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REVIEW ARTICLE

The Clinical Significance of Cardiac Markers in COVID-19 Patients: A Review Article

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ABSTRACT

SARS-CoV-2 is a highly contagious viral illness that started the COVID-19 pandemic in March 2020. Accumulating evidence suggests that the cardiovascular system is primarily affected by SARS-CoV-2. Cardiovascular complications such as myocarditis, acute coronary syndrome, heart failure, arrhythmias, and venous thromboembolism have been reported. The role of cardiac biomarkers in diagnosing and monitoring COVID-19 patients is becoming of particular interest, as it may provide insights into the underlying mechanisms of cardiovascular injury and inform clinical decision-making.

Troponins, specifically troponin I, have been widely studied and was proven to be elevated in COVID-19 patients with myocardial injury, indicating a negative prognostic indicator and association with poorer outcomes. Elevated levels of Natriuretic peptides, such as B-type natriuretic peptide (BNP), have been noted in severe COVID-19 cases and are associated with higher mortality rates. However, it is essential to consider that elevated natriuretic peptide levels in COVID-19 patients may also be influenced by factors other than heart failure. CK-MB, a subtype of creatine kinase, has been found to have significantly higher concentrations in COVID-19 patients with high disease severity or non-survivor status, suggesting its potential as a biomarker for risk stratification in this population. Myoglobin and lactate dehydrogenase (LDH) are additional cardiac markers that can indicate heart muscle damage, but their specificity in COVID-19 patients may be limited.

The widely used cardiac markers provide valuable diagnostic and prognostic information about cardiac injury and function in COVID-19 patients. Still, their performance characteristics and interpretation should be considered in the context of the individual patient and conjunction with other clinical assessments.

Keywords: SARS-CoV-2, myocarditis, acute coronary syndrome, heart failure, arrhythmias, troponin, B-type natriuretic peptide (BNP).

Introduction

COVID-19 is a highly contagious viral illness caused by SARS-CoV-2 that has resulted in over 6 million deaths worldwide[1]. The WHO declared the pandemic in March 2020 after the virus rapidly spread across the world. Mutant variants of the virus have contributed to ongoing outbreaks, with SARS-CoV-2 prone to genetic evolution and the development of mutations over time. The WHO has identified five variants of concern (VOCs) since the beginning of the pandemic: Alpha, Beta, Gamma, Delta, and Omicron. These variants were first reported in the UK, South Africa, Brazil, India, and South Africa, respectively, and have different characteristics than the original strains of SARS-CoV-2[1].

While the respiratory system is the primary target of SARS-CoV-2, the virus responsible for COVID-19, accumulating evidence suggests that the cardiovascular system is also primarily affected. Many studies have reported cardiovascular complications in COVID-19 patients, including myocarditis, acute coronary syndrome, heart failure, arrhythmias, and venous thromboembolism[2] COVID-19 also significantly affects patients with pre-existing cardiovascular disease, as it can reduce their cardiorespiratory reserve, worsen pre-existing conditions, or trigger the development of new cardiac issues. Individuals with comorbidities have higher mortality rates, and those with pre-existing cardiovascular disease have an exceptionally high risk[3]. Chinese studies have shown that the overall case fatality rate is 2-5%, while the death rate in patients with cardiovascular complications is 10.5%[4]. Among COVID-19 patients, acute myocardial injury with elevated cardiac troponin levels is the most reported abnormality, with an incidence rate of 8-30%. Arrhythmias are also frequently observed, occurring in around 16.7% of patients, with a higher incidence rate of 44.4% in severe cases compared to 8.9% in mild cases. ECG changes such as prolonged QTc (17.6%), sinus tachycardia (16.9%), first-degree AV block (4.6%), ventricular arrhythmias (1.8%), and sinus bradycardia (0.9%) have been reported[3]. Cardiovascular complications during hospitalization, such as acute cardiac injury (25.9%), heart failure (3.7%), cardiogenic shock (3.7%), acute coronary syndrome (3.7%), and myocarditis (2.8%) have been observed, which can have a detrimental effect on the patient's in-hospital outcome. Viral myocarditis and cardiac injury are the primary reasons for mortality in COVID-19 patients with cardiovascular complications[3].

Given the potential long-term consequences of COVID-19 on cardiovascular health, it is crucial to understand the pathophysiology of the disease better and identify strategies for preventing and managing cardiovascular complications in COVID-19 patients. In this context, the role of cardiac biomarkers in diagnosing and monitoring COVID-19 patients is of particular interest, as it may provide insights into the underlying mechanisms of cardiovascular injury and inform clinical decision-making. Herein, we review the clinical significance of prominent cardiac biomarkers to suggest proposed mechanisms of myocardial injury via the pathogenesis of COVID-19 infection and elucidate the most recent findings to assess the potential utility for risk stratification and managing cardiovascular complications in these patients.

