INVESTIGATION OF HIGH-SENSITIVITY TROPONIN I LEVELS AND THEIR CORRELATION WITH CLINICAL AND PARACLINICAL FACTORS IN PATIENTS WITH ARRHYTHMIAS

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ABSTRACT

Background: Elevated high-sensitivity cardiac troponin I (hs-cTnI) is frequently observed in patients with cardiac arrhythmias, complicating the diagnosis of underlying coronary artery disease (CAD). This study investigated the characteristics of hs-cTnI, its correlation with clinical factors, and its diagnostic utility for CAD in arrhythmia patients. **Methods:** A cross-sectional study was conducted on 244 patients admitted with arrhythmias (atrial fibrillation, ventricular tachycardia, and bradyarrhythmias) at a tertiary referral center. We analyzed correlations between hs-cTnI and hemodynamic/biochemical markers. Receiver Operating Characteristic (ROC) analysis was performed to determine the optimal cut-off value for predicting CAD. **Results:** Elevated hs-cTnI (>99th percentile) was present in 42.2% of the cohort, with the highest prevalence in the atrial fibrillation group. hs-cTnI exhibited a strong positive correlation with NT-proBNP ($r = 0.612$, $p < 0.001$) but no significant correlation with heart rate. Multivariate regression identified NT-proBNP and the presence of CAD as independent predictors of elevated hs-cTnI. Patients with CAD had significantly higher median hs-cTnI levels compared to those without (116.6 vs. 9.3 pg/mL, $p < 0.001$). An optimal cut-off of ≥ 36 pg/mL yielded an Area Under the Curve (AUC) of 0.84, offering 82% sensitivity and 76% specificity for CAD prediction. **Conclusion:** In arrhythmia patients, hs-cTnI elevation reflects both hemodynamic stress and potential ischemia. An optimized cut-off of 36 pg/mL improves diagnostic accuracy for CAD compared to the standard reference limit, helping to reduce false-positive rates.

Keywords: *High-sensitivity Troponin I, Arrhythmia, Coronary Artery Disease, NT-proBNP, Diagnostic value.*

I. INTRODUCTION

Cardiac arrhythmias represent one of the most frequent cardiovascular emergencies encountered in intensive care units and interventional cardiology settings. In clinical practice, the assessment of myocardial injury in patients presenting with arrhythmias plays a pivotal role in risk stratification and guiding therapeutic management [2]. Currently, cardiac troponins, particularly high-sensitivity cardiac troponin I (hs-cTnI) assays, are regarded as the "gold standard" for diagnosing myocardial cell injury [2, 3, 7]. However, the advent of these high-sensitivity assays has introduced significant challenges regarding result interpretation, particularly in arrhythmia patients who do not present with typical acute coronary syndrome (ACS).

Previous studies have demonstrated that hs-cTnI levels can be elevated across various arrhythmic contexts, including atrial fibrillation (AF), ventricular tachycardia (VT), and bradyarrhythmias [8]. The underlying mechanisms are postulated to involve oxygen supply-demand mismatch (type 2 myocardial infarction), excessive myocardial wall stress induced by hemodynamic changes, or direct myocardial injury resulting from tachycardia. Current literature has extensively documented a strong correlation between elevated hs-cTnI and biomarkers reflecting cardiac wall stress, such as NT-proBNP [1], as well as renal function impairment [6]. Nevertheless, distinguishing between "baseline" troponin elevation due to chronic structural heart disease and elevation caused by active coronary artery disease (CAD) remains a clinical dilemma [8]. In particular, defining an appropriate hs-cTnI cut-off value to predict CAD in this specific patient population remains unresolved, as the standard 99th percentile threshold (26 pg/mL) often yields a high rate of false positives [4, 5, 8].

In Vietnam, in-depth research data regarding hs-cTnI characteristics across specific arrhythmia subgroups, as well as the multivariate correlations between this index and other clinical and paraclinical factors (such as NT-proBNP and

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eGFR), remain limited. To address this gap, we conducted this study titled "Investigation of High-Sensitivity Troponin I Levels and Their Correlation with Clinical and Paraclinical Factors in Patients with Cardiac Arrhythmias," with the following specific objectives:

1. To investigate the characteristics of hs-cTnI levels across different arrhythmia groups (atrial fibrillation, ventricular tachycardia, and bradyarrhythmias).
2. To analyze the correlation between hs-cTnI concentrations and hemodynamic indices as well as blood biochemical markers.
3. To determine the value of hs-cTnI in predicting coronary artery disease (CAD) among arrhythmia patients and to identify the optimal cut-off value for this study population.

