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Genetic Study of Nuclear Factor Kappa B1 Gene (NFKB1) Polymorphism in Acute Coronary Syndrome

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ABSTRACT Acute coronary syndrome (ACS) is a leading cause of death and illness worldwide. Previous studies explored connection between NFKB1 gene polymorphism and its role in development of atherosclerosis. The aim of the present study was to know the correlation of NFKB1 gene polymorphism with acute coronary syndrome (ACS). Comprehensive clinical data, biochemical profiles, electrocardiograms, and blood samples were collected from 92 patients with ACS and NFKB1 gene polymorphism was analysed using polymerase chain reaction. In this study, male were more than female patients and in the age group of 61-70 years. Chest pain and dyspnea were common symptoms and diabetes and high blood pressure were risk factors. Non-ST-segment elevation myocardial infarction was the frequent ECG finding. No mutations were detected in NFKB1 gene exons 2 and 10, indicating this particular genetic variant was not linked to ACS in the studied population.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in India, driven by both population-level transitions, like epidemiological, nutritional, environmental, and socio-economic, and inherent biological risks. Recent evidence highlights genetic predisposition, altered metabolism, chronic inflammation, and epigenetic changes leading to CVD (Kalra et al. 2023). CVDs are the leading cause of death in the United States, resulting in more than 9 lac deaths in 2020 (Abirami et al. 2024). Coronary artery disease (CAD) has achieved epidemic proportions affecting 3.5 million Indians occurring 10 years earlier than the Western population of which 50 percent of the population is below 50 years and 25 percent of the population below 45 years. Hence, CAD has a significant hereditary element mainly observed in the younger population (Sasidhar et al. 2014). Nuclear factor kappa-B gene (NFKB), transcription factor, locates at chromosome 4q24, with 27 exons that regulates the expression of proinflammatory genes linked to atherosclerosis and regarded pathogenic through its implication in vascular inflammation, proliferation of smooth muscle cells in vessels, formation of foam cell (Lai et al. 2015). NFKB gene transfers in nucleus gets activated and in response to inflammatory stimulus like lipopolysaccharide, reactive oxygen species, and tumour necrosis factor alpha initiates transcription of inflammation related genes like cytokines and chemokines aiding in pathogenesis of chronic inflammatory diseases (Chen et al. 1999).

The NFKB gene contains five types of proteins namely, RelA (p65), RelB, c-Rel, NFKB1 (p50/p105) and NFKB2 (p52/p100). Out of five proteins heterodimers and homodimers induced, regulated via various signals, including viral, bacterial infections, growth factors, cytokines and various stressors. Resting cells, NFKB resides in cytoplasm, forming complexities with I-κB, keeping NFKB in inactive state, blocking translocation inside nucleus, binding of DNA and regulating gene expression (Oeckinghaus and Ghosh 2009). Classic/Canonical and Alternative/Non-canonical are two signalling pathways for the activation of NFKB (Shih et al. 2011).

There is a relationship between D allele of the functional NFKB1 ATTG ins/del promoter polymorphism and the increased risk of coronary heart disease compared to homozygous I allele carriers

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(Vogel et al. 2011). A study of the Chinese Han population showed, in NFKB1-94ins/del ATTG polymorphism that the distribution of mutant DD genotypes was noticeably higher in ACS patients increasing risk of ACS 1.329 times higher in mutant DD genotype compared to ID and II gene (Luo et al. 2020). Mutant DD genotype may increase risk of heart failure reducing left ventricular function, increasing ventricular remodelling (Mishra et al. 2013). A study done in 778 ACS and 1112 controls in Chinese Han population found that percentage of diabetes were high among ACS patients with NFKB1 gene rs28362491 mutant DD genotype (Jin et al. 2019). The NFKB1 gene rs28362491 DD genotype was linked to a higher incidence of myocardial infarction and more advanced coronary artery lesions, correlating with elevated circulating IL-6 levels, underscoring its pro-inflammatory contribution to disease severity (Luo et al. 2022). The -94 NFKB1 5'-ATTG-3' D allele is linked to endothelial dysfunction, evidenced by decreased reactive hyperemic FBF response and its impact on NOS3 gene expression. This polymorphism, prevalent in approximately 20 percent of the population, offers a precise genetic marker for enhanced cardiovascular risk assessment, illuminating a key molecular mechanism in atherosclerosis (Park et al. 2007).

Objective

The objective of this study was to study the genetic polymorphism of the nuclear factor kappa B1 gene in patients of acute coronary syndrome.

