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ASSOCIATION OF ATG5 GENE POLYMORPHISM WITH ACUTE CORONARY SYNDROME - OBSERVATIONAL STUDY

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ABSTRACT
Autophagy, regulated by autophagy-related genes, plays a critical role in cardiomyocyte survival during ischaemic injury and in atherosclerotic plaque stability. Autophagy-related 5 (ATG5) is essential for the ATG12–ATG5–ATG16L1 conjugation system, and polymorphisms in this gene may modulate susceptibility to ACS, although Indian data are limited. We conducted a prospective cross-sectional study of 85 adults with ACS at a tertiary care centre in Karnataka, India, from March 2024 to December 2025. Clinical, biochemical, electrocardiographic, echocardiographic data was recorded. Genomic DNA was extracted from peripheral blood; the ATG5 gene promoter region (NC_000006.12, g.106326240–106326809) was amplified by polymerase chain reaction and analysed by Sanger sequencing. Patients were categorized as ATG5 polymorphism present or absent and the groups were compared. The mean age was 63.40 ± 13.45 years, with 64.7% males. ST-segment elevation myocardial infarction was diagnosed in 52 patients and non-ST-segment elevation myocardial infarction in 33. The ATG5 rs506027 (g.106326589 G>A) polymorphism was detected in 22 of 85 patients (25.9%) — 9 homozygous and 13 heterozygous. Patients with polymorphism had significantly higher triglycerides (182.4 ± 44.8 vs 154.2 ± 36.8 mg/dL, p = 0.004) and low-density lipoprotein cholesterol (158.1 ± 19.8 vs 141.5 ± 32.8 mg/dL, p = 0.028. Left ventricular ejection fraction, major adverse cardiac events and mortality were compared between groups. The ATG5 rs506027 polymorphism was identified in 25.9% of Indian ACS patients and was associated with an adverse lipid profile, suggesting a possible link between altered autophagy and dyslipidaemia in ACS. Larger multi-centric studies with functional validation are needed to define its prognostic and therapeutic relevance.

KEYWORDS: Autophagy; Atherosclerosis; Myocardial Infarction; Dyslipidaemia; Polymerase Chain Reaction; Echocardiography

INTRODUCTION
Cardiovascular diseases account for nearly 17.9 million deaths annually and remain the leading global cause of mortality (Roth et al., 2017). South Asians experience premature ACS nearly a decade earlier than populations in high-income countries (Yusuf et al., 2004; Prabhakaran et al., 2018). Atherosclerosis, characterised by endothelial dysfunction, lipid accumulation, inflammation and extracellular-matrix remodelling, underlies most ACS events (Libby et al., 2011). Plaque rupture with superimposed thrombosis precipitates acute ischaemia (Fuster et al., 1988; Davies et al., 1993). Autophagy has emerged as a key homeostatic mechanism regulating plaque biology and cardiomyocyte survival (Levine and Kroemer, 2008; Gatica et al., 2015). Autophagy is a conserved lysosomal degradation pathway that maintains cellular homeostasis during ischaemia and oxidative stress (Tanida, 2011). In endothelial cells and macrophages, autophagy limits lipid accumulation, inflammation and plaque instability, whereas defective autophagy accelerates lesion progression (Singh et al., 2009; Liao et al., 2012). In cardiomyocytes, dysregulated autophagy contributes to adverse remodelling following myocardial infarction (Matsui et al., 2007). More than 40 autophagy-related genes regulate autophagosome formation and lysosomal fusion (Mizushima et al., 1998). Among these, autophagy related 5 (ATG5), located on chromosome 6q21, is essential for autophagosome biogenesis through the ATG12–ATG5–ATG16L1 conjugation system and LC3 lipidation (Wesselborg and Stork, 2015; Ye et al., 2018). ATG5 also participates in mitochondrial quality control, antigen presentation and apoptosis (Pierdominici et al., 2012; Kim et al., 2016). Genetic variants in ATG5 can alter autophagic activity and have been associated with autoimmune, respiratory, neurological and cardiovascular diseases (Martin et al., 2012; Kim et al., 2016). A French case-control study demonstrated that plasma ATG5 and Beclin-1 levels were inversely associated with acute myocardial infarction and showed superior diagnostic performance compared with conventional

biomarkers (Grazide et al., 2024). Reduced ATG5 expression in peripheral blood mononuclear cells has also been linked with elevated LDL cholesterol, apolipoprotein B and inflammatory cytokines in cardiovascular disease patients, changes reversed by rapamycin-induced autophagy (Khalil et al., 2020). Despite growing evidence, data regarding ATG5 polymorphism in Indian ACS patients remain limited. Therefore, this prospective study aimed to evaluate the prevalence of ATG5 gene polymorphism in Indian patients with ACS and examine its association with clinical profile, lipid parameters, cardiac function and in-hospital outcomes.

