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ORIGINAL RESEARCH

Systematic Review of Cardiac Biomarkers: Physiological Roles and Clinical Significance

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ABSTRACT

Background: Cardiac markers are biomolecules released into the bloodstream due to myocardial injury. These biomarkers play a critical role in diagnosing and managing cardiovascular diseases (CVDs), which remain a leading cause of morbidity and mortality worldwide. The timely detection of cardiac markers aids in risk stratification, guiding treatment strategies, and improving patient outcomes.This systematic review explores the physiology of key cardiac markers, including troponins (cTnI, cTnT), creatine kinase-MB (CK-MB), B-type natriuretic peptide (BNP), myoglobin, and emerging biomarkers like high-sensitivity C-reactive protein (hs-CRP) and microRNAs. We analyze their biochemical characteristics, release kinetics, specificity, and clinical applications. Additionally, the review highlights recent advancements in biomarker research, including high-sensitivity assays and multi-marker approaches, to enhance diagnostic accuracy.

Material & Methods: Search Strategy**:** A systematic literature search was conducted in PubMed, Scopus, and Web of Science using keywords: "cardiac markers," "troponins," "creatine kinase-MB (CK-MB)," "B-type natriuretic peptide (BNP)," and "myoglobin". Eligibility Criteria**:** Studies included were original research, clinical trials, and meta-analyses published in peer-reviewed journals from 2000-2024.Study Selection**:** Two independent reviewers screened abstracts and full texts. A third reviewer resolved disagreements.Data Extraction and Quality Assessment**:** Extracted data included study design, sample size, biomarker levels, and clinical outcomes. Quality assessment was conducted using the Newcastle-Ottawa Scale.

Results &Discussion: Following PRISMA guidelines, we conducted a comprehensive literature search to evaluate the physiological significance, diagnostic utility, and prognostic value of these biomarkers in conditions such as acute coronary syndrome (ACS), myocardial infarction (MI), and heart failure (HF). The review also discusses the integration of novel biomarkers in clinical practice, their limitations, and future research directions.

Conclusion: Understanding the role of cardiac markers in disease mechanisms and management can significantly impact clinical decision-making, leading to improved patient care. The integration of traditional and novel biomarkers may pave the way for more precise and personalized approaches in cardiology.

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Keywords: Cardiac markers, troponins, creatine kinase-MB(CK-MB), B-type natriuretic peptide(BNP) and Myoglobin

INTRODUCTION

Cardiovasculardiseases (CVDs) remain the leading cause of morbidity and mortality worldwide. Early diagnosis through reliable biomarkers is critical for timely intervention. This review follows PRISMA guidelines to evaluate the physiological role and clinical relevance of cardiac markers.Cardiac biomarkers are naturally occurring substances that are released into the bloodstream when the heart muscle experiences damage or undergoes stress. These

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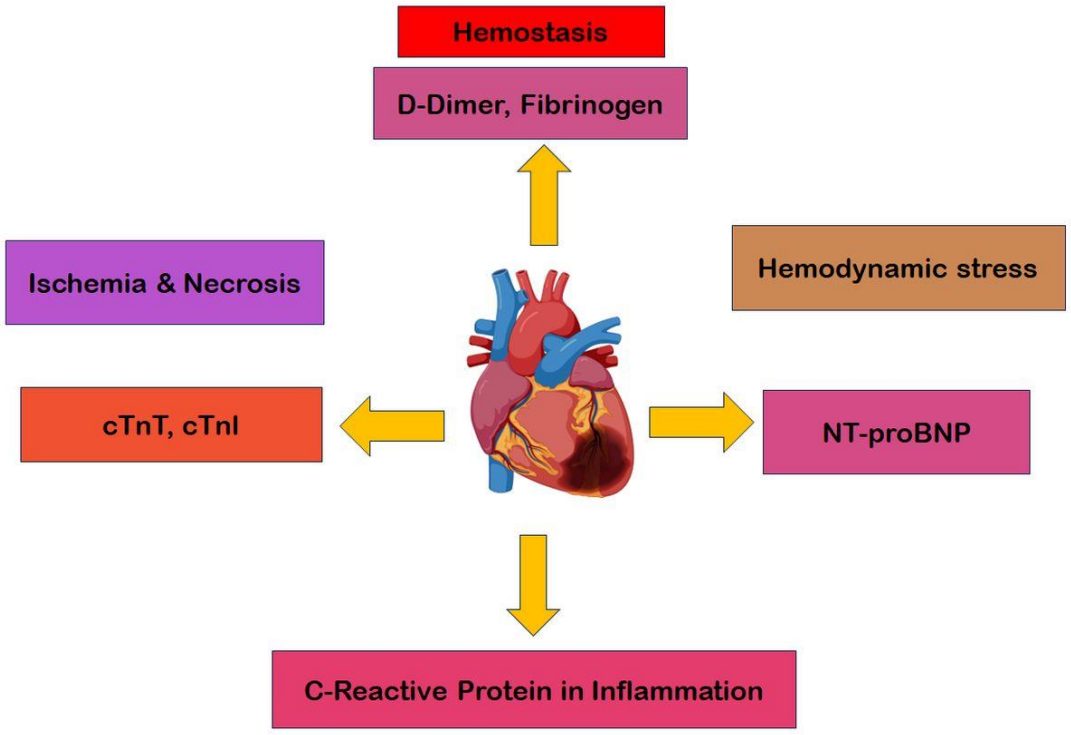
biomarkers serve as vital indicators for various conditions related to heart health. Their measurement plays a critical role in the diagnosis, risk assessment, and management of acute coronary syndrome (ACS), which is a group of conditions that pose a serious threat to life. ACS is commonly associated with the sudden onset of chest pain, which may radiate to one or both arms, the shoulders, stomach, or jaw. Additional symptoms often include shortness of breath, nausea, profuse sweating, and dizziness, all of which can signify the presence of a potentially life-threatening heart event[1].