MATERIAL AND METHODS

This cross-sectional study was conducted in Department of Medicine, BLDE (DU) Shri B M Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, India, from May 2023 to December 2024 with patients of ACS after approval from institutional ethical committee (IEC/NO-909/2023-24), and registered with the Clinical Trials Registry of India (CTRI/2023/05/052408) prospectively. The sample size was calculated using formula sample size (n) = ($\chi 2$ *p*(1-p)) /d2, where z score = 1.96, d is margin of error = 0.05, n = population size, p = population proportion = 0.06. The total of 100 patients presenting with typical anginal chest pain, dyspnoea were screened in the study. Out of which 92 patients were included based on inclusion criteria and 8 patients were excluded based on exclusion criteria in which 5 were valvular heart disease and 3 were ischemic cardiomyopathy. After taking informed consent, 92 patients underwent standardised assessment with detailed history, clinical examination, investigations like electrocardiogram, cardiac enzyme-Troponin I and coronary angiogram (if required). One ml of blood sample of the patient was collected in an EDTA tube for analysis of NFKB1 gene polymorphism in exon 10 and 2 as shown in Figure 1.

DNA Extraction and Primer Designing

From 300µl of peripheral blood genomic, the DNA was extracted using livgen blood genomic DNA extraction kit (cat no mp005). DNA concentration and purity were quantified using the Tecan multimode reader. Exon-specific oligonucleotide primers targeting NKB1 gene were designed with Primer 3, and synthesised by MWG Biotech, India. Table 1 shows PCR primers of exon 10 and exon 2.

Polymerase Chain Reaction

100 ml of 1 percent agarose gel was prepared (1gm of Agarose + 100 ml of 1X TAE buffer) to evaluate PCR products and the genomic DNA fragments were then separated based on size. PCR amplification of primer products was performed in a 20/ µL reaction volume comprising 0.5/ µL of template DNA (75-150/ ng/µL), 0.5/ iL of each primer (5/ pmol), 0.4/ µL of dNTPs (10/ pmol), 0.2/ µL of Taq DNA polymerase (3/ U/µL), and 4/ µL of 5X Taq buffer (Bio-Rad, USA), with molecular-grade water used to achieve the final volume.

DNA Sequencing (Capillary Based)

PCR products were subjected to capillary based Big-Dye terminator sequencing as shown in following Table 2 and Table 3. Prior to sequencing, the PCR products were subjected to cycle sequencing and plate processing. Cycle Sequencing as per the Sanger Sequencing protocol, Big-Dye labelling and chain termination were carried out by the cycle sequencing method. To label each base, the PCR amplicon was subjected to a cycle sequencing reaction with a single primer. Big-Dye TM terminator v3.1 was used for cycle sequencing (Applied Biosystems, USA) following the manufacturer's guidelines.