MATERIAL AND METHODS

Study design

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. Ethical approval was obtained from the Institutional Ethics Committee (IEC/NO-048/2023-24), and the study was prospectively registered with the Clinical Trials Registry of India (CTRI/2024/02/063859). Written informed consent was obtained from every participant.

Participants and sample size

Inclusion criteria: Individuals aged ≥18 years admitted with a clinical diagnosis of ACS based on standard guidelines (Amsterdam et al., 2014) were enrolled. Exclusion criteria: Patients with valvular or congenital heart disease and those with pulmonary embolism were excluded to eliminate potential confounding from these conditions. The sample size was calculated using the formula $n = Z^2 \times p \times q / d^2$, taking $p = 0.24$ for the combined frequency of deletion variants and SNPs in the ATG5 gene among acute myocardial infarction patients reported in the literature (Zhang et al., 2020), with 95% confidence and 9% absolute precision, yielding a required sample of 90 patients. A total of 90 patients with ACS were enrolled; 85 of them were included, and 5 patients were excluded due to exclusion criteria (four cases of valvular heart disease and one case of pulmonary embolism).

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 to assess regional wall motion abnormality (RWMA) and left ventricular ejection fraction (LVEF, biplane Simpson method). Laboratory investigations included complete blood count, blood urea, serum creatinine, electrolytes, fasting lipid profile and high-sensitivity cardiac troponin I. A 1 mL peripheral venous blood sample was obtained from each participant, collected in ethylenediaminetetraacetic acid (EDTA) tubes and sent to the genetics laboratory for analysis of ATG5 gene polymorphism (Figure 1). Based on detection of the rs506027 (g.106326589 G>A) variant, patients were grouped into ATG5 polymorphism-present (Group A) or polymorphism-absent (Group B).

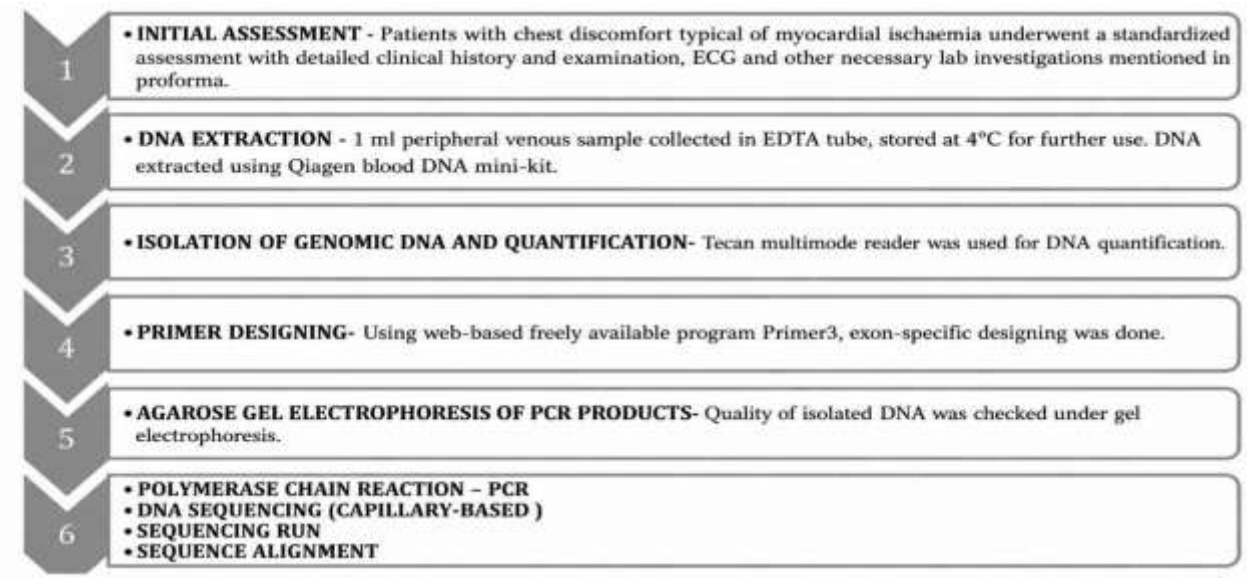

Figure 1. Workflow diagram outlining genetic analysis steps to study **ATG5** gene polymorphism.