Risk factors and pathophysiology of COVID-19 on the cardiovascular system

COVID-19 patients with pre-existing cardiovascular disease or risk factors appear to be at increased risk of cardiovascular complications and mortality. Age, hypertension, diabetes, obesity, and smoking are among the most commonly reported risk factors for cardiovascular complications in COVID-19 patients[5]. Older age, male gender, and pre-existing cardiovascular disease are consistently associated with a higher risk of cardiovascular complications in COVID-19 patients[6]. More specifically, progression of COVID-19 into a severe and critical stage could be driven by other factors, such as hypertension, diabetes, obesity, chronic lung diseases, heart, liver and kidney diseases, tumors, immunodeficiencies[7].

Several mechanisms have been proposed to explain the cardiovascular complications associated with COVID-19. These include direct viral infection of cardiomyocytes, inflammation-induced myocardial injury, hypercoagulability, and hypoxia-induced damage to the endothelium. The pathophysiology of COVID-19 is complex, and the relative contribution of these mechanisms to cardiovascular complications is not fully understood[8]. SARS-CoV-2 has been detected in the myocardium of COVID-19 patients, and autopsy studies have reported evidence of viral particles and myocardial inflammation. Up to 48% of patients have been reported to have cardiovascular histopathology findings, raising concerns about potential long-term myocardial injury[9]. Cardiac magnetic resonance studies revealed that up to 60% of patients recovered from COVID-19 still have evidence of myocardial inflammation independent of severity and overall course of the acute illness, and time from the original diagnosis, even in those without pre-existing cardiovascular disease[10]. In addition to direct myocardial injury, COVID-19 causes a dysregulated immune response, leading to a cytokine storm and systemic inflammation, which can cause damage to the myocardium[11]. Studies have identified autoantibodies against interferons type I and other autoantibodies promoting thrombosis or antagonizing cytokine signaling[12].

Hypercoagulability is also thought to play a role in the cardiovascular complications. COVID-19 patients have an increased risk of venous and arterial thromboembolism[8]. Several studies have suggested that D-dimer has the potential to be utilized as a biomarker to anticipate the prognosis and results of COVID-19 patients upon admission to medical facilities[13]. In COVID-19 patients, elevated levels of fibrinogen, tissue plasminogen activator (tPA), plasminogen activation inhibitor 1 (PAI-1), ST2(the receptor for interleukin-33), and von Willebrand factor (vWF) were noticed. In addition, the higher levels of t-PA, ST2, and vWF at admission were associated with lower survival rates, and patients with higher initial levels of vWF had more thrombotic events[14].

In conclusion, it is important to identify high-risk COVID-19 patients, including those with older age, male gender, and pre-existing cardiovascular disease, as well as other risk factors such as obesity, diabetes, and chronic kidney disease, to improve outcomes and reduce the burden of cardiovascular complications in COVID-19.

Overview of cardiac markers and their clinical significance in COVID-19

Cardiac markers are biochemical indicators of myocardial injury or dysfunction commonly used in diagnosing and managing cardiovascular diseases [Table 1]. In COVID-19, several cardiac markers have been investigated for their potential utility in identifying patients at increased risk of cardiovascular complications and monitoring disease progression[15].

Table 1: Summary of Main Cardiac Biomarkers and Their Respective Prognostic Roles in COVID-19

Biomarker	Source in Body	Function	Cardiac Significance	Summary of Major Research Findings
Troponin	Cardiac and skeletal muscle	Attachment site for Ca, coordinate actin-myosin cross linking during contraction	Biochemical evidence of myocardial ischemia in ACS, AMI, NSTEMI, STEMI	Higher risk of mortality from COVID-19 with elevated levels; higher negative predictive value for mortality in patients with negative results
Natriuretic Peptides (ANP, BNP) NT-proBNP	Atrial (ANP) and ventricular (BNP) myocytes	Response to cardiac dilation (increased volume and pressures), promote natriuresis, diuresis; counters RAAS activation	Severity or progression of CHF; may be elevated in hypertension or ACS	Higher levels seen in sicker COVID-19 patients; higher RR of cardiac injury as seen as elevated levels
Creatine Kinase (CK-MB)	Cardiac and skeletal muscle	Catalyzes transfer of phosphate groups between ATP and creatine to produce energy for contraction	Biochemical evidence of myocardial ischemia in ACS, AMI, NSTEMI, STEMI	Higher levels observed in more severe or non-survivor cases of COVID-19
Myoglobin	Cardiac and skeletal muscle	Carrier protein, facilitates oxygen delivery to muscle tissues	Biochemical evidence of myocardial ischemia in ACS, AMI, NSTEMI, STEMI	Higher levels observed in more severe COVID-19 infections

