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Review

Cite this article: Srour L, Ismail J, Zareef R, and Arabi M (2024) Cardiac biomarkers in COVID-19: what did we learn? *Cardiology in the Young* **34**: 1636–1644. doi: [10.1017/S1047951124025484](https://doi.org/10.1017/S1047951124025484)

Received: 23 February 2024
Revised: 12 May 2024
Accepted: 22 May 2024
First published online: 13 September 2024

Keywords: COVID-19; cardiac biomarkers; cardiovascular complications; SARS-CoV-2

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Abstract

Objectives: COVID-19, caused by the SARS-CoV-2 virus, has generated a global pandemic with a wide range of clinical manifestations. Cardiovascular complications are frequently observed in individuals with COVID-19, particularly those with preexisting cardiovascular risk factors or diseases. Cardiac biomarkers, including troponin, natriuretic peptides, and inflammatory markers, play a vital role in risk stratification, diagnosis, monitoring, and prognosis in COVID-19 patients. These biomarkers provide valuable insights into cardiac injury, myocardial stress, inflammation, and the prediction of adverse cardiovascular outcomes. This review aims to provide better understanding of how Cardiac biomarkers correlate to clinical manifestation of COVID-19. **Methods:** We retrieved studies from PubMed, Medline, and Google Scholars that included results on cardiac biomarkers in COVID-19. Total of 14 studies were reviewed. **Results:** 8 studies showed evidence of poor progression of the disease when there is increased troponin. 6 studies out of the 14 mentioned in this review showed positive correlation between mortality and elevation in cardiac biomarkers. This shows the significance of cardiac biomarkers in predicting the mortality in patients with COVID-19. **Conclusion:** It was shown that elevated cardiac biomarkers were associated significantly to poor outcome of covid-19 infection. The outcomes that were linked to increased cardiac biomarkers included increased length of hospitalization, need of life sustaining treatment, myocarditis, invasive and non-invasive respiratory support, and even death were linked to elevated cardiac biomarkers levels.

Introduction

Coronavirus disease 2019 (COVID-19) is a disease, caused by the severe acute respiratory coronavirus virus 2 (SARS-CoV-2), that emerged recently in 2019 and initiated a worldwide pandemic. Several hundred million cases were reported worldwide with a variety of symptoms. Clinically patients with COVID-19 can present in a range of clinical presentations, from being asymptomatic to having severe viral pneumonia and potentially progressing to cytokine storm (CS), acute respiratory distress syndrome, and death.¹ SARS-CoV-2, belonging to the coronavirus family, is a newly discovered strain characterized by its enveloped structure and single-stranded positive-sense RNA composition. It shares its viral family with other notable members such as Severe Acute Respiratory Syndrome Coronavirus-1 and Middle East respiratory syndrome-related coronavirus (SARS-CoV-1 and MERS-CoV).¹

Soon after the beginning of the pandemic, it became apparent that the degree of illness is associated with the presence of cardiovascular risk factors and pre-existing diseases.² Furthermore, it was observed that COVID-19 infection triggers elevation in cardiac biomarkers in hospitalized COVID-19 patients.³ Indeed, cardiac involvement may worsen the clinical outcomes for individuals with pre-existing cardiovascular disease (CVD). Direct and indirect consequences of SARS-CoV-2 infection have been attributed to the adverse cardiovascular effects observed in COVID-19,² which significantly contribute to the overall mortality and morbidity associated with COVID-19. Extensive studies have supported this notion. For example, a study evaluating risk for CVD after surviving COVID-19 revealed that the risk to develop heart failure (HF) was as high as 1.72 at 12 months following COVID-19. Notably, the incidence rate of HF was higher following the COVID-19 pandemic compared to the pre-pandemic numbers, raising serious concerns about a causal relationship between COVID-19 and the increased HF incidence.⁴

The cardiovascular implications associated with COVID-19 can be due to various mechanisms. Primarily, systemic oxidative stress caused by the low oxygen level in SARS-CoV-2 leads to damage of cardiomyocytes, as do mitochondrial impairment and intracellular acidosis.⁵ Secondly, dysregulation of the renin-angiotensin-aldosterone system can occur due to ACE2 receptor involvement in the cardiovascular system, leading to ventricular remodelling. Moreover, during COVID-19 infection, there is a prevalence of mononuclear inflammatory

infiltrate cells in the cardiac interstitial space.⁶ Lastly, both local and systemic immune system effects may contribute to impaired perfusion due to microvascular damage.

