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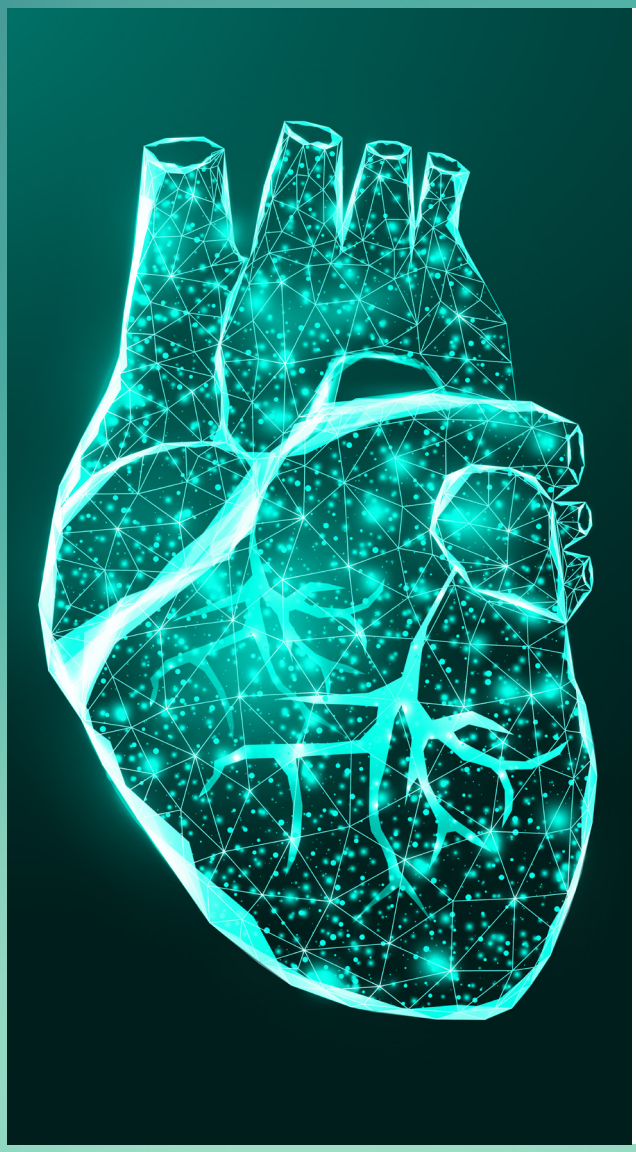





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RESEARCH ARTICLE

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Int J Cardiovasc Acad 2026;12(2):73-77

# Comparison of Mitral Annular Plane Systolic Excursion to 2D Speckle Tracking and Tissue Doppler Imaging in Patients with Type 2 Diabetes and Normal Subjects for Prediction of Subclinical Left Ventricular Systolic Dysfunction

**Vishwanath Hesarur, Megha Bubanale, Sanjay Porwal, Karan Chawla**

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## Abstract

**Background and Aim:** Type 2 diabetes mellitus (T2DM) is a significant risk factor for cardiovascular diseases, leading to subclinical left ventricular systolic dysfunction (LVSD). Early detection is crucial to prevent progression. To assess the utility of mitral annular plane systolic excursion (MAPSE) in detecting subclinical LVSD in asymptomatic T2DM patients and its correlation with 2D speckle-tracking echocardiography and tissue Doppler imaging (TDI) parameters.

**Materials and Methods:** A cross-sectional comparative study involving 200 participants (100 with T2DM and 100 controls) was conducted. Echocardiographic parameters, including MAPSE, global longitudinal strain (GLS), and TDI, were analysed. Statistical tests included t-tests and Pearson correlation analyses.

**Results:** T2DM patients showed significantly reduced MAPSE (1.2±0.3 cm vs. 1.4±0.2 cm, $P < 0.001$), GLS (-17.2±3.1% vs. -22.6±2.7%, $P < 0.001$), and TDI (0.08±0.02 m/s vs. 0.10±0.01 m/s, $P < 0.001$) compared with controls. MAPSE correlated positively with GLS (r=0.699, $P = 0.001$) and TDI [r=0.04, $P = 0.03$; 95% confidence interval (CI): 0.01-0.07] and negatively with HbA1c (r=-0.018, $P = 0.02$; 95% CI: -0.04-0.00) and diabetes duration (r=-0.117).

**Conclusion:** MAPSE <1.2 cm, a value supported by previous echocardiographic studies, identifies subtle impairment of longitudinal systolic function in asymptomatic T2DM patients. MAPSE demonstrates strong agreement with GLS and TDI and provides a simple, reproducible, and accessible marker for detecting subclinical LVSD, particularly in resource-limited settings.

**Keywords:** Diabetes mellitus, MAPSE, GLS, tissue doppler imaging, subclinical LVSD

## INTRODUCTION

Diabetes mellitus (DM) constitutes an ongoing metabolic dysfunction that has emerged as a critical global health issue, contributing significantly to cardiovascular morbidity and mortality. Subclinical left ventricular systolic dysfunction (LVSD), an early manifestation of diabetic cardiomyopathy,[1] often remains undiagnosed until overt heart failure develops. Advanced imaging techniques, such as 2D speckle-tracking echocardiography (STE) and tissue Doppler imaging (TDI), are of primary importance in diagnosing subclinical LVSD.[2,3] DM represents a chronic metabolic disorder that has emerged as a

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major global public health challenge, contributing substantially to cardiovascular morbidity and mortality. Among its cardiac manifestations, subclinical LVSD is recognized as an early hallmark of diabetic cardiomyopathy, often preceding clinically overt heart failure.[4]

Subclinical LVSD can remain undetected on conventional echocardiography, as left ventricular ejection fraction (LVEF) may appear preserved in the early stages. Advanced imaging modalities such as two-dimensional STE and TDI have been instrumental in detecting subtle myocardial deformation abnormalities. However, these methods may be technically demanding, cost-intensive, or not universally available in resource-constrained settings.[2]

Mitral annular plane systolic excursion (MAPSE), a simple M-mode echocardiographic measurement, reflects longitudinal left ventricular function and can serve as a practical surrogate marker for global systolic performance. Prior studies have demonstrated its correlation with both LVEF and global longitudinal strain (GLS), suggesting potential for early LVSD identification.[3,5]

Despite growing interest in MAPSE, limited data exist regarding its performance compared with GLS and TDI-derived systolic (S') velocities in asymptomatic patients with type 2 diabetes mellitus (T2DM). Therefore, this study aimed to evaluate the diagnostic value of MAPSE for detecting subclinical LVSD in T2DM patients with preserved LVEF and to examine its correlation with and to examine its correlation with GLS and TDI-derived systolic velocities.

## METHODS

### Study Design and Study Population

This was a cross-sectional comparative study conducted at a tertiary care medical centre between May 2024 and March 2025. The study included 200 patients divided into two groups: 100 asymptomatic patients with T2DM and 100 age- and sex-matched healthy controls. Inclusion criteria for the diabetic group included patients aged 18-70 years with a confirmed T2DM diagnosis. The control group consisted of healthy individuals without diabetes, cardiovascular disease, or other metabolic disorders. Exclusion criteria were overt heart failure, significant valvular disease, coronary artery disease, atrial fibrillation, poor echocardiographic windows, acute illness, or inability to provide informed consent. In addition to obtaining the patient history, a baseline electrocardiogram (ECG) evaluation and a review of medical records were performed to exclude occult ischemic heart disease.

### Data Collection

Comprehensive demographic, anthropometric, and clinical data were collected, including age, sex, body mass index (BMI), duration of diabetes, HbA1c levels, comorbidities (hypertension, dyslipidaemia), and medication history (antihypertensives, statins). All patients underwent a thorough physical examination, including assessment of vital signs. Transthoracic echocardiography was performed by experienced cardiologists using standardized protocols and high-resolution ultrasound systems, with patients in the left lateral decubitus position. Echocardiographic measurements included standard 2D, M-mode, pulsed-wave Doppler, and TDI imaging. MAPSE was measured in M-mode at both septal and lateral mitral annular sites. The mean MAPSE was calculated as the arithmetic average of the septal and lateral values for each subject. LVEF was obtained using the biplane Simpson's method. TDI S', early diastolic, and late diastolic velocities were recorded at the septal and lateral annuli. GLS was assessed using vendor-independent software (EchoPAC, GE Healthcare) by analyzing apical 2-, 3-, and 4-chamber views.[6] All echocardiographic measurements were averaged over three consecutive cardiac cycles to minimize beat-to-beat variability. To assess measurement reproducibility, intra- and inter-observer variabilities were calculated for 20 randomly selected subjects, yielding intraclass correlation coefficients of 0.92 and 0.89, respectively. All echocardiographic and statistical analyses were performed by personnel blinded to the participants' group allocation, with all data anonymized prior to analysis. Laboratory parameters, such as HbA1c, were also assessed.

### Ethics Committee Information

Ethical approval for this study was obtained from the Institutional Ethics Committee of Jawaharlal Nehru Medical College (references no: MDC/JNMCIEC/300, date: 13.05.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision). Each patient provided written informed consent before the start of the study.

### Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY). Quantitative variables are expressed as mean ± standard deviation, and qualitative data are expressed as frequencies and percentages. Group comparisons (T2DM vs control) were performed using independent-samples t-tests for continuous variables and chi-square tests for categorical variables. Correlations between MAPSE and GLS, TDI S', HbA1c, and diabetes duration were assessed using Pearson's correlation coefficients with corresponding 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$.

## RESULTS

A total of 100 T2DM patients and 100 age-matched healthy controls were included. As shown in Table 1, the mean age was slightly higher in the T2DM group than in controls (57.0±6.2

**Table 1. Comparison of echocardiographic parameters between type 2 diabetes mellitus patients and healthy controls**

| Variable | T2DM (n=100) | Controls (n=100) | t-value | *P*-value | 95% CI for mean difference |
|---|---|---|---|---|---|
| Age (years) | 57.0±6.2 | 54.0±5.8 | 2.09 | 0.038 | (0.17, 5.83) |
| Gender (M/F) | 54/46 | 52/48 | $\chi^2$=0.65 | 0.42 | - |
| HbA1c (%) | 8.65±1.78 | 5.85±0.63 | 12.89 | <0.001 | (2.36, 3.24) |
| LVEF (%) | 58.0±2.9 | 62.5±3.2 | 9.89 | <0.001 | (3.59, 5.41) |
| Septal MAPSE (cm) | 1.10±0.25 | 1.30±0.20 | 6.12 | <0.001 | (0.13, 0.27) |
| Lateral MAPSE (cm) | 1.30±0.25 | 1.50±0.20 | 6.48 | <0.001 | (0.14, 0.26) |
| Mean MAPSE (cm) | 1.20±0.30 | 1.40±0.20 | 5.73 | <0.001 | (0.13, 0.27) |
| GLS (%) | -17.2±3.1 | -22.6±2.7 | 12.00 | <0.001 | (4.61, 6.39) |
| TDI S' (m/s) | 0.08±0.02 | 0.10±0.01 | 8.24 | <0.001 | (0.014, 0.026) |
| E/e' ratio | 8.7±1.9 | 7.1±1.6 | 6.18 | <0.001 | (1.09, 2.11) |
| E/A ratio | 0.9±0.2 | 1.1±0.2 | 5.28 | <0.001 | (0.12, 0.28) |

LVEF: Left ventricular ejection fraction, MAPSE: Mitral annular plane systolic excursion, GLS: Global longitudinal strain, TDI: Tissue Doppler imaging, S': Derived systolic, CI: Confidence interval
Values are presented as mean ± standard deviation unless otherwise indicated. Independent-sample t-tests were used for continuous variables; $\chi^2$ test for gender distribution

vs. 54.0±5.8 years; $P$ = 0.038). The gender distribution was similar across groups ($P$ = 0.42). T2DM patients demonstrated significantly lower MAPSE, GLS, and TDI S' values compared with controls ($P$ < 0.001 for all measures), indicating early impairment of longitudinal systolic function despite a preserved ejection fraction.

MAPSE exhibited a strong positive association with GLS, supporting its use as a surrogate marker of global longitudinal systolic function [r=0.699, 95% CI: (0.58, 0.78); $P$ < 0.001] (Figure 1). The weak or absent relationships with HbA1c and diabetes duration suggest that structural myocardial dysfunction may occur independently of glycaemic status or disease chronicity.

MAPSE demonstrated a small, statistically significant negative correlation with HbA1c [r=-0.018, 95% CI: (-0.04, 0.00); $P$ = 0.02], as shown in Figure 2, suggesting that poorer glycemic control is associated with reduced longitudinal systolic displacement. No significant correlation was found between MAPSE and duration of diabetes ($P$ = 0.24).

A weak but statistically significant positive correlation was identified between MAPSE and TDI S' velocity [r=0.04, 95% CI: (0.01, 0.07); $P$ = 0.03], as shown in Table 2 and Figure 3, highlighting that reduced MAPSE reflects subtle impairments in tissue-level systolic function.

## DISCUSSION

In this study, we evaluated the diagnostic value of MAPSE for detecting subclinical LVSD in patients with T2DM and compared its performance with GLS and TDI. The findings demonstrate that diabetic patients exhibit significant reductions in MAPSE, GLS, and S' velocities despite a preserved ejection fraction, indicating early subclinical myocardial dysfunction.

### Demographic and Baseline Characteristics

The mean age and distribution between diabetic and control groups were comparable ($P$ = 0.038 for age; $P$ = 0.42 for gender), validating the matching process. The diabetic cohort had significantly higher HbA1c levels, consistent with impaired glycaemic control. The mean disease duration was 8.2 years, with a moderate prevalence of hypertension and dyslipidaemia, aligning with prior epidemiological data for middle-aged T2DM populations.

### MAPSE as a Marker of Longitudinal Systolic Function

The observed reduction in both septal and lateral MAPSE among diabetic patients compared with controls (1.2±0.3 cm vs. 1.4±0.2 cm; $P$ < 0.001) supports previous evidence that longitudinal myocardial fibres, located subendocardially, are

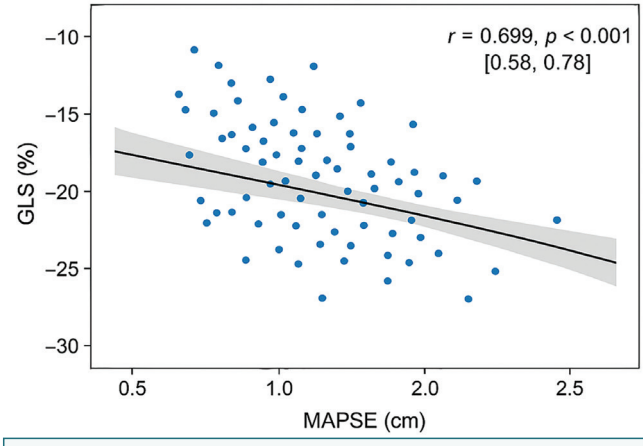


**Figure 1.** Correlation between mitral annular plane systolic excursion (MAPSE) and global longitudinal strain (GLS) in type 2 diabetes mellitus patients

**Table 2. Correlation between MAPSE and clinical or echocardiographic parameters in T2DM patients**

| Parameter | Pearson's r | 95% CI for r | *P*-value |
|---|---|---|---|
| GLS (%) | 0.699 | (0.58, 0.78) | <0.001 |
| TDI S' (m/s) | 0.04 | (0.01, 0.07) | 0.03 |
| HbA1c (%) | -0.018 | (-0.04, 0.00) | 0.02 |
| Duration of diabetes (years) | -0.117 | (-0.28, 0.05) | 0.24 |

T2DM: Type 2 diabetes mellitus, MAPSE: Mitral annular plane systolic excursion, GLS: Global longitudinal strain, TDI: Tissue Doppler imaging, S': Derived systolic, CI: Confidence interval
Pearson correlation coefficients computed for continuous variables. All tests two-tailed; significance level set at $P < 0.05$

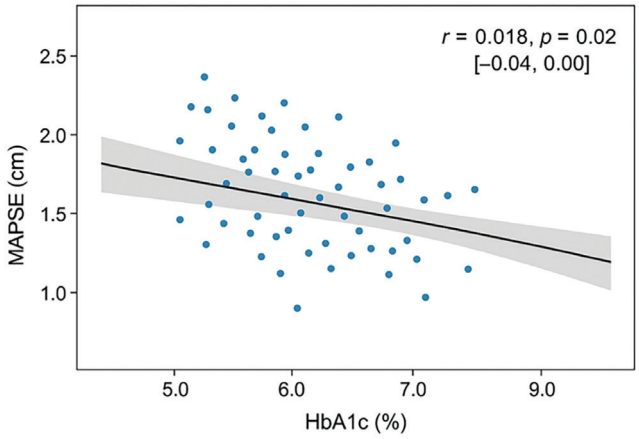


**Figure 2.** Correlation between mitral annular plane systolic excursion (MAPSE) and HbA1c in type 2 diabetes mellitus patients

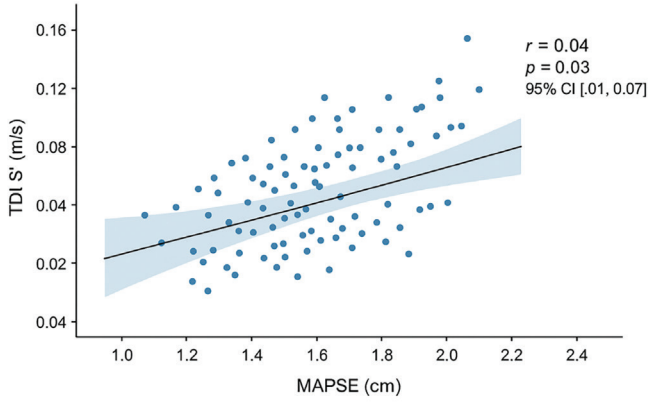


**Figure 3.** Correlation between mitral annular plane systolic excursion (MAPSE) and tissue Doppler imaging derived systolic (TDI S') velocity in type 2 diabetes mellitus patients

particularly vulnerable to hyperglycaemia-induced injury. These findings are consistent with Hu et al.[5] and Matos et al.,[3] who established that reduced MAPSE correlates strongly with global systolic dysfunction even when LVEF is preserved.

The strong positive correlation between MAPSE and GLS (r=0.699, $P < 0.001$) further supports the use of MAPSE as a simple surrogate measure of myocardial strain, particularly when advanced imaging modalities such as speckle-tracking are not available.

## Correlations with TDI and Metabolic Variables

The relationship between MAPSE and TDI S' was statistically significant (r=0.04, $P = 0.03$), although the magnitude of the correlation was minimal, indicating limited clinical relevance. This weak association may reflect technical variability in annular velocity measurements or the influence of regional motion abnormalities that can affect TDI values independently of global longitudinal function.

The correlation between MAPSE and HbA1c (r=-0.018, $P = 0.02$) was statistically significant, but extremely weak. This suggests that while poor glycaemic control is associated with myocardial dysfunction, MAPSE may be influenced by multiple overlapping pathophysiological mechanisms, including microangiopathy, oxidative stress, and myocardial fibrosis, rather than glycaemia alone.[1]

No significant correlation was observed between MAPSE and disease duration, implying that myocardial changes may occur early in the course of diabetes, potentially independent of clinically apparent disease duration.

The present findings are consistent with prior reports by Ernande and Derumeaux[1] and Mondillo et al.,[2] which emphasized that GLS and MAPSE both detect early myocardial dysfunction in people with diabetes before a decline in ejection fraction. Unlike previous studies, our analysis highlights the relative simplicity and reproducibility of MAPSE measurement, which can be particularly valuable in resource-limited clinical environments where STE software may not be available. This reinforces MAPSE as a feasible, low-cost tool for initial screening of diabetic cardiomyopathy.

These results confirm that diabetic patients can exhibit subclinical LVSD despite preserved LVEF. A MAPSE value <1.2 cm, supported by prior literature,[2] identified this impairment with reasonable sensitivity. Given its simplicity, MAPSE can serve as an early screening tool to identify patients who may benefit from closer echocardiographic surveillance or from lifestyle and

pharmacologic optimization.[3] Although the correlations with metabolic control were weak, the overall trend underscores that diabetic cardiomyopathy is multifactorial, involving metabolic, structural, and microvascular components rather than glycaemia alone.[1]

### Study Limitations

Its cross-sectional design precludes causal inferences about relationships among diabetes duration, glycaemic control, and LV function. The sample size was moderate and determined by feasibility rather than by a formal power calculation, which potentially limited the ability to detect smaller effects. Subclinical coronary artery disease could not be entirely excluded without angiography, although clinical screening and ECG were used to minimize this risk. No multivariate regression analysis was performed due to sample size constraints; hence, confounding by variables such as BMI and blood pressure cannot be fully excluded. Finally, this was a single-center study, and the results may not be generalizable to all diabetic populations. Despite these limitations, the study provides robust evidence that MAPSE is an effective parameter for early detection of LVSD.

## CONCLUSION

This study demonstrates that patients with T2DM exhibit a significant reduction in MAPSE, GLS, and tissue Doppler S' velocities compared to healthy controls, despite a preserved ejection fraction. A MAPSE value below 1.2 cm was indicative of subclinical LVSD and correlated strongly with GLS and moderately with TDI S'. These findings suggest that MAPSE is a simple, reproducible, and cost-effective echocardiographic parameter that can serve as a practical alternative for the early detection of subclinical LV dysfunction, particularly in resource-limited clinical settings where advanced strain analysis may not be available. Although the correlations between MAPSE and metabolic indices (HbA1c, disease duration) were weak, the overall data underscore that myocardial dysfunction in diabetes is multifactorial, reflecting the cumulative effects of metabolic, microvascular, and structural remodelling processes.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Institutional Ethics Committee of Jawaharlal Nehru Medical College (references no: MDC/JNMCIEC/300, date: 13.05.2024).

**Informed Consent:** Each patient provided written informed consent before the start of the study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.B., K.C., Concept: V.H., Design: M.B., S.P., Data Collection or Processing: S.P., K.C., Analysis or Interpretation: V.H., Literature Search: M.B., S.P., Writing: V.H., M.B., S.P., K.C.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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# Diagnostic Accuracy of a Smartphone-based 12-lead ECG for Detection of Common Bradycardias, Tachycardias, and Ectopic Arrhythmias

**Chandra Mohan[1], Kunal Gururani[1], Anurag Rawat[1], Yogendra Singh[2], Nitin Chandola[3], Deeksha Agarwal[3], Sengar Yashwardhan Pratap Singh[3], Milan Prabhakar[3]**

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## Abstract

**Background and Aim:** Electrocardiography (ECG) remains the cornerstone for diagnosing cardiac arrhythmias. The purpose of this study was to assess the diagnostic performance of a smartphone-based ECG device (Spandan Ultra 12-lead) compared with a standard 12-lead ECG device for detecting common cardiac arrhythmias (bradycardias, tachycardias, and ectopic arrhythmias), with a cardiologist as the reference standard.

**Materials and Methods:** The study was a prospective, cross-sectional, single-blind, observational, comparative diagnostic accuracy study conducted in 321 patients aged ≥20 years who exhibited signs of arrhythmias. For analysis of diagnostic performance, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), accuracy, F-score, positive and negative likelihood ratios [(positive likelihood ratio (PLR) and negative likelihood ratio (NLR)], Matthews correlation coefficient (MCC), and the Farrington-Manning score were used to provide a comprehensive evaluation.

**Results:** The mean age was 51.95±14.51 years; 50.47% were male. The smartphone-based ECG demonstrated higher sensitivity (86.54% vs. 77.80%), specificity (93.68% vs. 91.38%), PPV (72.58% vs. 64.61%), NPV (97.29% vs. 95.31%), accuracy (92.52% vs. 89.09%), F1 score (0.79 vs. 0.70), PLR (13.7 vs. 9.05), MCC (0.75 vs. 0.64), area under the curve (0.851 vs. 0.846), and lower NLR (0.14 vs. 0.24) compared with the standard 12-lead ECG. The Farrington-Manning non-inferiority test demonstrates that the smartphone-based ECG was non-inferior to the standard 12-lead ECG on all validation parameters.

**Conclusion:** The Spandan Ultra 12-lead smartphone-based ECG is a reliable diagnostic tool for detecting common bradycardias, tachycardias, and ectopic arrhythmias. Its simultaneous multichannel recording enables rapid and accurate rhythm assessment, demonstrating comparable diagnostic performance to that of the standard 12-lead ECG and serving as a complementary diagnostic tool for detecting common arrhythmias.

**Keywords:** Cardiac arrhythmias, 12-lead ECG, portable ECG, medical device

## INTRODUCTION

The World Health Organization states that cardiovascular diseases, particularly cardiac arrhythmias, are the leading cause of death worldwide because they are often asymptomatic and go undetected. Early and accurate diagnosis is essential to address this worldwide burden.[1] An arrhythmia is any abnormality in the rhythm or rate of a person's heartbeat. An irregular heartbeat (arrhythmia) can result from electrical

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impulses that are too slow (less than 60 beats per minute), too fast (more than 100 beats per minute), or erratic. An increased, decreased, or irregular heartbeat results from a defect in the electrical impulses that control the heart's rhythm.[2]

The sinoatrial node generates electrical impulses that control the rhythm of the heart. When electrical impulses do not function properly, an arrhythmia can develop. This malfunction can result in several life-threatening conditions, including stroke, heart failure, and death.[3] The most commonly seen types are bradycardia, atrial fibrillation (AF), ventricular tachycardia (VT), ventricular fibrillation (VF), supraventricular tachycardia (SVT), premature atrial contractions (PAC), and premature ventricular contractions (PVC). AF affected more than 33 million individuals globally in 2019,[4,5] while AF/atrial flutter remained the most common arrhythmia globally in 2021, with an estimated prevalence of 52.55 million.[6]

Electrocardiogram (ECG) signals are typically used to identify cardiac arrhythmias. Early diagnosis and treatment of cardiovascular problems depend mainly on ECG-detected cardiac arrhythmias. ECG is a non-invasive diagnostic technique that records the electrical activity of the heart using electrodes placed on the chest, upper, and lower limbs.[2] The gold standard for clinical cardiac examination remains the 12-lead ECG, which is recorded with 10 electrodes and is used in nearly all clinical settings.[7] Due to their large size and limited portability, standard 12-lead ECG devices are practically limited in their use in both local and remote settings.

However, in recent years, smartphone ECG devices have become more accessible, transforming the sector by providing portable, affordable, and convenient means for real-time arrhythmia detection. A smartphone-enabled ECG device helps identify different cardiac rhythm disturbances.[8] Many researchers have focused on the use of portable ECG devices in various scenarios for early diagnosis and effective treatment of cardiac issues.[9,10] Older equipment consisted of single-lead or limited-lead systems, which compromised diagnostic performance for detecting complex arrhythmias and ischemic changes, despite these improvements. Although some 12-lead ECG smartphone devices have been developed, data directly comparing their diagnostic performance with conventional 12-lead ECGs are limited.

One of these inventions is the Spandan Ultra 12-lead ECG (Sunfox Technologies, Dehradun) (Figure 1). Sunfox Technologies has designed a series of ECG devices, primarily point-of-care, which have proven effective in identifying various arrhythmias.[11-14] Previous models functioned as sequential ECG devices, recording one lead after another. Conversely, the Spandan Ultra 12-lead ECG is designed for diagnostic use, offering portability without compromising diagnostic quality. It is a multichannel instrument that can record and display all 12 leads simultaneously, enabling the capture of the entire electrical activity of the heart in 10 seconds. The present study was conducted to assess the diagnostic accuracy of the Spandan Ultra 12-lead ECG compared with the standard 12-lead ECG in diagnosing cardiac arrhythmias.

## METHODS

### Study Design and Setting

This prospective, cross-sectional, single-blinded observational comparative diagnostic accuracy study assessed the accuracy of smartphone-based ECGs in diagnosing various cardiac arrhythmias by comparing blinded interpretations of smartphone ECG tracings with diagnoses from standard ECGs. In this study, we describe the overall accuracy, sensitivity, and specificity of interpretations of cardiac rhythms recorded using the smartphone-based ECG. The research was conducted between June 6 and July 31, 2024, in the ECG room of a local hospital in Dehradun, Uttarakhand, India.

### Participants and Ethical Considerations

The study included 405 participants referred by a cardiologist for an ECG due to symptoms of arrhythmias. After applying inclusion and exclusion criteria, ECG test reports from 321 participants, obtained from both ECG devices, were deemed eligible for analysis. The sample size was determined using the Yamane formula. The formula is expressed as $n=N/(1+Ne^2)$.


**Figure 1.** Integration of Spandan Ultra 12-lead ECG device with smartphone for data acquisition

*ECG: Electrocardiogram*

Participants aged ≥20 years who presented with complaints suggestive of arrhythmias and who were able to provide informed consent were included in the study. Reports with poor ECG tracings (because of artifacts or baseline wandering), participants with loose skin or dense chest hair, interference from deep breathing, individuals in critical condition, patients experiencing hemodynamic instability, pregnant women, and participants who refused were not included in the study.

The study was approved by the Institutional Ethics Committee of Swami Rama Himalayan University (approval number: SRHU/HIMS/E-1/2024/06, date: 06.02.2024) and registered with ClinicalTrials Registry-India (CTRI no: CTRI/2024/07/070766) prior to initiation; it was conducted in accordance with the Declaration of Helsinki. Consent was given by the study participants both verbally and in writing after they received detailed information regarding the methods and procedures, possible risks, and benefits of participating in the study prior to their enrollment. The consent form stated that participants could withdraw from the study at any time without penalty.

### Data Collection and Procedure

Firstly, informed consent was obtained from the participants, and then trained clinical trial assistants completed the case report form (CRF) for the participants, which included detailed information about the participants' demographic details and their clinical history. The CRF assisted the cardiologist in making the diagnosis. The participants underwent ECG recordings with both ECG devices. Initially, a standard 12-lead ECG device was used, followed by a smartphone-based ECG device; both devices had automated interpretation capabilities. Arrhythmias were diagnosed by an experienced cardiologist by interpreting ECG reports, and the findings of the two ECG devices were compared. The reference standard used in this investigation to interpret cardiac arrhythmias from both devices was an experienced cardiologist. To minimize bias and enhance the reliability and accuracy of the study, the cardiologist was fully blinded to the computerized interpretations from both devices and conducted the assessments at least one week apart to ensure independence between readings.

To mitigate potential bias, the time interval between the standard 12-lead ECG and the smartphone-based ECG recordings was 2-3 minutes for most participants, and the maximum interval was less than 15 minutes. This time difference is due to the time required to remove the electrodes of a standard 12-lead ECG and to place the electrodes of the smartphone-based ECG.