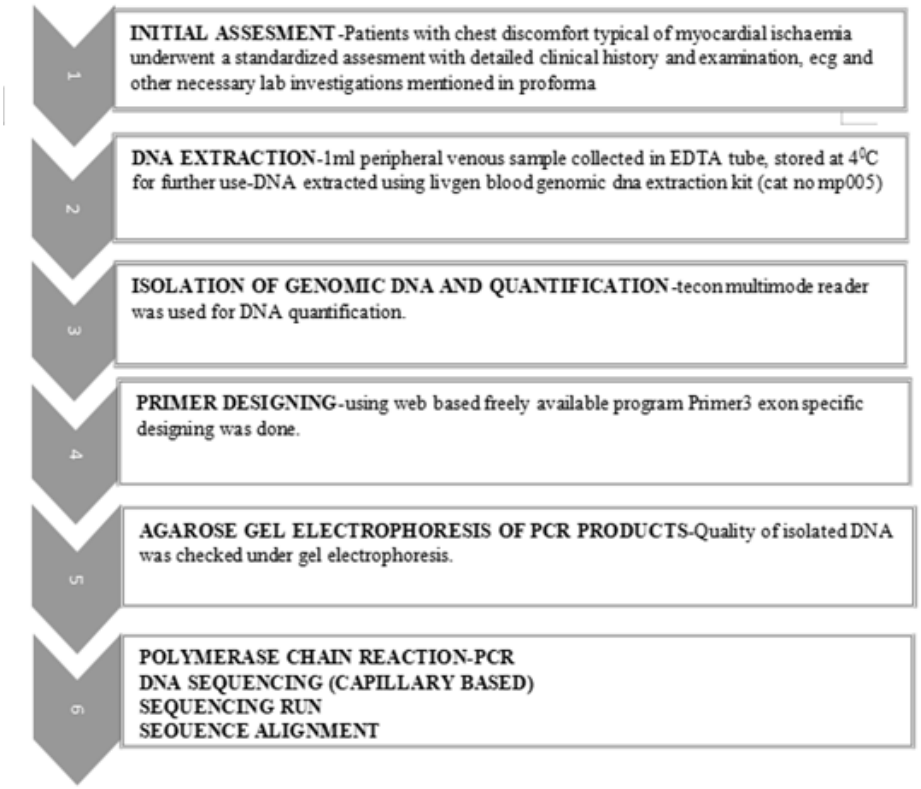

Fig. 1. Workflow diagram outlining genetic analysis steps to study NFKB1 gene polymorphism

Table 1: PCR Primers of NFKB1 gene of exon 10 and exon 2

Forward primer	*Reverse primer*	*Product size*	*Temperature*	*Primer name*
AAT GAA AGT TGG GGC GCA TT NF10 EXON	TGA TTG TAC CAC TGC ACT GC	388bp	60°C	NF10EXON
CCC AAG AGT TCC ATG GCC TC	CAT CTG GGC CCT GGC GGG CA	277bp	52°C	NF2 EXON

Table 2: Standardised master mix conditions for sequencing

S. No.	*Constituents*	*Quantity*
1	Molecular Biology grade water	6.3 µL
2	Big Dye Buffer (5X)	1.3 µL
3	Big Dye	1.0 µL
4	Template (PCR product)	1.0 µL
5	Forward Primer	0.2 µL
6	Reverse Primer	0.2 µL
	Total	**10 µL**

Table 3: The cycle sequencing conditions

Process	*Temperature*	*Time*
Initial Denaturation	98°C	10 seconds
Denaturation	98°C	10 seconds
Annealing	60°C	10 seconds
Elongation	72°C	5 minutes
Renaturation	72°C	5 minutes
Hold	4°C	

Sequencing Run

Sample information sheets containing analysis protocols and the sample details were prepared and imported into the data collection software. These samples were analysed using the ABI 3730 genetic analyser (Applied Biosystems, USA) to generate DNA sequences or electropherograms.

Sequence Alignment

Using Variant reporter software (ABI v1.1), produced sequences were aligned to corresponding reference sequences then screening of sequences was done to detect familiar variants like deletions, insertions and mutations. This technique was used to check the isolated genomic DNA from whole blood. In all the 92 acute coronary syndrome samples the presence of genomic DNA was confirmed and the same samples were taken for quantification based on Nanodrop.

Statistical Analysis

Data obtained was entered in Microsoft Excel spreadsheet, and statistical analysis was performed using a statistical package for the social sciences (version 20). Obtained results are presented as mean, standard deviation, counts and percentages, and diagrams.

RESULTS

Results of all 92 ACS patients were evaluated based on age, gender, risk factors, symptoms, hemodynamic and laboratory parameters, using SPSS v20 software.

Age and Gender Distribution, Risk Factors, Symptomatology

Following Table 4 depicts 100 participants diagnosed with coronary artery disease (CAD), mean age of patients in this study was 63.5 years, the highest proportion of individuals (39.1%) fell within the 61- to 70-year range. This was followed by the 51-60 years and 71-80 years age groups, both accounting for 19.6 percent. Only 1.1 percent of patients were under 40 years, indicating that the condition predominantly affects older adults. A gender-based breakdown revealed that males constituted a larger segment of the cohort (59.8%), whereas females represented 40.2 percent. This pattern supports the existing understanding that males are more frequently and earlier affected by CAD than females. Among the cohort, two major comorbidities, diabetes mellitus and hypertension, were identified in 66.3 percent of patients each, highlighting their prominent role in the disease's development. Tobacco use in the form of chewing was present in 73.9 percent of those who reported any tobacco use, indicating a strong behavioural and lifestyle component contributing to disease risk. Alcohol use was noted in 15.2 percent of individuals, and 7.6 percent reported a family history of myocardial infarction (MI). While genetic predisposition played a relatively smaller role, lifestyle-related factors appeared more influential in this population.

The predominant presenting symptom was chest discomfort, observed in 87 percent of the patients. Respiratory complaints such as breathlessness were reported by 37 percent, suggesting possible involvement of cardiac function beyond ischemia, potentially indicating early heart failure or severe ischemic burden. Less frequently, patients experienced abdominal pain (6.5%) or palpitations (3.3%), pointing toward less typical presentations of CAD, especially relevant in elderly and diabetic subgroups.