DNA extraction and ATG5 genotyping

Genomic DNA was extracted by the salting-out method using a commercial blood DNA mini-kit (Qiagen, Hilden, Germany) and quantified spectrophotometrically; optical density (OD) 260/280 ratios were between 1.5 and 2.0 for all samples, indicating good-quality DNA suitable for amplification. Primers targeting the promoter region of the ATG5 gene (NC_000006.12, g.106326240–106326809) were designed using the Primer3 platform and validated by in silico PCR (forward 5′-GGC ATG CTT CCC TAA CTT GA-3′; reverse 5′-CCC ACC CAT CCA AGA GTA CA-3′; amplicon 649 bp). Amplification was performed in 20 µL reactions containing 2 µL genomic DNA, 0.4 µL of each 5 pmol primer and 10 µL TaKaRa Premix Ex Taq (Takara Bio, Otsu, Japan), under the following cycling conditions: initial denaturation at 95 °C for 5 min; 35 cycles of 95 °C for 30 s, 56 °C for 30 s and 72 °C for 1 min; and a final extension at 72 °C fmin. Amplicons were verified by 1% agarose gel electrophoresis against a 100 bp ladder (Figure 2).

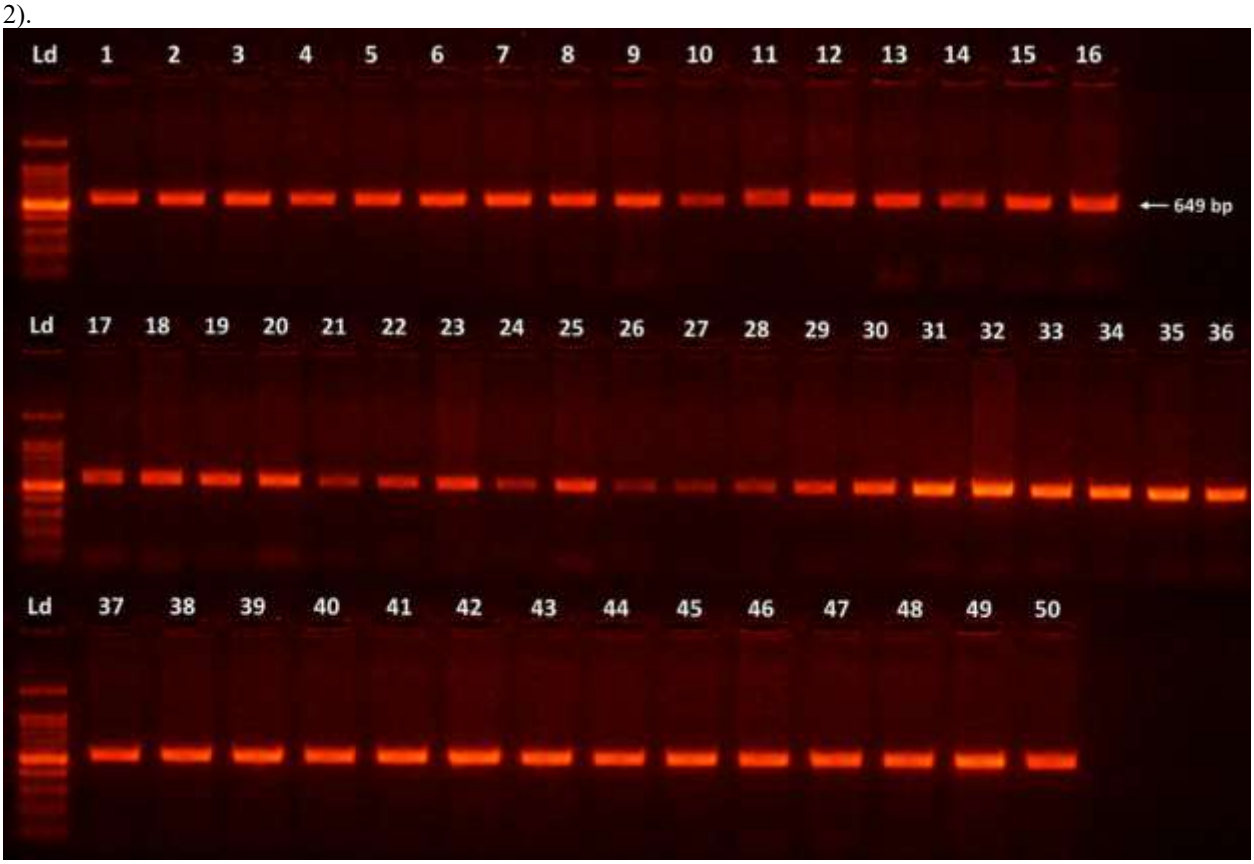

Figure 2. 1% agarose gel electrophoresis of **ATG5** gene amplicons.

Purified PCR products were subjected to Sanger sequencing using BigDye Terminator v3.1 chemistry on an automated capillary sequencer (Applied Biosystems, Foster City, CA, USA). Electropherograms were analysed with DNA Baser software and aligned to the reference ATG5 sequence to identify single-nucleotide polymorphisms.

