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Original article

Association of perilipin (PLIN1) gene mutations with acute coronary syndrome: Observational study

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Abstract
BACKGROUND: The lipid droplet's essential component, perilipin, is encoded by PLIN, which controls the droplet's release of free fatty acids. OBJECTIVES: To study PLIN 1 gene mutations in patients with ACS. METHODOLOGY: This research took place at a comprehensive regional hospital. Eighty-nine individuals were initially recruited. 84 patients diagnosed with ACS were included and 5 patients were excluded as per inclusion and exclusion criteria respectively. RESULTS: The c.205G>A(p.Ala69Thr) variant was the most common, present in 62.5% of mutation-positive cases. Silent mutations and missense mutations occurred in patients who had significantly higher mean total cholesterol (261.0 ± 24.9 mg/dL), triglycerides (169.4 ± 28.30 mg/dL). CONCLUSION: This study explores the PLIN1 gene mutations in acute coronary syndrome. The high frequency (62.5%) of the c.205G>A (p.Ala69Thr) variant in mutation-positive patients supports the potential benefits of genetic screening for early risk assessment, prompt management, and lowering the overall burden of disease in high-risk patients.
***Keywords:** Lipid droplet, missense mutation, silent mutation.*

Introduction

Acute Coronary Syndrome (ACS) is a prominent driver of heart-associated illness and fatalities. [1] Traditional cardiovascular risk factors such as tobacco exposure, elevated levels total cholesterol and triglycerides, obesity are well-established determinants. [2] However, these factors alone do not fully explain inter-individual variability in disease occurrence and progression. Increasing evidence indicates that inherited genetic factors contribute significantly to the individual susceptibility. [3] The PLIN1 gene encodes perilipin-1, regulates lipid storage and mobilization. Through its influence on lipolytic activity, perilipin-1 plays a central role in maintaining energy balance and lipid homeostasis. Disturbances in these pathways may contribute to metabolic abnormalities that accelerate atherosclerotic processes. [4] Therefore, PLIN1 gene mutations in patients with ACS are studied to explore their relationship with clinical characteristics, lipid parameters, and cardiovascular manifestations. [5]

Material and methods

This prospective cross-sectional study was conducted in the Department of General Medicine at Shri B M Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India, over 18 months from March 2024 to December 2025. The protocol was approved by the Institutional Ethics Committee (IEC/NO-049/2023-24), and the study was prospectively registered with the Clinical Trials Registry-India (CTRI/2024/03/063909). Written informed consent was obtained from every participant.

Inclusion criteria: Individuals aged ≥18 years admitted with a clinical diagnosis of ACS based on standard guidelines were included. Exclusion criteria: Patients with valvular or congenital heart disease and those with venous thromboembolism were excluded to prevent potential bias generated by these conditions. The formula $n = Z^2 \times p \times q / d^2$ was used for estimating sample size, taking $p = 0.24$ for the combined frequency of deletion variants and SNPs in the PLIN1 gene among ACS patients, with 95% confidence and 9% absolute precision, yielding a required sample of 89 patients, of which 84 patients with ACS were included after taking prior informed and written consent, further categorised as Group A (n = 8) and Group B (n = 76), depending on PLIN1 gene mutation being present and absent respectively**.** Five out of 89 patients were excluded who fit in the exclusion criteria (two had pulmonary thromboembolism, three had valvular heart disease).

Clinical evaluation

Detailed history and clinical examination were performed at admission. Variables recorded included age, sex, occupation, presenting symptoms, cardiovascular risk factors (diabetes mellitus, hypertension, smoking, alcohol and tobacco use), vital signs, anthropometry and a focused cardiovascular examination. All patients underwent 12-lead electrocardiography and bedside two-dimensional transthoracic echocardiography. Laboratory investigations included complete hemogram, renal function test, fasting lipid panel, in addition to high-sensitivity cardiac troponin I. For each participant, 1 mL of venous blood was collected from a peripheral vein into tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant and sent to the genetics laboratory for analysis of PLIN1 gene mutation (Figure 1). Based on detection of the rs146569237 (c.224 C>T) variant, patients were grouped into PLIN1 mutation-present (Group A) and mutation-absent (Group B).