Table 4: Demographic and clinical parameters of study population

Parameters	*Study population (n=92)*	*Percentage (%)*
Age (Years)		
18-40	1	1.1
41-50	13	14.1
51-60	18	19.6
61-70	36	39.1
71-80	18	19.6
e”80	6	6.5
Gender		
Male	55	59.8
Female	37	40.2
Risk Factors		
Diabetes Mellitus	66	66.3
Hypertension	66	66.3
Tobacco chewing	68	73.9
Alcohol addiction	14	15.2
Family h/o MI	6	7.6
Symptoms		
Chest pain	70	87
Dyspnoea	34	37
Palpitation	3	3.3
Abdominal pain	6	6.5

Hemodynamic and Laboratory Parameters

Following Table 5 shows among the 100 patients assessed, the average pulse rate was recorded at 86.4 beats per minute, with a standard deviation (SD) of 12.5, indicating mild variability in resting heart rate. The respiratory rate averaged 19.3 breaths per minute (±2.7), suggesting stable respiratory status in most individuals. The mean body temperature remained within normal limits, measuring 37.0°C, with minimal deviation (±0.3), which may suggest absence of systemic infection at the time of evaluation.

The mean hemoglobin level was 12.4 gm percent (±1.4), which is marginally lower than the ideal range, possibly pointing to mild anemia, which is commonly seen in chronic illness or elderly individuals with cardiovascular disease. The total leukocyte count showed a wide range, with a mean of 13.5 ×10³ cells/cu.mm and a high SD of 7.5, possibly reflecting inflammatory or stress-related leukocytosis in many patients. The erythrocyte sedimentation rate (ESR) had a mean value of 18.21 mm/hr (±9.71), consistent with a low-to-moderate inflammatory state often associated with cardiovascular pathology.

Renal function markers were within acceptable ranges, with a mean blood urea of 30.0 mg/dl (±16.6) and serum creatinine averaging 1.1 mg/dl (±0.66). This suggests that most patients had relatively preserved kidney function at presentation. Serum sodium levels averaged 136.0 mmol/l (±10.0), which falls close to the lower limit of normal, and potassium levels were 5.7 mmol/l (±0.6), slightly elevated. The latter may suggest mild hyperkalemia, potentially due to medications (for example, ACE inhibitors) or underlying cardiac or renal involvement.

The random blood sugar (RBS) averaged 129.6 mg/dl (±35.8), indicating elevated glucose in many patients, reflective of underlying or stress-induced hyperglycemia. Lipid profile assessment showed total cholesterol levels of 206.8 mg/dl (±50.6) and LDL cholesterol averaging 165.7 mg/dl (±40.0), both notably elevated, which are established risk factors for coronary artery disease. Triglyceride levels were also raised (mean 192.8 mg/dl, SD 65.0).

Notably, HDL cholesterol, considered cardioprotective, was considerably low at a mean of 30.8 mg/dl (±7.4), further underscoring the dyslipidemic profile of the study group.

The most striking laboratory abnormality was seen in Troponin I levels, with a mean value of 3692.5 ng/ml (±1200). This highly elevated concentration is consistent with acute myocardial injury and serves as a definitive marker supporting the diagnosis of ACS in the majority of patients.

Agarose Gel Electrophoresis of Exon 10 and Exon 2 of NFKB1 Gene

Following Figure 2 shows the PCR products of exon 10 with base pairs 388 and lane number 1-38 prepared with 100 ml of 1 percent agarose gel (1gm of Agarose +100 ml of 1X TAE buffer).

Figure 3 shows the PCR products targeting exon 2, with expected amplicon size of 277 base pairs electrophoresed, 1 percent agarose gel prepared by dissolving 1 gm agarose in 100 ml of 1X TAE buffer.

Distribution of Polymorphism in Study Population

Following Table 6 shows results of genetic testing for mutations in NFKB1 gene in exon specific target 10 and 2 shows all 92 patients of ACS had no genetic mutation detected.