### Statistical Analysis

Clinical and demographic features were summarized using descriptive statistics; categorical variables were presented as frequencies and percentages. To assess the diagnostic performance of the smartphone-based ECG device, confusion matrix elements such as true negatives (TN), false negatives (FN), false positives (FP), and true positives (TP) were determined. Overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used as key performance indicators. In addition, higher-level diagnostic statistics such as the F-score, positive and negative likelihood ratios (PLR and NLR), the Matthews correlation coefficient (MCC), and the Farrington-Manning score were applied to provide a comprehensive evaluation. For receiver operating characteristic (ROC) curve analysis, the DeLong test was used to compare smartphone-based and standard ECGs. Interpretation by a cardiologist based on the standard 12-lead ECG report was used as the reference standard. All analyses were performed with Microsoft Excel.

### Instructions for Operating the Spandan Ultra 12-lead ECG Device Recording System

To record an ECG using the Spandan Ultra 12-lead ECG device, an internet connection is not required. Ensure that the device is connected to the smartphone with a micro-USB cable. The electrodes had to be placed carefully to acquire accurate signals. The Goldberg lead placement procedure was followed, with right arm and left arm electrodes positioned on the right and left wrists or forearms, and right leg/neutral and left leg/foot electrodes positioned on the right and left legs, respectively. The chest electrodes were placed as follows: C1 (red) at the fourth intercostal space at the right sternal border, C2 (yellow) at the same level at the left sternal border, C3 (green) midway between C2 and C4, C4 (brown) at the fifth intercostal space at the midclavicular line, C5 (black) at the fifth intercostal space midway between C4 and C6, and C6 (purple) at the fifth intercostal space at the midaxillary line.

A description of the algorithm utilized by the smartphone-based ECG device for detecting arrhythmias is presented in Figure 2.

## RESULTS

The study initially enrolled 405 participants who presented with symptoms of arrhythmia. After applying the inclusion and exclusion criteria, ECGs from 321 participants were evaluated. All participants underwent testing with both ECG devices, and the reports from both ECGs were interpreted by a cardiologist. The Standards for Reporting Diagnostic Accuracy Studies checklist was followed in conducting the study (Figure 3). The mean age was 51.95±14.51 years; 162 patients (50.47%) were male and 159 patients (49.53%) were female. Of all participants, 50 presented with abnormal ECGs according to the cardiologist's interpretation of the smartphone-based 12-lead ECG; of these, first-degree atrioventricular (AV) block was present in 5 (10%)

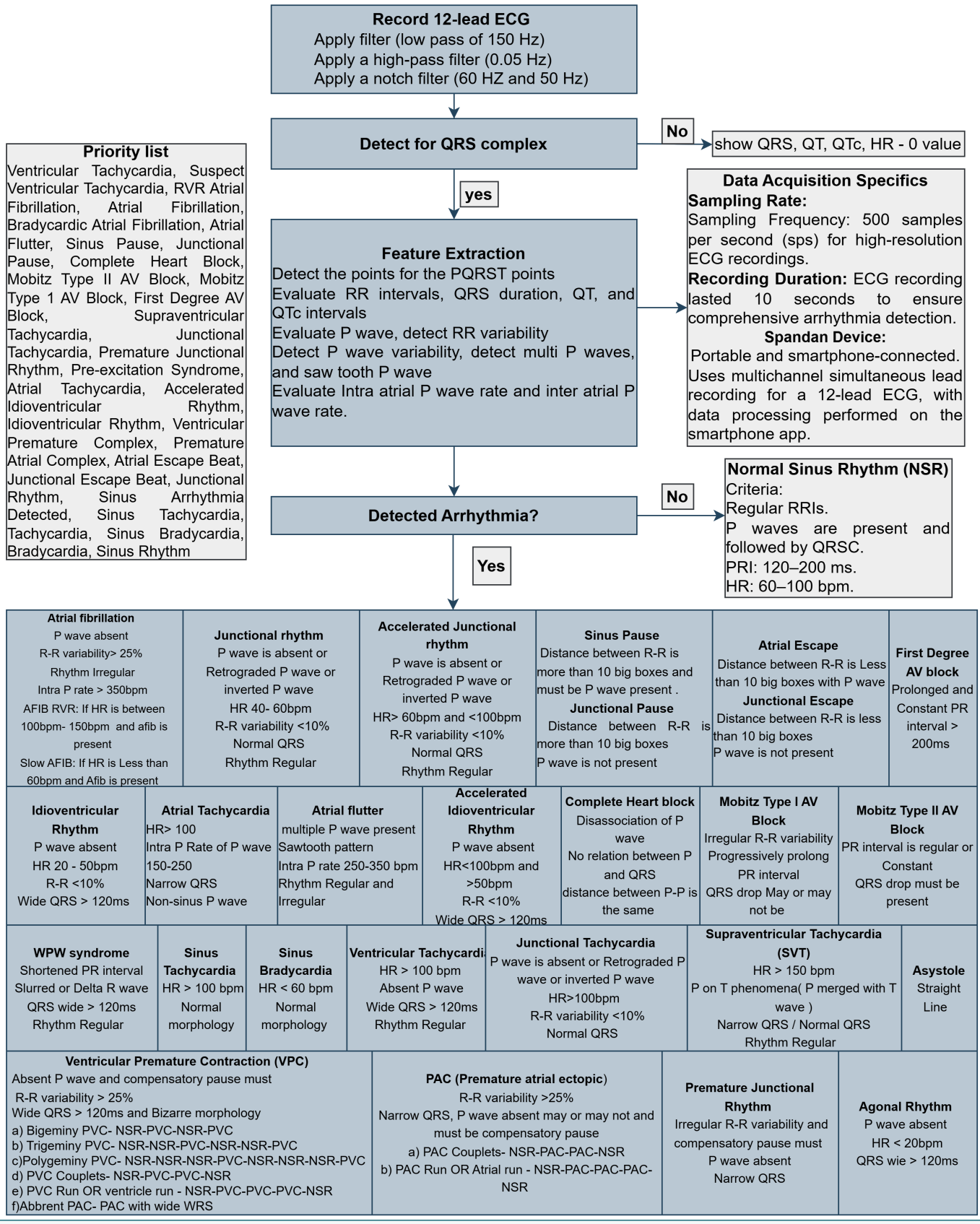


**Figure 2.** Spandan Ultra-12-lead ECG device algorithm for arrhythmia identification

*ECG: Electrocardiogram, HR: Heart rate, AV: Atrioventricular, PAC: Premature atrial contraction, NSR: Normal sinus rhythm*

cases, sinus bradycardia in 20 (40%) cases, sinus tachycardia in 14 (28%) cases, PAC in 6 (12%) cases, and PVC in 5 (10%) cases (Table 1). Among all participants, 38 patients (11.52%) were diabetic and were referred for an ECG test, of whom 19 were male and 19 were female.

The confusion matrix of ECG interpretation for both smartphone-based and standard 12-lead ECGs is summarized in Table 2. A smartphone-based ECG performed better than a standard 12-lead ECG in detecting TP cases (45 vs. 42) and true negative cases (252 vs. 244). The smartphone-based device also exhibited fewer false-negative cases (7 vs. 12) and false-positive cases (17 vs. 23) compared with the standard 12-lead ECG. For instance, a case of first-degree AV block was initially detected using both a standard 12-lead ECG and a smartphone-based ECG. Both interpretations were confirmed by the cardiologist, and it was therefore regarded as a true-positive case (Figure 4).

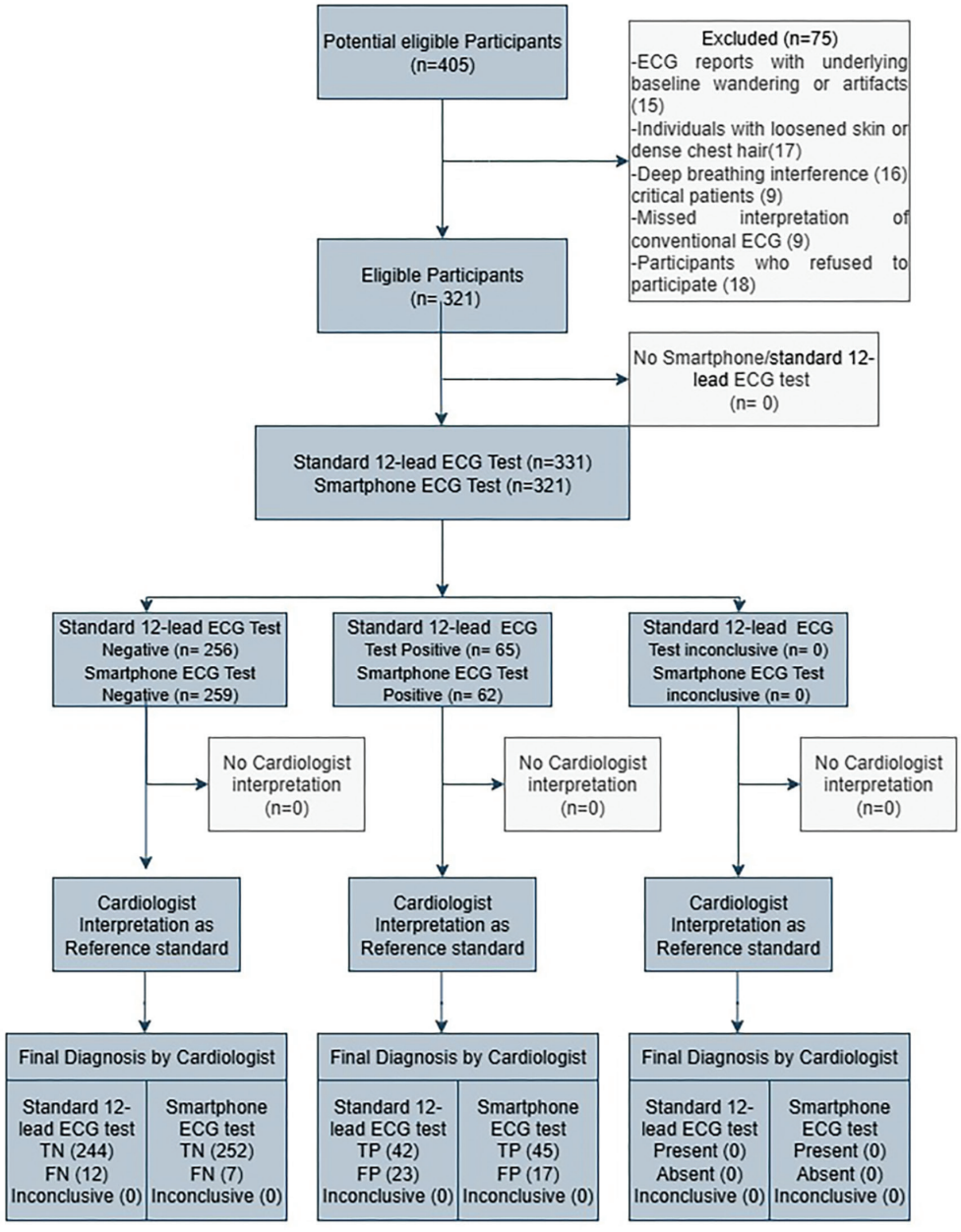


**Figure 3.** Standards for Reporting Diagnostic Accuracy Studies compliant flow diagram showing the number of patients assessed, excluded, and included in the validation of smartphone-based ECG compared with standard 12-lead ECG, using cardiologist interpretation as the reference standard

*ECG: Electrocardiography, TN: True negatives, FN: False negatives, FP: False positives*

The sensitivity, specificity, PPV, NPV, accuracy, precision, F1 score, MCC, PLR, and NLR of the smartphone-based ECG and the standard 12-lead ECG, along with their ECG interpretations compared with cardiologist diagnoses, are presented in Table 3. Compared to the standard 12-lead ECG, the smartphone-based ECG demonstrated higher specificity (93.68% vs. 91.38%), sensitivity (86.54% vs. 77.80%), PPV (72.58% vs. 64.61%), NPV (97.29% vs. 95.31%), and overall accuracy (92.52% vs. 89.09%). The smartphone-based ECG also demonstrated a higher F-score (0.79 vs. 0.70), a higher PLR (13.7 vs. 9.05), and a higher MCC (0.75 vs. 0.64), as well as a lower NLR (0.14 vs. 0.24). A comparison of the two ECGs reveals that the smartphone-based ECG has comparable diagnostic performance and may be a suitable alternative to the standard 12-lead ECG. These results underscore the smartphone-based ECG's strong predictive capability and reliability in distinguishing cases with and without disease.

The validation parameters for the smartphone-based ECG and the standard 12-lead ECG are shown in Table 4. The confidence intervals for a smartphone-based ECG indicated higher ranges of sensitivity (0.747-0.933 vs. 0.65-0.88), specificity (0.902-0.962 vs. 0.87-0.95), and accuracy (0.891-0.949 vs. 0.85-0.93) compared with the standard 12-lead ECG.

Table 5 summarizes the Farrington-Manning score non-inferiority test for sensitivity, specificity, and accuracy. The smartphone-based ECG has approximately 8.8% higher sensitivity and is statistically significant ($P$ = 0.007). It has approximately 2.3% higher specificity and is statistically

**Table 1. Participants with abnormal cases (50)**

| Abnormality | Number of abnormal cases | Percentage |
|---|---|---|
| 1st degree AV block | 5 | 10 |
| Sinus bradycardia | 20 | 40 |
| Sinus tachycardia | 14 | 28 |
| PAC | 6 | 12 |
| PVC | 5 | 10 |

AV: Atrioventricular, PAC: Premature atrial contractions, PVC: Premature ventricular contractions

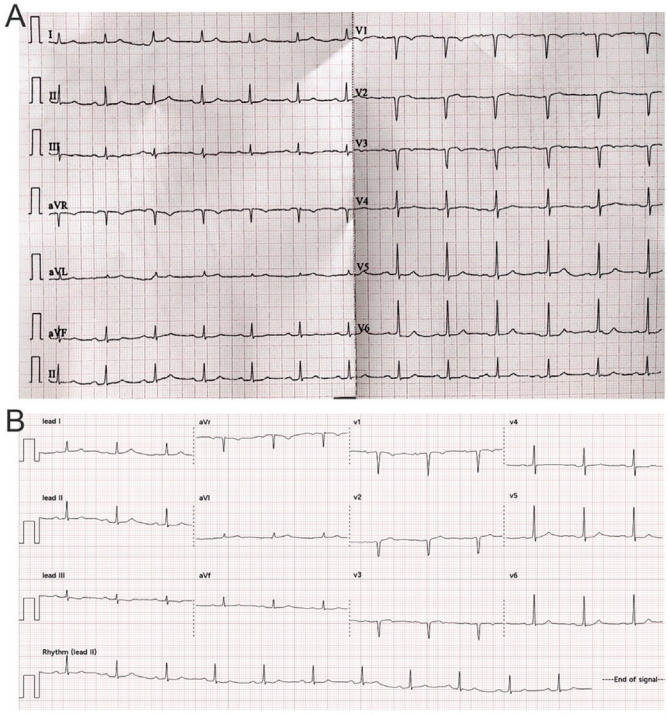


**Figure 4.** Example of a true positive case. (A) 1st degree AV block detected by the standard 12-lead ECG. (B) 1st degree AV block detected by the smartphone-based 12-lead ECG and confirmed by the cardiologist

*AV: Atrioventricular, ECG: Electrocardiography*

**Table 2. ECG interpretation confusion matrix of both ECG devices**

| Parameter | Smartphone-based ECG | Standard 12-lead ECG |
|---|---|---|
| True positive | 45 | 42 |
| True negative | 252 | 244 |
| False positive | 17 | 23 |
| False negative | 7 | 12 |

ECG: Electrocardiogram

**Table 3. Diagnostic performance of both the ECG devices**

| Validation parameter | Smartphone-based ECG | Standard 12-lead ECG |
|---|---|---|
| **Specificity** | 93.68% | 91.38% |
| **Sensitivity** | 86.54% | 77.80% |
| **PPV** | 72.58% | 64.61% |
| **NPV** | 97.29% | 95.31% |
| **Accuracy** | 92.52% | 89.09% |
| **Precision** | 72.58% | 64.61% |
| **F1 score** | 0.79 | 0.706 |
| **MCC** | 0.75 | 0.642 |
| **PLR** | 13.7 | 9.05 |
| **NLR** | 0.14 | 0.24 |

ECG: Electrocardiogram, PPV: Positive predictive value, NPV: Negative predictive value, MCC: Matthew's correlation coefficient, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio

**Table 4. Validation parameters for both the ECG devices**

| Validation parameter | Smartphone-based ECG | Standard 12-lead ECG |
|---|---|---|
| **95% CI of sensitivity (L-U)** | 0.747-0.933 | 0.65-0.88 |
| **95% CI of specificity (L-U)** | 0.902-0.962 | 0.87-0.95 |
| **95% CI of accuracy (L-U)** | 0.891-0.949 | 0.85-0.93 |

ECG: Electrocardiogram, CI: Confidence interval, L: Lower bound, U: Upper bound

| Table 5. Farrington-Manning (score) non-inferiority test | | | |
|---|---|---|---|
| **Metric** | **Sensitivity** | **Specificity** | **Accuracy** |
| **Difference** | 0.088 | 0.023 | 0.034 |
| **Variance under H0** | 0.006 | 0.001 | 0.001 |
| **T-tests** | 2.434 | 4.772 | 5.351 |
| **One-sided *P*-value = 1-Φ(z)** | 0.007 | <0.001 | <0.001 |

significant ($P < 0.001$). Similarly, it has approximately 3.4% higher accuracy and is highly statistically significant ($P < 0.001$).

The ROC curves for the comparisons between standard 12-lead ECG and cardiologist interpretation, and between smartphone-based ECG and cardiologist interpretation are shown in Figure 5. Cardiologist interpretation of the standard 12-lead ECG report was considered the reference standard for ROC analysis; the area under the curve (AUC) was 0.846 for the gold-standard ECG and 0.851 for the smartphone-based ECG. No statistically significant difference was observed between the two AUCs ($P = 0.937$), indicating comparable diagnostic performance.

## DISCUSSION

The present study evaluated the diagnostic performance of a smartphone-based ECG compared with the standard 12-lead ECG for detecting cardiac arrhythmias (common bradycardias, tachycardias, and ectopic arrhythmias). The study detected different types of arrhythmias, such as first-degree AV block, sinus tachycardia and sinus bradycardia, PAC, and PVC. The

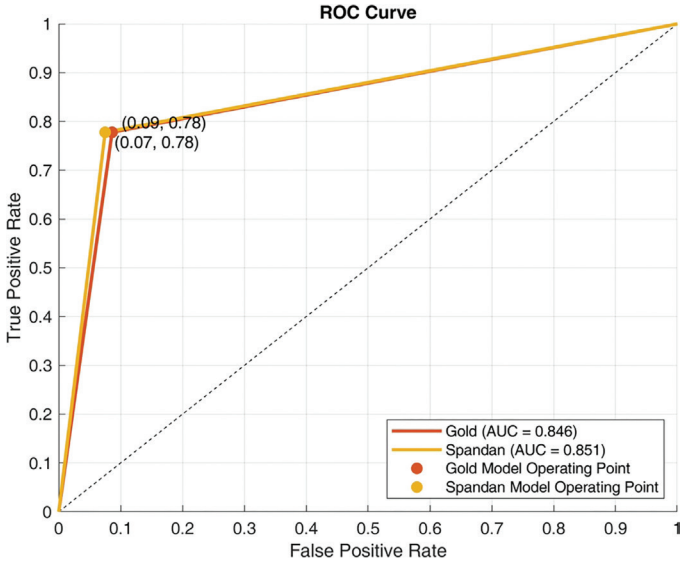


**Figure 5.** ROC curve comparison for both the ECG devices

*ECG: Electrocardiography, ROC: Receiver operating characteristic, AUC: Area under the curve*

mean age of participants in this study was 51.95±14.51 years, and the proportion of males was 50.47%, whereas the mean age of patients diagnosed with general arrhythmia in the study by Kwon et al.[15] was 55.1±12.8 years, and the proportion of males was 48.3%. In the study by Niu et al.[16] the mean age of participants was 63.77±13.90 years; in the study by Turnbull et al.[17] patients with arrhythmias had a mean age of 58±19 years.

The results of this study are consistent with previous reports on portable and mobile ECG devices, which have also shown improved accuracy compared with standard 12-lead, hospital-based ECG systems. Access to point-of-care healthcare devices is improved by handheld technologies, which are particularly advantageous when prompt clinical decision-making and time efficiency are required.[18] In the current study, the smartphone-based ECG device demonstrated increased sensitivity, which means it has performed better in detecting true abnormal cases and in minimizing missed arrhythmia cases compared with the standard 12-lead ECG. Likewise, the increased TN rate and the decreased FP rate indicate greater specificity. As in our research, Shahid et al.[19] had reported the Apple Watch's pooled sensitivity of 94.8% and specificity of 95% for detecting AF. In a trial by Himmelreich et al.[20] the 1L-ECG (AliveCor Kardia Mobile), determined by cardiologists, was 90.9% sensitive and 93.5% specific for any rhythm abnormality, figures very close to those found in our trial. In the study by Desteghe et al.[21] the sensitivity and specificity of MyDiagnostick in the cardiology ward were 81.8% and 94.2%, respectively, and those of AliveCor were 54.5% and 97.5%, respectively. In the geriatrics ward, MyDiagnostick's sensitivity and specificity were 89.5% and 95.7%, respectively, whereas AliveCor's were 78.9% and 97.9%.[21] The sensitivity of both devices was lower than that observed in our study, indicating they can detect fewer TP cases. Comparable to our study's accuracy of 92.52%, Turnbull et al.[17] in their study of 49 patients, recorded 843 cardiac rhythms; single-lead ECG produced a mean overall accuracy of 92%. Notably, Turnbull et al.[17] achieved greater accuracy for overall various arrhythmia types, e.g., AF accuracy was 91%, SVT 89%, VT 91%, VF 98%, asystole 100%, and PVC 91%.

In the present study, MCC was 0.75 and the F-score was 0.79, indicating an improved balance between recall and precision and greater overall classification reliability when utilizing a smartphone-based ECG device for arrhythmia detection. They were consistent with the findings reported in a recent AI-powered ECG model published by Tian et al.[22] For example, the knowledge-augmented ECG diagnosis foundation model leveraged large language models to incorporate domain-specific ECG signal knowledge and achieved an MCC of 0.72 and an F1 score of 0.776, which is slightly lower than in our research.[22] Importantly, the Farrington-Manning non-inferiority analysis confirmed that the smartphone-based ECG was non-inferior to standard 12-lead ECG across all validation

parameters, underscoring the reliability of the smartphone-based ECG for arrhythmia detection. Furthermore, the area under the ROC curve for the smartphone-based ECG was 0.851, indicating excellent diagnostic performance.

The clinical significance of this study lies in demonstrating that smartphone-based ECGs can achieve diagnostic accuracy comparable to standard 12-lead ECGs for diagnosing common cardiac arrhythmias, including bradycardias, tachycardias, and ectopic arrhythmias, with high sensitivity, specificity, accuracy, and overall diagnostic agreement. Compared with other single-lead or sequential multi-lead smartphone technologies, "Spandan Ultra 12-lead ECG" is a true 12-lead multichannel system capable of simultaneous recording within 10 seconds. This simultaneous multichannel recording preserves the spatial and temporal fidelity of electrical activity across all vectors with no beat-to-beat differences, meaning that each lead records identical cardiac cycles. This feature is absent in sequential 12-lead ECG recordings, which can be affected by cardiac rhythm and conduction changes. This simultaneous recording facilitates precise analysis of rhythm regularity, AV and intraventricular conduction, axis deviation, and ectopic activity. These technical advantages and performance are probably reflected in their high ROC curves, higher predictive values, and lower probability of missed cases, thus preventing diagnostic delays and assisting in clinical decisions, especially in cases of subtle and intermittent arrhythmias. In addition to its diagnostic and clinical benefits, this diagnostic aid has several technical advantages that increase its clinical utility. Its portable, water-resistant, and dust-resistant design with an IP55-rated construction enhances durability and enables use in any setting. Users no longer require conventional ECG paper to obtain multiple leads; recordings can be stored digitally without producing paper. If required, they can be printed on A4 paper, and the device is tolerant of variations in humidity and temperature. The addition of a unique hospital identification enables the direct linkage of recordings to patient records and the secure sharing of reports. While these findings establish diagnostic accuracy as a critical first step, the true clinical value lies in rapid point-of-care rhythm assessment. High-quality, diagnostic-grade tracings can be obtained within seconds, making the device suitable for time-sensitive settings such as emergency departments, outpatient clinics, and resource-limited or rural facilities. The device can help streamline care pathways, such as the acute coronary syndrome (ACS) pathway, by enabling immediate ECG acquisition and interpretation. This is because early detection of arrhythmias or ischemic changes expedites triage, guides urgent management, and reduces time to reperfusion therapy. Being lightweight, easy to operate, and not requiring internet connectivity, the Spandan Ultra is a promising device to increase access to accurate and immediate cardiac evaluation and to optimize the evaluation and management of arrhythmias.

## Study Limitations

This study has a few limitations. Because the sample was small and drawn from a single center, these findings may not generalize to larger populations. Secondly, only a few arrhythmias were studied; these included first-degree AV block (10%), sinus bradycardia (40%), sinus tachycardia (28%), PACs (12%), and PVCs (10%). Although these are common rhythm disturbances in day-to-day practice, rarer, more complex rhythms such as atrial flutter, SVT, VT, and higher-degree AV blocks were not included, thereby limiting the applicability of the findings across the full spectrum of cardiac arrhythmias. The limited intensity of the arrhythmia pattern may be associated with the pilot nature of the current study, because it was intended to test its feasibility and initial diagnostic capability. The study is monitored by an experienced cardiologist; thus, the quality of the ECGs recorded may differ when the device is operated by untrained users, depending on patient compliance, lead placement accuracy, and comorbidities. A significant limitation of this study is that the reference standard depended on a single experienced cardiologist for ECG interpretation. Although the cardiologist was entirely blinded throughout the investigation, and assessments were conducted at least one week apart to avoid any influence, the use of a single observer does not account for inter-observer variability, especially given the complexity of ECG signals. Consequently, this may limit the generalizability of the findings, particularly in cases of subtle or complex arrhythmias where interpretations may vary between experts.

Future studies with larger sample sizes and multicenter designs are required to further validate its diagnostic accuracy across different patient groups and a broader range of arrhythmias. Validation using well-established public ECG databases such as the Massachusetts Institute of Technology-Beth Israel Hospital (MIT-BIH) arrhythmia database, Physikalisch-Technische Bundesanstalt diagnostic ECG database, St. Petersburg Institute of Cardiological Technics database, and MIT-BIH ST-segment and T wave changes database will also be conducted to enable comprehensive testing of more complex or less common rhythm disorders. Such studies will help determine whether speed, portability, and accessibility translate into improved clinical outcomes, such as earlier diagnosis, reduced time to treatment, optimized management of arrhythmias, and improved patient-centered outcomes. More importantly, triage within ACS pathways may be faster using a 12-lead ECG acquired from a portable device at initial presentation, thereby enabling early detection of arrhythmias, ischemic changes, or occlusive myocardial infarction, prompt guideline-initiated treatment, and improved patient management. Moreover, the inclusion of multiple independent cardiologists in future analyses may further strengthen diagnostic validation, reduce inter-observer variability, and enhance the robustness of study findings.

## CONCLUSION

This study demonstrates that the Spandan Ultra 12-lead smartphone-based ECG has comparable diagnostic accuracy to the standard 12-lead ECG for the specific arrhythmias evaluated. The device reliably detected common, benign, non-life-threatening arrhythmias, including bradycardias, tachycardias, and ectopic rhythms. These findings support its potential role as a complementary tool for common arrhythmia screening and diagnostic assessment, rather than as a universal replacement for standard 12-lead ECG systems. Its capability to record all 12 leads at once through a multichannel system within seconds offers rapid, high-quality recordings, minimizing the risk of missed or delayed diagnoses and thereby enabling timely, precise clinical evaluation. The device also demonstrated high predictive reliability, low false-negative and false-positive rates, and strong ROC performance, supporting its use in clinical applications for precise arrhythmia detection. Unlike most smartphone-based ECG devices, which are limited to single-lead or sequential multi-lead recordings, Spandan Ultra provides diagnostic-grade data comparable to a standard 12-lead ECG, and hence it is particularly beneficial for comprehensive cardiac assessment. These results highlight its utility as a reliable and effective tool for physicians and cardiologists and a viable alternative to routine ECG for diagnosis when accuracy, speed, and reliability are essential to optimal patient care.

### Ethics

**Ethics Committee Approval:** The study was approved by the Institutional Ethics Committee of Swami Rama Himalayan University (approval number: SRHU/HIMS/E-1/2024/06, date: 06.02.2024) and registered with Clinical Trials Registry-India (CTRI no: CTRI/2024/07/070766).

**Informed Consent:** Both written and verbal informed consent were obtained from all the participants.

### Acknowledgments

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### Footnotes

### Authorship Contributions

Concept: C.M., K.G., A.R., Y.S., Design: C.M., K.G., A.R., Y.S., Data Collection or Processing: K.G., N.C., D.A., Analysis or Interpretation: A.R., N.C., D.A., Literature Search: N.C., S.Y.P.S., M.P., Writing: S.Y.P.S., M.P.

**Conflict of Interest:** N.C., D.A., S.Y.P.S. and M.P. are currently employed by Sunfox Technologies. None of the other authors has any conflict of interest.

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RESEARCH ARTICLE

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# The Role of Asymmetric Dimethylarginine in Early Detection of Coronary Artery Disease in Suspected Cases Using Machine Learning

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## Abstract

**Background and Aim:** Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide, underscoring the need for early detection of CAD before myocardial infarction (MI) develops.

**Materials and Methods:** This cross-sectional study included 471 Iraqi participants (126 controls, 126 confirmed CAD with MI and 149 suspected CAD without MI) assessed at cardiology departments in Baghdad. Biochemical parameters, including asymmetric dimethylarginine (ADMA), lipid profile, C-reactive protein, and cardiac troponin I, were measured. One-way analysis of variance showed significant differences in all parameters among confirmed CAD patients.

**Results:** Four machine learning models—logistic regression, support vector machine, random forest, and XGBoost—were applied to evaluate the detection capacity of ADMA under two clinical classes: C1) all groups (A, B, and C); and C2) A and C only. In C1, random forest achieved the highest overall area under the curve (AUC): (0.803), while logistic regression and support vector machine showed overfitting driven by MI. In C2, random forest (AUC: 0.822) and XGBoost (AUC: 0.781) maintained clinically relevant discriminatory power. Shapley Additive exPlanations analysis confirmed ADMA as the primary marker in early CAD. This study demonstrates that ADMA, combined with machine learning, enhances the detection of subclinical CAD and provides a more reliable risk-stratification tool prior to progression to acute coronary events.

