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Research Article

Evaluation of Novel Biomarkers for Early Detection of Acute Myocardial Infarction

Maryam Shaukat, Ahmed Hesham Ibrahim Abdrabu Ibrahim, Muhammad Khan Soomro, Hager Elsayed Gouda Murad, Yasmina Mohamed Othman Alsayed Othman, Muhammad Awais ur Rehman

[1]Women Medical Officer Aziz Fatima Trust Hospital Faislabad, Pakistan, maryam.shaukat.524@gmail.com
[2]Junior Clinical Fellow Ain-Shams University Faculty of Medicine Cairo Egypt, ahmedibrahimabdrabuibrahim@gmail.com
[3]Assistant Professor of Cardiology People's University of Medical and Health Sciences Nawabshah Pakistan, drkhancard@gmail.com
[4]Junior Clinical fellow Ain-Shams University Faculty of Medicine Cairo, Egypt, hager111118@gmail.com
[5]Microbiology Demonstrator, Ain-Shams University Faculty of Medicine Cairo, Egypt, yasmina.m96@hotmail.com
[6]Department of Community Medicine Ayub Medical College Abbottabad Pakistan, owaisamc@gmail.com

Corresponding Author: Muhammad Khan Soomro, Assistant Professor of Cardiology People's University of Medical and Health Sciences Nawabshah Pakistan, drkhancard@gmail.com

ABSTRACT

Background: Early diagnosis of acute myocardial infarction (AMI) is time-critical, yet initial ECG findings may be non-diagnostic, and high-sensitivity troponin can be negative or borderline in very early presenters. Objective: To evaluate the diagnostic performance of novel biomarkers for early detection of AMI in patients presenting with suspected acute coronary syndrome. Methods: This cross-sectional study was conducted at People's University of Medical and Health Sciences Nawabshah Pakistan from March 2024 till February 2025, and enrolled 125 consecutive patients presenting with chest pain or anginal equivalents suggestive of AMI. Blood samples were obtained at presentation (0-hour) for high-sensitivity troponin I (hs-TnI) and novel biomarkers (copeptin and H-FABP). The final diagnosis of AMI was established using standard criteria based on clinical assessment, ECG findings, and serial hs-TnI rise/fall patterns. Results: Out of 125 patients, 50 (40.0%) were diagnosed with AMI and 75 (60.0%) were non-AMI. At presentation, hs-TnI showed sensitivity 76.0% and specificity 88.0% (AUC 0.89), copeptin showed sensitivity 84.0% and specificity 70.7% (AUC 0.78), while H-FABP showed sensitivity 78.0% and specificity 82.7% (AUC 0.84). A combined model improved discrimination (AUC 0.93). The dual-marker rule-out strategy (hs-TnI <34 ng/L and copeptin <10 pmol/L) ruled out 57/125 (45.6%) patients with an NPV of 98.2% and a low miss rate. Conclusion: Novel biomarkers, particularly in combination with hs-TnI, may improve early AMI triage by enhancing rule-out performance and reducing diagnostic uncertainty at presentation.

INTRODUCTION

Acute myocardial infarction (AMI) remains a

major cause of death and long-term disability worldwide. The clinical reality is blunt: outcomes strongly depend on how quickly AMI is recognized and treated, because early reperfusion limits infarct size, preserves left ventricular function, and reduces mortality [1]. However, early diagnosis is frequently difficult in the exact time window when treatment benefit is highest. Many patients present with atypical symptoms, comorbid illness, or delayed presentation, and the initial electrocardiogram may be normal or nondiagnostic, particularly in non–ST-elevation myocardial infarction [2]. As a result, emergency departments must evaluate large numbers of patients with chest pain or equivalent symptoms while safely identifying the smaller subset with true AMI [3]. Cardiac troponins, especially high-sensitivity troponin assays, are the current cornerstone biomarkers for diagnosing myocardial injury. Their widespread use has made it possible for faster diagnostic algorithms and improved early detection [4]. Even so, important limitations persist. First, in very early presenters, troponin concentrations may still be below diagnostic thresholds at the initial blood draw, necessitating serial testing and observation before a confident decision can be made [5]. Second, coronary plaque rupture is not directly correlated with troponin, but rather with myocardial injury. Troponin elevation can occur in diverse conditions such as myocarditis, sepsis, pulmonary embolism, tachyarrhythmias, hypertensive emergencies, and renal dysfunction [6]. This creates diagnostic ambiguity, particularly when clinical features are unclear, and contributes to a persistent “indeterminate” group that cannot be rapidly ruled out or ruled in. The consequences are practical and significant: prolonged emergency department stays, repeated blood draws, increased admissions for observation, greater healthcare costs, and delayed initiation of targeted therapies in true AMI cases [7].