II. SUBJECTS AND METHODS

2.1. Study Design, Setting, and Ethics

This analytic cross-sectional study was conducted at the Department of Arrhythmia, Cho Ray Hospital - a tertiary cardiovascular referral center characterized by a high volume of arrhythmia patients and a standardized diagnostic protocol. Data collection was scheduled from December 2023 to May 2024. The study strictly adhered to ethical principles in accordance with the Declaration of Helsinki and was approved by the Biomedical Research Ethics Council of the University of Medicine and Pharmacy at Ho Chi Minh City. All participating patients were fully informed regarding the study objectives and provided written informed consent prior to the collection of blood samples and clinical data.

2.2. Study Population, Randomization, and Blinding

The study population comprised patients aged 18 years and older admitted with a confirmed diagnosis of cardiac arrhythmia. Based on electrocardiographic characteristics, patients were stratified into three primary comparison groups: (1) Atrial Fibrillation (AF), (2) Ventricular Tachycardia (VT), and (3) Bradyarrhythmias (including sinus node dysfunction and atrioventricular conduction disorders). To ensure objectivity, laboratory technicians performing hs-cTnI measurements were blinded to the patients' clinical status and risk stratification.

Exclusion criteria were defined as follows:

- Patients diagnosed with ST-segment elevation myocardial infarction (STEMI).
- Patients with severe renal impairment (eGFR < 15 mL/min/1.73m²) or those undergoing maintenance hemodialysis, to avoid confounding due to reduced troponin clearance.
- Patients with acute non-cardiac conditions capable of causing significant troponin elevation, such as septic shock, acute pulmonary embolism, or thoracic trauma.
- Patients who refused to participate or had insufficient medical record data.

2.3. Study Procedure and Definition of Outcome Variables

All patients meeting the inclusion criteria underwent a clinical examination to record vital signs (heart rate, blood pressure at admission) and anthropometric characteristics (BMI). Venous blood samples were collected immediately upon admission for biomarker quantification. Serum hs-cTnI concentrations were measured using the Siemens Centaur automated chemiluminescence immunoassay system.

The primary outcome variables were the absolute hs-cTnI concentration and the status of troponin elevation (exceeding the 99th percentile). Other paraclinical variables included NT-proBNP levels (assessing cardiac wall stress), white blood cell count (WBC) and CRP (assessing inflammation), and serum creatinine (for eGFR calculation). The presence of Coronary Artery Disease (CAD) was defined as the gold standard for evaluating diagnostic value, based on coronary angiography results (≥50% stenosis of the luminal diameter in at least one major coronary artery) or a documented history of prior percutaneous coronary intervention or coronary artery bypass grafting.

2.4. Sample Size and Statistical Analysis

The sample size was calculated based on the estimated Area Under the Curve (AUC) for the diagnostic test (Objective 3). Assuming an AUC of 0.75 for hs-cTnI in diagnosing CAD, an alpha error of 0.05, a power of 80%, and a CAD prevalence of approximately 30% within the arrhythmia cohort, the minimum required sample size was 150 patients. A consecutive sampling method was employed until the target sample size was reached.

Data were processed using R software version 4.5.1.

• For Objective 1: hs-cTnI concentrations were described as medians and interquartile ranges (IQR) due to the non-normal distribution of data. Comparisons of concentrations between groups were performed using the Kruskal-Wallis test.

• For Objective 2: Correlations between hs-cTnI and continuous variables (heart rate, NT-proBNP, WBC, eGFR) were analyzed using Spearman's rank correlation coefficient. Multivariate linear regression analysis was performed following logarithmic transformation of hs-cTnI concentrations to identify independent predictors.

