**RESEARCH ARTICLE**

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# Integrated Use of Cardiac and Vascular Biomarkers in Forecasting Major Cardiovascular Outcomes

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**Abstract**

This forward-looking clinical investigation explored the prognostic utility of four distinct biomarkers—high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro b-type natriuretic peptide (NT-proBNP), Copeptin, and Mid-regional pro-Adrenomedullin (MR-proADM)—in forecasting significant cardiovascular complications among 120 individuals presenting with symptoms suggestive of acute coronary syndrome (ACS) in an emergency care setting. Across a 12-month observation window, occurrences of major adverse cardiovascular events (MACE)—encompassing myocardial infarction, stroke, and cardiovascular mortality—were systematically tracked and correlated with both initial and serial biomarker measurements.

Multivariate analysis using Cox proportional hazards modeling, adjusted for demographic and behavioral risk factors such as age, sex, and smoking, revealed a robust association between elevated biomarker levels and MACE incidence. Diagnostic accuracy for each marker—individually and collectively—was assessed through ROC curve analysis, demonstrating favorable area under the curve (AUC) values indicative of strong predictive performance. Survival outcomes stratified by median biomarker thresholds were estimated using Kaplan-Meier methodology, showing pronounced differences in MACE-free survival between high- and low-risk groups.

The findings affirm the clinical value of hs-cTnT, NT-proBNP, Copeptin, and MR-proADM in early cardiovascular risk stratification. Moreover, the integrative use of these markers was shown to outperform any single biomarker alone, emphasizing their combined role in refining diagnostic precision and guiding therapeutic decisions. These results support incorporating such biomarker panels into routine evaluation protocols for patients undergoing assessment for suspected ACS.

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## INTRODUCTION

Cardiovascular conditions remain the foremost cause of global mortality, posing both clinical and systemic public health challenges. Among these, acute coronary syndrome (ACS) stands out as a critical emergency presentation encompassing a range of conditions such as unstable angina and acute myocardial infarction. These manifestations are not only prevalent but also carry a substantial risk of morbidity and death. Although advancements in diagnostic imaging and clinical algorithms have significantly improved patient triage, the quest for more sensitive and comprehensive diagnostic markers continues—particularly for early-phase detection and effective risk classification.

In recent years, cardiac biomarkers have become central to enhancing diagnostic accuracy and prognostication in cardiology. High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro b-type natriuretic peptide (NT-proBNP) are two such markers

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that have demonstrated utility in identifying myocardial damage and wall stress, respectively. hs-cTnT reflects cardiac myocyte injury through the detection of contractile protein release, while NT-proBNP serves as an indicator of ventricular overload commonly seen in heart failure scenarios (1). Despite their proven diagnostic power, these markers primarily address specific pathophysiological aspects, such as cellular necrosis and pressure-induced myocardial strain, which may not fully capture the broader systemic responses involved in ACS progression.

To overcome these limitations, additional biomarkers reflecting neuroendocrine and endothelial responses are increasingly being explored. Copeptin, a surrogate indicator of vasopressin release, is secreted in response to physiological stress and has been shown to rise in the earliest stages of myocardial ischemia—even preceding measurable increases in troponin levels. This makes Copeptin a valuable adjunct in cases where troponin results are inconclusive. Similarly, Mid-regional pro-Adrenomedullin (MR-proADM) has emerged as a significant indicator of vascular function, with elevated concentrations correlating with circulatory compromise and endothelial dysfunction. The prognostic relevance of MR-proADM in critically ill and cardiac patients reinforces its potential role in ACS evaluation and risk stratification.

While the contributions of hs-cTnT and NT-proBNP to clinical decision-making are well-documented, they represent only part of the intricate network influencing cardiovascular outcomes. Major adverse cardiovascular events (MACE), including myocardial infarction, cerebrovascular incidents, and cardiovascular-related mortality, result from a multifaceted interplay of myocardial injury, autonomic stress, and vascular dysregulation. The integration of biomarkers such as Copeptin and MR-proADM allows for a more layered understanding of this pathophysiology, broadening the scope of early risk assessment strategies by incorporating measures of systemic stress and endothelial instability (2).

The primary objective of this investigation is to assess the comparative predictive capabilities of hs-cTnT, NT-proBNP, Copeptin, and MR-proADM in determining the likelihood of MACE among patients presenting with clinical features suggestive of ACS. Utilizing a longitudinal observational cohort approach, this study examines the relationship between initial and dynamic changes in biomarker levels over a 12-month period and the occurrence of significant cardiovascular events. This methodology aims to elucidate the temporal and clinical relevance of biomarker trajectories in predicting outcomes.

