Section: Medicine

Systematic Review Article

RECENT ADVANCES IN BIOMARKERS FOR EARLY DETECTION OF MYOCARDIAL INFARCTION: A SYSTEMATIC REVIEW

Hafsa Saifullah

MBBS, Fatima Jinnah Medical University, Lahore, Pakistan

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Corresponding Author:
Dr. Hafsa Saifullah
MBBS, Fatima Jinnah Medical University, Lahore, Pakistan
Email: hafsasaifullah06@gmail.com

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ABSTRACT

Background: High-sensitivity cardiac troponins (hs-cTn) are the diagnostic gold standard for acute myocardial infarction (AMI) but face limitations in ultra-early detection and specificity. The objective is to systematically review complementary biomarkers and diagnostic technologies for earlier AMI detection.

Materials and Methods: We searched PubMed, Scopus, and Web of Science (2003–2025) for clinical studies evaluating diagnostic accuracy of biomarkers (copeptin, H-FABP {Heart-Type Fatty Acid–Binding Protein}, MPO {myeloperoxidase}, IMA {Ischemia-Modified Albumin}, microRNAs {Ribonucleic acids}, cell-free DNA {Deoxyribonucleic acid}, metabolomics) and technologies (biosensors, POC {point-of-care} devices, AI {Artificial Intelligence}).

Results: Copeptin and H-FABP enable detection within 1 hour of symptom onset. MicroRNAs and cell-free DNA show high early sensitivity but lack standardization. Biosensors and AI-multimarker panels enhance rapid, decentralized diagnosis.

Conclusion: Complementary biomarkers and technologies address hs-cTn limitations, warranting multicenter validation for clinical translation.

Keywords: Myocardial infarction, biomarkers, high-sensitivity troponin, copeptin, microRNA, metabolomics, point-of-care diagnostics, biosensors, artificial intelligence.

INTRODUCTION

Acute myocardial infarction (AMI) continues to be a major global health burden, accounting for millions of hospitalizations and deaths annually. Early identification of MI is essential to initiate reperfusion strategies—such as percutaneous coronary intervention (PCI) or fibrinolysis—which significantly improve outcomes and decrease infarct size (Thygesen et al., 2018).[1]

Diagnosis of MI relies on the integration of clinical presentation, serial electrocardiogram (ECG) findings, and biochemical markers of myocardial injury. Troponins are the cornerstone of laboratory diagnosis, with high-sensitivity cardiac troponin I and T (hs-cTnI / hs-cTnT) enabling earlier detection of minor myocardial injury that was previously undetectable with conventional assays (Reichlin et al., 2009; Apple & Collinson, 2012).[2,3]

Despite these advancements, some diagnostic challenges remain:

- Troponin elevation is time-dependent, typically rising 2–4 hours after symptom onset.
- Non-ischemic elevations (e.g., CKD {chronic kidney disease}, CHF {congestive heart failure}, sepsis, myocarditis) reduce specificity (Chapman et al., 2017).[4]
- Type 2 MI and myocardial injury frequently overlap in biomarker profiles (Sandoval & Jaffe, 2019).[5]
- Very early presenters (<1 hour from symptom onset) may have false-negative troponin results.

Therefore, interest has shifted to complementary ultra-early biomarkers that reflect ischemia, inflammation, neurohormonal activation, or reversible myocardial stress, providing diagnostic value before irreversible necrosis occurs (Salvagno GL et al., 2016).[6]

This review synthesizes two decades of research on emerging biomarkers, evaluates their clinical utility, and discusses integration with modern diagnostic technologies, including biosensors and artificial intelligence.

MATERIALS AND METHODS

Search Strategy: This systematic review was conducted and reported in accordance with the PRISMA 2020 guidelines. A search was conducted across PubMed, Scopus, and Web of Science (2003–2025). Search terms included:
"myocardial infarction", "acute coronary syndrome", "early diagnosis", "biomarkers", "troponin", "H-FABP", "copeptin", "microRNA {Ribonucleic acid}", "cell-free DNA {Deoxyribonucleic acid}", "metabolomics", "biosensors", "nanotechnology", "artificial intelligence".

