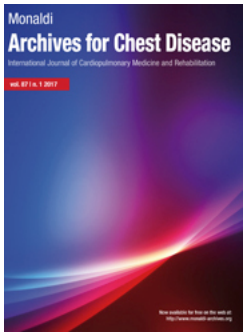

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Growth differentiation factor-15 as a predictor of acute myocardial infarction: a multivariable modeling approach

Halala Hatem Mohammed,[1] Fatima Mohammed Ahmed,[2] Sardar Nori Ahmed[1]

[1]Pharmacy Biophysics and Clinical Biochemistry Department, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region; [2]Research Centre, Akre University for Applied Sciences, Duhok, Kurdistan Region, Iraq

Correspondence: Halala Hatem Mohammed, Pharmacy Biophysics and Clinical Biochemistry Department, College of Medicine, Hawler Medical University, 44001 Erbil, Kurdistan Region, Iraq. Tel.: +964 750 891 3154. E-mail: halala.mustafa9@gmail.com

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Abstract

Globally, acute myocardial infarction (AMI) is a predominant cause of morbidity and mortality. Identifying reliable biomarkers to enhance risk prediction models remains a priority. This study assesses the role of growth differentiation factor-15 (GDF-15) as a predictor of AMI and its incremental value in refining current risk assessment models. A case-control study was established involving 45 AMI cases and 45 controls. Demographic, clinical, and biochemical parameters were evaluated. Logistic regression models were developed to assess the relationship between GDF-15 and AMI, adjusting for conventional risk factors and biomarkers. The prediction ability of models with and without GDF-15 was compared using the area under the curve (AUC). GDF-15 values were markedly elevated in AMI patients relative to controls. Incorporating GDF-15 into predictive models substantially improved their discriminative ability, demonstrating that GDF-15 was a robust independent predictor of AMI, enhancing diagnostic sensitivity and specificity across multiple models. Adjusting for demographic, lifestyle, and clinical risk factors, inclusion of GDF-15 led to notable AUC enhancements in Model 2 (32.88%) and Model 3 (19.66%). Models 4 and 5, which included additional biomarkers, demonstrated modest AUC improvements (2.57% and 0.61%, respectively), highlighting GDF-15's incremental value, even in models already incorporating a wide range of established biomarkers. In conclusion, GDF-15 is a robust and independent predictor of AMI, consistently improving the diagnostic performance of multivariable models. Its incorporation enhanced sensitivity, specificity, predictive values, and AUC (up to 0.999), underlining its effectiveness in risk stratification and early diagnosis of AMI.

Key words: acute myocardial infarction, growth differentiation factor-15, area under curve, logistic regression, risk prediction.

Introduction

Myocardial infarction (MI) and coronary artery disease (CAD) rank among the primary causes of morbidity and mortality globally [1]. These disorders arise from the restriction of the heart's blood flow caused by plaque accumulation in the coronary arteries and are affected by various internal and external factors, including medical history, lifestyle choices, emotional stress, and environmental changes [2]. The increased mortality and financial implications linked to myocardial infarction and coronary artery disease underscore the necessity for prompt chest pain diagnosis and quick management, which can significantly decrease mortality and improve patient outcomes. Markers of myocardial necrosis are crucial in this process, facilitating precise diagnosis, predicting disease severity and extent, and guiding the development of efficient treatment methods [3].

Recently, GDF-15 has been an interesting biomarker indicative of myocardial damage. It functions as a systemic biomarker that responds to stress and is classified as a divergent member of the transforming growth factor β superfamily [4,5]. Its activity is generally minimal in normal tissues but markedly elevates under pathological conditions, including hypoxia, cardiovascular comorbidities, and oxidative stress [6]. Elevated GDF-15 levels have been associated with the spectrum of cardiovascular disease (CVD), including MI [7].