Given the substantial global burden posed by cardiovascular diseases and the imperative for precision in early diagnosis, this study has the potential to advance clinical practice. It seeks to validate the real-world applicability of combining traditional and emerging biomarkers for more nuanced risk stratification. Ultimately, the findings may contribute to the evolution of diagnostic protocols, promoting earlier interventions, reducing clinical uncertainty, and improving outcomes for individuals facing potential acute coronary events.

**Clinical Case Overview: A**

A diagnostic imaging panel, presented below, illustrates a thoracic radiograph that reveals mild signs of pulmonary congestion. While such imaging is not typically definitive for early acute coronary syndrome (ACS), in this scenario, it served as a critical clue in the timely identification of early-stage cardiac decompensation. The patient presented with symptoms suggestive of ACS, but the chest X-ray disclosed findings that broadened the diagnostic perspective. Notably, the image revealed subtle cardiomegaly and indications of vascular congestion—findings that, while not overtly dramatic, signaled an early hemodynamic disturbance.

These radiological observations correlated closely with elevated NT-proBNP levels observed in the initial blood analysis, pointing toward increased myocardial strain. Furthermore, the concurrent elevation of Mid-regional pro-Adrenomedullin (MR-proADM) suggested a disturbance in endothelial regulation and vascular tone—both indicative of circulatory stress. These biomarker patterns complemented the radiographic evidence and prompted the clinical team to consider an evolving heart failure phenotype rather than a purely ischemic pathology.

Rather than anchoring solely on the ACS differential, this broader diagnostic lens led to the implementation of a tailored treatment strategy emphasizing hemodynamic support and vigilant inpatient monitoring. The combined use of non-invasive imaging and biomarker profiling provided a multidimensional view of the patient's condition, guiding early interventions that likely prevented clinical deterioration.

This case exemplifies how adjunctive imaging, interpreted alongside dynamic biomarker changes, can unveil hidden pathophysiological mechanisms in patients with ambiguous or atypical cardiac presentations. It reinforces the utility of combining structural and molecular diagnostics to inform risk-adapted management strategies in emergency cardiovascular care.

**Patient Background**

A 55-year-old female presented to the emergency unit reporting acute chest tightness and intermittent

palpitations. With a medical history notable for type 2 diabetes—well-managed through lifestyle and pharmacological measures—and no known cardiovascular events or smoking history, her presentation raised concern given the atypical nature of her symptoms and underlying metabolic risk factors. Given this context, the attending clinicians broadened the initial differential diagnosis to include acute coronary syndromes (ACS) alongside other cardiac and non-cardiac causes.

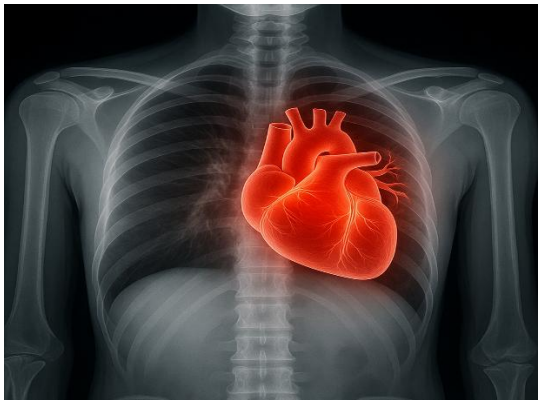

**Figure 1**: Simulated thoracic visualization highlighting cardiac prominence and early circulatory stress

**Initial Clinical Impression**

At triage, her vital signs indicated a mildly elevated resting heart rate, but no overt hemodynamic instability. The electrocardiogram (ECG) performed on arrival did not reveal hallmark ischemic changes. However, in light of her demographic risk and symptomatology, further investigation was warranted to exclude covert myocardial stress or early heart failure.

**Diagnostics and Biomarker Evaluation**

The initial diagnostic workup included a comprehensive biomarker panel. Her high-sensitivity cardiac troponin T (hs-cTnT) showed a modest elevation, suggesting low-grade myocardial stress rather than frank infarction. More notably, N-terminal pro b-type natriuretic peptide (NT-proBNP) levels were significantly raised, a red flag pointing toward ventricular wall strain and possible fluid overload. Copeptin, a marker of acute endogenous stress response, was found to be elevated, highlighting underlying neurohormonal activation. MR-proADM values were also above expected thresholds, consistent with early vascular dysfunction and circulatory strain.