Inclusion Criteria

- Clinical cohort studies, RCTs {Randomized controlled trials}, review articles, meta-analyses
- Studies evaluating diagnostic accuracy of biomarkers for AMI
- Published between January 2003 and December 2023

Exclusion Criteria

- Letters

Data Extraction

Extracted variables included:

- Study population and sample size
- Biomarker type
- Time to elevation (kinetics)
- Diagnostic accuracy: sensitivity, specificity
- Assay technology (Enzyme Linked Immunosorbent Assay, Reverse Transcriptase Polymerase Chain Reaction, biosensor)
- Comparative performance with troponin
- Limitations and confounders

Quality Assessment

- Cohort studies: Newcastle–Ottawa Scale
- Systematic reviews: AMSTAR-2 criteria

Records identified from databases (n = 4,800) (PubMed, Scopus, WoS)
↓
Duplicates removed (n = 1,900)
↓
Records screened (n = 2,900)
↓
Full-text assessed (n = 180)
↓
Excluded (n = 160)
•Letters (25)
•Others (135)
↓
Studies included (n = 20)
(Qualitative synthesis only)

RESULTS

High-Sensitivity Cardiac Troponins (hs-cTn)
High-sensitivity troponin assays detect extremely low concentrations of circulating troponin, and are capable of measuring below the 99th percentile in more than 50% of healthy individuals—fulfilling analytical criteria for high-sensitivity tests (Apple & Collinson, 2012).[3]

Advantages

- Allow 0/1-hour and 0/2-hour accelerated rule-out algorithms (Reichlin et al., 2009).[2]
- Detect micro-necrosis with high precision.
- Widely validated across clinical settings.

Limitations

- Troponin rise is delayed, especially in early presenters.
- Elevated in nonischemic conditions (CKD, myocarditis).
- Distinguishing type 2 MI from type 1 MI remains difficult (Sandoval & Jaffe, 2019).[5]

Early-Rising Protein Biomarkers

Heart-Type Fatty Acid–Binding Protein (H-FABP)

- Low molecular weight cytosolic protein
- Released within 30 minutes to 1 hour after myocardial membrane injury
- Peaks earlier than troponin
- Chan et al. (2003) demonstrated that H-FABP significantly improved early diagnostic sensitivity, especially within the first 2 hours.[7]

Copeptin

Copeptin is the C-terminal part of the vasopressin prohormone, released during acute endogenous stress.

- Rises immediately at symptom onset, making it the earliest detectable biomarker
- Excellent negative predictive value when combined with hs-cTn

Keller et al. (2010) showed that the combination of copeptin + troponin improved early rule-out accuracy.[8]
Maisel et al. (2013) demonstrated similar findings in European cohorts.[9]

Myeloperoxidase (MPO)

- Reflects oxidative stress and plaque instability
- Increases before troponin in some cases

Baldus et al. (2003) reported its value in identifying vulnerable plaque and early coronary inflammation.[10]

Ischemia-Modified Albumin (IMA)

- Produced when ischemic free radicals modify N-terminal albumin
- Elevates in ischemia even without necrosis

IMA showed good sensitivity but low specificity (Sbarouni et al., 2011).[11]

Molecular Biomarkers: microRNAs & Cell-Free DNA

MicroRNAs (miRNAs)

Circulating cardiac-specific microRNAs are emerging as promising ultra-early biomarkers.

Table 1: Summary of types of microRNAs and key findings

miRNA	Source	Elevation Time	Key Findings
miR-1	Cardiomyocytes	<1 hour	Early marker of injury
miR-133a	Cardiomyocytes	1–2 hours	High diagnostic sensitivity
miR-208b	Cardiac muscle	3 hours	Correlates with infarct size
miR-499	Ventricular myocardium	2–4 hours	High specificity

D'Alessandra et al. (2010) confirmed miRNAs outperform CK-MB and are comparable to troponin in early presenters.[12]

Kuwabara et al. (2011) reported significant elevations in cardiovascular disease patients, indicating myocardial damage.[13]

Challenges:

- Lack of assay standardization
- Pre-analytical variability (hemolysis affects miRNA levels)

Cell-Free DNA (cfDNA)

cfDNA originates from apoptosis and necrosis of cardiomyocytes.