**Conclusion:** DMA showed significant differences across groups. Random forest retained its diagnostic ability in suspected cases, supporting early detection. ADMA indicated potential for early detection of CAD in the suspected group. Random forest and XGBoost demonstrate the strongest diagnostic performance for clinical decision-making.

**Keywords:** Coronary artery disease, asymmetric dimethylarginine, machine learning, early detection

## INTRODUCTION

Coronary artery disease (CAD), also known as ischemic heart disease (IHD), continues to cause substantial morbidity and mortality worldwide. In 2023, cardiovascular diseases (CVD) claimed an estimated 19.2 million lives, making them the leading cause of death worldwide.[1] Disability-adjusted life years (DALYs) for the number of individuals suffering from CVD reached 437 million in the same year, indicating the growing global burden.[2] According to the Institute for Health Metrics and Evaluation, age-standardized DALY rates for IHD remain among the greatest globally.[3] Projections suggest that by 2050,

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the population with IHD may increase to more than double the 2021 level, and associated deaths and DALYs could increase by 80% and 62%, respectively.[4] In the Middle East and North Africa data from 2021 reported particularly high rates of IHD, both in distribution and mortality, compared to many other regions.[5] CAD begins when atherosclerotic plaque develops in the coronary arteries, impeding blood flow and causing myocardial infarction (MI). The non-modifiable risk factors included age and genetics, whereas modifiable risk factors included hypertension, diabetes, smoking, and dyslipidemia. Early detection rises in IHD concerns improved risk and effective preventive strategies are more critical.[6] CAD also imposes a marked economic burden on healthcare systems worldwide. The expenditure includes direct costs from hospitalization, medication, and surgical procedures as well as indirect costs from productivity loss, disability, and premature mortality. Low and middle-income regions including many developed countries aspect additional challenges due to rapidly growing populations, changing lifestyles, and limited resources assigned for disease management.[7] These rising numbers of morbidity and mortality necessitate examination of how CAD develops at the biological and biochemical levels and how early identification can prevent progression to severe clinical conditions.

CAD is a multifactorial disease that begins with endothelial injury, inflammation, and the gradual accumulation of lipids, particularly low-density lipoprotein (LDL) cholesterol, which migrates beneath the endothelial cells of the coronary arteries, allowing oxidation and leading to macrophage recruitment and foam cell formation. As the plaque develops as a result of foam accumulation and deposition causing arterial narrowing over time which limits myocardial oxygen supply leading to stenosis and thereby ischemia and clinical manifestations such as angina or MI.[8] The role of asymmetric dimethylarginine (ADMA) is to reduce nitric oxide production by inhibiting nitric oxide synthase from L-arginine. This decline in nitric oxide concentration leads to endothelial dysfunction and increases vascular stiffness and narrowing.[9] Preventive approaches are now recognized as central to reducing the growing concern about CAD. Lifestyle interventions, including diet modification, regular exercise, and weight management, are essential strategies. Lipid-lowering medications have been highly effective in reducing risk. Public health education programs play an important role in prevention.[10] Early diagnosis of CAD, regardless of advances in clinical evaluation, remains a concern because symptoms may be silent or non-specific until the disease is advanced by MI, making the management of the disease challenging. Traditional diagnostic tools, instrumentation, and lab tests such as electrocardiography, cardiac enzymes, angiography, and stress testing are commonly used.[11]

## Previous Related Works

Several investigations have emphasized the continuing importance of traditional lipid and metabolic parameters in the assessment of CAD. For example, Xia et al.[12] found that high-density lipoprotein cholesterol (HDL-C) levels were independently associated with the severity and extent of coronary atherosclerosis, indicating that even in the statin era, HDL-C remains a meaningful marker of CAD burden. Several studies have reported that the triglyceride (TG)/HDL-C[13-15] and LDL-C/HDL-C[16-18] are robustly associated with CAD. Jiang et al.[19] mention that high levels of oxidized LDL induce metabolic stress in primary human aortic endothelial cells. Another study mentioned that a high level of lipoprotein (a) increases the risk of developing CAD independently and additively in both individuals with or without a family history of CAD.[20] Nathir et al.[21] mention that a high level of apoprotein B increases the risk of CAD. Numerous studies mention alteration of the protein levels, such as desmosine,[22] matrix metalloproteinase (MMP-1 and MMP-2),[23] osteoprotegerin,[24] fibroblast growth factor-23.[25] Elevated level of ADMA, as a metabolite (methylated amino acids), inhibits nitric oxide, which leads to endothelial dysfunction.[26] Inflammatory proteins are key to the development of CAD because they drive the process of atherosclerosis, from plaque initiation to rupture. Major inflammatory proteins linked to CAD include C-reactive protein (CRP), which is a general marker of inflammation, and various cytokines like interleukin-6 (IL-6), IL-1, and tumor necrosis factor-alpha, which play specific roles in plaque development and instability.[27,28] These proteins are not just markers but also contribute to the disease progression, making them potential targets for future therapies.[29] After reviewing the relevant classical studies, it is appropriate to discuss the new statistical models that enable earlier diagnosis and disease prediction.

Machine learning (ML) has been increasingly applied to CAD detection, risk stratification, and outcome prediction, using a wide range of clinical, biochemical, and imaging parameters. In parallel, a growing number of studies have applied ML or artificial intelligence techniques to CAD detection or risk stratification. Many cross-sectional ML studies incorrectly refer to their findings as predictions, when in fact a cross-sectional diagnostic dataset can only support classification of existing disease status rather than forecasting future outcomes. Table 1 summarizes previous studies using ML to investigate biochemical parameters in patients with CVD. Previous studies reported area under the curve (AUC) values ranging from approximately 0.68 to 0.94. Commonly used features included lipid profiles, age, and blood pressure, and these features were used for disease prediction rather than diagnostic classification. However, these findings are presented in comparison to those of the present study, which focuses on disease classification and diagnosis of CAD.[30-35] To avoid this misjudgment, our study

**Table 1. Previous works focused of machine learning based on routine clinical assessments**

| No | Dataset/sample size | Parameters used | Model(s) | Performance | Ref. |
|---|---|---|---|---|---|
| 1 | 193 non-CAD, 1647 CAD who received lipid-lowering agent, and 354 who did not receive lipid-lowering agent participants (CAD vs. non-CAD) | Lipid profile (TC, TG, HDL-C, LDL-C, sdLDL), demographic, and clinical data | KNN, LR, SVM, DT, MLP, XGBoost | Best AUC: 0.94 (XGBoost); lipids were top predictors | [30] |
| 2 | 9,640 (1699 CAD and 6796), adults (Taiwan) groups were balanced for enhanced ML | Age, sex, BMI, SBP/DBP, LFT, RFT, lipid panel (TC, LDL-C, HDL-C, TG), smoking, alcohol | Gradient boosting, RF, LR | Best AUC: 0.846 (GBM); age & LDL-C major predictors | [31] |
| 3 | 3316 (Rhine-Neckar region of Germany), CVD and CAD | Lp(a), troponin T, BMI, TC, LDL-C, HDL-C, TG, statin use, age | AutoML (GBM+ensemble) | AUC: 0.910 (CVD overall), 0.841 (CAD subgroup) | [32] |
| 4 | 7260 (6955 non-CHD, 305 CHD) clinical subjects (routine screening data) of Suita- Osaka- Japan | Routine clinical variables: age, BMI, SBP, DBP, body fat, smoking, FBG, LPT, and IMT | XGBoost, RF, LR (with SHAP explainability) | Accuracy: 0.871 SHAP ranked LDL-C, TG, and BP as the strongest features | [33] |
| 5 | 1568 subjects (suspected of CAD), Healthcare, Milwaukee, USA. | Lp(a), ApoB/ApoA-I, TC/HDL-C, TG/HDL-C, LDL/HDL, carotid IMT | LR | AUC Lp(a): 0.712, (Lp(a)+cIMT other lipid ratio: 0.678-684 | [34] |
| 6 | 2,350 CAD surgical patients | Clinical comorbidities, lab data, demographics, and operation details | LR, SVM, XGBoost, CatBoost | AUC: 0.855; CatBoost best for high-risk subgroup | [35] |

CAD: Coronary artery disease, CVD: Cardiovascular diseases, CHD: Coronary heart disease, ApoB/ApoA-I: Apolipoprotein B to apolipoprotein A-I ratio, BMI: Body mass index, DBP: Diastolic blood pressure, DT: Decision tree, FBG: Fasting blood glucose, GBM: Gradient boosting machine, HDL-C: High-density lipoprotein cholesterol, IMT: Intima-media thickness, KNN: K-nearest neighbors, LDL-C: Low-density lipoprotein cholesterol, LFT: Liver function test, Lp(a): Lipoprotein (a), LR: Logistic regression, SHAP: Shapley Additive exPlanations, ML: Machine learning, MLP: Multilayer perceptron, RF: Random forest, RFT: Renal function test, SBP: Systolic blood pressure, sdLDL: Small-dense low-density lipoprotein, SVM: Support vector machine, TC: Total cholesterol, TG: Triglyceride, AUC: Area under the curve

specifically focuses on early CAD classification and diagnosis and does not claim long-term prognostic prediction.

### Research Gap

Although numerous studies have applied ML to CAD detection and risk prediction, several research gaps remain. Most studies treated CVD as a major challenge, while others focused on CAD versus non-CAD to develop ML models that distinguish between intact and healthy individuals; one exception was a study by Sun et al.,[18] which included a suspected group. This study employed only logistic regression, did not include any ML models, and used relatively routine biochemical parameters. Most previous models focused on limited clinical or lipid parameters and on prediction using cross-sectional datasets and did not integrate broader biochemical and inflammatory markers that reflect the complex pathophysiology of CAD. In addition, many studies relied on large retrospective datasets to distinguish between CAD and non-CAD disease using "predictors" terms of routine laboratory tests, including almost healthy individuals with mild hyperlipidemia and only one focused on suspected CAD. Thus, there is a need for a comprehensive (not predictive) classification approach based on specific CAD-related parameters, in addition to routine biochemical tests, to improve diagnostic accuracy and early risk assessment of CVD. The present work aims to investigate whether the ADMA levels in the suspected CAD group can classify and/or detect CAD early, and this work is designed for diagnostic classification of existing CAD, not for prediction due to the cross-sectional nature of the study.

## METHODS

A total of 471 individuals whose ages ranged from 41 to 72 years were selected in the present work. Patients were selected from the Clinic of Cardiology at Ebn Al-Bitar and Medical City Hospital and Medical City (Madinat Al-Tib) Hospital in Baghdad, Iraq. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and approval was granted by the Al-Karkh University of Science (approval number: RS2-432KUS102025, date: 05.06.2022). Hospitalized patients, individuals who came to the hospital, were referred from non-specialized clinics or were directly admitted to the department of cardiology for further diagnosis and management from March 2022 to Aug 2025. The American Heart Association/American College of Cardiology (AHA/ACC) guideline[36] diagnostic criteria for CAD were adopted by the department and were as follows: Diagnostic confirmation consistently relies on ischemic symptoms, electrocardiography changes, biochemical parameters such as blood pressure, lipid panel, cTln, sugar, and CRP, and computed tomography coronary angiography ≥50-90% coronary stenosis considered significant CAD and ≥90% indicating severe, MI related to the disease. This protocol was performed by the staff of the cardiology department and began with blood collection before any diagnostic evaluation. The patients were divided into two CAD groups based on the cardiologist's assessment. Group B (confirmed CAD) included patients with ischemic symptoms, elevated cardiac troponin I (cTnI), and severe coronary artery stenosis ≥90% in one or more major vessels, confirmed by invasive coronary angiography,

indicating MI CAD. Group C (suspected CAD) comprised patients with mild ischemic manifestations, angiographic stenosis of 50-90%, and normal troponin levels. The inclusion criteria were as follows: diagnosis by cardiology staff of CAD, with or without suspected MI, based on AHA/ACC criteria. Patients aged 45 years or older were evaluated for suspected CAD and underwent coronary angiography. The exclusion criteria included 1) a history of CAD or coronary revascularization procedures, 2) chronic systemic or inflammatory diseases, 3) liver or renal failure, and 4) malignancy, 5) non-fasted patient. It should be noted that patients with a prior history of CAD or coronary revascularization procedures were excluded because the aim of this study was to investigate early detection of CAD in patients without established disease. The levels of ADMA and cTnI were measured in the research laboratory at Al-Karkh University as cardiac centers do incorporate ADMA in their routine diagnostic protocol and use only qualitative cTnI for rapid decision-making regarding treatment strategy.

## Study Design

This study was a cross-sectional diagnostic investigation with the main experimental part conducted in the cardiology department. Angiographic imaging and biochemical tests, such as the rapid cTnI test, CRP, and lipid panel were performed in the cardiology department. Sample size was determined pragmatically based on patient availability during the study period; patients with missing data were excluded, and only complete, verified data were included. The final sample comprises 345 patients. The patients were divided into two groups: the first group, B (n=149, confirmed CAD), included patients with symptoms of severe ischemia and stenosis >90% and positive cTnI, reflecting MI. Group C (n=196) included patients with mild ischemia and stenosis of 50-89% and negative cTnI. Group A comprised 126 control individuals (n=126). The control group (n=126) consisted of individuals who had no clinically documented CAD, selected from the same source population and with the same age and sex distribution as the patient groups to minimize selection bias. The sample was selected from two sites, Al-Karkh University of Science and Al-Nokhba Clinical Laboratory Center, and consisted of individuals who came for routine checkups. Controls had no history of MI, angiographically confirmed coronary lesions, hyperlipidemia, diabetes, or hypertension. A venous blood sample was collected between 7:00 and 9:00 am after 10-14 hours of fasting. The remaining serum sample was stored at -20 °C for further biochemical analysis at the private clinical laboratory in Baghdad. The biochemical reagent of related parameters with the corresponding assay sensitivity, intra and inter-assay precision (CV%) were as follows: ADMA, (0.30 µmol/L, 10-12%) cTnI (0.3 ng/L, 10%) was determined by ELISA manufactured by Biomatic, Ontario, Canada, cholesterol (0.1 mg/dL, 1.1%), TG (0.1 mg/dL, 1.67%, and HDL (0.3 mg/dL, 2.68%) manufactured by Agappe, Greek were determined using a enzymatic colorimetric method on an autoanalyzer (Agappe, Mispa Chem Dx, Greek).

## Statistical Analysis

All experimental results were cleaned and formatted; the data were carefully split for ML, and no data leakage was observed. The Shapiro-Wilk test was applied to assess the normality of data distribution. Statistical analysis was performed using Python version 3.12.3. Descriptive statistical analysis expressed as mean ± standard deviation to describe the mean and deviation. One-way analysis of variance (ANOVA) was used to investigate overall variance among groups (A, B, and C) and to evaluate group-level differences in biochemical parameters.

## Bias Control

Several potential sources of bias were considered in the current study. To minimize bias, only patients who met the inclusion and exclusion criteria of the study were enrolled. The ML analysis indicated overfitting because models were trained on the complete dataset without external validation.

## Machine Learning Analysis

Early diagnostic classification was performed using ML with four models, including logistic regression, random forest (RF), support vector machine (SVM), and XGBoost, with evaluation metrics including accuracy, sensitivity, specificity, positive classification value, recall (F1-score), AUC, mean absolute error, and log loss, to investigate whether ADMA concentration could detect early CAD across different groups and to compare the performance of the models. To assess internal validity and reduce performance variability arising from a single train-test split, k-fold cross-validation was used for model evaluation. To ensure the clinical reliability of the evaluation and to reduce the effect of MI on model outcomes, ML analysis was performed in two classes. In the first class (C1), all study groups (A, B, and C) were included to assess the diagnostic ability of ADMA. In the second class (C2), the analysis was restricted to groups A and C, excluding patients with MI and severe stenosis. This approach allowed us to evaluate the performance of the models under more subtle clinical conditions in which differences in ADMA levels are less well defined and early CAD detection is critical. Decision curves and net benefits were used to display the model's behavior. In the present study, Shapley Additive exPlanations (SHAP) analysis identified ADMA and CRP as the most influential features in the early-stage C2 model, highlighting their importance in detecting subclinical CAD. Specifically, high ADMA values (Figure 1) were associated with a positive SHAP contribution of approximately 0.35, indicating a strong influence on the model; CRP showed a SHAP contribution reaching approximately 0.3. TG, total cholesterol (TC), and cTnI

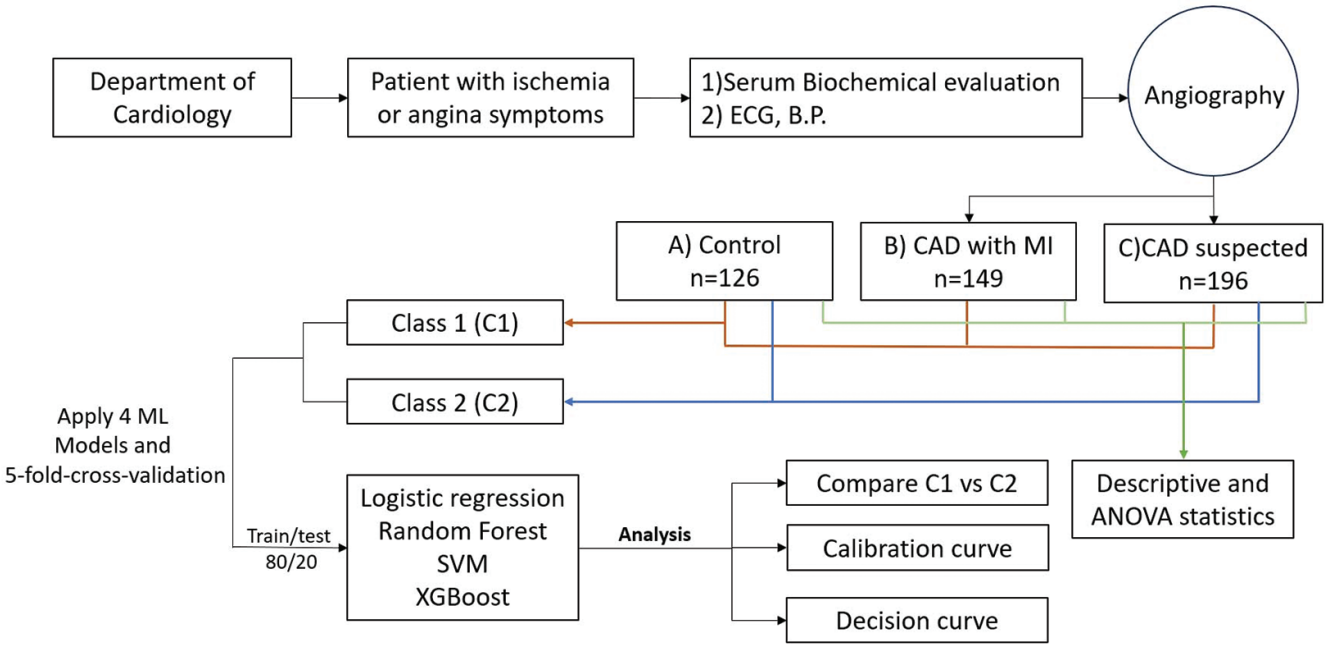


**Figure 1.** Overview of the methodology of the present work

*ECG: Electrocardiography, B.P.: Blood pressure, CAD: Coronary artery disease, MI: Myocardial infarction, ML: Machine learning, SVM: Support vector machine, ANOVA: Analysis of variance*

had lower SHAP contributions at this stage, generally below 0.2. These findings are clinically meaningful, because they reflect the pathophysiological sequence in which ADMA, an indicator of endothelial dysfunction, and CRP act as early measurable signals before substantial lipid derangements progress to MI. Notably, over 60% of the high-risk classifications in C2 were driven primarily by elevated ADMA and CRP, underscoring the importance of these markers in early diagnosis and potential preventive interventions. Figure 1 summarizes the methodological steps evaluated in the present work.

## RESULTS

Based on the cross-sectional nature of the current study, the results reflect the distribution of confirmed CAD cases (group B), suspected CAD cases (group C), and controls among Iraqi participants from March 2022 to Aug 2025. A total of 471 blood samples were collected in the present study from n=277 (58.8%) females and n=194 (41.2%) males. Participants were divided into three groups as presented in Table 2.

Biochemical parameters, including AMDA, cTnI, CRP, TC, TG, and HDL-C, were evaluated in both study groups and are presented in Table 3.

The results indicated significant variations in the study groups compared with the control. A significant difference was also observed between groups B and C. The levels of cTnI, ADMA, and CRP were significantly elevated in group B compared to group C, as a direct effect of MI on these parameters.

The performance metrics of the ML models were evaluated for class 1 (C1) to assess classification performance and provide a clear understanding of their effectiveness, as shown in Table 4.

**Table 2. Characteristics of anthropometrics and demographic parameters**

| Group | n | Sex | n (%) | Age (year) | BMI (m²/kg) | BP (mmHg) | Smokers n (%) | Stenosis |
|---|---|---|---|---|---|---|---|---|
| A | 126 (26.8%) | F | 55 (43.7%) | 52.34±7.59 | 26.05±1.25 | 12.14±0.24 | 22 (31.0%) | N/A |
| | | M | 71 (56.3%) | 56.69±8.64 | 25.56±1.35 | 12.05±0.29 | 19 (34.5%) | |
| B | 149 (31.6%) | F | 57 (38.3%) | 54.83±8.35 | 27.25±2.19 | 13.63±1.10 | 42 (45.7%) | 93.59±4.39 |
| | | M | 92 (61.7%) | 59.21±7.39 | 26.91±2.01 | 13.48±1.02 | 33 (57.9%) | |
| C | 196 (41.6%) | F | 82 (41.8%) | 58.12±8.40 | 27.44±2.57 | 12.89±1.01 | 44 (38.6%) | 71.84±9.89 |
| | | M | 114 (58.2%) | 58.24±8.73 | 27.15±2.62 | 12.83±0.97 | 42 (51.2%) | |

BMI: Body mass index, BP: Blood pressure, N/A: Not available

**Table 3. ANOVA and mean ± SD of biochemical parameters**

| Parameter | A (min, max) | B | C | F-statistic | *P*-value |
|---|---|---|---|---|---|
| ADMA (µmol/L) | 0.49±0.12 (0.24, 0.91) | 1.62±0.64 (0.67, 2.34) | 0.81±0.16 (0.45, 1.81) | 3.0792 | 0.04 |
| cTnI (ng/L) | 0.148±0.08 (0.07, 0.36) | 23.91±7.10 (11.0, 46.7) | 0.39±0.12 (0.18, 0.91) | 1780.177 | <0.01 |
| CRP (mg/dL) | 5.66±0.87 (4.1, 8.0) | 17.93±5.32 (8.2, 35.0) | 7.30±1.33 (4.52, 11.7) | 62.5648 | <0.01 |
| TC (mg/dL) | 160.8±15.73 (123, 248) | 209.0±31.39 (184, 341) | 217.87±33.4 (89, 307) | 32.468 | <0.01 |
| TG (mg/dL) | 119.0±20.4 (80.7, 182) | 193.4±60.79 (135, 371) | 223.5±53.12 (115, 350) | 43.9723 | <0.01 |
| HDL-C (mg/dL) | 50.2±6.12 (39, 63) | 39.64±6.47 (19.6, 60.3) | 49.05±31.06 (25, 73) | 35.1223 | <0.01 |

ANOVA: Analysis of variance, SD: Standard deviation, ADMA: Asymmetric dimethylarginine, cTnI: Cardiac troponin I, CRP: C-reactive protein, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol

**Table 4. Independent hold-out test performance metrics of CAD classification in class 1 models**

| Model | Accuracy | Sensitivity | Specificity | F1-score | AUC | MAE | Log loss |
|---|---|---|---|---|---|---|---|
| Logistic regression | 0.737 | 1 | 0 | 0.848 | 0.648 | 0.387 | 0.565 |
| Random forest | 0.811 | 0.886 | 0.6 | 0.873 | 0.803 | 0.262 | 1.124 |
| SVM | 0.737 | 1 | 0 | 0.848 | 0.648 | 0.339 | 0.534 |
| XGBoost | 0.8 | 0.914 | 0.48 | 0.871 | 0.79 | 0.279 | 0.46 |

CAD: Coronary artery disease, AUC: Area under the curve, F1-score, harmonic mean of precision and recall, MAE: Mean absolute error, SVM: Support vector machine

Comparison of the performance of the four ML models reveals notable variability in their diagnostic capabilities. RF demonstrated the best overall balance, achieving the highest accuracy. Strong sensitivity combined with moderate specificity results in reliable detection of both CAD-positive and CAD-negative subjects, while XGBoost specificity shows a bias toward FP. Logistic regression and SVM models exhibited overfitting due to the models' high sensitivity and low specificity. As discussed above and presented in Table 3, it is clear that most models exhibited overfitting or values approaching overfitting and were unable to distinguish between negative and positive cases in the C1 model analysis. To assess internal validity and to establish that performance was not dependent on a single train-test split, k-fold cross-validation was performed, as presented in Table 4.

As shown in Table 5, the 5-fold cross-validation results were consistent with the independent hold-out evaluation, indicating that RF and XGBoost exhibited the strongest overall classification ability, with AUC values of 0.854 and 0.879, respectively. Some variation in individual metrics was observed. The stability of the model confirms that the selected ensemble methods exhibit good generalizability and a reduced tendency to overfit.

The C1 evaluation allowed exploration of the ability of ADMA to distinguish individuals with any form of CAD from healthy participants. Markedly elevated ADMA, reflecting the acute myocardial injury present in group B patients, caused a very strong class separation, which likely contributed to overfitting of some models above. This MI-driven class produced relatively imbalanced metric values across several models, particularly in those demonstrating close-to-perfect sensitivity but poor specificity. Consequently, the high-performance C1 metrics reflect the ease of differentiating advanced MI-CAD rather than true diagnostic discrimination across disease stages, thereby restricting direct clinical interpretability for early CAD classification and diagnosis.

After analyzing the C1 models, it is to investigate the C2 model, which does not include the group B patients. Table 6 illustrates the 4 ML model groups, A and C. The results indicate that all classes a clinically meaningful detection capability, though with notable variability in performance.

RF showed the highest selectivity with an AUC of 0.822. XGBoost followed closely, with an AUC of 0.781-the highest among models with balanced sensitivity and specificity. Logistic regression and SVM demonstrated weaker variable selection. Sensitivity remained high across most models (0.75-1.00), whereas specificity was low (0.36-0.64), indicating overfitting for most models except XGBoost and RF, which recorded acceptable values of 0.72 and 0.64, respectively. Comparison of the C1 and C2 models' performances indicated that the C2 models exhibited a slight decrease in accuracy, dropping by 4-12% across models and a reduction in sensitivity, especially in RF and XGBoost. The specificity increased markedly to 1.00 in the SVM model, showing a better balance between true positive and true negative detection, with an AUC of 0.657-0.822, demonstrating that ADMA has diagnostic value for non-MI CAD, particularly under conditions in which biochemical abnormalities are more subtle.

To verify the model's generalizability for early detection, internal validation was performed using k-fold cross-validation, as shown in Table 7. As shown in Table 6, RF and XGBoost maintained the strongest overall performance, with AUC values of 0.768 and 0.767 respectively, consistent with the independent holdout test. Despite variations in sensitivity and specificity, the model ranking remained unchanged, indicating the robustness of these methods for early detection of CAD. Cross-validation results, therefore, support the validity of the hold-out analyses, whereas calibration and decision-curve assessments were based exclusively on the final detection test for clinical interpretability. Further clarification was obtained using calibration-curve analysis to assess how well each C1 model converts detected values into true clinical measurements, as illustrated in Figure 2. Logistic regression and SVM models exhibit notably poor calibration, as shown by their calibration curves. RF shows improved calibration, with variation above the reference suggesting overfitting. High accuracy combined with moderate specificity indicates that it distinguishes disease severity more effectively; however, it tends to misclassify lower-risk individuals (group C) as higher risk. XGBoost is closest to the perfect calibration line, especially at mid- to high detection probabilities, among the tested models. XGBoost provides the most accurate risk estimates for groups B and C while still partially separating groups B and C from healthy controls.

The calibration curves comparing the models in class 2 highlight important differences in their behavior, as presented in Figure 3. RF shows better alignment, but still deviates at the upper end, indicating slight overfitting in suspected cases. Conversely, XGBoost aligns most closely with the diagonal reference, especially in mid- to high-probability ranges, indicating remarkable calibration and more clinically reliable risk estimates for suspected CAD, compared with controls.

Table 8 compares the calibration for both classes (C1 and C2); RF identified the highest diagnostic performance in the C1 class, with accuracy and specificity of 81.1% and 60% respectively, while RF showed reliable performance in the C2 class. XGBoost also showed strong generalizability across both classes, but had slightly lower specificity and accuracy than RF in C2. Conversely, logistic regression and SVM exhibited an improvement in C2 by about 36%. Overall, RF provides the most robust and clinically meaningful classification, especially for multi-group CAD stratification. Based on class 2, all models showed improved specificity, resulting in a more balanced analysis. RF demonstrated improved and clinically useful performance with a specificity of 64%, confirming its robustness across severity levels. XGBoost also remained strong, with improved specificity (52%), indicating stable generalization. Table 5 summarizes the key metrics that change across C1 and C2 for the two classes.

