Review Article

# From CK-MB to MicroRNAs: Evolving Biomarker Strategies for Early Diagnosis of Myocardial Infarction

**Vijjapu Devi Deepak[1], Sharon Rose Kombathula[2], Athulya Asokan[3], Ghina Naiyer[4], Patricia Sharon[5], Kalash Dwivedi[6], Boykhurozov Jasurbek Asilbek o'g'li[7], Akramkhon Sharipov[8] Surajit Bose[9], Srojidinov Sardor Shamsiddinovich[10]**

**[1-9]Students at Tashkent State Medical University, Tashkent Uzbekistan.**

**[10]Assistant at the department of Propaedeuticsof internal medicine, Tashkent State Medical University, Tashkent Uzbekistan.**

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## Abstract

Myocardial infarction (MI) remains a major cause of morbidity and mortality worldwide, and accurate early diagnosis is critical to improving clinical outcomes. High-sensitivity cardiac troponins (hs-cTn) are the current gold standard biomarkers due to their excellent sensitivity, yet they have limitations including delayed elevation in very early infarction and reduced specificity in patients with renal dysfunction or non-ischemic myocardial injury. This systematic review evaluated the diagnostic performance of traditional biomarkers (CK, CK-MB, myoglobin, hs-cTn) and emerging molecular approaches including circulating microRNAs (miRNAs) and multi-marker strategies. Seven studies and one meta-analysis were included, encompassing over 23,000 patients. Classical biomarkers such as CK and CK-MB demonstrated limited sensitivity but retained niche value in peri-procedural MI due to higher specificity, with CK-MB achieving up to 96% specificity. High-sensitivity troponins provided superior early detection with sensitivities approaching 90% but showed reduced positive predictive value in unselected emergency department populations. Circulating miRNAs, particularly miR-499 and miR-133a, achieved pooled sensitivities and specificities around 0.88, highlighting their potential for ultra-early MI detection. Furthermore, computational models like the ARTEMIS algorithm integrating hs-cTn with clinical variables achieved AUCs of 0.92–0.98, surpassing traditional threshold-based diagnostics and enabling personalized probability-based assessment. Overall, the findings suggest that while hs-cTn remains the primary diagnostic biomarker, combining it with molecular markers and advanced computational models can improve early diagnosis, specificity, and clinical decision-making in myocardial infarction.

**Keywords:** Myocardial infarction, cardiac biomarkers, high-sensitivity troponin, microRNA, multi-marker strategy, diagnostic accuracy, machine learning.

**Corresponding Author:** Vijjapu Devi Deepak & Kalash Dwivedi; Students at Tashkent State Medical University, Tashkent Uzbekistan