Unlike other cardiovascular indicators, GDF-15 plasma concentrations remain comparatively constant during both acute and stable phases of CAD. This stability provides substantial predictive insights for both the short- and long-term [8]. Individuals with ACS and elevated GDF15 levels exhibit an increased risk of all-cause and cardiovascular mortality, along with recurrent MI, even when controlling for traditional biomarkers such as hs-troponin T, cystatin C, hs-CRP, and NT-proBNP [9,10].

Despite its potential, the independent predictive value of GDF-15 remains inconsistent, showing a reduced association with myocardial infarction (MI) after adjusting for clinical characteristics and other prognostic biomarkers [10]. This study aims to evaluate the diagnostic potential of GDF-15 in acute myocardial infarction (AMI) and to investigate its incremental value when added to traditional and biomarker-based predictive models. The objective is to determine whether GDF-15 enhances diagnostic accuracy, with particular emphasis on its performance in models with

limited clinical or biochemical inputs, thereby supporting its role as a valuable and potentially early diagnostic biomarker.

Materials and Methods

Subjects and sample collection

In this case-control study, the participants were divided into control group and an AMI group. The control group included 45 clinically healthy individuals and the AMI group comprised another 45 consecutive patients admitted to the CCU of the Erbil Cardiac Center in the Surgical Specialty Hospital, after experiencing sudden chest pain and confirming the diagnosis of AMI. The diagnosis was verified using coronary angiography, along with positive troponin T (cTnT) and creatine kinase isoenzyme BB (CK-BB) values. Each patient was evaluated for CVD risk factors, encompassing obesity, physical activity, hypertension, hyperlipidemia, diabetes mellitus, familial history, and smoking status.

GDF-15 estimation

A 5 ml fasting venous blood specimen was obtained from each patient and let to coagulate for 30 minutes in gel tubes. The samples were subsequently centrifuged at 3000 rpm for 15 minutes, and the supernatant was extracted for analysis. Plasma GDF-15 concentrations were quantified with a Human GDF-15 ELISA Kit (catalog number: E-EL-H0080, Elabscience Biotechnology Inc., Houston, TX, USA), with a normative reference range of 7–18.47 ng/ml.

Inclusion and exclusion criteria

Adults 45 years of age or older with a verified diagnosis of acute myocardial infarction met the inclusion requirements. The exclusion criteria were as follows:

- Heart failure, defined by a clinical diagnosis using both electrocardiographic findings and NT-proBNP levels, which are the primary diagnostic tools at the Erbil Cardiac Center. Patients with severe heart failure, characterized by a left ventricular ejection fraction (EF) of ≤40%, were excluded from the study.
- Other cardiovascular conditions, including stroke and any history of significant heart disease other than AMI.

- Autoimmune or inflammatory disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus).
- Liver disease, including chronic liver disease or cirrhosis.
- Chronic kidney disease, particularly those with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2.
- Malignancies, including any history of cancer within the past five years.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Scientific Committee of the College of Medicine, Hawler University (Approval Code: 13, Date: 11/9/2024) and the Ethical Committee of the Erbil General Directorate of Health, Ministry of Health (Reference no: 24102021-10-38, Date: 15/9/2024). Written informed consent was obtained from all participants before their involvement in the study.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism (version 10). Categorical variables were represented as percentages, and comparisons were assessed using the Chi-square test. For normally distributed variables, the mean and standard error of the mean were used to describe continuous data and compared using Student's t-test. For non-normally distributed data, medians with interquartile ranges (25th and 75th percentiles) were reported and analyzed using the Mann-Whitney U test. Data that were non-normally distributed underwent log transformation to approximate a normal distribution prior to statistical analysis. Logistic regression analysis was utilized to investigate a potential independent association between blood GDF-15 levels and AMI, with results shown as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). To evaluate the diagnostic efficacy of serum GDF-15 in AMI, the diagnostic performance of GDF-15 was analyzed, and receiver operating characteristic (ROC) curves were produced for modified models utilizing MedCalc statistical software. An area under the curve (AUC) exceeding 0.70 signifies diagnostic value, with statistical significance established at $p < 0.05$. To compare the AUCs between models with and without GDF-15, DeLong's test for correlated receiver operating characteristic (ROC) curves. This test was used to assess whether the differences in AUC values