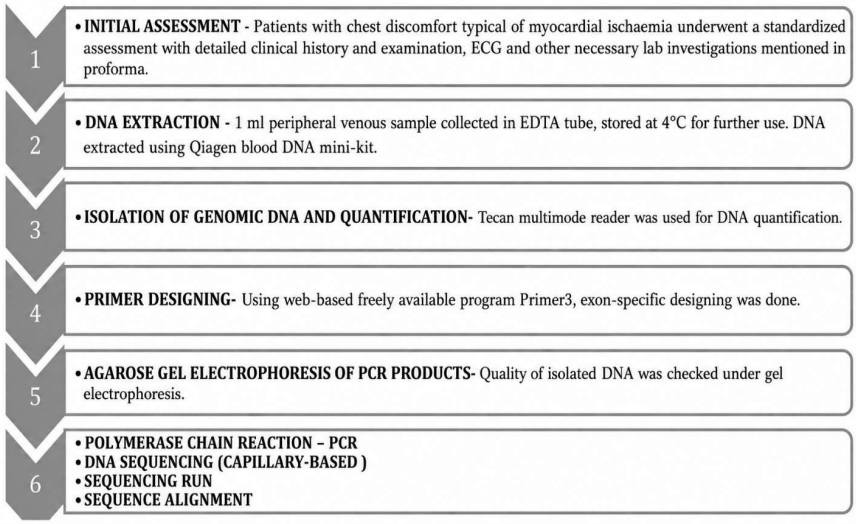


Figure 1. Flowchart depicting the methodology of genetic analysis for **PLIN1** gene mutation study.

DNA extraction and PLIN1 genotyping

Extracting DNA by the salting-out method was done, and using a commercial Qiagen blood DNA extraction kit (Hilden, Germany), these were measured spectrophotometrically; optical density (OD) 260/280 ratios were between 1.5 and 2.0 for all samples, indicating good-quality DNA suitable for amplification.

Designing of primers targeting the upstream regulatory region of the PLIN1 target sequence was done by using the Primer 3 platform and validated by in silico PCR

(upstream 5′-CAGACTGGAAGGTAGGCAGTG-3′;

downstream 5′-GGGAGGTGGGACAACTTGAA-3′ amplicon 260bp;

upstream 5′-CCGGGGGGCCGATCGAAGATA-3′

downstream 5′-CTGGAATAAAGCGGCTACAG-3′; amplicon 280bp).

Amplicons were verified by 1% agarose gel electrophoresis against a 100 bp ladder (Figure 2).

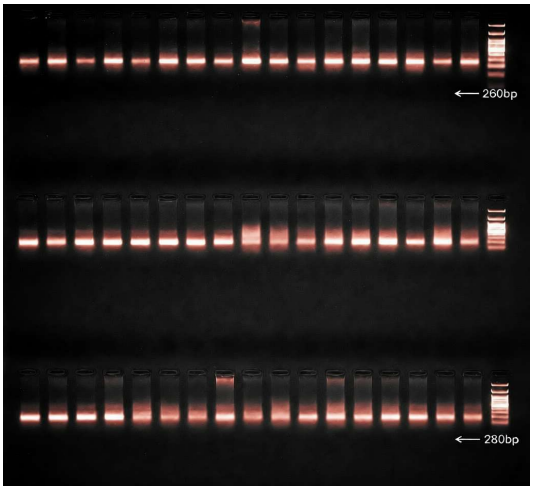


Figure 2. Electrophoretic visualization of **PLIN1** PCR products

With the help of BigDye Terminator, purified PCR products underwent sanger sequencing. Electropherograms were analysed with DNA based software and aligned to the reference PLIN1 sequence to identify single-nucleotide polymorphisms. Based on detection of the rs146569237 (c.224 C>T) variant, patients were grouped into PLIN1 mutation-present (Group A) and mutation-absent (Group B).

