a), and Apo-B are linked to an increased risk of myocardial infarction (MI). This study aimed to evaluate the prevalence of elevated Apo-B, Lp(a), and Hcy levels in MI patients from rural areas of Coimbatore District, Tamil Nadu, India.

METHODS This case-control study was conducted at a tertiary care hospital from January to December 2021, following institutional ethics committee approval (IHEC/188/BIOCHEMISTRY/2020). Fifty MI patients (aged 30-80 years) and 50 age-sex matched healthy controls were recruited after obtaining informed written consent. Patients with previous MI, CAD, chronic kidney disease, or those on lipid-lowering therapy were excluded. Blood samples were collected under sterile conditions and analyzed for Apo-B, Lp(a) and Hcy using immunoturbidimetric methods. Statistical analysis was performed using SPSS version 24, with independent t-tests and Pearson correlation analysis.

RESULTS The average levels of Apo-B, Lp(a) and Hcy in MI patients were 103.2 ± 5.9, 19.7 ± 1.6, and 29.5 ± 2.5, respectively, significantly higher than in the control group. A t-test confirmed a strong association between these risk markers and MI (p = 0.000), indicating their significant role in MI occurrence. ROC curve analysis demonstrated excellent discriminatory ability for Hcy (AUC = 0.868, sensitivity 85%, specificity 90%) with an optimal cut-off of 25 µmol/L.

CONCLUSIONS Our findings confirm a strong association between elevated Apo-B, Hcy, and Lp(a) levels and the onset of first-episode MI, especially in patients without prior CVD or lipid-lowering treatment. This underscores the importance of screening for these risk factors, particularly in underserved rural populations, to enhance early detection and preventive care.

KEYWORDS apolipoprotein B, cardiovascular risk factors, homocysteine, lipoprotein(a), myocardial infarction

INTRODUCTION

Cardiovascular disease (CVD) affects the heart and blood vessels and is the leading global cause of death, responsible for 17.9 million deaths in 2019, accounting for 32.00% of all deaths globally (1). Coronary artery disease (CAD), the most common form of CVD, affects approximately 126 million people worldwide, representing 1.72% of the global population (2). The global cost of CVD was $863 billion in 2010, and is projected to surpass $1 trillion by 2030 (3).

CAD results from atherosclerosis, which leads to myocardial infarction (MI). Risk increases with age and is higher in men, though post-menopausal women also face increased risk (4). Risk factors for CVD include hypertension, diabetes, smoking, and dyslipidemia (5, 6). Smoking contributes to 53.00% of MIs in men and promotes atherosclerosis via oxidative stress (7). Hypertension leads to atherosclerotic plaque formation and contributes to 49.00% of CVD cases, with 42.00% of Indian adults affected (8). Diabetes doubles the risk of MI through the production of advanced glycation end-products, accelerating vascular damage (9). Dyslipidemia, particularly elevated LDL and low HDL, further contributes to atherosclerosis (10).

In India, the prevalence of CAD is increasing. CAD deaths rose from 2.26 million in 1990 to 4.77 million in 2020, with an estimated 350,000–400,000 deaths attributed to MI annually (11). Emerging risk factors include hyperhomocysteinemia, lipoprotein(a) (LP(a)), and apolipoprotein B Apo-B (12). Apolipoproteins are critical for lipid transport in plasma. Apo B-100, a major component of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL), plays a pivotal role in cholesterol transport and CAD risk (13). Elevated Apo B levels are strongly associated with MI and CAD, even when LDL levels appear normal (14). Apo B-containing lipoproteins penetrate arterial walls and promote plaque formation, exacerbating atherosclerosis (15).

Lp(a) has been identified as an independent risk factor for CAD. Structurally similar to LDL, it contains apolipoprotein A attached to Apo B-100 (16). Lp(a) inhibits plasminogen, promoting fibrin and cholesterol deposition at vascular injury sites (17). Elevated Lp(a) levels (> 50 mg/dL) are found in approximately 25.00% of South Asians, significantly raising their risk of CVD (18).

Homocysteine (Hcy) is a sulfur-containing amino acid, and elevated levels (hyperhomocysteinemia) increase the risk of MI and CAD by promoting oxidative stress, endothelial dysfunction, and smooth muscle proliferation (19). Up to 83.30% of young MI patients in India have high Hcy levels (20). Hyperhomocysteinemia impairs nitric oxide activity, worsening endothelial function (21).