between models were statistically significant, accounting for the correlation between the models. The percentage improvement in the AUC for each model was calculated using this formula:

$$\%\ \text{Improvement} = \left(\frac{\text{AUC with GDF 15} - \text{AUC without GDF 15}}{\text{UC without GDF 15}}\right) \times 100$$

Results

The results showed that participants with AMI were considerably older with a higher BMI and a higher percentage of hypertension and smoking ($p \leq 0.050$). No significant variations were identified in family history, diabetes, physical activity, and obesity between the two groups ($p > 0.05$). Clinically, a comparison between the two groups revealed significant differences in the levels of cardiac, inflammatory, renal function, metabolic, and lipid markers ($p < 0.0001$) (Table 1).

The result of binary logistic regression presented in Table 2, the adjusted models demonstrate a robust and consistent association between GDF-15 and AMI. The crude model (Model 1) showed an odds ratio (OR) of 3.791 (95% CI: 2.136–6.727, $p < 0.0001$). After adjusting for various demographic, clinical, and biochemical factors, the OR remained significant across all models, peaking at 4.512 (95% CI: 1.235–16.479, $p = 0.023$) in Model 4.

Table 3 outlines the diagnostic performance of predictive models for acute myocardial infarction (AMI). Incorporating GDF-15 consistently enhanced diagnostic accuracy across all models. In Model 2, sensitivity improved from 60% to 97.78%, the positive likelihood ratio (PLR) increased from 3.86 to 22.0, and the negative likelihood ratio (NLR) decreased from 0.47 to 0.023. incorporation of GDF-15 In Model 3 resulted in prefect sensitivity (100%) and negative predictive value (100%), while maintaining high specificity (91.11%). Similarly, Model 4 with GDF-15 exhibited almost perfect diagnostic performance, achieving a sensitivity of 97.78% and a specificity of 100%, in contrast, diminished sensitivity (91.11%) and an elevated NLR (0.093) have been observed in model without GDF-15. Finally, Model 5 demonstrated balanced performance with GDF-15, achieving 95.56% sensitivity and specificity; however, its exclusion slightly increased sensitivity (100%) at the expense of reduced specificity (91.11%).

The AUC was conducted to evaluate the discriminative ability of the models built by logistic regression. The discriminative ability of models with and without GDF-15 was compared to demonstrate the predictive power of GDF-15 for AMI across sequential models. In the crude

model (Model 1), the AUC was 0.967 (95% CI: 0.922–1.000, $p < 0.0001$), indicating excellent discrimination. Including GDF-15 in Models 2-5 consistently improved the AUC compared to models without GDF-15. In Model 2, the AUC increased from 0.742 (95% CI: 0.639–0.844, $p < 0.0001$) to 0.986 (95% CI: 0.962–1.000, $p < 0.0001$), and in Model 3, from 0.824 (95% CI: 0.739–0.909, $p < 0.0001$) to 0.986 (95% CI: 0.965–1.000, $p < 0.0001$). The addition of GDF-15 provide significant incremental predictive value beyond traditional risk factors as evidenced by % Improvement of 32.88% for model 2 and 19.66% for model 3 respectively. The statistical significance of the differences in AUC values between models with and without GDF-15 was assessed using the DeLong test, which confirmed the significant improvements in Model 2 and Model 3 ($p < 0.001$). In contrast, Model 4, which incorporated lipid and glucose metabolism biomarkers (LDL, HDL, and HbA1c) alongside GDF-15, achieved near-perfect predictive accuracy with an AUC of 0.999 (95% CI: 0.995–1.000, $p < 0.0001$). The AUC for Model 4 without GDF-15 was slightly lower at 0.974 (95% CI: 0.945–1.000, $p < 0.0001$), emphasizing the modest but meaningful improvement contributed by GDF-15. The DeLong test results for Model 4 showed a p-value of 0.0814, suggesting that while the improvement was present, it was not statistically significant at the 0.05 threshold. Finally, Model 5, which adjusted for biomarkers reflecting inflammation (CRP), cardiac injury (troponin), renal function (creatinine), and metabolic status (uric acid), also demonstrated excellent predictive performance. The AUC for Model 5 with GDF-15 was 0.993 (95% CI: 0.982–1.000, $p < 0.0001$), compared to 0.987 (95% CI: 0.970–1.000, $p < 0.0001$) in model without GDF-15. While the improvement in Model 5's AUC was relatively modest (0.61%), it highlights GDF-15's incremental value, even in models already incorporating a wide range of established biomarkers. The DeLong test for Model 5 showed a p-value of 0.3590, indicating no statistically significant improvement (Table 4 and Figures 1 and 2).