**Email:**kalashdwivedi77@hotmail.com

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## Introduction

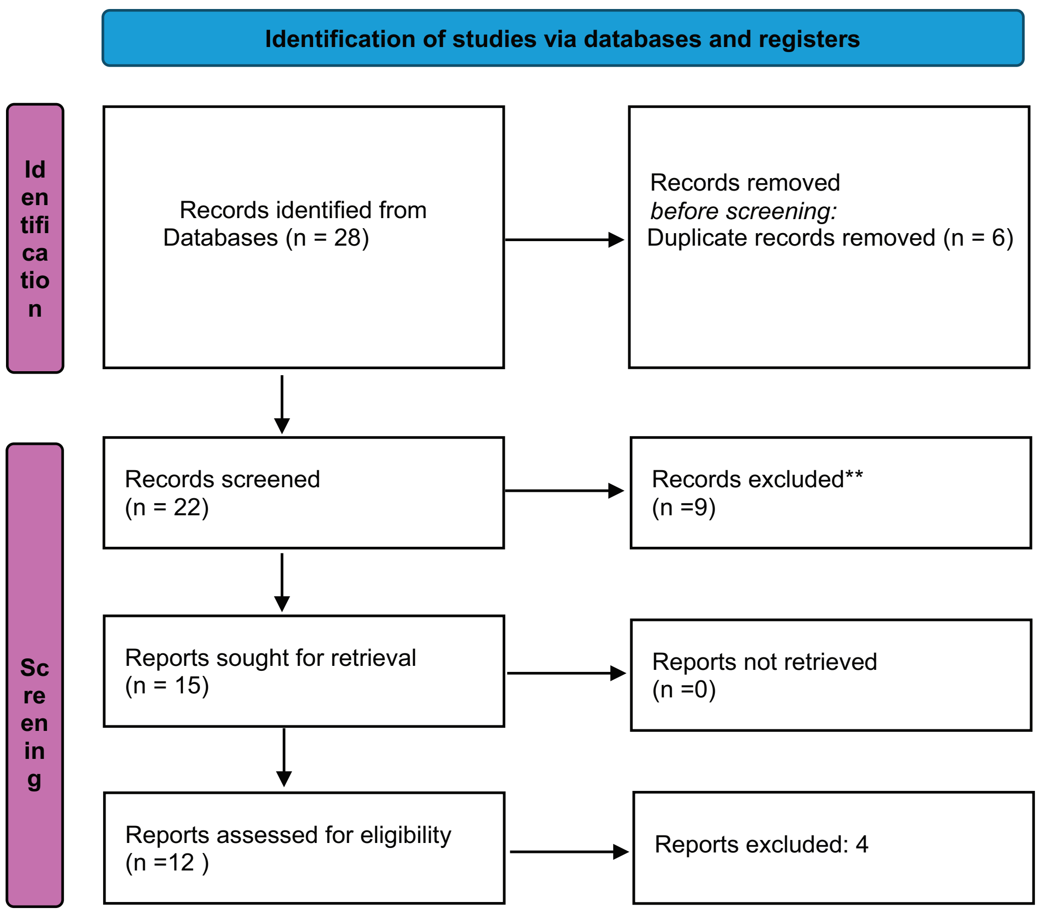
Myocardial infarction (MI) remains a leading cause of global morbidity and mortality, with timely and accurate diagnosis being critical to improving patient outcomes. High-sensitivity cardiac troponins (hs-cTn) remain the cornerstone biomarkers for MI diagnosis due to their high sensitivity and specificity for myocardial injury[8]. However, even hs-cTn testing has diagnostic limitations, including delayed elevation during very early infarction and potential false positives in renal dysfunction or other cardiac injuries[9]. This has driven the search for emerging biomarkers and multi-marker diagnostic strategies to enhance early detection, improve specificity, and reduce diagnostic uncertainty. Circulating microRNAs (miRNAs) have gained attention as novel biomarkers for early MI detection due to their tissue specificity and rapid release after myocardial injury. Tilea et al. reported that total serum miRNA levels achieved sensitivities of 78–82% and provided diagnostic value in the early phase of acute myocardial infarction[10]. Similarly, Deddens et al. highlighted that miRNAs could fill the pre-troponin diagnostic window, offering an adjunctive role to traditional assays[11]. Multi-marker approaches, integrating hs-cTn with inflammatory and molecular markers such as myeloperoxidase (MPO) and high-sensitivity C-reactive protein (hs-CRP), have been shown to enhance diagnostic performance and risk stratification[12]. Bokhari et al. (2025) emphasized that the multi-marker strategy improves early diagnosis and prognostic assessment while addressing single-biomarker limitations[13].Despite promising data, the routine clinical integration of these novel biomarkers faces key challenges. Variability in assay standardization, heterogeneity in biomarker expression, and the absence of large multicentre validation studies limit their widespread adoption[14] Recent reviews advocate for personalized diagnostic algorithms combining hs-cTn with emerging biomarkers to improve early detection, reduce false negatives, and advance precision cardiology[15-16]. Future studies focusing on multicentre validation and standardized multi-marker panels will be essential to translate these advances into routine practice. This study evaluated the diagnostic accuracy of cardiac biomarkers in myocardial infarction. It compared traditional markers (hs-cTn, CK-MB, myoglobin) with emerging biomarkers (miRNAs, multi-marker panels). The focus was on early detection and improved risk stratification.

## Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 guidelines to evaluate the diagnostic accuracy of cardiac biomarkers in myocardial infarction (MI). The research question was developed using the PICO framework, where the population comprised patients with suspected or confirmed myocardial infarction (STEMI or NSTEMI), the intervention or index test was cardiac biomarkers including high-sensitivity troponin (hs-cTnI and hs-cTnT), CK-MB, myoglobin, microRNAs (miRNAs), and multi-biomarker panels, the comparator was the standard diagnostic criteria for MI based on clinical presentation, ECG findings, and imaging, and the outcome was diagnostic sensitivity and specificity for MI detection. A comprehensive literature search was performed across Google Scholar, PubMed/MEDLINE, SpringerLink, ScienceDirect, Scopus, and Web of Science, while Sci-Hub was used to retrieve full texts when access was restricted. The search strategy combined keywords such as “myocardial infarction,” “acute coronary syndrome,” “cardiac biomarkers,” “troponin,” “CK-MB,” “myoglobin,” “miRNA,” “sensitivity,” and “specificity,” using Boolean operators. The search was limited to human studies, published in English between 2000 and 2023, to include studies using contemporary biomarker assays.

