Original Article

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A Study on Plasma Fibrinogen as a Risk Factor for Premature Acute Myocardial Infarction

Internal Medicine Section

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ABSTRACT

Introduction: Acute Myocardial Infarction (AMI), a significant coronary event, is increasingly prevalent among younger populations, presenting unique challenges in risk assessment and prevention. Premature AMI, defined as occurring before the age of 55, is often linked to non traditional risk factors such as elevated Plasma Fibrinogen (PFg), a key component in atherothrombosis and vascular inflammation.

Aim: To determine the prevalence of elevated PFg levels in premature AMI patients (<55 years) and evaluate its association with AMI among patients admitted to a tertiary care hospital in Puducherry, India.

Materials and Methods: A hospital-based case-control study was conducted in the Coronary Care Unit (CCU) and Intensive Care Units (ICU) under the Department of General Medicine at a tertiary care teaching hospital in rural Puducherry, India. Over 18 year among 112 patients: 56 with AMI (cases) and 56 age- and sex-matched controls without AMI. Data were collected through clinical evaluations, Electrocardiography (ECG), Echocardiography (ECHO) and biochemical assays. PFg levels were classified as normal (<340 mg/dL) or elevated (>340 mg/dL) and the associations with AMI were analysed.

Results: The mean PFg level in AMI patients was significantly higher (409±52.3 mg/dL) than that in controls (226±46.2 mg/dL) (p<0.001). Elevated PFg levels were observed in 48.2% of AMI patients, correlating strongly with traditional risk factors such as smoking and lipid abnormalities.

Conclusion: Elevated PFg is a significant risk factor for premature AMI. Incorporating PFg measurement into cardiovascular risk assessments could aid in the early identification and targeted intervention for this at-risk population.

Keywords: Acute-phase reactants, Atherothrombosis, Premature myocardial infarction

INTRODUCTION

The AMI, or heart attack, is a critical coronary event that significantly contributes to the overall burden of cardiovascular disease, with an alarming rise being observed among younger populations [1]. Acute Coronary Syndrome (ACS), a subset of Coronary Artery Disease (CAD), is symptomatic and includes MI, presenting as an absolute medical emergency [2]. A recent meta-analysis reported a global MI incidence of 3.8% in individuals under 60 years of age, with CAD now reaching pandemic levels in developing regions [3,4]. India markedly contributes to the global CAD burden, accounting for 38% of mortality, with its rising prevalence of MI among young Indians estimated at 11-16%, which is certainly of interest [5,6]. MI incidence rates, as reported by the Framingham Heart Study (FHS), escalate with age; however, the onset in the younger population highlights the need for targeted preventive measures [7].

Premature AMI, variably defined as occurring between the ages of ≤40-55 years, often lacks traditional risk factors, including dyslipidaemia, Hypertension (HTN), or Diabetes Mellitus (DM) [8,9]. Moreover, a consensus statement revealed that the average age of ACS among young Indians is 56.3 years [10]. Understanding the aetiology, pathophysiology and prevention of AMI in these age groups presents challenges, as this condition results in a significant loss of life prior to individuals reaching their fifth decade [3,11]. Non traditional risk factors, such as genetic predisposition, psychological stress, dysregulated inflammatory pathways and the presence of acute-phase reactants such as Lipoprotein(a) [Lp(a)] and Fibrinogen (Fg), are associated with an increased risk. Unfortunately, these patients present with a poor short-term prognosis and require aggressive secondary prevention once AMI has occurred [8].

