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Utility of cardiac biomarkers and biosensors for diagnosis of acute myocardial infarction

Rupali Shinde[1], Isha Juwarwala[1], Vishal Modi[2], and Chandni V. Chandarana[1]*

[1]Department of Quality Assurance, SSR College of Pharmacy, Sayli, Silvassa, U.T. of Dadra Nagar Haveli, 396230, India

[2]Department of Pharmaceutical Chemistry, Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar, Gujarat, 382421, India

Abstract

Acute myocardial infarction (AMI) is the most prevalent condition that results in sickness and death worldwide. An early and accurate diagnosis of AMI is critical for prompt and appropriate treatment. Cardiac biomarkers, including myoglobin, creatinine phosphokinase (CK), and cardiac troponins, have been widely used for AMI diagnosis. More recently, new biomarkers such as heart-type fatty acid-binding protein and matrix metalloproteinases have shown promise in improving AMI diagnosis. At present, cardiac biomarkers and biosensors are used in the diagnosis and prognosis of AMI. This review article gives information on cardiac biomarkers specific to AMI and its diagnostic methods. These biomarkers have several advantages, including their high specificity for cardiac injury and their sensitivity to even small extent of cardiac damage. In addition, cardiac biomarkers can be used to assess the severity of AMI and predict the risk of complications or mortality. Recently, biosensors that can detect cardiac biomarkers in real time have been developed, allowing for an earlier and more accurate diagnosis of AMI. The utility of cardiac biomarkers and biosensors in the diagnosis of AMI underscores the importance of early and accurate diagnosis and treatment of this life-threatening condition.

Keywords: Acute myocardial infraction; Cardiac biomarker; Colorimetric; Electrochemical method; Aptamer

***Corresponding author:**
Chandni V. Chandarana
(chandnichandarana7343@gmail.com)

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1. Introduction

Myocardial infarction or heart attack occurs when blood flow to part of the myocardium is reduced or completely interrupted[1]. Myocardial infarction could be "silent" and progress undetected, and that it can be catastrophic and result in sudden death due to hemodynamic deterioration and a collapse of the blood vessels[2]. Chest pain is the most typical symptom, with longer-lasting chest pain that occurs in the center or left side of the chest as well as discomfort that can spread from the shoulder to the arm or neck. Additional signs include shortness of breath, nausea, cold sweat, or exhaustion. The primary factor for coronary artery disease is myocardial infraction, and high blood pressure, smoking, diabetes, overweight, high cholesterol, unhealthy diets, and excessive alcohol consumption are risk factors. According to the World Health Organization (WHO), myocardial infarction is the main cause of death and disability worldwide[3].

Electrocardiograms (ECGs) are a popular approach for noticing and diagnosing irregular cardiac rhythms as well as injury to the tissue that transports electrical information or is conductive. Despite its insensitivity, the ECG is still the recommended diagnostic method for identifying an individual with MI. The first disadvantage is that it only records electrical activity at a certain time and must be repeated as a patient's clinical condition changes[4]. The second disadvantage is that the physician could make personal decision, despite the wave pattern in ECG is similar to expected normal results. Finally, ECG is ineffective in individuals with NSTEMI (the contraction waves segmenting the ECG depiction)[5]. Finally, even if an ECG can detect acute myocardial ischemia, myocardial infarction history, conduction abnormality defect, or arrhythmia, it is a very inadequate test for detecting early blockage of coronary arteries. To get around the limitations and problems with ECG, cardiac biomarkers that are suitable for sensing are collectively an alternative option[6].

2. Background of myocardial infarction

Myocardial infarction is characterized by the standard rise and decline of biochemical indicators (e.g., troponin and creatine kinase-MB [CK-MB]) with at least one of the following conditions:

- The signs of ischemia
- The new ischemia-related ECG changes
- The new unhealthy Q waves.

Acute myocardial infarction (AMI) can be identified using any recent imaging evidence or pathologic (morphologic) results on the pathologic changes of myocardial viability[7].

3. Background of cardiac biomarkers

The initial biomarker for the detection of AMI was aspartate transaminase (AST). CK, which was discovered in the 1950s, was the first enzyme to be recognized as a cardiac biomarker. AST and lactate dehydrogenase were also recognized as cardiac biomarkers in the 1960s[6]. The spectrum of cardiac biomarkers was completely altered in the 1980s since the discovery of cardiac troponins. Cardiovascular troponins, such as both troponin T and I, are released into the circulation when the heart muscle cells are injured[8].

3.1. Myoglobin

Heme protein includes myoglobin, which has been utilized as an AMI marker for about 60 years. Both skeletal muscle and heart muscle contain myoglobin. The large quantity of myoglobin in skeletal muscle and the fact that brief, modest skeletal muscle injuries raise the level of myoglobin in the blood indicate that myoglobin is not cardiac-specific[9]. The fundamental advantage of using myoglobin as a cardiac marker is that it enables early detection of AMI because it appears before the emergence of other heart symptoms as a result of cell damage. The rapid release of myoglobin is probably attributed to its small size and cytoplasmic location. As an early marker of AMI, myoglobin has a high negative predictive value. Most hospitals choose not to use myoglobin as marker because the high concentration of myoglobin in skeletal muscle and the broad range of specificity (60–90%) tend to give an unsatisfactory clinical evaluation of chest pain[10]. A primary drawback of myoglobin is that it is not specific to cardiac tissue, as it can be found in abundance in skeletal muscles. Instead of being utilized alone as a diagnostic marker, myoglobin should be utilized with CK-MB or troponins[11]. Myoglobin is no longer used as a marker because cardiac troponins, which are highly sensitive, serve as early marker of AMI. Myoglobin is included in studies that integrate sickness detection because TnI and NT-pro-BNP, which are more reliable in diagnoses, have been developed and have shown a good association with CK-MB[12].

3.2. High-sensitivity cardiac troponin

Since the initial application of troponin testing, multiple generations of more sophisticated and dependable assays have been created and employed to aid in the quicker and more precise diagnosis of heart attacks. The high-sensitivity cardiac troponin test (hs-cTnT) is the latest generation of the cardiac enzyme testing that allows for detection of very low levels of troponin T, helping to diagnose heart attacks more quickly. If the test is negative, it can also help "rule out" heart damage from coronary artery disease[12]. Modern high-sensitivity cardiac troponin (hs-cTn) assays measure cardiac troponin (cTn) concentrations that are 10–100 fold lower than those of conventional assays. These assays enable faster, higher-precision, and more accurate assessments even with extremely low concentrations of cTn that are undetected by conventional tests. Recent recommendations state that hs-cTn assays with imprecision ≤10% are "acceptable" by guideline standards, whereas assays with imprecision >10% but <20% are "clinically usable"[13].