An association was made between elevated cardiac biomarkers and the severity of COVID-19. These cardiac biomarkers include high-sensitivity troponin I (hs-TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and D-dimer.⁷ Up to 36% of patients hospitalized for COVID-19 showed increased cardiac biomarkers, which were identified as independent predictors of unfavourable clinical outcomes in COVID-19 patients.⁸

In this review paper, by examining the available literature, we aim to understand the association between cardiac biomarkers and COVID-19-related cardiovascular complications. Furthermore, we will explore the mechanisms underlying the cardiac involvement observed in COVID-19, shedding light on the pathophysiological processes that contribute to the development and progression of CVD in COVID-19 patients.

Methods

We conducted a thorough and up-to-date investigation into the biomarkers associated with CVD in SARS-CoV-2 infection. Our research encompassed various studies and reports available in the literature. We primarily relied on PubMed, Medline, and Google Scholar as the main sources for our search. These databases were chosen for their relevance in having suitable materials. The keywords cardiac biomarkers, cardiovascular complications, SARS-CoV-2, COVID-19, troponin, CK-MB, and proBNP were used to conduct the search.

After obtaining the search results, a filtering process was implemented to select the most pertinent papers. This was achieved through the application of inclusion and exclusion criteria that were carefully formulated.

The inclusion criteria consisted of selecting publications within the timeframe of January 2019 to July 2023, written in the English language, and papers that included results on cardiac biomarkers in COVID-19. It is important to note that two different authors evaluated the articles for inclusion/exclusion by reading the abstracts of papers resulting from the search independently. As a result of our search, we retrieved studies that explored the relationship between COVID-19 and CVD biomarkers, and we assembled their findings in our review.

To present the collected information, we organized the studies into a table (Table 1), highlighting the respective methodologies and outcomes of each investigation. Furthermore, we complemented and strengthened the information provided in our review by including several narrative reviews obtained from our search.

COVID-19 and cardiac manifestations

Subsequent to the COVID-19 pandemic, an increasing body of evidence suggests the existence of cardiac manifestations that can have profound implications for individuals' cardiovascular health, as shown in Figure 1.⁹ Notably, myocarditis, characterized by inflammation of the heart muscle, emerges as a prominent cardiac manifestation.¹⁰ The SARS-CoV-2 virus has been shown to invade cardiac cells and trigger an immunological response, which then causes inflammation of the myocardium. Myocarditis following COVID-19 has been observed in both symptomatic and asymptomatic individuals, and it can give rise to myocardial injury, impaired cardiac function, and the potential development of HF.¹¹ Studies have demonstrated that individuals in the recovery

Table 1. Common cardiac biomarkers' half-life and origin^{61,62}

Biomarker	Origin	Half-life
BNP	Cardiac ventricles	<20 mins
NT-proBNP	Cardiac ventricles	120 mins
Troponin I, C	Cardiac thin filament	120 mins
Myoglobin	Cardiomyocyte, muscles	120–180 mins
CK	Heart, brain, muscles	120–240 mins
CK-MB	Myocardium	11 hrs

BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; CK = creatine kinase; CK-MB = creatine kinase MB.

phase of COVID-19 may experience tenacious myocardial inflammation, emphasizing the necessity for continuous monitoring of cardiac health in these patients.^{12,13}

Furthermore, in addition to myocarditis, COVID-19 is linked to an augmented risk of thromboembolic events, encompassing venous thromboembolism and arterial thrombosis.¹⁴ The systemic inflammatory response triggered by the viral infection induces a prothrombotic state, thereby facilitating the formation of blood clots. COVID-19-related thromboembolic events can impact the coronary arteries, leading to myocardial infarction, or affect other blood vessels, resulting in ischaemic stroke or pulmonary embolism.¹⁵ Studies have emphasized the criticality of implementing anticoagulation therapy in the management of COVID-19 patients to mitigate the potential life-threatening complications associated with thromboembolic events.^{16,17}