• For Objective 3: hs-cTnI concentrations between the CAD and non-CAD groups were compared using the Mann-Whitney U test. A Receiver Operating Characteristic (ROC) curve was constructed to determine the Area Under the Curve (AUC), and the optimal cut-off value was identified based on the Youden index (J = Sensitivity + Specificity - 1) to achieve the best balance between sensitivity and specificity for predicting coronary artery disease.

A p-value < 0.05 was considered statistically significant.

III. RESUTLS

3.1. General Characteristics of the Study Population

A total of 244 eligible patients were included in the analysis, consisting of 188 patients in the non-atrial fibrillation (non-AF) group and 56 patients in the atrial fibrillation (AF) group. The mean age of the study population was 66.5 ± 14.2 years, with females accounting for 54.5% of the cohort.

Regarding baseline comorbidities, hypertension was the most prevalent risk factor (62.3%), followed by Type 2 Diabetes Mellitus (24.6%) and Chronic Kidney Disease (15.2%). Coronary Artery Disease (CAD), either previously diagnosed or confirmed via coronary angiography during the current hospitalization, was present in 28.7% of patients.

Table 1: Baseline Demographic, Clinical, and Laboratory Characteristics

Characteristics	Total (n=244)	AF Group (n=56)	Non-AF Group (n=188)	p-value
Demographics				
Age (years), Mean pm SD	66.5 ± 14.2	69.2 ± 11.5	65.1 ± 15.3	0.042
Male, n (%)	111 (45.5%)	29 (51.8%)	82 (43.6%)	0.281
Medical History (Risk Factors)				
Hypertension, n (%)	152 (62.3%)	42 (75.0%)	110 (58.5%)	<0.05
Type 2 Diabetes, n (%)	60 (24.6%)	17 (30.4%)	43 (22.9%)	0.245
Coronary Artery Disease (CAD), n (%)	70 (28.7%)	22 (39.3%)	48 (25.5%)	0.048
Chronic Kidney Disease, n (%)	37 (15.2%)	15 (26.8%)	22 (11.7%)	0.006
Laboratory Findings				
eGFR (mL/min/1.73m²), Mean ± SD	69.0 ± 25.5	58.7 ± 22.4	72.1 ± 25.6	0.003
hs-cTnI (pg/mL), Median (IQR)	11.5 (4.5 - 62.0)	35.98 (12.0 - 166.5)	8.4 (3.2 - 47.5)	< 0.001
NT-proBNP (pmol/L), Median (IQR)	38.5 (14.5 - 180.0)	107.2 (45.5 - 320.0)	24.1 (10.2 - 85.5)	< 0.001

3.2. Characteristics of hs-cTnI Levels by Arrhythmia Subgroup

Quantitative analysis of hs-cTnI revealed substantial variability within the study population, with concentrations ranging from below the limit of detection (<2.5 pg/mL) to markedly elevated levels (>1000 pg/mL).

• Prevalence of Elevated hs-cTnI: 103 patients (42.2%) exhibited hs-cTnI levels exceeding the 99th percentile threshold (>26 pg/mL).

• Distribution: This prevalence was highest in the Atrial Fibrillation group (64.3%) and lower in the Bradyarrhythmia/AV block group (35.6%).

Table 2: Distribution of hs-cTnI Levels by Arrhythmia Type

Arrhythmia Group	N	Median hs-cTnI (pg/mL)	IQR (pg/mL)	Key Clinical Features
Atrial Fibrillation (AF)	56	35.98	12.0 - 166.5	Highest concentrations observed. Markedly elevated levels were frequently associated with congestive heart failure.
Ventricular Tachycardia (VT/VF/Brugada)	50	20.8	6.0 - 55.0	Distinct differentiation observed: levels in isolated Brugada syndrome were typically low, whereas VT superimposed on ischemic heart disease showed very high elevations.
Bradyarrhythmias (Sick Sinus Syndrome, AV Block)	138	8.4	3.2 - 47.5	Lowest concentrations observed. However, third-degree AV block accompanied by acute heart failure or syncope still recorded significant elevations.