3.3. Cardiac troponins I and T

Cardiac troponins I and T are proteins that regulate and modulate the actin-myosin connection mediated by calcium. In the diagnosis of myocardial infarction, elevated cardiac troponin concentrations are regarded as the benchmark. Muscle and cardiac troponin are both present. Serum troponin testing was found to have a high level of specificity when compared to measurement of

enzymes in cardiac muscle for the identification of cardiac muscle injury[14]. Although both cardiac troponins I and T are early markers of AMI, cardiac troponin I has a cardiac focus, whereas cardiac troponin T is not cardiac-specific because it is also raised in other degenerative diseases[15].

4. Biomarkers of AMI

Biomarkers of AMI are some of the most recent biomarkers and they are associated with numerous pathologic processes (Figure 1)[16].

4.1. Myeloperoxidase (MPO)

MPO may be involved in human atherogenesis according to several lines of evidence. The enzymes and their byproducts of oxidation result in atherosclerotic lesions, as detected by immunohistochemical and biochemical investigations[17-20]. White persons who have complete or partial MPO deficiency, which affects 1 in every 2000 – 4000 of them, appear to have a lower risk of developing cardiovascular disease (CVD)[21]. In addition, those who have a promoter polymorphism that is associated with a reported 2-fold reduction in MPO expression appear to have cardioprotection as evidenced by a significant reduction in angiographic indicators of cardiac mortality, non-fatal myocardial infarction, and coronary artery disease[22-24]. There is an angiographic link between coronary artery disease and expected rises in systemic MPO levels. A patient whose diagnostic cardiac catheterization was performed in a tertiary referral hospital is 15–20 times more likely to have abnormal coronary angiograms, which were defined as >50% stenosis in one or more major coronary arteries, as compared to a subject in the lowest quartile. It was still statistically significant to associate the C-reactive protein (CRP) with the Framingham risk score. Furthermore, it has been demonstrated that in patients who present with acute coronary symptoms or chest pair, it is possible to forecast the likelihood of a severe adverse cardiac event using MPO concentrations in the blood and serum, mortality of a non-fatal myocardial infarction, or the requirement for revascularization[24]. In addition, several biochemical and genetic studies have demonstrated a strong link between MPO and the risk of CVD[25].

4.2. Matrix metalloproteinases (MMPs)

The immediate role of MMPs is the breakdown and removal of extracellular matrix (ECM) molecules as well as cell-surface molecules. Physiological functions of MMPs include angiogenesis, wound healing, and embryogenesis, and they may also lead to pathological hazards such

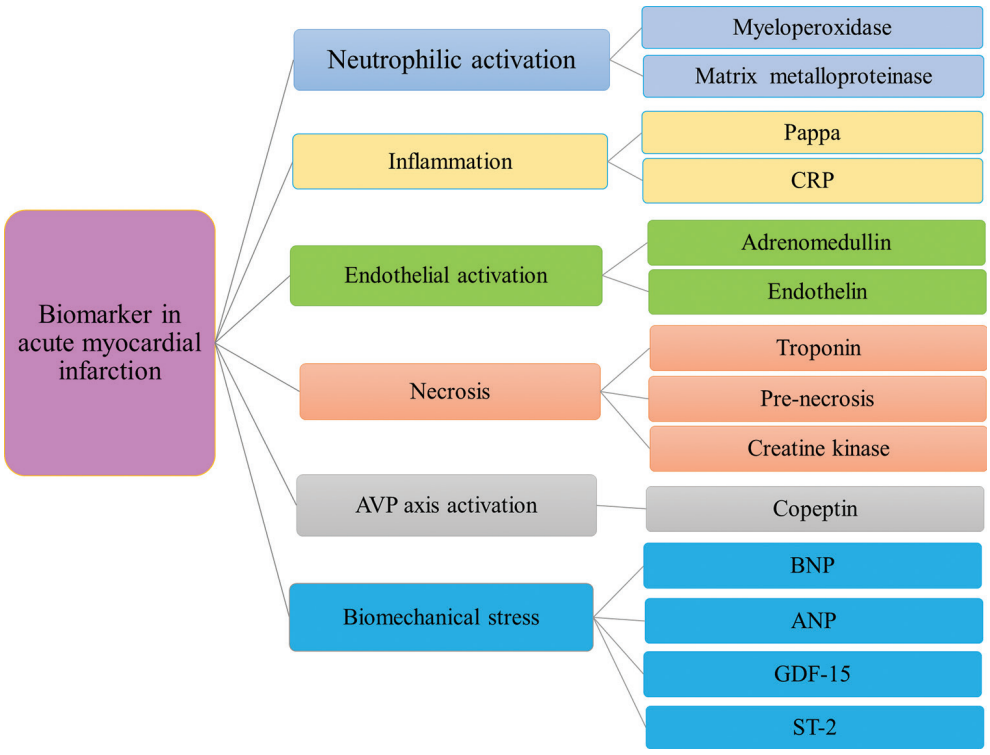

Figure 1. Association of biomarkers of acute myocardial infarction with pathophysiological mechanism.
Abbreviations: ANP: Atrial natriuretic peptide; BNP: B-type natriuretic peptide; CRP: C-reactive protein; GDF-15: Growth differentiation factor-15; ST-2: Suppression of tumorigenicity 2.

as cancer, ischemia, myocardial infarction, and dilated cardiomyopathy.

The majority of MMPs are produced as zymogens and secreted in this manner, but there is also a subfamily that is membrane-bound (membrane-type MMPs)[26]. Tissue inhibitors of metalloproteinases (TIMPs), which belong to a class of tightly binding, naturally occurring proteins, control the activity of MMPs[27]. Long-term remodeling activities, including embryogenesis, inflammation, tumor invasion, angiogenesis, and wound healing, are all facilitated by MMPs. Recent research has revealed that MMP-2 (also known as gelatinase A or type IV collagenase) performs a combination of cellular activities rapidly (within seconds to minutes), which impacts the ECM. Using mice model in which *MMP* gene has been deleted, it has also been revealed that MMP-2 and MMP-9 play an important role in the increase in aneurysms of the abdominal aorta. Both MMP-2 and MMP-9 degrade type I and type II interstitial collagen, type III and type IV collagen, elastin, and other ECM components. The digestion of the intercellular MMP-2, troponin I, myosin light chain, and poly(ADP-ribose) polymerase present in cardiomyocytes may be a factor in cardiac dysfunction[26].

