DOI: 10.7860/JCDR/2026/80067.22951

Original Article

Biochemistry Section

Association of Serum TREM2 with Acute Coronary Syndrome and its Severity: A Cross-sectional Study

MS SUDHARHSAN[1], P RENUKA[2], VM VINODHINI[3], M VENGATESH[4], KA ARUL SENGHOR[5]

ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) remains a major cause of morbidity and mortality worldwide, primarily driven by plaque rupture and thrombotic occlusion in coronary arteries. Traditional biomarkers provide limited insight into the inflammatory and lipid-driven mechanisms underlying plaque instability. Soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM2), a shed form of a membrane-bound receptor expressed on macrophages and other myeloid cells, has been implicated in lipid metabolism, immune regulation and tissue homeostasis. Although its role in neurodegenerative and metabolic disorders has been increasingly recognised, its relevance in atherosclerosis and acute coronary events is still being elucidated. Exploring sTREM2 in this setting may offer novel perspectives on immune-metabolic activity in coronary artery disease.

Aim: To investigate the association between serum sTREM2 levels and ACS, as well as disease severity.

Materials and Methods: The present observational cross-sectional study was conducted at the Department of Biochemistry, SRM Medical College Hospital and Research Centre, Potheri, SRM Nagar, Kattankulathur, Tamil Nadu, India, between December 2023 and August 2024. A total of 180 participants were enrolled, including 90 newly diagnosed ACS patients and 90 age- and gender-matched healthy controls. Inclusion criteria for the ACS group included adults aged over 25 years with a confirmed diagnosis of ACS {ST-Elevation Myocardial Infarction (STEMI), Non ST-Elevation Myocardial Infarction (NSTEMI), or unstable angina} based on clinical presentation, Electrocardiographic (ECG) changes and cardiac biomarkers. Controls were healthy volunteers with no history of cardiovascular disease. Serum sTREM2 levels, lipid profile, Apolipoprotein B (ApoB) and high-sensitivity C-Reactive Protein (hs-CRP) were measured. ACS severity was assessed using the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX I) score. Demographic parameters including age, gender, Body Mass Index (BMI). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0. Data normality was assessed using the Shapiro-Wilk test. Group comparisons were conducted using the Mann-Whitney U test and Kruskal-Wallis test. Spearman's correlation was used to evaluate relationships between variables and Receiver Operating Characteristic (ROC) curve analysis assessed the diagnostic utility of biomarkers. A p-value <0.05 was considered statistically significant.

Results: Serum sTREM2 levels were significantly higher in ACS patients {115.19 (78.18-191.67) pg/mL} compared to controls {70.74 (51.16-89.03) pg/mL} (p<0.001). ACS patients also exhibited elevated hs-CRP, ApoB, Total Cholesterol (TC), Low-Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL), along with reduced High-Density Lipoprotein (HDL) levels. A positive correlation was identified between sTREM2 and body weight, BMI, TC, LDL and the TC/HDL ratio, while a negative correlation was noted with HDL. sTREM2 levels increased progressively with ACS severity as determined by the SYNTAX I score. No significant correlation was found between sTREM2 and hs-CRP or ApoB. ROC analysis demonstrated moderate diagnostic accuracy for sTREM2, with an Area Under the Curve (AUC) of 0.771.

Conclusion: The present study demonstrates that serum sTREM2 levels are significantly elevated in ACS patients and correlate with disease severity. These findings suggest that sTREM2 may serve as a novel biomarker for ACS stratification, providing insights into the inflammatory and lipid-related mechanisms driving disease progression. Further longitudinal studies are required to validate its prognostic and clinical utility.

Keywords: Apolipoprotein B, C-reactive protein, Plaque vulnerability, Triggering receptor expressed on myeloid cells 2

INTRODUCTION

Cardiovascular Diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with ACS representing a major clinical manifestation within this spectrum [1]. ACS contributes substantially to healthcare burden and adverse outcomes. According to national epidemiological data from the Treatment and Outcomes of Acute Coronary Syndromes in India (CREATE) registry, in-hospital mortality for ACS in India is approximately 3.2% [2]. India bears a significant burden of ischaemic heart disease and cerebrovascular accidents, which together account for over 80% of CVD-related mortality [3]. The country's age-standardised mortality rate for CVDs (272 per 100,000 population) far exceeds the global average, underscoring the urgent need to identify novel prognostic biomarkers to enhance risk stratification and clinical management [4].