Moreover, COVID-19 can exacerbate pre-existing cardiovascular conditions or precipitate the development of new cardiac abnormalities. Severe COVID-19 disease course and unfavourable cardiovascular outcomes are more likely to occur in people with underlying CVDs, such as hypertension, coronary artery disease, or HF.⁹ The viral infection induces cardiac stress, inflammation, and endothelial dysfunction, which may lead to acute decompensation or deterioration of pre-existing cardiac conditions.¹⁸ Additionally, COVID-19 directly affects the electrical conduction system of the heart, giving rise to arrhythmias such as atrial fibrillation or ventricular tachycardia.^{19,20}

Consequently, in the post-COVID-19 phase, cardiac manifestations, including myocarditis, thromboembolic events, and the exacerbation of pre-existing cardiovascular conditions, impose notable risks to individuals' cardiovascular health.

Mechanisms of cardiac injury in COVID-19

The mechanisms underlying cardiac injury in COVID-19 involve a multifaceted interplay of direct viral effects, immune response dysregulation, endothelial dysfunction, and thrombotic processes.²¹ These intricate mechanisms contribute to the pathogenesis of myocardial inflammation, myocardial infarction, and exacerbation of pre-existing cardiovascular conditions.

1. Direct viral myocardial injury: The SARS-CoV-2 virus gains entry into cardiac cells by binding to ACE2 receptors, which are abundantly expressed in cardiomyocytes and endothelial cells.²² Viral invasion causes cellular damage and disrupts normal functioning of the heart. In addition, the replication of viruses in cardiac cells and their subsequent release triggers local and systemic inflammation. Cardiovascular function may be adversely affected by the combination of direct viral

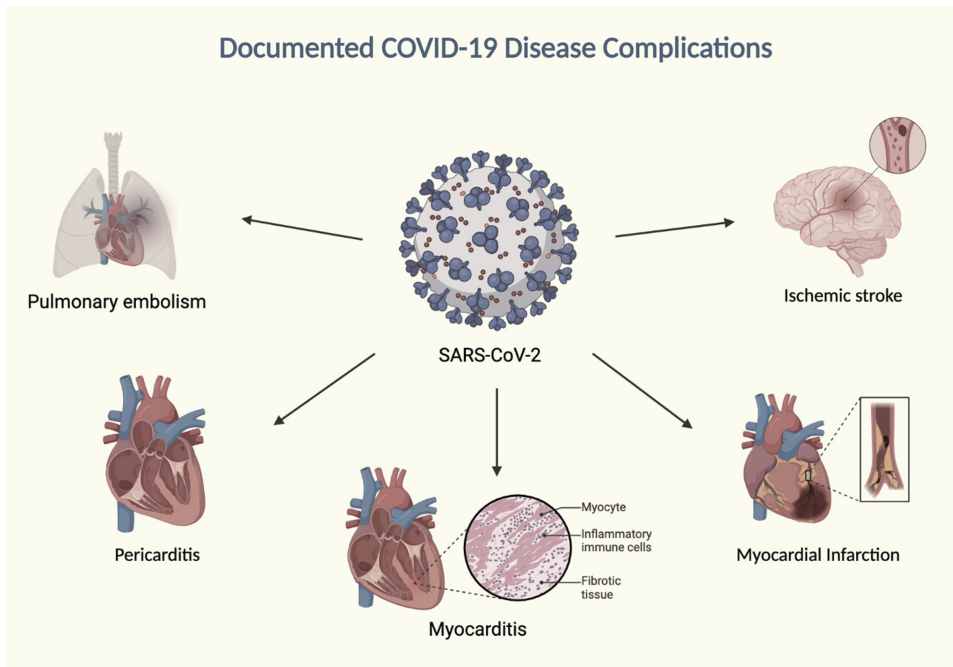


Figure 1. COVID-19 cardiovascular complications; COVID-19 infection is often associated with cardiovascular manifestations such as pulmonary embolism, pericarditis, myocarditis, myocardial infarction, and ischaemic strokes. COVID-19 = coronavirus disease 2019.