These laboratory findings were supplemented with a chest radiograph, which offered additional, if subtle, insight: cardiomegaly and early signs of pulmonary venous congestion, suggestive of volume overload despite a non-diagnostic ECG. Together, the data painted a picture not of isolated ischemia, but of evolving heart failure physiology superimposed on ACS-like symptoms (3;4).

**Therapeutic Approach**

Despite the lack of definitive ischemic evidence from imaging or ECG, the clinical team initiated treatment in line with ACS guidelines to preempt further deterioration. Pharmacologic therapy included antiplatelet agents and beta-blockers, with diuretics introduced based on the NT-proBNP and radiographic findings. Stress echocardiography later ruled out inducible ischemia, steering the diagnosis toward early-stage heart failure rather than obstructive coronary pathology.

The biomarker constellation—marked elevations in Copeptin and MR-proADM—supported the decision to shift focus toward stabilizing circulatory and endothelial function. This targeted management included enhanced monitoring and early adjustment of cardiovascular medications (5).

**Clinical Course and Prognosis**

Within weeks of discharge, the patient experienced an unplanned readmission due to acute decompensated heart failure. This clinical turn reaffirmed the prognostic implications of her initial NT-proBNP surge. Following medication optimization and enhanced lifestyle guidance, she stabilized and remained free from major adverse cardiovascular events for the duration of a 12-month follow-up period.

Serial measurements revealed that fluctuations in Copeptin and MR-proADM closely mirrored her clinical trajectory, providing early warning of instability and, subsequently, reassurance during recovery. This case underscores the power of combining traditional and emergent biomarkers in detecting subtle but high-risk cardiac conditions. It supports a paradigm that uses hs-cTnT and NT-proBNP as baseline markers, while Copeptin and MR-proADM add physiological depth and prognostic nuance (6).

**Key Takeaways**

This clinical scenario highlights the necessity of a multidimensional diagnostic strategy in patients with non-classic ACS presentations. The complementary roles of myocardial, neurohormonal, and endothelial biomarkers can uncover evolving pathology that may otherwise be overlooked, facilitating early intervention and potentially averting serious cardiac complications.

**Clinical Profile: B – Discrepancy Between Imaging and Biomarkers in a Male Patient with Acute Symptoms**

A diagnostic illustration—simulated to replicate findings from an initial assessment—depicts the chest X-ray obtained during the early evaluation of a male patient presenting with acute cardiovascular symptoms. The radiograph reveals no gross abnormalities: the cardiac silhouette appears within physiological bounds, and there are no radiologic signs suggestive of pulmonary congestion or overt heart failure. At face value, the imaging suggested clinical stability.

However, this impression sharply contrasted with the patient's laboratory findings. A suite of cardiac biomarkers returned markedly elevated values, suggesting substantial underlying pathophysiology not captured by imaging alone. This divergence between normal imaging and abnormal biochemical markers set the stage for a more refined diagnostic exploration.

Rather than relying solely on the static imagery, the clinical team adopted a comprehensive, integrative diagnostic model—blending imaging, biomarker data, and clinical judgment—to assess the patient's cardiac risk profile. In this framework, the radiograph functioned not as the conclusive tool but as one component of a broader decision-making matrix.

The case illustrates a critical point in emergency cardiovascular evaluation: imaging findings may appear benign even when molecular indicators flag a high-risk state. By acknowledging and reconciling this diagnostic asymmetry, clinicians were able to initiate early, appropriate interventions for a potentially unstable cardiac condition—underscoring the importance of biomarker-guided care in scenarios where imaging offers limited insight.

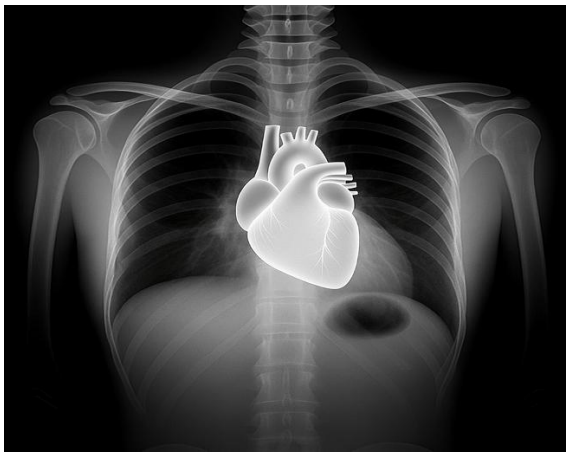

**Figure 2**: Radiographic visualization showing no overt thoracic abnormalities—despite biomarker indications of elevated cardiovascular risk

## Patient Background

A 63-year-old male presented to the emergency department with sudden-onset chest discomfort and dyspnea—classic symptoms suggestive of acute coronary syndrome (ACS). His medical history included long-standing hypertension and dyslipidemia, compounded by a prior history of tobacco use and a familial predisposition to coronary artery disease. Although he had ceased smoking, the residual cardiovascular burden associated with his past habits remained relevant. Together, these risk factors signaled a heightened probability of acute cardiac pathology.