Illustration of the electropherogram displaying the nucleotide sequence of exon 10 in the NFKB1 gene, with well-defined peaks indicating high-qual-

Table 5: Hemodynamic and laboratory parameters in study population

Parameter	*Mean*	*SD*	*Parameter*	*Mean*	*SD*
Pulse Rate (beats/min)	86.4	12.5	Sodium (mmol/l)	136.0	10.0
Respiratory Rate (cycles/min)	19.3	2.7	Potassium (mmol/l)	5.7	0.6
Temperature (°C)	37.0	0.3	Total Cholesterol (mg/dl)	206.8	50.6
Haemoglobin (gm%)	12.4	1.4	Triglycerides (mg/dl)	192.8	65.0
Total Count (cells/cu.mm ×10³)	13.5	7.5	HDL (mg/dl)	30.8	7.4
RBS (mg/dl)	129.6	35.8	LDL (mg/dl)	165.7	40.0
Blood Urea (mg/dl)	30.0	16.6	Troponin I (ng/ml)	3692.5	1200
Creatinine (mg/dl)	1.1	0.66	ESR (mm/hr)	18.21	9.71

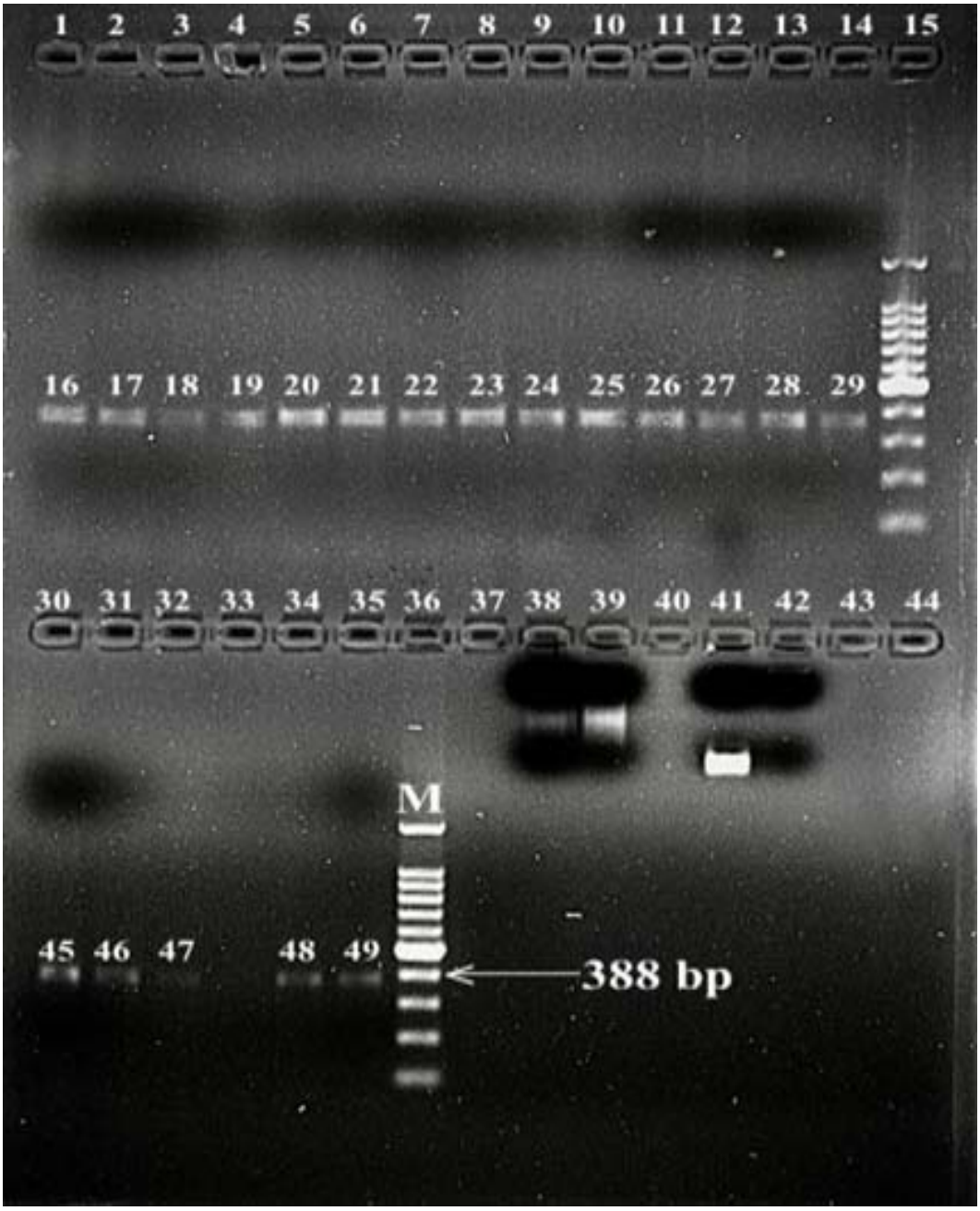

Fig. 2. Agarose gel image of exon 10 in NFKB1 gene

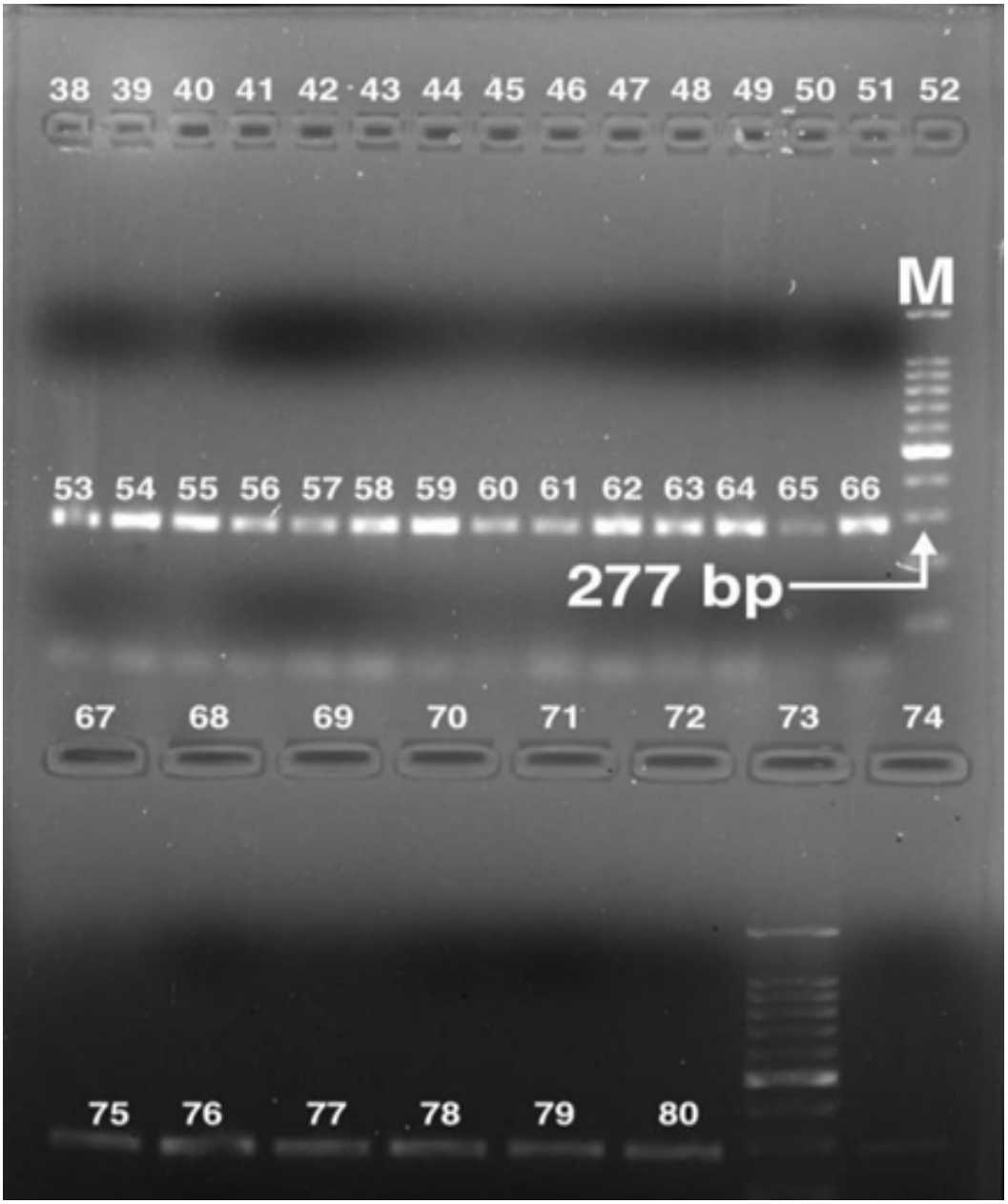

Fig. 3. Agarose gel image of exon 2 in NFKB1 gene

Table 6: Distribution of NFKB1 gene mutation results in ACS patients

NFKB1 gene mutation in Exon 10 and Exon 2	*Patients (n=92)*	*Percentage (%)*
Present	0	0
Absent	92	100
Total	92	100

ity sequencing is shown in following Figure 4. A specific nucleotide position is marked, suggesting no mutation.