4.3. Inflammation

Inflammation is a commonplace in AMI due to tissue loss and cell death in the heart. Pro-inflammatory cytokines, chemokines, and other inflammatory mediators are produced at the site of injury, attracting immune cells, and causing extra tissue damage and inflammation. Surgery may aggravate the symptoms of initial ischemia and worsen the AMI patients' prognosis. Biomarkers such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and CRP are associated with inflammation in cases of AMI. Increasing concentrations of these biomarkers are associated with an increased risk of adverse cardiovascular events, such as recurrent myocardial infarction, heart failure, and death[28].

4.4. Pregnancy-associated plasma protein A

The ECM of unstable plaques contains high levels of pro-atherosclerotic metalloproteinase and pregnancy-associated plasma protein A (PaPPA)[28]. Circulating PaPPA was observed in patients with unstable angina and significantly increased AMI, which is correlated with troponin, but not with growth factors or CRPs similar to insulin. PaPPA >2.9 mIU/L predicts a 4.6-fold increase in the risk of cardiovascular mortality, myocardial infarction, or revascularization even in the absence of elevated troponin levels[29]. When it binds to the binding sites on endothelium, endothelial dysfunction can be reversed by cleaving insulin-like growth factor-1, causing the nitric oxide emission. PaPPA has been found to be a repair-promoting and inflammation-responsive protein in other injured tissues[30].

4.5. Adrenomedullin

The kidneys, lungs, adrenal medulla, heart, and liver express adrenomedullin (ADM), which is a peptide with 52 amino acids. It advances within the heart and also uses natriuretic peptides (NPs) in response to volume and pressure overload[31]. It has a potent diuretic and natriuretic effect and is a powerful vasodilator. ADM levels in plasma are markedly increased in heart failure and AMI, connected to the seriousness of the condition, and of prognostic significance in AMI-related death[32].

4.6. Troponin

Greaser and Gergely demonstrated in 1971 that the troponin complex is composed of three components. Due to their distinct features, these sections were given the designations TnC, TnI, and TnT. TnC has the binding capacity for Ca2+; TnI possesses the ability to inhibit ATPase activity; and TnT binds to tropomyosin[33].

Troponin C is produced in both cardiac and skeletal muscle. Troponin T and I isoforms are known as cardiac troponins due to their heightened sensitivity to and specificity for cardiac myocytes (cTn). As a result, identifying cTn-T or cTn-I in the blood is a very reliable way to detect cardiac damage[8].

4.7. Creatinine kinase

An enzyme called CK, also known as creatine phosphokinase (CPK), is present in many different tissues. CK is expressed in skeletal muscle, heart, and brain and is a cardiac-specific enzyme with a clinical sensitivity of 90% for detecting AMI, but it has low specificity. The time required for CK to reach the peak is 20–30 h and the time of return to the normal level is 24–48 h. A result, CK is ineffective in the quick identification of AMI[34].

4.8. C-terminal pro-arginine vasopressin

C-terminal pro-arginine vasopressin (copeptin), a more stable alternative to arginine vasopressin, is well known for its effects on the harmony of the cardiovascular and endocrine systems[35]. In the development of AMI, it is believed that vasopressin encourages expansion afterload, peripheral vasoconstrictor activity, and ventricular stress. Myocyte protein expression then rises, resulting in hypertrophy and vasoconstriction of the coronary arteries. The V1 receptor mediates these effects, whereas actions on the V2 receptor cause the renal tubules to retain water. The current focus of pharmaceutical therapy is on these receptors[36,37].

4.9. Heart-type fatty acid-binding protein (H-FABP)

Tissues with lower expression of H-FABP include the brain, kidney, skeletal tissue, adrenal gland, and mammary gland tissues, as well as blastocysts[38,39]. H-FABP is a valuable tool for assessing patients with chest pain in the emergency department, and its concentration is elevated as early as 30 min after myocardial injury. Peaking at 6–8 h and reverting to baseline after 24 h, H-FABP is sensitive enough for the early detection of AMI. This protein exhibits an 82% negative predictive value in testing[40].

4.10. B-type natriuretic peptide

One of the most well-known indicators of biomechanical stress is B-type natriuretic peptide (BNP)[16]. Produced in response to the tense cardiomyocytes in the ventricle[40], BNP binds to and activates receptors, lowering central venous pressure, natriuresis, and systemic vascular resistance. Research has shown that BNP offers predictive information after myocardial infarction[41]. Although this biomarker has a half-life, it is released, along with the N-terminal (NT)-pro-BNP, a peptide that is considerably stronger in serum and is simple to test. The biology of this substance is still not well understood, particularly with regard to the post-translational metabolism of the peptides, which may interfere with the precise measurement of BNP levels[42].

4.11. Atrial natriuretic peptide

Both atrial natriuretic peptide (ANP) and BNP have comparable neurohormonal effects and secretory profiles after AMI. ANP levels have been precisely measured in other studies, although with mixed results. It has been established that N-ANP is connected to late mortality after AMI[43]. Interference and analyte unreliability commonly affect ANP assays[44]. ANP was deemed to give meager prognostic information due to unsatisfactory outcomes. Nevertheless, the identification of a new midregional (MR)-pro-ANP fragment[45]. The peptide is much more stable than ANP. MR-pro-ANP is at least as good at predicting mortality and heart failure as MR-pro-ANP due to the test epitopes being positioned internally on the pro-ANP molecules (and hence stability to exoprotein activity) as NT-pro-BNP[46]. When MR-pro-ANP levels were divided into quartiles, the highest quartile was associated with a hazard ratio (HR) of 3.87 (vs. NT-pro-BNP's HR 3.25), including a higher likelihood of mortality at follow-up. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve for each biomarker was similar (0.83). Thus, MR-pro-ANP is a powerful predictor of adverse outcomes after an AMI.

4.12. Growth differentiation factor-15

Growth differentiation factor-15 (GDF-15) is a distant member of transformation growth factor (TGF) and can be activated in response to tissue damage. Multiple types of cardiovascular cells have the potential to produce GDF-15 under pathological circumstances. GDF-15 levels are higher in the blood and are related to increased cardiac metabolic risk factors. The fact that GDF-15 is drastically elevated in CVD and that the level of GDF-15 is directly associated with the frequency of CVD[47-49] increases the possibility that it might be an useful disease biomarker. According to a meta-analysis, high levels of GDF-15 were associated with a higher risk of death in patients with CVD[49,50]. GDF-15 further supports NT-pro-BNP and CRP as well as standard hazard factors in the detection of acute coronary syndrome (ACS), and it is a standalone indicator of all-cause mortality in ACS patients[51,52].