The use of cardiac enzymes to evaluate patients with suspected acute myocardial infarction (MI), commonly known as a heart attack, dates back to the mid-20th century. However, the biomarkers used at that time are no longer clinically relevant today. Over the years, advancements in medical science have led to the development of more sensitive and specific biomarkers that are now the standard in clinical practice[2]. These modern biomarkers provide healthcare professionals with more accurate and timely information, enabling better diagnosis and treatment[3].

Among the various cardiac biomarkers, troponins have emerged as the most critical and widely used markers for diagnosing acute myocardial ischemia, a condition in which the heart muscle is deprived of oxygen due to a blocked or narrowed artery. Troponins are proteins found in heart muscle cells and are released into the bloodstream when the heart muscle is injured. Unlike older biomarkers such as creatine kinase (CK), which typically shows elevated levels 6 to 12 hours after a patient arrives at the emergency department, troponins can be detected much earlier, usually within 2 to 3 hours of an acute myocardial infarction (AMI)[4]. This rapid elevation allows for quicker identification of heart attacks, enabling faster intervention and potentially improving patient outcomes[5].

Schematic diagram showing Cardiac Biomarkers



MATERIAL & METHODS

Search Strategy: A thorough and systematic literature search was meticulously carried out across multiple reputable databases, including PubMed, Scopus, and Web of Science. This search aimed to identify relevant studies by utilizing a set of carefully selected keywords. These keywords were strategically chosen to encompass a wide range of cardiac biomarkers, including "cardiac markers," "troponins," "creatine kinase-MB (CK-MB)," "B-type natriuretic peptide (BNP)," and "myoglobin." The intention behind this comprehensive search strategy was to ensure that all pertinent articles and studies related to these biomarkers were considered, thus capturing a full spectrum of relevant research in the field.

Eligibility Criteria: The studies eligible for inclusion in this review were original research articles, clinical trials, and meta-analyses. These studies had to be published in peer-reviewed journals to guarantee the

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scientific credibility and reliability of the findings. To ensure that the review focused on contemporary advancements, only studies published between the years 2000 and 2024 were considered. This time frame was chosen to reflect the most recent and relevant data in the field of cardiac biomarkers, particularly with regard to their clinical utility and diagnostic accuracy.

Study Selection: The process of selecting the studies involved two independent reviewers who each screened both the abstracts and full texts of the studies to determine their relevance and inclusion in the review. Any disagreements or discrepancies in the selection process were resolved through consultation with a third reviewer, ensuring that the final list of studies met the rigorous criteria set for this review. This methodical approach helped maintain objectivity and reliability in the selection process.

Data Extraction and Quality Assessment: Data extraction focused on key aspects such as the study design, sample size, the specific biomarkers measured, and the associated clinical outcomes observed in each study. This detailed data collection allowed for a comprehensive comparison across studies. Additionally, the quality of each included study was rigorously assessed using the Newcastle-Ottawa Scale (NOS), a tool designed to evaluate the methodological quality of non-randomized studies. This process ensured that only studies meeting a high standard of scientific rigor were included in the final review, providing confidence in the validity and reliability of the results.