Discussion

A major strength of this study lies in its comprehensive evaluation of GDF-15 across multiple predictive models. The systematic adjustment for confounding variables, encompassing conventional cardiovascular risk factors and biochemical markers, underscored the supplementary significance of GDF-15. The strength of these findings is underscored by the observed enhancements in diagnostic metrics across all models. Moreover, utilization of AUC,

likelihood ratios (PLR and NLR), and predictive values provides a comprehensive assessment of diagnostic efficacy, confirming the dependability and clinical relevance of the findings.

This study validated diagnostic utility of GDF-15 in AMI and highlighted one of the highest reported AUC values (0.999), affirming its exceptional diagnostic precision in this context. The findings align with the established understanding of GDF-15 as a stress-responsive cytokine that is increased in response to hypoxia, inflammation, and oxidative stress, all of which are critical factors in the onset and progression of AMI. Its release from cardiomyocytes and other tissues following myocardial infarction renders it a sensitive marker for early cardiac stress [11-13]. A recent meta-analysis has shown that elevated GDF-15 levels are significantly linked to elevated risks of major adverse cardiac events (MACEs) and all-cause mortality in patients with ACS, hence proving its potential predictive usefulness in clinical practice [14].

Clinically, incorporation of GDF-15 into diagnostic methods may resolve existing gaps in AMI detection, particularly in instances of diagnostic inconsistency, such as conflicting troponin readings or unusual manifestations. Enhancing diagnostic accuracy with GDF-15 facilitates timely treatment interventions, improves patient outcomes, and provides substantial advantages in resource-limited settings [15]. Moreover, recent outcomes of an individual meta-analysis showed that GDF-15 is consistently adds prognostic data for cardiovascular death and heart failure hospitalization, increasing its clinical value in the treatment of AMI [13].

Our results support previous studies that have determined the prognostic relevance of GDF-15 in cardiovascular diseases, particularly acute myocardial infarction (AMI). A longitudinal cohort research study conducted by Bradley et al. (2023) showed the prognostic relevance of GDF-15 in predicting hospitalization and mortality in patients at risk for or diagnosed with heart failure (HF) [16]. This supports our findings, as the diagnostic efficacy of GDF-15 observed in our study indicates its broader potential to identify individuals with elevated risks of cardiovascular events, similar to the heart failure patients in the Bradley et al. trial. This relationship underscores the significance of GDF-15 in the diagnosis of AMI, encompassing not only immediate detection but also the prediction of long-term cardiovascular outcomes, thereby enhancing clinical decision-making.