A total of 28 records were initially identified. After removing 6 duplicates and screening 22 records based on title and abstract, 12 full-text articles were assessed for eligibility. Studies were included if they were original clinical research evaluating cardiac biomarkers for MI diagnosis, reported sensitivity and specificity or provided sufficient data to calculate these metrics, included sample size and population characteristics, and were published within the specified period. Studies were excluded if they were reviews, case reports, animal studies, lacked diagnostic accuracy data, or were unavailable in full text. After applying these inclusion and exclusion criteria, 8studies met the eligibility criteria and were included in the final systematic review. Data extraction was performed independently by two reviewers using a standardized form, collecting information on author, year, country, patient population, sample size, biomarker type, study design, methodology, diagnostic sensitivity and specificity, key findings, and limitations.

**Figure 1: PRISMA Flow Diagram for Systematic Review of Cardiac Biomarkers in Myocardial Infarction Diagnosis.**



## Result

**Table 1: Diagnostic Performance of Cardiac Biomarkers in Myocardial Infarction: Systematic Review of Included Studies.**

| Author | Title | Year | Country | Population (Patients) | Sample Size | Biomarkers / Methodology | Type of Study | Sensitivity / Specificity | Key Finding | Limitation |
|---|---|---|---|---|---|---|---|---|---|---|
| **Chao Cheng et al.** | MiRNAs as Biomarkers of Myocardial Infarction: A Meta-Analysis | 2014 | Multiple (Meta-analysis) | MI patients from 19 studies | 19 studies | Meta-analysis of circulating miRNAs (miR-1, miR-133a, miR-208b, miR-499) from databases | **Meta-analysis** | Total miRNAs: Sens. 0.78; Spec. 0.82; **miR-499:** Sens. 0.88, Spec. 0.87 | MiRNAs, especially **miR-499** and **miR-133a**, are promising diagnostic biomarkers for MI | Heterogeneous methodologies; some studies had <100 patients |
| **An Hsu et al.** | Systemic Approach to Identify Serum microRNAs as Potential Biomarkers for AMI | 2014 | Taiwan | STEMI patients & healthy controls | 70 (8+8 initial; 31+31 validation) | Screening of 270 serum miRNAs; validation with qRT-PCR | **Case-control** | AUC 0.863 for miR-486-3p / miR-191-5p ratio | Serum miRNAs show potential for **early STEMI diagnosis** | Initial screening sample size small; findings require larger cohorts |
| **Stanley Chia et al.** | Utility of Cardiac Biomarkers in Predicting Infarct Size, LVEF, and Clinical Outcome After PCI | 2008 | Unknown (Multicenter Trial) | STEMI patients undergoing PCI | 378 | Serial CK, CK-MB, Troponin I/T measurements; correlated with SPECT and LVEF | **Prospective cohort** | **TnI72h:** Sens. 90%, Spec. 70% for large infarct size | **TnI72h** predicts infarct size, low LVEF, and 180-day outcomes | Lower specificity for predicting reduced LVEF (52%) |
| **Johannes Tobias Neumann et al.** | Personalized diagnosis in suspected myocardial infarction | 2023 | International (13 cohorts) | ED patients with suspected MI | 23,411 (training 2,575) | Machine learning (ARTEMIS model) using hs-cTn and 11 clinical variables | **Diagnostic model development & validation** | Serial hs-cTn model AUC 0.92–0.98 | AI model provides **personalized MI probability**, improving safety and efficiency | Requires **digital infrastructure** and **large datasets** |