RESULTS

Troponins (cTnI, cTnT): Highly specific for myocardial injury; elevated in acute coronary syndrome (ACS) and myocardial infarction (MI).Cardiac troponin plays a crucial role in regulating the contraction of heart muscle by acting as a calcium-dependent "switch" that controls the transition between contraction and relaxation. It is currently regarded as the gold standard biomarker for diagnosing myocardial infarction. The cardiac troponin complex consists of three proteins: troponin T (TNT), troponin I (TNI), and troponin C (TNC). Due to distinct differences in the amino acid sequences between the cardiac and skeletal isoforms of TNT and TNI, specialized monoclonal antibody-based immunoassays have been developed to specifically detect the cardiac forms of TNT and TNI.
For patients with acute coronary syndrome (ACS), cardiac troponins are highly beneficial, offering sensitivity, specificity, and valuable insights into the symptoms. As a result, they have become the primary cardiac biomarker used for ACS cases. Additionally, cardiac troponins are more sensitive to even small levels of myocardial damage when compared to CK-MB tests. Although troponin is the gold standard biomarker for myocardial infarction, it has limited utility in identifying reinfarction. This limitation arises because a second myocardial infarction occurring 7 to 10 days after the initial event may be challenging to detect using cardiac troponin alone due to its prolonged half-life [6].

CK-MB: Previously a gold standard for MI diagnosis; now used adjunctively due to lower specificity than troponins.Since the 1960s, a blood test measuring creatine kinase has been utilized to detect myocardial infarction. The identification of CK-MB, a specific isoenzyme of creatine kinase predominantly found in the heart, has significantly enhanced the accuracy of diagnosing myocardial damage. Researchers have employed this test for assessing acute myocardial infarction (AMI) since the 1970s. CK-MB is one of three isoenzymes of the creatine kinase enzyme, primarily located in the heart, but also present in lower amounts in skeletal muscle [7]. Elevated levels of creatine kinase are commonly observed in cases of myocardial infarction, and as such, CK-MB is crucial in differentiating whether the rise in creatine kinase is due to cardiac or skeletal muscle injury [8].

Brain natriuretic peptide (BNP and NT-pro BNP): Brain natriuretic peptide (BNP) and its N-terminal fragment, NT-proBNP, are continuously released into the bloodstream from the ventricles in response to myocardial stretch. The precursor to BNP, known as proBNP, is a peptide composed of 108 amino acids that is cleaved into two fragments: the 76-amino acid BNP and the 32-amino acid NT-proBNP[9]. NT-proBNP has a sixfold longer half-life than BNP, and it is cleared from the body through several mechanisms, including renal and other pathways [10]. Elevated levels of BNP and NT-proBNP are commonly found in individuals with heart failure, making them useful biomarkers for diagnosis. BNP plays a key role in regulating a variety of physiological and pathological processes [11]. It is involved in mechanisms such as natriuresis, diuresis, vasodilation, and the inhibition of the sympathetic nervous system, in addition to its influence on the renin-angiotensin-aldosterone system [12,13]. Research has shown that BNP also contributes to the regulation of diseases associated with these pathways [14].

Myoglobin: Early marker of myocardial injury but lacks specificity.Myoglobin is a protein responsible for oxygen binding, forming a complex with iron in the muscle tissues of both the skeletal and cardiac systems. Following a myocardial infarction, myoglobin is released into the bloodstream within an hour. Its levels begin to increase steadily within 2 to 4 hours after the onset of myocardial injury, reaching their peak around 8–12 hours, and typically return to normal within 24–36 hours. Although myoglobin is found in significant quantities in skeletal muscles, it is an early marker of acute myocardial infarction but

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lacks specificity to the heart. Therefore, myoglobin alone should not be used to diagnose acute myocardial infarction; it is more effective when combined with other heart-specific biomarkers, such as TNI or TNT, to enhance diagnostic accuracy [15].