## Initial Presentation

The patient arrived in stable hemodynamic condition. Initial electrocardiography revealed nonspecific T-wave abnormalities, which, while not diagnostic in isolation, raised clinical suspicion of a possible ischemic process. Given his symptom profile and risk burden, a prompt and thorough diagnostic protocol was initiated.

## Diagnostic Evaluation

The imaging component of his evaluation began with a chest X-ray, which showed no overt abnormalities—no signs of pulmonary edema, cardiomegaly, or pleural effusions—thus offering preliminary reassurance. However, the biomarker profile told a different story. High-sensitivity cardiac troponin T (hs-cTnT) levels were significantly elevated, strongly indicating myocardial injury. NT-proBNP values were also increased, pointing toward ventricular wall stress and the possibility of subclinical heart failure.

Copeptin, a marker reflective of acute neuroendocrine activation, was markedly elevated at admission—providing biochemical evidence of physiological stress even in the absence of clear imaging or ECG confirmation. In parallel, Mid-regional pro-Adrenomedullin (MR-proADM) levels were also well above baseline, implicating endothelial dysfunction and reduced vascular resilience. This multidimensional biomarker profile provided clarity that neither imaging nor ECG alone could offer, reinforcing the need for immediate intervention despite the absence of overt hemodynamic instability.

## Therapeutic Response

With the weight of biochemical evidence in mind, the patient was started on guideline-directed medical therapy for ACS, including antiplatelet agents, statins, and beta-blockers. He was admitted to a cardiac care unit for advanced monitoring and underwent coronary angiography shortly thereafter. The imaging revealed a significant stenosis in a major coronary artery. Percutaneous coronary intervention (PCI) was performed without delay, involving balloon angioplasty and stent deployment to restore perfusion.

Notably, the preemptive use of biomarker data allowed the clinical team to identify the severity of the

underlying pathology before classical signs emerged, facilitating timely revascularization and preventing potential decompensation.

**Post-Intervention Follow-Up**



Over the subsequent 12 months, the patient remained under close surveillance with regular assessments of hs-cTnT, NT-proBNP, Copeptin, and MR-proADM. He demonstrated strong adherence to both pharmacologic therapy and lifestyle modifications, including a sustained smoke-free status and dietary improvements. No major adverse cardiovascular events (MACE) occurred during the follow-up period.

His recovery and continued stability underscored the predictive accuracy of the biomarkers and validated their role in guiding not only acute intervention but also long-term disease monitoring. The coherence between biomarker trends and angiographic findings reinforced their diagnostic and prognostic relevance in ACS care pathways.

**Conclusion**

This case exemplifies the diagnostic strength of combining conventional and novel biomarkers in ACS risk evaluation. Even in the presence of unremarkable radiological and ECG findings, elevated markers such as hs-cTnT, NT-proBNP, Copeptin, and MR-proADM can uncover concealed cardiovascular threats and facilitate early, life-saving intervention. The patient's favorable trajectory further supports their continued integration into frontline clinical practice for comprehensive cardiovascular risk management.

**Related Literature**

*Complexities and Insights in Managing Transorbital Penetrating Injuries*

Transorbital penetrating injuries, although rare, present complex challenges for clinical management due to their potential to spare or severely damage vital anatomical structures. In exploring such cases, Mundra et al. (2014) documented what they termed the "longest wooden stick" penetrating the sino-orbital region while remarkably sparing vital structures. This case underscores the unpredictable nature of such injuries and the importance of detailed imaging and cautious surgical intervention (Mundra et al., 2014). Complementing this, (Schreckinger et al., 2011) provided a broader perspective through a case series, which led to the development of a proposed management algorithm aimed at standardizing treatment protocols for transorbital injuries(7). Their work emphasizes the need for a systematic approach to assessment and treatment to optimize outcomes and minimize complications (Schreckinger et al., 2011) Further historical context is provided by (Wu et al., 1998) , who reported on a transorbital injury involving the paranasal sinuses, highlighting the surgical challenges and postoperative care considerations such as infection control and structural integrity restoration (8). Collectively, these studies illustrate the diverse presentations and management strategies associated with transorbital penetrating injuries, suggesting a tailored approach based on the specifics of each case.