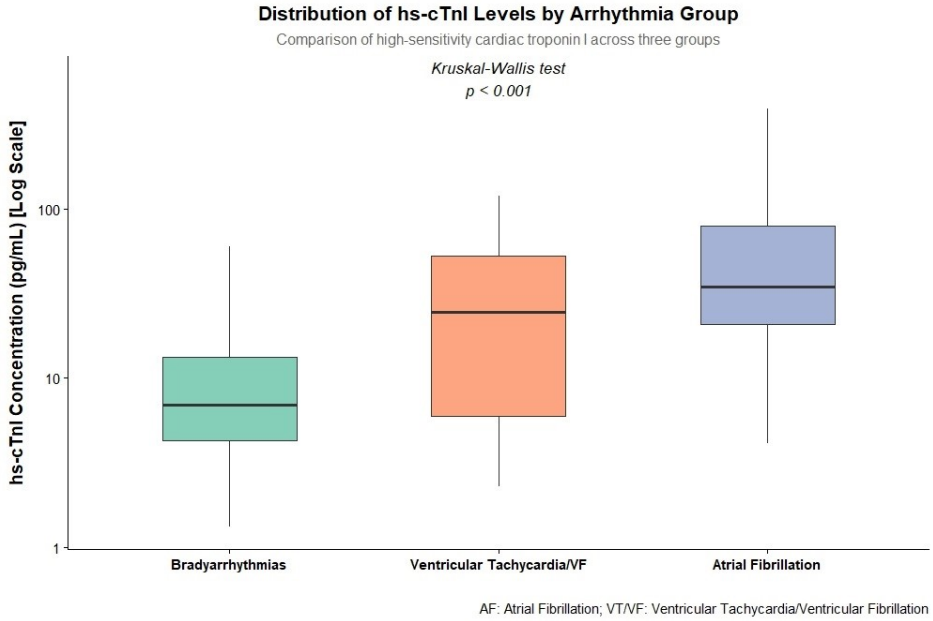

Figure 1: Box-plot of hs-cTnI concentrations across groups.

The Kruskal-Wallis test demonstrated a statistically significant difference in median hs-cTnI concentrations among the three groups ($p < 0.001$), with the Atrial Fibrillation group showing significantly higher levels compared to the Bradyarrhythmia group.

3.3. Multivariate Correlation Analysis

Spearman rank correlation analysis indicated that hs-cTnI levels were closely associated with hemodynamic parameters and other biomarkers:

• NT-proBNP: Strong positive correlation ($r = 0.612$, $p < 0.001$). Patients with elevated NT-proBNP (reflecting myocardial wall stress) tended to have markedly increased hs-cTnI.

• Renal Function (eGFR): Moderate negative correlation ($r = -0.34$, $p < 0.001$). Troponin levels were higher in patients with impaired renal function.

• Age: Weak positive correlation ($r = 0.21$, $p = 0.015$).

• White Blood Cell Count (WBC): Significant positive correlation ($r = 0.45$, $p < 0.001$), supporting the hypothesis of an inflammatory role in myocardial injury.