**Table 5. 5-fold cross-validation performance for internal validation of class 1**

| Model | Accuracy | Sensitivity | Specificity | F1-score | AUC |
|---|---|---|---|---|---|
| Logistic regression | 0.777 | 0.916 | 0.398 | 0.857 | 0.815 |
| Random forest | 0.794 | 0.872 | 0.581 | 0.861 | 0.854 |
| SVM | 0.826 | 1 | 0.35 | 0.894 | 0.769 |
| XGBoost | 0.826 | 0.916 | 0.581 | 0.885 | 0.879 |

AUC: Area under the curve; F1-score, harmonic mean of precision and recall, SVM: Support vector machine

**Table 6. Independent hold-out test performance metrics of CAD classification in class 2 models**

| Model | Accuracy | Sensitivity | Specificity | F1-score | AUC | MAE | Log loss |
|---|---|---|---|---|---|---|---|
| Logistic regression | 0.692 | 0.9 | 0.36 | 0.783 | 0.657 | 0.405 | 0.604 |
| Random forest | 0.708 | 0.75 | 0.64 | 0.759 | 0.822 | 0.309 | 0.584 |
| SVM | 0.754 | 1 | 0.36 | 0.833 | 0.686 | 0.374 | 0.549 |
| XGBoost | 0.692 | 0.8 | 0.72 | 0.762 | 0.781 | 0.342 | 0.565 |

CAD: Coronary artery disease, AUC: Area under the curve; F1-score, harmonic mean of precision and recall, MAE: Mean absolute error, SVM: Support vector machine

**Table 7. 5-fold cross-validation performance for internal validation of class 1**

| Model | Accuracy | Sensitivity | Specificity | F1-score | AUC |
|---|---|---|---|---|---|
| Logistic regression | 0.674 | 0.857 | 0.39 | 0.762 | 0.667 |
| Random forest | 0.736 | 0.816 | 0.613 | 0.791 | 0.768 |
| SVM | 0.739 | 1 | 0.334 | 0.824 | 0.676 |
| XGBoost | 0.746 | 0.826 | 0.621 | 0.799 | 0.767 |

AUC: Area under the curve; F1-score, harmonic mean of precision and recall, SVM: Support vector machine

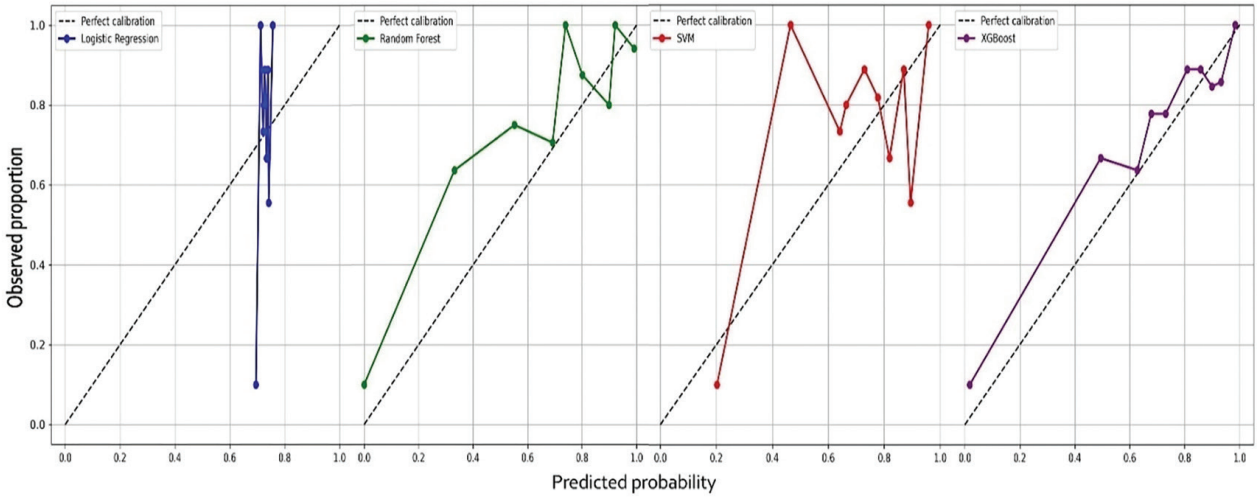


**Figure 2.** Calibration curve of the four models under study for all groups
*SVM: Support vector machine*

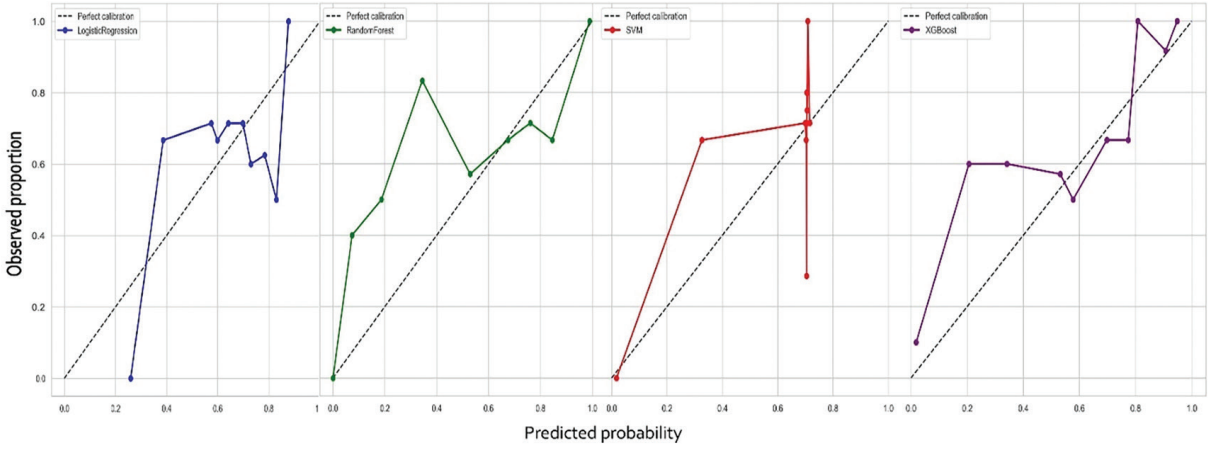


**Figure 3.** Calibration curve of the four models under study of all groups
*SVM: Support vector machine*

As demonstrated by the decision curve analysis (Figure 4), excluding group B in class 2 resulted in a noticeable shift in the clinical utility of the models. In the C1, all models recorded a higher overall net benefit across clinically relevant threshold probabilities, particularly at pt=0.01-0.03. This superior performance is expected, as group B patients already exhibit advanced and easily distinguishable disease characteristics, which contribute to a clearer separation between positive and negative cases (Figure 4a). However, in C2, as illustrated in Figure 4b, the net benefit curves shifted to approximately 0.61 at the same thresholds, representing an estimated 16% reduction. The class 2 evaluation provides more clinically applicable and functional diagnostic performance in early CAD detection, where biomarker levels and symptoms are less definitive and more challenging to classify.

Collectively, these findings indicate that although the inclusion of confirmed CAD improves model performance metrics, its exclusion yields a more meaningful appraisal of diagnostic capability in pre-event disease states. Accordingly, RF appears to be the most reliable approach for identifying early high risk of CAD, as evidenced by its stability and consistently positive net benefit under both modeling conditions. A shift in results contributions is observed when comparing the SHAP results from the C1 to the C2 models as shown in Figure 5. In Figure 5a, TG shows the highest mean SHAP contribution of 0.131, followed by TC (0.114). These results indicate that in C2 cases, hyperlipidemia plays the strongest role in distinguishing disease from non-disease states. Troponin (cTnI) remains an important marker (0.106), consistent with myocardial injury in these subjects. ADMA, while elevated (0.108), appears to

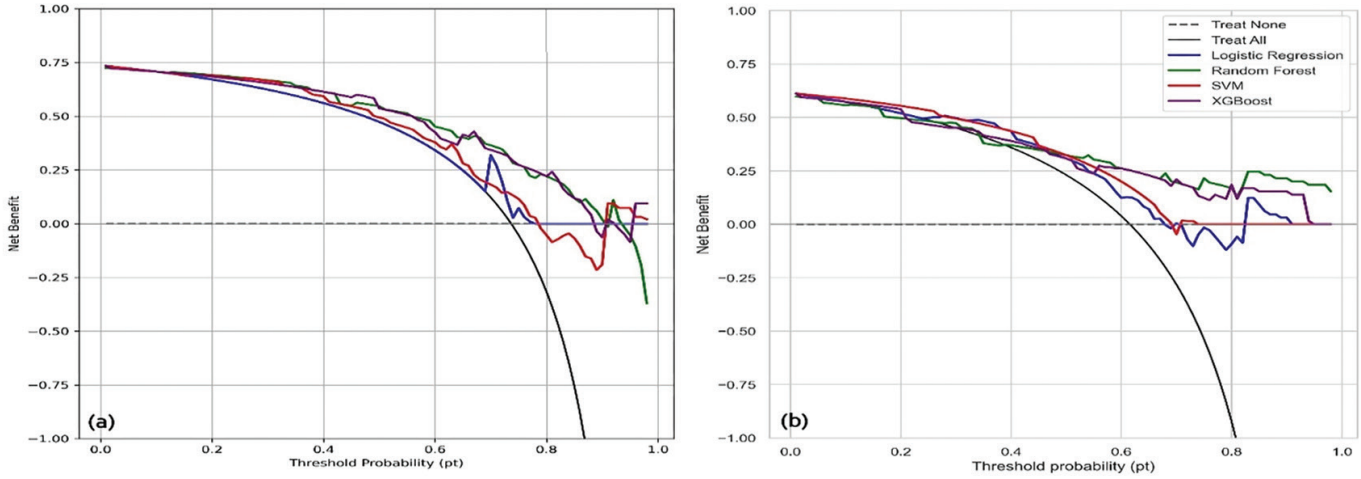


**Figure 4.** Decision curve analysis of (a) class 1 models and (b) class 2 models

*SVM: Support vector machine*

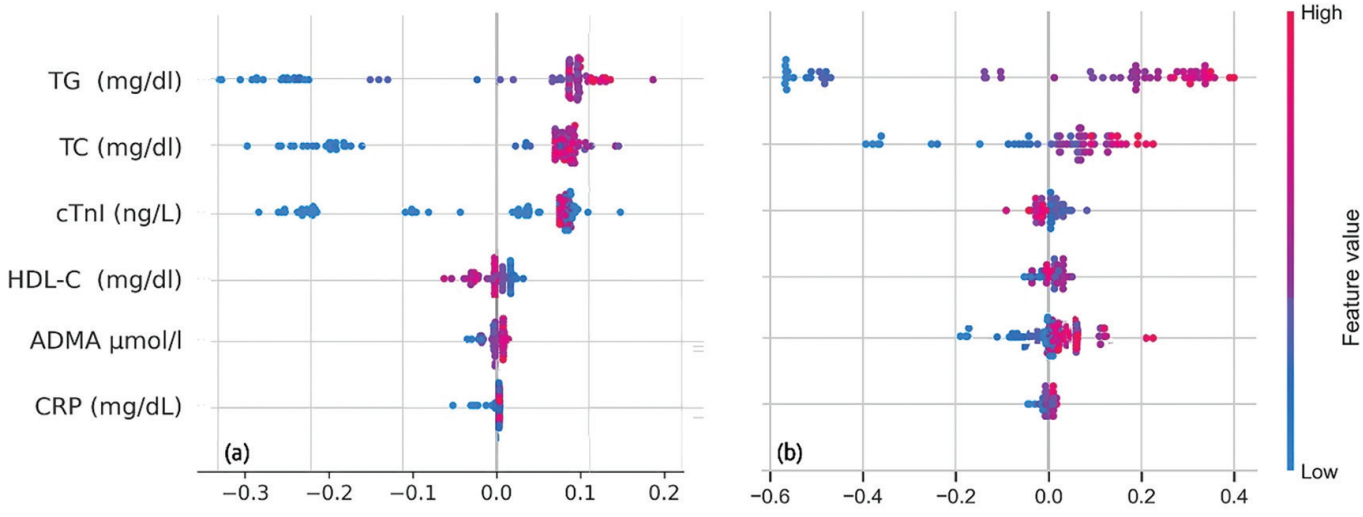


**Figure 5.** SHAP plots illustrating the directional contribution of biochemical parameters of (a) class 1 and (b) class 2

*SHAP: Shapley Additive exPlanations, TG: Triglyceride, TC: Total cholesterol, cTnI: Cardiac troponin I, HDL-C: High-density lipoprotein cholesterol, ADMA: Asymmetric dimethylarginine, CRP: C-reactive protein*

**Table 8. Comparison of performance of 4 ML for key metrics across the two classes (C1 and C2)**

| Model | C1 | C2 | Interpretation |
|---|---|---|---|
| Logistic regression | Sensitivity 100%, specificity 0%, AUC: 0.648 | Sensitivity 90%, specificity 36%, AUC: 0.657 | Strong overfitting toward CAD-positive cases |
| SVM | Sensitivity 100%, specificity 0%, AUC: 0.648 | Sensitivity 100%, specificity 36%, AUC: 0.686 | Model is unable to learn class separation in risk spectrum |
| Random forest | Accuracy 81.1%, sensitivity 88.6%, specificity 60%, AUC: 0.803 | Accuracy 70.8%, sensitivity 75%, specificity 64%, AUC: 0.822 | Moderately robust, improved reliability |
| XGBoost | Accuracy 80%, sensitivity 91.4%, specificity 48%, AUC: 0.79 | Accuracy 69.2%, sensitivity 80%, specificity 52%, AUC: 0.781 | Most clinically applicable across scenarios |

ML: Machine learning, AUC: Area under the curve, C1: Class 1 (all groups), C2: Class 2 (A and C groups), SVM: Support vector machine, CAD: Coronary artery disease

be masked by other more dominant risk markers in severe conditions. CRP exhibits the lowest influence (0.004). In Figure 5b, with severe MI cases removed and the comparison limited to early versus healthy CAD, the importance profile changes significantly. ADMA was the most influential feature (0.134), followed closely by CRP (0.131), indicating that endothelial dysfunction and inflammation provide stronger detection cues in early stages of CAD. cTnI (0.091) and TC (0.097) show reduced but still notable contributions, while TG drops sharply to 0.010, a >90% reduction compared to Figure 5a. HDL-C remains a consistently minor, yet protective, factor in both models.

## DISCUSSION

CAD remains a major global health concern, and early detection before the onset of MI is essential to improve clinical outcomes. This study evaluates the diagnostic performance of ADMA and conventional biochemical parameters and explores advanced ML to enhance CAD risk stratification. Accordingly, the discussion will interpret these results in the context of current evidence, emphasizing their implications for early CAD diagnosis and clinical applicability.

In the present cohort, one-way ANOVA revealed significant differences in most biochemical parameters, with patients in group B showing higher levels of TC, TG, ADMA, CRP, and cTnI, and lower HDL-C, compared with those in the suspected CAD and control groups, supporting a graded worsening of cardiometabolic risk across the spectrum of disease. This pattern is consistent with recent evidence that serum ADMA rises in parallel with the extent and severity of coronary atherosclerosis and may serve as a marker of atherosclerotic burden and adverse outcomes in CAD patients.[37] Likewise, our finding of a less favorable lipid profile in the study groups agrees with contemporary studies showing that elevated TG-rich lipoproteins and reduced HDL-C are independently associated with a greater prevalence and extent of CAD, and higher residual cardiovascular risk despite standard therapy.[38] These ANOVA results indicate that the significant biochemical differences between groups in the present study reflect well-established pathophysiological gradients of dyslipidemia, endothelial dysfunction, and inflammation in CAD compared with controls. Also, differences between groups B and C were observed as a clear MI-driven effect that caused a significant elevation of some biochemical parameters. Since the previous ML work was also cross-sectional but reported prediction results, their findings must be interpreted as diagnostic classification rather than as evidence of prediction from a cross-sectional study. Therefore, the comparison is based on classification performance.

In the present work, ML models indicated differential performance in two distinct classifications, C1 and C2. For the C1, the RF model achieved the most balanced outcomes, with an accuracy of 81.1%, sensitivity of 88.6%, specificity of 60%, and an AUC of 0.803, indicating moderate robustness. However, logistic regression and SVM showed 100% sensitivity and 0% specificity, meaning that all subjects were classified as CAD-positive. This behavior indicates overfitting to the severe CAD signal driven by group B, in which markedly elevated AMDA provided a strong separation, leading to the complete misclassification of healthy individuals. Analysis was restricted to the first class (C1), indicating early or subtle disease, RF maintained strong discrimination with an AUC of 0.822 and reduced overall accuracy (70.8%) and enhanced specificity through models, explaining that earlier inflated performance metrics were triggered by class imbalance. While XGBoost showed slightly higher specificity, better performance in k-fold AUC, and closer calibration, RF was favored due to its higher sensitivity, which is critical for early diagnostic classification and for minimizing missed CAD cases.

By comparison, many prior studies achieved higher AUCs in broader CAD versus non-CAD settings, but did not separate MI from non-MI populations. For example, Zhang et al.[30] conducted a cohort study of 1,647 participants (CAD vs. healthy) and used 6 machine-learning models [k-nearest neighbors, logistic regression (LR), SVM, decision tree, multilayer perceptron, and XGBoost] to predict CAD. They found that the XGBoost algorithm recorded the best score by achieving an AUC of 0.94 using lipid panels and demographic data.[30] Cheng et al.[31] by using a set data of 9,640 adults and using three ML models (Gradient Boosting, RF, and LR) reported an AUC of 0.846 with gradient boosting using routine anthropometric, clinical and physiological parameters (age, sex, body mass index, systolic blood pressure/diastolic blood pressure, liver function test, renal function test, lipid panel, smoking, and alcohol consumption). Bibi et al.[32] investigated 3,316 individuals using a gradient boosting model reported an AUC of 0.910 for overall CVD and 0.841 for CAD subgroups using lipid profile and troponin data. Another cohort study of 7,260 subjects reported an accuracy of 0.871 using XGBoost and ranked LDL-C, TG, and blood pressure as the top features.[33] None of these prior studies explicitly isolated an MI subgroup and a non-MI suspected CAD group, nor did any study report that CAD patients with current MI were excluded from the present work. As observed in the present work and as it well documented that CAD driven MI strongly affects the levels of TC, TG, HDL-C, and cTnI[39,40] that act on strong class separation between control and CAD groups which may affect the results of ML models. The present work addresses a more refined clinical question regarding screening for early CAD before MI.

In the C2 models, the output results become substantially more challenging because biomarker abnormalities are less pronounced and MI is absent. Despite this, RF maintained

the most reliable diagnostic performance overall, with the highest AUC (0.822) and well-balanced sensitivity and specificity of 75% and 64%, respectively, suggesting that it can identify biochemical risk signatures associated with early CAD development. XGBoost demonstrated slightly higher specificity (72%), which is advantageous for reducing unnecessary interventions. Few previous studies have evaluated early CAD separately from MI but recent report indicate that ML tends to perform less effectively in mild disease due to weaker biomarker contrast for example study performed by Kim et al.[41] in suspected CAD populations reported AUCs in the range of 0.68-0.78 when relying on lipid ratios and carotid intima-media thickness alone with accuracy of 74.6%. These findings support the notion that our C2 performance values reflect a real-world diagnostic challenge rather than indicating model limitations, reinforcing the promise of ML for CAD detection before high-risk features, such as elevated troponin, appear. In contrast to models that perform well only when MI present, our results demonstrate that early CAD detection is feasible before irreversible cardiac damage occurs and support the clinical value of ML as a decision-support tool in screening contexts. Although few prior studies have isolated non-MI CAD populations for diagnostic purposes, they provide a more realistic assessment of early diagnostic utility, emphasizing the importance of distinguishing risk from overt disease.

It should be clarified that d espite the XGBoost model indicating slightly higher specificity of 72% than RF with 64% and higher k-fold AUC with values 0.879 and 0.854 respectively, and closer calibration to the ideal values (line) in certain metrics, RF was selected as the primary classifier because of its higher sensitivity. In early CAD screening, sensitivity is critical to minimize the risk of missing true-positive cases, which could have serious clinical consequences. Therefore, despite XGBoost's advantages in specificity and calibration, RF provides a better balance for identifying high-risk patients, aligning with the study's objective of early identification. Future studies could investigate ensemble strategies combining the models to optimize sensitivity and specificity.

### Study Limitations

The present work has several limitations. First, the cross-sectional design limits the ability to infer causal relationships between ADMA levels and the presence of CAD. Second, the sample size remains modest, which may limit the statistical power and generalizability of the findings. Third, despite multiple ML models being evaluated, they were trained and evaluated on data from only two cohorts in Baghdad and lacked external validation. The absence of external validation may restrict the evaluation of model robustness and increase the risk of overfitting, thereby reducing confidence in the models' performance when applied to independent populations.

## CONCLUSION

This study demonstrates the clinical potential of ADMA and ML-based analytics for improving the early detection of CAD prior to the onset of MI. The findings emphasize the importance of biomarkers of endothelial dysfunction in the early detection of CAD and support the integration of predictive modeling into preventive cardiology strategies.

Significant elevations of ADMA correlate with CAD severity-driven MI.

ML models confirmed that ADMA independently contributes to CAD detection, especially in the absence of myocardial infarction.

RF and XGBoost demonstrated the strongest diagnostic balance, indicating their suitability as clinical decision support tools.

SHAP analysis highlighted endothelial dysfunction and inflammation as the leading features in early CAD, before overt cardiac injury (troponin rise).

Excluding MI cases provided a more realistic early-screening scenario, showing clinical feasibility for early detection CAD prior to irreversible cardiac damage.

### Ethics

**Ethics Committee Approval:** The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and approval was granted by the Al-Karkh University of Science (approval number: RS2-432KUS102025, date: 05.06.2022).

**Informed Consent:** Written informed consent was obtained from all participants before inclusion.

### Availability of Data and Materials

The data supporting the results of this work are available upon reasonable request from the corresponding author.

### Acknowledgements

The authors acknowledge the volunteers who provided blood samples.

### Footnotes

### Authorship Contributions

Concept: M.M.S.,A.S.F.A., M.H.Z., Design: M.M.S., Data Collection or Processing: M.M.S., A.S.F.A., Analysis or Interpretation: M.M.S., A.S.F.A., M.H.Z., Literature Search: M.M.S., M.H.Z., Writing: M.M.S., M.H.Z.

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RESEARCH ARTICLE

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# Validation of "Get With the Guidelines" Risk Score (GWTG) to Predict the In-hospital Mortality among the Patients Admitted with Congestive Cardiac Failure

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## Abstract

**Background and Aim:** Heart failure (HF) is a leading cause of cardiovascular morbidity and mortality. Prognostic models such as the Get With the Guidelines-HF (GWTG-HF) score are validated for predicting in-hospital mortality, but data from critically ill populations in South India are limited. To validate the predictive accuracy of the GWTG-HF score for hospital mortality in acute decompensated HF (ADHF) cases managed in a tertiary intensive care unit (ICU).

**Materials and Methods:** In this prospective observational study, 67 adults admitted with HF over three months were enrolled. Patients with chronic kidney disease, thyroid disorders, valvular heart disease, pulmonary arterial hypertension, or pregnancy were excluded. Clinical, laboratory, and hemodynamic data were collected, and GWTG-HF scores were calculated at admission. Patients were stratified into low (0-33), moderate (34-50), and high (>50) risk groups. Outcomes included in-hospital mortality and ICU stay. Statistical tests included analysis of variance, Kruskal-Wallis, chi-square/Fisher's exact, and receiver operating characteristic (ROC) curve analysis.

**Results:** Of 67 patients, 61 (91%) survived and 6 (9%) died. Mortality increased across risk groups: 0% in low, 9.3% in moderate, and 28.6% in high ($P = 0.012$). Non-survivors had higher mean GWTG-HF scores (47.7±7 vs. 38.4±8.1; $P = 0.013$) and lower sodium levels (128±4 vs. 134.6±6.3 mmol/L; $P = 0.007$). ROC analysis showed good discrimination (area under the curve: 0.754). At a cut-off ≤47, sensitivity was 66.7%, specificity 85.2%, and negative predictive value 96.3%. ICU stay was longer in higher-risk groups ($P = 0.041$).

**Conclusion:** The GWTG-HF score demonstrated good predictive performance for in-hospital mortality in ICU patients with ADHF. Its strong negative predictive value supports its use for identifying low-risk patients, while incorporating biomarkers such as N-terminal pro-brain natriuretic peptide may enhance prognostic accuracy.

**Keywords:** ADHF, GWTG-HF score, mortality, risk stratification, cardiac failure, heart failure

## INTRODUCTION

Heart failure (HF), arising from structural and functional cardiac abnormalities, represents the final stage of most heart diseases and contributes substantially to cardiovascular illness and death. Although there has been progress in diagnosis and management of HF there is sparse satisfactory information regarding outcomes of HF.[1] Many clinical scores have been derived and validated for in-hospital survival, but

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their applicability in real world population has been seldom evaluated.[2] Get With the Guidelines-HF (GWTG-HF) score is one of the scores to evaluate outcomes of HF. Other scores include, the acute decompensated HF (ADHF) national registry, OPTIMIZE-HF outcome of a prospective trial of IV milrinone for exacerbates of chronic HF, enhanced feedback for effective cardiac treatment.

Although hospitalizations for HF have surged, standardized models for risk assessment in ADHF admissions are still lacking. Medical decision-making may benefit from the use of clinical risk prediction technologies. A patient who is thought to be at a lesser risk might be treated with less extensive therapies and monitoring on a hospital ward or telemetry unit, whereas a patient who is believed to be at a higher risk might need more severe care in an intensive care unit (ICU) or coronary care unit.

The analysis sought to validate a straightforward risk assessment tool for hospital mortality in ADHF patients that can be integrated into everyday practice.

### Aim

Validate GWTG-HF score for its predictability of outcome in congestive HF patients, admitted in ICU in a South Indian tertiary care center.

## METHODS

A prospective observation study was conducted in a tertiary care center in South India. Over a period of three months 67 patients admitted with congestive HF were studied and followed up for their outcomes in the hospital.

All patients (more than 18 years) getting admitted with diagnosis of congestive cardiac failure were included in the study. Pregnant women, patients with chronic kidney disease, thyroid disorders HF due to organic valvular disease or due to pulmonary arterial hypertension were not included in the study.

The routine investigations like complete blood count, renal function test, 12-lead electrocardiogram, 2D echocardiography, N-terminal pro-brain natriuretic peptide (NT-proBNP) were done as per routine standard of care. The GWTG score was determined for each patient upon admission. A patient's score was calculated by adding the points assigned to each predictor's value. The score values range from 0 to 100. Participants were categorized into three groups (low, moderate, high) according to the GWTG-HF risk score.

Based on previous clinical studies,[3-7] availability of data on the time of presentation the following data was collected: -demographic details (age, gender), clinical data (pulse rate, blood pressure), diagnosis, comorbidities [diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), hypothyroidism], laboratory parameters were recorded. All the patients were followed up till their stay in hospital. patient outcome, number of days in ICU and GWTG-HF score

The protocol received approval from the Institutional Ethics Committee of Ramaiah Medical College (ref. no: MSRMC/EC/SP03/122022, reg. no: ECR/215/Inst/KA/2013/RR22) on 15 December 2022 for three months, with all activities conducted in line with committee guidelines.

ClinicalTrials registry: Not applicable.

### GWTG-HF Score

GWTG-HF risk score has 7 predictor variables. These variables are age, heart rate, systolic blood pressure (SBP), sodium, race, COPD and blood urea nitrogen (BUN). Every predictor variable has been assigned points according to their values within various ranges as illustrated in Table 1.[4] A total score is generated by adding points from each variable.

### Statistical Analysis

The study was stratified into three groups based on the GWTG-HF risk score: low (0-33), moderate (34-50), and high (>50), as presented in Table 2. Continuous variables including age, SBP, BUN, and heart rate were summarized as mean ± standard deviation (SD). Categorical variables such as COPD prevalence and Black race were expressed as percentages.

Laboratory parameters—including white blood cell count, red blood cell count, hemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC)—were reported as mean ± SD. ICU stay duration was expressed as median with interquartile range (IQR) due to its non-normal distribution. Additional metrics such as number of deaths, predicted mortality (based on GWTG-HF score), and observed mortality rates were also tabulated.

Comparisons across the three risk groups were performed using one-way analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed variables (e.g., ICU stay, NT-proBNP), and chi-square or Fisher's exact test for categorical variables. Corresponding *P*-values are provided in Table 1 to indicate statistical significance.

Baseline patient data were analyzed with descriptive statistics. Continuous measures were expressed as mean ± SD or median (IQR) and compared between discharged and in-hospital deaths using ttests or Mann-Whitney U tests. Categorical variables were presented as counts and percentages, with chisquare or Fisher's exact tests applied where appropriate. A *P*-value below 0.05 was considered significant.

Receiver operating characteristic (ROC) curve analysis was employed to assess the discriminative performance of the GWTG-HF risk score in predicting in-hospital mortality among patients admitted to the ICU with HF. The ROC curve plots sensitivity (true positive rate) against 1- specificity (false positive rate) across a range of threshold values.

The area under the curve (AUC) was calculated[8] as a measure of the model's overall accuracy. Multiple cut-off values were assessed, and the optimal threshold was determined using the Youden's index (J = sensitivity + specificity - 1), which identifies the point on the ROC curve that maximizes the combined sensitivity and specificity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported for the selected cut-off.

## RESULTS

Patients were stratified into three groups according to the GWTG-HF risk score: low (0-33; n=17), moderate (34-50; n=43), and high (>50; n=7) as shown in Table 2. A clear stepwise increase in mortality was observed across groups. No deaths occurred in the low-risk group, compared with 4 deaths (9.3%) in the moderate group and 2 deaths (28.6%) in the high-risk group ($P$ = 0.012, Fisher's exact test). The observed mortality rates corresponded well with the predicted mortality estimates (<1%, 1-5%, and 5-10% for the low, moderate, and high groups, respectively).

Length of ICU stay also differed significantly between groups, with median stays of 5.5 days (range 2-16), 8.75 days (range

**Table 1. GWTG-HF score**

| Systolic BP | Points | BUN | Points | Sodium | Points | Age | Points |
|---|---|---|---|---|---|---|---|
| 50-59 | 28 | ≤9 | 0 | ≤130 | 4 | ≤19 | 0 |
| 60-69 | 26 | 10-19 | 2 | 131 | 3 | 20-29 | 3 |
| 70-79 | 24 | 20-29 | 4 | 132 | 3 | 30-39 | 6 |
| 80-89 | 23 | 30-39 | 6 | 133 | 3 | 40-49 | 8 |
| 90-99 | 21 | 40-49 | 8 | 134 | 2 | 50-59 | 11 |
| 100-109 | 19 | 50-59 | 9 | 135 | 2 | 60-69 | 14 |
| 110-119 | 17 | 60-69 | 11 | 136 | 2 | 70-79 | 17 |
| 120-129 | 15 | 70-79 | 13 | 137 | 1 | 80-89 | 19 |
| 130-139 | 13 | 80-89 | 15 | 138 | 1 | 90-99 | 22 |
| 140-149 | 11 | 90-99 | 17 | ≥139 | 0 | 100-109 | 25 |
| 150-159 | 9 | 100-109 | 19 | | | ≥110 | 28 |
| 160-169 | 8 | 110-119 | 21 | | | | |
| 170-179 | 6 | 120-129 | 23 | | | | |
| 180-189 | 4 | 130-139 | 25 | | | | |
| 190-199 | 2 | 140-149 | 27 | | | | |
| ≥200 | 0 | ≥150 | 28 | | | | |

| Heart rate | Points | Black race | Points | COPD | Points | Total score | Probability of death |
|---|---|---|---|---|---|---|---|
| | | | | | | 0-33 | <1% |
| | | | | | | 34-50 | 1-5% |
| ≤79 | 0 | Yes | 0 | Yes | 2 | 51-57 | >5-10% |
| 80-84 | 1 | | | | | 58-61 | >10-15% |
| 85-89 | 3 | | | | | 62-65 | >15-20% |
| 90-94 | 4 | No | 3 | No | 0 | 66-70 | >20-30% |
| 95-99 | 5 | | | | | 71-74 | >30-40% |
| 100-104 | 6 | | | | | 75-78 | >40-50% |
| ≥105 | 8 | | | | | ≥79 | >50% |

The range of scores reflects the probability of mortality as indicated in the Table 1

GWTG-HF: Get With the Guidelines-heart failure, BUN: Blood urea nitrogen, COPD: Chronic obstructive pulmonary disease, BP: Blood pressure

2-60), and 8 days (range 2-21) for the low-, moderate-, and high-risk groups, respectively ($P = 0.041$).