Statistical analysis

The collected data was organized using Microsoft Excel and later analysis was done using IBM SPSS (Version 26). Quantitative variables are reported as mean ± standard deviation (SD) and were compared between study groups using the independent-samples t-test after assessing the underlying assumptions of data distribution and homogeneity of variances. Qualitative variables are presented as frequencies and percentages, with group differences evaluated using Pearson's chi-squared test. All analyses were two-tailed and p- value < 0.05 was considered indicative of statistical significance.

RESULTS

Baseline demographic and clinical profile

A total of 85 ACS patients were included. Based on the presence or absence of ATG5 gene polymorphism, these patients were divided into Group A (n = 22) and Group B (n = 63), respectively. The mean age was 63.40 ± 13.45 years, with 20% were in the 30-50 years age group, 43.5% of patients in the 51–70-year age group and 36.5% aged 71–90 years. The common age group in Group A was 71-90, and in Group B it was 51-70. Fifty-five patients (64.7%) were male and 30 (35.3%) were female of which Group A had 10 males (45.5%) and 12 females (54.5%), while Group

B had 45 males (71.4%) and 18 females (28.6%). A non-significant trend toward higher female representation (54.5% vs 28.6%, p = 0.067) was noted in Group A. Hypertension was the most common modifiable risk factor in the study groups (40.9% in Group A vs 34.9% in Group B). Chest pain was the dominant presenting symptom in 80 patients (94.1%), followed by dyspnoea (24.7%); this did not differ between groups (p = 0.600 and p = 0.398, respectively). Baseline age, sex distribution, modifiable risk factors and symptom distribution were comparable between the two groups (Table 1).

Table 1. Demographic and clinical data.

Variable	**Group A (n = 22)**		**Group B (n = 63)**		**p-value**
	n	**%**	**n**	**%**	
Age (years)					0.221
18–30	0	0.0	0	0.0	
31–50	7	31.8	10	15.9	
51–70	7	31.8	30	47.6	
71–90	8	36.4	23	36.5	
Sex					
Male	10	45.5	45	71.4	0.067
Female	12	54.5	18	28.6	0.067
Modifiable risk factors					
Diabetes mellitus	4	18.2	22	34.9	0.339
Hypertension	9	40.9	22	34.9	0.617
Smoking	6	27.3	14	22.2	0.771
Alcohol use	4	18.2	15	23.8	0.769
Tobacco chewing	4	18.2	23	36.5	0.182
Symptom distribution					
Chest pain	20	90.9	60	95.2	0.600
Dyspnoea	7	31.8	14	22.2	0.398
Palpitation	0	0.0	2	3.2	1.000
Abdominal pain	0	0.0	1	1.6	1.000

Vital signs and most laboratory parameters did not differ between the two groups (Table 2). However, serum creatinine and serum potassium were significantly lower in Group A (0.81 ± 0.24 vs 1.08 ± 0.68 mg/dL, p = 0.008; and 3.87 ± 0.70 vs 4.27 ± 0.63 mmol/L, p = 0.016, respectively). The fasting lipid profile showed a markedly atherogenic pattern in patients of Group A: triglyceride levels (182.4 ± 44.8 vs 154.2 ± 36.8 mg/dL, p = 0.004) and LDL cholesterol (158.1 ± 19.8 vs 141.5 ± 32.8 mg/dL, p = 0.028) were significantly higher, and HDL cholesterol tended to be lower (37.1 ± 7.9 vs 41.2 ± 10.2 mg/dL, p = 0.093). Total cholesterol was comparable between groups (Figure 3).

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

Parameter	**Group A**		**Group B**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Pulse rate (beats/min)	88	24	83	17	0.185
Systolic blood pressure (mmHg)	132	38	136	26	0.586
Diastolic blood pressure (mmHg)	78	17	82	13	0.346

Parameter	Group A		Group B		p-value
	Mean	SD	Mean	SD	
Troponin I (ng/L)	3457	6869	2676	5222	0.581
Haemoglobin (g/dL)	14.4	6.4	13.2	2.1	0.566
Blood urea (mg/dL)	31.6	20.0	36.5	23.3	0.381
Serum creatinine (mg/dL)	0.81	0.24	1.08	0.68	0.008*
Serum potassium (mmol/L)	3.87	0.70	4.27	0.63	0.016*
Total cholesterol (mg/dL)	203.6	25.6	201.5	43.6	0.838
Triglycerides (mg/dL)	182.4	44.8	154.2	36.8	0.004*
LDL-C (mg/dL)	158.1	19.8	141.5	32.8	0.028*
HDL-C (mg/dL)	37.1	7.9	41.2	10.2	0.093

*Statistically significant ($p < 0.05$). LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