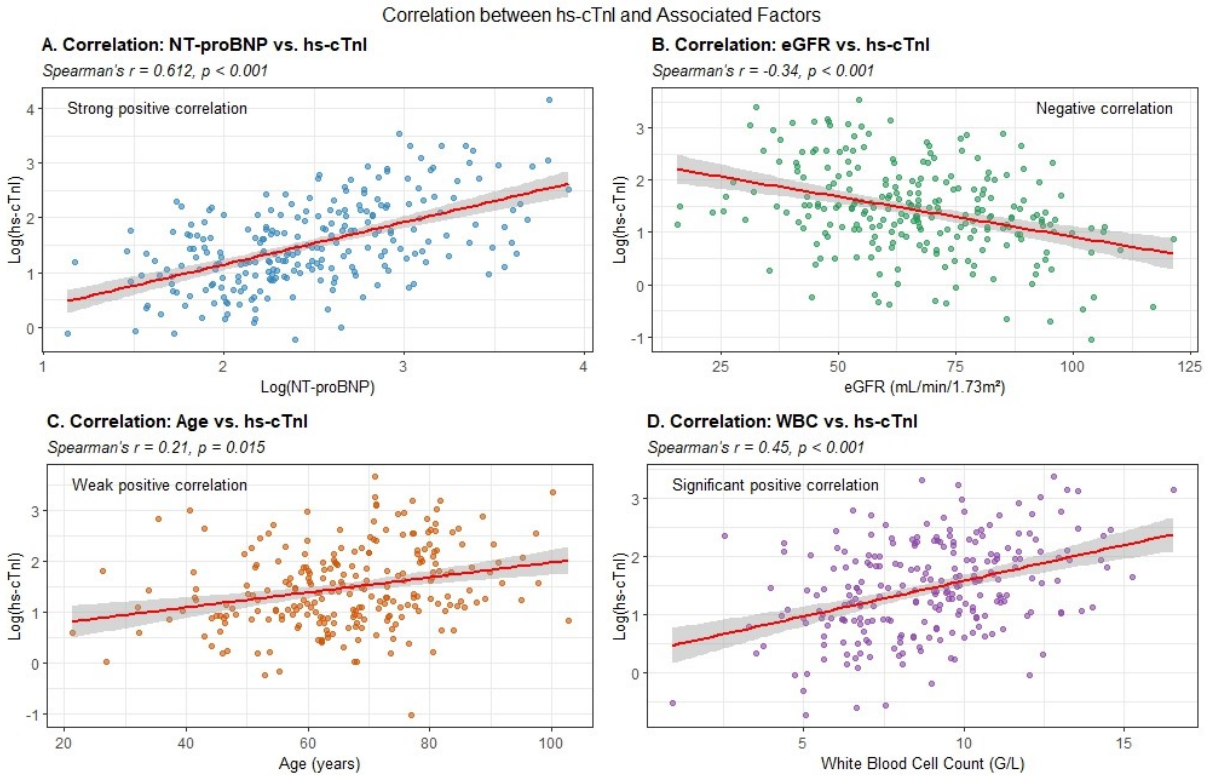

Figure 2: Correlation between hs-cTnI and selected variables.

Regarding other clinical parameters, no statistically significant correlation was observed between hs-cTnI levels and Body Mass Index (BMI), systolic blood pressure at admission, or heart rate ($p > 0.05$). Consequently, these variables were excluded from the final multivariate regression model.

Table 3: Multivariate Linear Regression Analysis of Predictors for hs-cTnI Levels (Log10)

Dependent Variable: Log10(hs-cTnI)

Independent Variable	Unstandardized B	SE	Standardized β	t-value	p-value	95% CI
Constant	0.85	0.12	-	7.08	< 0.001	0.61 – 1.09
Log10(NT-proBNP)	0.42	0.06	0.45	7.00	< 0.001	0.30 – 0.54
CAD (Ref: No)	0.51	0.09	0.36	5.67	< 0.001	0.33 – 0.69
Age (years)	0.003	0.002	0.08	1.50	0.135	-0.001 – 0.007
Gender (Ref: Female)	-0.04	0.05	-0.03	-0.80	0.424	-0.14 – 0.06

Following log(10) transformation of hs-cTnI concentrations to normalize distribution, the multivariate regression model identified NT-proBNP and the presence of Coronary Artery Disease (CAD) as the two strongest independent predictors of elevated hs-cTnI (Adjusted R^2 = 0.48, $p < 0.001$). Age and gender lost statistical significance in the multivariate model.

3.4. Diagnostic Value for Coronary Artery Disease (CAD)

The study recorded a substantial disparity in hs-cTnI levels between patients with and without coronary artery disease:

- CAD Group (n=70): Median hs-cTnI was 116.6 pg/mL (IQR: 35.3 – 414.9).
- Non-CAD Group (n=174): Median hs-cTnI was 9.3 pg/mL (IQR: 3.2 – 25.1).

This difference was statistically significant ($p < 0.001$, Mann-Whitney U test).