4.13. Suppression of tumorigenicity 2

When hearts are being strained mechanically, the blood levels of suppression of tumorigenicity 2 (ST-2), an IL-1-receptor-like protein, were found to be raised[16]. In the IL-1 receptor family, there are two isoforms of ST-2: Soluble (ST2L) and transmembrane (ST2)[53]. It was later discovered that ST2 targets IL-33, a kind of interleukin that only develops when myocytes are under biomechanical stress and seem to play a cardioprotective role[54]. Cardiomyocyte hypertrophy caused by phenylephrine and angiotensin II was shown to be significantly decreased by IL-33 in studies using mice. The connection between ST-2 and IL-33 may also alleviate the burden of the atheroma. However, it has a weak correlation with NT-pro-BNP after an AMI and both of these biomarkers are predictive of cardiac failure or death 6 months after a myocardial infarction. A study found that the IL-33/ST-2 pathway is the therapeutic target of AMI[55]. Level of ST2 is higher in both autoimmune diseases and acute asthma. It is necessary to verify the specificity of ST-2 for cardiac tissue stretching before applying it at the clinical settings (Table 1 and Figure 2)[56].

5. Methods for detecting and diagnosing AMI

5.1. Colorimetric assay for diagnosing AMI

The principles of conventional ELISA testing are also applied to colorimetric immunoassays. Specific binding occurs between an antigen or antibody and its complementary antibody or antigen. A secondary antibody or antigen that is enzyme-labeled is added during the detection stage to trigger an enzymatic reaction when it binds to the primary antibody. The outcome of this reaction is an appreciable color change, as a result of the transformation of the substrate

Table 1. Biomarker for diagnosis of myocardial infarction

Diagnostic indicator (marker)	Time required for marker level to peak after onset (h)	Time required for marker level to peak after onset (h)	Specificity (%)	Sensitivity (%)
Myoglobin (MYO)	4–6	20–25	80	92
Cardiac troponin I (cTnI)	12–24	5–9	98.4	98.7
Cardiac troponin T (cTnT)	18–36	5–14	100	99
Creatinine kinase (CK)	20–30	24–48	91	24
Glucose dehydrogenase (GDH)	48–72	10–15	-	-
N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)	No clinical consensus	No clinical consensus	72.6	50.7
Heart-type fatty acid-binding protein (H-FABP)	6	0.5–1	68	89.7
Creatine kinase-myoglobin binding (CK-MB)	12–24	3–4	92	44.8
B-type natriuretic peptide (BNP)	No clinical consensus	No clinical consensus	90	86

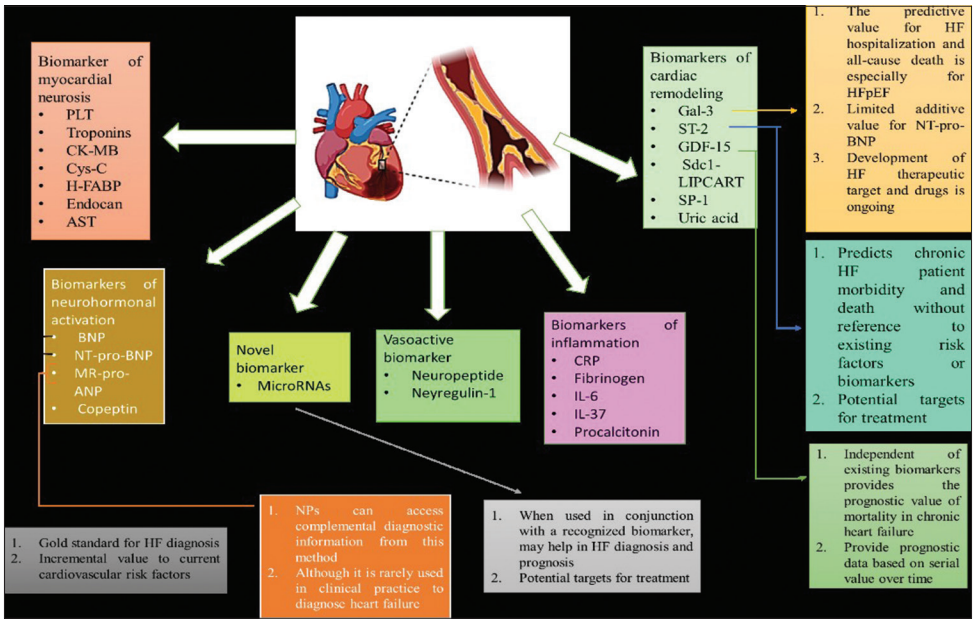

Figure 2. Therapeutical potential and functional role of biomarkers of acute myocardial infarction.
Abbreviations: AST: Aspartate transaminase; BNP: B-type natriuretic peptide; CK-MB: Creatine kinase-myoglobin binding; Copeptin: C-terminal pro-arginine vasopressin; CRP: C-reactive protein; Cys-C: Cystatin C; Gal-3: Galectin-3; GDF-15: Growth differentiation factor-15; H-FABP: Heart-type fatty acid-binding protein; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; IL: Interleukin; MR-pro-ANP: Midregional pro-atrial natriuretic peptide; NP: Natriuretic peptide; NT-pro-BNP: N-terminal pro-B-type natriuretic peptide; PLT: Platelet; SP-1: Specificity protein 1; ST-2: suppression of tumorigenicity 2.

into a colorful product[57]. The process for ELISA-based colorimetric immunoassays often entails covering a solid surface (such as a microplate) with a capture antibody or an antigen specific to the target analyte. After blocking to reduce non-specific binding, the sample is introduced to let the target analyte attach to the antigen or antibody that will capture it. The analyte's distinct epitope is then bound by an enzyme-labeled detecting antibody or antigen, which is then added. A substrate solution is added after incubation and washing steps are performed to remove unbound components. An enzyme label catalyzes a reaction with a substrate that results in the production of a colored product. The analyte concentration is directly proportional to the intensity of color measured spectrophotometrically[58]. In 2010, Kim *et al.* developed a test of lateral flow strips comprising a sample pad, conjugate pad, nitrocellulose membrane, and absorbent pad. After the cTnl antigen is added to the sampling pad, two separate gold nanoparticles (AuNP) conjugates are deposited onto the conjugated pad and then flow out. First, cTnI reacts with AuNP containing anti-troponin antibodies I, followed by a second AuNP interacting with the first AuNP by BSA and anti-BSA antibody interactions. This method shows higher signal intensity than the conventional lateral flow assay (LFA) method, and after passing through the NC membrane, conjugated AuNPs were immobilized onto the surface and finally, by dipping the cut LFA strip into troponin

I-containing well plates, the color intensity was assessed. The limit of detection is as low as 0.01 ng/mL[59]. In 2020, Wen *et al.* developed a calorimetric biosensor on poly (dimethyl siloxane) (PDMS)-AuNPs composite film with silver, which is used as a biosensor for TnI detection[2,3]. An immune-sensing biochip for the rapid and accurate detection of cardiac biomarkers such as TnI, CK-MB, and myoglobin in blood using a nitrocellulose membrane for antibody immobilization enables a quick and effective detection of AMI[12].

