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Evaluating GDF-15 As A Marker of Atherosclerotic Severity Using TIMI Score Stratification in Non-ST Segment Elevation Acute Coronary Syndrome

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ABSTRACT

Background: GDF-15, a cytokine of the TGF-β superfamily, is expressed in atherosclerotic plaque macrophages. While several biomarkers have been widely studied in Acute coronary syndrome (ACS), data linking GDF-15 to angiographic severity in non-ST segment elevation acute coronary syndrome (NSTE-ACS), as measured by TIMI score, remain limited. This study investigates the association between GDF-15 levels, atherosclerotic burden, and clinical outcomes in NSTE-ACS patients to enhance risk stratification and guide management.

Methods: The study included 100 diagnosed cases of NSTE-ACS, including 34 patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) and 66 with Unstable Angina (UA). Patients were stratified into three risk groups based on the TIMI risk score: low (0–2), intermediate (3–4), and high (≥5). Blood samples were collected at admission, and serum GDF-15 levels were measured using enzyme-linked immunosorbent assay (ELISA).

Results: Of the 100 NSTE-ACS patients, 46% were classified as low risk, 39% as intermediate risk, and 15% as high risk based on TIMI scores. High-risk status was more common among males and UA patients. A significant association was found between diagnosis and risk categories ($P = 0.014$). GDF-15 levels significantly increased across risk groups, with the highest levels in the high-risk group ($P < 0.001$). The ROC curve analysis showed excellent predictive value for GDF-**15**, with an **AUC of 0.985** ($p < 0.001$). An optimal cut-off value of >**954 pg/mL** demonstrated **100% sensitivity** and **92.94% specificity** in identifying high cardiovascular risk.

Conclusion: GDF-15 levels strongly correlate with TIMI risk scores in NSTE-ACS, supporting its role as a promising biomarker for risk assessment and disease severity stratification.

Keywords: Growth differentiation factor-15, Non-ST Segment Elevation Acute Coronary Syndrome, TIMI risk score

1. INTRODUCTION

Acute coronary syndrome (ACS) is a leading cause of morbidity and mortality, affecting approximately 1.5 million people annually. Early diagnosis and evidence-based treatment are critical to improving clinical outcomes.[1] Among ACS cases, non–ST elevation ACS (NSTE-ACS) accounts for about 70% [2] and includes unstable angina (UA) and non–ST elevation myocardial infarction (NSTEMI).[3] Despite advancements in treatment, NSTE-ACS remains clinically challenging due to its heterogeneous presentation and high risk of recurrence. [4,5]

Given the variability in patient risk, early risk stratification is essential for timely and appropriate management.[6] Several scoring systems have been developed to guide treatment decisions; among them, the Thrombolysis in Myocardial Infarction (TIMI) score is widely used. It is based on clinical features at presentation and includes a binary evaluation of myocardial injury using biomarkers such as creatine kinase-MB (CK-MB) or cardiac troponin (cTn).[7]

While the TIMI score is useful in clinical decision-making, it does not fully capture the extent or complexity of myocardial injury. Cardiac biomarkers enhance prognostic accuracy by detecting myocardial damage that may not be evident from clinical data alone. Elevated biomarkers, when combined with a high TIMI score, indicate a higher risk of adverse events. Although troponin is central in diagnosing myocardial injury, it has limitations—especially in high-risk patients with unstable angina who may present with normal troponin levels. Moreover, troponin does not reflect all underlying pathophysiological processes in ACS, prompting investigation into additional biomarkers for improved risk prediction. [8]

Growth Differentiation Factor-15 (GDF-15), previously known as MIC-1, is a member of the TGF-β superfamily, initially identified in activated macrophages. [9] It is a stress-responsive cytokine released from multiple cell types, including cardiomyocytes and macrophages, in response to inflammation, hypoxia, oxidative stress, and tissue injury. [12] In healthy individuals, GDF-15 levels gradually rise with age and are largely unaffected by sex or race. [10,11]

Following myocardial ischemia, GDF-15 levels increase rapidly and remain elevated for several days after reperfusion. [13] These observations suggest that circulating GDF-15 may reflect distinct biological pathways and offer complementary prognostic information in patients with NSTE-ACS. [14]

This study aims to assess the clinical relevance of GDF-15 in NSTE-ACS and evaluate its potential as a complementary prognostic marker alongside the TIMI risk score.

2. MATERIALS AND METHODS

Among the 100 NSTE-ACS patients enrolled in this cross-sectional study, 34 were diagnosed with NSTEMI and 66 with UA. All participants were admitted to the Emergency Department of SMS Medical College and Hospital, Jaipur.

