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# Role of Cardiac Biomarkers in COVID-19: What Recent Investigations Tell Us?

Shahzad Khan, MBBS, PhD[a], Sahibzada Tasleem Rasool, MBBS, PhD[b], and Syed Imran Ahmed, MClinPharm, PhD[c]

*From the* [a] *Department of Pathophysiology, Wuhan University School of Medicine, Hubei, Wuhan, China,* [b] *School of Medicine, King Faisal University, Al-Ahsa, Kingdom of Saudi Arabia and* [c] *College of Science, School of Pharmacy, University of Lincoln, Lincoln, United Kingdom.*

**Abstract:** ***Purpose of review*: Although the respiratory system is the main target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is evident from recent data that other systems, especially cardiovascular and hematological, are also significantly affected. In fact, in severe form, COVID-19 causes a systemic illness with widespread inflammation and cytokine flood, resulting in severe cardiovascular injury. Therefore, we reviewed cardiac injury biomarkers' role in various cardiovascular complications of COVID 19 in recent studies. *Recent findings*: Cardiac injury biomarkers were elevated in most of the complicated cases of COVID-19, and their elevation is directly proportional to the worst outcome. Evaluation of cardiac biomarkers with markers of other organ damage gives a more reliable tool for case fatalities and future outcome. *Summary*: Significant association of cardiac biomarkers in COVID-19 cases helps disease management and prognosis, especially in severely ill patients. (Curr Probl Cardiol 2021;46:100842.)**

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## Introduction

Cardiac biomarkers are mainly a measurable protein produced as a result of some pathological processes in the cardiovascular system. To be clinically useful, they ought to be of high sensitivity, specificity, and cost-effectiveness. In clinical practice, cardiac biomarkers are now a frequently used technique to identify the presence and progression of cardiovascular diseases.[1••-3] In current clinical practice, cardiac biomarkers are routinely used in combination with other diagnostic tools such as electrocardiography, echocardiography, and radiodiagnostics. The prime objective of cardiac biomarkers in cardiology is mainly an adjuvant diagnostic technique which in many circumstances could be of extremely useful in the care of the patient.[2]

Cardiac biomarkers are important in various cardiovascular conditions such as Congestive heart failure (CHF), ischemic heart diseases (IHD), diabetic cardiomyopathy (DCM), acute coronary syndromes (ACS), and acute myocardial infarction (AMI). Various notable cardiac biomarkers include natriuretic peptides, like b-type natriuretic peptide (BNP), N-terminal pro-b- type natriuretic peptide (Nt-proBNP) and mid regional proatrial natriuretic peptide (MR- pro ANP), cardiac troponin T (CTnT), cardiac troponin I (CTnI), soluble source of tumorigenicity 2 (sST2), galectin-3 (Gal-3), and growth differentiation factor-15 (GDF-15). Recently various micro ribonucleic acids (miRNAs) are also successfully used as cardiac biomarkers. Some important cardiac biomarkers and their importance is shown in Table 1.

## COVID-19 Infection and Cardiovascular Involvement

Although the SARS novel coronavirus (SARS-CoV-2) or COVID-19 is a viral illness in which lungs are the primary and severely affected target as the name suggests but in fact, it is a system illness in which most of the organ systems are affected with varying degree. The severity of the disease depends on factors such as the age of the patient, immune status, and preexisting comorbidities. The disease gradually progresses and evolves, and the signs and symptoms depend on the viral infiltration and replication and host immune response. The disease progression over time can be divided into 3 stages, early infection stage, a pulmonary stage, and a severe hyper inflammation stage in which systemic complications are likely to result (Table 2). In the first stage, viral infiltrate and replicate, and lymphopenia is observed. Later as the disease progresses, lung involvement increases, resulting in various respiratory signs and symptoms. In this stage, radiographic imaging can also detect lung involvement. As the disease progresses, the body's immune system tries to