Emerging biomarkers like Apo-B, Lp(a) and Hcy provide additional layers of risk assessment for CVD. Apo B has been found to be a better predictor of cardiovascular events compared to LDL-C (22), even in patients treated with statins (23). Elevated Lp(a) levels correlate strongly with coronary events in individuals without traditional lipid abnormalities (24). Elevated Hcy concentrations, linked to endothelial dysfunction, offer potential for early detection and intervention in CAD (25).

This study addresses a critical gap in cardiovascular risk assessment, particularly in the Indian population where traditional risk factors may not fully explain MI occurrence. The identification of these novel biomarkers could lead to improved risk stratification, earlier intervention, and reduced cardiovascular mortality in resource-limited settings, especially in rural Tamil Nadu where access to advanced cardiac care is limited.

The primary aim of this study is to investigate the role of specific biochemical markers—Apo-B, Lp(a), and Hcy—in patients diagnosed with MI. The study seeks to quantitatively measure the levels of these biomarkers in MI patients and to evaluate their significance in the context of cardiovascular risk. Additionally, a comparative analysis was conducted between the levels of Apo-B, Lp(a), and Hcy in MI patients and those in non-cardiac control subjects to identify any significant differences. A key objective also includes examining the prevalence and likelihood of elevated levels of these markers specifically among MI patients residing in rural areas of the Coimbatore District in Tamil Nadu.

METHODS

Study design and setting

This case-controlled study was conducted over a one-year period from January 2021 to December 2021 among patients diagnosed with

acute MI admitted to the ICU of a tertiary care hospital and healthy individuals attending the outpatient department of that hospital. The study included 50 MI patients (cases) and 50 age- and sex-matched healthy individuals (controls).

Ethical considerations

Ethical approval for the study was obtained from the institutional ethics committee of Karpagam Faculty of Medical Sciences and Research (IHEC/188/BIOCHEMISTRY/2020) prior to study initiation. Informed written consent was secured from all participants after explaining the study objectives, procedures, risks, and benefits. Patient confidentiality was maintained throughout the study, and all data were de-identified before analysis. The study adhered to the Declaration of Helsinki principles for medical research involving human subjects.

Study population and inclusion/exclusion criteria

The inclusion criteria for cases were patients aged 30-80 years, diagnosed with MI by a cardiologist based on clinical presentation, ECG changes, and elevated cardiac biomarkers. Patients with chronic kidney disease, previous MI or CAD treated with percutaneous coronary intervention or thrombolytic therapy, or those on statins or lipid-lowering drugs were excluded. The controls included individuals without a history of CAD or MI or similar exclusion criteria.

Sample size calculation

The sample size was calculated using the prevalence of elevated Hcy (83.30%) among MI patients reported in previous Indian studies, with a power of 80.00% and significance level of 0.05, and allowing for a 10.00% non-response rate, resulting in a total of 100 participants (50 cases and 50 controls).

Materials and instrumentation

The following materials and equipment were used:

- Immunoturbidimetric assay kits for Apo-B, Lp(a), and Hcy measurement (ERBA EM 360)
- Automated clinical chemistry analyzer (ERBA EM 360)
- Centrifuge (Eppendorf 5810R) for serum separation
- Freezer (-20°C) for sample storage
- Standard laboratory consumables including plain tubes, ethylenediaminetetraacetic acid (EDTA) tubes, micropipettes, and tips

Laboratory protocol and methodology

Blood collection and processing:

- Five milliliters of venous blood was collected in plain tubes after 12-hour fasting
- Samples were allowed to clot at room temperature for 30 minutes
- Centrifugation was performed at 3,000 rpm for 10 minutes at room temperature
- Serum was separated and stored at -20°C until analysis (within 48 hours)

Biochemical analysis

- Apo-B, Lp(a) and Hcy levels were measured using immunoturbidimetric methods
- Quality control measures included daily calibration using manufacturer's standards
- Internal quality control samples were run with each batch
- Normal reference ranges: Apo-B (< 100 mg/dL), Lp(a) (< 30 mg/dL), Hcy (< 15 μmol/L)

Data collection

Information was gathered on participants' socio-economic status, medical history, lifestyle factors, and family history of illness. Vital signs, including pulse, blood pressure, and respiratory rate, were recorded. Detailed cardiovascular risk factor assessment was performed including smoking history, hypertension status, diabetes mellitus, family history of CAD, and current medications.