| Author | Title | Year | Country | Population (Patients) | Sample Size | Biomarkers / Methodology | Type of Study | Sensitivity / Specificity | Key Finding | Limitation |
|---|---|---|---|---|---|---|---|---|---|---|
| **Whady Hueb et al.** | MASS-V: Accuracy of Myocardial Biomarkers in the Diagnosis of MI After Revascularization | 2015 | Brazil | Stable multivessel CAD undergoing CABG/PCI | 202 | cTnI and CK-MB vs cardiac MRI (late gadolinium enhancement) | **Prospective study** | **cTnI:** Sens. 100%, Spec. 3.6–42.1%; **CK-MB:** Sens. 44.4–69.2%, Spec. 73.2–96.4% | CK-MB was **more accurate than cTnI** for procedure-related MI | cTnI specificity very low; clinical interpretation difficult |
| **Anoop S V Shah et al.** | Patient selection for high sensitivity cardiac troponin testing and diagnosis of MI | 2017 | UK & USA | ED patients (unselected and clinician-selected) | 8,500 | hs-cTnI in ED with independent adjudication | **Prospective cohort** | PPV: 11.8% (unselected), 59.7% (selected UK), 16.4% (US) | **Clinical selection** for troponin testing improves PPV for type 1 MI | Troponin elevation often reflects **injury, not MI** in unselected patients |
| **Suleyman Aydin et al.** | Biomarkers in Acute Myocardial Infarction: Current Perspectives | 2018 | Turkey | Literature-based (no patients) | N/A | Review of enzymatic (CK, CK-MB, TnI/T) & non-enzymatic (hFABP, GPBB, MPO) biomarkers | **Review** | TnI remains **gold standard** | Provides a **comprehensive biomarker overview** | Lacks original patient data; translational gap remains |

**Table 2: Time Course of Cardiac Biomarkers After Myocardial Infarction.**

| Biomarker | Onset After MI | Peak Time | Return to Baseline | Clinical Significance |
|---|---|---|---|---|
| CK | 4–6 hours | 18–24 hours | 2–3 days | Early marker, but low specificity |
| CK-MB | 4–6 hours | 18–24 hours | 2–3 days | More specific than CK for cardiac injury |
| cTnI | 3–6 hours | 18–24 hours | 5–10 days | Gold standard for MI, high sensitivity |
| cTnT | 3–6 hours | 18–24 hours | 7–14 days | Useful for late diagnosis, prolonged elevation |
| hs-cTn | 1–3 hours | 10–24 hours | 5–14 days | Detects very early injury, may detect minor damage |
| hFABP | 1–3 hours | 6–8 hours | 24–36 hours | Very early marker, useful for early detection |
| miR-499 | 1–4 hours | 6–12 hours | 1–2 days | Emerging early diagnostic biomarker |
| miR-133a | 1–4 hours | 6–12 hours | 1–2 days | Early biomarker, complements troponins |

The evaluation of myocardial infarction (MI) biomarkers across multiple studies has revealed a diverse spectrum of diagnostic capabilities, spanning from classical enzymatic markers to emerging molecular and computational approaches. The studies collectively demonstrate that each biomarker strategy offers unique strengths and limitations in terms of sensitivity, specificity, and clinical usability.

Classical biomarkers such as creatine kinase (CK) and CK-MB were historically used as frontline diagnostic tools for myocardial infarction but have limited sensitivity and specificity. The study by Stanley Chia et al.[3] assessed 378 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). Serial measurements of CK, CK-MB, and troponins I and T were correlated with infarct size and left ventricular ejection fraction (LVEF) as determined by single-photon emission computed tomography (SPECT). Among these markers, troponin I measured at 72 hours (TnI72h) demonstrated the strongest correlation with infarct size ($r > 0.70$, $p < 0.001$) and independently predicted adverse clinical outcomes at 180 days. A TnI72h threshold of 55 ng/ml achieved 90% sensitivity for detecting large infarcts (≥10% of myocardium), while specificity was 70% for infarct size and 52% for predicting LVEF ≤ 40%. These results show that troponin I is highly sensitive but moderately specific, especially for functional outcomes.

The MASS-V trial by Whady Hueb et al.[5] provided a peri-procedural perspective on biomarker utility. Among 202 patients undergoing on-pump and off-pump coronary artery bypass grafting (CABG) or PCI, cardiac troponin I (cTnI) exhibited 100% sensitivity for diagnosing procedure-related myocardial infarction (type 5 MI) but very low specificity, ranging from 3.6% to 42.1% depending on the procedure. CK-MB offered a more balanced profile, with specificity between 73% and 96% and sensitivity between 44% and 69%. These findings highlight that post-procedural troponin elevations often represent myocardial injury rather than clinically meaningful infarction, whereas CK-MB can better discriminate true peri-procedural MI.