Diagnosis of NSTE-ACS was made by trained cardiologists, based on a combination of clinical presentation, electrocardiographic changes, and laboratory investigations. Diagnostic criteria included chest pain lasting more than 20 minutes along with ST-segment depression ≥0.1 mV and/or T-wave inversion in two or more contiguous leads on ECG.

Risk stratification was conducted using the Thrombolysis in Myocardial Infarction (TIMI) score.

Severity of coronary artery disease (CAD) was assessed using the vessel score (ranging from 0 to 3), defined by the presence of ≥50% stenosis in major epicardial coronary arteries, including the left main coronary artery, left anterior descending (LAD), right coronary artery (RCA), or left circumflex artery (LCX).

All patients were evaluated in accordance with the latest European Society of Cardiology (ESC) guidelines for the management of acute myocardial infarction.

Inclusion and Exclusion criteria

The study included patients over 18 years of age with anginal chest pain and a confirmed diagnosis of NSTE-ACS (NSTEMI or unstable angina) who provided written informed consent. Exclusion criteria were STEMI, chronic kidney or liver disease, malignancy, autoimmune or inflammatory disorders, recent major surgery, active infection or sepsis, chronic muscular disease, pregnancy, lactation, or refusal to consent.

Data collection

All participants were informed about the study protocol and provided written consent. Confidentiality was maintained, and demographic and clinical details were recorded using a semi-structured proforma.

Routine biochemical investigations were conducted using the Beckman Coulter AU 5100 analyser. Electrocardiography (ECG) was performed using the Edan SE-1201, and echocardiography using the GE Vivid E9 systems. Left ventricular ejection fraction (LVEF) was calculated by Simpson's biplane method. Coronary angiography (CAG) findings were documented in patients who underwent the procedure. Growth differentiation factor-15 (GDF-15) levels were measured using the Elabscience® ELISA kit, and troponin T was assessed using the RADIOMETER AQT 90 FLEX analyser.

Statistical analysis

Statistical analysis was performed using SPSS software. Patients were categorized into low, intermediate, and high-risk groups based on TIMI scores. Categorical variables were compared using the Chi-square test, while continuous variables, including GDF-15 levels, were analyzed using one-way ANOVA with Bonferroni post hoc correction for multiple comparisons. The predictive value of GDF-15 for identifying high-risk patients was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated to assess discriminative ability, and the optimal cutoff value was determined using Youden's index.

Ethical consideration

A study protocol was designed before undertaking this study, which was approved by the Institutional Ethics Committee vide letter number 231/MC/EC/2021 dated 21/03/2022. It was justified that this study imposed no harm or any risk factor on the patient involved.

3. RESULTS

The study included 100 participants, of whom 34.0% were diagnosed with NSTEMI and 66.0% with UA. Using the **TIMI score for risk stratification**, 46.0% of participants were classified as low risk, 39.0% as intermediate risk, and 15.0% as high risk. The baseline clinical characteristics are listed in Table 1.

	Low risk (n=46)	Medium risk (n=39)	High risk (n=15)	P
Clinical and hemodynamic data				
Age, years	54.37 ± 10.72	63.05 ± 10.21	66.07 ± 8.75	< 0.001
Men, n, %	33 (47.14)	25 (35.71)	12 (17.14)	0.490
Body mass index, kg/m^2	27.56 ± 2.45	27.03 ± 2.20	27.44 ± 1.93	0.565
Hypertension, n, %	11 (31.43)	15 (42.86)	9 (25.71)	0.033
Diabetes mellitus, n, %	8 (25)	16 (50)	8 (25)	0.011
Smoking (current), n, %	19 (39.58)	21 (43.75)	8 (16.67)	0.465
Left ventricular ejection fraction, %	51.24 ± 9.02	48.05 ± 10.63	50.67 ± 8.63	0.302
Biochemical and hematological data				
Total cholesterol, mg/dL	178.65 ± 45.14	184.74 ± 50.08	170.33 ± 48.02	0.595
Low-density lipoprotein, mg/dL	114.91 ± 38.77	106.53 ± 29.00	112.53 ± 27.29	0.516
High-density lipoprotein mg/dL	53.22 ± 10.76	52.92 ± 9.43	49.47 ± 10.26	0.448
Triglyceride, mg/dL	178.15 ± 119.19	171.92 ± 57.00	161.40 ± 53.22	0.820
Creatinine, mg/dL	1.00 ± 0.21	0.96 ± 0.27	0.99 ± 0.28	0.797
Random blood sugar, mg/dL	111.60 ± 68.61	132.17 ± 75.85	129.47 ± 54.04	0.367
Hemoglobin, g/dL	13.41 ± 2.14	13.37 ± 2.27	12.10 ± 2.54	0.127
Trop- T, ng/mL	0.66 ± 3.00	1.23 ± 3.73	0.18 ± 0.59	0.493
GDF-15, pg/mL	687.26 ± 75.96	884.72 ± 104.84	1191.40 ± 138.08	< 0.001
Number of diseased vessels, n (mean ± SD)	46 (1.04 ± 0.94)	39 (2.05 ± 0.56)	15 (2.73 ± 0.88)	<0.001
Location of stenosis, n, %				
LMCA	3 (20.00)	6 (40.00)	6 (40.00)	0.007
LAD	26 (37.68)	32 (46.38)	11 (15.94)	0.037
LCx	15 (38.46)	18 (46.15)	6 (15.38)	0.442
RCA	11 (25.00)	26 (59.09)	7 (15.91)	<0.001