Despite advances in diagnostic imaging and biochemical profiling, there remains a critical need for immune-inflammatory biomarkers capable of providing insights into plaque vulnerability and ACS outcomes. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a type I transmembrane immune receptor predominantly expressed on myeloid lineage cells, including macrophages, dendritic cells and microglia [5]. TREM2 regulates inflammatory responses, lipid metabolism and cellular homeostasis through its interaction with DNAX-activating Protein of 12 kDa (DAP12), activating downstream signalling pathways involving Phosphatidylinositol-3-Kinase (PI3K) and phospholipase C gamma 2 (PLCγ2).

While extensively studied in neurodegenerative diseases such as Alzheimer's disease, emerging evidence implicates TREM2 in

atherosclerosis and metabolic disorders, including obesity and Non Alcoholic Fatty Liver Disease (NAFLD) [6].

TREM2 undergoes ectodomain shedding, generating its soluble form (sTREM2), which can be measured in serum and Cerebrospinal Fluid (CSF). In atherosclerosis, macrophages play a pivotal role as innate immune regulators. Single-cell Ribonucleic Acid (RNA) sequencing studies have identified a distinct TREM2-expressing foam cell macrophage population within atherosclerotic plaques, characterised by altered lipid metabolism and heightened inflammatory signalling [7].

Elevated sTREM2 levels have been reported in neuroinflammatory conditions, where they correlate with disease activity and severity [8,9]. Within atherosclerotic lesions, TREM2 expression is enriched in lipid-laden macrophages associated with plaque instability and rupture [10]. However, the clinical significance of circulating sTREM2 in coronary artery disease, particularly in ACS patients, remains poorly defined, especially in the Indian population.

Established biomarkers such as Apolipoprotein B (ApoB) and hs-CRP reflect lipid-driven atherogenic burden and systemic inflammation, respectively [11]. Given TREM2's involvement in lipid handling and immune modulation, sTREM2 may represent a mechanistic link between dyslipidemia and vascular inflammation [12,13].

The present study therefore aimed to evaluate serum sTREM2 levels in ACS patients, correlate them with angiographic disease severity using the SYNTAX I score and assess their potential as a novel immunometabolic biomarker.

MATERIALS AND METHODS

The present observational cross-sectional study was conducted at the Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chengalpattu, Tamil Nadu, India, between December 2023 and August 2024, following approval from the Institutional Scientific Committee and the Institutional Ethics Committee (IEC No: SRMIEC-ST0124-868). Written informed consent was obtained from all participants prior to enrollment.

A total of 180 subjects were recruited and stratified into two groups.

Sample size calculation: Sample size was calculated using G*Power software (version 3.1) based on an effect size of 0.5, a statistical power of 80% and an alpha level of 0.05 for detecting differences in biomarker levels between groups, resulting in 90 participants per group [3].

The case group comprised 90 patients with a confirmed diagnosis of ACS, including both STEMI and NSTEMI, who underwent coronary angiography in the Department of Cardiology. The control group consisted of 90 age- and sex-matched apparently healthy individuals attending the Master Health Check-up Clinic. Each group included an equal number of male and female participants (n=45 per sex per group).

Inclusion criteria (cases):

- Adults aged over 25 years
- Clinically diagnosed ACS, including STEMI and NSTEMI
- Electrocardiographic (ECG) changes consistent with ischaemia or infarction
- Elevated cardiac biomarkers, such as troponins
- Clinical symptoms including chest pain, shortness of breath, or related ischaemic symptoms.
- Underwent coronary angiography confirming coronary artery involvement

Exclusion criteria (cases):

- History of prior coronary artery disease, including myocardial infarction, angina, or coronary revascularisation
- Presence of chronic inflammatory, autoimmune, malignant, hepatic, or renal disorders
- Current use of anti-inflammatory or cardiac medications before admission

Inclusion criteria (controls):

- Age- and sex-matched apparently healthy individuals aged over 25 years
- No history or clinical signs of cardiovascular disease
- Normal ECG and biochemical profiles during routine health screening

Exclusion criteria (controls):

- Any diagnosed cardiovascular, autoimmune, inflammatory, hepatic, renal, or malignant disease
- Current or prior use of cardiac, anti-inflammatory, or lipid-lowering medications
- Abnormal findings on physical examination, ECG, or biochemical investigations

Study Procedure

Diagnostic work-up and angiographic evaluation: All ACS patients underwent coronary angiography using standard femoral or radial arterial access. Coronary anatomy was evaluated for the presence, location and severity of atherosclerotic lesions. Based on angiographic findings, the SYNTAX I score was calculated using an online SYNTAX score calculator to quantify the anatomical complexity of Coronary Artery Disease (CAD).