A recent meta-analysis published in Frontiers in Cardiovascular Medicine (2023) validated the independent predictive value of GDF-15 for complications in CAD. Additionally, this study

highlighted the relationship between GDF-15 and biomarkers indicative of inflammation, myocardial injury, and renal dysfunction [10]. These outcomes closely confirm our results, wherein GDF-15 independently improved diagnostic models for AMI, enhancing both sensitivity and specificity. Further, the study indicated a correlation between GDF-15 and critical pathophysiological mechanisms, including oxidative stress and inflammation, which stratifies with our observations, suggesting that its utility as an indicator for AMI complements its broader prognostic significance for cardiovascular diseases.

In line with the PLATO study's findings, in which the prognostic significance of GDF-15 has been reassessed in 16,876 patients with ACS, this study identifies GDF-15 as an independent predictor of AMI with enhanced diagnostic accuracy. The PLATO study showed that higher GDF-15 concentrations were associated with an increased risk of all-cause mortality, whereas our study focuses on the diagnostic utility of GDF-15 for early AMI detection. When taken as a whole, these findings demonstrate the diverse potential of GDF-15 as a biomarker for both short-term diagnosis and long-term prognostic evaluation in the treatment of cardiovascular disease [9].

Our investigation quantitatively evaluated the diagnostic utility of GDF-15, revealing that it provided significant incremental value to predictive models beyond traditional risk factors and biomarkers. Accordingly, our findings establish GDF-15 as an independent predictor of AMI and demonstrate its ability to enhance the diagnostic model. Overall the study results are consistent with the results of the Mathijs et al. trial. The latter highlighted the prognostic significance of GDF-15 in predicting long-term all-cause mortality among STEMI patients treated with primary percutaneous coronary intervention (PPCI), indicating that it offered considerable additional value to predictive models beyond conventional risk factors and biomarkers. These findings show the versatility of GDF-15 as a biomarker, providing immediate diagnostic utility in acute settings, as shown in this study, and long-term prognostic insights, as indicated in the Mathijs et al. trial [17]. Comparably, a retrospective investigation by He et al. on the diagnostic accuracy of GDF-15 and high-sensitivity troponin T (hscTnT) in elderly AMI patients underscored the significant role of GDF-15 in diagnosing AMI. The study they conducted emphasized the combined utility of GDF-15 and hs-CTnT, stating GDF-15's high specificity (93.75%) and its association with disease intensity. Our study extends these insights by demonstrating that GDF-15 independently enhances the performance of diagnostic models by the notable improvements in sensitivity (up to 100%)

and specificity (up to 100%). These studies indicate that GDF-15 enhances the efficacy of AMI detection and serves as a novel biomarker for AMI diagnosis and disease monitoring [2]. The study conducted at Qilu Hospital on GDF-15 and coronary microvascular dysfunction (CMD) in STEMI patients highlighted the incremental predictive value of the biomarker in identifying CMD following primary percutaneous coronary intervention (PPCI). The referenced study found an accuracy score of 0.867 for GDF-15 in predicting CMD, with notable enhancements in reclassification metrics (NRI: 0.854; IDI: 0.151), highlighting its prognostic significance in post-procedural complications. While their study focused on the predictive value of GDF-15 for CMD, our study emphasized its acute diagnostic potential in AMI. Both studies reinforced the versatility of GDF-15 as a biomarker, providing important insights into various aspects of cardiovascular disease diagnosis and prognosis [18]. In alignment with the study on premature myocardial infarction, which recognized GDF-15 as a critical factor associated with the risk of early-onset MI, our research emphasized the diagnostic utility of GDF-15 in MI. The study by Dogan et al. on patients under 45 years with premature MI found that GDF-15 was an independent risk factor for MI in younger patients. While this study focused on the role of GDF-15 in a younger population and its association with atherosclerosis, our research emphasized GDF-15's significance in the acute diagnosis of AMI in older patients, particularly its ability to improve predictive models beyond conventional biomarkers. Together, these studies demonstrate the increasing significance of GDF-15 not only as a diagnostic marker for acute MI but also as a potential risk factor for early cardiovascular events, suggesting its broader relevance in both young and older populations [7]. Future research should explore the utility of GDF-15 together with other emerging biomarkers to establish a multimodal diagnostic approach for AMI. This is consistent with recent studies advocating for the integration of GDF-15 with high-sensitivity troponin and NT-proBNP, possibly enhancing diagnostic accuracy and prognostic stratification for AMI [19]. Additionally, beyond its diagnostic role, GDF-15's involvement in key pathophysiological processes may present opportunities for targeted therapies in AMI, warranting further investigation.