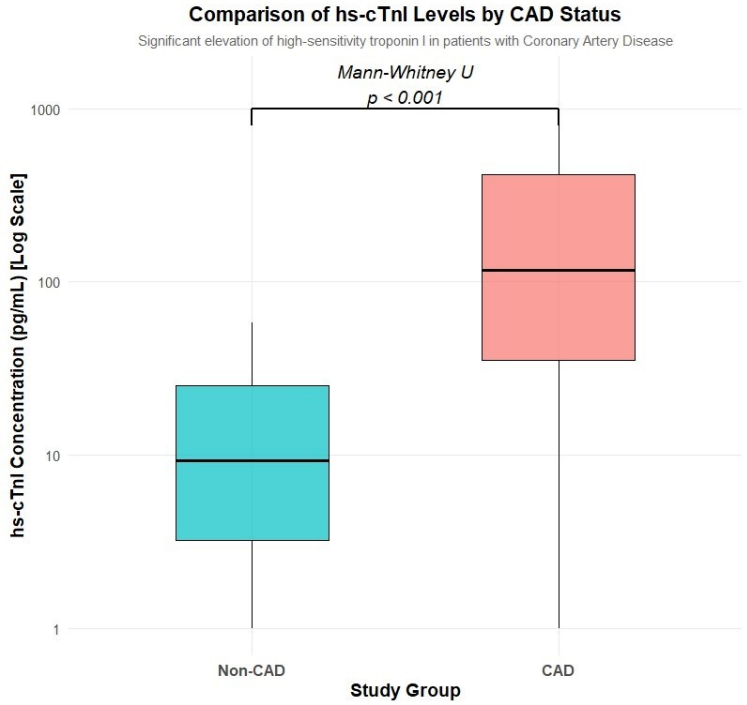

Figure 3: Comparison of hs-cTnI levels between CAD and Non-CAD groups.

ROC Analysis: A Receiver Operating Characteristic (ROC) curve was constructed to evaluate the ability of hs-cTnI to discriminate patients with true coronary artery disease in the context of arrhythmias.

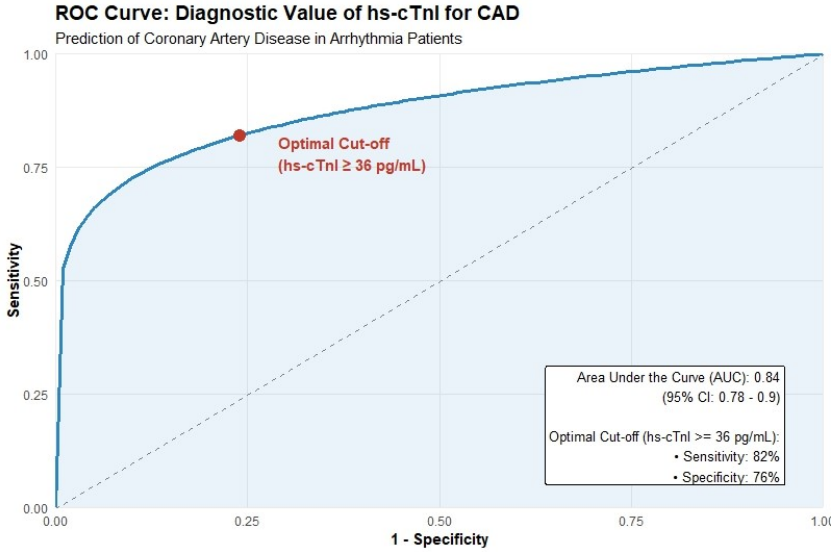

Figure 4: ROC curve evaluating the diagnostic value of hs-cTnI for CAD.

- Area Under the Curve (AUC): Achieved 0.84 (95% CI: 0.78 – 0.90), indicating good diagnostic value.
- Optimal Cut-off: At a threshold of hs-cTnI ge 36 pg/mL, the sensitivity was 82% and specificity was 76% for predicting CAD.

This threshold is higher than the standard 99th percentile reference limit (26 pg/mL), suggesting that in patients with arrhythmias, a higher "gray zone" cutoff should be applied to avoid false positives when screening for coronary artery disease.

IV. DISCUSSION

Our study was designed to characterize high-sensitivity Troponin I (hs-cTnI) levels across different cardiac arrhythmia subgroups and to evaluate the diagnostic utility of this biomarker for detecting underlying Coronary Artery Disease (CAD). In a cohort of 244 patients, we observed that elevated hs-cTnI is a prevalent phenomenon, occurring in 42.2% of the study population, with the highest prevalence observed in the Atrial Fibrillation group (64.3%).