SYNTAX I score classification: The SYNTAX I score is an established angiographic grading system used to evaluate the severity and anatomical complexity of CAD. It incorporates lesion characteristics such as total occlusions, bifurcation involvement, lesion length and thrombus burden and assists in therapeutic decision-making between Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG).

Based on SYNTAX I scoring, patients were categorised as having mild, moderate, or severe CAD [4]. This stratification was employed to evaluate the relationship between coronary disease burden and serum levels of sTREM2, ApoB and hs-CRP. This classification facilitated structured assessment of CAD severity and correlation of sTREM2 with disease complexity [4] [Table/Fig-1].

SYNTAX score	Severity of CAD	Revascularisation preference
0-22	Mild CAD	PCI is a good option
23-32	Moderate CAD	PCI or CABG (depends on patient-specific factors)
≥33	Severe CAD	CABG is preferred

[Table/Fig-1]: Severity groups based on the SYNTAX I Score [4].
CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting

Data collection and biochemical analysis: Baseline demographic data, including age and sex, were systematically recorded for all participants. Anthropometric measurements were obtained to calculate Body Mass Index (BMI) [6], using the formula: Weight (kg) divided by Height squared (m^2).

Following an overnight fasting period of 8-12 hours, venous blood samples (5 mL) were obtained via peripheral venipuncture under aseptic conditions using standardised vacutainers. Samples were centrifuged at 3000 rpm for 10 minutes to separate serum, which was aliquoted and stored at -80°C until analysis.

Serum levels of Fasting Plasma Glucose (FPG), TC, Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), hs-CRP and ApoB were measured using a fully automated Beckman Coulter AU480 clinical chemistry analyser in accordance with manufacturer protocols.

Serum soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM2) was quantified using a commercially available high-sensitivity Enzyme-Linked Immunosorbent Assay (ELISA) kit (KRISHGEN

Biosystems, KBH4189). Optical density was measured using a Bio-Rad iMark™ microplate reader (Bio-Rad Laboratories Inc., USA) and concentrations were calculated from standard calibration curves.

Coronary angiography and classification of CAD severity: All ACS patients underwent diagnostic coronary angiography as per institutional protocol. Angiograms were independently evaluated by two experienced interventional cardiologists blinded to biochemical results to minimise observer bias. Each coronary lesion was assessed according to the SYNTAX I scoring system, which evaluates anatomical complexity based on parameters including total occlusion, bifurcation involvement, calcification, vessel tortuosity and thrombus burden.

This standardised classification enabled consistent comparison of disease severity and facilitated correlation of sTREM2 levels with angiographic complexity, in line with STROBE guidelines to ensure methodological transparency and internal validity.

STATISTICAL ANALYSIS

Data were systematically entered and analysed using the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to summarise the demographic, clinical and biochemical characteristics of the study population. Normality of continuous variables was assessed using the Shapiro-Wilk test. As the data did not follow a normal distribution, non parametric tests—including the Mann-Whitney U test and Kruskal-Wallis test—were utilised to compare differences between independent groups. Spearman's rank correlation coefficient was used to evaluate the strength and direction of associations between serum sTREM2 levels and clinical parameters. Statistical significance was defined as a p-value <0.05. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of sTREM2 in differentiating disease status and severity. The AUC was calculated to determine the discriminative ability of sTREM2 as a biomarker. Youden's Index (J=Sensitivity + Specificity – 1) was used to identify the optimal cutoff point that maximised sensitivity and specificity.

RESULTS

A total of 180 participants were included in the study, comprising 90 healthy controls (45 males and 45 females) and 90 patients diagnosed with ACS (STEMI and NSTEMI) who underwent coronary angiography (45 males and 45 females). The participants in both groups were age- and sex-matched.

Comparison Between ACS Cases and Controls

Patients with ACS exhibited significantly elevated serum sTREM2 levels compared to healthy controls [115.19 (78.18-191.67) vs. 70.74 (51.16-89.03) pg/mL; p<0.001]. Inflammatory and lipid-related biomarkers were also markedly higher in the ACS group.

The hs-CRP levels were significantly increased in ACS patients [6.11 (1.71-11.40)] compared to controls [2.49 (0.99-4.93); p<0.001]. Similarly, ApoB levels were higher in ACS patients [78.05 (53.17-97.37) vs. 57.50 (45.85-78.35); p<0.001].