Statistical Package for the Social Sciences (SPSS), version 26 was used to assess the data which was entered in Microsoft excel. Continuous variables were summarized as mean ± standard deviation (SD). Comparisons between groups were performed using the independent-samples t-test after assessing data distribution and homogeneity of variances. Categorical variables were reported as frequencies and percentages, and associations between groups were evaluated using the Chi-square test.

Results

Baseline demographic and clinical profile

This study included 84 patients categorised as Group A (n = 8) and Group B (n = 76), depending on PLIN1 gene mutation being present or absent respectively. Most common age group in Group A was 51-70 years age group (75%), and most common age group in Group B was >70 years age group (25%). When stratified by PLIN1 mutation status, age distribution was non-significant across the three groups (p=0.704), indicating that age was not associated with the presence or type of PLIN1 mutations. In Group A, males were 85.7% and females were 12.5%, whereas in Group B, males were 57.9% and females were 42.1%, however, p = 0.237 was not statistically significant. Baseline age, sex distribution, modifiable risk factors and symptom distribution were comparable between the two groups (Table 1).

Table 1. Demographic and clinical data.

Parameter	Group A(n=8)	Group B(n=76)	Chi-square test value	p-value
Age Group (Years)				
18-30 years	0 (0.0%)	0 (0.0%)	0.702	0.704
31-50 years	0 (0.0%)	13 (17.1%)		
51–70 years	6 (75.0%)	44 (57.9%)		
>70 years	2 (25.0%)	19 (25.0%)		
Gender			1.39	0.237
Male	7 (87.5%)	44 (57.9%)		
Female	1 (12.5%)	32 (42.1%)		
Symptom Distribution				
Chest Pain	7 (87.5%)	62 (81.6%)	0.055	0.814
Dyspnea	2 (25.0%)	35 (46.1%)	0.342	0.559

Palpitation	1 (12.5%)	3 (3.9%)	0.93	0.335
Abdominal Pain	1 (12.5%)	11 (14.5%)	0.001	1.000
Modifiable Risk Factors				
Diabetes Mellitus	2 (25.0%)	18 (23.7%)	0.001	1.000
Hypertension	2 (25.0%)	24 (31.6%)	0.03	1.000
Smoking	2 (25.0%)	12 (15.8%)	0.19	0.663
Alcohol Consumption	1 (12.5%)	7 (9.2%)	0.001	1.000
Tobacco Chewing	0 (0.0%)	12 (15.8%)	0.52	0.468

Vital signs, including pulse rate and respiratory rate, as well as laboratory parameters such as total leukocytes, blood urea, serum creatinine, serum electrolytes and troponin I, were comparable among the two groups. Among the lipid parameters, total cholesterol (261.0 ± 24.09 versus 225.0 ± 31.3 mg/dL, p = 0.003), triglycerides (169.4 ± 28.30 versus 131.7 ± 32.6 mg/dL, p = 0.006) showed markedly higher values in Group A than in Group B. Although LDL cholesterol was higher in Group A (183.23 ± 40.38 versus 156.9 ± 25.1 mg/dL), the results failed to reject the null hypothesis (p = 0.110). Similarly, HDL cholesterol levels were comparable between the two groups (32.15 ± 10.36 versus 29.9 ± 9.5 mg/dL, p = 0.572).