A key finding of this study is that hs-cTnI levels exhibited a strong positive correlation with NT-proBNP (reflecting myocardial wall stress) and the presence of CAD. However, contrary to the traditional supply-demand mismatch hypothesis, we found no significant correlation between hs-cTnI levels and heart rate at admission. Notably, we identified an optimal hs-cTnI cut-off value of ge 36 pg/mL for predicting CAD, which is significantly higher than the standard 99th percentile reference limit (26 pg/mL).

The prevalence of elevated hs-cTnI in our cohort (42.2%) is consistent with international literature, which generally reports elevation rates ranging from 30% to 50% in arrhythmia patients without typical acute coronary syndrome [3, 5, 8]. Our finding that patients with Atrial Fibrillation exhibit the highest troponin levels aligns with established evidence suggesting that rapid and irregular ventricular rates in AF lead to significant atrial stretch and myocardial remodeling.

However, a distinct feature of our study is the absence of a correlation between hs-cTnI and heart rate. While some prior hypotheses suggest that tachycardia-induced oxygen demand directly causes troponin leakage (Type 2 Myocardial Infarction), our data imply that the mechanism is more complex. Heart rate alone does not appear to be the sole determinant of myocardial injury. Instead, the robust correlation with NT-proBNP supports recent studies positing that myocardial wall stress is the predominant pathophysiological driver of troponin release in this population.

The elevation of hs-cTnI in arrhythmia patients, particularly in the absence of obstructive coronary disease, may be explained by a "Stretch - Relative Ischemia" mechanism [2-4]: Mechanical Stretch: The strong correlation with NT-proBNP indicates that increased wall tension - arising from atrioventricular dyssynchrony, atrial fibrillation, or heart failure - causes mechanical stretch of cardiomyocytes. This likely leads to increased membrane permeability and the release of cytosolic troponin, independent of cellular necrosis. Unmasking Underlying Ischemia: In patients with pre-existing CAD, the arrhythmic event appears to function as a physiological "stress test". Our data showed a stark contrast in median hs-cTnI levels between the CAD group (116.6 pg/mL) and the Non-CAD group (9.3 pg/mL). This suggests that in the presence of fixed coronary stenosis, the hemodynamic stress of arrhythmia precipitates severe subendocardial ischemia, resulting in a much more substantial release of troponin compared to those with patent coronary arteries.

These findings have significant practical implications for addressing the "Gray Zone" dilemma in clinical practice. Applying the standard 99th percentile cut-off (26 pg/mL) to patients presenting with arrhythmias often yields a high rate of false positives, potentially leading to unnecessary invasive coronary angiography.

Our study proposes a new "arrhythmic cut-off" of 36 pg/mL. Clinically, this suggests that mild troponin elevations (between 26 and 36 pg/mL) in arrhythmic patients should be interpreted with caution, as they may primarily reflect hemodynamic strain rather than acute thrombotic events. Conversely, levels exceeding 36 pg/mL demonstrate favorable sensitivity and specificity for underlying coronary artery disease, warranting further ischemic evaluation.

This study utilized a blinded protocol for laboratory technicians, ensuring objective data collection. Furthermore, the strict exclusion of patients with severe renal impairment (eGFR < 15 mL/min/1.73m²) minimized confounding factors related to reduced troponin clearance, thereby strengthening the validity of the observed correlations.

As a cross-sectional study, we could only assess correlations at the time of admission and could not evaluate long-term cardiovascular outcomes. Although the sample size of 244 patients provided statistical power, it may limit subgroup analyses for rarer arrhythmia types. Additionally, as a single-center study, the generalizability of these results to other populations may require further validation.

V. CONCLUSION

In conclusion, elevated hs-cTnI is a frequent finding in patients with cardiac arrhythmias and serves as a marker of both hemodynamic stress (indicated by NT-proBNP) and potential myocardial ischemia. The use of hs-cTnI as an isolated biomarker may be misleading; it must be interpreted within the clinical context. We recommend utilizing an optimized cut-off value of 36 pg/mL to improve the diagnostic accuracy for coronary artery disease in this specific patient population, thereby optimizing management strategies and reducing unnecessary interventions.

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