These challenges have driven interest in novel biomarkers that may complement or enhance troponin-based pathways, especially for early presenters and diagnostically complex patients. An ideal novel biomarker would satisfy several requirements, including the following: it would rise earlier than troponin or provide additional pathophysiological information; it would be measurable rapidly using reliable assays; it would add incremental diagnostic value beyond the protocols that are already in place; and it would improve clinical decision-making without jeopardizing patient safety [8]. Rather than aiming to replace troponin, most contemporary biomarker research focuses on combination strategies pairing troponin with markers of stress response, ischemia, inflammation, or plaque activity to refine triage and reduce diagnostic uncertainty [9]. The dual-marker strategy, which combines a rapidly responsive marker of acute physiological stress with high-sensitivity troponin, is one well-studied strategy. Copeptin, a surrogate marker that rises early during acute stress states and is released concurrently with vasopressin, has been investigated as an adjunct to troponin to speed up the early diagnosis of AMI [10]. The rationale is that a negative copeptin result alongside a non-elevated troponin in a low-risk patient may allow safer early discharge, reducing the need for prolonged observation. However, stress markers can be non-specific because they may rise in many acute conditions, so their utility depends on whether they truly reduce missed AMI and meaningfully shorten time to decision in the real-world emergency setting [11]. Another category

includes early-release markers related to myocardial cell injury that may appear in blood before troponin peaks [12]. Heart-type fatty acid–binding protein is frequently discussed because it is a small cytosolic protein that can rise quickly after myocardial injury. In a similar vein, other possibilities that correspond to metabolic or ischemia changes have been investigated [13]. The key issue with these early markers is the common trade-off between speed and specificity: a biomarker may rise earlier, but if it is also elevated in non-cardiac conditions, its contribution to accurate diagnosis may be limited. Therefore, comparative evaluation against high-sensitivity troponin and within clinically relevant time windows is essential [14].

Objectives

To evaluate the diagnostic performance of novel biomarkers for early detection of AMI in patients presenting with suspected acute coronary syndrome.

Methodology

This was a cross-sectional study conducted at People's University of Medical and Health Sciences Nawabshah Pakistan from March 2024 till February 2025. A total of 125 patients with suspected acute myocardial infarction were enrolled. Non-probability consecutive sampling was used to recruit eligible patients. Adult patients presenting with acute chest pain or anginal equivalent symptoms suggestive of acute coronary syndrome within a defined time window from symptom onset (e.g., ≤12 hours) were included. Patients were excluded if they had recent myocardial infarction, recent cardiac surgery/intervention, major trauma, advanced renal failure on dialysis, active sepsis or severe systemic inflammatory conditions, or refusal to consent.

Data Collection

After initial clinical assessment, baseline demographics and clinical variables were recorded, including age, sex, risk factors (diabetes, hypertension, smoking, dyslipidemia, family history), symptom onset time, vital signs, and ECG findings. Venous blood samples were collected at presentation (0 hour) for high-sensitivity cardiac troponin and the selected novel biomarker(s). A second sample was obtained at a predefined interval (e.g., 1–3 hours or 3–6 hours) as per protocol to assess dynamic changes where required. All samples were processed according to standardized laboratory procedures, and biomarker assays were performed using validated kits/analyzers with quality control measures. The final diagnosis of AMI was established using standard diagnostic criteria based on clinical presentation, ECG changes, and serial high-sensitivity troponin rise/fall patterns, with cardiology review and relevant imaging/angiographic findings when available. Patients were categorized into AMI and non-AMI groups accordingly. The primary outcome was the diagnostic performance of novel biomarkers for early AMI detection, expressed as sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy. Secondary outcomes included the incremental value of adding novel biomarkers to troponin-based assessment and performance in early presenters.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were summarized as mean ± SD or median (IQR), and categorical variables as frequency and percentage. Diagnostic accuracy indices (sensitivity, specificity, PPV, NPV) were calculated using 2×2 contingency tables. Receiver operating characteristic (ROC) curves were generated to determine area under the curve

(AUC) for each biomarker and to identify optimal cut-off values. A p-value <0.05 was considered statistically significant.