Baseline characteristics varied substantially across risk categories. Patients in the moderate and high-risk groups were older (72.1±9.2 and 74.4±11.7 years, respectively) compared with the low-risk group (58.1±15.3 years; $P < 0.001$). SBP decreased significantly with higher risk strata (150.2±28.1 mmHg in low vs. 129.4±20.3 mmHg in moderate and 100.0±12.6 mmHg in high-risk groups; $P < 0.001$).

Markers of renal dysfunction and cardiac stress showed strong associations with risk category. BUN levels were markedly elevated in the high-risk group (48.1±35.2 mg/dL) compared with the low (17.1±5.9 mg/dL) and moderate groups (17.9±10.0 mg/dL; $P < 0.001$). Similarly, NT-proBNP concentrations were highest in the high-risk category (16.820±10.920 pg/mL) compared with the moderate (5.059±6.370 pg/mL) and low-risk groups (9.122±9.360 pg/mL; $P < 0.001$).

In contrast, hematological indices—including white blood cell count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, and MCHC—did not differ significantly across the three groups ($P > 0.05$ for all). However, the prevalence of COPD increased with higher risk category (5.9% in low, 11.6% in moderate, and 28.6% in high; $P = 0.031$). No patients identified as Black in this cohort.

Among the 67 patients included, 61 (91%) were discharged and 6 (9%) died during hospitalization. Age, gender, diagnosis, and key comorbidities did not differ between groups ($P > 0.05$), and hemodynamic parameters such as blood pressure and heart rate were also comparable (Table 3).

However, serum sodium levels were significantly lower in patients who died compared with those discharged (128±4 vs. 134.6±6.3 mmol/L, $P = 0.007$). In addition, the mean GWTG-HF risk score was higher among patients with outcome of death (47.7±7 vs. 38.4±8.1, $P = 0.013$). Although not statistically significant, non-survivors had a numerically longer hospital stay (median 18.5 vs. 4.5 days, $P = 0.117$) and higher BUN and NT-proBNP values.

Overall, these findings suggest that lower sodium levels and higher GWTG-HF risk scores were strongly associated with in-hospital mortality, while other clinical, hemodynamic, and laboratory variables did not show significant differences.

The discriminative ability of the GWTG-HF risk score for predicting in-hospital mortality was evaluated using ROC curve analysis. Graph 1 given below shows AUC was 0.754 [95% confidence interval (CI): 0.58-0.93], indicating good overall discrimination. At an optimal cut-off value of ≤47, the model achieved a sensitivity of 66.7% and a specificity of 85.2%. The corresponding PPV was 30.8%, while the NPV was notably high

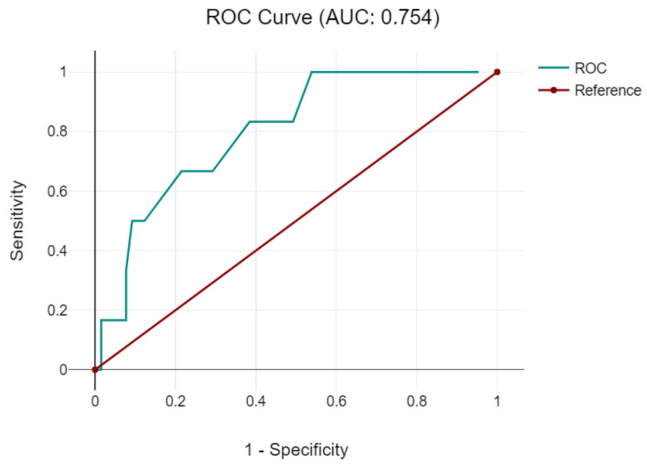
**Table 2. Patient outcomes and biomarkers across low, moderate, and high risk score groups**

| Parameter | Low score (0-33) | Moderate score (34-50) | High score (>50) | *P*-value |
|---|---|---|---|---|
| **Number of patients** | 17 | 43 | 7 | - |
| **Deaths (n)** | 0 | 4 | 2 | 0.012 (Fisher's exact) |
| **Mortality rate (%)** | 0% | 9.3% | 28.6% | 0.012 (Fisher's exact) |
| **Predicted mortality** | <1% | 1-5% | 5-10% | - |
| **ICU stay (days)** | 5.5 (2-16) | 8.75 (2-60) | 8 (2-21) | 0.041 (Kruskal-Wallis) |
| **Age (years)** | 58.1±15.3 | 72.1±9.2 | 74.4±11.7 | <0.001 (ANOVA) |
| **Systolic BP (mmHg)** | 150.2±28.1 | 129.4±20.3 | 100.0±12.6 | <0.001 (ANOVA) |
| **Heart rate (bpm)** | 89.6±13.3 | 90.0±20.1 | 92.0±24.1 | 0.331 (ANOVA) |
| **BUN (mg/dL)** | 17.1±5.9 | 17.9±10.0 | 48.1±35.2 | <0.001 (ANOVA) |
| **NT-proBNP (pg/mL)** | 9.122± 9.360 | 5.059±6.370 | 16.820±10.920 | <0.001 (Kruskal-Wallis) |
| **WBC (cells/µL)** | 9.891±3.160 | 10.957±5.620 | 9.956±3.050 | 0.56 |
| **RBC (millions/µL)** | 4.29±0.63 | 4.30±0.66 | 4.52±0.72 | 0.58 |
| **Hemoglobin (g/dL)** | 11.49±2.04 | 11.79±1.79 | 11.91±2.54 | 0.78 |
| **Hematocrit (%)** | 37.1±6.3 | 36.7±6.8 | 37.6±7.1 | 0.82 |
| **MCV (fL)** | 87.1±10.4 | 87.3±11.9 | 88.6±9.8 | 0.66 |
| **MCH (pg)** | 26.6±4.8 | 27.6±3.2 | 28.1±3.9 | 0.49 |
| **MCHC (g/dL)** | 30.9±1.3 | 31.2±2.9 | 31.6±2.1 | 0.62 |
| **COPD prevalence (%)** | 5.9% | 11.6% | 28.6% | 0.031 (chi-square) |
| **Black race (%)** | 0% | 0% | 0% | - |

ICU: Intensive care unit, BUN: Blood urea nitrogen, NT-proBNP: N-terminal pro-brain natriuretic peptide, WBC: White blood cell, RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: MCH concentration, COPD: Chronic obstructive pulmonary disease, ANOVA: Analysis of variance, BP: Blood pressure

at 96.3% as shown in Table 4, supporting the score's strength in ruling out adverse outcomes. Overall, the model's performance was graded as good.

Logistic regression analysis was performed to assess independent predictors of inhospital mortality. In univariable analysis, hyponatremia and COPD appeared associated with adverse outcomes, while other variables including SBP, BUN, age, and heart rate were not significant. However, after adjustment in the multivariable model, none of the predictors retained statistical significance. The GWTG-HF score showed a directional trend toward increased risk (odds ratio: 1.46, 95% CI 0.80-5.87, $P = 0.438$), but with wide CIs reflecting limited sample size. Notably, no patients with COPD died, producing an apparent protective effect in univariable regression; this represents complete separation, a statistical artifact of small samples, rather than a true protective role. Overall, these findings suggest that while the GWTG-HF score captures relevant prognostic information, its independent predictive value in this cohort was modest (Table 5).




**Graph 1.** ROC curve demonstrating discriminative ability of the GWTG-HF score (AUC: 0.754)

*ROC: Receiver operating characteristic, AUC: Area under the curve, GWTG-HF: Get With the Guidelines-heart failure*

**Table 3. Comparison of baseline characteristics and clinical parameters of patients with outcome of discharge and death**

| Characteristic | Total (n=67) | Discharged (n=61) | Dead (n=6) | *P*-value (dead vs. discharged) |
|---|---|---|---|---|
| Age (years) | 69.4±12.7 | 69.3±13.2 | 71.7±12.3 | 0.66 |
| Gender (male) | 36 (53.7%) | 34 (54.1%) | 2 (50%) | 1.00 |
| Gender (female) | 31 (46.3%) | 27 (45.9%) | 4 (50%) | 1.00 |
| Diagnosis: ADHF | 50 (74.6) | 46 (75.4%) | 4 (66.7%) | 0.65 |
| Diagnosis: ACS | 17 (32.8%) | 15 (24.5%) | 2 (33.3%) | 0.63 |
| Hypertension | 51 (76.1%) | 46 (75.4%) | 5 (83.3%) | 1.00 |
| Diabetes mellitus | 50 (74.6%) | 44 (72.1%) | 6 (100%) | 0.32 |
| Hypothyroidism | 9 (13.4%) | 9 (14.7%) | 0 (0%) | 0.57 |
| COPD | 9 (13.4%) | 9 (14.7%) | 0 (0%) | 0.57 |
| Black race | 0 | 0 | 0 | - |
| Systolic BP (mmHg) | 132±26.3 | 134.3±26.5 | 119.3±18.1 | 0.10 |
| Diastolic BP (mmHg) | 78.1±13.3 | 78.3±13.3 | 80.7±15.4 | 0.72 |
| Heart rate (bpm) | 89±20.4 | 89±20.1 | 91.7±39.6 | 0.87 |
| Sodium (mmol/L) | 134.1±6.4 | 134.6±6.3 | 128±4 | 0.007 |
| BUN (mg/dL) | 20.3±11.3 | 20±16.3 | 27.3±26 | 0.25 |
| NT-proBNP (pg/mL) | 6242.5±7402.6 | 6242.5±7402.6 | 8001.8±10462.4 | 0.64 |
| GWTG score | 39.6±8.5 | 38.4±8.1 | 47.7±7 | 0.013 |
| Length of stay (days) | 5 (4) | 4.5 (3) | 18.5 (24.5) | 0.117 |

ADHF: Acute decompensated heart failure, ACS: Acute coronary syndrome, COPD: Chronic obstructive pulmonary disease, BUN: Blood urea nitrogen, NT-proBNP: N-terminal pro-brain natriuretic peptide, GWTG: Get With the Guidelines, BP: Blood pressure

**Table 4. Performance characteristics of the GWTG score**

| Parameter | AUC | Cut-off | Sensitivity | Specificity | PPV | NPV | Performance grade |
|---|---|---|---|---|---|---|---|
| GWTG score | 0.754 | ≤47 | 0.667 | 0.852 | 0.308 | 0.963 | Good |

GWTG: Get With the Guidelines, AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value

**Table 5. Univariable and multivariable logistic regression analysis for predictors of inhospital mortality**

| Variable | Univariable OR (95% CI) | *P*-value | Multivariable OR (95% CI) | *P*-value |
|---|---|---|---|---|
| SP | 0.974 (0.93-1.00) | 0.134 | 1.035 (0.76-1.29) | 0.787 |
| BUN | 1.017 (0.88-1.07) | 0.800 | 0.899 (0.46-1.07) | 0.626 |
| Sodium | 0.828 (0.67-0.91) | 0.019 | 0.809 (0.28-1.16) | 0.510 |
| Age | 1.016 (0.95-1.11) | 0.683 | 0.902 (0.56-1.22) | 0.617 |
| Heart rate | 1.003 (0.95-1.08) | 0.941 | 0.960 (0.79-1.23) | 0.727 |
| COPD | 0.001 (0.00-0.01) | <0.001 | 0.417 (0.18-1.00) | 0.063 |
| GWTG score | 1.134 (1.04-1.36) | 0.701 | 1.458 (0.80-5.87) | 0.438 |

BUN: Blood urea nitrogen, COPD: Chronic obstructive pulmonary disease, GWTG: Get With the Guidelines OR: Odds ratio, CI: Confidence interval

## DISCUSSION

This study evaluated the prognostic utility of the GWTG-HF risk score in a cohort of ICU-admitted patients with ADHF. The findings underscore the relevance of this clinical tool in stratifying in-hospital mortality risk, while also highlighting potential limitations in high-acuity settings.

The GWTG-HF score estimates hospital mortality risk in HF patients, particularly in ICU settings, based on seven parameters: age, SBP, BUN, sodium, heart rate, race, and COPD status (Figure 1).

Patients with chronic kidney disease, valvular heart disease, pulmonary hypertension, and thyroid disorders were excluded because these conditions independently alter key prognostic variables such as BUN, sodium, and hemodynamic status, which could have confounded the score's predictive accuracy. However, their exclusion also limits external validity, as these comorbidities are common in real-world HF populations and may affect generalizability of our findings.

Among these, SBP, BUN, and age contribute more heavily to the final score, reflecting their stronger association with adverse outcomes. Specifically, lower SBP, elevated BUN, and advanced age have been consistently linked to increased mortality risk in HF populations. This scoring model offers a practical framework for early risk stratification and targeted clinical decision-making in critically ill patients. While SBP is widely recognized as a strong predictor of HF outcomes due to its correlation with cardiac output and perfusion status,[9] our findings revealed that several high-risk patients (GWTG-HF score >50) survived despite low SBP values. Their elevated risk scores were primarily driven by low SBP and/or high BUN, yet these patients did not experience mortality during ICU admission. This discrepancy suggests that while SBP heavily influences the score, its isolated predictive strength may vary depending on patient context and compensatory factors.

Conversely, some patients in the moderate-risk group who died had higher sodium levels than expected. Although hyponatremia is a well-established marker of poor prognosis

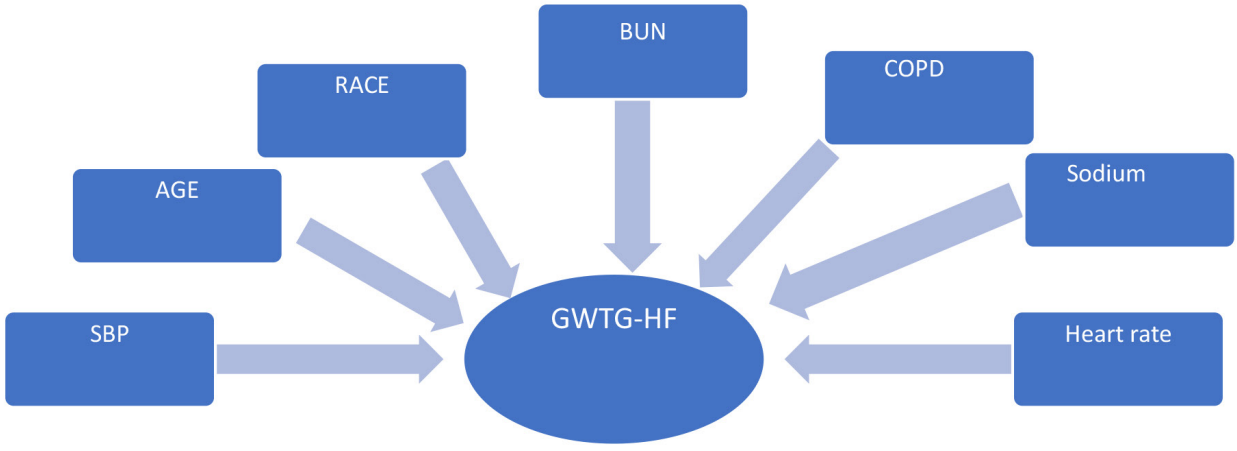



**Figure 1.** Parameters of GWTG-HF risk score

*GWTG-HF: Get With the Guidelines-heart failure, SBP: Systolic blood pressure, BUN: Blood urea nitrogen, COPD: Chronic obstructive pulmonary disease*

in HF,[10,11] the GWTG-HF model assigns relatively low weight to serum sodium. This may partially explain why certain high-sodium patients were under classified despite adverse outcomes, implying that sodium may warrant greater emphasis in future iterations of risk models.

The role of heart rate as a predictor remains debated across HF risk models. While some studies support its prognostic relevance,[5,12,13] others report minimal impact on mortality prediction.[3,14] Our dataset reflects only a modest variation in heart rate across risk categories, underscoring the ongoing need for consensus regarding its integration into standardized scoring systems.

A key observation was that 9% of patients succumbed during their ICU stay, with mortality disproportionately affecting postmenopausal females and patients with significant comorbidity burdens—100% had diabetes mellitus and 83.3% had hypertension. These findings align with existing literature linking metabolic syndrome with adverse HF outcomes.

Risk stratification using the GWTG-HF score revealed clear clinical and biochemical gradients across low, moderate, and high-risk groups. Lower-risk patients exhibited higher SBP and serum sodium, with lower BUN and heart rate, reflecting preserved hemodynamic and renal function. In contrast, high-risk patients demonstrated classic markers of decompensation—hypotension, hyponatremia, elevated BUN, and tachycardia, as well as higher COPD prevalence—corroborating the score's clinical validity.

The score's performance was further evaluated through outcome comparison. While low-risk patients had excellent alignment between predicted and observed mortality (0%), the moderate and high-risk groups experienced higher-than-predicted mortality, indicating a tendency toward risk underestimation in sicker patients. This suggests that the GWTG-HF score, while broadly useful, may require local recalibration or enhancement to maintain accuracy in critically ill patients.

However, multivariable regression did not confirm independent associations for the GWTG-HF score or its individual components, reflecting collinearity and the limited number of deaths in this cohort. Notably, sodium and COPD did not retain predictive value after adjustment, and the absence of deaths among COPD patients produced a statistical artifact in univariable analysis. These shortcomings highlight the constraints of small sample size and event rates, which limit the stability of regression estimates. Overall, the findings suggest that while the GWTG-HF score captures relevant prognostic information and performs well in ruling out adverse outcomes, its independent predictive value in critically ill populations remains modest. Larger, multicenter studies are needed to validate and recalibrate the score.

Haematological data added another dimension, pointing to progressive anaemia and altered red cell indices in higher-risk groups. These findings reinforce the concept of systemic compromise as HF advances. Moreover, NT-proBNP was markedly elevated in patients who died (mean ~8001.8 pg/mL), highlighting its potential as a complementary biomarker for short-term prognostication.

Our data revealed markedly elevated NT-proBNP levels (~8001.8 pg/mL) in non-survivors, suggesting its potential as an adjunctive biomarker. Recent studies have validated NT-proBNP's prognostic value in both acute and chronic HF settings. For instance, Nguyen et al.[15] identified NT-proBNP ≥1858 pg/mL as an independent predictor of 90-day mortality and rehospitalization in HFrEF patients. Similarly, Ali et al.[16] demonstrated a 5-4 fold increase in ICU admission or death risk with NT-proBNP >1826 pg/mL. These findings support the integration of NT-proBNP into existing risk models to improve predictive accuracy.

### Study Limitations

This study has several limitations. It was a single-centre study with a small sample size and only six deaths, limiting statistical reliability of ROC estimates, cut-off optimization, and predictive values. The exclusive focus on ICU-admitted patients introduces severity bias, while exclusion of patients with chronic kidney disease, valvular heart disease, pulmonary hypertension, or thyroid disorders further narrows generalizability. These comorbidities are common contributors to ADHF and their exclusion may bias the cohort toward less complicated cases. Outcomes were restricted to in-hospital mortality, without long-term follow-up. The cut-off value of ≤47 was identified post hoc and should be interpreted as exploratory. Aggressive ICU interventions (e.g., vasopressors, mechanical ventilation, renal replacement therapy) may have confounded associations between admission scores and outcomes, underscoring the need for local recalibration of the GWTG-HF score in high-acuity settings. Additionally, underrepresentation of certain predictors, such as black race and COPD, restricted assessment of their true impact. Although NT-proBNP levels were collected and found to be prognostically relevant, they were not integrated into the GWTG-HF model. Future multicenter studies with larger cohorts, longer follow-up, and recalibration for ICU populations are needed to refine the score and enhance its predictive accuracy.

## CONCLUSION

In ICU patients with ADHF, the GWTG-HF score reliably predicts hospital mortality and is especially useful for identifying lowrisk cases. Refinement with additional biomarkers such as NT-proBNP may improve predictive accuracy in high-acuity settings.

## Ethics

**Ethics Committee Approval:** The protocol received approval from the Institutional Ethics Committee of Ramaiah Medical College (ref. no: MSRMC/EC/SP03/122022, reg. no: ECR/215/Inst/KA/2013/RR22) on 15 December 2022.

**Informed Consent:** Written informed consent was obtained from all participants prior to enrollment.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: Y.R., A.K., A.H., M.A.S., M.S., Concept: Y.R., A.K., M.A.S., Design: Y.R., A.K., M.A.S., Data Collection or Processing: Y.R., A.H., M.S., Analysis or Interpretation: Y.R., A.K., M.S., Literature Search: Y.R., A.K., M.S., Writing: Y.R., A.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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# Readability Assessment of Patient Information Leaflets for Commonly Used Cardiovascular Drugs

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## Abstract

**Background and Aim:** Adequate comprehension of drug information leaflets is essential for safe medication use, particularly in cardiology where elderly patients and polypharmacy are common. This study evaluated the readability of patient information leaflets for commonly used cardiovascular drugs in Türkiye.

**Materials and Methods:** Instructions for use (IFU) and short product information (SPI) sections of 28 cardiovascular drugs (10 NOACs, 9 antiarrhythmics, and 9 antiplatelets) were analyzed using two validated Turkish readability formulas: Ateşman, Bezirci and Yılmaz. Structural text parameters were also quantified.

**Results:** SPI sections contained significantly higher word, sentence, and character counts than IFU sections ($P < 0.001$). Despite these differences, overall Ateşman readability scores did not differ significantly between IFU and SPI. However, SPI sections of antiarrhythmic drugs demonstrated significantly lower readability and required higher estimated educational levels compared with their IFU counterparts ($P < 0.05$).

**Conclusion:** The readability of cardiovascular drug leaflets, particularly SPI sections of antiarrhythmic medications, may exceed the educational level of a substantial proportion of elderly patients. Simplification of written drug information may improve patient understanding and medication safety.

**Keywords:** Readability, drug leaflets, cardiology, NOAC, antiarrhythmic, antiplatelet, elderly patients, patient education

## INTRODUCTION

The readability of patient information leaflets is a key determinant of patients' ability to understand medication instructions, potential adverse effects, and safety precautions. In cardiovascular medicine, where patients are often elderly and exposed to complex treatment regimens, inadequate readability may compromise safe drug use.[1,2]

Regulatory authorities such as the European Medicines Agency (EMA) emphasize that written drug information should be understandable to the general population and recommend readability testing using real users. However, formula-based readability indices remain widely used as objective screening tools.[3,4]

This study aimed to evaluate the readability of instructions for use (IFU) and short product information (SPI) sections of commonly prescribed cardiovascular drugs in Türkiye and to estimate the educational level required for adequate comprehension.

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## METHODS

### Study Design and Drug Selection

This descriptive, cross-sectional study analyzed patient information leaflets of cardiovascular drugs registered on the Turkish Medicines and Medical Devices Agency (TİTCK) website at the time of the study. All NOACs and antiplatelet agents were included. For antiarrhythmic drugs, one representative drug was selected for each active substance to ensure coverage across the class.

This study did not involve any human participants, identifiable personal data, biological material, or interventional procedures. The analysis was based solely on publicly available pharmaceutical package inserts/prospectuses. In accordance with national regulations and international guidelines, this type of methodological/document-based research is exempt from ethics committee approval. Therefore, ethics committee approval was not required for this study.

### Data Source

IFU and SPI sections were obtained from the official TİTCK website.

### Readability Assessment

Readability was evaluated using the Ateşman[5], Bezirci and Yılmaz[6] formulas, both validated for Turkish texts. Calculations were performed manually by two independent researchers, and discrepancies were resolved by consensus.

- **Ateşman[5] Formula:** Readability score=198.825 - (40.175×avg. syllables per word) - (2.610×avg. words per sentence).
- **Bezirci and Yılmaz[6] Formula:** Readability score=$\sqrt{OKS} \times [(H3\times0.84)+(H4\times1.5)+(H5\times3.5)+(H6\times26.25)]$ (OKS: Average sentence length, H3-H6: Average number of 3 to ≥6 syllable words per sentence).
- **Ateşman[5] Readability Index:** Scores are interpreted on a 0-100 scale, where 1-29 indicates "very difficult," 30-49 "difficult," 50-69 "moderately difficult," 70-89 "easy," and 90-100 "very easy." Although the Ateşman formula may mathematically produce values outside this interval, scores are conventionally interpreted within the 0-100 readability scale.
- **Bezirci and Yılmaz[6] Formula:** This formula estimates the educational level required for comprehension: 1-8 corresponds to primary education, 9-12 to secondary education, 13-16 to high school, and >16 to academic education.

Calculations were performed manually by two independent researchers. Discrepancies between the two evaluations were reviewed jointly and resolved by consensus. Although inter-rater agreement statistics were not formally calculated, the formula-based nature of the readability indices ensured objective and reproducible measurements.

### Statistical Analysis

Normality of continuous variables was assessed using the Shapiro-Wilk test. IFU and SPI sections belonging to the same drug were compared using paired-sample t-tests, as these sections represent matched textual components of the same leaflet. Data are presented as mean ± standard deviation.

Given the exploratory nature of the study and the fixed number of available drug leaflets, no a priori power analysis was performed. Statistical significance was set at $P < 0.05$. Analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

SPI sections demonstrated significantly higher word counts, sentence numbers, and character counts compared with IFU sections (all $P < 0.001$). Specifically, the mean word count was markedly higher in SPI sections than in IFU sections, accompanied by a greater number of sentences and overall text length. Despite these pronounced structural differences, overall Ateşman[5] readability scores were comparable between IFU and SPI sections, indicating similar general readability levels (Table 1).

When stratified by drug class, distinct patterns emerged. For antiarrhythmic drugs, SPI sections exhibited significantly lower Ateşman[5] readability scores compared with IFU sections (71.5±2.68 vs. 65.6±3.10; $P = 0.012$), along with significantly higher estimated educational level requirements (7.44±0.88 vs. 8.78±0.66; $P = 0.014$) (Table 2).

In contrast, for NOACs, SPI sections demonstrated higher readability scores compared with IFU sections, whereas no significant differences in readability scores or required educational levels were observed between IFU and SPI sections of antiplatelet drugs.

**Table 1. Differences between IFU and SPI**

| Variables | IFU | SPI | *P*-value |
|---|---|---|---|
| Number of words | 2379.2±448 | 7325.8±2666 | **0.001** |
| Number of characters | 185518±3408 | 56730.2±18947 | **0.001** |
| Number of difficult words | 2314.0±439 | 7009.1±2487 | **0.001** |
| Number of short words (<5 characters) | 462.5±107 | 1556±709 | **0.001** |
| Number of characters without spaces | 16168.5±2963 | 49385.6±16290 | **0.001** |
| Number of sentences | 391.0±64 | 1311.8±467 | **0.001** |
| Number of paragraphs | 322.7±55 | 1022.4±389 | **0.001** |
| Mean word length | 2.76±0.05 | 2.78±0.15 | 0.754 |
| Average sentence lenght | 6.07±0.41 | 5.56±0.44 | **0.001** |
| Ateşman[5] readability index | 72±1.93 | 72.43±5.59 | 0.464 |
| Readability level | 7.21±0.63 | 7.57±1.06 | 0.132 |

IFU: Instructions for use, SPI: Short product information

**Table 2. Readability index and levels of cardiac drug groups according to IFU and SPI**

| | IFU | | SPI | | *P*-value | |
|---|---|---|---|---|---|---|
| | Ateşman[5] readability index | Readability level | Ateşman[5] readability index | Readability level | Ateşman[5] readability index | Readability level |
| NOAC | 72.15±1.62 | 7.15±0.55 | 77.09±1.59 | 6.85±0.55 | **0.001** | 0.317 |
| Anti-platelet | 72.6±1.18 | 7.0±0.3 | 72.51±2.91 | 7.33±0.81 | 0.345 | 0.317 |
| Anti-arrhythmic | 71.5±2.68 | 7.44±0.88 | 65.6±3.1 | 8.78±0.66 | **0.012** | **0.014** |

IFU: Instructions for use, SPI: Short product information

## DISCUSSION

This study demonstrated that the readability of drug information leaflets used in cardiology is relatively low, potentially limiting patient understanding. Readability metrics offer objective insights into whether a document is likely to be understood by the average patient. Given the pharmacological complexity of cardiovascular drugs and their associated risks, enhancing the clarity of written information is critical for safe medication use.

Our findings align with previous literature indicating that low readability of drug leaflets may not only impede patient comprehension but also heighten anxiety and reduce adherence.[7,8] This is especially pertinent for elderly or polymedicated individuals, who often face greater difficulty in interpreting medical content due to age-related cognitive decline, visual impairment, and limited health literacy.

In a national survey conducted in Türkiye involving 1,944 participants, 28.2% were taking one medication, while 17.3% were taking five or more.[9] Polypharmacy, particularly in elderly populations with low educational attainment, poses a significant barrier to safe and effective drug use.[10,11] According to Turkish Statistical Institute data, only a small proportion of elderly individuals have completed higher education, whereas nearly half have only primary-level education.[12] Given that most drug leaflets in the present study required an estimated education level corresponding to the 7$^{th}$-8$^{th}$ grade for adequate comprehension, these findings raise important concerns regarding accessibility, patient autonomy, and medication safety.

Similar findings have been reported in recent international studies evaluating the readability of patient information leaflets and other health-related materials. A large systematic overview of readability research covering more than 29,000 health information materials across 438 studies found that most patient education documents exceed the recommended sixth-to-eighth grade reading level required for the general population.[13] In addition, recent investigations of medication leaflets and digital medicine information systems have demonstrated that complex terminology and long sentence structures remain common, potentially limiting patient comprehension and safe medication use.[14] Furthermore, contemporary studies evaluating the readability of drug leaflets in different therapeutic areas have reported that many materials still require educational levels above those of a considerable proportion of patients.[15] Taken together, these findings suggest that limited readability of medication information leaflets represents a persistent and global challenge rather than a country-specific issue.