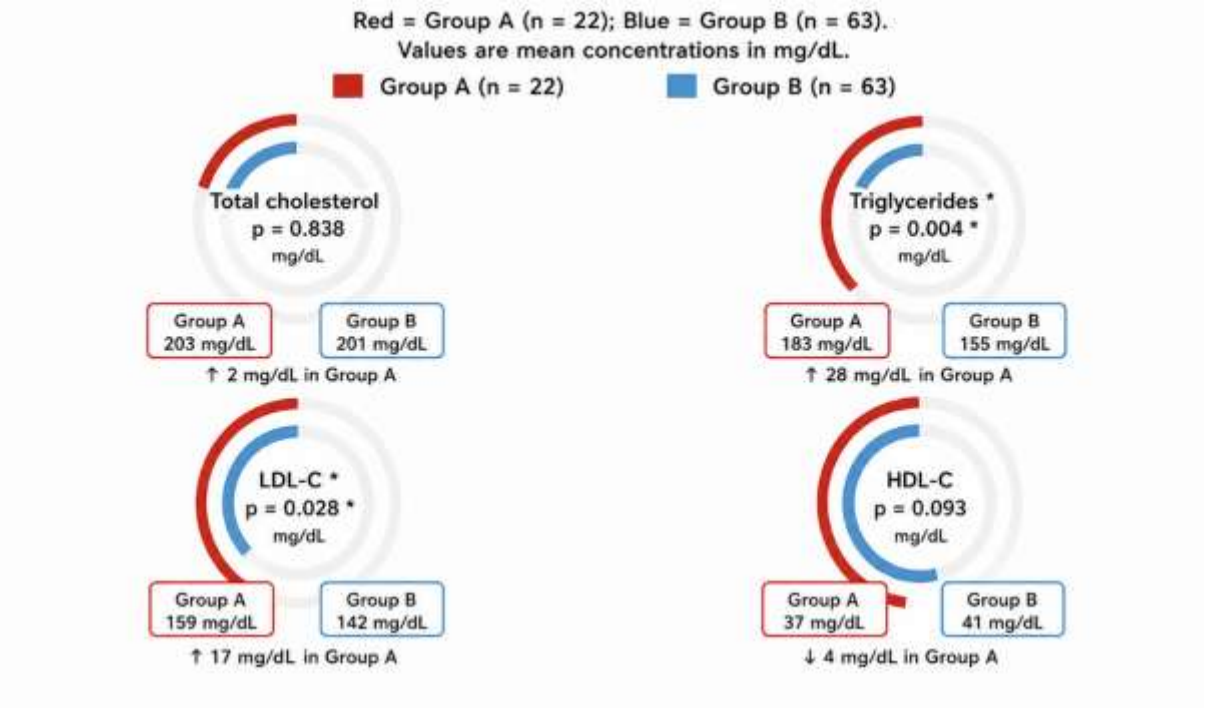

Figure 3. Lipid profile in Group A (n = 22) versus Group B (n = 63). Triglycerides and LDL cholesterol were significantly higher among patients harbouring the **ATG5** rs506027 polymorphism (Group A). *$p < 0.05$ (independent-samples t-test).

Cardiac investigations

On electrocardiography, STEMI was diagnosed in 52 patients and NSTEMI in 33; the distribution of the two phenotypes did not differ significantly between ATG5 groups ($p = 0.299$). Two-dimensional echocardiography showed regional wall motion abnormalities in 89.4% of patients overall, with anterior wall involvement in 30 (35.3%), inferior wall in 29 (34.1%) and global or multiple-wall involvement in 12 (14.1%). The distribution of RWMA did not differ significantly between groups ($p = 0.801$). Among patients in Group A, 9 patients (40.9%) had LVEF <40%, while 13 patients (59.1%) had LVEF ≥40%. Among patients in Group B, 19 patients (30.2%) had LVEF <40%, whereas 44 patients (69.8%) had LVEF ≥40%. Although a higher proportion of patients in Group A had reduced LVEF (<40%) compared to those in Group B, (40.9% vs 30.2%), the difference was not statistically significant ($p = 0.509$; Table 3).

Table 3. Echocardiographic findings in Group A and Group B.

Parameter	Group A (n = 22)		Group B (n = 63)		p-value
	n	%	n	%	
LVEF					
<40%	9	40.9	19	30.2	0.509
>40%	13	59.1	44	69.8	
RWMA					
Anterior wall	10	45.5	20	31.7	
Inferior wall	5	22.7	24	38.1	
Global/multiple walls	4	18.2	8	12.7	0.801
No RWMA	1	4.5	8	12.7	
Concentric LVH/other	2	9.1	3	4.8	

LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormality; LVH, left ventricular hypertrophy; SD, standard deviation.

Major adverse cardiac events

All 85 patients were assessed for major adverse cardiac events (MACE). Heart failure was the most common in-hospital complication (54.5% in Group A vs 49.2% in Group B, p = 0.805). Cardiac arrhythmia, cardiogenic shock and in-hospital mortality each occurred in only one patient, all from the ATG5 polymorphism–absent group; overall in-hospital mortality was 1.2%. There were no statistically significant differences in adverse events between groups (Table 4).