Biomarker	Source in Body	Function	Cardiac Significance	Summary of Major Research Findings
Lactate Dehydrogenase (LDH)	Nearly all living cells	Converts pyruvate to lactate and NAD+ to NADH during anaerobic respiration	Biochemical evidence of myocardial ischemia in ACS, AMI, NSTEMI, STEMI	Higher levels observed in more severe COVID-19 infections
D-Dimer	Throughout the body	Fibrin degradation product following fibrinolysis of thrombus from cross-linkage of fibrin proteins	Biochemical evidence of thrombotic state (venous, arterial thromboembolism), ACS, chronic inflammation; may be elevated in other conditions (sepsis, malignancy)	Higher levels observed in more severe COVID-19 infections

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; NT-proBNP, N-terminus pro-Brain Natriuretic Peptide; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase; ACS, acute coronary syndrome; AMI, acute myocardial infarction; NSTEMI, non-ST elevated myocardial infarction; ST Elevated Myocardial Infarction; Ca, calcium ions; CHF, congestive heart failure.

Troponin, a protein found in cardiac muscle cells, is one of the most frequently studied cardiac markers in COVID-19. When there is damage to the myocardium, troponin is released into the bloodstream. COVID-19 patients with elevated troponin levels have a higher risk of cardiovascular complications and mortality. The imbalance of the renin-angiotensin-aldosterone (RAAS) system caused by angiotensin-converting enzyme 2 (ACE2) depletion is thought to be responsible for elevated troponin levels or myocardial damage in COVID-19 patients. This mechanism complicates the clinical course, inflammatory response, endothelial dysfunction, and microvascular damage resulting from COVID-19 infection[16]. Other cardiac markers that have been investigated in COVID-19 include B-type natriuretic peptide (BNP), which is released by the heart in response to increased myocardial wall stress, and D-dimer. This fibrin degradation product is a marker of hypercoagulability[15].

The clinical significance of cardiac markers in COVID-19 has yet to be fully understood and varies depending on the specific marker and the patient population. Several studies have reported elevated levels of cardiac markers in COVID-19 patients with severe disease or those who develop cardiovascular complications, suggesting they are helpful for risk stratification and identifying patients who benefit from more aggressive management[16,17]. In addition to their potential clinical utility, cardiac markers may provide

insights into the underlying mechanisms of cardiovascular injury in the progression of COVID-19. For example, elevated troponin levels in COVID-19 patients may indicate direct viral myocardial injury or inflammation-induced damage. In contrast, elevated BNP levels may suggest myocardial wall stress and the subsequent development of heart failure[17]. However, using cardiac markers in COVID-19 remains controversial, as some studies have reported high rates of false positives and variability in test results[18].

Several cardiac markers have been investigated in COVID-19 patients, including troponins, natriuretic peptides, creatine kinase (CK), myoglobin, and lactate dehydrogenase (LDH). While these markers provide unique information about cardiac injury and function, their performance characteristics in COVID-19 patients may vary.