5.2. Electrochemical immunoassay for diagnosing AMI

The electrochemical assay focuses mainly on the interaction between the transducer and the target molecules. It works by detecting electrochemical signals produced by the particular interaction, which, when caught by the immobilized surface antibodies, leads to a charge exchange between host and guest molecules and a change in current or voltage on the targeted surface.

- Amperometric approach, which measures the electric current created by the displacement by a regulated potential.
- Potentiometric approach, which detects the potential difference caused by the accumulation or reduction of ions at the sensor interface when exposed to a continuous current or zero current sources, for instance, a field-effect transistor (FET), a semiconductor device that functions by electric field modulating charges and can convert specific biological interactions into electrical signals.
- Impedimetric approach, which measures changes in the impedance of a material depending on a current or potential disturbance on the sensor surface[60].

Label-free electrochemical detection is recognized as an affordable, responsive, and sustainable method for biomarker analysis. High sensitivity, selectivity, and low cost are all features of electrochemical detection (electron transfer directly generates an electronic signal, so expensive equipment is not needed for signal transduction). Many electrochemical biosensors are constructed using capacitance, amperometry, or potentiometry. Amperometry biosensors are the most popular because it is easy to use. It is possible to immobilize the recognition components on the transducer surface with the aid of gels, polymeric membranes, conductive salts, etc., which pose one of the most crucial problems while using this technique. An aptamer-based biosensor for Tnl detection, with a gold electrode serving as the transducer, had a detection range of 0.03 to 2 ng/mL when tested on 89 human samples. Electrochemical biosensors are suitable for diagnosing AMI due to their significant surface area, low density, thermal stability, and exceptional electrical, porous, and mechanical characteristics[12].

5.3. Aptamers biosensor for diagnosing AMI

The glassy carbon electrodes (GCE) used in the aptamer biosensor serve as recognition molecules. When aptamers attach precisely to the analyte in a solution, they can provide an electrochemical signal. The current corresponds with the analyte concentration; hence, the aptamer-based biosensor may be used to find cTnl in a sample. In 2014, a new aptamer biosensor for cTnl detection was developed. They added hydroxyl groups to the GCE by submerging it in a hydrophilic solution of NH_4OH: H_2O_2: amination solution and H_2O (1-1-10) at 72°C for 20 minutes and of 3-amino-propyltryethoxysilane: H_2O amination solution by attaching it to the surface of the GCE as an amino group. Carbon di-imide hydrochloride and N-hydroxy succinimide are used to activate the GCE. A biosensor uses aptamers and cognition molecules standing still on the surface of GCE. When the cTnl in solution is attached to the immobilized the concentration of the cTnl in the solution affects the current generated by the binding process[12]. Their low stability, fragility, and sensitivity to denaturation caused by temperature changes account for their limited storage life. They cannot also be created artificially. It results in high expenses and uncertainty from batch to batch. Therefore, they could be blamed for the discrepancy in cTnl levels detected by various so-called point-of-care (POC) equipment. With this synthetic method of production, high reproducibility and good yields are feasible. In comparison to antibodies, they are more stable over time and less vulnerable to high temperatures. There is always a potential for them to become denaturized, which would then allow for the benefit of their folding shape. Their storage, transport, and manipulation are therefore made easier. Aptamers, sometimes referred to as "APTA-sensors," are becoming more and more popular to be used in sensitive and precise testing and as a cheaper alternative to unstable and costly antibodies in sensors[3].

5.4. Fluorescence immunoassay for diagnosing AMI

For cTnl detection, alkaline phosphatase (ALP) chemiluminescence chemistry is used. In the beginning, monoclonal anti-cTnl was applied to the carboxylic acid-modified magnetic beads through EDC coupling to create a particular antigen-antibody association[61]. This innovative method is designed for cTnl detection. It has been claimed that microwave-accelerated and metal-enhanced fluorescence (MA-MEF) is used to identify proteins. Only a little time is required for incubation thanks to microwave acceleration[62]. Multianalyte chip assay is an additional technique for identifying biomolecules. A multianalyte sensor surface was sandwiched with several biomarkers,