The PFg, an acute-phase reactant and a component of the coagulation cascade, has emerged as a key risk factor for CAD [12-14]. Studies have demonstrated its role in promoting atherothrombosis, vascular inflammation and endothelial dysfunction, all of which contribute to increased cardiovascular risk [13,15]. The FHS linked elevated PFg levels to a higher incidence of cardiovascular disease, comparable to traditional risk factors such as smoking [7]. In Iran, a case-control study showed hyperfibrinogenaemia in 81.8% of premature MI patients, which correlated with disease severity [16,17]. The rising incidence of premature AMI necessitates the identification of modifiable risk factors, particularly in young populations where traditional predictors often fall short [18]. Understanding the role of Fg in the pathogenesis of AMI may aid in risk stratification and the implementation of targeted preventive measures. Given the limited data on these risk factors, especially among young Indians, the present study aimed to investigate whether PFg can serve as a risk factor for premature AMI and to determine the prevalence of PFg levels in premature AMI among patients aged under 55 years admitted to the Coronary Care Unit (CCU) of a tertiary care teaching hospital and to investigate the association between PFg levels and premature AMI.

MATERIALS AND METHODS

Study setting: The study was conducted in the CCU and Intensive Care Units (ICU) under the Department of General Medicine at a tertiary care teaching hospital in rural Puducherry, India. This department is equipped with advanced facilities that enhance the quality of care for AMI patients, including ECG and ECHO, which are accessible year-round for both inpatients and outpatients.

This was a hospital-based case-control study matched by sex and age, conducted over a period of 18 months following Institutional Ethics Committee approval. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

The study compared PFg levels in individuals with and without AMI {according to World Health Organisation (WHO) criteria}, confirmed via ECG, ECHO and cardiac enzymes and admitted to the ICU.

Inclusion criteria for cases:

- Both male and female patients
- WHO criteria for AMI (at least two of the three components):
- History of ischaemic chest discomfort
- Typical ECG changes {ST-elevated MI (STEMI)/Non ST elevated MI (NSTEMI)/Unstable Angina (UA)}
- Presence of elevated cardiac enzymes
- Age under 55 years
- Patients presenting within 12 hours of the onset of symptoms.

Inclusion criteria for controls:

- Healthy adults aged under 55 years (matched with cases)
- Both male and female individuals (matched with cases)
- Normal healthy individuals without AMI
- Patients without elevated cardiac enzymes.

Exclusion criteria: Patients aged >55 years, presented with Cerebrovascular Accident (CVA) or a history of CVA, with known other cardiac problems like valvular heart disease, known CAD, underwent Coronary Artery Bypass Graft (CABG), Percutaneous Coronary Intervention (PCI) and other surgeries related to cardiac, with present or previous history of renal dysfunction or chronic liver disease, with infection or inflammation or Peripheral Vascular Disease (PVD), presenting after 12 hours of onset of symptoms, pregnant females and non consenting participants were excluded from the study.

Sample size calculation: Mr. Thai Thanh Truc's sample size application was used as a sample size calculator tool [19] (version 1.0, Sydney, Australia). The observed percentage was 81.8% for cases, while in controls it was 57.5%, based on the study conducted by Wilhelmsen L et al., [20]. The calculated sample size was 112, based on a 1:1 ratio, with a type I error rate of 95% and a power of 80%. (Group I: With MI - 56; Group II: Without MI - 56). The calculation formula was used accordingly.

Sampling procedure: Systematic random sampling techniques were employed to select two groups of individuals who met the eligibility criteria for the study: patients with AMI (Group I) and those without AMI (Group II) in a 1:1 ratio.

Study Procedure

Data from patients were collected through a structured case proforma sheet during face-to-face interviews. Following these non invasive procedures, ECG changes were observed and a 2D ECHO was performed. Blood samples were collected for biochemical analysis, which included cardiac biomarkers (troponin I) and PFg levels. PFg levels were classified as normal fibrinogen levels (<340 mg/dL) and hyperfibrinogenaemia (>340 mg/dL).

Operational definitions:

Premature myocardial infarction: Premature MI is defined as "MI that occurs in men before the age of 55 and in women before the age of 65" [21].