Table 4. Major adverse cardiac events in Group A and Group B.

Major adverse cardiac events	Group A (n = 22)		Group B (n = 63)		p-value
	n	%	n	%	
Heart failure	12	54.5	31	49.2	0.805
Arrhythmia	0	0.0	1	1.6	1.000
Cardiogenic shock	0	0.0	1	1.6	1.000
In-hospital mortality	0	0.0	1	1.6	1.000

Mutation analysis of the ATG5 gene

Sequencing of the ATG5 promoter region (NC_000006.12, g.106326240–106326809) in all 85 samples identified a single G>A transition at position g.106326589, corresponding to the SNP rs506027 (Table 5).

Table 5. Mutation analysis of the **ATG5** gene.

Gene	Chromosomal location	Reference sequence	Region covered (g.)	Variant identified	SNP identifier	Variant type
ATG5	6q21	NC_000006.12	106326240–106326809 (promoter)	G > A at g.106326589	rs506027	SNV

SNV, single-nucleotide variant.

Of the 85 patients, 22 (25.9%) were positive for the ATG5 rs506027 polymorphism (Group A) and 63 (74.1%) were negative (Group B); 9 of the 22 carriers were homozygous and 13 were heterozygous. No additional novel variants were detected within the sequenced region (Table 6). An electropherogram obtained via capillary-based DNA sequencing showed both homozygous (A/A) and heterozygous (G/A) forms of the g.106326589 G>A variant in the ATG5 gene sequence (Figure 4).

Table 6. Distribution of **ATG5** gene polymorphism in Group A and Group B.

ATG5 gene polymorphism	**Group A (n = 22)**		**Group B (n = 63)**	
	n	**%**	**n**	**%**
Homozygous variant	9	40.9	—	—
Heterozygous variant	13	59.1	—	—
Polymorphism absent	—	—	63	74.1
Total	22	25.9	63	74.1

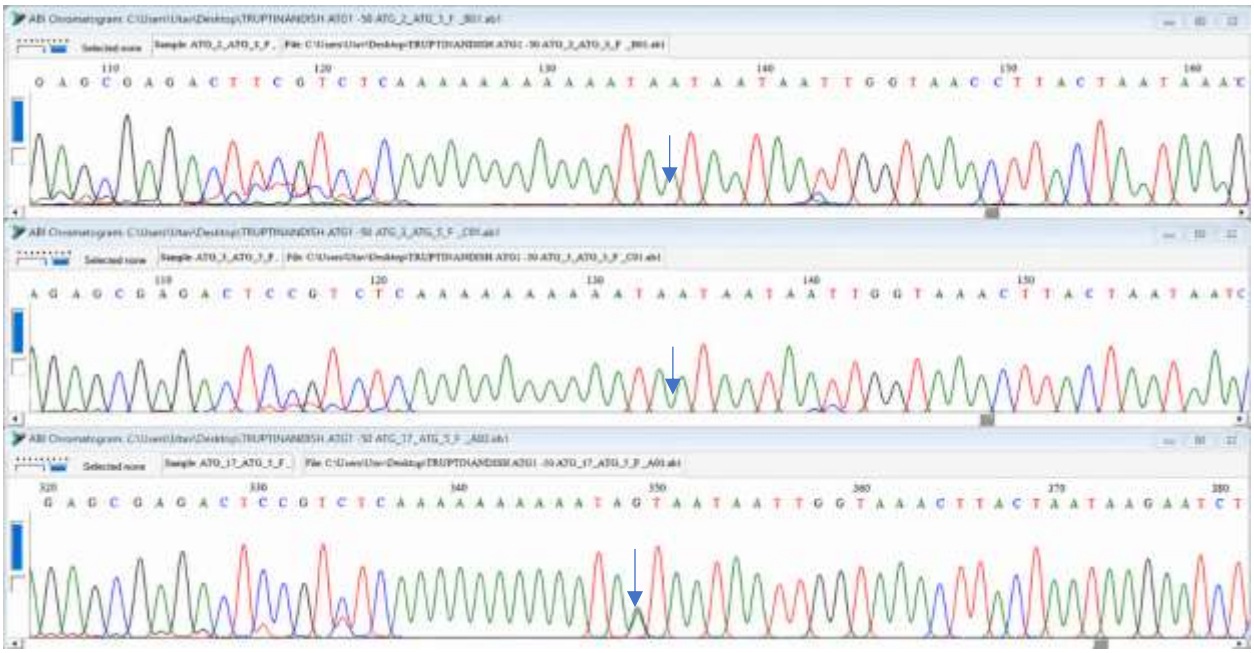

Figure 4. Electropherogram of the **ATG5** gene sequence showing the homozygous (A/A) and heterozygous (G/A) forms of the g.106326589 G>A variant.