Troponin is a protein complex in cardiac and skeletal muscle integral to myocardial contractility[19]. Troponins are widely used as a biomarker for heart muscle damage They are released into the bloodstream when cardiac myocytes are injured, making them a valuable diagnostic tool for cardiac events such as infarction. Troponin levels are typically elevated in patients with acute coronary syndrome (ACS), such as unstable angina and myocardial infarction. However, they may also be seen in patients with heart failure and other types of cardiac injury[20]. SARS-CoV-2 virus is an established cause of myocardial damage and subsequent complications, including myocarditis and pericarditis, especially in elderly patients and those with prior cardiovascular risk factors. A high level of high-sensitivity troponin (hs-cTn) is an adverse prognostic indicator when associated with infectious-inflammatory heart damage, such as in cases of myopericarditis[21]. De Michieli et al[22]. performed a study to assess the use of hs-cTn for risk stratification in 367 COVID-19 patients[22]. The study found that 46% of COVID-19 patients had myocardial injury identified through hs-cTn testing, and these patients had a higher risk of mortality and major adverse events such as respiratory failure, cardiac arrest, and shock. Baseline and maximum hs-cTn levels were independent predictors of major adverse events. A single hs-cTn level of <6 ng/L at presentation identified patients with a more favorable prognosis. [22] Malik et al.[23], performed a meta-analysis of ten studies with 3982 hospitalized COVID-19 patients. They found that patients with elevated troponin I levels had higher odds of poor outcomes, such as admission to intensive care units, oxygen saturation <90%, invasive mechanical ventilation, and in-hospital mortality[23]. More recently, in April 2023, Losiniecki et al.[24] published a study that included 65,580 COVID-19 patients from a single healthcare system to assess the utility of measuring troponin I level in the first 24 hours of admission for predicting in-hospital mortality. Their results showed that a negative troponin I value was associated with reduced odds of death during admission and cardiac complications. The negative predictive value of a negative troponin value for all-cause in-hospital mortality was 85.7%[24]. Despite being widely considered the gold standard cardiac biomarker for diagnosing the myocardial injury and increasing evidence of elevation in COVID-19 patients, the specificity of troponins in COVID-19 patients may be limited, as elevated levels can also occur in patients with respiratory failure or sepsis[21–

[23,25,26]. Troponin increases in COVID-19 patients may be related to chronic myocardial injury due to comorbidities or acute nonischemic myocardial injury[25]. Umeh et al. conducted a retrospective study of COVID-19 patients with elevated troponin levels and found that elevated levels without ST-segment elevation on ECG were not independently associated with increased mortality in hospitalized COVID-19 patients[27]. Thus, the clinical history, troponin levels, and cardiac ultrasound findings can help predict myocardial injury, risk stratifying these patients, and thereby improving patient outcomes[21].

The natriuretic peptides (NPs) are hormones the atrial and ventricular myocytes secrete to regulate fluid and electrolyte balance and blood pressure. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted in response to the stretching of the cardiac chambers due to increased blood volume or pressure to promote sodium and water excretion by the kidneys. C-type natriuretic peptide (CNP) is mainly produced by endothelial cells to regulate vascular tone[28]. Natriuretic peptides have been extensively studied as biomarkers for various cardiovascular conditions, including heart failure, hypertension, and acute coronary syndrome diagnosis and progression[29 30]. Elevated levels of BNP have been observed in COVID-19 patients with cardiac complications[30]. In COVID-19 patients, elevated levels of natriuretic peptides have been reported and are associated with increased mortality. However, natriuretic peptides may be elevated in COVID-19 patients due to factors other than heart failure, such as acute respiratory distress syndrome (ARDS) or pulmonary embolism (PE)[31].

Benhuri et al., performed a meta-analysis to compare natriuretic peptide levels in patients with severe COVID-19 versus those with non-severe COVID-19. They identified nine studies with 1,575 Chinese patients. Compared to those with non-severe COVID-19, the severe cases had significantly higher levels of BNP (mean difference was 70 pg/mL) and NT-proBNP (mean difference was 519 pg/mL)[32]. Another meta-analysis by Dalia et al.[33] collected data on 5967 COVID-19 patients from 20 studies to investigate the impact of congestive heart failure (CHF) and cardiac biomarkers on outcomes[33]. The mean difference in Troponin-I, CK-MB, and NT-proBNP levels was higher in deceased and severely infected patients. Pre-existing CHF and hypertension were also associated with higher in-hospital mortality. The RR of in-hospital mortality was 2.35 and 1.52 among patients with pre-existing CHF and hypertension, respectively[33]. Both meta-analyses confirmed that cardiovascular risk factors are key contributors to the development of severe illness in COVID-19, and elevated natriuretic peptide levels may be helpful to biomarkers to identify severe cardiac damage and failure in these patients[32,33].

Creatine kinase-MB (CK-MB) is a subtype of creatine kinase. This enzyme catalyzes the transfer of phosphate groups between ATP and creatine, producing phosphocreatine and ADP, which are used as energy sources for muscle contraction. It may be used as a diagnostic marker for acute myocardial infarction (AMI), although troponin measurements have widely replaced this. Elevated levels of CK-MB are typically observed within 4-6 hours of the onset of symptoms and peak within 18-24 hours. CK-

MB levels return to normal within 48-72 hours after the infarction. Nonetheless, CK-MB testing is usually done in conjunction with other cardiac biomarkers, such as troponin, to aid in the diagnosis of AMI and to guide the treatment and management of the patient, especially in cases of reinfarction following initial resolution[34].