Myocardial infarction: MI is clearly defined as "abnormal cardiac biomarkers that indicate the occurrence of AMI in the context of evidence for AMI" [22]. Specifically, AMI is defined as "the identification of elevated cardiac troponin levels that are rising and/or falling, as well as high cardiac troponin values exceeding the 99th percentile Upper Reference Limit (URL)" [23,24].

STATISTICAL ANALYSIS

Microsoft Excel (Version 2007) was utilised for data entry and the statistical data were analysed using the Statistical Package for the Social Sciences (SPSS) software (IBM Corp., Armonk, Version 20.0, New York). Normality was assessed using a Q-Q plot and the Kolmogorov-Smirnov test. Descriptive statistics for categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as the mean and standard deviation or median without Interquartile Range (IQR).

For inferential statistics, Pearson's Chi-square test and independent t-test were employed based on the normality of the data. Pearson's correlation was utilised to examine the association between mortality (the dependent variable) and two independent variables, namely arrhythmia and heart failure (ejection fraction). Similarly, the association between heart failure as the dependent variable and laboratory parameters as independent variables was assessed.

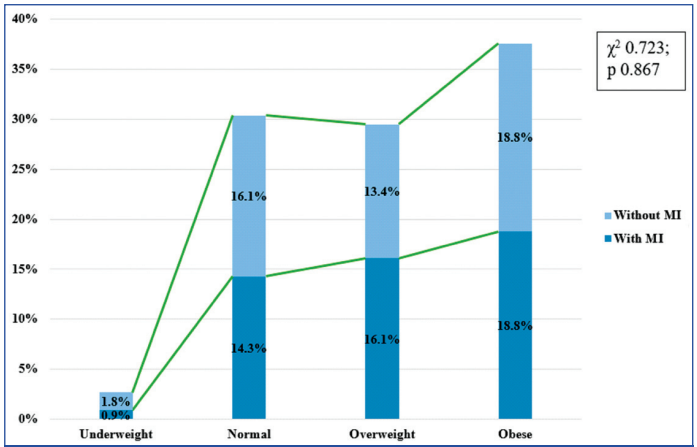
RESULTS

Among the study participants matched for age and gender, the mean age of the patients with MI was 48.2±5.93 years. Of the participants, 41 (36.6%) were male and the remaining 15 (13.4%) were female in both groups. The risk factors among the study participants indicates that smokers and alcohol consumers had a risk of developing MI that was 1.419 and 1.911 times higher than non smokers and non alcohol consumers, respectively and these differences were statistically significant (p-value <0.001 and p-value <0.002, respectively) as presented in [Table/Fig-1]. Similarly, a family history of ischaemic episodes was associated with an increased risk of MI; those with a positive family history had a 2.276 times higher risk of MI, which was statistically significant (p-value <0.001) when compared to those with no family history.

Variables	Total (N=112)	With MI (n=56)	Without MI (n=56)	RR; p-value*
Smoking history				
Smoker	22 (19.6)	18 (16.1)	4 (3.6)	1.419; <0.001
Non smoker	90 (80.4)	38 (33.9)	52 (46.4)	
Alcohol consumption				
Consumes alcohol	18 (16.1)	15 (13.4)	3 (2.7)	1.911; 0.002
Not consumes alcohol	94 (83.9)	41 (36.6)	53 (47.3)	
Family history of ischaemic events				
Presence of ischaemic events	18 (16.1)	17 (15.2)	1 (0.9)	2.276; <0.001
No events	94 (83.9)	39 (34.8)	55 (49.1)	
Physical activity				
Physically inactive	87 (77.1)	36 (32.1)	51 (45.5)	1.933; <0.001
Physically active	25 (22.3)	20 (17.9)	5 (4.5)	

[Table/Fig-1]: Risk factors in patients with MI and based on MI status (N=112). *Pearson's Chi-square: Nominal and non parametric; RR: Risk ratio; p value <0.05 is statistically significant indicated by boldface. Values given in brackets were percentage