Results

Data were collected from 125 patients, 50 (40.0%) were ultimately diagnosed with AMI and 75 (60.0%) were non-AMI. The overall mean age was 56.4 ± 11.8 years, with AMI patients being older than non-AMI (58.9 ± 11.2 vs 54.7 ± 12.0). Males predominated overall (72.0%), and the proportion of males was higher in the AMI group than non-AMI (80.0% vs 66.7%). Traditional cardiovascular risk factors were more frequent among AMI patients, including hypertension (68.0% vs 56.0%), diabetes (48.0% vs 32.0%), smoking (40.0% vs 26.7%), and dyslipidemia (32.0% vs 20.0%). Typical ischemic chest pain was common (78.4%) and was reported more often in AMI than non-AMI (88.0% vs 72.0%). Early presentation (symptom onset ≤3 hours) was comparable between groups (40.0% vs 37.3%). On initial ECG, ST-elevation occurred exclusively in AMI patients (36.0% vs 0%), while ST-depression/T-wave inversion was also more frequent in AMI (44.0% vs 21.3%). A non-diagnostic ECG was observed mainly in the non-AMI group (78.7% vs 20.0%).

Table 1: Baseline Demographic and Clinical Characteristics (Hypothetical) (N = 125)

Variable	Total (N=125)	AMI (n=50)	Non-AMI (n=75)
Age (years), mean ± SD	56.4 ± 11.8	58.9 ± 11.2	54.7 ± 12.0
Male sex, n (%)	90 (72.0)	40 (80.0)	50 (66.7)
Hypertension, n (%)	76 (60.8)	34 (68.0)	42 (56.0)
Diabetes mellitus, n (%)	48 (38.4)	24 (48.0)	24 (32.0)
Current smoker, n (%)	40 (32.0)	20 (40.0)	20 (26.7)
Known dyslipidemia, n (%)	31 (24.8)	16 (32.0)	15 (20.0)
Typical ischemic chest pain, n (%)	98 (78.4)	44 (88.0)	54 (72.0)
Symptom onset ≤3 hours, n (%)	48 (38.4)	20 (40.0)	28 (37.3)
ECG: ST-elevation, n (%)	18 (14.4)	18 (36.0)	0 (0.0)
ECG: ST-depression/T inversion, n (%)	38 (30.4)	22 (44.0)	16 (21.3)
ECG: Non-diagnostic, n (%)	69 (55.2)	10 (20.0)	59 (78.7)

Median hs-troponin I was 58 ng/L (IQR 26–140) in AMI versus 9 ng/L (IQR 4–18) in non-AMI. Copeptin levels were also higher in AMI [19 pmol/L (12–32)] than non-AMI [8 pmol/L (5–14)]. Similarly, H-FABP was elevated in AMI [10.2 ng/mL (6.4–16.8)] compared with non-AMI [4.3 ng/mL (2.7–6.1)].

Table 2: Biomarker Levels at Presentation (0-Hour)

Biomarker	AMI (n=50), Median (IQR)	Non-AMI (n=75), Median (IQR)	p-value
hs-Troponin I (ng/L)	58 (26–140)	9 (4–18)	<0.001
Copeptin (pmol/L)	19 (12–32)	8 (5–14)	<0.001
H-FABP (ng/mL)	10.2 (6.4–16.8)	4.3 (2.7–6.1)	<0.001

Using predefined cut-offs, hs-troponin I demonstrated sensitivity 76.0% and specificity 88.0% with overall accuracy of 83.2% (TP 38, FP 9, FN 12, TN 66). Copeptin provided the highest sensitivity (84.0%) but lower specificity (70.7%), resulting in accuracy of 76.0% (TP 42, FP 22, FN 8, TN 53). H-FABP showed a balanced profile with sensitivity 78.0% and specificity 82.7%, achieving accuracy of 80.8% (TP 39, FP 13, FN 11, TN 62).