Furthermore, although the EMA recommends user-based readability testing, most drug information leaflets continue to be evaluated primarily through formula-based indices. While such indices provide standardized and reproducible assessments of textual complexity, they do not capture real-world patient comprehension, contextual understanding, or behavioral outcomes. Therefore, the present results should be interpreted as indicators of potential difficulty rather than direct measures of patient understanding.

An additional noteworthy finding of this study is the significantly lower readability observed in the SPI sections of antiarrhythmic medications. Given that patients often rely on SPI due to its easier accessibility and condensed format, reduced readability in this section may paradoxically increase the risk of misunderstanding, particularly for drugs with narrow therapeutic windows and potentially serious adverse effects. This highlights the need for targeted revision of SPI texts, especially for high-risk cardiovascular medications.

Taken together, these findings underscore the importance of adapting written drug information to the needs of elderly and low-literacy populations. Simplifying sentence structure, reducing medical jargon, and incorporating patient-centered design principles may improve the usability of drug leaflets. Future studies should combine readability assessments with user-testing approaches to better evaluate how revised leaflets influence patient understanding, adherence, and clinical outcomes.

### Study Limitations

Several limitations should be acknowledged. First, the study relied solely on formula-based readability indices and did not include user testing or direct assessment of patient comprehension. Second, visual and graphical elements of leaflets were not evaluated. Third, selection of representative antiarrhythmic drugs may introduce selection bias. Finally, inter-rater reliability statistics were not calculated for manual measurements.

## CONCLUSION

In conclusion, the readability of patient information leaflets for cardiovascular drugs—particularly the SPI sections of antiarrhythmic agents—may exceed the educational level of a considerable proportion of elderly patients. This mismatch between text complexity and patient literacy may compromise medication safety and informed decision-making. Regulatory authorities and pharmaceutical manufacturers should consider implementing standardized readability thresholds, simplifying technical terminology, and incorporating user-testing procedures during leaflet development. Such measures may enhance patient comprehension, improve adherence, and ultimately contribute to safer medication use in cardiovascular care.

### Ethics

**Ethics Committee Approval:** This study did not involve any human participants, identifiable personal data, biological material, or interventional procedures. The analysis was based solely on publicly available pharmaceutical package inserts/prospectuses. In accordance with national regulations and international guidelines, this type of methodological/document-based research is exempt from ethics committee approval. Therefore, ethics committee approval was not required for this study.

**Informed Consent:** Patient informed consent was waived because the study did not involve human participants, animal subjects, or identifiable personal data.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: H.S., Concept: M.G., Design: H.S., R.A.E., Data Collection or Processing: M.G., U.A., Analysis or Interpretation: H.S., Literature Search: M.G., Writing: U.A.

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# Clinical Characteristics, Treatment Strategies, and Short-term Outcomes in Octogenarian Patients with Acute Coronary Syndrome

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## Abstract

**Background and Aim:** Octogenarians (≥80 years) with acute coronary syndrome (ACS) represent a high-risk group due to comorbidities, frailty, and atypical clinical presentations, which pose significant management challenges. There is limited evidence to guide optimal management, especially regarding the choice between conservative and invasive strategies. This study examines the clinical characteristics, treatment approaches, and short-term outcomes in this population.

**Materials and Methods:** In this multi-center observational study, 197 octogenarian ACS patients were enrolled between January 2022 and August 2024. Patients were categorized into conservative (57.4%) and invasive (42.6%) management groups. Demographics, comorbidities, clinical presentation, and geriatric assessments (Fried Frailty Scale, Confusion Assessment Method, Geriatric Depression Scale) were collected. Outcomes assessed included in-hospital and 30-day mortality, reinfarction, bleeding (Bleeding Academic Research Consortium ≥3), and target vessel revascularization (TVR).

**Results:** The cohort was predominantly non-ST-elevation ACS (88.3%) with high frailty (53.8%). Selection bias was notable: the conservative group had more peripheral vascular disease (38.9% vs. 19.0%, $P = 0.003$) and delirium (42.5% vs. 26.2%, $P = 0.02$), while the invasive group had higher Global Registry of Acute Coronary Events scores ($P = 0.039$) and body mass index ($P = 0.028$). In-hospital (5.9% vs. 7.9%) and 30-day mortality (9.6% vs. 15.9%) were lower in the invasive group, though these differences were not statistically significant. The invasive group had a higher TVR rate (13.1% vs. 0.0%, $P < 0.001$) and a trend toward lower reinfarction (3.5% vs. 10.6%, $P = 0.12$). Major bleeding rates were similar (13.1% vs. 9.7%, $P = 0.61$).

**Conclusion:** Geriatric syndromes have a substantial impact on ACS management in octogenarians. Frailty and delirium are associated with a preference for conservative care. In appropriately selected patients, invasive treatment appears safe and associated with numerical reduction of recurrent ischemic events without increasing short-term risk. Comprehensive geriatric assessment is essential for individualized treatment planning.

**Keywords:** Octogenarian, frailty, acute coronary syndrome

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## INTRODUCTION

Ischemic heart disease (IHD) is the top global cause of death, and advanced age is its main non-modifiable risk factor linked to higher morbidity and mortality.[1,2] Acute coronary syndrome (ACS) in the elderly, especially octogenarians (≥80 years), is rising and presents a growing challenge.[3,4]

Octogenarian patients with ACS represent a distinct and highly vulnerable population. They have more comorbidities, frailty, polypharmacy, and face higher complications from both disease and treatment. Compared to younger patients, octogenarians often present with atypical symptoms, such as dyspnea, dizziness, or syncope. These atypical symptoms delay ACS diagnosis and increase rates of conservative management.[5-7] This management disparity is exacerbated by the underrepresentation of the elderly in major clinical trials, resulting in gaps in evidence-based guidelines.[8] Early invasive strategies are associated with better outcomes in ACS but also with higher complication rates in this subgroup. Management choice depends on comorbidities, functional status, and life expectancy.[9,10]

Given these challenges, a thorough understanding of clinical characteristics, treatment patterns, and outcomes in this cohort is essential for optimizing management. This study investigates the clinical profiles, treatment strategies (conservative versus invasive), and short-term outcomes of octogenarian patients with ACS. The findings aim to inform evidence-based, individualized decision-making for this high-risk group.

## METHODS

### Study Design

This multi-center observational study provides real-world insights into the management and outcomes of octogenarians with ACS by comparing invasive and conservative management strategies. Conducting a randomized controlled trial (RCT) in this high-risk population presents significant ethical and practical challenges; therefore, an observational design was chosen to reflect actual clinical practice.

### Objective

To investigate the characteristics, treatment approaches, and outcomes of octogenarian patients hospitalized with ACS.

### Population of Study

A total of 212 patients aged 80 and older presenting with ACS were evaluated for eligibility. Of these, 197 were enrolled between January 2022 and August 2024. Fifteen patients were excluded—seven declined to participate, and eight could not be reached after discharge. Patients or their representatives provided written consent to the study. Data from the included patients were collected during the study period, and a complete case analysis was performed. The study was approved by the Local Research Ethics Committee, Cairo University Faculty of Medicine (approval no: MD-371-2021, date: 04.10.2022).

### Inclusion Criteria

Age ≥80 years old. Patients presented with ACS [non-ST-segment elevation (NSTE)-ACS or ST-segment elevation myocardial infarction (STEMI)].

### Exclusion Criteria

1. Patient refusing to participate in the study.

2. Patients who presented with elevated cardiac troponin levels due to non-ischemic causes such as renal impairment, heart failure (HF), myocarditis, sepsis, or rhabdomyolysis were excluded.

### Methodology

All the patients were subjected to the following during the index hospitalization:

- Demographics and risk factors: Age, gender, hypertension [systolic blood pressure (SBP) ≥140 and diastolic blood pressure (DBP) ≥90 mmHg],[11] diabetes mellitus (HbA1c > 6.5 and FBS >126),[12] smoking, dyslipidemia [low-density lipoprotein (LDL) cholesterol >70 mg/dL, triglycerides >150 mg/dL][13], family history of IHD,[14] previous coronary artery bypass grafting (CABG), history of percutaneous coronary intervention (PCI).
- Comorbidities: Chronic kidney disease,[15] hepatic impairment,[16] peripheral vascular disease (PVD),[17] cerebrovascular disease (ischemic stroke or transient ischemic attack),[18] chronic obstructive pulmonary disease.[19]
- ACS data:
    - Clinical presentation: Symptom characteristics (typical vs. atypical chest pain, diaphoresis, nausea, vomiting, dyspnea, syncope).
    - ACS type: NSTE-ACS and STEMI.
    - Timing: Duration of chest pain, time from first medical contact to revascularization.
    - Hemodynamic support: Use of vasopressors, intra-aortic balloon counterpulsation (IABP), in-hospital or out-of-hospital resuscitation.
    - Management strategy: The choice between conservative and invasive strategies was made at the discretion of

the treating physician, based on assessment of patient characteristics, comorbidities, geriatric syndromes, and clinical presentation, rather than following predefined standardized criteria. This approach reflects real-world clinical practice in this complex patient population.

- Conservative strategy: A management approach in which coronary angiography is not routinely performed, but is reserved for patients with refractory symptoms or objective evidence of recurrent ischemia, despite optimal medical therapy. The initial focus is on pharmacological stabilization.
- Invasive strategy: This approach involves routine coronary angiography within a recommended timeframe, with the intention to perform PCI or, less commonly, CABG if the coronary anatomy is suitable.[20]

• Electrocardiographic (ECG): Rhythm, ST-segment changes, and conduction abnormalities.

• Transthoracic echocardiography: The echocardiographic studies were performed during the first 48 hours of hospitalization.[21]

• Laboratory assessment: Including cardiac enzymes [creatine kinase-MB, high-sensitivity troponin, glomerular filtration rate (GFR), creatinine, hemoglobin, total leucocytic count, platelets count, alanine aminotransferase, aspartate aminotransferase, HbA1c, total cholesterol, high-density lipoprotein, LDL, and triglycerides].

• Coronary angiographic assessment: This included evaluation of single versus multivessel disease, left main (LM) coronary artery or equivalent involvement, lesion characteristics (type, length, calcification), and access site complications. We also recorded the incidence of contrast-induced acute kidney injury.[22,23]

• Frailty was assessed using the Fried Frailty Scale. Additional evaluations included the Confusion Assessment Method (CAM) and the Geriatric Depression Scale (GDS).

- Fried Frailty Phenotype Scale:[24]
  - Administration: Patients were assessed across five predefined criteria: unintentional weight loss, self-reported exhaustion, low physical activity (Minnesota leisure time activity questionnaire), slow walking speed (4-meter walk), and weak handgrip strength (dominant hand, measured with a Jamar dynamometer).
  - Scoring and Interpretation: Each criterion present was scored as 1 point. Patients were categorized as follows:
- Robust (not frail): 0 criteria present.
- Pre-frail: 1-2 criteria present.
- Frail: ≥3 criteria present.
- CAM:[25]
  - Administration: The CAM was administered daily throughout hospitalization by the attending nurse to screen for acute delirium. The assessment evaluated: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness.
  - Scoring and interpretation: A patient was diagnosed with delirium (CAM-positive) if they displayed both features (1) and (2) plus either feature (3) or (4).
- GDS-15:[26]
  - Administration: The 15-item short form of the GDS was used. Patients were asked to answer "yes" or "no" to 15 questions about how they felt over the past week.
  - Scoring and interpretation: Each answer suggestive of depression scores 1 point. The total score was interpreted as:
- Normal (no significant depression): 0-5 points.
- Suggestive of mild/moderate depression: 6-10 points.
- Suggestive of severe depression: 11-15 points.

In this study, a score of ≥6 was used to define clinically significant depressive symptoms.

## Patient Outcomes

- Primary outcome:
  - In-hospital mortality: Death from any cause during hospital admission.
- Secondary outcomes:
  - Target vessel revascularization (TVR): A repeat revascularization procedure (either PCI or CABG) performed on the original culprit vessel treated during the index ACS event.[27]
  - Reinfarction: According to the fourth universal definition of myocardial infarction:[28]

- In patients with PCI for the index myocardial infarction: A recurrence of symptoms and new ECG changes plus a re-elevation of cardiac troponin values by >20% from the previous trough level, with a peak value exceeding the 99$^{th}$ percentile upper reference limit (URL).
- In patients without PCI (conservative arm): The detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL and with at least one of the following: (1) symptoms of ischemia, (2) new ischemic ECG changes, (3) development of pathological Q-waves, or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- In-hospital HF: The development of new or worsening symptoms and signs of HF (e.g., dyspnea, orthopnea, pulmonary edema, hypoperfusion) requiring intensification of diuretic therapy or the initiation of intravenous vasoactive agents (e.g., diuretics, inotropes, vasopressors) during the index hospitalization.
- Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding:[29]
  - BARC 3a: Overt bleeding with a hemoglobin drop of 3 to <5 g/dL odds ratio (OR) transfusion of whole blood or packed red blood cells.
  - BARC 3b: Overt bleeding with a hemoglobin drop ≥5 g/dL OR cardiac tamponade OR bleeding requiring surgical intervention or intravenous vasoactive drugs.
  - BARC 3c: Intracranial hemorrhage OR subcategories confirmed by autopsy, imaging, or lumbar puncture.
  - BARC 5: Fatal bleeding.
- Stroke: Rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting >24 hours or leading to death, with no apparent non-vascular cause, confirmed by a neurologist and neuroimaging (computed tomography or magnetic resonance imaging).[30]
- Readmission: An unplanned admission to any hospital for any cause within a specified timeframe after the index discharge (30 days).

## Medical Follow-up

Throughout the one-month follow-up period after discharge, all patients remained on guideline-directed medical therapy. This included antithrombotic and anti-ischemic agents, with additional HF medications as clinically indicated. The therapeutic regimen typically consisted of antithrombotic agents, statins, beta-blockers, nitrates, and renin-angiotensin-aldosterone inhibitors.[20] Survival was assessed at one month following hospital discharge.

## Statistical Analysis

A formal sample size calculation was not performed a priori for this study. The final sample size of 197 participants was determined based on feasibility and convenience sampling over a defined enrollment period.

This approach was justified for the following reasons:

- Real-world constraints in a specific population: This study focused exclusively on octogenarians (≥80 years) presenting with ACS. This population is distinct and challenging to enroll due to higher mortality, more complex comorbidities, and frequent exclusion from clinical trials. A consecutive sample over 30 months was the most pragmatic approach to obtain a meaningful, real-world cohort representative of this demographic at our institution.
- Explorative and hypothesis-generating nature: As an observational study, its primary aim was to describe characteristics, management patterns, and associated outcomes, rather than to test a single prespecified hypothesis with a definitive effect size. The sample size is sufficient to provide precise estimates of prevalence (e.g., frailty, depression) and to identify clinically relevant trends and associations that can inform the design of future, larger-scale or randomized studies.
- Post-hoc evaluation of precision: Despite the lack of a prior power calculation, the obtained sample provides measurable precision. For example, with 197 participants, the proportion of a given outcome (e.g., the overall 30-day mortality rate of 13.4%) has a 95% confidence interval (CI) of approximately ±4.8%. This indicates a reasonable level of precision for estimating event rates within this cohort.

Therefore, although this sample may be underpowered to detect small differences in less common endpoints, it constitutes a clinically relevant effort to characterize the presentation and care of a critically important, understudied patient group in a real-world setting. A complete case approach was utilized in this study; patients with missing data for any variable included in a specific analysis were excluded from that analysis.

Descriptive statistics were used to summarize the demographic and clinical characteristics of patients. Continuous variables were presented as mean with standard deviation for normally distributed data or median with interquartile range for skewed data, while categorical variables were expressed as percentages. The normality of continuous data was assessed using the Shapiro-Wilk test. Additionally, histogram charts and measures of central tendency and dispersion were examined to further assess the distributions' normality. Group comparisons were conducted using Student's t-test for normally distributed continuous variables and the Mann-Whitney U-test for skewed continuous variables. Categorical variables were compared between groups using the chi-square ($\chi^2$) test, as appropriate. Variables with a *P*-value <0.2 in univariate analysis, along with clinically relevant factors such as age, sex, and type of ACS, were considered for inclusion in the multivariable logistic regression model. A backward stepwise selection method was employed to identify independent predictors of mortality. A two-sided *P*-value of less than 0.05 was considered statistically significant. For the comparison of clinical outcomes between the invasive and conservative management groups, OR with 95% CIs were calculated to estimate the effect size and precision of the treatment strategy. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL), Version 27.0 for Windows.

## RESULTS

This multicenter observational study enrolled 197 octogenarian patients (range: 80-95 years) who were diagnosed with ACS between January 2022 and August 2024. The study aimed to assess their clinical characteristics, treatment approaches, and in-hospital and short-term outcomes. The study also compared conservative (57.4%) vs. invasive (42.6%) management among the study patients. All patients in the invasive arm received PCI.

Table 1 shows the baseline characteristics of the studied patients. The mean age in this study was 84.8±3.9, with 56% of the patients were male. The studied patients showed NSTE-ACS dominance, accounting for 88.3% of cases, and it was significantly more frequent in the conservative group ($P$ = 0.004). The management strategy was invasive management in 73.9% of STEMI patients (17 out of 23) and in 38.5% of NSTE-ACS patients (67 out of 174). The decision to proceed with either coronary intervention or conservative management was made individually for each patient based on their clinical condition.

There were differences between the two management strategies in baseline characteristics (Table 1). The invasive group had a significantly higher average body mass index (BMI) (30.45±3.52 kg/m²) compared to the conservative group (29.33±3.45 kg/m²) ($P$ = 0.028). Patients in the conservative group had a significantly higher history of PVD (38.9%) compared to the invasive group (19.0%) ($P$ = 0.004).

Octogenarians presented with atypical ACS symptoms rather than classic chest pain. Only one-fifth of the patients presented with chest pain. There was a trend of late presentation of patients presenting with chest pain, with a chest pain duration of 10.0±16.1. The conservative group showed a non-significantly longer duration of chest pain (11.2±18.6 vs. 8.4±12.0, $P$ = 0.23). The other presenting symptoms included dyspnea, diaphoresis, nausea, vomiting, syncope, and cardiac arrest. While the difference between groups in individual symptoms is not statistically significant, the overall trend suggests a higher likelihood of conservative management for these patients (Table 2). DBP is relatively low in the whole group (66.2±15.2); however, the conservative group exhibited a significantly higher DBP (67.96±16.40 mmHg) upon admission compared to the invasive group (63.68±12.99 mmHg) ($P$ = 0.049). Cardiac resuscitation on presentation (out-of-hospital or in-hospital) was numerically higher in the invasive group. The use of vasopressors and IABP was also higher in the invasive group; however, the *P*-values were not significant.

The invasive group showed a statistically higher incidence of Q-wave myocardial infarction (42.4% vs. 54.7%, $P$ = 0.03). All patients with anterior STEMI were treated invasively ($P$ < 0.001). On the contrary, some patients with inferior (3 patients) and lateral (3 patients) STEMI were treated conservatively.

The overall ejection fraction in the study was 50.6±14.1 with no significant difference between the two groups. Significant aortic stenosis and left ventricular thrombus were detected in 9.4% and 4.1% of the study patients, respectively. The conservative group had a significantly higher prevalence of mitral regurgitation (57.5%) compared to the invasive group (42.8%) ($P$ = 0.045) (Table 3).

Interestingly, the majority of patients were frail (53.8%) and prefrail (46.2%) according to the Fried Frailty Scale. There was a trend of increased frailty in the conservative group (58.4% vs. 47.6%). Delirium was significantly higher in the conservative group (42.5%) compared to the invasive group (26.2%) ($P$ = 0.019). The invasive group had significantly higher GRACE scores ($P$ = 0.039), indicating a higher overall risk profile in patients selected for invasive management. Patients with GRACE scores ≥140 were predominantly treated invasively (Table 4).

Regarding the laboratory, the mean GFR in the study was 49.0±22.7. There was a trend of lower creatinine (1.7±1.1 vs. 1.4±0.9, $P$ = 0.09) in the invasive group. The invasive group also showed a trend of higher HbA1c (6.1±1.2 vs. 6.5±1.3, $P$ = 0.05) and lower total cholesterol values (183.4±50.6 vs. 170.7±42.5, $P$ = 0.07) (Table 5).

**Table 1. Baseline criteria, comorbidities, and baseline medications for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n=113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| Age (years) | 84.8±3.9 | 84.8±3.9 | 84.2±3.6 | 0.27 |
| Male gender | 111 (56.3) | 67 (59.3) | 44 (52.4) | 0.33 |
| BMI (kg/m$^2$) | 29.8±3.5 | 29.3±3.5 | 30.5±3.5 | **0.03** |
| Smoker | 50 (25.4) | 31 (27.4) | 19 (22.6) | 0.66 |
| Dyslipidemia | 169 (85.8) | 95 (84.1) | 74 (88.1) | 0.42 |
| Hypertension | 170 (86.3) | 97 (85.8) | 73 (86.9) | 0.83 |
| Diabetes mellitus | 101 (51.3) | 55 (48.9) | 46 (54.8) | 0.40 |
| Ischemic heart disease | 144 (73.1) | 84 (74.3) | 60 (71.4) | 0.65 |
| History of PCI | 60 (30.5) | 40 (35.4) | 20 (23.8) | 0.08 |
| Previous CABG | 13 (6.6) | 8 (7.1) | 5 (6.0) | 0.75 |
| Family history for IHD | 51 (25.9) | 29 (25.7) | 22 (26.2) | 0.93 |
| Atrial fibrillation | 57 (28.9) | 35 (31.0) | 22 (26.2) | 0.56 |
| PVD | 60 (30.5) | 44 (38.9) | 16 (19.0) | **0.003** |
| CVD | 51 (25.9) | 30 (26.5) | 21 (25.0) | 0.81 |
| CKD | 79 (40.1) | 45 (39.8) | 34 (40.5) | 0.93 |
| COPD | 52 (26.4) | 33 (29.2) | 19 (22.6) | 0.30 |
| Liver disease | 9 (4.6) | 4 (3.5) | 5 (6.0) | 0.42 |
| **Medications** | | | | |
| Aspirin | 127 (64.5) | 77 (68.1) | 50 (59.5) | 0.27 |
| Clopidogrel | 145 (73.6) | 83 (73.4) | 62 (73.8) | 1.00 |
| Ticagrelor | 9 (4.6) | 4 (3.5) | 5 (6.0) | 0.50 |
| Beta blocker | 63 (32.0) | 33 (29.2) | 30 (35.7) | 0.42 |
| ACEI | 38 (19.3) | 23 (20.3) | 15 (17.8) | 0.80 |
| ARB | 37 (18.8) | 18 (15.9) | 19 (22.6) | 0.32 |
| ARNI | 39 (19.8) | 26 (23.0) | 13 (15.4) | 0.26 |
| Diuretics | 56 (28.4) | 33 (29.2) | 23 (27.3) | 0.90 |
| CCB | 49 (24.9) | 25 (22.1) | 24 (28.5) | 0.39 |
| PPI | 43 (21.8) | 22 (19.4) | 21 (25.0) | 0.45 |
| Insulin | 43 (21.8) | 25 (22.1) | 18 (21.4) | 0.99 |
| Oral hypoglycemic drugs | 62 (31.5) | 31 (27.4) | 31 (36.9) | 0.21 |
| Vasopressors | 29 (14.7) | 14 (12.4) | 15 (17.8) | 0.39 |
| IABP | 4 (2.0) | 1 (0.8%) | 3 (3.5%) | 0.42 |

SD: Standard deviation, CABG: Coronary artery bypass grafting, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor-neprilysin inhibitor, BMI: Body mass index, CCB: Calcium channel blocker, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, IABP: Intra-aortic balloon counterpulsation, IHD: Ischemic heart disease, PCI: Percutaneous coronary intervention, PPI: Proton pump inhibitor, PVD: Peripheral vascular disease

Based on the data from the invasive strategy group (n=84), coronary angiography revealed significant and severe coronary artery disease. The vast majority of patients (98%) had at least one diseased vessel, with multi-vessel disease being common; 31.0% had one-vessel disease, 28.6% had two-vessel disease, and 38.1% had three or more diseased vessels. The lesions were complex, predominantly type B (42.9%) or type C (39.3%), with a high prevalence of moderate or greater calcification (65.5%). The LM artery and its equivalent were frequently affected (26.2% and 20.2%, respectively). Following angiography, the invasive group patients underwent an intervention as follows: 67.9% received stents (most requiring stents longer than 15 mm and larger than 2.5 mm), and 11.9% were referred for CABG. The invasive procedures were associated with a 16.7% rate of access site complications and a 15.5% incidence of contrast-induced nephropathy.

**Table 2. Clinical presentation and ECG findings for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n=113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| **NSTE-ACS** | 174 (88.3) | 107 (94.7) | 67 (79.8) | **0.004** |
| **STEMI** | 23 (11.7) | 6 (5.3) | 17 (20.2) | |
| Chest pain | 45 (22.8) | 24 (21.2) | 21 (25.0) | 0.65 |
| Chest pain duration | 10.0±16.1 | 11.2±18.6 | 8.4±12.0 | 0.23 |
| Dyspnea | 74 (37.6) | 44 (38.9) | 30 (35.7) | 0.75 |
| Diaphoresis | 53 (26.9) | 29 (25.6) | 24 (28.6) | 0.77 |
| Nausea/vomiting | 45 (22.8) | 27 (23.9) | 18 (21.4) | 0.81 |
| Syncope | 17 (8.6) | 9 (8.0) | 8 (9.5) | 0.90 |
| OHCA | 2 (1.0) | 0 (0.0) | 2 (2.3) | 0.35 |
| In-hospital resuscitation | 9 (4.6) | 3 (2.6) | 6 (7.1) | 0.25 |
| SBP (mmHg) | 120.6±25.3 | 123.3±25.0 | 117.0±25.4 | 0.08 |
| DBP (mmHg) | 66.2±15.2 | 68.0±16.4 | 63.7±13.0 | 0.049 |
| Heart rate (bpm) | 82.3±19.6 | 82.8±17.4 | 81.7±22.4 | 0.72 |
| Killip class | 1.9±0.9 | 1.8±0.8 | 2.0±0.9 | 0.19 |
| ECG | | | | |
| Pathological Q-wave | 94 (47.7) | 48 (42.4) | 46 (54.7) | **0.03** |
| Anterior STEMI | 14 (7.1) | 0 (0.0) | 14 (16.7) | **<0.001** |
| Lateral STEMI | 4 (2.0) | 3 (2.6) | 1 (1.2) | 0.83 |
| Inferior STEMI | 4 (2.0) | 3 (2.6) | **1 (1.2)** | 0.83 |
| LBBB | 1 (0.5) | 0 (0%) | 1 (1.2) | 0.88 |

SD: Standard deviation, DBP: Diastolic blood pressure, LBBB: Left bundle branch block, NSTE-ACS: Non-ST segment elevation-acute coronary syndrome, ECG: Electrocardiographic, OHCA: Out of hospital cardiac arrest, SBP: Systolic blood pressure, STEMI: ST-segment elevation myocardial infarction

**Table 3. Echocardiographic data for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n=113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| Aortic root diameter (cm) | 3.3±1.6 | 3.2±0.7 | 3.4±2.2 | 0.45 |
| Left atrial diameter (cm) | 4.6±2.8 | 4.7±1.2 | 4.6±3.9 | 0.97 |
| LVED (cm) | 5.1±0.7 | 5.2±0.7 | 5.1±0.8 | 0.47 |
| LVES (cm) | 3.6±0.8 | 3.6±0.8 | 3.5±0.9 | 0.51 |
| Ejection fraction (%) | 50.6±14.1 | 50.0±14.4 | 51.3±13.6 | 0.53 |
| WMSI | 1.4±0.5 | 1.5±0.5 | 1.4±0.5 | 0.38 |
| Mitral incompetence | 101 (51.3) | 65 (57.5) | 36 (42.8) | **0.045** |
| Significant aortic stenosis | 18 (9.4) | 9 (7.9) | 9 (10.7) | 0.62 |
| LV thrombus | 8 (4.1) | 5 (4.4) | 3 (3.5) | 0.99 |

SD: Standard deviation, LV: Left ventricle, LVED: Left ventricular end-diastole, LVES: Left ventricular end-systole, WMSI: Wall motion systolic index

No significant difference was found between the two groups regarding discharge medications. Aspirin was the most commonly used antiplatelet (77.2%), followed by clopidogrel (64%), with ticagrelor prescribed in only 4.6%. 31.5% of the patients received direct oral anticoagulants on discharge, with the main indications being atrial fibrillation and LV thrombus. 85.3% of the patients received statins (Table 6).

The in-hospital and 30-day mortality were 7.1% and 13.2%, respectively. The in-hospital and 30-day mortality were numerically higher in the conservative group (7.9% vs. 5.9%; OR: 0.73, 95% CI 0.24-2.27; $P = 0.79$, and 15.9% vs. 9.6%; OR: 0.56, 95% CI 0.23-1.35; $P = 0.27$, respectively). More than 10% of the invasive patients had TVR. Reinfarction was less frequent in the invasive group (10.6% vs. 3.5%), while bleeding (BARC ≥3) was more frequent in the invasive group (9.7% vs. 13.1%), though

**Table 4. Geriatric assessment and GRACE risk score for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n=113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| **Frailty** | | | | |
| Pre-frail | 91 (46.2) | 47 (41.6) | 44 (52.4) | 0.13 |
| Frail | 106 (53.8) | 66 (58.4) | 40 (47.6) | |
| **Delirium** | | | | |
| Delirium by CAM | 70 (35.5) | 48 (42.5) | 22 (26.2) | **0.02** |
| **Geriatric Depression Scale** | | | | |
| Suggestive | 63 (32) | 34 (30.1) | 29 (34.5) | 0.78 |
| Indicative | 60 (30.5) | 36 (31.9) | 24 (28.6) | |
| **GRACE risk score** | | | | |
| Low | 91 (46.2) | 60 (53.1) | 31 (36.9) | **0.04** |
| Moderate | 83 (42.1) | 44 (38.9) | 39 (46.4) | |
| High | 23 (11.7) | 9 (8.0) | 14 (16.7) | |

SD: Standard deviation, CAM: Confusion assessment method

**Table 5. Laboratory for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n= 113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| GFR (mL/min) | 49.0±22.7 | 47.8±23.9 | 50.5±21.0 | 0.41 |
| Creatinine (mg/dL) | 1.6±1.0 | 1.7±1.1 | 1.4±0.9 | 0.09 |
| CK-MB (U/L) | 48.1±56.6 | 49.1±61.8 | 46.8±49.2 | 0.79 |
| High-sensitive troponin (pg/mL) | 402.5±696.9 | 424.7±840.3 | 373.5±439.1 | 0.62 |
| Hemoglobin (gram/dL) | 11.8±1.9 | 11.6±2.0 | 11.9±1.6 | 0.33 |
| Total leucocytic count (x$10^3$/cmm) | 10.5±5.7 | 10.8±5.8 | 10.2±5.6 | 0.53 |
| Platelets count (x$10^3$/cmm) | 266.8±35.3 | 243.5±21.7 | 297.3±25.0 | 0.25 |
| ALT (U/L) | 47.9±181.6 | 59.4±238.4 | 32.6±27.2 | 0.31 |
| AST (U/L) | 43.0±130.2 | 50.3±170.1 | 33.3±28.2 | 0.37 |
| Albumin (g/dL) | 3.6±0.5 | 3.5±0.5 | 3.6±0.4 | 0.08 |
| Hemoglobin A1c (%) | 6.3±1.2 | 6.1±1.2 | 6.5±1.3 | 0.05 |
| Cholesterol (mg/dL) | 178.0±47.6 | 183.4±50.6 | 170.7±42.5 | 0.07 |
| Low-density lipoprotein (mg/dL) | 105.2±39.9 | 108.9±42.6 | 100.2±35.6 | 0.13 |
| High-density lipoprotein (mg/dL) | 43.3±10.2 | 43.7±10.2 | 42.9±10.2 | 0.59 |
| Triglycerides (mg/dL) | 141.8±66.0 | 145.6±67.3 | 136.7±64.3 | 0.35 |

SD: Standard deviation, GFR: Glomerular filtration rate, CK-MB: Creatine kinase-MB, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

neither difference was statistically significant (Supplementary Table 1 and Figure 1). On the other hand, the invasive group exhibited a higher incidence of hospital stays, which tended to be longer in the conservative group (6.4±3.9 vs. 5.4±4.0, *P* = 0.08).