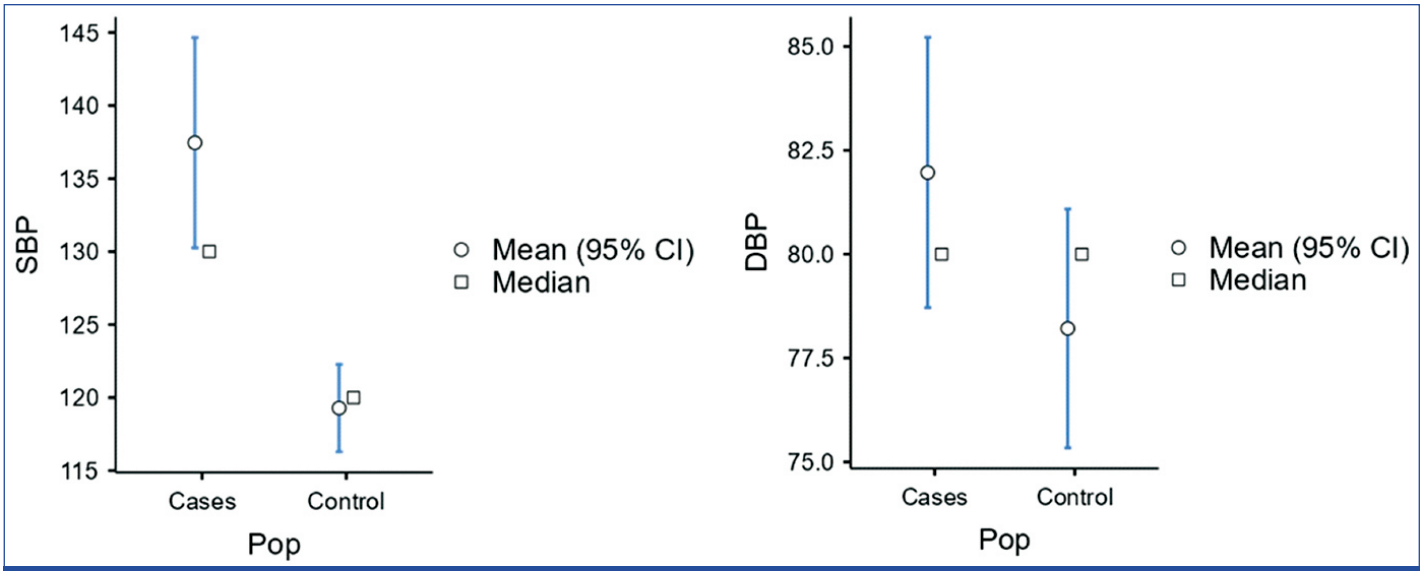
The BMI was classified based on the Asian BMI classification and is presented in [Table/Fig-2]. The overall mean BMI among the study participants was 23.5±2.44 kg/m^2 and this was not statistically significant (p-value=0.847).



[Table/Fig-2]: BMI characteristics among the patients with MI and based on MI status (N=112).

The mean SBP among patients with and without MI was 137.5±27.2 mmHg and 119.3±11.4 mmHg, respectively, which was statistically significant (t=4.60; p-value <0.001). In contrast, the mean DBP was 82.0±12.4 mmHg for those with MI and 78.2±11.0 mmHg for those without MI, which was not significant (t=1.69; p-value=0.093) [Table/Fig-3]. The laboratory parameters among study participants with and without MI are presented in [Table/Fig-4].

A correlation coefficient analysis [Table/Fig-8] was applied to various variables among MI patients, focusing on PFg and other risk factors. Troponin I exhibited a positive correlation with moderate strength to PFg (ρ=0.598; p-value <0.001), indicating a statistically significant result that is very unlikely to be due to chance. The findings of this analysis support the study's hypothesis that individuals with MI who test positive for troponin I will have higher PFg levels, which



[Table/Fig-3]: Systolic and diastolic blood pressure among the patients with MI and based on MI status (N=112).