DISCUSSION

A prospective study of 85 Indian patients hospitalised with ACS was conducted to explore the association of ATG5 gene polymorphism, specifically the rs506027 (g.106326589 G>A) promoter-region variant, and to describe the demographic, biochemical and clinical characteristics of affected patients.

The mean age (63.4 ± 13.5 years) and the male preponderance (64.7%) observed in this cohort are consistent with major Indian ACS registries. The Kerala ACS Registry reported a mean age of 60.1 ± 12.3 years and 76.3% male representation among 25,748 admissions (Mohanan et al., 2013), while the CREATE registry of 20,937 Indian ACS patients described a comparable age distribution and 77.2% males (Xavier et al., 2008). A non-significant trend toward female predominance among rs506027 carriers (54.5% vs 28.6%, p = 0.067) is biologically plausible: ATG5 lies in a chromosomal region targeted by several autoimmunity-related loci, and autophagy-related polymorphisms have repeatedly shown female-skewed associations with systemic lupus erythematosus and related diseases (Pierdominici et al., 2012; Zhou et al., 2011).

The conventional risk-factor burden in this cohort — 30.6% with diabetes, 36.5% with hypertension and 55.3% with any form of tobacco use — is broadly in line with the Global Burden of Disease estimates for India (Gupta et al., 2008; Prabhakaran et al., 2018). The INTERHEART study established that South Asians develop their first myocardial infarction nearly a decade earlier than Western populations, and that diabetes (OR 2.37) and current smoking (OR 2.87) are leading population-attributable risks in this region (Yusuf et al., 2004).

Chest pain was the predominant presenting symptom in this study and was observed in 94.1% of patients, followed by dyspnoea in 24.7% of cases. The frequency of chest pain was comparable between Group A and Group B (90.9%

vs 95.2%, p = 0.600). Similarly, the prevalence of dyspnoea was comparable between the two groups, with no statistically significant difference observed (31.8% vs. 22.2%, p = 0.398). Palpitations and abdominal pain were infrequently reported, while syncope was not observed in any patient. These findings are comparable with previous ACS studies (Canto et al., 2000), in which chest pain was reported as the most common presenting symptom among patients with myocardial infarction, with dyspnoea being the next frequent presentation, particularly in elderly patients and those with comorbidities. The lack of significant symptomatic variation between the groups in the present study suggests that ATG5 polymorphism may not substantially influence the initial clinical presentation of ACS.

Interestingly, the ATG5 polymorphism carriers in this study had lower serum creatinine, which may simply reflect the higher proportion of women in this subgroup or chance, given the modest sample size. Lower baseline creatinine has been associated with better outcomes in ACS (Gibson et al., 2003), although whether this relationship is preserved in genetically defined subgroups is unknown. The mildly lower serum potassium in the polymorphism group remained within physiological limits and is unlikely to be clinically meaningful.

Two-dimensional echocardiographic evaluation demonstrated that regional wall motion abnormalities (RWMA) were common among ACS patients, reflecting the underlying ischaemic insult. Although a higher proportion of patients in Group A had reduced LVEF (<40%) compared to those in Group B, (40.9% vs 30.2%), the difference was not statistically significant (p = 0.509), which does not support a definitive association between ATG5 polymorphism and impaired myocardial function in this cohort. Diastolic dysfunction and segmental wall motion abnormalities were frequently observed in both groups. Experimental and clinical studies of autophagy-related pathways have shown that impaired ATG5-mediated autophagy is associated with adverse ventricular remodelling, cardiomyocyte dysfunction and reduced cardiac performance after ischaemic injury (Matsui et al., 2007).

The 25.9% carrier frequency of the rs506027 variant in this cohort is markedly higher than the frequency of rare promoter variants reported by Zhang et al. in 378 Chinese AMI patients, where a single deletion variant (g.106326168_70delTCT) and one SNP were identified in only one patient (0.26%) (Zhang et al., 2020). The discrepancy likely reflects ethnic differences in allele frequency rather than a methodological artefact: an intergenic PRDM1–ATG5 variant has been reported at a 28% minor allele frequency in Chinese systemic lupus erythematosus patients (Zhou et al., 2011), and the ATG5 promoter SNP rs2245214 had an allele frequency of approximately 40% in European children with asthma (Martin et al., 2012). This pattern suggests that common ATG5 variants are widely distributed in human populations but with considerable interethnic variation, and that rs506027 may represent a common functional or regulatory variant in South Asians warranting confirmation in larger studies.