**TABLE 1.** Important cardiac biomarkers, their source, and notable functions

| Biomarker | Source | Notable function | Pathogenetic relevance |
|---|---|---|---|
| BNP and NT-proBNP | Cardiomyocytes of ventricle | Natriuresis, diuresis, vasodilation, inhibition of renin and aldosterone | Cardiac biomechanical stress |
| cTnT and cTnI | Cardiomyocytes | Cardiac muscle contraction, works with calcium and actin filaments | Cardiac myocyte necrosis |
| ST2 and sST2 | Cardiomyocytes, Endothelial cells, Fibroblasts | Cardioprotective, prevent myocardial fibrosis, and cardiomyocyte apoptosis | Cardiomyocytes inflammation |
| GDF-15 | Cardiomyocytes | Cardioprotective, inhibits apoptosis of cardiomyocytes, involve in cardiomyocyte hypertrophy | Cardiomyocytes inflammation |
| Galectin-3 | Macrophages, Neutrophils, Endothelial cells, Epithelial cells | The proliferation of myofibroblast, promote fibrogenesis, tissue repair, and myocardial remodeling | Cardiomyocytes fibrosis |
| MGP species | Vascular smooth muscle cells | Vitamin K-dependent potent inhibitor of vascular calcification, levels with decreased vitamin K is associated with increased intimal calcification and increased CVD risk | Cardiovascular calcification and injury |

BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; CTnT, cardiac troponin T; GDF-15, growth and differentiation factor-15; MGP, matrix gla protein; NT-proBNP, N-terminal proBNP; sST2, soluble ST2; ST2, suppression of tumorigenicity 2.

control and limit the viral damage, but unfortunately, this results in an exaggerated hyperinflammatory response, causing extensive collateral tissue damage and severely affecting many organs. In this stage, cardiac and vascular systems are no exception, and cardiovascular injury can be severe and fatal.[4••-6•]

## The Pattern of Cardiovascular Involvement in COVID 19

There are various patterns of cardiovascular involvement in COVID 19. First of all, cardiovascular disease present as pre-existing comorbidity which becomes apparent or becomes more complicated and decompensated during COVID 19. Second cardiovascular system involvement results due to systemic inflammatory response during the course COVID

**TABLE 2.** Various stages of COVID 19[4••,5]

| Stages of COVID 19 | | |
|---|---|---|
| **Early infection stage** | **Second pulmonary stage** | **Late stage** |
| Characterized by viral infiltration and replication | Characterized by lung involvement | Characterized by systemic involvement |
| Clinical features may be mild and nonspecific | Pulmonary signs and symptoms are present | Systemic inflammation causes multiple organ damage especially cardiovascular system |
| Lymphopenia can be present | Chest radiography can detect abnormality | Cardiac biomarkers, inflammatory biomarkers, and other systemic investigation are positive |

**TABLE 3.** Cardiovascular comorbidities and mortalities in COVID 19[23••,24••,69••,70••-72••]

| Cardiovascular comorbidities and mortalities in COVID 19 |
|---|
| Coronary artery disease 10% to 17% |
| Hypertension from 35% to 57%, |
| Congestive heart failure (CHF) 6% to 7% (non-ICU patients) |
| Congestive heart failure (CHF) 42.9% (ICU patients) |
| COVID-related deaths having underlying CVD 30% to 35% |

19. The third cardiovascular system can be affected during treatment due to the side effects of some medication or secondary hospital-acquired infections and complications. Table 3 shows significant cardiovascular comorbidities and mortalities found in COVID 19.