Variables	Total (N=112) Mean±SD	With MI (n=56) Mean±SD	Without MI (n=56) Mean±SD	p-value*
FBS (mg/dL)	115.1±46.1	129.9±56.9	100.2±24.5	<0.001
PPBS (mg/dL)	194.4±76.4	226.0±96.5	162.7±20.9	<0.001
CHO-T (mg/dL)	196.9±51.1	215.3±58.6	178.6±33.8	<0.001
TGL (mg/dL)	143.9±37.5	156.9±47.4	130.8±15.6	<0.001
LDL (mg/dL)	75.8±30.1	85.4±35.3	66.3±19.8	<0.001

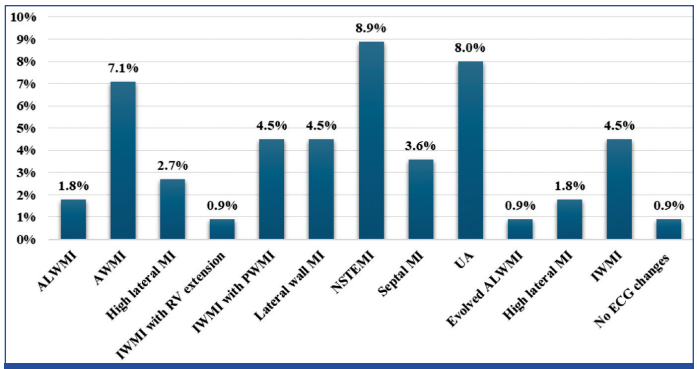
[Table/Fig-4]: Laboratory values of patients with and without MI (N=112).
*Independent t-test: continuous and parametric; p value <0.05 is statistically significant indicated by boldface. FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; CHO-T: Total cholesterol; TGL: Triglycerides; LDL: Low-density lipoprotein

The mean PFg among patients with and without MI was 409±52.3 mg/dL and 226±46.2 mg/dL, respectively and this difference was statistically significant (p-value <0.001; t=19.6; 95% CI: 164-201). Overall, about 58 patients (51.8%) had normal fibrinogen levels (<340 mg/dL), while the remaining 54 patients (48.2%) exhibited hyperfibrinogenaemia (>340 mg/dL). Among the patients with MI, only 1.8% had normal fibrinogen levels, while the remaining 48.2% had hyperfibrinogenaemia, which was statistically significant (χ^2=104; p-value <0.001) [Table/Fig-5].

Variables	Total (N=112)	With MI (n=56)	Without MI (n=56)	p-value
Plasma fibrinogen (mg/dL)	318±104	409±52.3	226±46.2	<0.001[a]
Categorisation				
Normal fibrinogen (<340 mg/dL)	58 (51.8)	2 (1.8)	56 (50.0)	<0.001[b]
Hyperfibrinogenaemia (>340 mg/dL)	54 (48.2)	54 (48.2)	0	

[Table/Fig-5]: Plasma fibrinogen among the study participants (N=112).
[a]Independent t-test: continuous and parametric; [b]Fisher's exact test: Nominal and non parametric; p value <0.05 is statistically significant indicated by boldface. SD: Standard deviation. Cells with '0' will be considered as 0.5. Values given in brackets were percentage

Among the 56 study participants with MI, the mean troponin I level was 13966±12430 ng/L. The ECG changes among patients with MI are presented in [Table/Fig-6]. [Table/Fig-7] demonstrates the association between fibrinogen levels and patients with MI.