Figure 5 shows the electropherogram depicting the nucleotide sequence of exon 2 in the NFKB1 gene, with distinct peaks indicating high-quality sequencing data. A particular nucleotide position is highlighted, pointing to no potential variant or mutation.

DISCUSSION

This was a prospective cross-sectional study where the aim of the study was to look for NKB1 gene polymorphism in patients admitted with acute coronary syndrome. This study was conducted in 92 patients who fulfilled the inclusion criteria and were analysed based on clinical history, blood investigations, ECG, 2D-ECHO and NFKB1 gene polymorphism. In this study, the most common age group with ACS was between 61-70 years, while a study done in tertiary care center in Harayana among 9945 patients, ACS was seen most commonly in the age group of 51-60 years (Nayak et al. 2022) . Both studies converge on the fact that advancing age is a dominant risk factor. This supports the pathophysiological understanding that aging promotes vascular endothelial dysfunction, inflammation, and accumulated exposure to cardiovascular risk factors. This study highlights male preponderance with 55 patients (59.8%) been male, 37 patients (40.2%) been female with ACS which matches the results of the study done in 1000 ACS patients in tertiary care hospital in India showing male group of 700 patients (70%) with ACS while female group had 300 patients (30%), showing significant male predominance (Mahapatra et al. 2024). The comparatively increased proportion of female patients in this study may suggest a shift in trends, where cardiovascular risks in women are being more effectively identified and documented. Based on risk factors this study concluded that tobacco chewing was the most commonly found risk factor comprising 68 patients (73.9%), following which diabetes (66.3%) and hypertension (66.3%) were significantly associated risk factors. Smoking (16%) and alcohol consumption (14%) were the least common associated risk factors found in this study.