Limitations

Notwithstanding these promising results, this study possesses many limitations. The case-control design, although effective for discovering relationships, may introduce selection bias and limit the

generalizability of the findings to broader populations. Furthermore, the restricted sample size, although sufficient for statistical evaluations, needs validation in larger and more heterogeneous populations. A notable disadvantage is the lack of longitudinal data, which could clarify the role of GDF-15 in predicting recurrent cardiovascular events and long-term outcomes. Subsequent research aimed at overcoming these limitations is essential to confirm the clinical applicability of GDF-15.

Conclusions

The study indicates that GDF-15 is a strong predictor of AMI. Its incorporation regularly enhanced the diagnostic performance of multivariable models. Logistic regression analysis indicated that GDF-15 consistently served as an independent predictor across all models, with odds ratios ranging from 3.45 to 4.51 ($p < 0.05$). Diagnostic metrics showed that models including GDF-15 had superior sensitivity (up to 100%), specificity (up to 100%), and predictive values relative to models without GDF-15. Furthermore, the area under the curve (AUC) values and the positive and negative likelihood ratios (PLR and NLR) consistently demonstrated enhanced diagnostic accuracy for models that included GDF-15, achieving AUCs of 0.999 in adjusted models. These findings highlight the potential of GDF-15 to complement existing biomarkers, improving the early detection and management of AMI. With further validation, GDF-15 could become an integral component of precision medicine approaches in cardiology.

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Table 1. Clinical and basic characteristics of the study participants.

Variables	MI group	Control group	p-value
Age (years) Mean ± SE	59.22±1.033	56.39±0.8958	0.0416
BMI(Kg/m)^2 Mean ± SE	29.59±0.7522	27.40±0.5970	0.0254
Family History No. (%)	28 (60.87)	25 (54.35)	0.5268
Hypertension No. (%)	32 (69.57)	17 (36.96)	0.0017
Diabetes No. (%)	25 (54.35)	17 (36.96)	0.0940
Physical activity No. (%)	19 (41.30)	26 (56.52)	0.1443
Smoking No. (%)	21 (45.65)	12 (26.09)	0.050
GDF-15 ng/ml Median (IQR)	2.090(0.885)	0.4825(0.441)	<0.0001
C-RP mg/dl Median (IQR)	1.125(1.373)	0.3000(0.361)	<0.0001
Troponin ng/ml Median (IQR)	3.087(4.45)	0.01950(0.038)	<0.0001
Creatinine mg/dl Median (IQR)	0.9250(0.35)	0.3850(0.32)	<0.0001
Uric acid mg/dl Median (IQR)	6.385(2.635)	3.700(2.13)	<0.0001
TC mg/dl Median (IQR)	223.5(57.3)	108.5(29)	<0.0001
TG mg/dl Median (IQR)	174.5(56.2)	112.5(63.75)	<0.0001
HDL-C mg/dl Median (IQR)	40.00(15)	49.50(15.25)	<0.0001
LDL-C mg/dl Median (IQR)	86.80(33.2)	61.00(20.65)	<0.0001
HbA1c Median (IQR)	7.900(2.05)	5.290(0.87)	<0.0001
FBS Median (IQR)	180.0(58)	103.0(24.55)	<0.0001

BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar. Parametric data are presented as mean ± SD and analyzed by Student's t-test; Non-parametric data are presented as median (IQR) and analyzed by the Mann-Whitney test.