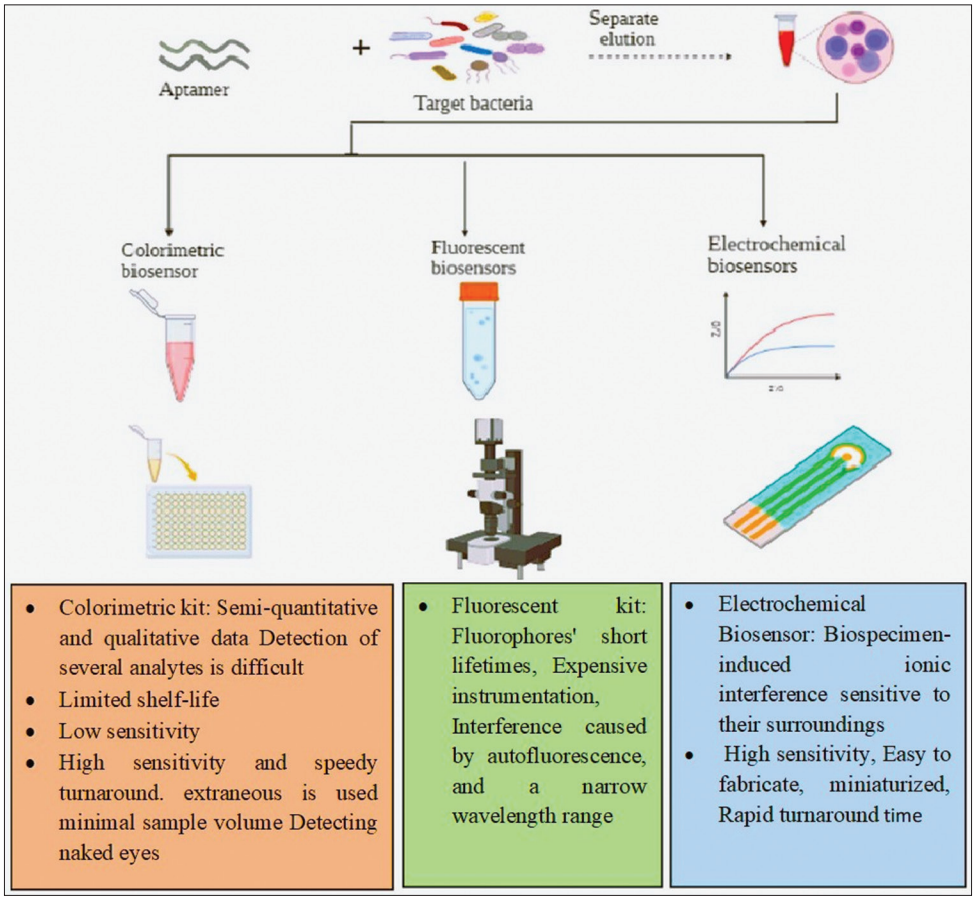

Figure 3. Biosensor for diagnosing acute myocardial infarction.

including cTnl, and activated by an integrated optical waveguide made of silicon oxynitride.

In a multianalyte platform like this, many biomarkers are simultaneously detected, and due to their high sensitivity, this sort of biochip can act as a POC apparatus. Markers that can be detected in ELISA-based assays such as cTnl may be detected using a colorimetric and fluorescent immunoassay. These assays are quick and have great sensitivity, but the procedures involved are time-consuming and laborious (Figure 3)[63-66].

6. Conclusions

The utility of cardiac biomarkers and biosensors in AMI diagnosis cannot be overstated. The high specificity and sensitivity of cardiac troponin, connected with advances in biosensor technology, have significantly improved diagnostic accuracy. Biosensors, such as electrochemical and optical biosensors, offer rapid and precise detection of cardiac biomarkers, enabling timely intervention of diseases.

Diagnosis of AMI is therefore dependent on the use of cardiac biomarkers and biosensors. These techniques enable the rapid identification and early detection of AMI, resulting in better patient outcomes and immediate medical intervention. Myoglobin, cardiac troponins, and CK are examples of cardiac biomarkers that are frequently used to identify AMI. Biosensors based on principles such as fluorescence, auditory, and colorimetry have also been found to be promising diagnostic methods for AMI. AMI diagnosis has also been proven to be more sensitive and specific when biomarkers linked to oxidative stress and inflammation, such as MMPs and MPO, are used. Further, development of cardiac biomarkers and biosensors might generate even more precise and effective AMI detection methods in the future.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

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Writing – original draft: Rupali Shinde
Writing – review & drafting: Isha Juwarwala, Vishal Modi, Chandni V. Chandarana

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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References

1. Ojha N, Dhamoon AS, 2022, Myocardial infarction. In: StatPearls. Treasure Island, FL: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/nbk537076 [Last accessed on 2023 Jun 06].
2. Savonnet M, Rolland T, Cubizolles M, *et al.*, 2021, Recent advances in cardiac biomarkers detection: From commercial devices to emerging technologies. *J Pharm Biomed Anal*, 194: 113777.

   https://doi.org/10.1016/j.jpba.2020.113777
3. Ahammad AJS, Choi YH, Koh K, *et al.*, 2011, Electrochemical detection of cardiac biomarker troponin I at gold nanoparticle-modified ITO electrode by using open circuit potential. *Int J Electrochem Sci*, 6: 1906–1916.
4. Mahajan VS, Jarolim P, 2011, How to interpret elevated cardiac troponin levels. *Circulation*, 124: 2350–2354.

   https://doi.org/10.1161/circulationaha.111.023697
5. Rashid S, Malik A, Khurshid R, *et al.*, 2019, The diagnostic value of biochemical cardiac markers in acute myocardial infarction. In: Myocardial Infarction. London, UK: IntechOpen.

   https://doi.org/10.5772/intechopen.76150
6. Falahati A, Sharkey SW, Christensen D, *et al.*, 1999, Implementation of serum cardiac troponin I as marker for detection of acute myocardial infarction. *Am Heart J*, 137: 332–337.

   https://doi.org/10.1053/hj.1999.v137.92412
7. Garg P, Morris P, Fazlanie AL, *et al.*, 2017, Cardiac biomarkers of acute coronary syndrome: From history to high-sensitivity cardiac troponin. *Intern Emerg Med*, 12: 147–155.

   https://doi.org/10.1007/s11739-017-1612-1
8. Van Nieuwenhoven FA, Kleine AH, Wodzig KH, *et al.*, 1995, Discrimination between myocardial and skeletal muscle injury by assessment of the plasma ratio of myoglobin over fatty acid-binding protein. *Circulation*, 92: 2848–2854.

   https://doi.org/10.1161/01.cir.92.10.2848
9. Lewandrowski K, Chen A, Januzzi J, 2002, Cardiac markers for myocardial infarction. A brief review. *Am J Clin Pathol*, 118: S93–S99.

   https://doi.org/10.1309/3ek7-yvv9-228c-e1xt
10. Tilea I, Varga A, Serban RC, 2021, Past, present, and future of blood biomarkers for the diagnosis of acute myocardial infarction-promises and challenges. *Diagnostics* (*Basel*), 11: 881.

    https://doi.org/10.3390/diagnostics11050881
11. Reyes-Retana JA, Duque-Ossa LC, 2021, Acute myocardial infarction biosensor: A review from bottom up. *Curr Probl Cardiol*, 46: 100739.

    https://doi.org/10.1016/j.cpcardiol.2020.100739
12. High-sensitivity Troponin Test: Normal and High Levels. Available from: https://www.medicinenet.com/high_sensitivity_troponin_test_ranges_and_values/article.htm [Last accessed on 2023 Jun 06].
13. Vasile VC, Jaffe AS, 2017, High-sensitivity cardiac troponin for the diagnosis of patients with acute coronary syndromes. *Curr Cardiol Rep*, 19: 92.

    https://doi.org/1010.1007/s11886-017-0904-4
14. Collinson PO, Boa FG, Gaze DC, 2001, Measurement of cardiac troponins. *Ann Clin Biochem*, 38: 423–449.

    https://doi.org/10.1177/000456320103800501
15. Shave R, Dawson E, Whyte G, *et al.*, 2002, The cardiospecificity of the third-generation cTnT assay after exercise-induced muscle damage. *Med Sci Sports Exerc*, 34: 651–654.

    https://doi.org/10.1097/00005768-200204000-00014
16. Chan D, Ng LL, 2010, Biomarkers in acute myocardial infarction. *BMC Med*, 8: 34.