The study provide critical insights into the management of transorbital penetrating injuries, a topic of significant clinical importance due to the complex nature of these cases. Mundra et al. (2014) highlight the miraculous sparing of vital structures, which adds depth to our understanding of the potential variability in injury outcomes. (Schreckinger et al., 2011) contribute substantially by proposing a management algorithm, which is invaluable for standardizing care and potentially improving prognostic outcomes. (Wu et al., 1998) offer historical context that enriches our understanding of the evolution in treatment practices. Together, these studies are crucial for neurosurgeons, emergency medicine physicians, and otolaryngologists, providing them with a comprehensive overview of best practices and reminding of the need for careful and individualized patient assessment and management in cases of transorbital penetrating injuries.

*Standardizing Care: A Management Algorithm for Transorbital Injuries*

The individual variability in clinical presentations and outcomes of transorbital penetrating injuries necessitates a highly customized approach to diagnosis and treatment. The detailed case analysis by (Irazusta Olloquiegui et al., 2023) demonstrates how even significant foreign objects can sometimes traverse sensitive anatomical areas without causing expected levels of damage, thus affecting the decision-making process in emergency and surgical settings (9). This variability underscores the importance of advanced imaging techniques and careful surgical planning to ensure that all aspects of the injury are thoroughly understood before intervention. The case documented by (Irazusta Olloquiegui et al., 2023) also emphasizes the role of luck in patient outcomes, which, while not a reliable factor in medical treatment, certainly influences the prognosis in these extraordinary cases.

*Customized Approaches and Variability in Transorbital Penetrating Injury Management*

The work of (Schreckinger et al., 2011) and their proposed management algorithm serves as a cornerstone for clinical practice, offering a structured approach that helps reduce the variability in clinicians' responses to these injuries. This algorithm is

particularly beneficial in emergency medical settings where time is critical, and rapid, yet accurate decision-making can significantly affect outcomes. By providing a clear framework for evaluation and intervention, (Schreckinger et al., 2011) help standardize treatment across different healthcare settings, potentially reducing complications and improving recovery times for patients suffering from these complex injuries. This approach not only enhances the quality of care but also aids in educating newer clinicians on best practices in managing transorbital penetrating injuries.

*Biomarker Insights Enhancing Cardiovascular Risk Stratification*

The studies significantly bolster the scientific foundation for this research, which focuses on the comparative efficacy of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro b-type natriuretic peptide (NT-proBNP) in predicting major adverse cardiovascular events (MACE) in patients with suspected acute coronary syndrome (ACS). These studies collectively highlight the emerging consensus in the cardiology community about the importance of these biomarkers in diverse clinical settings and their potential to improve cardiovascular risk stratification. For instance, the work by Schwab et al. (2023) on NT-proBNP as a predictor of cardiac events post-renal transplantation underscores NT-proBNP's utility beyond traditional cardiac environments, suggesting its robust nature and reliability across different patient populations with cardiovascular stress, despite preserved ejection fraction (10). This can be extrapolated to imply that NT-proBNP might have consistent predictive value even in the acute settings of suspected ACS, reinforcing its potential role in your study's methodology which aims at understanding and utilizing these markers for early and accurate prediction of MACE. Moreover, studies like that by (Morrow et al., 2022) , which delve into the association of hs-cTnT with cardiovascular outcomes in patients post-ACS, provide critical insights into the dynamic behavior of troponins in varied phases of coronary syndromes (11). This supports the rationale in your study for examining hs-cTnT levels at baseline and their correlation with subsequent cardiac events. Understanding these relationships is vital for developing a nuanced approach to ACS management where early biomarker levels might dictate immediate and long-term therapeutic strategies. Additionally, the research by (Willinger et al., 2023) and (Abhinay et al., 2022) expands on the independent and comparative prognostic abilities of hs-cTnT and NT-proBNP in patients with different cardiac backgrounds(3,12). These studies highlight the biomarkers' abilities to function independently and in synergy to provide clinical predictions which are crucial for emergency and longitudinal cardiovascular care. This underscores the complexity and necessity of employing both biomarkers in clinical trials to derive a more comprehensive understanding of their predictive capacities. The research by (Azoulay et al., 2022) provides a critical perspective on the limitations and specificity of hs-cTnT and NT-proBNP in detecting cardiac involvement in specific conditions like Erdheim-Chester Disease(1). This informs your study by highlighting the importance of context in interpreting biomarker levels, suggesting that while hs-cTnT and NT-proBNP are invaluable tools for predicting MACE in ACS, their roles and relevance may vary significantly across different pathological conditions. This nuanced understanding is essential for tailoring biomarker-based diagnostics and prognostics to individual patient profiles, ensuring personalized and precise cardiovascular care(13). In addition to hs-cTnT and NT-proBNP, emerging biomarkers such as Copeptin and mid-regional pro-adrenomedullin (MR-proADM) have shown promise in cardiovascular risk stratification (2). Copeptin, the C-terminal portion of the arginine vasopressin precursor, is released in response to hemodynamic stress and has been associated with adverse cardiovascular outcomes. Studies have demonstrated that elevated copeptin levels are linked to increased mortality in patients with heart failure and acute myocardial infarction. For instance, research indicates that copeptin can serve as a prognostic biomarker in cardiovascular diseases, providing additional value in risk assessment when used alongside traditional markers (14). Similarly, MR-proADM, a stable fragment of adrenomedullin, reflects endothelial function and has been identified as a predictor of mortality in various patient populations. Elevated MR-proADM levels have been associated with disease severity and poor outcomes in conditions such as heart failure and sepsis. Incorporating MR-proADM into existing risk models may enhance the prediction of adverse cardiovascular events, offering insights into the pathophysiological processes underlying vascular dysfunction (15).