damage and a subsequent inflammatory response. The induction of cytopathic effects is one of the manifestations of direct viral myocardial injury. Studies have shown that SARS-CoV-2 infection in cardiac cells leads to structural and functional changes, such as alterations in cell morphology, disruption of cellular organelles, and impairment of contractile function.²³ These cytopathic effects directly contribute to the dysfunction of cardiac cells and compromise the overall cardiac performance. Moreover, viral infection within cardiac cells can activate apoptotic pathways, leading to programmed cell death.²³ Viral RNA has been detected in myocardial tissue, supporting the notion of viral invasion and replication within the heart.²⁴

2. Dysregulated immune response and CS: COVID-19 is characterized by dysregulated immune responses and an excessive release of pro-inflammatory cytokines, known as a CS.^{25,26} This dysregulation can lead to an uncontrolled inflammatory response, causing collateral damage to cardiac tissue. The CS is characterized by elevated levels of interleukin-6 (IL-6), tumour necrosis factor-alpha, and other pro-inflammatory molecules.²⁷ These cytokines can directly affect the heart by promoting myocardial inflammation, impairing contractile function, and disrupting the electrical conduction system.²⁷ In addition, the immune response involves the infiltration of immune cells into cardiac tissue, leading to further inflammation and tissue damage.²⁸
3. Endothelial dysfunction and thrombotic processes: COVID-19 is associated with widespread dysfunction in the endothelial cells, contributing to vascular abnormalities and thrombotic complications.²⁹ The virus can infect endothelial cells and induce endotheliitis, impairing the normal regulation of vascular tone and promoting vasoconstriction.³⁰ This endothelial dysfunction leads to microvascular injury, impaired perfusion, and tissue ischaemia in the heart.³⁰ Furthermore, the risk of thromboembolism can increase with systemic inflammation reactions and release of prothrombotic factors in COVID-19.³¹ COVID-19-associated coagulopathy, characterized by elevated

D-dimer levels, fibrinogen levels, and prolonged prothrombin time, further contributes to the formation of microvascular and macrovascular thrombi, including myocardial infarction and pulmonary embolism.^{32,33}

Hence, the mechanisms of cardiac injury in COVID-19 involve direct viral myocardial injury, dysregulated immune responses, endothelial dysfunction, and thrombotic processes. These complex mechanisms contribute to myocardial inflammation, myocardial infarction, and the exacerbation of pre-existing cardiovascular conditions. Besides, each mechanism of cardiac injury secondary to COVID-19 infection can be translated into an increase in the level of specific cardiac biomarkers that are shown in the figure (Fig. 2).

Role of cardiac biomarkers in COVID-19

Cardiac biomarkers have emerged as important tools for risk stratification, diagnosis, monitoring, and prognosis in individuals with COVID-19. The measurement of specific biomarkers allows for the assessment of cardiac injury, myocardial stress, inflammation, and the prediction of adverse cardiovascular outcomes. Figure 2 highlights the corresponding disruption in cardiac biomarkers levels secondary to myocardial injury.

1. Troponin and cardiac injury: Cardiac troponins, particularly high-sensitivity cardiac troponin (hs-cTn), are well-established biomarkers of myocardial injury.³⁴ A large proportion of patients with COVID-19 have been observed to have higher levels of hs-cTn, and these results are related to an unfavourable clinical outcome.³⁵ The underlying mechanisms of cardiac injury in COVID-19 include direct viral invasion, myocardial oxygen supply-demand mismatch, cytokine-induced inflammation, and microvascular dysfunction.³⁶ Elevated hs-cTn levels have been associated with increased risk of severe disease, need for ICU admission, and mortality.³⁷ Hence, serial monitoring of hs-cTn levels can aid in the early detection of myocardial injury, risk stratification,