## *Covid-19 and Cardiovascular Diseases*

Severe acute respiratory syndrome coronavirus 2 or (SARS-CoV-2) is responsible for the coronavirus disease of 2019 or (COVID-19). COVID 19 can affect the cardiovascular system (CVS) in a variety of ways. COVID 19 associated cardiovascular diseases (CVD) can be classified as primary CVD (resulting from direct viral injury) such as arrhythmias, acute coronary syndrome (ACS), and myocarditis and secondary CVD (resulting from an exaggerated systemic inflammatory response) such as a cardiac injury during multiple organ failure (MOF) in septic shock of SARS-CoV-2. There is considerable overlap between primary CVD and secondary CVD, which makes the distinction very difficult, especially when the disease is severe or the disease course is rapid, or the patient is older or the presence of other comorbidities.[7] We will briefly discuss these CVD and then present the importance of cardiac biomarkers in the diagnostics and therapeutics of COVID 19.

## Acute Coronary Syndrome (ACS)

Investigations have shown that viral infections are associated with coronary plaque inflammation, may promote plaque rupture, and can initiate thrombosis. It is believed that COVID19 is likely to behave likewise and patients with COVID19 can present with the acute coronary syndrome (ACS).[8-10] The COVID 19 patients can present with non-ST segment elevation (NSTEMI) as well as with ST-segment elevation (STEMI). However, COVID-19 patients may present without classic symptoms of angina. Alternatively, other conditions may mimic ACS, such as myocarditis and pericarditis. Therefore, a complete investigation with electrocardiography (ECG), echocardiogram, and cardiac biomarkers is mandatory.[11••,12••] In a small-scale study, COVID 19 33% of patients presented with chest pain and 78% with ST-segment elevation. On echocardiography, 35% of them had regional wall motion abnormality, and half of them had to go through coronary angiography in which 67% confirmed with coronary occlusion.[13]

## Acute Myocardial Injury

The possible mechanism of cardiac injury is believed to be through multiple overlapping factors such as severe inflammatory response with uncontrolled cytokine activation. Atherosclerotic plaque can destabilize and rupture and can initiate a thrombo-embolic cascade resulting in myocardial infarction (MI). Myocardial oxygen supply and demand mismatch, arrhythmia, and electrolyte abnormality can all lead to myocardial injury.

Since SARS-COV-2 enter through angiotensin-converting enzyme 2 (ACE 2) receptors, which are abundant in lungs, myocytes, and vascular endothelial cells,[14••] which can result in direct vascular endothelial cells and cardiomyocytes injury.[15••,16••] This hypothesis is backed by recent histopathologic proofs, which confirmed that the SARS-CoV-2 invasion resulted in endothelial cells inflammation, microcirculatory disturbances, and tissue ischemia.[17,18••] There are mixed data about the presence of SARS-CoV-2 in cardiac tissue on histopathology analysis. Some data show endomyocardial biopsy (EMB) analysis did not find the SARS-CoV-2 even in the presence of diffuse myocardial edema and diffuse T-lymphocyte infiltration.[19••,20••]

In contrast, a recent autopsy study of cardiac tissue of 39 cases from Germany found SARS-CoV-2 in 24 of 39 patients (61.5%) with a viral load above 1000 copies per $\mu$g RNA in 16 of 39 patients (41.0%). The study also reported a higher cytokine response and expression of many proinflammatory genes in these 16 patients compared with 15 patients without any SARS-CoV-2 in the heart. This result indicates that severe cardiac injury is more likely in cases with higher virus load. The same study revealed that the

localization of SARS-CoV-2 was most likely in interstitial cells or macrophages of myocardial tissue rather than the cardiomyocytes.[21••] Alternatively, other EMB studies also found SARS-CoV-2 in cardiac macrophages but did not find cardiomyocytes.[22••] According to reports, 25% of COVID 19 patients have a myocardial injury and show elevated cardiac troponin (CTn).[23••-26••] According to studies, the rapid increase of cardiac biomarkers, including CTn, CRP (C-reactive protein), D-dimer, NT-probrain natriuretic peptide (NT-pro BNP) especially during the late course of disease indicate poor prognosis with case fatality.[25]