The mean age of study participants with high cardiovascular risk was (66.07±8.75) years. It is evident from the table that 17.14% of males were in the high cardiovascular risk category. A significantly higher proportion of hypertensive patients (25.71%) were in the high-risk group compared to normotensive patients (9.23%) ($p < 0.05$). A similar trend was observed in patients with diabetes mellitus (DM), where 25% were in the high-risk category. Using the chi-square test, DM was found to be significantly associated with cardiovascular risk ($p = 0.011$).

In contrast, 16.67% of high-risk, 43.75% of medium-risk, and 39.58% of low-risk patients were smokers. However, this distribution across risk categories was not statistically significant ($p = 0.465$).

LMCA involvement showed a significant association with risk category, with 40% of affected patients in the high-risk group versus 10.59% with normal LMCA ($p = 0.007$). Similarly, 15.94% of LAD-involved patients were high risk compared to 12.90% without LAD involvement ($p = 0.037$).

RCA involvement was strongly associated with TIMI risk levels ($p < 0.001$), with 59.09% of affected patients in the intermediate-risk group and 25% in the low-risk group, compared to 62.50% among non-RCA patients.

The mean serum GDF-15 level was highest among participants in the **high cardiovascular risk** group (**1191.40 ± 138.08 pg/ml**), followed by the **medium-risk** group (**884.72 ± 104.84 pg/ml**) and the **low-risk** group (**687.26 ± 75.96 pg/ml**). Statistical analysis revealed that GDF-15 levels in the high-risk category were **significantly higher** than those in both the low- and medium-risk groups.

Other clinical and biochemical parameters, including body mass index (BMI), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), random blood sugar (RBS), hemoglobin (Hb), and troponin T levels, did not differ significantly across the risk groups.

Correlation between TIMI score and markers

	GDF-15	NO OF VESSELS	TROP-T
Correlation Coefficient*	0.770	0.410	0.245
Significance Level (P)	<0.0001	<0.0001	0.0141
N	100	100	100

*Spearman rank correlation coefficient

Table 2. Correlation of TIMI Score with Serum GDF-15, Number of Vessels, and Troponin-T

As shown in Table 2, Spearman rank correlation analysis demonstrated a strong positive correlation between TIMI score and serum GDF-15 levels ($\rho = 0.770$, $p < 0.0001$), indicating that higher GDF-15 concentrations are significantly associated with higher TIMI risk scores.

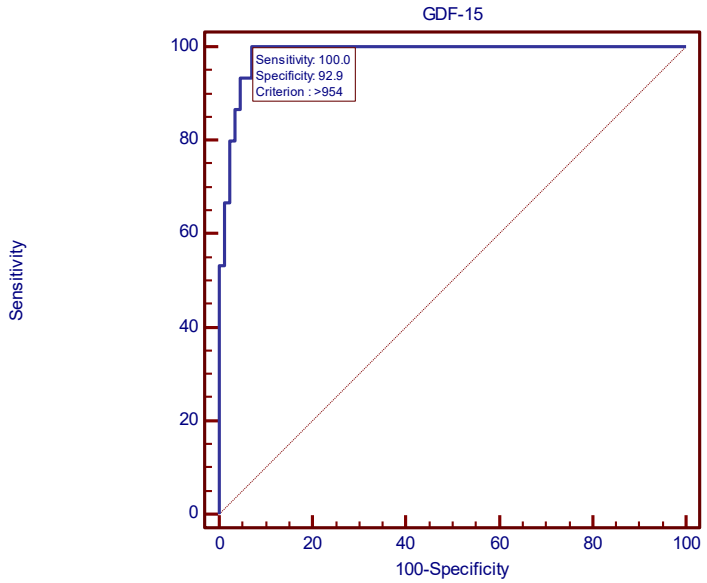

Figure 1. Receiver operating curve (ROC) for evaluating the diagnostic role of growth differentiation factor-15 (GDF-15)