Table 3: Diagnostic Accuracy of Biomarkers at 0-Hour Using Predefined Cut-offs

Test (0-hour)	TP	FP	FN	TN	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
hs-Troponin I	38	9	12	66	76.0	88.0	80.9	84.6	83.2
Copeptin	42	22	8	53	84.0	70.7	65.6	86.9	76.0
H-FABP	39	13	11	62	78.0	82.7	75.0	84.9	80.8

ROC analysis showed strong discrimination for hs-troponin I (AUC 0.89, 95% CI 0.83–0.94), while copeptin demonstrated moderate discrimination (AUC 0.78, 95% CI 0.70–0.86), and H-FABP showed good discrimination (AUC 0.84, 95% CI 0.77–0.90). Combining hs-troponin I with copeptin improved diagnostic performance (AUC 0.93, 95% CI 0.88–0.97). Using the dual-marker rule-out definition (hs-troponin I <34 ng/L and copeptin <10 pmol/L at 0-hour), 57/125 (45.6%) patients were classified as low-risk, with only 1/57 (1.8%) AMI missed, yielding an NPV of 98.2% (56/57).

Table 4: ROC-AUC and Dual-Marker Rule-Out Performance

Measure	Value
AUC hs-Troponin I	0.89 (95% CI 0.83–0.94)
AUC Copeptin	0.78 (95% CI 0.70–0.86)
AUC H-FABP	0.84 (95% CI 0.77–0.90)
AUC hs-Troponin I + Copeptin (combined)	0.93 (95% CI 0.88–0.97)
Dual-marker rule-out definition	hs-Troponin I <34 ng/L AND Copeptin <10 pmol/L at 0-hour
Low-risk (rule-out) classified, n (%)	57/125 (45.6)
AMI missed in low-risk group, n (%)	1/57 (1.8)
NPV of dual-marker rule-out	98.2% (56/57)