Statistical analysis

The data were entered and analyzed using SPSS Version 24 for Windows. Categorical variables, such as gender, are presented as frequencies and percentages, while continuous variables, like age, are expressed as mean ± standard deviation. Normality of data distribution was assessed using the Shapiro-Wilk test. Pearson correlation was applied to assess the relationship between Apo-B, Lp(a), Hcy, and lipid levels. An independent samples t-test was used to determine the association between Apo-B, Lp(a), Hcy levels, and MI. receiver operating characteristic (ROC) curve analysis was

Table 1. General characteristics of study participants

Parameters	Cases (Mean ± SD)	Controls (Mean ± SD)	*p*-value
Age (years)	57.46±1.6	55.26±1.4	0.164
Gender (males/females)	42/8	41/9	NS
Smoking (%)	56.00	12.00	< 0.001*
Hypertension (%)	40.00	8.00	< 0.001*
Diabetes (%)	46.00	6.00	< 0.001*
Total cholesterol (mg/dL)	185.6±9.4	209.0±6.7	0.115
Triglyceride (mg/dL)	180.0±21.9	159.9±9.1	0.579
HDL (mg/dL)	43.6±1.45	51.1±1.4	0.121
LDL (mg/dL)	112.5±6.0	119.0±5.5	0.149
VLDL (mg/dL)	35.8±4.3	31.9±1.8	0.500
Apolipoprotein B (mg/dL)	103.2±5.9	93.1±3.7	0.026***
Lipoprotein(a) (mg/dL)	19.7±1.6	14.4±1.4	0.007**
Homocysteine (µmol/L)	29.5±2.5	15.0±1.3	< 0.0001*

***$p < 0.05$ statistically significant; **$p < 0.01$ highly significant; *$p < 0.001$ very highly significant
M/F, male/female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; NS, not significant; SD, standard deviation

performed to determine the optimal cut-off values for biomarkers with calculation of area under the curve (AUC), sensitivity, and specificity. A $p < 0.05$ was considered statistically significant.

RESULTS

General characteristics of the study population

The study participants included 50 MI cases and 50 healthy controls. Most participants were aged between 51 and 60 years, with no significant differences in age or gender distribution between the two groups. Notably, traditional cardiovascular risk factors were significantly more prevalent in MI patients compared to controls: 56.00% of MI patients were smokers (controls: 12.00%), 40.00% had hypertension (controls: 8.00%), and 46.00% had diabetes mellitus (controls: 6.00%), highlighting the multifactorial nature of MI risk in this population.

Biochemical marker analysis

Elevated levels of Apo-B (103.2 ± 5.9 vs. 93.1 ± 3.7 mg/dL, $p = 0.026$), Lp(a) (19.7 ± 1.6 vs. 14.4 ± 1.4 mg/dL, $p = 0.007$), and Hcy (29.5 ± 2.5 vs. 15.0 ± 1.3 µmol/L, $p < 0.0001$) in cases compared to controls demonstrated a statistically significant association with MI development. While traditional lipid markers like total cholesterol, triglycerides, high-density lipoprotein (HDL), and LDL did not show statistically significant differences between groups, the marked elevation of these specific biomarkers underscores their potential diagnostic and prognostic importance in cardiovascular risk assessment (Table 1).

Table 2. Correlation analysis

Parameter	r (Correlation Coefficient)	*p*-value
Homocysteine vs Apo-B	0.521	< 0.0001*
Homocysteine vs lipoprotein(a)	0.489	< 0.01**
Apo-B vs LDL	0.315	0.001*
HDL vs total cholesterol	-0.102	0.210

**Highly significant at $p < 0.01$; *very highly significant at $p < 0.001$
r, Pearson Correlation Coefficient; Apo-B, apolipoprotein B; DL, high-density lipoprotein; LDL, low-density lipoprotein;

Correlation analysis

Strong positive correlations were observed between Hcy and both Apo-B ($r = 0.521$, $p < 0.0001$) and Lp(a) ($r = 0.489$, $p < 0.01$), suggesting interconnected pathophysiological mechanisms underlying their roles in atherothrombosis (Table 2).