Multiple logistic regression analysis showed that SBP <100 mmHg, Killip II, GFR, low EF, and HF were positively associated with mortality. STEMI diagnosis was associated with a reduction in the odds of mortality (Supplementary Table 2 and Figure 2).

## DISCUSSION

ACS in octogenarians presents a major clinical challenge due to the high prevalence of comorbidities, frailty, and neuropsychiatric disorders, as well as the risks associated with both invasive and conservative treatments.[3] This prospective observational study of 197 octogenarians with ACS provides real-world data on clinical characteristics, treatment pathways, and short-term outcomes in this vulnerable population.

Consistent with contemporary literature, our cohort demonstrated a high burden of NSTE-ACS, accounting for 88.3%

**Table 6. Discharge medications for the total, conservative, and invasive patients [data are expressed as mean ± SD or count (percentage)]**

| | Total (n=197) | Conservative (n=113) | Invasive (n=84) | *P*-value |
|---|---|---|---|---|
| Aspirin | 152 (77.2) | 84 (74.3) | 68 (81.0) | 0.36 |
| Clopidogrel | 126 (64.0) | 68 (60.2) | 58 (69.1) | 0.26 |
| Ticagrelor | 9 (4.6) | 4 (3.5) | 5 (6.0) | 0.50 |
| DOAC | 62 (31.5) | 38 (33.6) | 24 (28.6) | 0.55 |
| Statin | 168 (85.3) | 93 (82.3) | 75 (89.3) | 0.24 |
| Beta blocker | 125 (63.5) | 73 (64.6) | 52 (61.9) | 0.81 |
| RAAS blocker | 75 (38.1) | 39 (34.5) | 36 (42.9) | 0.30 |
| Nitrates | 61 (31.0) | 34 (30.1) | 27 (32.1) | 0.88 |
| CCB | 30 (15.2) | 16 (14.2) | 14 (16.7) | 0.78 |

SD: Standard deviation, CCB: Calcium channel blocker, DOAC: Direct oral anticoagulant, RAAS: Renin-angiotensin-aldosterone system

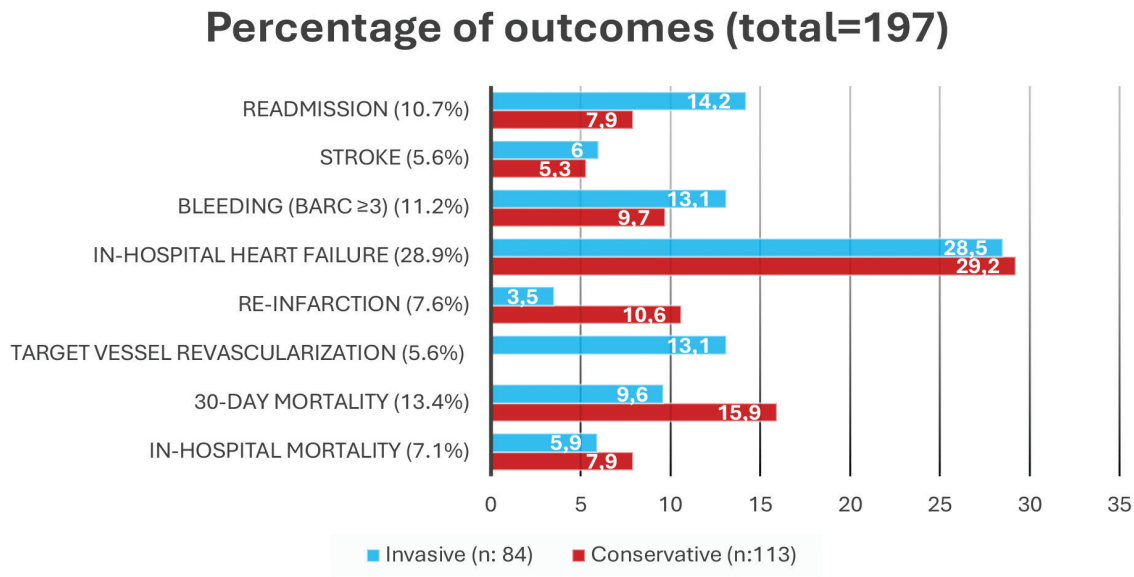


**Figure 1.** The outcome data for total patients (presented on the vertical axis) with comparison between the conservative and invasive arms regarding the different outcome data

*BARC: Bleeding Academic Research Consortium*

of all ACS presentations, a finding that was significantly more frequent in the conservative group (94.7% vs. 79.8%, $P = 0.004$). This observation is explained by the complex chronic coronary artery disease in the elderly progressing into ACS rather than acute plaque rupture, leading to STMEI that is commonly encountered in the younger patients.[31,32]

The decision to pursue an invasive strategy was not random but reflected a careful selection process guided by clinical judgment and risk stratification. Patients in the invasive group, despite a higher proportion of high-risk features (such as higher GRACE scores and a greater incidence of anterior STEMI), demonstrated characteristics indicative of better overall functional reserve. Compared to the conservative group, the invasive group had significantly higher BMI (30.5±3.5 vs. 29.3±3.5, $P = 0.03$), lower prevalence of PVD (19.0% vs. 38.9%, $P = 0.003$), and lower rates of delirium (26.2% vs. 42.5%, $P = 0.02$), with a trend toward lower frailty rates (47.6% vs. 58.4%, $P = 0.13$). Conservative management appears to be favored in octogenarian patients with a higher burden of comorbidities, including low BMI, PVD, and cognitive impairment, despite the potential for favorable long-term outcomes with an invasive approach. Comprehensive geriatric assessment is therefore critical in decision-making for elderly patients with ACS.[3,33,34]

The primary outcome of in-hospital mortality was numerically lower in the invasive group (5.9% vs. 7.9%, $P = 0.79$). Similarly, the 30-day mortality was lower in the invasive group (9.6% vs. 15.9%), but this difference was not statistically significant ($P = 0.27$). This lack of a significant short-term mortality

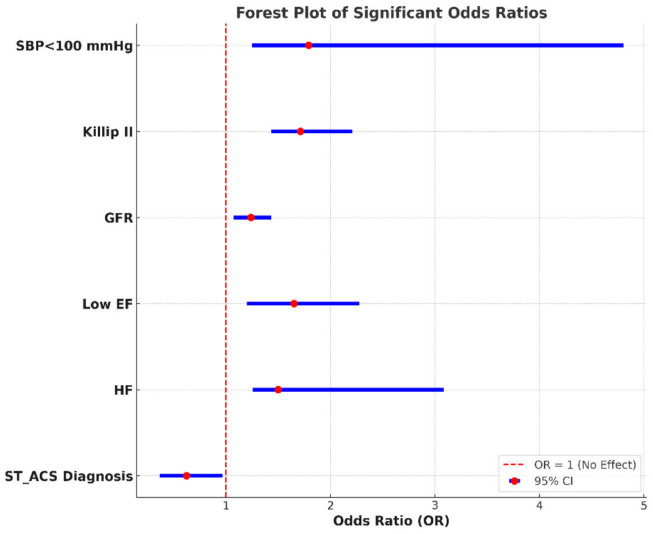


**Figure 2.** Forest plot for the significant predictors of mortality. Bars represent the ORs for each variable. Red lines indicate the 95% confidence intervals (CIs)

*EF: Ejection fraction, GFR: Glomerular filtration rate, HF: Heart failure, SBP: Systolic blood pressure, ST-ACS: ST-segment elevation acute coronary syndrome*

benefit aligns with the primary outcome of the SENIOR-RITA trial, the largest RCT to date in this population, which found no difference in the composite endpoints of cardiovascular death and myocardial infarction between routine invasive and conservative strategies.[35,36]

This study provides evidence supporting the benefit of the invasive strategy in reducing future ischemic events. The invasive group had a significantly higher rate of TVR (13.1% vs. 0.0%, $P < 0.001$), as expected since the conservative group did not undergo the initial procedure. Additionally, the invasive group demonstrated a numerical trend toward a lower reinfarction rate (3.5% vs. 10.6%, $P = 0.12$). These findings are consistent with major RCTs and meta-analyses. Our findings, particularly the numerical but non-significant reduction in mortality with an invasive strategy, resonate with observations from key RCTs in similar elderly populations. The After Eight study[37] was an open-label RCT involving patients aged 80 years or older with NSTE-ACS, which showed that the invasive strategy significantly reduced a composite endpoint of myocardial infarction, urgent revascularization, stroke, and death. However, like our study, the After Eight trial did not find a statistically significant difference in all-cause mortality between the invasive and conservative groups. This suggests that while an invasive approach may improve overall cardiovascular outcomes, the mortality benefit in these vulnerable patients remains challenging, even in a randomized setting. A meta-analysis by Kotanidis et al.[9] reported that the invasive strategy was associated with a significant reduction in the one-year risk of recurrent myocardial infarction (hazard ratio 0.62, 95% CI 0.44-0.87) and urgent revascularization (hazard ratio 0.41, 95% CI 0.18-0.95). These data support the benefit of an invasive approach in reducing future ischemic events and the need for repeat procedures, even among octogenarians.

A critical finding is the absence of a significant difference in major bleeding complications (BARC bleeding >3) between the invasive (13.1%) and conservative (9.7%) groups ($P = 0.61$). This finding can suggest that the increased bleeding risk imposed by the invasive approach can be decreased by proper patient selection, procedural planning, and adjustment of antithrombotic drugs. This is further supported by the non-significant difference in the use of high-risk medications such as glycoprotein IIb/IIIa antagonists and the similar rates of discharge medications between the two groups. The comparable rates of in-hospital HF and stroke also indicate that the invasive strategy did not introduce a disproportionate risk of these major complications.

The length of hospital stay was numerically shorter in the invasive group (5.4±4.0 days) than in the conservative group (6.4±3.9 days). This trend toward shorter hospital stays with the invasive strategy suggests that it may lead to more rapid stabilization and discharge than conservative management.

Our study highlights the profound influence of geriatric syndromes on treatment selection and outcomes. As mentioned earlier, conservative management was associated with higher delirium and frailty rates. Frailty is increasingly recognized as a powerful, independent predictor of adverse outcomes, including mortality, functional decline, and bleeding, often surpassing the predictive power of chronological age or traditional risk scores.[38,39] This association between cognitive disorder and conservative approach denotes selection bias against the intervention approach in such patients, which may lead to increased long-term adverse cardiac events. A retrospective analysis by Roman et al.[40] compared revascularization rates between frail and non-frail patients. The study showed that revascularization is associated with a reduction in cardiovascular mortality in frail patients, suggesting that they could benefit from an invasive approach.[40] On the other hand, the MOSCA-FRAIL study[41] included frail elderly patients (≥70 years) with NSTEMI. This trial found no significant difference in the primary composite outcome of death or new myocardial infarction at one year between the two groups. The MOSCA-FRAIL study highlighted the impact of frailty on outcomes and showed that comorbidities, such as frailty, can dilute the benefits of revascularization. Our observational findings, showing a trend towards lower mortality in the invasive group but without statistical significance, are consistent with the nuanced and often challenging results observed in this trial.

We suggest that a comprehensive geriatric assessment guide the individualized decision-making in such high-risk patients.

The counterintuitive finding that STEMI diagnosis was associated with a reduction in the odds of mortality in our regression analysis could be explained by the increased use of invasive management in octogenarian STEMI patients. In our study, more STEMI patients (73.9%) received invasive management compared to NSTE-ACS patients (38.5%). The early aggressive invasive management in STEMI patients may mitigate the high risk imposed by STEMI presentation compared to NSTE-ACS patients, who had more conservative management.

### Study Limitations

This study is underpowered to detect statistically significant differences in less frequent outcomes, such as mortality. This limitation is due to the observational design and the challenges of recruiting a large cohort of octogenarian ACS patients. The absence of an a priori sample size or power calculation represents a significant methodological limitation. Consequently, our study may be susceptible to type I or II errors. This study should therefore be viewed as primarily descriptive and hypothesis-generating, providing real-world insights to inform future, adequately powered research. Our 30-day follow-up period provided insights into short-term outcomes, but limited the assessment of long-term morbidity and mortality, which are crucial considerations in this elderly population. Furthermore, although we assessed frailty and delirium, using a single frailty scale (Fried Frailty Scale) may not capture the full spectrum of functional decline. Despite using logistic regression to adjust for confounders, the authors acknowledge that a more robust method, such as propensity score matching, could mitigate baseline imbalances in future observational studies. The observational design of this study carried a potential limitation in the form of unmeasured confounders that influenced the treatment decision, such as subjective assessments of frailty and overall prognosis (e.g., the "eyeball assessment") that may not have been fully captured by the objective geriatric assessment conducted in this study. We described that the selection bias was evident in this descriptive study due to multiple comorbidities of the octogenarians. Finally, as a multicenter trial, multicenter heterogeneity may introduce variability in the management of such patients. This growing patient population requires future studies with large sample sizes, longer follow-up, and formal geriatric assessment to better inform optimal management strategies for these high-risk patients.

## CONCLUSION

This study describes the characteristics of octogenarian patients presenting with ACS, a high-risk population with increased ischemic and bleeding risks. Several key findings emerged. First, selection bias was evident, as the choice between invasive and conservative management was strongly influenced by geriatric factors beyond traditional risk scores. Patients managed conservatively had a significantly higher prevalence of geriatric syndromes, particularly delirium, and a greater burden of comorbidities such as PVD. In contrast, the invasively managed group, despite higher GRACE scores, demonstrated better functional reserve indicators, such as higher BMI. These findings indicate that clinical decision-making in this population is appropriately guided by comprehensive geriatric assessment. Second, the invasive strategy was associated with a trend toward lower reinfarction rates. Randomized trials are required to support the effectiveness of invasive therapy in reducing recurrent ischemic events in this high-risk population. Third, the safety profile of the invasive strategy was acceptable, with no statistically significant increase in short-term adverse outcomes, including in-hospital or 30-day mortality or major bleeding complications.

In summary, current ACS management practices in octogenarians vary and are influenced by individual characteristics and comorbidities. Early invasive strategy shows a numerical trend towards reduced recurrent ischemic events; however, geriatric syndromes such as frailty and delirium remain strong determinants of conservative management. Future research should prioritize the development of standardized, validated geriatric risk assessment tools.

### Ethics

**Ethics Committee Approval:** The study was approved by the Local Research Ethics Committee, Cairo University Faculty of Medicine (approval no: MD-371-2021, date: 04.10.2022).

**Informed Consent:** Patients or their representatives provided written consent to the study.

### Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: W.A., Concept: M.A., Design: E.L., M.A., Data Collection or Processing: H.N., Analysis or Interpretation: K.M., E.L., W.A., Literature Search: H.N., Writing: K.M., H.N.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Supplementary Tables 1-2.** https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/b7d9ce90-b725-4545-8d09-2a4843782dcb.pdf

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LETTER TO THE EDITOR

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# Letter to the Editor: In Response to Cardiac Toxicity of Cancer Therapies: Mechanisms, Surveillance, and Clinical Implications

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**Keywords:**

Dexrazoxane, cardioprotection, genetics, cardiotoxicity

## To the Editor,

We read with great interest the recent article titled "Cardiac Toxicity of Cancer Therapies: Mechanisms, Surveillance, and Clinical Implications", published in the *International Journal of Cardiovascular Academy*.[1] The review presents an insightful overview of the mechanisms and monitoring strategies for therapy-induced cardiotoxicity. However, we highlight two emerging aspects that warrant further discussion.

While the paper provides an exhaustive review of cardiac toxicity mechanisms and surveillance methods, it neglects to mention the emerging role of molecular and genetic predictors in cardio-oncology. According to recent studies, a patient's genetics and ethnicity play a major role in their susceptibility to therapy-induced cardiomyopathy. For example, Black race/African ancestry is associated with 71% higher odds of cardiotoxicity after cancer chemotherapy.[2] Several common genetic variants have been identified as either increasing or reducing the risk of cancer therapy-induced cardiomyopathy. These genetic variants influence drug metabolism, efficacy, and susceptibility to adverse effects.[3]

Secondly, the description of the drug, dexrazoxane in the Management and Prevention section claims its administration as controversial based on issues of decreased efficacy of chemotherapy and secondary malignant neoplasms, especially among children. The latest evidence and global consensus, though, offer a more balanced view. International Late Effects of Childhood Cancer Guideline Harmonization Group concluded that "if cardiac damage risk is high, it could be reasonable to administer dexrazoxane to children and cancer patients with adults exposed to anthracyclines", highlighting an individualized risk-benefit evaluation (de Baat et al.,[4]). It recommends dexrazoxane as a clinically justifiable cardioprotective approach when properly administered in high-risk populations.

In conclusion, we appreciate the authors for their valuable contribution and hope these perspectives may guide future discussion in this evolving field by acknowledging the importance of genetic screening and updated dexrazoxane evidence would further strengthen the article's clinical applicability and comprehensiveness.

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CASE REPORT

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# Insights into Coronary Artery Perforations: A Cath Lab Nightmare

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## Abstract

Coronary artery perforation (CAP) is an uncommon yet clinically significant complication that may occur during percutaneous coronary intervention. Ongoing advances in interventional devices and techniques have enabled treatment of increasingly complex lesions, including heavily calcified or tortuous vessels and chronic total occlusions, thereby contributing to a higher incidence of CAP. Early recognition and implementation of appropriate treatment strategies are crucial for reducing mortality and complications associated with CAP. In this case series, we report nine cases of CAP that were successfully managed with timely recognition and appropriate intervention, achieving favorable in-hospital outcomes without in-hospital mortality or need for urgent surgical intervention.

**Keywords:** Coronary artery perforations, covered stents, percutaneous coronary intervention

## INTRODUCTION

Coronary artery perforation (CAP) is an uncommon yet potentially life-threatening complication of percutaneous coronary intervention (PCI) which leads to serious complications such as myocardial infarction, pericardial effusion, cardiogenic shock, tamponade, and even death.[1] Ellis classified coronary perforations based on their angiographic appearances as follows: grade I (extraluminal crater), grade II (myocardial or pericardial blushing), grade III (prominent contrast streaming from a ≥1 mm tear), and grade IV (cavity spilling).[2,3] The risk of CAP increases in complex coronary anatomy and during the use of oversized balloons, high-pressure post-dilatation, atheroablative devices, hydrophilic guidewires, and in calcified or tortuous vessels.[2] Management strategies vary according to the severity of perforation and may include prolonged balloon inflation, covered stent implantation, pericardiocentesis, or surgical intervention.[4]

Despite its low incidence, CAP requires immediate recognition and timely intervention to prevent adverse outcomes. In this retrospective descriptive case series, we report nine angiographically confirmed cases of CAP encountered during PCI at a single tertiary care center over a one-year period. The present case series outlines the angiographic severity, procedural context, and management strategies employed in each case, providing a consolidated account of our institutional experience in the recognition and intraprocedural management of CAP.

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## CASE REPORTS

### Case 1

A 55-year-old female presented with symptoms of unstable angina and had a history of uncontrolled diabetes mellitus, and hypertension. Angiogram revealed 80% long segment stenosis (calcified lesion) in the proximal and mid left anterior descending artery (LAD) and 60-70% stenosis in the proximal obtuse marginal artery (OM1). Treatment included rotablation of the LAD using a 1.5 mm burr, followed by the deployment of a 2.75×48 mm drug-eluting stent (DES). Post-procedure, two perforations (Ellis grade III) were noted at the distal edge of the stent. Two attempts of intermittent sustained balloon tamponade were unsuccessful. Consequently, the patient was managed with a 2.8×16 mm GraftMaster™ RX coronary stent graft system (Abbott Vascular, Santa Clara, CA) (covered stent), yielding satisfactory results. The patient remained hospitalized for three days, during which a repeat echocardiogram showed minimal effusion.

### Case 2

A 46-year-old female with a history of diabetes mellitus and hypertension was admitted to our tertiary care center with unstable angina. Electrocardiogram (ECG) showed T-wave inversions in lateral leads while the echocardiogram was unremarkable, demonstrating concentric left ventricular hypertrophy. Angiogram revealed 80% stenosis in mid LAD and thus the patient was treated with direct stenting to the diseased segment. Post-stenting, a perforation (Ellis Grade III) was noted at the distal edge of the stent, which was immediately addressed with intermittent prolonged balloon tamponade. However, this intervention failed after two attempts. For rescue, a 3.5×16 mm GraftMaster™ (covered stent) was deployed, which sealed the perforation after complete inflation. Post-procedure, the patient was hospitalized for four days. During this time, the patient experienced minimal pericardial effusion; however, this was successfully managed without any drainage.

### Case 3

A 60-year-old male presented with chief complaints of breathlessness on exertion (New York Heart Association Class II) and exertional chest discomfort for the past eight to nine months. The patient's medical history included uncontrolled diabetes and coronary artery bypass grafting (five years ago), involving two grafts [reversed saphenous vein graft (rSVG) to OM1 and rSVG to posterior descending artery]. ECG and echocardiogram were normal. The coronary angiogram showed 85% occlusion in proximal rSVG-OM1 graft and 80% occlusion in the mid graft segment, 70% stenosis in proximal LAD, diffuse disease in the non-dominant left circumflex artery (LCX), and a totally occluded native right coronary artery (RCA) in the mid-segment with distal RCA filling retrogradely through collaterals. A 4.5×20 mm Supralimus Grace DES (Sahajanand Medical Technologies Limited, Surat, Gujarat, India) was deployed in the rSVG-OM1 graft. During this procedure, an Ellis grade I perforation was noted, which was attributed to overzealous inflation in a venous graft. However, the perforation was sealed spontaneously and was managed conservatively. Subsequent echocardiograms did not show any significant pericardial effusion.

### Case 4

A 65-year-old male presented with anterior wall myocardial infarction. He was a chronic smoker, diabetic, and had a family history of coronary artery disease. Coronary angiogram revealed 95% stenosis in proximal to mid-LAD and 99% stenosis in proximal diagonal 1 (D1) branch. After successful thrombolysis with streptokinase, the patient underwent elective PCI to the LAD. The D1 and LAD both were wired because of the steep angle. Post-stenting, while performing non-compliant (NC) balloon inflation, an Ellis grade III perforation was observed at mid-LAD. Balloon tamponade was unsuccessful in halting the extravasation. Thus, a 3.5×19 mm GraftMaster™ stent (covered stent) was successfully deployed, sealing the perforation with no residual extravasation. Subsequently, the D1 and the proximal LAD lesions were successfully stented. Echocardiographic assessment following PCI demonstrated no pericardial effusion. The patient remained hemodynamically stable without the need for surgical intervention and was discharged after 48 hours of monitoring.

### Case 5

A 70-year-old hypertensive male was admitted with acute onset retrosternal chest discomfort. The ECG showed inferior wall myocardial infarction for which the patient was treated with thrombolysis using streptokinase. An echocardiogram revealed hypokinesia in the territory of the RCA. Coronary angiogram revealed double vessel disease with 95% occlusion and diffuse disease in ostial to mid-RCA, as well as 99% stenosis in the distal segment of the non-dominant LCX. Consequently, an elective PCI was performed in ostial to mid-RCA. Post-stenting, a large Ellis grade III perforation was observed in the mid portion of the RCA, which was immediately managed using a 3.5×26 mm GraftMaster™ stent (covered stent) in the mid-RCA and a 3.5×19 mm GraftMaster™ stent (covered stent) in the proximal to mid-RCA. Post-procedure, the patient did not develop significant pericardial effusion. On the fourth day, the patient was discharged in stable condition.

### Case 6

A 62-year-old male with a medical history of diabetes mellitus and hypertension was admitted for unstable angina. The ECG and echocardiogram were unremarkable. Coronary angiography revealed 90% occlusion of proximal LAD (at level of D1) and 90% stenosis in mid-RCA. After successfully stenting the RCA lesion, the LAD lesion was crossed using a wire and predilated with a 3×15 mm Sapphire II pro balloon (Orbus Neich). A check angiogram showed Ellis grade II perforation, attributed to the use of an oversized balloon in a smaller artery. This was managed successfully with a 3×29 mm DES. Post-procedure, the patient did not develop any significant pericardial effusion. Clinical stability was maintained, allowing discharge on the second day after the intervention.

### Case 7

A 70-year-old hypertensive female was admitted for non-ST-segment elevation myocardial infarction. The ECG was suggestive of ST coving and T-wave inversion in the inferior leads, while the echocardiogram indicated inferior wall hypokinesia. Coronary angiogram revealed diffuse disease, with 85% stenosis in the mid and distal RCA and 80% stenosis in the ostial to mid-LAD with calcification. After successfully stenting RCA lesion, rotablation of the calcified LAD lesion was performed using a 1.5 mm rotablation burr. Following adequate lesion preparation, a 3×24 mm Biomime Aura DES (Meril Life Sciences Pvt. Ltd., India) was deployed in the mid-LAD. An Ellis grade III perforation was observed after NC balloon expansion. Balloon tamponade was immediately performed, followed by the implantation of a 3 ×19 mm covered stent. The ostial and proximal lesion were also covered with a stent after the perforation was sealed off. An echocardiogram showed significant pericardial effusion, which was drained using a pigtail catheter. Post-procedure, the patient remained stable and was discharged after seven days.

### Case 8

A 62-year-old female with a history of diabetes mellitus and hypertension presented with chief complaints of exertional chest discomfort radiating towards the back and left shoulder for the past seven to eight days. The ECG was suggestive of biphasic T-waves in V2-V5, while the echocardiogram showed hypokinesia of anterior wall. Coronary angiogram revealed 70% stenosis in proximal RCA, 95% stenosis in mid-RCA and 80-85% stenosis in proximal LAD. After stenting the RCA lesions, the LAD lesion was crossed with a wire and after adequate lesion preparation, a 3×60 mm BioMime Aura DES was deployed in proximal to mid-LAD. Subsequently, a 3×12 mm NC Quantum Apex™ balloon at 12-18 atm (Boston Scientific, Natick, MA, USA) was used for inflation in the mid segment of the stent. After the procedure, an Ellis grade III perforation was observed. Therefore, balloon tamponade was performed immediately, followed by the deployment of a 3.5×26 mm GraftMaster™ (covered stent). The echocardiogram did not show any significant pericardial effusion. Post-procedure, the patient was stable and was discharged after three days.

### Case 9

A 53-year-old diabetic male presented with chief complaints of exertional chest discomfort radiating to the back and left shoulder for the past seven-eight days. The patient had a medical history of acute coronary syndrome eight years ago, for which stenting was performed in the proximal to mid-LAD. ECG was suggestive of T-wave inversion in inferior leads, and the echocardiogram showed inferior and posterior wall akinesia. Coronary angiogram revealed 80% long-segment stenosis in the proximal to mid-RCA with a patent stent in proximal to mid-LAD. Elective PCI was performed in the proximal to mid-RCA using a 3×44 mm Supraflex Cruz DES (Sahajanand Medical Technologies Limited, Surat, Gujarat, India). Post-stenting, NC balloon was used for adequate stent deployment, after which a large Ellis grade II perforation was observed, which was managed conservatively with intermittent sustained balloon tamponade till the defect sealed off. Post procedure, no pericardial effusion was observed in echocardiography. Clinical stability was maintained, allowing discharge on the third day after the intervention.

Figure 1 demonstrates angiogram showing coronary perforation in each case. Summary of each case is represented in Table 1. As this was a retrospective descriptive case series involving standard clinical care, formal ethics committee approval was waived in accordance with institutional policy. Written informed consent for publication of clinical data and angiographic images was obtained from all patients.

## DISCUSSION

In the present series of nine cases, CAP was categorized according to the Ellis classification, and management decisions were tailored based on angiographic severity and hemodynamic status. The perforations occurred during routine PCI procedures and were immediately recognized angiographically. These cases illustrate the intraprocedural decision-making process adopted in our catheterization laboratory.