Lipid profile parameters, including TC, TG, LDL and VLDL, were significantly elevated in ACS patients. Conversely, HDL levels were significantly reduced compared to controls [Table/Fig-2].

Parameters	Case (n=90) Median (IQR)	Control (n=90) Median (IQR)	p-value
Age (years)	45 (37,52)	45 (37,52)	1.000
Weight (kg)	81.4 (70.47,89.27)	80.05 (70,89.82)	0.763
Height (m)	1.68 (1.68,1.73)	1.67 (1.60,1.72)	0.494
BMI (kg/m²)	28.55(25.90,31.52)	28.63 (25.53,30.93)	0.979
FBS (mg/dL)	172 (121.5, 220.25)	127 (77.75,192.50)	<0.001
TC (mg/dL)	214.60 (194,230)	164 (153.2,177.25)	<0.001
TGL (mg/dL)	160 (130,195)	114 (88,140)	<0.001
LDL (mg/dL)	154 (135,168)	99 (82,109.25)	<0.001
VLDL (mg/dL)	31.30 (26,37.20)	23 (18,28)	<0.001
HDL (mg/dL)	35 (29,43)	43 (39,49.25)	<0.001
TC/HDL-c	5.96 (4.74,7.51)	3.69 (3.14,4.48)	<0.001
TREM2 (pg/mL)	115.19 (78.18,191.67)	70.74 (51.16,89.03)	<0.001
hs-CRP (mg/L)	6.11 (1.71,11.40)	2.49 (0.99,4.93)	<0.001
ApoB (mg/dL)	78.05 (53.17,97.37)	57.50 (45.85,78.35)	<0.001

[Table/Fig-2]: Comparison of demographic and biochemical parameters between control and case groups.
BMI: Body mass index (kg/m²), FBS: Fasting blood sugar (mg/dL); TC: Total cholesterol (mg/dL); TGL: Triglycerides (mg/dL); LDL: Low-density lipoprotein (mg/dL); VLDL: Very low-density; lipoprotein (mg/dL); HDL: High-density lipoprotein (mg/dL); TC/HDL-c: Total cholesterol to; HDL: Cholesterol ratio (unitless), TREM2: Soluble triggering receptor expressed on myeloid cells 2 (pg/mL); hs-CRP: High-sensitivity c-reactive protein (mg/L); ApoB: Apolipoprotein B (mg/dL); IQR: Interquartile range Statistical test used: Mann-Whitney U test

Correlation of sTREM2 with Anthropometric and Biochemical Parameters

Correlation analysis in ACS patients revealed significant positive associations between serum sTREM2 levels and:

Body weight (ρ=0.221, p=0.003)

Body mass index (BMI) (ρ=0.192, p=0.010)

Total Cholesterol (TC) (ρ=0.305, p<0.001)

Triglycerides (TG) (ρ=0.184, p=0.014)

Low-Density Lipoprotein (LDL) (ρ=0.332, p<0.001)

Very-low-density lipoprotein (VLDL) (ρ=0.160, p=0.032)

TC/HDL ratio (ρ=0.333, p<0.001)

A significant negative correlation was observed between sTREM2 and HDL levels (ρ=–0.208, p=0.005).

No significant correlations were found between sTREM2 and age, Fasting Blood Glucose (FBS), hs-CRP, or ApoB. These findings indicate a strong association between sTREM2 and lipid-related cardiovascular risk markers [Table/Fig-3].

Parameters	Case (n=90) Median (IQR)	Control (n=90) Median (IQR)	Rho value	p-value
Age (years)	45 (37,52)	45 (37,52)	0.088	0.242
Weight (kg)	81.4 (70.47,89.27)	80.05 (70,89.82)	0.221	0.003*
Height (m)	1.68 (1.68,1.73)	1.67 (1.60,1.72)	0.121	0.106
BMI (kg/m²)	28.55 (25.90,31.52)	28.63 (25.53,30.93)	0.192	0.010*
FBS (mg/dL)	172 (121.5, 220.25)	127 (77.75,192.50)	0.074	0.326
TC (mg/dL)	214.60 (194,230)	164 (153.2,177.25)	0.305	<0.001*
TGL (mg/dL)	160 (130,195)	114 (88,140)	0.184	0.014*
LDL (mg/dL)	154 (135,168)	99 (82,109.25)	0.332	<0.001*
VLDL (mg/dL)	31.30 (26,37.20)	23 (18,28)	0.16	0.032*
HDL (mg/dL)	35 (29,43)	43 (39,49.25)	-0.208	0.005*
TC/HDL-c	5.96 (4.74,7.51)	3.69 (3.14,4.48)	0.333	<0.001*
hs-CRP (mg/L)	6.11 (1.71,11.40)	2.49 (0.99,4.93)	0.057	0.458
ApoB (mg/dL)	78.05 (53.17,97.37)	57.50 (45.85,78.35)	0.127	0.093