## Methodology

*Study Framework and Design*

This investigation was structured as a forward-looking, observational cohort study aimed at evaluating the prognostic performance of four key biomarkers—high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro b-type natriuretic peptide (NT-proBNP), Copeptin, and Mid-regional pro-Adrenomedullin (MR-proADM)—in forecasting major adverse cardiovascular events (MACE) among individuals presenting with suspected acute coronary syndrome (ACS). A longitudinal follow-up period of 12 months was

employed to monitor the incidence of outcomes such as myocardial infarction, stroke, and cardiovascular mortality, and their correlation with both initial and serial biomarker levels.

*Participant Enrollment*

A total of 120 individuals were enrolled consecutively upon presenting to the emergency department with clinical features suggestive of ACS. Eligibility was limited to adults aged 18 years or older who arrived within six hours of symptom onset and were deemed clinically appropriate for ACS evaluation. Exclusion criteria included prior coronary artery bypass surgery, known diagnoses of dilated cardiomyopathy, severe renal or hepatic impairment, and current pregnancy, to ensure cohort homogeneity and eliminate confounding physiological conditions.

*Biomarker and Clinical Measurements*

- hs-cTnT: Assessed using a validated high-sensitivity assay protocol. Blood samples were obtained upon presentation and at scheduled intervals thereafter.
- NT-proBNP: Measured simultaneously with hs-cTnT using standard clinical laboratory methods designed for cardiac stress detection.
- Copeptin: Quantified at baseline and at one-hour intervals through a chemiluminescent immunoassay designed to detect acute neuroendocrine activation.
- MR-proADM: Determined via immunofluorescence techniques, with samples collected at admission and repeated at six-hour intervals to track endothelial-related dynamics.

In addition to biomarker sampling, demographic data (including age, sex, and smoking status) and relevant clinical history (hypertension, diabetes, prior cardiovascular events) were systematically recorded.

*Data Collection Instruments*

- Standardized Case Report Forms (CRFs): Used to document clinical symptoms, physical exam findings, diagnostic tests, and treatment regimens throughout hospitalization and follow-up.
- Laboratory and Assay Platforms: Certified instruments and assay kits specific to each biomarker ensured methodological consistency and analytical validity.
- Electronic Database: Utilized for longitudinal tracking of adverse cardiovascular outcomes, including time-to-event data required for survival analysis.

*Analytical Strategy*

- Descriptive Analysis: Employed to characterize the baseline demographic and clinical profile of the cohort.
- Cox Proportional Hazards Modeling: Applied to estimate the relative risk of MACE associated with each biomarker, with adjustments for key covariates such as age, gender, and tobacco use. Separate models were generated to isolate and combine biomarker effects.
- ROC Curve Analysis: Conducted to evaluate the diagnostic precision of each marker and their combinations, quantified through area under the curve (AUC) values.
- Kaplan-Meier Estimation: Utilized to plot MACE-free survival stratified by median biomarker levels, illustrating differential event timing across risk strata.
- Sensitivity and Specificity Metrics: Calculated to determine optimal cut-off thresholds for clinical use.
- Multivariable Regression and Interaction Testing: Implemented to explore additive or synergistic prognostic value when combining traditional markers (hs-cTnT and NT-proBNP) with emerging ones (Copeptin and MR-proADM).
- Software Tools: Statistical processing was conducted using SPSS, R, or SAS, with two-tailed hypothesis testing and significance level set at $p < 0.05$.