The advent of high-sensitivity cardiac troponin (hs-cTn) assays has improved early detection but has also introduced new diagnostic challenges. Anoop S. V. Shah et al.[6] evaluated 8,500 emergency department patients in the UK and US to determine how patient selection affects the diagnostic yield of hs-cTn. In unselected patients, troponin positivity was 13.7%, but the prevalence of type 1 MI was only 1.6%, yielding a positive predictive value (PPV) of 11.8%. When testing was restricted to clinician-selected patients with higher pre-test probability, PPV increased to 59.7% in the UK and 16.4% in the US. This demonstrates that hs-cTn testing without careful patient selection can lead to overdiagnosis, whereas selective use preserves diagnostic accuracy.

Emerging molecular biomarkers, particularly circulating microRNAs (miRNAs), offer a promising complement to troponin-based diagnostics. Chao Cheng et al.[1] conducted a meta-analysis of 19 studies evaluating miRNAs as diagnostic markers of myocardial infarction. The pooled sensitivity and specificity of miRNA panels were 0.78 and 0.82, respectively. Among individual markers, miR-499 achieved 0.88 sensitivity and 0.87 specificity, and miR-133a demonstrated a similar profile, suggesting that specific miRNAs could serve as highly accurate diagnostic tools. Building on this, An Hsu et al.[2] performed a two-phase study in Taiwan, initially profiling 270 serum miRNAs in 8 STEMI patients and 8 matched controls, followed by validation in 31 patients and 31 controls. They identified a miR-486-3p/miR-191-5p ratio that achieved an AUC of 0.863, indicating strong discriminatory ability. These results suggest that miRNAs could provide early molecular signals of myocardial infarction, particularly useful in cases where troponin elevations are equivocal or delayed.

Finally, integration of biomarkers with computational models represents a new frontier. Johannes Tobias Neumann et al.[4] developed the ARTEMIS machine learning model to generate individualized MI probabilities using hs-cTn data, electrocardiography, and clinical variables. Across 23,411 patients in 13 international cohorts, the model achieved AUCs of 0.92–0.98 for serial hs-cTn measurements, outperforming guideline-based rule-in/rule-out algorithms and enabling flexible, efficient diagnostic decision-making. This approach allows personalized, context-aware interpretation rather than reliance on fixed thresholds.

Collectively, the results illustrate that classical biomarkers retain value in specific settings, high-sensitivity troponins excel in early detection but require contextual interpretation, miRNAs show promise for molecular-level precision, and machine learning models like ARTEMIS represent the future of probabilistic, patient-specific MI diagnostics.

## Discussion

A comparison of the available biomarkers reveals clear differences in their diagnostic performance, clinical applicability, and role in modern MI evaluation. Classical enzymatic biomarkers like CK and CK-MB have largely been supplanted by troponins due to their limited sensitivity and delayed peak, but their comparative specificity in peri-procedural settings remains valuable. In the MASS-V trial[6], CK-MB demonstrated higher specificity (up to 96%) than troponin I (as low as 3.6%) in detecting clinically meaningful peri-procedural MI. This highlights a scenario where traditional biomarkers remain relevant: when distinguishing between procedural myocardial injury and true infarction, CK-MB avoids the overdiagnosis inherent to highly sensitive assays.

Troponins, particularly high-sensitivity troponin assays, have transformed the landscape of acute MI diagnosis. They are now the gold standard for early detection due to their ability to detect even small amounts of myocardial necrosis. The work of Stanley Chia et al.[3] demonstrates the prognostic and diagnostic utility of troponin I, which correlated strongly with infarct size and LVEF. However, as Anoop Shah et al.[6] demonstrated, the utility of hs-cTn is heavily dependent on pre-test probability and patient selection. Widespread, unselective use results in low PPV due to the high prevalence of non-ischemic myocardial injury in hospital populations. Therefore, troponins offer unmatched sensitivity but moderate to poor specificity in certain contexts, necessitating careful clinical interpretation or adjunctive testing.

MicroRNAs represent a fundamentally different diagnostic approach, targeting upstream molecular changes associated with ischemia and cell stress rather than necrosis alone. Chao Cheng et al.[1] and An Hsu et al.[2] provide compelling evidence that miRNAs like miR-499 and miR-133a can achieve sensitivities and specificities rivaling or exceeding those of troponins in some cohorts. Moreover, their expression patterns may change before irreversible necrosis occurs, potentially enabling ultra-early detection. While promising, the clinical translation of miRNA biomarkers is limited by assay heterogeneity, lack of standardization, and the need for rapid, point-of-care testing platforms. Compared to troponins, which are widely available, miRNAs remain primarily a research tool.