    https://doi.org/10.1186/1741-7015-8-34
17. Hazen SL, Heinecke JW, 1997, 3-chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima. *J Clin Invest*, 99: 2075–2081.

    https://doi.org/10.1172/JCI119379
18. Thukkani AK, McHowat J, Hsu FF, *et al.*, 2003, Identification of alpha-chloro fatty aldehydes and unsaturated lysophosphatidylcholine molecular species in human atherosclerotic lesions. *Circulation*, 108: 3128–3133.

    https://doi.org/10.1161/01.cir.0000104564.01539.6a
19. Beckmann JS, Ye YZ, Anderson PG, *et al.*, 1994, Extensive nitration of protein tyrosines in human atherosclerosis detected by immunohistochemistry. *Biol Chem Hoppe*

Seyler, 375: 81–88.

https://doi.org/10.1515/bchm3.1994.375.2.81

20. Hazell LJ, Baernthaler G, Stocker R, 2001, Correlation between intima-to-media ratio, apolipoprotein B-100, myeloperoxidase, and hypochlorite-oxidized proteins in human atherosclerosis. *Free Radic Biol Med*, 31: 1254–1262.

https://doi.org/10.1016/s0891-5849(01)00717-1

21. Kutter D, Devaquet P, Vanderstocken G, *et al.*, 2000, Consequences of total and subtotal myeloperoxidase deficiency: Risk or benefit ? *Acta Haematol*, 104: 10–15.

https://doi.org/10.1159/000041062

22. Nikpoor B, Turecki G, Fournier C, *et al.*, 2001, A functional myeloperoxidase polymorphic variant is associated with coronary artery disease in French-Canadians. *Am Heart J*, 142: 336–339.

https://doi.org/10.1067/mhj.2001.116769

23. Pecoits-Filho R, Stenvinkel P, Marchlewska A, *et al.*, 2003, A functional variant of the myeloperoxidase gene is associated with cardiovascular disease in end-stage renal disease patients S-172. *Kidney Int Suppl*, 63: S172–S176.

https://doi.org/10.1046/j.1523-1755.63.s84.32.x

24. Brennan ML, Penn MS, Van Lente F, *et al.*, 2003, Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med*, 17: 1595–1604.

https://doi.org/10.1056/NEJMoa035003

25. Baldus S, Heeschen C, Meinertz T, *et al.*, 2003, Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation*, 108: 1440–1445.

https://doi.org/10.1161/01.CIR.0000090690.67322.51

26. Wang W, Schulze CJ, Suarez-Pinzon WL, *et al.*, 2002, Intracellular action of matrix metalloproteinase-2 accounts for acute myocardial ischemia and reperfusion injury. *Circulation*, 106: 1543–1549.

https://doi.org/10.1161/01.cir.0000028818.33488.7b

27. Kwan JA, Schulze CJ, Wang W, *et al.*, 2004, Matrix metalloproteinase-2 (MMP-2) is present in the nucleus of cardiac myocytes and is capable of cleaving poly (ADP-ribose) polymerase (PARP) *in vitro*. *FASEB J*, 18: 690–692.

https://doi.org/10.1096/fj.02-1202fje

28. Morrow DA, Braunwald E, 2003, Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. *Circulation*, 108: 250–252.

https://doi.org/10.1161/01.cir.0000078080.37974.d2

29. Lund J, Qin QP, Ilva T, *et al.*, 2003, Circulating pregnancy-associated plasma protein a predicts outcome in patients with acute coronary syndrome but no troponin I elevation. *Circulation*, 108: 1924–1926.

https://doi.org/10.1161/01.cir.0000096054.18485.07

30. Bayes-Genis A, Conover CA, Schwartz RS, 2000, The insulin-like growth factor axis: A review of atherosclerosis and restenosis. *Circ Res*, 86: 125–130.

https://doi.org/10.1161/01.res.86.2.125

31. Nishikimi T, Asakawa H, Iida H, *et al.*, 2004, Different secretion patterns of two molecular forms of cardiac adrenomedullin in pressure-and volume-overloaded human heart failure. *J Card Fail*, 10: 321–327.

https://doi.org/10.1016/j.cardfail.2003.12.002

32. Miyao Y, Nishikimi T, Goto Y, *et al.*, 1998, Increased plasma adrenomedullin levels in patients with acute myocardial infarction in proportion to the clinical severity. *Heart*, 79: 39–44.

https://doi.org/10.1136/hrt.79.1.39

33. Mohan G, Kaur R, Singh T, 2017, Cardiac biomarkers in acute coronary syndrome. *Curr Trends Diagn Treat*, 1: 80–88.

https://doi.org/10.5005/jp-journals-10055-0019

34. Duma RJ, Siegel AL, 1965, Serum creatinine phosphokinase in acute myocardial infarction: Diagnostic value. *Arch Intern Med*, 115: 443–451.

https://doi.org/10.1001/archinte.1965.03860160069011

35. Itoi K, Jiang YQ, Iwasakiz Y, *et al.*, 2004, Regulatory mechanisms of corticotropin-releasing hormone and vasopressin gene expression in the hypothalamus. *J Neuroendocrinol*, 16: 348–355.

https://doi.org/10.1111/j.0953-8194.2004.01172.x

36. Gheorghiade M, Gattis WA, O'Connor CM, *et al.*, 2004, Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA*, 291: 1963–1971.

https://doi.org.10.1001/jama.291.16.1963

37. Abraham WT, Shamshirsaz AA, McFann K, *et al.*, 2006, Aquaretic effect of lixivaptan, an oral, non-peptide, selective v2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol*, 47: 1615–1621.

https://doi.org/10.1016/j.jacc.2005.11.071

38. Rezar R, Jirak P, Gschwandtner M, *et al.*, 2020, Heart-type fatty acid-binding protein (H-FABP) and its role as a biomarker in heart failure: What do we know so far? *J Clin Med*, 9: 164.

https://doi.org/10.3390/jcm9010164

39. Atay E, Guzel M, Amanvermez R, *et al.*, 2019, Role of Gal-3 and H-FABP in the early diagnosis of acute coronary syndrome. *Bratisl Lek Listy*, 120: 124–130.

https://doi.org/10.4149/bll_2019_020

40. Levin ER, Gardner DG, Samson WK, 1998, Natriuretic

peptides. *N Engl J Med*, 339: 321–328.

https://doi.org/10.1056/NEJM199807303390507

41. De Ames JA, Morrow DA, Bentley JH, *et al.*, 2001, The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*, 345: 1014–1021.