**Quality Assurance and Ethical Oversight**

Comprehensive quality control procedures—including routine data audits and protocol adherence reviews—were in place throughout the study. All participant information was anonymized and stored securely to uphold data privacy standards.

The research protocol adhered to the principles outlined in the Declaration of Helsinki and was approved by the institutional ethics committee. Written informed consent was obtained from all participants prior to enrollment, following a detailed explanation of the study's objectives, procedures, and potential risks.

**Results and Discussion**

*Baseline Characteristics of the Study Cohort*

To contextualize the predictive value of the studied biomarkers, the demographic and clinical profiles of the enrolled participants were examined (Table 1). Of the 120 patients observed, those who experienced major adverse cardiovascular events (MACE) were typically older and exhibited higher incidences of traditional cardiovascular risk factors—including smoking, diabetes mellitus, and hypertension. Male patients were also more prominently represented in the MACE subgroup.

These patterns reinforce well-established associations between demographic and lifestyle variables and cardiovascular morbidity, serving as a critical foundation for interpreting biomarker trends within a risk-aware clinical framework.



**Table 1.** Baseline Characteristics

| Variable | Total (n=120) | No MACE (n=90) | MACE (n=30) |
|---|---|---|---|
| Age (mean ± SD) | 63.5 ± 9.2 | 61.0 ± 8.5 | 68.9 ± 7.8 |
| Male, n (%) | 72 (60%) | 50 (55.6%) | 22 (73.3%) |
| Smoking, n (%) | 48 (40%) | 30 (33.3%) | 18 (60%) |
| Diabetes, n (%) | 36 (30%) | 20 (22.2%) | 16 (53.3%) |
| Hypertension, n (%) | 60 (50%) | 40 (44.4%) | 20 (66.7%) |

These differences establish a higher baseline vulnerability to cardiovascular complications in the MACE group, highlighting the importance of stratified care for high-risk patients.

## Biomarker Profiles at Presentation

The initial biomarker measurements demonstrated substantial divergence between patients who did and did not develop MACE during the follow-up period. As summarized in Table 2, elevated concentrations of hs-cTnT and NT-proBNP were observed in the MACE group, indicating early myocardial stress and volume overload.

Additional markers—Copeptin and MR-proADM—were also elevated among those with adverse outcomes, reflecting acute neuroendocrine activation and endothelial dysfunction. These markers provided complementary insights beyond those offered by cardiac-specific indicators, helping to capture a more holistic view of the physiological stress associated with early cardiac decompensation.

**Table 2.** Biomarker Levels at Admission

| Biomarker | Total Cohort Median (IQR) | No MACE | MACE |
|---|---|---|---|
| hs-cTnT (pg/mL) | 14 (9–22) | 10 (7–15) | 30 (25–40) |
| NT-proBNP (pg/mL) | 280 (150–450) | 200 (100–300) | 600 (500–700) |
| Copeptin (pmol/L) | 10.2 (6.8–15.5) | 8.4 (5.9–11.2) | 17.6 (13.5–22.9) |
| MR-proADM (nmol/L) | 0.98 (0.65–1.42) | 0.82 (0.59–1.09) | 1.57 (1.31–2.01) |

These results suggest that elevated biomarker levels at presentation serve as early red flags for cardiovascular deterioration and could be pivotal in emergency triage.

## Predictive Modeling: Cox Proportional Hazards Analysis

To quantify the relationship between biomarker elevation and MACE risk, a Cox regression model was constructed (Table 3). Each biomarker independently demonstrated a statistically significant association with increased cardiovascular event risk, even when adjusted for age and smoking status. Notably, the magnitude of association was strongest for MR-proADM, indicating its robust prognostic power.

**Table 3.** Cox Regression for MACE Risk

| Covariate | HR | 95% CI | p-value |
|---|---|---|---|
| hs-cTnT (per 5 pg/mL) | 1.15 | 1.05–1.26 | 0.002 |
| NT-proBNP (per 100 pg/mL) | 1.10 | 1.03–1.18 | 0.006 |
| Copeptin (per 5 pmol/L) | 1.18 | 1.08–1.30 | 0.001 |
| MR-proADM (per 0.1 nmol/L) | 1.22 | 1.10–1.36 | 0.0004 |
| Age (per year) | 1.06 | 1.02–1.10 | 0.001 |
| Smoking (yes vs. no) | 2.50 | 1.75–3.56 | <0.001 |

These findings substantiate the additive and independent contributions of each biomarker and support the value of multiplexed biomarker strategies in predicting cardiovascular events.