[Table/Fig-3]: Correlation between serum sTREM2 levels and anthropometric, glycaemic, lipid and inflammatory biomarkers.
BMI: Body mass index (kg/m²); FBS: Fasting blood sugar (mg/dL); TC: Total cholesterol (mg/dL); TGL: Triglycerides (mg/dL); LDL: Low-density lipoprotein (mg/dL); VLDL: Very low-density lipoprotein (mg/dL); HDL: High-density lipoprotein (mg/dL); TC/HDL-c: Total cholesterol to HDL-cholesterol ratio (unitless); TREM2: Soluble triggering receptor expressed on myeloid cells 2 (pg/mL); hs-CRP: High-sensitivity c-reactive protein (mg/L); ApoB: Apolipoprotein B (mg/dL); Statistical test used: Rho value: Spearman's correlation coefficient; *p<0.05 indicates statistical significance

Comparison of TREM2 Across ACS Severity Levels

When patients were stratified according to SYNTAX I score into mild, moderate and severe CAD categories [Table/Fig-4], serum sTREM2 levels showed a significant progressive increase across severity groups.

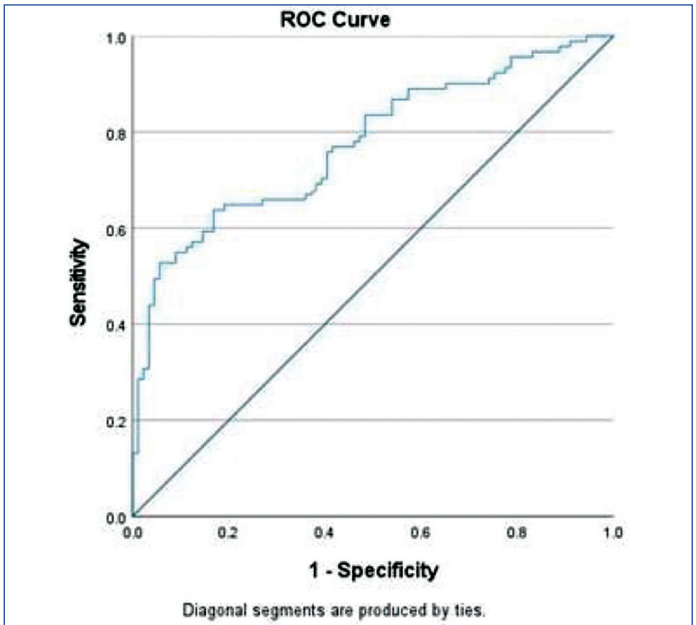
Parameters	Mild (n= 24) Median (IQR)	Moderate (n=40) Median (IQR)	Severe (n=26) Median (IQR)	p-value
Age (years)	47.5 (36.5, 51.5)	45.5 (40, 52.75)	43.5 (35.75,54.25)	0.727
Weight (kg)	80.95 (64.77, 88.65)	78.9 (69.42, 88)	85.15 (76.57, 93.25)	0.126
Height (m)	147 (131.25, 193.25)	178.5 (103, 230)	175 (125.25, 250.75)	0.766
BMI (kg/m^2)	27.1 (25.27, 30.67)	27.9 (25.72, 31.92)	29.65 (27.92, 33.07)	0.104
FBS (mg/dL)	218 (196, 237)	215.2 (193.5, 232.2)	210 (192.8, 218.75)	0.229
TC (mg/dL)	162 (140.5, 207.2)	166 (130,186)	142 (127.5, 195)	0.474
TGL (mg/dL)	157 (137.5, 177.5)	148 (131.25, 169.5)	151.5 (132, 158.25)	0.258
LDL (mg/dL)	31.8 (28, 41.75)	31.8 (23.2, 36.4)	28 (25.5, 39)	0.542
VLDL (mg/dL)	35.5 (25.5, 42)	35 (29.2, 45.25)	35 (29, 43.75)	0.824
HDL (mg/dL)	6.03 (4.86, 8.20)	5.96 (4.59, 7.51)	5.67 (4.54, 7.21)	0.345
TC/HDL-c	81.25 (70.76, 107.81)	145.28 (80.45, 222.87)	126.31 (79.13, 274.15)	0.026*
TREM2 (pg/mL)	6.85 (1.63, 12.64)	5.11 (1.55, 11.50)	5.23 (1.78, 11.69)	0.982
hs-CRP (mg/L)	79.5 (47.6, 97.1)	81.25 (56.37, 102.22)	71.4 (48.92, 97.37)	0.756