## Heart Failure

Congestive heart failure (CHF) patients are at higher risk of getting SARS-CoV-2 infection, an ominous sign because the severe respiratory disease itself can result in CHF decompensation.[27] On the other hand, patients with COVID 19 can get new onset congestive heart failure (CHF) as retrospective data have been shown from various studies from China and the USA. There may be various causes of CHF in COVID 19 victims. In some cases, cardiomyopathies have been reported although the exact pathogenesis of ventricular failure has to be explored.[25••,28••]

Increased levels of serum brain natriuretic peptide (BNP) may indicate the contribution of cardiac failure in pulmonary edema frequently seen in COVID 19 patients, which is mainly because of acute respiratory distress syndrome (ARDS).[29] In contrast, some cases of COVID-19 have shown raised BNP levels without significant ventricular failure.[25••,30••] Therefore, it is essential to evaluate cardiac contribution during the treatment of pulmonary edema, which may be overlooked. During the treatment of CHF, Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) should not be discontinued until there is proof of shock or acute kidney injury in COVID as directed by The American College of Cardiology, American Heart Association and Heart Failure Society of America.[31••] Since ACE-2 receptors are used by SARS-COV-2 to penetrate human cells, there is a debate about the use of ACEI and ARB (ACEI and ARB use can result in the upregulation of ACE-2 receptors).[32••] Despite this connection, recent studies have not found any association between the ACE inhibitor and ARB with COVID-19.[33••,34••]

## Shock and Multisystem Organ Failure

Shock with or without multisystem organ failure (MOF) is a hallmark of severe COVID-19. The shock can be multifactorial, usually septic shock, though the cardiogenic shock is also commonly seen if CHF or

myocarditis is also present.[31••] Septic shock frequently results in disseminated intravascular coagulation (DIC), which is an important reason for the high incidents of thromboembolism seen in COVID 19.[35••]

## Thromboembolic Events in COVID 19

Patients with COVID-19 infection are at high risk for venous and arterial thromboembolism in COVID 19. In our previous article, we have briefly discussed the factors leading to increased thromboembolism and heparin use in this.[35••] These factors include severe inflammatory response, cytokine storm, and widespread endothelial damage.[36••,37••] Various studies from Italy, China, USA, and other parts of the world have reported increased thromboembolic events in admitted patients of COVID 19. Many studies have found thromboembolism in COVID 19 autopsies as well.

Autopsies report of 80 deceased SARS-CoV-2 positive patients from Hamburg (Germany), reported deep vein thrombosis in 40% of patients. This study has claimed to be the biggest autopsy study of SARS-CoV-2-infected patients (Until April 2020).[38••] A case series from Italy reported at least one thromboembolic event in 28 out of 362 hospitalized patients of COVID-19 (7.7%) while the rate was 31% in ICU patients.[39••,40••] Subsequently, over activation of coagulation cascade can result in various unwanted thromboembolic such as cerebrovascular accident (CVA), disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT) and pulmonary embolism (PE) even with no or few predisposing factors present before.[40••,39••,41••] Pulmonary embolism (PE) has been mentioned as the most frequently seen complication and carries a higher risk of death[40••,39••] because it can increase ventricular strain, lead to cor pulmonale, and degenerate compensated CHF. For better evaluation of thromboembolic events, estimation of cardiac biomarkers is especially helpful in these settings for risk stratification.[42••-44•] On the other hand, estimation of D-dimer levels ($>1$ $\mu$g/L) and fibrin degradation products are also very helpful and are strongly associated with in-hospital mortality.[36••,25••]

## Arrhythmias

There are reports available that show COVID 19 can result in arrhythmias, especially where the coexisting myocardial injury is also present. This verdict is proved by a study that showed the incidence of malignant arrhythmias were higher in subjects with proven myocardial injury (17.3% versus 1.5%).[24••] Various forms of arrhythmias have been

reported in COVID 19 which include nonshockable such as asystole (89.7%), pulseless electrical activity (4.4%), as well as shockable (5.9%) such as ventricular fibrillation and pulseless ventricular tachycardia.[45••]