Novel Markers: High-sensitivity C-reactive protein (hs-CRP), heart-type fatty acid-binding protein (H-FABP), and microRNAs are emerging as potential biomarkers for early cardiac event detection.The liver produces C-reactive protein (CRP), an important acute-phase reactant. In response to various inflammatory cytokines, CRP levels in the bloodstream rapidly increase [16]. Recent research has provided more insight into the potential role of inflammation in the development of major health conditions like diabetes and cardiovascular diseases. Epidemiological studies have consistently shown that CRP is a strong, independent predictor of future cardiovascular events, such as myocardial infarction, ischemic stroke, peripheral vascular disease without prior heart disease, and sudden cardiac death [17]. CRP's significance lies in its early appearance in the bloodstream during a variety of systemic inflammatory conditions. However, challenges exist in diagnosing CRP due to its lower stability, extended detection periods, and cross-reactivity with other blood proteins [18].Heart-fatty acid binding protein (H-FABP) is a small cytosolic protein primarily found in cardiac tissue, where it facilitates the transport of fatty acids from the plasma membrane to the mitochondria and peroxisomes for oxidation, as well as to the endoplasmic reticulum for lipid synthesis [19]. While it is most abundant in the myocardium, it can also be detected in lesser amounts in tissues such as the brain, kidneys, and skeletal muscle. Following myocyte injury, H-FABP is quickly released into the bloodstream [20]. Its levels begin to rise within 30 minutes after a myocardial infarction, peak around 6 to 8 hours later, and typically return to normal levels within 24 hours [21]. Additionally, H-FABP may serve as a valuable biomarker for predicting mortality [22].Micro-RNAs (miRNAs) are short noncoding RNA molecules that regulate gene expression through their seed region, which consists of a sequence of six to eight nucleotides that binds to target messenger RNA (mRNA) [23]. These molecules primarily downregulate translation at the post-transcriptional level by two key mechanisms: translational repression and mRNA degradation. Real-time quantitative polymerase chain reaction (qPCR) is widely regarded as the most reliable method for quantitatively measuring miRNA expression levels. MiRNAs are involved in regulating various biological processes, such as lipid metabolism, glucose balance, vascular function, and endothelial cell activity [24,25]. Previous research indicated that a panel of miRNAs improved the predictive accuracy of traditional Framingham risk models, although no individual miRNA was found to significantly reduce the risk of acute myocardial infarction (MI) in a clinically meaningful way [26].

Table 1: Summary of important cardiac biomarkers used in diagnosing and monitoring heart-related conditions.

Biomarkers	Type	Normal Range	Clinical Use	Associated conditions
Troponin I	Protein	< 0.04 ng/mL	Most sensitive and specific for myocardial injury	Acute Myocardial Infarction (AMI), Myocarditis, Heart failure
Troponin T	Protein	< 0.01 ng/mL	Indicates myocardial damage, often used interchangeably with troponin I	Acute Myocardial Infarction (AMI), Myocarditis, Heart failure
CK-MB (Creatinekinase-MB)	Enzyme	< 5 ng/mL	Detects myocardial injury, less specific than troponins	Acute Myocardial Infarction (AMI), Cardiac surgeries
BNP(B-Type Natriuretic Peptide)	Peptide	< 100 pg/mL	Assists in diagnosing heart failure and assessing its severity	Heart failure, Pulmonary hypertension, Renal failure
cTn(Cardiac Troponin)	Protein	< 0.04 ng/mL	Used for detecting acute myocardial injury	Acute Myocardial Infarction (AMI), Myocardial damage
Myoglobin	Protein	< 70 ng/mL	Early marker for myocardial injury, less specific	Acute Myocardial Infarction (AMI), Muscle injury
hs-CRP(High-sensitivity C-reactive protein)	Protein	< 1.0 mg/L	Indicates inflammation, can help assess cardiovascular risk	Atherosclerosis, Risk for cardiovascular disease

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DISCUSSION

The biomarkers that have been extensively reviewed are crucial in various aspects of cardiovascular disease (CVD), including diagnosis, prognosis, and monitoring the effectiveness of treatments. Among these biomarkers, troponins are recognized as the most sensitive and specific indicators of cardiac injury, making them indispensable for detecting heart-related conditions with high accuracy. On the other hand, B-type natriuretic peptide (BNP) plays an essential role in the evaluation of heart failure, as it helps to assess the severity and prognosis of this condition. Furthermore, the incorporation of emerging biomarkers into clinical practice holds the potential to significantly improve diagnostic precision and offer a more comprehensive understanding of cardiovascular health. These novel markers could lead to earlier detection, better risk stratification, and more tailored treatment strategies for individuals with CVD.

CONCLUSION

Cardiac markers play a crucial role in the detection and diagnosis of myocardial injury and heart failure. These biomarkers provide valuable insights into the presence and extent of heart damage, aiding healthcare professionals in making timely and accurate clinical decisions. In particular, markers such as troponins, B-type natriuretic peptide (BNP), and creatine kinase-MB (CK-MB) are widely used to assess patients with suspected heart conditions. However, as the understanding of cardiovascular diseases continues to evolve, there is a growing need for the identification and validation of new, more specific biomarkers that can offer enhanced diagnostic capabilities. Future research should focus on the discovery of novel biomarkers that can provide a clearer understanding of cardiac injury at various stages, from acute to chronic conditions. Furthermore, integrating multi-marker approaches, which involve analyzing multiple biomarkers simultaneously, holds significant potential for improving diagnostic accuracy and precision. By combining several markers, clinicians may be able to differentiate between various types of heart conditions and provide a more comprehensive assessment of a patient's cardiovascular health. These advancements in biomarker research are likely to contribute to more personalized treatment strategies and ultimately lead to better patient outcomes in the management of heart disease.

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