[Table/Fig-6]: ECG changes among the study participants with MI (n=56).
*MI: Myocardial infarction; ALWMI: Anterolateral wall MI; AWMI: Anterior wall; IWMI: Inferior wall; PWMI: Posterior wall; RV: Right ventricle; NSTEMI: Non ST segment elevation MI; UA: Unstable angina; ECG: Electrocardiogram

Variables	Normal fibrinogen (<340 mg/dL) (n=2)	Hyperfibrinogenaemia (>340 mg/dL) (n=54)	p-value*
Age (in years)	47.50±3.53	48.19±6.01	0.874[a]
Gender			
Male	2 (100.0)	39 (72.2)	0.384[b]
Female	0	15 (27.8)	
Smoking history			
Smoker	0	18 (33.3)	0.322[b]
Non smoker	2 (100.0)	36 (66.7)	
Alcohol consumption			
Consumes alcohol	0	15 (27.8)	0.384[b]
Not consumes alcohol	2 (100.0)	39 (72.2)	
Family history of ischaemic events			
Presence of ischaemic events	1 (50.0)	16 (29.6)	0.538[b]
No events	1 (50.0)	38 (70.4)	
Physical activity			
Physically inactive	0	34 (63.0)	0.283[b]
Physically active	2 (100.0)	20 (37.0)	

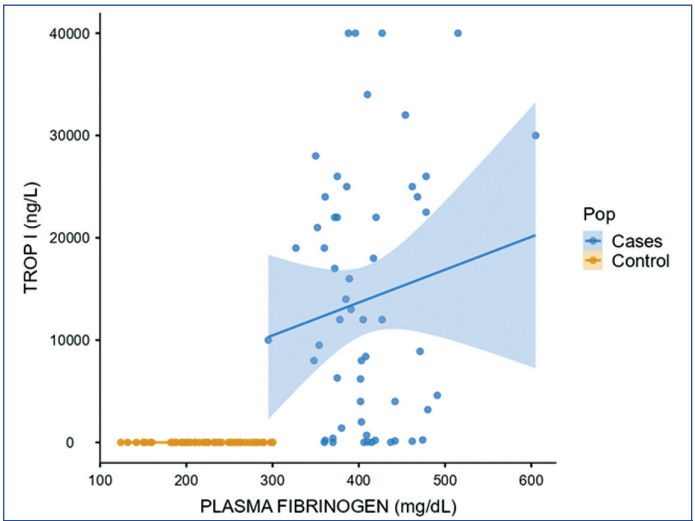
BMI (kg/m²)			
Underweight (<18.5)	0	1 (1.9)	0.771[b]
Normal (18.5-22.9)	1 (50.0)	15 (27.8)	
Overweight (23-24.9)	0	18 (33.3)	
Obesity (>25)	1 (50.0)	20 (37.0)	
Troponin I	14500.00±6363.96	13946.61±12632.06	0.951[a]
SBP	125.00±7.07	137.92±27.62	0.515[a]
DBP	75.00±7.07	82.22±12.53	0.424[a]
FBS	228.00±39.59	126.28±54.35	0.012[a]
PPBS	438.50±40.305	218.17±88.68	0.001[a]
CHO	253.00±4.24	213.89±59.19	0.359[a]
TGL	201.00±21.21	155.31±47.35	0.183[a]
LDL	118.00±8.48	84.17±35.39	0.186[a]

[Table/Fig-7]: Association of fibrinogen levels in patients with MI (N=56).
*[a]Independent t-test: continuous and parametric; [b]Pearson's Chi-square test: Nominal and non parametric; p value <0.05 is statistically significant indicated by boldface. Values given in brackets were percentage. SD: Standard deviation; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; CHO-T: Total cholesterol; TGL: Triglycerides; LDL: Low-density lipoprotein

Variables	Correlation (r or rho)	p-value[#] (2-tailed)
Plasma fibrinogen with risk factors		
With FBS	0.219	0.020[a]
With PPBS	0.296	0.002[a]
With troponin I	0.598	<0.001[a]
With cholesterol	0.362	<0.001[a]
With triglycerides	0.274	0.003[a]
With Low-density lipoprotein	0.279	0.003[a]
With BMI	0.074	0.438[b]

[Table/Fig-8]: Correlation between the plasma fibrinogen and the risk factors for MI among the study participants (N=112).
[#a]Spearman's correlation; [b]Pearson's correlation. Correlation is significant at the 0.01 level (2-tailed)

increases their likelihood of developing an early MI. The scatterplot showing the correlation between PFg and troponin I is presented in [Table/Fig-9].