Table 2. Multivariate logistic regression models evaluating GDF-15 as a predictor of AMI with sequential adjustments for confounders.

Adjusted models	β	Wald	SE	OR	95%CI	p-value
Model 1: Crude, no adjustment	1.333	20.731	0.293	3.791	2.136-6.727	<0.0001
3Model 2: Adjusting for age, gender, BMI, smoking, physical activity	1.411	19.495	0.320	4.101	2.192-7.672	<0.0001
Model 3: Adjusting for hypertension, diabetes statues, hyperlipidemia, family history	1.395	13.242	0.383	4.033	1.903-9.548	<0.0001
Model 4: Adjusted for LDL, HDL, HbA1c	1.507	5.196	0.661	4.512	1.235-16.479	0.023
Model 5: Adjusting for CRP, Troponin, creatinine, uric acid	1.240	5.124	0.548	3.454	1.181-10.104	0.024

Table 3. Comparison of diagnostic performance of predictive models for AMI with and without GDF-15.

Models	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
Model 1 (Crude Model)	>1.02	100.0	95.56	95.7	100.0	22.50	0.0
Model 2							
With GDF-15	>0.30816	97.78	95.56	95.7	97.7	22.0	0.023
Without GDF-15	>0.59461	60.0	84.44	79.4	67.9	3.86	0.47
Model 3							
With GDF-15	>0.10734	100.0	91.11	91.8	100.0	11.25	0.0
Without GDF-15	>0.52254	71.11	80.0	78.0	73.3	3.56	0.36
Model 4							
With GDF-15	>0.35618	97.78	100.0	100.0	97.8	0.0	0.022
Without GDF-15	>0.49555	91.11	95.56	95.3	91.5	20.50	0.093
Model 5							
With GDF-15	>0.41308	95.56	95.56	95.56	95.56	21.50	0.047
Without GDF-15	>0.23002	100.0	91.11	91.8	100.0	11.25	0.0

Table 4. Comparison of AUC values for predictive models with and without GDF-15 in assessing risk of AMI.

Models	AUC (95%CI)	SE	p-value	ΔAUC (95%CI)	Z-statistic	p-value
Model 1 (Crude Model)	0.967 (0.922-1.000)	0.023	<0.0001	-	-	-
Model 2						
With GDF-15	0.986 (0.962-1.000)	0.052	<0.0001	0.244 (0.139-0.349)	4.556	<0.0001
Without GDF-15	0.742 (0.639-0.844)	0.12	<0.0001			
Model 3						
With GDF-15	0.986 (0.965-1.000)	0.011	<0.0001	0.162 (0.0759-0.248)	3.692	0.0002
Without GDF-15	0.824 (0.739-0.909)	0.044	<0.0001			
Model 4						
With GDF-15	0.999 (0.995-1.000)	0.051	<0.0001	0.0242 (-0.003-0.0514)	1.742	0.0814
Without GDF-15	0.974 (0.945-1.000)	0.002	<0.0001			
Model 5						
With GDF-15	0.993 (0.982-1.000)	0.009	<0.0001	0.00543 (-0.006-0.0170)	0.917	0.3590
Without GDF-15	0.987 (0.970-1.000)	0.005	<0.0001			

AUC, Area under the ROC curve; SE, Standard error. ΔAUC represents the difference in AUC between models with and without GDF-15; p-values for ΔAUC are calculated using DeLong's test for paired ROC curves (DeLong et al., 1988).