Zinellu et al.[35], conducted a meta-analysis to assess the association between CK-MB and COVID-19 patients. They included 55 studies involving 11,791 COVID-19 patients in their analysis. The results demonstrated that CK-MB concentrations were significantly higher in patients with high disease or non-survivor status than those with low severity or survivor status. The rate of patients with CK-MB values above the normal range was also higher in the high disease severity or non-survivor group (RR = 2.84). In other words, elevated CK-MB concentrations were significantly associated with severe disease and mortality in COVID-19 patients, suggesting its potential utility for risk stratification in this population[35].

Myoglobin and lactate dehydrogenase (LDH) are additional cardiac markers that can be used to diagnose and monitor cardiac myocyte damage. Myoglobin is a protein found in cardiac and skeletal muscle tissue and is released into the bloodstream when heart cells are damaged. Elevated levels of myoglobin in the serum can be detected within a few hours of the onset of an AMI. However, its usefulness as a diagnostic marker is limited by its low specificity due to its presence in other tissues[36]. Similarly, LDH is an enzyme found in many tissues, including the heart, and is released into the bloodstream when cells are damaged. LDH testing can help detect AMI, as elevated levels of LDH in the serum can persist for several days after the onset of symptoms. However, LDH testing is less specific than other cardiac biomarkers, such as troponin and CK-MB, since it can be elevated in a variety of other conditions[37].

A study by Ergenc et al., investigated lactate dehydrogenase (LDH) isoenzymes levels in 111 hospitalized COVID-19 patients to identify the tissue responsible for LDH elevation[37]. The severity of lung involvement was scored using computed tomography (CT). The study found that higher levels of LDH3 were an independent risk factor for COVID-19 deterioration, and LDH elevation was mainly due to lung, liver, and muscle damage. The study suggests that LDH levels, particularly LDH3, may be useful in predicting COVID-19 severity[37].

Severe acute respiratory syndrome coronavirus-2 may cause a post-viral condition known as post-COVID-19 syndrome or long-COVID.

Yong et al.[38], conducted a meta-analyze to assess twenty-four biomarkers from 23 studies in Long-COVID. Higher levels of C-reactive protein, D-dimer, lactate dehydrogenase, and leukocytes were found in COVID-19 survivors with post-COVID-19 syndrome than in those without post-COVID-19 syndrome. After sensitivity analyses, lymphocytes and interleukin-6 were significantly higher in post-COVID-19 syndrome cases than in non-post-COVID-19 syndrome cases. No significant differences were noted in the remaining biomarkers investigated (e.g., ferritin, platelets, troponin, and fibrinogen). Subgroup analyses suggested the biomarker changes were mainly driven by post-COVID-19 syndrome cases diagnosed via the manifestation of organ abnormalities rather

than symptomatic persistence, as well as post-COVID-19 syndrome cases with a duration of fewer than six months or more[38].

Overall, while these cardiac markers provide unique information about cardiac injury and function, their performance characteristics in COVID-19 patients may vary. Troponins and natriuretic peptides are the most investigated markers in COVID-19 patients, with elevated levels associated with increased mortality. However, using these markers in diagnosing and monitoring COVID-19 patients is challenging, and further research is needed to determine the optimal use of each marker in this population.

Conclusion:

Several cardiac markers have been investigated in COVID-19 patients, including troponins, natriuretic peptides, creatine kinase (CK), myoglobin, and lactate dehydrogenase (LDH). Troponins, specifically troponin I, have been widely studied and found to be elevated in COVID-19 patients with myocardial injury, indicating a negative prognostic indicator and association with poorer outcomes. Elevated levels of Natriuretic peptides, such as B-type natriuretic peptide (BNP), have been noted in severe COVID-19 cases and are also associated with higher mortality rates. However, it is important to consider that elevated natriuretic peptide levels in COVID-19 patients may also be influenced by factors other than heart failure. CK-MB, a subtype of creatine kinase, has been found to have significantly higher concentrations in COVID-19 patients with high disease severity or non-survivor status, suggesting its potential as a biomarker for risk stratification in this population. Myoglobin and lactate dehydrogenase (LDH) are additional cardiac markers that can indicate heart muscle damage, but their specificity in COVID-19 patients may be limited. Overall, these cardiac markers provide valuable diagnostic and prognostic information about cardiac injury and function in COVID-19 patients, but their performance characteristics and interpretation should be considered in the context of the individual patient and in conjunction with other clinical assessments.

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The authors declare that they have no competing interests.

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All Authors have contributed equally to the manuscript by gatheringinformation, rigorously reviewing available literature, draftingthe manuscript, and providing critical reading and feedback to oneanother.

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