https://doi.org/10.1056/nejmoa011053

42. Vasile VC, Babuin L, Giannitsis E, *et al.*, 2008, Relationship of MRI-determined infarct size and cTnI measurements in patients with ST-elevation myocardial infarction. *Clin Chem*, 54: 617–619.

https://doi.org/10.1373/clinchem.2007.095604

43. Richards AM, Nicholls MG, Yandle TG, *et al.*, 1998, Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: New neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation*, 97: 1921–1929.

https://doi.org/10.1161/01.cir.97.19.1921

44. Squire IB, O'Brien RJ, Demme B, *et al.*, 2004, N-terminal pro-atrial natriuretic peptide (N-ANP) and N-terminal pro-B-type natriuretic peptide (N-BNP) in the prediction of death and heart failure in unselected patients following acute myocardial infarction. *Clin Sci*, 107: 309–316.

https://doi.org/10.1042/CS20040087

45. Morgenthaler NG, Struck J, Thomas B, *et al.*, 2004, Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. *Clin Chem*, 50: 234–236.

https://doi.org/10.1373/clinchem.2003.021204

46. Khan SQ, Dhillon O, Kelly D, *et al.*, 2008, Plasma N-terminal B-type natriuretic Peptide as an indicator of long-term survival after acute myocardial infarction: Comparison with plasma midregional pro-atrial natriuretic peptide. The LAMP (Leicester Acute Myocardial Infarction Peptide) study. *J Am Coll Cardiol*, 51: 1857–1864.

https://doi.org/10.1016/j.jacc.2008.01.041

47. Ho JE, Mahajan A, Chen MH, *et al.*, 2012, Clinical and genetic correlates of growth differentiation factor 15 in the community. *Clin Chem*, 58: 1582–1591.

https://doi.org/10.1373/clinchem.2012.190322

48. Schopfer DW, Ku IA, Regan M, *et al.*, 2014, Growth differentiation factor 15 and cardiovascular events in patients with stable ischemic heart disease (The Heart and Soul Study). *Am Heart J*, 167: 186–192.e1.

https://doi.org/10.1016/j.ahj.2013.09.013

49. Zhang S, Dai D, Wang X, *et al.*, 2016, Growth differentiation factor-15 predicts the prognoses of patients with acute coronary syndrome: A meta-analysis. *BMC Cardiovasc Disord*, 16: 82.

https://doi.org/10.1186/s12872-016-0250-2

50. Xie S, Lu L, Liu L, 2019, Growth differentiation factor-15 and the risk of cardiovascular diseases and all-cause mortality: A meta-analysis of prospective studies. *Clin Cardiol*, 42: 513–523.

https://doi.org/10.1002/clc.23159

51. Daniels LB, Clopton P, Laughlin GA, *et al.*, 2011, Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: The Rancho Bernardo Study. *Circulation*, 123: 2101–2110.

https://doi.org/10.1161/circulationaha.110.979740

52. Bodde MC, Hermans MPJ, van der Laarse A, *et al.*, 2019, Growth differentiation factor-15 levels at admission provide incremental prognostic information on all-cause long-term mortality in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Cardiol Ther*, 8: 29–41.

https://doi.org/10.1007/s40119-019-0127-4

53. Wang XY, Zhang F, Zhang C, *et al.*, 2020, The biomarkers for acute myocardial infarction and heart failure. *Biomed Res Int*, 2020: 2018035.

https://doi.org/10.1155/2020/2018035

54. Sanada S, Hakuno D, Higgins LJ, *et al.*, 2007, IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest*, 117: 1538–1549.

https://doi.org/10.1172/JCI30634

55. Seki K, Sanada S, Kudinova AY, *et al.*, 2009, Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. *Circ Heart Fail*, 2: 684–691.

https://doi.org/10.1161/circheartfailure.109.873240

56. Díez J, 2008, Serum soluble ST2 as a biochemical marker of acute heart failure. Future areas of research. *J Am Coll Cardiol*, 52: 1466–1467.

https://doi.org/10.1016/j.jacc.2008.07.045

57. Zhou L, Liu Y, Lu Y, *et al.*, 2022, Recent advances in the immunoassays based on nanozymes. *Biosensors* (*Basel*), 12: 1119.

https://doi.org/10.3390/bios12121119

58. Yang J, Wang X, Sun Y, *et al.*, 2023, Recent advances in colorimetric sensors based on gold nanoparticles for pathogen detection. *Biosensors* (*Basel*), 13: 29.

https://doi.org/10.3390/bios13010029

59. Choi DH, Lee SK, Oh YK, *et al.*, 2010, A dual gold nanoparticle conjugate-based lateral flow assay (LFA) method for the analysis of troponin I. *Biosens Bioelectron*,

25: 1999–2002.

https://doi.org/10.1016/j.bios.2010.01.019

60. Benjamin SR, Santos LKB, Silva JEG, *et al.*, 2023, Electrochemical Immunosensors and Biomimetic Sensors for the Detection of the Myocardial Infarction Biomarkers. United States: Crimson Publishers.

61. Liu J, Zhang L, Wang Y, *et al.*, 2014, An improved portable biosensing system based on enzymatic chemiluminescence and magnetic immunoassay for biological compound detection. *Measurement*, 47: 200–206.

https://doi.org/10.1016/j.measurement.2013.08.057

62. Aslan K, Grell TAJ, 2011, Rapid and sensitive detection of troponin I in human whole blood samples by using silver nanoparticle films and microwave heating. *Clin Chem*, 57: 746–752.

https://doi.org/10.1373/clinchem.2010.159889

63. Qureshi A, Gurbuz Y, Niazi JH, 2012, Biosensors for cardiac biomarkers detection: A review. *Sens Actuators B Chem*, 171–172: 62–76.

https://doi.org/10.1016/j.snb.2012.05.077

64. Masson JF, Battaglia TM, Khairallah P, *et al.*, 2007, Quantitative measurement of cardiac markers in undiluted serum. *Anal Chem*, 79: 612–619.

https://doi.org/10.1021/ac061089f

65. Plowman TE, Durstchi JD, Wang HK, *et al.*, 1999, Multiple-analyte fluoroimmunoassay using an integrated optical waveguide sensor. *Anal Chem*, 71: 4344–4352.

https://doi.org/10.1021/ac990183b

66. Wolf M, Juncker D, Michel B, *et al.*, 2004, Simultaneous detection of C-reactive protein and other cardiac markers in human plasma using micromosaic immunoassays and self-regulating microfluidic networks. *Biosens Bioelectron*, 19: 1193–1202.

https://doi.org/10.1016/j.bios.2003.11.003