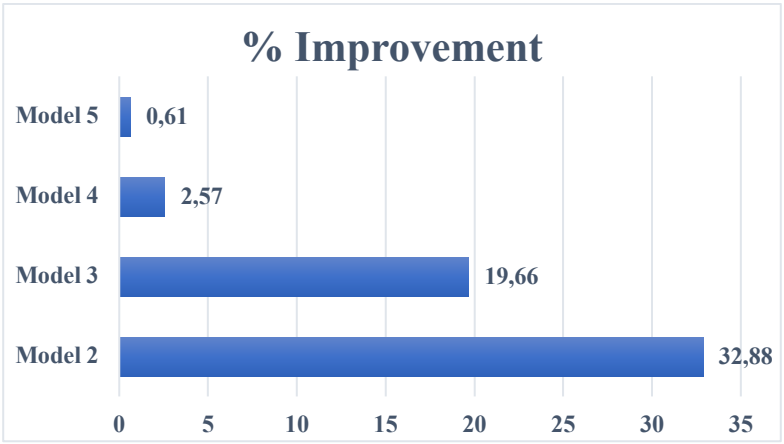

Figure 1. Percentage improvement in predictive performance across multivariable models for AMI.

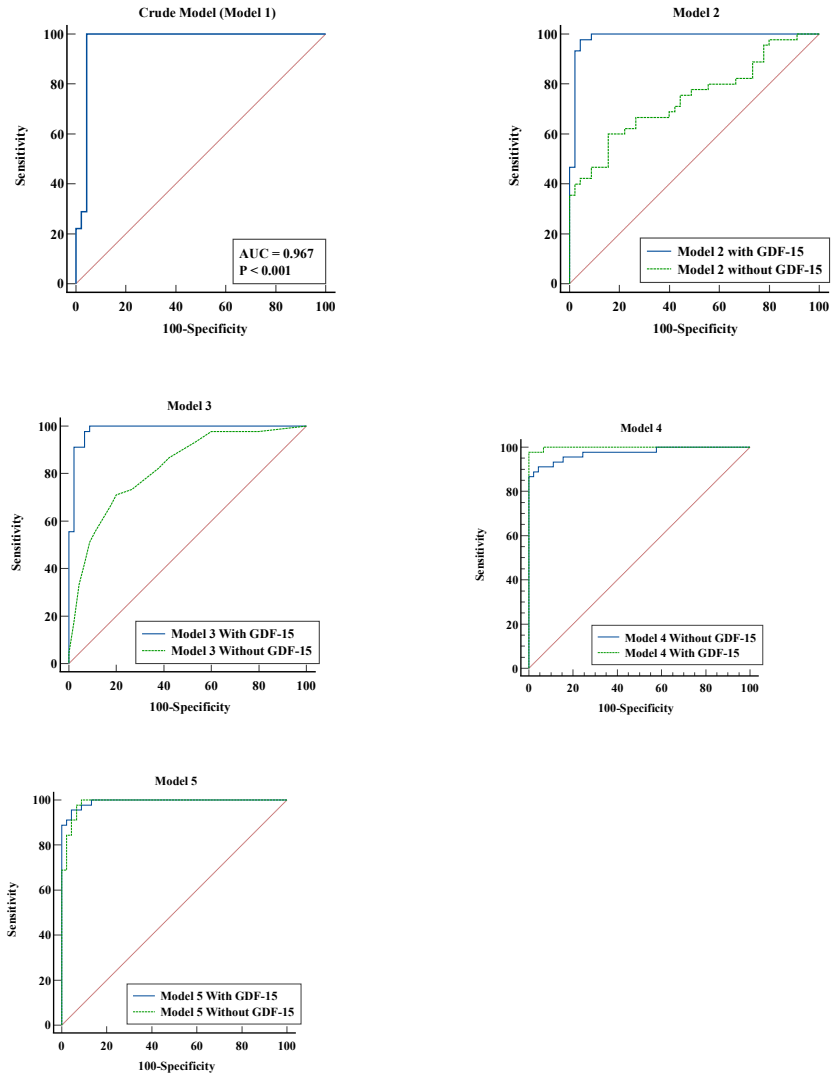

Figure 2. The area under the curve (AUC) for crude model and multivariable models predicting AMI.