**Table 1. Summary of each case**

| Case no | Age (years) | Gender | Cause of perforation | Ellis grade | Treatment | In-hospital clinical outcome |
|---|---|---|---|---|---|---|
| 1 | 55 | Female | Distal stent edge perforation post-rotablation and DES | III | Covered stent | Minimal effusion; no drainage; discharged stable |
| 2 | 46 | Female | Distal stent edge perforation post-direct stenting | III | Covered stent | Minimal effusion; no drainage; discharged stable |
| 3 | 60 | Male | Overzealous balloon inflation in venous graft | I | Conservative | No significant effusion; discharged stable |
| 4 | 65 | Male | NC balloon overexpansion post-stenting | III | Covered stent | No effusion; discharged stable |
| 5 | 70 | Male | Post-stent deployment perforation in RCA | III | Covered stent | No significant effusion; discharged stable |
| 6 | 62 | Male | Oversized pre-dilatation balloon | II | Drug-eluting stent | No effusion; discharged stable |
| 7 | 70 | Female | NC balloon overexpansion post-DES | III | Covered stent | Significant effusion; pericardiocentesis done; discharged stable |
| 8 | 62 | Female | NC balloon overinflation | III | Covered stent | No significant effusion; discharged stable |
| 9 | 53 | Male | NC balloon overinflation | II | Balloon | No effusion; discharged stable |

LAD: Left anterior descending artery, NC: Non-compliant, RCA: Right coronary artery, DES: Drug-eluting stent

Appropriate sizing of the guidewire and balloon is important in reducing the risk of CAP.[5] Initial management of CAP includes proximal balloon inflation to temporarily occlude antegrade flow and limit contrast extravasation, alongside prompt discontinuation of intravenous anticoagulation and correction of coagulopathy. This conservative strategy is often adequate for Ellis grade I and II perforations as well as distal vessel injuries to achieve haemostasis. In many cases, however, balloon tamponade serves only as a bridging measure until definitive therapy can be instituted.[6] The Ellis grade III and IV CAPs can lead to severe complications and may necessitate more invasive treatments, such as surgery or emergency pericardiocentesis.[7]

Covered stents have transformed the management of CAP. Expanded polytetrafluoroethylene covered stents have enabled treatment of CAP in catheterization laboratory, eliminating the need for emergency surgery especially for perforations in proximal and middle segments of large epicardial arteries. Studies indicate a high success rate for covered stent implantation, with angiographic success rates ranging from 92% to 96%. Currently, the implantation of covered stents is the treatment of choice for Ellis grade III perforations in arteries >2 mm diameter.[7] The Ellis grade III CAPs are particularly life-threatening and can induce a cycle of ischemia and tamponade physiology due to coronary blood extravasation. In managing these scenarios, balloon tamponade at the perforation site, along with pericardiocentesis and auto-perfusion is recommended. Simultaneous volume resuscitation and inotropic support are essential, with procedural efficiency improved by having a balloon catheter prepared and ready for rapid insertion.

A recently described double guide catheter technique has been introduced to minimize time loss during balloon deflation. In this approach, the target coronary artery is sub-selectively engaged using a 7F guiding catheter via second femoral access. While maintaining balloon inflation, the initial guidewire is withdrawn, after which the balloon is gradually deflated as the second guiding catheter is positioned to allow rapid delivery of definitive therapy. The covered stent is placed over-the-wire at the coronary perforation. Following successful management, a few minutes may be required to stabilize hemodynamics before performing a final check angiogram. In cases of Ellis grade III CAP, prompt notification of the cardiothoracic surgical team is essential, as surgical repair may be necessary if percutaneous measures are unsuccessful, although this is uncommon.[5]

Furthermore, several embolic agents have been reported for therapeutic use, including microcoils, polyvinyl alcohol particles, gelatin sponge, thrombin, fibrin glue, cyanoacrylate adhesive, newer agents such as Onyx, as well as autologous blood clots and fat. Microcoils are among the most feasible and commonly used methods for therapeutic embolization. Appropriately sized microcoils, typically selected up to 1.5 times the diameter of the target vessel, are deployed through microcatheters and promote sealing of the perforation by inducing thrombosis.[4]

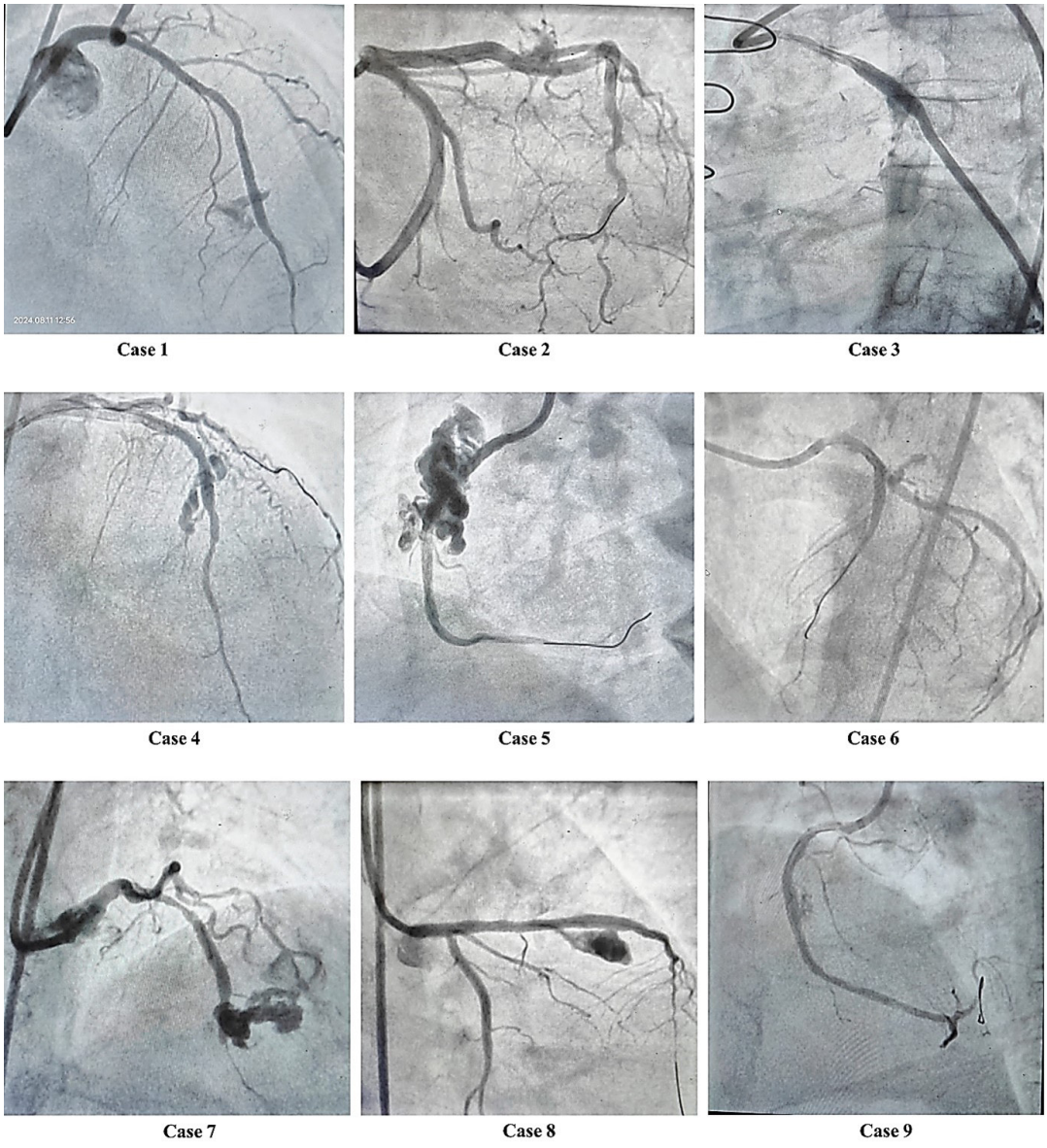


**Figure 1.** Angiogram showing coronary perforation in each case

Our experience from these nine cases emphasizes the importance of immediate angiographic recognition of CAP and prompt escalation of therapy according to perforation severity. By documenting cases encountered in routine clinical practice at a single tertiary care center, this series illustrates the spectrum of Ellis grades and the corresponding management strategies employed in real time. This report provides a consolidated institutional perspective on the recognition and intraprocedural management of CAP.

## Study Limitations

This case series has several limitations. First, it is a retrospective descriptive case series without a predefined protocol. Second, outcomes are limited to in-hospital follow-up without systematic mid-term or long-term outcome assessment. Third, details regarding activated clotting time monitoring and protamine administration were not consistently documented in procedural records and therefore could not be systematically analyzed. Fourth, quantitative vessel-to-balloon ratios were not consistently documented in procedural records, limiting detailed analysis of device-to-artery sizing as a mechanism of perforation. Lastly, routine serial post-procedural cardiac biomarker measurements were not uniformly available for all patients, particularly those presenting with acute coronary syndromes and elevated baseline troponin levels. Therefore, biochemical myocardial injury specifically attributable to the perforation event could not be reliably assessed. Although no

patient developed hemodynamic instability, required urgent surgical intervention, or experienced in-hospital mortality, subclinical myocardial necrosis cannot be excluded.

## CONCLUSION

In conclusion, this case series presents nine cases of CAP encountered during PCI, encompassing a spectrum of Ellis grades and varied procedural contexts. Management was guided by angiographic severity and hemodynamic status, with conservative measures proving adequate for lower-grade perforations and covered stent implantation required for higher-grade lesions. All cases were successfully managed during index hospitalization. This series highlights the importance of prompt angiographic recognition and timely escalation of therapy in the management of CAP and provides a descriptive account of real-world perforation management at a tertiary care center.

### Ethics

**Informed Consent:** Written informed consent for publication of clinical data and angiographic images was obtained from all patients.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: S.P., P.M., Concept: S.P., P.M., Data Collection or Processing: S.P., P.M., Analysis of Interpretation: S.P., P.M., Literature Search: S.P., P.M., Writing: S.P., P.M.

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CASE REPORT

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# Amphetamine-type Stimulant-induced Cardiomyopathy with Reversible Left Ventricular Dysfunction: A Case Report

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## Abstract

The global prevalence of methamphetamine and other amphetamine-type stimulants (ATS) continues to rise, contributing substantially to cardiovascular morbidity and mortality. ATS-associated cardiomyopathy (ATSAC) is an increasingly recognized but underdiagnosed cause of heart failure in young adults. This case report aims to describe the clinical presentation, management, and outcome of ATSAC and to highlight its potential reversibility with stimulant cessation and guideline-directed medical therapy (GDMT). A 24-year-old male with a long-standing history of polysubstance ATS abuse presented with progressive dyspnea and symptoms of acute decompensated heart failure. Comprehensive clinical evaluation, laboratory testing, echocardiography, and cardiac magnetic resonance imaging excluded alternative etiologies of cardiomyopathy. On admission, the patient demonstrated severe left ventricular systolic dysfunction with a left ventricular ejection fraction of 14%. GDMT for heart failure was initiated, alongside sustained cessation of stimulant use and multidisciplinary follow-up. Serial echocardiographic assessments over 12 months documented marked clinical and functional improvement. This case illustrates that ATSAC should be considered in young patients presenting with otherwise unexplained cardiomyopathy. Importantly, it demonstrates that significant—and potentially complete—recovery of cardiac function is achievable with early recognition, abstinence from stimulant use, and appropriate medical management. Further research is warranted to identify predictors of reversibility, clarify underlying mechanisms of myocardial injury, and develop standardized diagnostic and therapeutic strategies for ATSAC.

**Keywords:** Amphetamine, methamphetamine, cardiomyopathies, ventricular dysfunction, heart failure

## INTRODUCTION

Amphetamines were first synthesized in the late 1920s, and by the late 1940s, they had achieved considerable medical and commercial success as antidepressants and weight-loss medications. In the late 1980s, crystal methamphetamine (METH) "ice" emerged, further contributing to widespread use. More recently, 3,4-methylenedioxymethamphetamine (MDMA), commonly known as "ecstasy", has gained popularity due to its ease of availability and relatively low cost. Although regulatory restrictions were introduced once the high addictive potential of these substances became evident, diversion to the illicit market has fueled a continuing global epidemic.

METH exerts profound effects on multiple organ systems, with the most clinically significant manifestations involving the central nervous and cardiovascular systems. In the brain, METH stimulates euphoria and heightened alertness through increased dopamine release in the nucleus accumbens, reinforcing addictive use behaviors.[1] However, chronic or high-dose exposure leads to reduced dopamine synthesis and receptor downregulation, resulting in deficits in memory,

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attention, and decision-making. Long-term use is strongly associated with psychiatric complications, including psychosis, depression, paranoia, delusions, violent behavior, and an alarmingly high lifetime suicide attempt rate, reported in up to 30% of users.[2]

Cardiovascular complications are equally concerning. The heightened catecholaminergic state induced by METH, combined with direct vasoconstriction, oxidative stress, and endothelial dysfunction, contributes to hypertension, vasospasm, and ischemia. METH use has been linked to hemorrhagic stroke, intracardiac thrombi in approximately one-third of patients with methamphetamine-associated cardiomyopathy (MACM), and a high incidence of atrial and ventricular arrhythmias.[3]

MDMA, a semi-synthetic entactogenic phenylethylamine, also produces a spectrum of adverse effects. Acute symptoms may include appetite loss, trismus and bruxism, nausea, muscle aches, fatigue, excessive perspiration, and ataxia. More severe complications have been documented, including psychosis, hyperthermia, seizures, cardiac arrhythmias, rhabdomyolysis, disseminated intravascular coagulation, hyponatremia, hepatotoxicity, aplastic anemia, pneumomediastinum, cerebral hemorrhage, and multiorgan failure. Fatal outcomes most commonly result from malignant hyperthermia, heat stroke, or acute hepatic failure.[4]

Given the escalating use of METH and MDMA worldwide, alongside their well-documented neuropsychiatric and cardiovascular toxicities, there is an urgent need for continued research to better understand their mechanisms, complications, and public health implications.

We present this case to highlight the potential reversibility of amphetamine-type stimulant-associated cardiomyopathy (ATSAC) in the absence of myocardial fibrosis, as demonstrated by cardiac magnetic resonance (CMR) imaging. The patient achieved complete recovery of left ventricular function following stimulant cessation and guideline-directed medical therapy (GDMT), underscoring the importance of early recognition and abstinence in improving outcomes.

## CASE REPORT

### Patient History

A 24-year-old male student presented to the emergency department with a one-month history of progressive shortness of breath, which had worsened over the preceding week, causing severe dyspnea and orthopnea. Initially reluctant to disclose substance use, he later admitted to a six-year history of periodic consumption of amphetamine-type stimulants (ATS), including METH, MDMA, and amphetamine, sometimes combined with alcohol.

Five years earlier, while under the influence of stimulants, he sustained traumatic injuries in an accident with significant blood loss, requiring intensive care admission and multiple sessions of dialysis for acute kidney injury. Renal function subsequently recovered, but echocardiography at that time revealed a reduced left ventricular ejection fraction (LVEF) of approximately 40%. As he was asymptomatic, no further cardiological investigations were pursued. Following recovery, he abstained from stimulants for a period but relapsed due to deteriorating mental health and depression. He was not on any regular medication and had no significant family history of cardiomyopathy.

### Examination on Admission

On presentation, the patient was alert and oriented to time, place, and person but appeared diaphoretic. Vital signs showed tachycardia (heart rate 120 bpm), blood pressure 150/90 mmHg, respiratory rate 27 breaths/min, $SpO_2$ 88%, and temperature 36.6 °C.

Electrocardiography revealed sinus tachycardia with T-wave inversion in leads V4-V6, as well as evidence of ventricular hypertrophy (Figure 1).

### Investigations

Laboratory findings revealed elevated NT-proBNP (2800 pg/mL), slightly increased platelet count ($367\times10^3$/μL), and C-reactive protein (8.62 mg/L). High-sensitivity troponin I was marginally elevated at 0.016 ng/mL (normal <0.014 ng/mL) without dynamic change on repeat testing. The estimated glomerular filtration rate was 99 mL/min. Thyroid function tests were normal. Laboratory findings demonstrated markedly elevated NT-proBNP, mild troponin elevation without dynamic change, and increased inflammatory markers, while renal and thyroid function remained within normal limits.

Bedside transthoracic echocardiography showed a dilated left ventricle (left ventricular end-diastolic diameter 6.9 cm) with severely reduced LVEF of 21% and global hypokinesis (Table 1). Other chambers were also dilated: right-ventricular end-diastolic diameter 4.1 cm, LA 4.8 cm, RA 4.4 cm. Pulmonary artery systolic pressure was elevated (42 mmHg), and mild mitral regurgitation was present.

Lung ultrasonography revealed large bilateral pleural effusions, estimated at approximately 1500 mL on the right and 1000 mL on the left, consistent with significant volume overload and contributing to the patient's respiratory distress. Thoracentesis was performed sequentially, resulting in significant symptomatic relief.

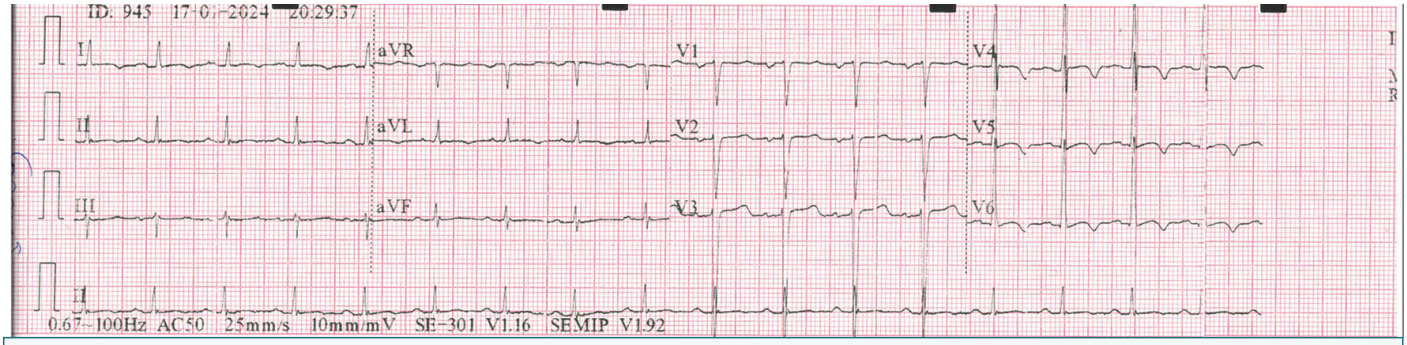


**Figure 1.** Electrocardiogram (ECG) on hospital day 3 ECG showing sinus tachycardia, T-wave inversions in leads V4-V6, and evidence of left ventricular hypertrophy

**Table 1. Echocardiographic and cardiac MRI findings at presentation**

| Parameter | Value |
|---|---|
| LVEDD (cm) | 6.9 |
| LVEF (%) | 21% (echo); 14% (CMR) |
| LV function | Global hypokinesis |
| RVEDD (cm) | 4.1 |
| LA diameter (cm) | 4.8 |
| RA diameter (cm) | 4.4 |
| PASP (mmHg) | 42 |
| Mitral regurgitation | Mild |
| LVEDV (mL, CMR) | 313 |
| Stroke volume (mL, CMR) | 44 |
| Cardiac output (L/min, CMR) | 5.0 |
| LVEDV/BSA (mL/m², CMR) | 226 |
| LGE-CMR | No fibrosis/necrosis |

MRI: Magnetic resonance imaging, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, RVEDD: Right-ventricular end-diastolic diameter, PASP: Pulmonary artery systolic pressure, LGE: Late gadolinium enhancement, CMR: Cardiac magnetic resonance

Initial imaging revealed severe biventricular dilation and global systolic dysfunction with markedly reduced LVEF (21% by echocardiography, 14% by CMR). Importantly, late gadolinium enhancement [(LGE)-CMR] did not demonstrate fibrosis or necrosis, suggesting absence of irreversible myocardial damage. Echocardiographic and CMR imaging findings at presentation and during follow-up are summarized in Table 1.

A post-procedure chest radiograph showed vascular congestion, interstitial edema, Kerley B lines, cardiomegaly, and free costophrenic sinuses (Figure 2).

Post-procedural chest X-ray demonstrating cardiomegaly, pulmonary vascular congestion, interstitial edema, and Kerley B lines. Pleural effusions were resolved after drainage, with free costophrenic sinuses visible.

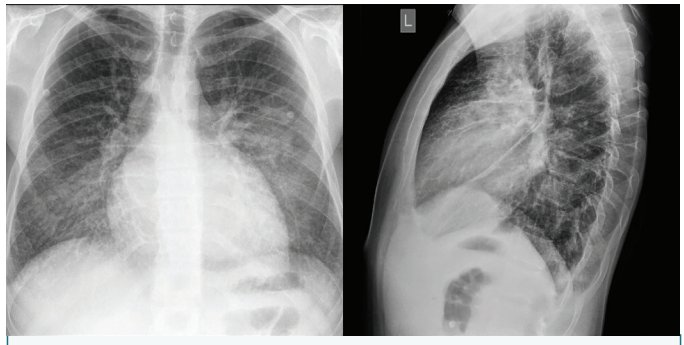


**Figure 2.** Chest radiograph following thoracentesis

## Management and Hospital Course

The patient was initiated on inotropic support and intravenous diuretic therapy. Ivabradine was introduced for initial rate control given the patient's marked tachycardia and low ejection fraction (EF), in whom early initiation of beta-blockers was considered unsafe. Beta-blocker therapy (carvedilol) was subsequently introduced gradually once hemodynamic stability was achieved. Enoxaparin was administered to prevent intracardiac thrombus formation. GDMT for heart failure was then initiated, including sacubitril/valsartan, carvedilol, dapagliflozin, eplerenone, and torasemide. This approach aligns with guideline principles that prioritize stabilization in acute heart failure with reduced ejection fraction (HFrEF) and allow the use of adjunctive agents for rate control in sinus rhythm when beta-blockers cannot be promptly up-titrated.

Despite clinical improvement, repeat thoracentesis was required on day three, draining an additional 1000 mL of transudative fluid from the right pleural space.

Coronary angiography was deferred as per ESC/ACC/AHA guideline recommendations, given the patient's young age, absence of cardiovascular risk factors, typical history of stimulant abuse, and CMR imaging findings that did not suggest ischemic injury. CMR imaging was performed, showing severely

impaired systolic function [EF 14%, left ventricular end-diastolic diameter (LVEDV) 313 mL, stroke volume 44 mL, cardiac output 5.0 L/min, LVEDV/BSA 226 mL/m²]. Importantly, no evidence of intramyocardial fibrosis, necrosis, or active inflammation was detected on early or LGE (Figure 3).

CMR demonstrating severely reduced left ventricular systolic function (LVEF 14%), increased LV end-diastolic volume (LVEDV 313 mL), and no evidence of fibrosis, necrosis, or inflammation on LGE.

As the patient's condition stabilized, inotropic support was discontinued. Primary prevention of sudden cardiac death was discussed. Although implantable cardioverter-defibrillator (ICD) therapy was considered, the absence of sustained ventricular arrhythmia, sudden cardiac arrest, or prior ventricular tachycardia, together with the potentially reversible etiology, led to the decision to defer ICD implantation until after reassessment at three months of optimized medical therapy.

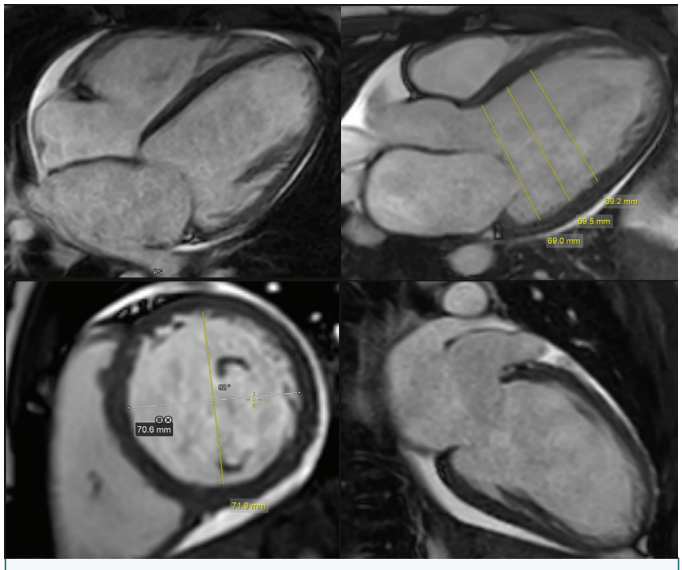


**Figure 3.** Cardiac magnetic resonance imaging

The patient was hospitalized for seven days. At discharge, he was prescribed sacubitril/valsartan, carvedilol, dapagliflozin, eplerenone, and torasemide. He was counseled regarding strict abstinence from stimulants and offered referral to a rehabilitation center, which he declined, though he committed to cessation of drug use.

### Follow-up and Outcome

Serial echocardiographic findings demonstrating progressive recovery of cardiac function are summarized in Table 2. At two months, there was partial recovery of systolic function (LVEF 35%) and reduction in LV dimensions. At 12 months, LVEF normalized to 50%, chamber sizes were within reference ranges, and pulmonary pressures had resolved. He reported significant improvement in both physical and psychological well-being. He continued on GDMT, with the exception of loop diuretics, which were discontinued.

Abstinence from stimulant use during follow-up was assessed based on patient self-report and clinical evaluation, as routine toxicological screening was not performed.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Caucasus University (approval no: CU-17-45/2025). Informed consent was obtained from the patient included in the study.

## DISCUSSION

The global incidence of ATS use, including MACM or ATSAC, continues to rise. In 2022, approximately 0.6% of the world's population aged 15-64 reported ATS use in the preceding year.[5] Among these substances, METH is the most widely consumed stimulant, and its cardiovascular complications are the best documented. Reported manifestations include malignant hypertension, arrhythmias, aortic dissection, myocardial infarction secondary to vasospasm or coronary artery disease, stroke, pulmonary arterial hypertension, endothelial

**Table 2. Echocardiographic recovery during follow-up**

| Parameter | Admission | 2 months | 12 months |
|---|---|---|---|
| LVEDD (cm) | 6.9 | 5.8 | ~5.0 |
| LVEF (%) | 21% | 35% | 50% |
| RVEDD (cm) | 4.1 | Improved | Normalized |
| LA diameter (cm) | 4.8 | Reduced | Normalized |
| RA diameter (cm) | 4.4 | Reduced | Normalized |
| PASP (mmHg) | 42 | Improved | <30 |
| Mitral regurgitation | Mild | Trivial | None |

Echocardiography demonstrated progressive improvement in ventricular function and remodeling following stimulant cessation and GDMT. By 12 months, LVEF normalized to 50% and all chamber sizes were within reference ranges

LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, RVEDD: Right-ventricular end-diastolic diameter, PASP: Pulmonary artery systolic pressure, GDMT: Guideline-directed medical therapy

dysfunction, and dilated cardiomyopathy (DCM). Recent large-scale analyses indicate METH users face a 32% higher overall risk of cardiovascular disease, including significantly elevated rates of heart failure and pulmonary hypertension. The mechanistic basis for these injuries spans catecholamine-mediated vasoconstriction, direct myocardial cell toxicity, oxidative stress, and inflammation, as well as structural and electrical remodeling of the heart.

Alternative etiologies were carefully considered. Viral myocarditis was deemed unlikely due to the absence of clinical features suggestive of acute infection, lack of dynamic troponin elevation, and CMR findings demonstrating no evidence of myocardial edema, inflammation, or LGE on CMR. Genetic cardiomyopathy was also considered less likely in the absence of a family history and given the marked reversibility of left ventricular dysfunction following stimulant cessation.

In recent years, the use of other stimulants such as MDMA, 4-fluoroamphetamine, Adderall, and α-PVP has also increased, largely due to low cost and wide availability. MDMA is particularly prevalent among young adults, with the highest reported incidence in the Netherlands, where 9.3% of individuals aged 15-34 reported use in 2023.[6] In Georgia, a 2021 survey revealed that over half of psychoactive substance users had consumed MDMA in the past year, and amphetamine use rose from negligible levels in 2016 to 10% in 2022.[7] These drugs are often used in social and party contexts, but also by students and young adults aiming to enhance academic or occupational performance.

Our case highlights the frequent pattern of polysubstance abuse, as many patients combine different ATS with alcohol. Another concern in the Georgian context is the purity of stimulants sold on the illicit market: more than half (57%) of MDMA products are either adulterated or entirely substituted with other substances.[8] This significantly increases the risk of unexpected toxicities, complicates diagnosis, and underscores the importance of public health interventions such as drug-checking programs, surveillance, and education campaigns. A widespread misconception persists that MDMA is safer than METH; however, accumulating evidence demonstrates its cardiotoxic potential, which is comparable to other amphetamines.

ATS-related cardiotoxicity is multifactorial, involving catecholamine excess, oxidative stress, reactive oxygen species-mediated injury, and inflammation, ultimately leading to myocardial fibrosis and DCM. Clinical outcomes depend strongly on whether patients achieve abstinence. Improvement in cardiac function following METH cessation was independently associated with the extent of myocardial fibrosis, whereas continued use was linked to progressive heart failure and poor prognosis.[9] Similarly, the degree of irreversible fibrosis is considered a major predictor of recovery. A smaller study suggested that patients presenting with a reverse Takotsubo pattern and less ventricular dilatation may achieve earlier recovery of function.[10]

Currently, no randomized trials have evaluated specific pharmacologic therapies for MACM. Until such data are available, GDMT for HFrEF remains the standard of care.[11] Endomyocardial biopsy is the gold standard for assessing myocardial fibrosis, but LGE-CMR has emerged as a valuable, non-invasive tool for detecting fibrosis and inflammation and may help predict left ventricular recovery.[12]

In the present case, our patient had several years of stimulant use with intermittent abstinence. Importantly, CMR did not reveal evidence of myocardial fibrosis. Following sustained ATS abstinence and initiation of GDMT, he demonstrated substantial recovery, with LVEF improving from 21% at baseline to 50% after 12 months. This favorable outcome is consistent with existing evidence that highlights abstinence and limited fibrosis as key determinants of reversibility in MACM.

This case has several limitations. First, objective toxicological confirmation of ATS use (e.g., urine drug screening) was not performed at presentation, and the diagnosis relied on patient-reported history in conjunction with clinical findings. Second, abstinence during follow-up was assessed based on patient self-report and clinical evaluation without routine toxicological monitoring. Third, although alternative etiologies were carefully considered and deemed unlikely based on clinical, laboratory, and imaging findings, definitive exclusion of all potential causes, including viral or genetic cardiomyopathies, cannot be fully established. Despite these limitations, the temporal association between stimulant cessation and marked recovery of cardiac function strongly supports a causal relationship.

## CONCLUSION

ATSAC should be suspected in young patients with unexplained cardiomyopathy, as stimulant cessation and guideline-directed therapy can lead to meaningful recovery. This case underscores the importance of early recognition, integrated multidisciplinary care, and ongoing research to clarify the mechanisms of myocardial injury, identify predictors of reversibility, and define optimal management strategies that integrate cardiovascular care with substance use treatment.

## Ethics

**Informed Consent:** This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Caucasus University (approval no: CU-17-45/2025). Informed consent was obtained from the patient included in the study.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: T.K., V.S., M.L., N.G., T.V., Concept: T.K., V.S., M.L., N.G., T.V., Design: T.K., V.S., M.L., N.G., T.V., Data Collection or Processing: T.K., V.S., M.L., N.G., T.V., Analysis or Interpretation: T.K., V.S., M.L., N.G., T.V., Literature Search: T.K., V.S., M.L., N.G., T.V., Writing: T.K., V.S., M.L., N.G., T.V.

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