Table 2. Haemodynamic and laboratory parameters in Group A and Group B

Parameter	Normal Reference Range	Group A		Group B		t-test (t value)	p-value
		Mean	SD	Mean	SD		
Pulse rate (beats/min)	60–100 beats/min	92.38	18.18	89.24	24.47	0.448	0.664
Respiratory Rate (cycles/min)	12–20 cycles/min	19.25	3.04	19.97	3.93	0.618	0.551
Total Count (cells/cumm)	4,000–11,000 cells/cumm	5311.92	8311.182	2945.63	5576.31	0.787	0.455
Blood urea (mg/dL)	15–40 mg/dL	30.87	11.08	29.13	9.58	0.428	0.680
Serum creatinine (mg/dL)	0.6–1.3 mg/dL	0.88	0.22	0.93	0.28	0.594	0.566
Serum sodium (mmol/L)	135–145 mmol/L	138.88	3.46	137.88	3.89	0.768	0.462
Serum potassium (mmol/L)	3.5–5.0 mmol/L	4.51	0.54	4.38	0.57	0.644	0.536
Troponin I (pg/ml)	<34 pg/mL	2374.58	2777.43	1527.49	3436.60	0.801	0.443
Total cholesterol (mg/dL)	<200 mg/dL	261	24.09	225	31.3	3.895	0.003*
Triglycerides (mg/dL)	<150 mg/dL	169.4	28.30	131.7	32.6	3.529	0.006*
LDL-C (mg/dL)	<100 mg/dL	183.23	40.38	156.9	25.1	1.808	0.110
HDL-C (mg/dL)	>40 mg/dL	32.15	10.36	29.9	9.5	0.589	0.572

*(p < 0.05) considered as rejection of null hypothesis. LDL-C: low-density lipoprotein

cholesterol; HDL-C: high-density lipoprotein cholesterol; SD: standard deviation.

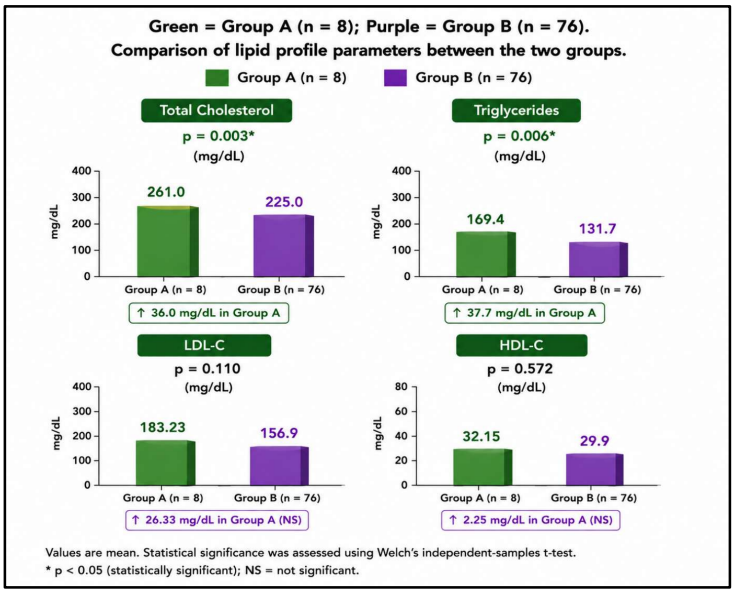


Figure 3. Assessment of lipid levels among PLIN1 rs146569237 mutation carriers (Group A, n= 8) and non-mutation carriers (Group B, n = 76). Total cholesterol and triglyceride values in mutation carriers were significantly higher, whereas, LDL-C and HDL-C levels did not differ significantly between the groups. *p < 0.05 (independent-samples t-test).

Major adverse cardiac events

All 84 patients were assessed for major adverse cardiac events (MACE). As depicted below, heart failure was the most frequently reported adverse cardiac event (28.6% in Group A versus 42.1% in Group B, p = 0.818). Cardiac arrhythmia occurred in 2 patients, cardiogenic shock didn't occur at all, overall in-hospital mortality was 2.4% (n=2), with 97.6% (n=82). Two deaths occurred in Group B (2.6%), while all patients with either missense or silent mutations survived (100%). However, the results failed to reject the null hypothesis (p=1.000).