ROC curve analysis and diagnostic performance

ROC curve analysis revealed excellent discriminatory ability for both biomarkers in predicting MI risk. Hcy demonstrated superior performance with an AUC of 0.868, sensitivity of 85.00%, and specificity of 90.00% at an optimal cut-off value of 25 µmol/L. Apo-B showed good discriminatory ability with an AUC of 0.809, sensitivity of 78.00%, and specificity of 82.00% at a cut-off value of 95 mg/dL. These findings suggest that both biomarkers, particularly Hcy, could serve as reliable screening tools for MI risk assessment in clinical practice (Table 3, Figure 1).

Table 3. ROC analysis of biomarkers

Biomarker	AUC	Sensitivity	Specificity	Cut-off value	*p*-value
Homocysteine	0.868	85.00%	90.00%	25 µmol/L	< 0.0001*
Apolipoprotein B	0.809	78.00%	82.00%	95 mg/dL	0.006**

**Highly significant at $p < 0.01$; *very highly significant at $p < 0.001$ ROC, receiver operating characteristic; AUC, area under the curve

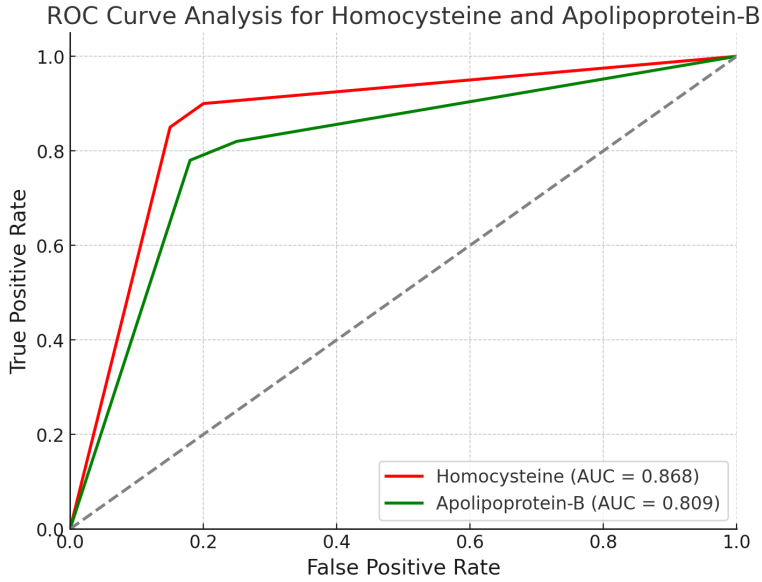

Figure 1. ROC curve analysis for Hcy and Apo-B in predicting myocardial infarction risk. The curves demonstrate the diagnostic performance of both biomarkers, with Hcy showing superior discriminatory ability (AUC = 0.868) compared to Apo-B (AUC = 0.809). The optimal cut-off values were 25 µmol/L for Hcy and 95 mg/dL for Apo-B, providing clinically relevant thresholds for risk assessment.

Prevalence of elevated biomarkers

Among MI patients, 48.00% had elevated Hcy levels (> 25 µmol/L), 22.00% had elevated Lp(a) levels (> 30 mg/dL), and 18.00% had elevated Apo-B levels (> 100 mg/dL), compared to only 6.00%, 4%, and 8%, respectively in the control group, demonstrating the clinical significance of these biomarkers in MI risk stratification.

DISCUSSION

CVD remains a leading cause of morbidity and mortality globally, with about 20.00% of individuals suffering MI dying within the first year, half within 30 days. Despite advanced diagnostic tools like ECG, elevated cardiac markers, and symptom analysis, the high mortality rate underscores the need for early detection and prevention (26).

The identification of CVD risk factors, such as dyslipidemia, hypertension, diabetes, smoking, and a family history of CVD, has reduced MI incidence over the years (27). Preventive measures like lifestyle changes, diet control, and medical intervention have led to a 50.00% decline in MI cases over the last three decades (28).

However, emerging biomarkers such as Hcy, Apo-B, and Lp(a) remain underutilized in clinical practice. Our study demonstrates that Hcy was significantly elevated in 48.00% of MI patients compared to only 6.00% in controls (29), with levels nearly double those of healthy individuals. This finding is particularly relevant in the Indian context, where genetic polymorphisms affecting Hcy metabolism are common. Apo-B, reflecting atherogenic particles and better predicting cardiovascular risk than LDL-C alone, was elevated in 18.00% of MI cases (30). Lp(a), associated with arterial calcification and thrombosis, was elevated in 22% of MI patients (31, 32).