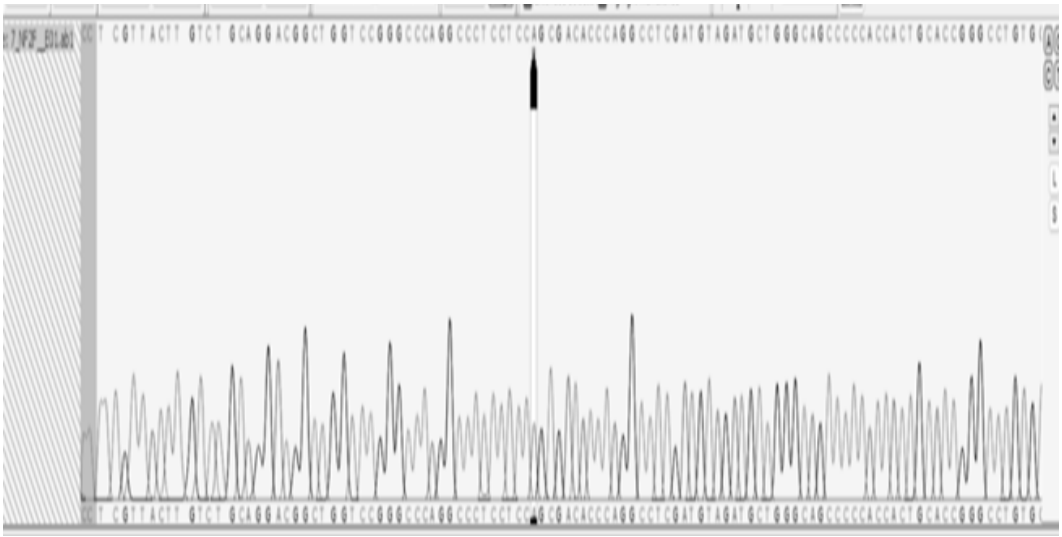

Fig. 4. Electropherogram showing gene analysis of Exon 10

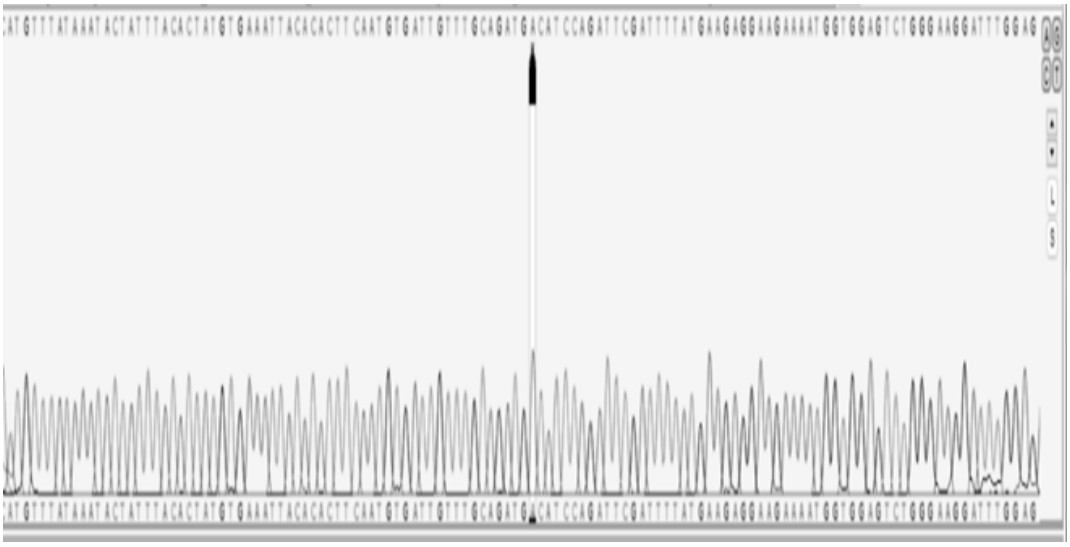

Fig. 5. Electropherogram showing gene analysis of Exon 2

Positive family history was found in 6 patients (7.6%) which is similar to study done in 13,071 South Asian participants conclude that smokeless tobacco, diabetes mellitus, hypertension, positive family history in young coronary artery disease patients were associated risk factors in ACS (Agrawal et al. 2023). The congruent results derived from both studies underscore the imperative for enhanced community-based tobacco control strategies like non-smoking tobacco products, which frequently receive insufficient attention in mainstream cessation programs. Moreover, consistent comorbidities like diabetes and hypertension across both studies affirms their central role in accelerating atherosclerotic changes in the coronary vasculature.

In this study chest pain (87%) was the most common symptom observed among patients followed by dyspnea (37%), while abdominal pain (6.5%), palpitations (3.3%) and syncope (1.1%) were least common. Which differs from a study done among 20,881 patients registered under Global Registry of Acute Coronary Events who showed unusual presentation of ACS with 1763 patients (8.4%) presenting without chest pain followed by presyncope/syncope (Brieger et al. 2004). A study done in Bhutan among 67 ACS patients, common symptoms observed were chest pain (29.7%), shortness of breath (26.4%), and nausea/vomiting (17.0%) (Chempay et al. 2025). This discrepancy suggests notable variability in symptom presentation across populations and healthcare settings.In this study no genetic mutation in exons 10 and 2 of NFKB1 gene were found which differs from the study done in South India on 100 ACS cases and 100 case controls, who found four novel missense mutations in exon 2 of NFKBIL1 gene in ACS patients implying role of NFKBIL1 gene in structural and functional changes in transcription factor, which in turn increased risk of MI (Naik and Rajasekhar 2018). A study done in Chinese population among 609 CAD patients and 423 controls, found that two common NFKB1 (-94 delATTG) and NFKBIA (rs8904) polymorphism were not associated with CAD (Coto García et al. 2019). In a study done in 2011 among 253 cases, -94 ins/del ATTG polymorphism of NFKB1 gene, frequency of II, ID and DD genotypes was 41.5 percent, 45.5 percent and 13 percent, respectively. Frequency of D allele were higher in control group compared to ACS cases and compared to D non carriers, D carriers had significant low fibrinogen and CRP level implying protective role of -94 ins/del ATTG polymorphism in causing ACS (Boccardi et al. 2011). A study done in 2021 with 462 patients in Iran found no correlation between ATTG

polymorphism of NFKB1 gene and cardio metabolic risk factors in patients of acute coronary syndrome (Darabi et al. 2023). While this study did not identify pathogenic variants in NFKB1 exons 2 and 10, it does not exclude the gene's involvement in ACS pathophysiology. Different findings in other studies suggest that non-coding variants, particularly promoter polymorphisms like in-94 delATTG and genes like NFKBIL1 may have a role in ACS.

CONCLUSION

This study investigated potential genetic variation in exons 10 and 2 of the NFKB1 gene, which showed no mutation in the study cohort of Karnataka, India. Their results suggest the differential ethnic genetic variations.

RECOMMENDATIONS

The present study was conducted with a smaller study group, at a single centre, limited to one institute only. Further multicentre studies focusing on different exons with larger sample sizes will be beneficial in providing more accurate results.

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