Table 3. Composite cardiovascular endpoints in Group A versus Group B

Major adverse cardiac events	Group A (n = 8)		Group B (n = 76)		p-value
	n	%	n	%	
Heart failure	2	28.6	32	42.1	0.818
Arrhythmia	0	0.0	2	2.6	1.000
Cardiogenic shock	0	0.0	0	0	1.000
In-hospital mortality	0	0.0	2	2.6	1.000
In-hospital survival	8	100	74	97.36	

Among 84 clinical samples analysed, single nucleotide variants (SNVs) were identified in 8 samples (Table 4). Sample 5 harboured a heterozygous c.224C>T variant resulting in a p.(Pro75Leu) substitution (rs146569237), which was classified as a variant of uncertain significance in ClinVar. Sample 12 exhibited a heterozygous c.120C>G synonymous variant with no amino acid change. Sample 29 showed a heterozygous c.131C>T variant leading to a p.(Thr44Ile) substitution, which was not reported in ClinVar. Samples 41, 45–47, and 50 carried a heterozygous c.205G>A variant resulting in a p.(Ala69Thr) substitution; this variant was also not reported in ClinVar. However, the heterozygous peak observed for the c.205G>A variant required confirmation by reverse-primer sequencing.

Table 4. Detailed genetic analysis of PLIN1 gene of exon 3 and exon 9 mutations

Sample No.	cDNA position	Amino acid position	SNP ID	Variant type	Functional Consequence	Clinical Significance
5	c.224 C>T (heterozygous)	p.(Pro75Leu)	rs146569237	SNV	missense_variant, coding sequence_variant	Uncertain Significance in ClinVar
12	c.120C>G (heterozygous)	p.(=)	-	SNV	Silent mutation	-
29	c.131C>T (heterozygous)	p.(Thr44Ile)	-	SNV	Missense mutation	Not reported in ClinVar
41,45-47,50	c.205G>A (heterozygous peak not clear, to be rechecked with reverse primer)	p.(Ala69Thr)	-	SNV	Missense mutation	Not reported in ClinVar

The distribution of PLIN1 gene mutations in the study population is shown in Table 5. A heterozygous PLIN1 gene variant was identified in all participants of Group A (n = 8, 9.5%), whereas none of the participants in Group B carried the mutation. The remaining 76 participants (90.5%) were negative for the PLIN1 gene mutation.

Table 5. Allocation of the identified **PLIN1** mutations

PLIN1 mutations	Group A (n = 8)		Group B (n = 76)	
	n	%	N	%
Mutation present (Heterozygous)	8	9.5	—	—
Mutation absent	—	—	76	90.5
Total	8	9.5	76	90.5

Representative Sanger sequencing electropherograms of Exon 3 are shown in Figure 4. The chromatograms demonstrate the nucleotide c.205G>A at the indicated position, with the arrows marking the site analysed for sequence variation. Differences in peak patterns at the marked loci were used to assess the presence of nucleotide alterations in Exon 3.

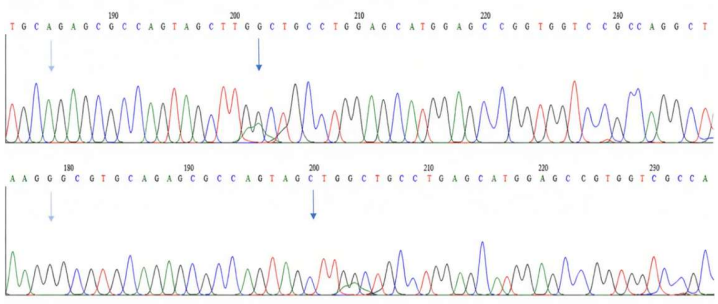


Figure 4. Electropherogram showing gene analysis of Exon 3

Representative Sanger sequencing electropherograms of Exon 9 are shown in Figure 5. The chromatograms demonstrate the nucleotide c.120C>G at the indicated position, with the arrows marking the site analysed for sequence variation. Differences in peak patterns at the marked loci were used to assess the presence of nucleotide alterations in Exon 9.