Mechanistically, ATG5 is indispensable for the elongation of the phagophore and for LC3-II generation during autophagosome biogenesis (Mizushima et al., 1998; Ye et al., 2018). Genetic ablation of ATG5 in murine cardiomyocytes increases susceptibility to ischaemia–reperfusion injury, accelerates pathological remodelling and exacerbates lipid accumulation in macrophages (Matsui et al., 2007; Liao et al., 2012; Wesselborg and Stork, 2015). In humans, Grazide and colleagues demonstrated that circulating ATG5 and Beclin-1 levels were inversely associated with AMI in a French case-control study and provided incremental discriminative value over traditional biomarkers (Grazide et al., 2024). Khalil and colleagues reported a marked downregulation of ATG5 and LC3 gene expression in peripheral blood mononuclear cells from cardiovascular patients, accompanied by apolipoprotein B overexpression, elevated LDL and increased interleukin-6 and tumour necrosis factor-α — abnormalities partially reversed by autophagy induction with rapamycin in patient-derived macrophages (Khalil et al., 2020). These findings, together with the established role of autophagy in hepatic and macrophage lipid handling (Singh et al., 2009; Christian et al., 2013), offer a plausible explanation for the higher triglyceride and LDL levels we observed in our ATG5 polymorphism carriers: reduced or dysregulated autophagic activity may impair lipid droplet turnover and impede LDL clearance, thereby contributing to the dyslipidaemic phenotype.

Clinically, the observations of this study carry two practical implications. First, the relatively high carrier frequency (25.9%) in a hospitalised ACS population suggests that ATG5 promoter genotyping may be a feasible adjunct to conventional risk assessment, particularly when integrated with lipid screening — identification of carriers might prompt earlier, more intensive lipid-lowering therapy and structured screening of first-degree relatives (Ginsburg et al., 2005; Bhardwaj et al., 2014). Second, the lipid signal supports the hypothesis that pharmacological induction of autophagy (for example by metformin, statins or rapamycin analogues) may offer a complementary therapeutic axis in atherosclerotic cardiovascular disease, an idea that deserves prospective evaluation (Khalil et al., 2020; Lavandero et al., 2015).

Finally, MACE analysis revealed that heart failure was the most common complication, occurring in 50.6% of patients overall (43 of 85) and in-hospital mortality was 1.2%. These rates reflect the severe nature of ACS and its complications (Matsui et al., 2007). Despite the significant biochemical signal, ATG5 polymorphism status did not influence the acute presentation, the extent of RWMA, LVEF and in-hospital adverse events. Several considerations are relevant. First, the rs506027 variant is a common SNP rather than a rare loss-of-function mutation, so its effect on autophagic flux is likely to be modest. Second, the acute manifestations of ACS reflect the interaction of plaque rupture, thrombosis and immediate ischaemia — processes in which traditional haemodynamic and prothrombotic

mechanisms predominate; subtle differences in autophagy may matter more in chronic atherogenesis, long-term remodelling or recurrent events than at the time of the acute episode (Lavandero et al., 2015). Third, our short follow-up — limited to the index hospitalisation — and the small number of events (one death, one arrhythmia, one cardiogenic shock) preclude meaningful conclusions about hard outcomes. Higher serum autophagy levels have been shown to correlate positively with the Rentrop score in chronic ischaemia, supporting a compensatory and protective role for autophagy (Kaplan and Demircan, 2018). Longer-term follow-up of ATG5-variant carriers, with measurement of plasma autophagy markers, may therefore reveal effects that are not evident in the acute window. Genetic factors play an independent role in the development and progression of coronary artery disease. Therefore, a better understanding of the molecular pathways influenced by these genes, along with the integration of genetic testing into routine clinical practice, may facilitate the development of targeted therapies aimed at specific genetic determinants. Furthermore, advances in genetic research can help identify asymptomatic individuals with a higher inherited risk, particularly among relatives of patients with acute coronary syndrome (ACS), thereby supporting effective primary prevention strategies. In this context, the present study represents one such effort by investigating the association between ATG5 gene polymorphism and ACS.

CONCLUSION

ACS remains a leading cause of mortality worldwide, highlighting the need for timely intervention and diagnostic tools incorporating biological and genetic markers. This study identified the ATG5 rs506027 promoter polymorphism in 25.9% of Indian ACS patients and demonstrated significant associations with higher triglyceride and LDL cholesterol levels. These findings suggest a possible role of altered autophagy in metabolic and inflammatory pathways contributing to ACS. Larger case-control studies with functional validation, autophagy biomarker assessment and long-term follow-up are needed to confirm the clinical utility of this variant in risk stratification and therapeutic decision-making in cardiovascular disease.

Limitations

The present study was limited by its relatively small sample size, single-centre design and lack of a healthy control group; hence, the positive correlation of ATG5 gene obtained in this study cannot be generalized. Larger multi-centric studies with long-term follow-up and functional analysis of the rs506027 variant are therefore needed.

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