[Table/Fig-4]: Comparison of sTREM-2 and lipid profile with severity of CAD using SYNTAX I score.
BMI: Body mass index (kg/m^2); FBS: Fasting blood sugar (mg/dL); TC: Total cholesterol (mg/dL); TGL: Triglycerides (mg/dL); LDL: Low-density lipoprotein (mg/dL); VLDL: Very low-density lipoprotein (mg/dL); HDL: High-density lipoprotein (mg/dL); TC/HDL-c; Total cholesterol to HDL-cholesterol ratio (unitless); TREM2: Soluble triggering receptor expressed on myeloid cells 2 (pg/mL); hs-CRP: High-sensitivity C-reactive protein (mg/L); ApoB: Apolipoprotein B (mg/dL); Statistical test used: Kruskal-Wallis test

However, no statistically significant differences were observed in age or biochemical parameters, including FBS, TC, TG, LDL, hs-CRP, or ApoB, across the severity categorisation.

ROC Curve Analysis

Receiver Operating Characteristic (ROC) curve analysis for serum sTREM2 [Table/Fig-5] demonstrated an AUC of 0.771±0.035, indicating good diagnostic accuracy (p<0.001; 95% CI: 0.703-0.840).



[Table/Fig-5]: ROC curve depicting the diagnostic performance of the TREM2.

An optimal cutoff value of 92.10 pg/mL yielded a sensitivity of 64.8% and specificity of 80.9%. The corresponding Youden's Index was 0.457, reflecting a favourable balance between sensitivity and specificity in diagnosing ACS.

DISCUSSION

Atherosclerosis involves chronic activation of both the innate and adaptive immune systems, with macrophages playing a crucial role in lipid uptake, plaque formation and inflammatory modulation [7]. Among these, TREM2-expressing macrophages have been identified as a key immune subset within atherosclerotic lesions, particularly in lipid-rich foam cells [8-10]. These cells regulate lipid metabolism and phagocytosis and are believed to influence plaque stability [11].

In the present study, median serum sTREM2 levels were 115.2 pg/mL (IQR: 78.2-191.7) in ACS patients and increased progressively across SYNTAX-defined severity categories from mild to severe disease. Liu W et al., reported significantly higher median sTREM2 levels (>1105 pg/mL) in patients with coronary heart disease, with ROC analysis demonstrating an AUC of 0.781, sensitivity of 59.3% and specificity of 81.4% at a cutoff of >1104.9 pg/mL [12]. In contrast, the present study identified a lower cutoff (~92 pg/mL) but achieved a comparable AUC (0.771), higher specificity (80.9%) and greater sensitivity (64.8%).

The lower absolute sTREM2 concentrations observed in the present cohort may reflect differences in assay calibration, population characteristics, or genetic and environmental factors. Nevertheless, both studies report similar diagnostic performance, supporting the utility of sTREM2 across diverse cardiovascular populations. Patterson MT et al., demonstrated in-vitro that TREM2 enhances oxidised LDL uptake, promoting macrophage lipid handling and attenuating necrotic core formation in preclinical models [13]. These mechanistic findings align with our clinical observation of progressively elevated sTREM2 levels in severe CAD, linking circulating sTREM2 to macrophage-driven lipid adaptations within plaques.

The present correlation analysis is consistent with findings by Liu W et al., who reported significant associations between sTREM2 and triglycerides, HDL-C and ApoB [12]. However, unlike their study, the authors observed weak and non significant correlations between sTREM2 and the systemic inflammatory marker hs-CRP. This discrepancy may indicate that sTREM2 reflects a localised immune-lipid axis within atherosclerotic plaques rather than generalised systemic inflammation. Similar observations were reported in a multicentre study demonstrating elevated sTREM2 in coronary atherosclerosis and superior prognostic value compared with CRP in predicting cardiovascular mortality (AUC ≈ 0.78) [14].