[Table/Fig-9]: Scatterplot showing the relation between the plasma fibrinogen with troponin I among the cases and controls.

DISCUSSION

The present case-control study assessed the role of PFg as a risk factor for early AMI, focusing on its relationships with traditional and non traditional CV risk factors. The study found that patients with early AMI had higher PFg levels, which correlated with inflammatory markers, lipid abnormalities and troponin I, suggesting PFg's potential as a biomarker for targeted therapies and early risk assessment in younger populations. This aligns with evidence emphasising the thrombogenic and inflammatory processes as pivotal in the pathophysiology of premature AMI.

Elevated PFg levels in patients with early AMI are consistent with existing literature highlighting its role in atherothrombosis. Elevated fibrinogen enhances blood viscosity, promotes platelet aggregation and stabilises clots, which are critical factors in the pathogenesis of AMI [25-29]. Hyperfibrinogenemia is a significant predictor of adverse cardiovascular outcomes, particularly in younger populations [16,27,30]. In the present study, distinct fibrinogen levels were observed between patients with and without MI, emphasising its potential as a diagnostic marker. A study by von Eyben FE et al., reported similar findings, demonstrating fibrinogen's independent predictive value for AMI and its significant role in thrombogenesis and inflammation [28].

The study found that male patients had a higher prevalence of premature AMI (73.2%) compared to females (26.8%), indicating a significant gender disparity in CV risk. This finding aligns with established literature suggesting that males are more likely to develop premature MI than females, likely due to hormonal, genetic and lifestyle factors. Studies such as those by von Eyben FE et al., have documented similar trends, suggesting that the proatherogenic effects of testosterone and lower levels of cardioprotective oestrogen in men contribute to the observed differences [28]. Additionally, female patients exhibited stronger associations between fibrinogen levels and metabolic conditions, such as DM. Liu Q et al., found that DM disproportionately increased CV risk in women [11]. Conversely, Gao XY et al., found no gender differences in the predictive value of fibrinogen, a finding inconsistent with the results of this study [27].

Smoking and alcohol consumption were also significant risk factors, as noted in similar studies, including those by Shojaie M et al., [16]. Moreover, smoking showed a significant correlation with fibrinogen levels ($p<0.001$), which is consistent with findings from the study by von Eyben FE et al., [28], where smoking amplified MI risk when combined with high fibrinogen. Smoking-induced oxidative stress and endothelial injury upregulated fibrinogen synthesis, exacerbating thrombogenicity. The proinflammatory and prothrombotic synergy underscores the need for cessation strategies in high-risk populations [28,31,32]. The study by Wilhelmsen L et al., also highlighted this robust correlation [20]. Furthermore, the study by von Eyben FE et al., emphasised the importance of addressing smoking in young patients with elevated fibrinogen levels [28].

The elevated PFg levels were 409±52.3 mg/dL and were found in 48.2% of MI patients, which is consistent with the study by Shojaie M et al., where hyperfibrinogenemia was detected in 81.8% of premature MI cases, with an odds ratio of 3.3 ($p=0.036$) [16]. The study by von Eyben FE et al., also documented high fibrinogen levels in premature AMI patients, underscoring its association with elevated CV risk [28]. Similarly, Mills JD et al., linked elevated fibrinogen levels in relatives of premature CAD patients to genetic predisposition [33].