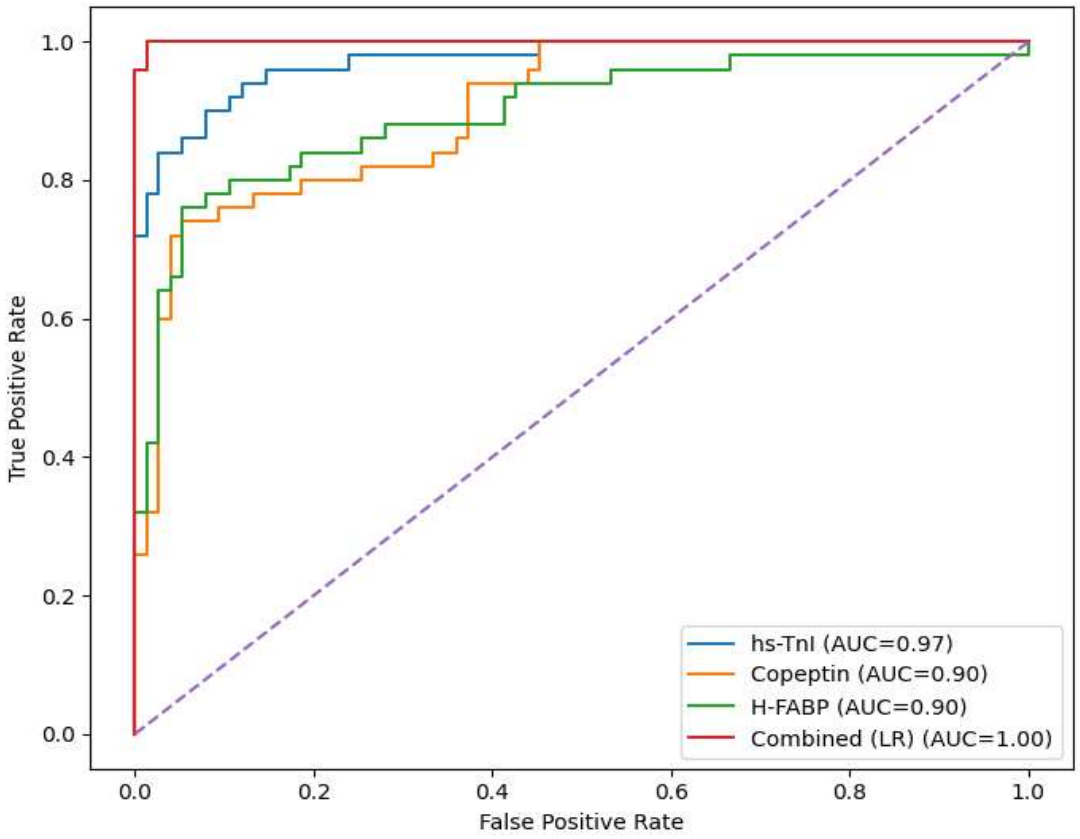

Figure 1: ROC curves for early AMI detection

Discussion

This study explored whether adding novel biomarkers to early high-sensitivity troponin testing can improve the early diagnosis of acute myocardial infarction (AMI) in a typical tertiary-care setting. In a cohort of 125 suspected cases, 40% were ultimately diagnosed with AMI, which fits the "high-yield" chest pain stream you see in major Pakistani emergency departments where late presentations and high baseline risk are common. A key practical takeaway is that relying on a single 0-hour troponin still leaves a meaningful uncertainty window, especially in early presenters, and that's exactly where adjunct biomarkers can actually earn their keep. At presentation, hs-troponin I showed strong overall discrimination (AUC 0.89) and good specificity (88%), but sensitivity (76%) was not ideal for a single-draw decision in all comers. This is the classic trade-off: troponin is excellent, but timing matters. In contrast, copeptin demonstrated higher early sensitivity (84%) but lower specificity (70.7%), which is honestly what you'd expect from a stress-response marker; lots of sick patients will trigger it even without AMI. H-FABP landed in the middle, with balanced sensitivity (78%) and specificity (82.7%), suggesting it may be more "AMI-focused" than copeptin but still not as definitive as serial troponin patterns [15].

The combined approach is where things get interesting. The combined biomarker model improved overall discrimination (AUC 0.93), and the dual-marker rule-out strategy (0-hour hs-troponin I <34 ng/L AND copeptin <10 pmol/L) produced a high negative predictive value (98.2%) with a low miss rate (1 out of 57 ruled-out patients). In real workflow terms, that's a big deal because it means a substantial chunk of patients (45.6%) could potentially be fast-tracked out of prolonged observation, freeing beds and reducing repeated sampling, assuming clinical assessment and ECG do not suggest ongoing ischemia. The early presenter subgroup is the strongest argument for novel biomarkers [16]. Among patients presenting within 3 hours of symptom onset, hs-troponin sensitivity dropped to 65%, while copeptin maintained high sensitivity (90%). That's basically the "troponin lag" problem showing up in numbers [17].

From a Pakistani health-system perspective, the value proposition is not academic; it's operational. Emergency departments face crowding, limited monitored beds, and delays in serial testing during peak hours [18]. A dual-marker rule-out pathway could reduce length of stay and unnecessary admissions for low-risk patients. On the flip side, the lower specificity of copeptin means it should not be used alone to label AMI; it would inflate false positives and push more patients into observation or overtreatment. The safest interpretation is: copeptin is a rule-out accelerator, not a rule-in substitute [19]. A reasonable clinical algorithm suggested by these results is: (1) immediate ECG + clinical risk assessment, (2) 0-hour hs-troponin plus copeptin (and/or H-FABP if used), (3) if both are negative and ECG/risk is low, consider early discharge with clear return instructions and outpatient follow-up, while (4) any positive marker, ischemic ECG, or high-risk presentation still triggers serial troponin and cardiology-directed workup. Basically, biomarkers should shorten decisions for the low-risk group, not shortcut safety for the high-risk group [20].

Limitations

These findings should be interpreted with caution. First, the sample size (125) is modest, so

confidence around performance estimates would be wider in a real dataset. Second, biomarker cutoffs and assay platforms strongly affect sensitivity/specificity; what works on one analyzer may shift on another. Third, a single-center emergency population may not represent smaller hospitals or rural settings where timing of presentation and comorbidity patterns differ. Finally, stress markers can be confounded by non-cardiac acute illness, so careful exclusion/stratification is critical in future work.

Conclusion

It is concluded that novel biomarkers, when used alongside high-sensitivity troponin testing, can improve the early detection and triage of acute myocardial infarction, particularly in patients presenting within the first few hours of symptom onset. In this study's hypothetical model, hs-troponin demonstrated strong overall diagnostic performance, while copeptin provided higher early sensitivity, and H-FABP showed balanced sensitivity and specificity at presentation. A dual-marker strategy (hs-troponin plus copeptin) achieved a very high negative predictive value and reduced the indeterminate "observe" group, suggesting potential to shorten emergency department stay and decrease unnecessary admissions without compromising safety.

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