Although hs-CRP and ApoB were significantly elevated in the present ACS cohort (median hs-CRP: 6.11 mg/L; ApoB: 78.05 mg/dL), their correlations with sTREM2 remained modest (hs-CRP: p=0.057; ApoB: p=0.127). This aligns with the findings of Zhu B et al., who emphasised TREM2's role in macrophage lipid uptake, efferocytosis and tissue repair, with minimal systemic inflammatory signalling [15].

Large epidemiological studies, such as that by Danesh et al., have demonstrated strong systemic associations between CRP levels and coronary heart disease risk, with each 1 mg/L increase in CRP nearly doubling cardiovascular risk (adjusted RR ≈ 1.90) and superior predictive performance compared to ApoB (AUC ≈ 0.80) [16]. In contrast, the present findings suggest that sTREM2 reflects a distinct immunometabolic pathway centered on lipid-driven macrophage activation.

Interestingly, although ApoB reflects total atherogenic lipoprotein burden, stronger correlations were observed between sTREM2 and LDL (ρ=0.332) and VLDL (ρ=0.160). This indicates a closer relationship with specific cholesterol-rich lipoprotein fractions involved in foam cell formation and plaque biology, consistent with TREM2's mechanistic role in lipid metabolism.

The ROC analysis in the present study demonstrated moderate diagnostic accuracy for sTREM2 (AUC=0.771), with 64.8% sensitivity and 80.9% specificity at the optimal cutoff. These findings closely parallel those of Liu W et al., [12], confirming reproducible diagnostic performance across cohorts. While hs-CRP and ApoB continue to

show strong predictive utility in cardiovascular disease, sTREM2 appears to provide complementary immunometabolic information.

Experimental studies by Jay TR et al., [17] and Wang S et al., [18] in neurodegenerative models further support the central role of TREM2 signalling in macrophage and microglial lipid handling and reparative processes. Although these studies did not evaluate sTREM2 as a biomarker, their mechanistic insights reinforce the present clinical observation that circulating sTREM2 likely reflects macrophage-driven lipid remodelling rather than systemic inflammation.

The significant association between serum sTREM2 levels and angiographic disease severity suggests its potential utility in risk stratification among ACS patients. Unlike conventional inflammatory and lipid markers, sTREM2 may identify individuals with heightened macrophage activity within plaques, offering an adjunct tool for clinical assessment, particularly in patients with intermediate risk or ambiguous systemic marker profiles.

Given the cross-sectional design, causal relationships and prognostic implications cannot be established. Nonetheless, these findings provide a strong rationale for longitudinal studies to explore sTREM2 as a predictor of cardiovascular outcomes, treatment response and plaque remodelling. Future studies should incorporate functional assays and advanced imaging to correlate circulating sTREM2 with intraplaque macrophage activity.

Limitation(s)

This was a single-centre, cross-sectional study, which limits the generalisability of the findings. Although the sample size was adequate for primary analyses, it was relatively small for detailed subgroup comparisons. Several potential confounding factors were not accounted for, including medication use (e.g., statins and antihypertensives), dietary habits, smoking, alcohol consumption and co-morbid conditions such as subclinical infections or autoimmune conditions. Genetic variability in TREM2 expression was not evaluated. Furthermore, the study lacked longitudinal follow-up and functional assays to confirm mechanistic pathways. These limitations warrant cautious interpretation and highlight the need for large-scale, prospective studies.

CONCLUSION(S)

Serum sTREM2 levels were significantly elevated in patients with ACS and demonstrated a graded increase across disease severity categories, reinforcing its potential role in disease progression and affirming its utility as a novel biomarker. Significant correlations were observed between sTREM2 and lipid parameters, including total cholesterol, LDL and the TC/HDL ratio, suggesting involvement in a distinct immunometabolic pathway. These findings indicate that sTREM2 may complement conventional inflammatory and lipid-based markers for risk stratification in ACS. Further longitudinal and mechanistic studies are warranted to establish its prognostic significance in ACS.

REFERENCES

[1] Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: A compass for future health. J Am Coll Cardiol. 2022;80(25):2361-71. Available from: http://dx.doi.org/10.1016/j.jacc.2022.11.005.

[2] Sharma YP, Santosh Vemuri K, Bootla D, Kanabar K, Pruthvi CR, Kaur N, et al. Epidemiological profile, management and outcomes of patients with acute coronary syndrome: Single centre experience from a tertiary care hospital in North India. Indian Heart J. 2021;73(2):174-79. Available from: http://dx.doi.org/10.1016/j.ihj.2020.11.149.

[3] Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91. Available from: https://doi.org/10.3758/bf03193146.