When comparing these biomarkers head-to-head, troponins remain the best-established for routine diagnosis, CK-MB retains niche utility post-revascularization, and miRNAs represent the most promising next-generation tool for early or specific diagnosis. However, none of these approaches fully resolve the specificity issue inherent in biomarker-based diagnosis. This is where computational approaches like the ARTEMIS model by Johannes Tobias Neumann et al.[4] offer a transformative solution. By integrating hs-cTn with demographic, clinical, and ECG data, ARTEMIS moves beyond binary thresholds to generate patient-specific MI probabilities. Its AUC of 0.92–0.98 in multiple cohorts demonstrates that incorporating context directly into the diagnostic model outperforms biomarkers alone. In practical terms, such models could reduce unnecessary admissions from troponin-positive non-MI patients and allow safe early discharge for low-probability cases.

The comparative analysis therefore illustrates a continuum of biomarker evolution: CK-MB and troponins mark structural injury, miRNAs provide early molecular signals, and machine learning models synthesize this information into clinically actionable probabilities. Each has trade-offs: CK-MB is specific but less sensitive, troponins are sensitive but can overdiagnose, miRNAs are promising but not yet standardized, and AI models require digital infrastructure. In clinical practice, the future likely lies in multimodal strategies combining troponins for sensitivity, miRNAs for specificity, and computational models for context-aware decision-making.

## Conclusion

The diagnosis of myocardial infarction has advanced from reliance on classical enzymatic biomarkers to a nuanced, multimodal, and increasingly personalized approach. Classical markers like CK-MB still offer value in post-procedural settings due to their superior specificity compared to troponin, but they lack the sensitivity required for early detection. High-sensitivity troponins have become the gold standard, providing excellent sensitivity and facilitating rapid rule-in and rule-out protocols, yet they are vulnerable to overdiagnosis in low-risk or unselected populations. Emerging molecular biomarkers such as circulating microRNAs offer a compelling glimpse into the future of precision cardiology, with the potential for ultra-early and highly specific diagnosis. Studies have demonstrated that miRNAs like miR-499 and miR-133a can achieve sensitivities and specificities approaching 0.88, making them attractive adjuncts to traditional testing, though clinical implementation awaits standardization and point-of-care adaptation.

Machine learning approaches like the ARTEMIS model represent the next stage of biomarker evolution, integrating high-dimensional clinical and biomarker data into probabilistic diagnostic tools that outperform threshold-based algorithms. These models can mitigate the limitations of individual biomarkers by providing context-aware risk assessment, improving diagnostic efficiency, and potentially reducing unnecessary admissions.

In summary, the future of MI diagnosis is likely to be hybrid, combining the sensitivity of high-sensitivity troponins, the specificity of molecular biomarkers, and the interpretive power of computational models. Such an approach promises to enhance diagnostic accuracy, optimize patient management, and reduce healthcare burden. Continued research, validation, and clinical integration will be essential to fully realize the benefits of this evolving diagnostic paradigm, ultimately translating biomarker innovation into improved patient outcomes.

## Abbreviations

MI – Myocardial Infarction, AMI – Acute Myocardial Infarction, STEMI – ST-Segment Elevation Myocardial Infarction, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Grafting, CAD – Coronary Artery Disease, CK – Creatine Kinase, CK-MB – Creatine Kinase Myocardial Band, cTnI – Cardiac Troponin I, cTnT – Cardiac Troponin T, hs-cTn – High-Sensitivity Cardiac Troponin, TnI72h – Troponin I at 72 hours, LVEF – Left Ventricular Ejection Fraction, SPECT – Single-Photon Emission Computed Tomography, MRI – Magnetic Resonance Imaging, AUC – Area Under the Curve, PPV – Positive Predictive Value, qRT-PCR – Quantitative Real-Time Polymerase Chain Reaction, hFABP – Heart-type Fatty Acid Binding Protein, GPBB – Glycogen Phosphorylase Isoenzyme BB, MPO – Myeloperoxidase, ARTEMIS – AI-based Model for MI Diagnosis, ED – Emergency Department, Sens. – Sensitivity, Spec. – Specificity.

## Financial Burden and Conflicts of Interest

All authors of this review, bear the financial burden of this research. There were no conflicts of interest reported by any of the authors.

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