Arrhythmias in COVID 19 may be due to side effects of drug treatment such as hydroxychloroquine, which is known to prolong corrected QT Interval (QTc). Prolonged QTc is associated with ECG findings called Torsades de Pointes, which can potentially degenerate into ventricular fibrillation, associated with higher mortality rates.[46••-48••] The risk can be further increased if concomitant macrolides (especially azithromycin) or fluoroquinolones are used (due to adverse drug reaction)[47••,46••,49] or if these drugs are given without dose adjustment in patients with renal insufficiency.[50••,51••] Furthermore, electrolyte monitoring is equally essential because electrolyte imbalance, especially hypokalemia in COVID 19, can significantly increase the risk of arrhythmias. One reason for this may be because SARS-CoV-2 enters cells through ACE-2 receptors, and increased availability of angiotensin 2 can result in excess excretion of potassium leading to hypokalemia.[52••]

## Use of Cardiac Biomarkers in COVID 19

### *Cardiac Biomarkers and COVID 19 Pneumonia*

Cardiac biomarkers can play an essential role in the diagnosis, management, and prognosis of COVID 19. However, usually, cardiac biomarkers are increased in various cardiac pathologies, but they can be increased in some pulmonary diseases as well. If there are preexisting lung comorbidity, which is frequently present in COVID 19 patients, cardiac biomarkers may indicate a mixed pathology. Previous studies have shown increased cardiac biomarkers in various lung pathologies. For example, a study showed, elevated Nt-proBNP at the time of discharge in chronic obstructive pulmonary disease (COPD) patients, was associated with increased risk of re-hospitalization and mortality. Additionally, CTnT is also linked with poor prognosis in pulmonary embolism[53] and with stable ischemic heart disease of type2-diabetes mellitus(T2DM) patients.[54]

A study of 730 community-acquired pneumonia (CAP) patients showed that biomarkers pro adrenomedullin (pro-ADM), proendothelin-1, troponin, proBNP, and IL-6 levels were significantly increased in patients who also suffered cardiovascular events during the early (1 month) and late (up to 1 year) follow up period. These cardiac events included acute coronary syndrome, acute myocardial infarction, unstable angina, new or worsening arrhythmia, atrial fibrillation, atrial flutter,

acute heart failure, cerebrovascular accident, stroke, and transient ischemic attack. This study showed the importance of cardiac biomarkers in managing long-term cardiovascular complications in CAP patients.[55••]

## Cardiac Biomarkers and COVID 19 Cardiac Diseases

As discussed earlier, multiple preexisting or new-onset cardiac pathologies in COVID-19 can lead to increased cardiac biomarkers (especially in ICU patients).[56••-58••,12••] These comorbidities are also known as acute COVID−19 cardiovascular syndrome (ACovCS). They can be due to myocardial oxygen-energy demand-supply mismatch, due to direct viral infection, due to thromboembolic complications, due to endothelial injury or many other factors mentioned earlier.[35••,19••] Researchers have investigated the role of cardiac biomarkers in COVID 19 disease. For instance, a recently published study revealed higher troponin (CTn) levels among critically ill patients and in nonsurvivors compared to patients who were not critically ill or survived. The same study also reported significantly elevated CK in nonsurvivors. Another finding from the same study showed that although LDH was significantly higher in critically ill versus not critically ill, LDH was not significantly higher in COVID 19 survivors versus nonsurvivors. Surprisingly, BNP was not significantly higher in any of the groups of patients, whether critically ill or not critically ill or survivors or nonsurvivors. These results suggest that elevated CTn and CK in COVID-19 patients could be due to direct myocardial injury and can be used to estimate mortality risk.[57••] A study from Wuhan, China, reported higher creatinine kinase-myocardial band (CK-MB), CK, lactate dehydrogenase (LDH), myoglobin, and TnI among nonsurvivors when compared with survived. In this study, cardiac biomarkers were comparatively raised in patients above 65 years with preexisting CVD than those who were younger or without prior CVD.[59••] Several other investigations have also shown a significantly higher risk of death in COVID 19 patients with elevated circulating cardiac biomarkers.[60••-62••,58••]