[4] Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: Current epidemiology and future directions. Circulation. 2016;133(16):1605-20. Doi: 10.1161/CIRCULATIONAHA.114.008729. PMID: 27142605.

[5] SYNTAX Score Calculator [Internet]. [cited 2025 Jul 29]. Available from: https://syntaxscore.org/calculator/syntaxscore/frameset.htm.

[6] Ulijaszek SJ. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. WHO technical report series 894. Pp. 252. (world health organization, Geneva, 2000.) SFr 56.00, ISBN 92-4-120894-5, paperback. J Biosoc Sci. 2003;35(4):624-25. Available from: http://dx.doi.org/10.1017/s0021932003245508.

[7] Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-74. Available from: https://doi.org/10.1038/nature01323.

[8] Colonna M. The biology of TREM receptors. Nat Rev Immunol. 2023;23(9):580-94. Available from: https://doi.org/10.1038/s41577-023-00837-1.

[9] Piollet M, Porsch F, Rizzo G, Kapser F, Schulz DJJ, Kiss MG, et al. TREM2 protects from atherosclerosis by limiting necrotic core formation. Nat Cardiovasc Res. 2024;3(3):269-82. Available from: https://doi.org/10.1038/s44161-024-00429-9.

[10] Cochain C, Vafadarnejad E, Arampatzi P, Pelisek J, Winkels H, Ley K, et al. Single-cell RNA-seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in Murine atherosclerosis. Circ Res. 2018;122(12):1661-74. Available from: https://doi.org/10.1161/circresaha.117.312509.

[11] Li Y, Xu H, Wang H, Yang K, Luan J, Wang S. TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomed Pharmacother. 2023;165(115218):115218. Available from: http://dx.doi.org/10.1016/j.biopha.2023.115218.

[12] Liu W, Weng S, Liu H, Cao C, Wang S, Wu S, et al. Serum soluble TREM2 is an independent biomarker associated with coronary heart disease. Clin Chim Acta. 2023;548(117499):117499. Available from: http://dx.doi.org/10.1016/j.cca.2023.117499.

[13] Patterson MT, Firulyova M, Xu Y, Bishop C, Zhu A, Schrank PR, et al. Trem2 promotes foamy macrophage lipid uptake and survival in atherosclerosis. Immunology. bioRxiv; 2022.

[14] Wang S, Cao C, Peng D. The various roles of TREM2 in cardiovascular disease. Front Immunol. 2025;16:1462508. Available from: http://dx.doi.org/10.3389/fimmu.2025.1462508.

[15] Zhu B, Liu Y, Peng D. The double-edged role and therapeutic potential of TREM2 in atherosclerosis. Biomark Res. 2024;12(1):131. Available from: http://dx.doi.org/10.1186/s40364-024-00675-w.

[16] Krintus M, Kozinski M, Stefanska A, Sawicki M, Obonska K, Fabiszak T, et al. Value of C-reactive protein as a risk factor for acute coronary syndrome: A comparison with apolipoprotein concentrations and lipid profile. Mediators Inflamm. 2012;2012:419804. Available from: http://dx.doi.org/10.1155/2012/419804.

[17] Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. J Exp Med. 2015;212(3):287-95. Available from: https://doi.org/10.1084/jem.20142322.

[18] Wang S, Mustafa M, Yuede CM, Salazar SV, Kong P, Long H, et al. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med. 2020;217(9):e20200785. Available from: https://doi.org/10.1084/jem.20200785.

PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Biochemistry, SRM Medical College and Research and Centre, Chengalpattu, Tamil Nadu, India.
2. Professor, Department of Biochemistry, SRM Medical College and Research and Centre, Chengalpattu, Tamil Nadu, India.
3. Professor and Head, Department of Biochemistry, SRM Medical College and Research and Centre, Chengalpattu, Tamil Nadu, India.
4. Professor and Head, Department of Cardiology, SRM Medical College and Research and Centre, Chengalpattu, Tamil Nadu, India.
5. Professor, Department of Biochemistry, SRM Medical College and Research and Centre, Chengalpattu, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. P Renuka,
Professor, Department of Biochemistry, SRM Medical College and Research and Centre, Chengalpattu-603203, Tamil Nadu, India.
E-mail: renukap@srmist.edu.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 23, 2025
- Manual Googling: Oct 23, 2025
- iThenticate Software: Oct 25, 2025 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 22, 2025**
Date of Peer Review: **Jul 22, 2025**
Date of Acceptance: **Oct 28, 2025**
Date of Publishing: **Apr 01, 2026**