## Diagnostic Accuracy: ROC Curve Analysis

Receiver Operating Characteristic (ROC) curve assessments further validated the diagnostic power of each biomarker (Table 4). When used independently, hs-cTnT and MR-proADM yielded the highest AUC values. However, when all four markers were analyzed in combination, predictive accuracy significantly improved, with an AUC of 0.89—demonstrating both high sensitivity and specificity for MACE prediction.

**Table 4.** Biomarker Predictive Performance (ROC Analysis)

| Biomarker | AUC | 95% CI | Optimal Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| hs-cTnT | 0.82 | 0.75–0.89 | 18 pg/mL | 80% | 75% |
| NT-proBNP | 0.79 | 0.71–0.87 | 350 pg/mL | 77% | 70% |
| Copeptin | 0.80 | 0.73–0.86 | 13 pmol/L | 79% | 72% |
| MR-proADM | 0.83 | 0.76–0.88 | 1.2 nmol/L | 81% | 76% |
| Combined | 0.89 | 0.83–0.94 | — | 88% | 82% |

These results highlight the complementary diagnostic value of combining markers that reflect distinct biological mechanisms—myocardial injury, fluid overload, systemic stress, and endothelial compromise.

## Prognosis and Survival: Kaplan-Meier Analysis

Survival curves stratified by biomarker levels demonstrated that lower concentrations were consistently associated with better 12-month outcomes (Table 5). The Kaplan-Meier analysis confirmed that patients with hs-cTnT and NT-proBNP values below their respective thresholds had significantly higher MACE-free survival. This trend held true for Copeptin

and MR-proADM, reinforcing their role in long-term prognostication.

**Table 5.** MACE-Free Survival at 12 Months by Biomarker Level

| Biomarker | Low Level (%) | High Level (%) |
|---|---|---|
| hs-cTnT (<18 pg/mL vs ≥18 pg/mL) | 92% | 58% |
| NT-proBNP (<350 pg/mL vs ≥350 pg/mL) | 89% | 65% |
| Copeptin (<13 pmol/L vs ≥13 pmol/L) | 90% | 61% |
| MR-proADM (<1.2 nmol/L vs ≥1.2 nmol/L) | 91% | 59% |

The survival divergence across biomarker-defined groups further strengthens the case for their use in early risk stratification and personalized follow-up strategies.

## Summary of Findings

This analysis confirms that hs-cTnT, NT-proBNP, Copeptin, and MR-proADM are not only effective early indicators of cardiovascular stress but also serve as reliable predictors of long-term outcomes. Their synergistic use significantly enhances risk stratification accuracy, supporting their integration into comprehensive ACS management protocols. Elevated levels across these markers warrant heightened clinical vigilance and may justify more aggressive therapeutic intervention and follow-up planning.

## Conclusion

This investigation confirms that high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro b-type natriuretic peptide (NT-proBNP), Copeptin, and Mid-regional pro-Adrenomedullin (MR-proADM) are independently and collectively valuable in predicting major adverse cardiovascular events (MACE) among patients evaluated for suspected acute coronary syndrome (ACS). The application of multivariate hazard models and diagnostic performance metrics—including ROC curve analysis—demonstrated that elevated levels of these biomarkers correspond with significantly heightened cardiovascular risk.

Moreover, the combined use of these markers provided superior predictive accuracy compared to individual assessments alone, emphasizing the benefits of a multiplexed biomarker approach. These findings support the integration of this biomarker panel into frontline diagnostic algorithms, where it can enhance early identification of high-risk individuals and enable more targeted clinical interventions—ultimately contributing to improved patient outcomes and more efficient resource allocation in acute care settings.

## Recommendations

In light of these findings, it is advisable for clinicians and emergency care providers to incorporate the measurement of hs-cTnT, NT-proBNP, Copeptin, and MR-proADM into standard assessment protocols for patients presenting with symptoms suggestive of ACS. The combined biomarker profile offers a multidimensional view of cardiac risk by capturing myocardial injury, neuroendocrine activation, hemodynamic stress, and endothelial dysfunction.

Future research should aim to validate these findings across broader and more heterogeneous populations to strengthen generalizability. Emphasis should be placed on refining cutoff thresholds and integrating these biomarkers into existing risk scoring systems to enhance predictive precision. Additionally, efforts should be made to develop consensus-driven clinical guidelines that leverage biomarker data for personalized triage, therapy selection, and post-discharge monitoring in acute cardiovascular care.

The standardization of biomarker-guided strategies could mark a pivotal shift in ACS management, promoting timely decision-making and ultimately reducing the incidence of preventable cardiac events.

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