Zemmour et al. (2018) reported that methylation-specific patterns can accurately identify cardiomyocyte-derived cfDNA.[14]

cfDNA increases before troponin rises, making it extremely valuable for ultra-early diagnosis.

Advantages:

- Highly sensitive
- Reflects molecular-level cell death

Limitations:

- Complex and expensive assays
- Lower availability in routine settings

Metabolomic Biomarkers

Metabolomics captures biochemical alterations during ischemia:

- Acylcarnitines
- Lysophospholipids
- Branched-chain amino acids
- Purines (hypoxanthine)

Sabatine et al. (2005) demonstrated metabolic shifts detectable even before traditional biomarkers.[15]

Multi-omics approaches integrating metabolomics + proteomics + transcriptomics enhance diagnostic precision (Leon-Mimila P et al, 2019).[16]

Technological Advancements in MI Diagnostics

Wearable and Implantable Biosensors

Advances in nanotechnology have enabled:

- Continuous biomarker monitoring
- Sweat-based and interstitial fluid-based diagnostics
- Microfluidic sensors capable of detecting minute analyte concentrations

Dincer et al. (2019) documented low-cost biosensors ideal for POC diagnostics.[17]

Electrochemical Biosensors

Mageswaran N et al (2025) reviewed biosensors capable of detecting premature coronary artery disease with:

- High sensitivity
- Rapid turnaround time
- Suitability for prehospital settings (ambulance, rural areas)[18]

Multimarker + Artificial Intelligence (AI) Approaches

Multimarker Panels

Combining biomarkers for diagnostic accuracy:

- hs-cTn + copeptin
- hs-cTn + H-FABP
- hs-cTn + miRNA panels
- Oxidative stress + metabolomic signatures

The Twerenbold et al. (2017) studied that High-sensitivity troponin assays speed up MI evaluation by reducing the early diagnostic gap and enabling quicker serial testing. Because mild elevations may occur in non-ischemic conditions, changes over time help confirm or exclude ischemia. When incorporated into standardized ED (emergency department) protocols with rapid triage algorithms, hs-cTn testing allows safe MI rule-out or rule-in within hours, improving safety, shortening ED stays, and reducing costs.[19]

AI-Based MI Detection

Machine learning models integrate large datasets (omics, clinical data, ECG) for pattern recognition.

Deo (2015) outlined machine learning algorithms capable of predicting myocardial ischemia with high accuracy. AI improves diagnostic precision, early detection in atypical presentations, risk stratification.[20]

Summary and Future Directions

Key Findings

- hs-cTn remains indispensable, but limitations in ultra-early detection justify the search for complementary biomarkers.
- Copeptin, H-FABP, miRNAs, cfDNA, and metabolomic patterns provide earlier detection than troponin.
- Biosensors and wearable devices are shifting diagnosis toward rapid, decentralized, and continuous monitoring.
- Combining biomarkers using AI significantly increases diagnostic accuracy.

Current Gaps

1. Need for large, multicenter clinical trials.
2. Standardization of molecular assays (microRNAs, cfDNA).
3. Cost-effectiveness studies.
4. Integration of biomarker assays into prehospital settings.
5. Regulatory frameworks for AI-assisted diagnostics.

CONCLUSION

Over the past two decades, remarkable progress has been made in the development of novel biomarkers and diagnostic platforms for myocardial infarction.

Emerging biomarkers offer the promise of earlier detection—before irreversible myocardial damage—and enhanced specificity in complex clinical scenarios. In parallel, biosensors and artificial intelligence are revolutionizing point-of-care diagnostics. Future clinical translation will depend on robust validation, cost-effectiveness, and seamless integration into healthcare systems.

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