Dyslipidaemia, including elevated LDL and TGL, strengthens fibrinogen's involvement in lipid-driven atherogenesis. Fibrinogen correlated positively with LDL cholesterol ($\rho=0.279$), reinforcing its role in dyslipidaemia-driven atherosclerosis. The FHS and the study by Gao XY et al., highlighted fibrinogen's contribution to thrombogenesis and atherothrombosis, with significant correlations to Gensini scores in young MI patients [7,27]. Research by Cremer P et al., documented that fibrinogen's interaction with Lp(a) and foam cell formation in plaques is consistent with the present study's findings [34]. These results emphasise the systemic inflammation and severity of CAD linked to fibrinogen and lipid abnormalities.

Metabolic disorders, particularly DM, showed a significant association with higher fibrinogen levels (FBS: $\rho=0.219$, $p=0.020$; PPBS: $\rho=0.296$, $p=0.002$). The study by Liu Q et al., identified fibrinogen as a mediator of the proinflammatory and prothrombotic states induced by hyperglycaemia [11]. Hyperglycaemia amplifies Fg production, contributing to CV complications in patients with DM [35]. Chen L et al., also found that elevated Fg levels are linked to metabolic syndrome and CV risk [36]. This study supports the connection between

fibrinogen and glycaemic indices, emphasising the need to address metabolic dysfunction to reduce CV risks associated with elevated Fg.

The Fg levels correlated significantly with cardiac markers, including troponin I (ρ=0.598; p<0.001), indicating myocardial injury and vascular inflammation. The study by Shojaie M et al., similarly found a significant correlation between Fg levels and Gao XY et al., demonstrated Fg's association with plaque rupture, highlighting its role in thrombotic complications [16,27]. Yuan D et al., confirmed its predictive value for adverse CV events during follow-up, reinforcing Fg's utility as a biomarker for assessing myocardial damage and guiding early therapeutic interventions [37].

Thus, from the present study, the authors recommend that clinicians adopt a comprehensive risk assessment strategy that includes Fg levels alongside traditional CV markers to lessen the impact of early AMI. Public health initiatives should emphasise lifestyle changes to reduce Fg levels and their associated risks. Targeted therapies aimed at Fg reduction should also be explored. Future investigations must concentrate on prospective studies to validate these findings and evaluate the efficacy of Fg-lowering interventions in reducing the incidence and severity of premature MI.

The present study evaluates the risk of PFg in Puducherry, focusing on patients with early MI to identify disparities in CV risk among younger individuals. The case-control methodology allows for direct comparisons between Fg levels and other risk factors. The study highlights the potential for integrating Fg measurement into CV risk assessment protocols to enhance early detection and prevention strategies.

Limitation(s)

Addressing the study's limitations is also important, as the generalisation of these findings is not possible since the data were gathered from a single tertiary care facility. Furthermore, a larger sample size might have provided greater statistical power and more nuanced insights into subgroup differences. While traditional risk indicators have been taken into account, unmeasured variables such as genetic predispositions or psychosocial stressors could have influenced the outcomes. Additionally, the absence of follow-up data restricts the study's ability to assess long-term outcomes or the potential benefits of Fg-lowering interventions. Moreover, the study does not explore the direct impact of fibrinogen-modifying treatment, leaving a gap in actionable clinical interventions.

CONCLUSION(S)

The substantial significance of PFg as a standalone risk factor for initial AMI was highlighted by this study. Even after adjusting for common risk factors, including smoking, high blood pressure and dyslipidaemia, increased thrombogenesis and CV risk were all significantly correlated with elevated Fg levels. These findings emphasise Fg's importance as a biomarker for its role in the pathophysiology of AMI, particularly in younger individuals. The findings underline the necessity of including Fg measurements in CV risk evaluation, facilitating the timely identification and management of individuals at risk.

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Authors' contribution: VR, SS- Conceptualisation; VR, SS, KSC- Methodology; MM, VR- Software; SS, KSC- Validation; MM, VR- Formal analysis; MM- Investigation; MM, VR- Resources; VR- Data curation; MM, VR- Writing - Original draft preparation; SS, KSC- Writing - Review and Editing; KSC- Visualisation; SS- Supervision; MM, VR, SS- Project administration.

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