ROC analysis of GDF-15 showed that GDF-15 was significantly helpful in assessing the severity of ACS with an AUC of 0.985 ($p < 0.001$). An optimal cut-off value of >954 pg/mL for serum GDF-15 demonstrated 100% sensitivity and 92.94% specificity in identifying patients at high cardiovascular risk.

4. DISCUSSION

This study demonstrated a significant association between serum GDF-15 levels and TIMI risk scores in patients with acute coronary syndrome (ACS). GDF-15 concentrations were significantly higher in patients categorized as high risk compared to those in low-risk and moderate-risk groups, suggesting its utility as a reliable biomarker for ACS severity and risk stratification. The ability of GDF-15 to effectively distinguish high-risk patients supports its potential role in clinical decision-making and early identification of high-risk cases.

GDF-15, previously known as macrophage inhibitory cytokine-1 (MIC-1), is a divergent member of the transforming growth factor-beta (TGF-β) superfamily, involved in maintaining tissue homeostasis [15–18]. It is typically expressed at low levels under physiological conditions, with higher baseline expression noted only in the placenta during pregnancy [19]. GDF-15 levels tend to increase slowly with age and are relatively unaffected by sex or ethnicity [20]. However, under pathological conditions such as inflammation, hypoxia, oxidative stress, or tissue injury, GDF-15 is rapidly upregulated by various cell types, including cardiomyocytes, macrophages, endothelial cells, and hepatocytes [21]. Elevated levels have been reported following cardiovascular events such as heart failure, atrial fibrillation, atherosclerosis, and pressure overload [16,21].

Our findings are consistent with several previous studies. For instance, Hagström et al. in the PLATO trial observed that higher GDF-15 levels were independently associated with increased risk of mortality, recurrent MI, and bleeding in non-ST-elevation ACS patients treated with either ticagrelor or clopidogrel [22]. Likewise, Eggers et al. [23] and Schaub et al. [24] showed that GDF-15 predicted all-cause mortality more accurately than hs-Troponin T or natriuretic peptides in the emergency triage of chest pain patients.

A comprehensive meta-analysis by Wang et al. [25] involving over 43,000 ACS patients found that elevated GDF-15 was significantly associated with mortality (RR = 6.75, 95% CI: 5.81–7.84) and recurrent MI (RR = 1.95, 95% CI: 1.72–2.21). These findings reinforce the prognostic value of GDF-15 in ACS. Similarly, Zhang et al. (2016) demonstrated a significant association between GDF-15 levels and adverse outcomes, reporting a mortality RR of 6.08 and a recurrent MI RR of 1.76 in patients with the highest versus lowest GDF-15 levels [26]. Subgroup analysis further supported the clinical utility of specific cut-off values, showing progressively increased risk with rising GDF-15 concentrations.

In line with these studies, our research identified a GDF-15 threshold of >954 pg/ml as an effective cut-off for distinguishing high-risk ACS patients. This reinforces the relevance of GDF-15 as a non-invasive, accessible biomarker for guiding risk stratification, prognosis, and management strategies in clinical cardiology.

5. CONCLUSION

The present study underscores the significant role of serum GDF-15 as a biomarker for risk stratification in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). A strong positive correlation was observed between GDF-15 levels and TIMI risk scores, with markedly elevated concentrations in high-risk patients. These findings demonstrate that GDF-15 can effectively differentiate high-risk individuals from those at low to moderate risk, thereby facilitating early clinical decision-making.

Notably, GDF-15 outperformed traditional markers such as troponin T in terms of correlation strength, and its high sensitivity and specificity reinforce its potential as a robust prognostic biomarker. Supported by existing literature and our results, routine assessment of serum GDF-15 may enhance current risk stratification protocols, enabling timely intervention and improved outcomes in ACS management.

6. LIMITATION

This study is limited by its cross-sectional design and absence of follow-up data, which restricts the evaluation of the long-term prognostic value of GDF-15. It was a single-center, observational study with a relatively small sample size and uneven distribution across risk groups. As a hospital-based study, it is also subject to selection bias and may not be fully generalizable to the broader ACS population.

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