Diabetic patients in our study showed higher MI risk, which may be partially explained by oxidative stress and mitochondrial dysfunction. Chronic hyperglycemia promotes advanced gly-

cation end-product formation, leading to increased reactive oxygen species production and mitochondrial respiratory chain impairment (33). This creates a cascade of cellular damage affecting cardiac myocytes and vascular endothelium. Elevated Hcy levels such as those observed in our diabetic MI patients, may further exacerbate oxidative stress through inhibition of cellular antioxidant systems, creating a synergistic effect that accelerates atherothrombosis.

We acknowledge that dietary patterns and vitamin B12/folate status significantly influence Hcy levels. This represents a limitation of our study, as we did not assess these parameters. The high prevalence of vegetarian diets in Tamil Nadu may contribute to B12 deficiency, potentially explaining the elevated Hcy levels observed in our study population (34). Future studies should include comprehensive nutritional assessment, particularly B-vitamin status, to better understand the mechanisms underlying hyperhomocysteinemia in our population.

The strong correlations observed between Hcy and both Apo-B (r = 0.521) and Lp(a) (r = 0.489) suggest shared pathophysiological pathways. Hcy promotes oxidative stress and endothelial dysfunction, while Apo-B facilitates lipid transport and plaque formation. Lp(a) inhibits fibrinolysis and promotes thrombosis. The synergistic effects of these biomarkers may explain why patients with multiple elevations have a particularly high MI risk.

The excellent diagnostic performance of Hcy (AUC = 0.868) and good performance of Apo-B (AUC = 0.809) support their potential clinical utility. The cut-off values identified (25 µmol/L for Hcy, 95 mg/dL for Apo-B) could be adopted in routine clinical practice for risk stratification, particularly in resource-limited settings where advanced cardiac imaging may not be readily available.

The study emphasizes incorporating these biomarkers into routine clinical assessments for CVD risk stratification. Early screening and interventions based on these parameters may further reduce MI incidence and could help prevent cardiovascular-related mortality. Standardizing the use of these tests could revolutionize CVD prevention, particularly in high-risk populations such as those in rural Tamil Nadu where access to specialized cardiac care is limited.

Clinical Implications and Recommendations: Based on our findings, we recommend routine screening for Hcy, Apo-B, and Lp(a) in individuals with a family history of CAD, diabetes, or other traditional risk factors. The cut-off values identified in this study could be used for risk stratification. Patients with elevated levels should receive intensified preventive care, including lifestyle modifications, dietary counselling, and consideration of B-vitamin supplementation in cases of hyperhomocysteinemia.

CONCLUSION

This study represents one of the first comprehensive assessments of Hcy, Lp(a), and Apo-B levels in MI patients from rural Tamil Nadu, comparing them with healthy controls. Our findings confirm a significant correlation between elevated levels of these biomarkers and first-episode MI, especially in patients without prior CVD or lipid-lowering treatment. The excellent diagnostic performance of these biomarkers, particularly Hcy, supports their clinical utility for risk assessment and early intervention.

These markers have rarely been studied in the Indian population for predicting future CVD risk, and they are seldom evaluated even in patients with confirmed CVD. Early detection and assessment of these markers, particularly in individuals with a family history of CVD or with previous MI, could be instrumental in identifying high-risk cases and reducing CVD-related morbidity and mortality in underserved rural populations.

Future research should focus on longitudinal studies to establish causality, intervention trials targeting these biomarkers, and the cost-effectiveness of analyses for implementing routine screening in primary care settings.

Strengths

- To the best of our knowledge, this is one of the first studies in Tamil Nadu to assess the combined impact of Apo-B, Lp(a) and Hcy in MI patients from rural areas

- Important confounding variables, such as the use of statins and other lipid-lowering drugs, were controlled through strict exclusion criteria

- Testing was conducted before initiating therapy for MI patients, ensuring unbiased biomarker measurements

- ROC curve analysis provided clinically relevant cut-off values for risk assessment
- Strong statistical methodology with appropriate correlation and diagnostic performance analyses

Limitations

- Sample size, while adequate for the primary objectives, could be larger for subgroup analyses
- The single-center design may limit generalizability to other populations
- The cross-sectional design prevented establishment of causality
- Dietary patterns, vitamin B12, and folate status, which are known confounders of Hcy levels, were not assessed.
- The majority of participants belonged to lower socioeconomic classes, potentially limiting generalizability
- Long-term follow-up data was not available to assess prognostic value

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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