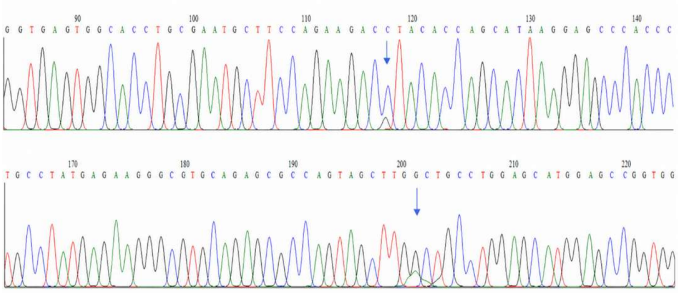


Figure 5. Electropherogram showing gene analysis of Exon 9

Discussion

In this study, PLIN1 mutations were identified in 9.5% of ACS patients, with the majority of mutation carriers belonging to the 51–70 year age group (75%). However, no statistically significant association was observed between age and PLIN1 mutation status ($p = 0.704$). In October 2023, Khera et al. conducted a large multicenter cardiovascular genomic study across the United States and Europe and demonstrated that inherited lipid-related genetic variants contributed to acute coronary syndrome risk, particularly among individuals older than 50 years. [6] The predominance of PLIN1 mutation carriers in the 51–70-year age group in this study supports the concept that genetic predisposition may manifest clinically during middle and late adulthood when traditional cardiovascular risk factors accumulate.

In this study, the difference in gender distribution between Group A and Group B was not statistically significant ($p = 0.237$). Likewise, in September 2024, Mars N et al. conducted a genomic association study in Finland and demonstrated that pathogenic lipid-associated genetic variants occurred with comparable frequency in both sexes despite a greater burden of coronary artery disease among men. [7] The absence of a significant sex-specific association with PLIN1 mutations in our study is in agreement with recent evidence suggesting that lipid metabolism gene variants are not inherently gender dependent.

An important observation in this study was the significantly elevated total cholesterol and triglyceride levels among mutation carriers. In September 2022, Wei et al. conducted a study in China and observed that ACS patients had lower HDL and higher triglycerides than controls, with elevated PLIN1 levels correlating with these adverse changes. The statistically significant association between PLIN1 mutations and dyslipidemia in the current study supports the hypothesis that these genetic variants contribute to cardiovascular risk by disrupting lipid homeostasis. [8]

PLIN1 variants were identified in 8 out of 84 patients (9.5%). The most common mutation was c.205G>A (p.Ala69Thr), detected in five patients. Other identified variants included c.224C>T (p.Pro75Leu), c.131C>T (p.Thr44Ile), and a synonymous c.120C>G variant. In February 2024, Desgrouas et al. from France highlighted the critical role of PLIN1 in lipid droplet homeostasis and identified PLIN1 as a key regulator of triglyceride storage and adipocyte metabolism. [9] The presence of rs146569237 in our ACS cohort highlights the need for larger population-based studies and functional analyses to determine its pathogenic significance.

Heart failure was the most prevalent MACE in this study. Among patients suffering from PLIN1 gene mutations, there was no statistical significance to show any relation between PLIN1 gene mutation and short-term outcomes for cardiac health. Likewise, in February 2022, Bhatt DL et al., based out of the United States of America, in their analysis of acute coronary syndromes, reported heart failure to be one of the commonest complications after ACS. [10] The lack of significant differences in MACE among the mutation carriers in this study may reflect the limited sample size and short duration of follow-up rather than the absence of a biological effect.

Conclusion

PLIN1 gene variants were identified in 9.5% of patients presenting with ACS. The c.205G>A (p.Ala69Thr) variant was the most frequently detected mutation in which mutation carriers demonstrated significantly higher total cholesterol and triglyceride levels, suggesting a potential role of PLIN1 variants in dyslipidaemia and altered lipid metabolism. These findings suggest that PLIN1 variants may contribute to ACS susceptibility through their effects on lipid homeostasis rather than directly influencing early prognosis. Larger multicenter studies with extended follow-up and functional genomic analyses are needed to clarify the pathogenic role of PLIN1 variants and their potential utility as biomarkers for cardiovascular risk stratification.

Limitations

The research was restricted to a single facility and featured a limited cohort, which could have an impact on the results. More research using larger, more varied cohorts from multi-centre trials will yield more thorough and reliable findings.

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