As discussed earlier, that preexisting cardiac disease can adversely affect the outcome in COVID19. A recently conducted meta-analysis of 20 individual studies has confirmed the unfavorable influence of preexisting CHF in the prognosis and survival of COVID 19 patients. The study found that of CTnI, CK-MB, and NT-proBNP was higher in deceased and severely infected patients and suggested that higher NT-pro BNP and CK-MB levels in COVID-19 patients are associated with worse outcomes.[63••] Another meta-analysis of 21 studies with 3377 patients studied not only the pattern of cardiac biomarkers elevation in COVID 19 but also various hematological and biochemical biomarkers. This study revealed elevated cardiac

biomarkers (creatine kinase-MB and cardiac troponin I) in patients with both severe and fatal COVID-19. The study further reported that nonsurvivors of COVID 19 had significantly elevated cardiac troponin levels at the presentation which could be due to viral myocarditis or be a part of multiple organ damage secondary to septic shock because liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase), renal biomarkers (blood urea nitrogen, creatinine), and coagulation imbalances (increased prothrombin time and D-dimer) which show a picture of multiple organ damage were also raised simultaneously.[64••]

Proofs of the strong association of troponins (CTnI and CTnT) with COVID19 have not been found. A study from the Netherlands[65] between April 1 and May 12, 2020, totaling 51 patients found no relation between elevated CTnT, NT-proBNP, and ventricular dysfunction. This finding supports the results of another investigation,[26••] which found that the cTnI level was only slightly increased in all COVID 19 patients.[66••] However, the study found that cTnI levels were significantly increased in severe COVID 19 cases compared to milder COVID 19 cases. Hence the study strongly suggested serial measurement of CTnI and CTnT to identify patients with a possible cardiac injury during COVID-19.[26••]

A unique cardiac mortality prediction model in COVID 19 has been proposed in a recent meta-analysis of 17,794 patients.[67••] This model recommends combined evaluation of aspartate aminotransferase (AST) with CTnI and advanced age and suggests that high CTnI (more than 13.75 ng/L) combined with either advanced age (more than 60 years) or elevated AST level (more than 27.72 U/L) is the best model for prediction of poor outcomes. Since cardiac injury is frequently a part of multiorgan damage of septic shock of SARS-CoV-2, this combined assessment of cardiac injury biomarkers with liver injury biomarker and advanced age seems plausible. The role of cardiac biomarkers in the better prediction of future mortality has been investigated in a recent study. The study was conducted on 3219 SARS-CoV-2 positive patients and observed the role of cardiac biomarkers in an effective prognosis of 28-day mortality. This study found cardiac biomarkers very useful and suggested much lower cutoff levels of hs-cTnI, NT-proBNP, CK-MB, and myoglobin than the current reference standards for the prognosis of mortality in COVID-19 patients.[68••]

## Conclusion

After reviewing results from most recent studies on COVID19 patients, it is evident that direct or indirect cardiac involvement is not uncommon in COVID19. The degree of cardiac injury is variable, and

severity depends on the age of the patient, preexisting cardiac disease, and the pathophysiology involved in cardiac injury. Cardiac biomarkers increase in most of the COVID19 patients, though their prognostic power for worst outcome increases with the severity of the disease, and lower threshold of cardiac biomarkers would be applicable for diagnosis and prognosis. A combined evaluation of cardiac biomarkers with markers of other organ damage is likely to give a better picture of the future outcome because the septic shock of SARS-CoV-2 is frequently associated with multiorgan damage. A better description of the role and use of cardiac biomarkers in COVID 19 is quite likely in the future.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance.
- •• Of major importance.

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