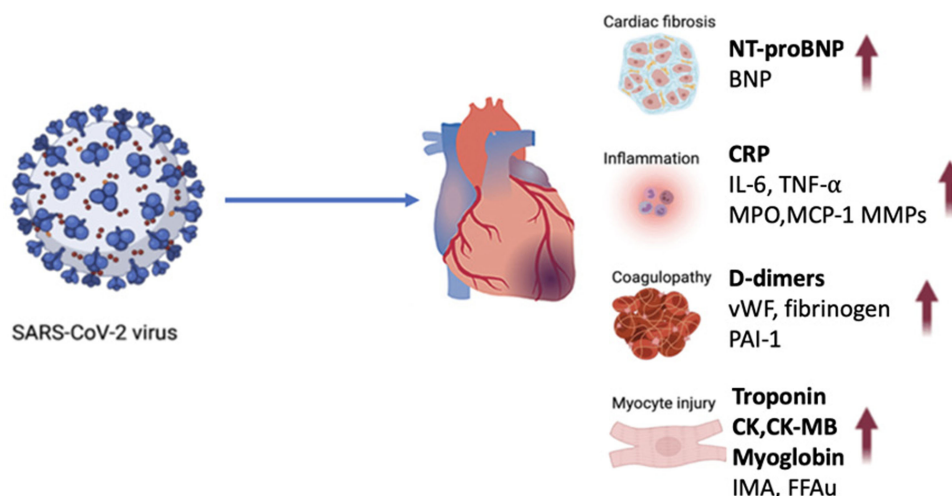


Figure 2. Cardiac damage caused by COVID-19 and cardiac biomarkers associated with corresponding mechanisms. COVID-19 = coronavirus disease 2019.

and guiding therapeutic interventions in individuals with COVID-19.

- Natriuretic peptides and myocardial stress: Natriuretic peptides, including brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are released in response to myocardial stress and stretch.³⁸ Elevated levels of BNP and NT-proBNP have been observed in individuals with COVID-19 and are associated with myocardial dysfunction, heart failure, and adverse outcomes.³⁹ The presence of cardiac stress or reduced heart function is reflected in the increased levels of these biomarkers. Numerous scientific investigations have offered proof indicating a connection between higher levels of NT-proBNP and an elevated risk of severe COVID-19 and unfavourable results.^{40,41} For example, one study that included 4675 patients hospitalized with COVID-19 discovered that COVID-19 patients with elevated NT-proBNP levels upon admission demonstrated a substantially increased probability of needing ICU admission and had a greater risk of mortality when compared to those with lower NT-proBNP levels.⁴² Thus, natriuretic peptides also provide valuable prognostic information and assist in risk stratification.⁴³ Serial measurements of BNP or NT-proBNP can help monitor the progression of myocardial stress.
- Inflammatory biomarkers and systemic inflammation: Inflammatory biomarkers, such as C-reactive protein (CRP), procalcitonin, and interleukin-6 (IL-6), have been shown to be elevated in individuals with severe COVID-19 and are associated with a higher risk of adverse outcomes.⁴⁴ Elevated CRP and IL-6 levels reflect the extent of systemic inflammation, which is associated with disease severity, multiple organ dysfunctions, and increased mortality.⁴⁵ The systemic inflammatory response to COVID-19 can contribute to cardiac injury, myocardial dysfunction, and thrombotic complications.
- Myoglobin: Myoglobin was shown to be linked to prognosis in patients with COVID-19 in some studies.⁴⁶ Researchers, such as Zhong et al., found that patients with a length of hospital stay fewer than 14 days had lower myoglobin values than patients with a hospital stay longer than 14 days.⁴⁷ Seraji et al. performed a meta-analysis and found that elevated myoglobin was strongly associated with patient mortality (WMD = 159.77 ng/mL; 95% CI = 99.54–220.01; $p < 0.001$).⁴⁸
- Creatine kinase (CK) and creatine kinase MB were also shown to be related to the prognosis of COVID-19. Zinello

et al. did a literature review in 2021 on cardiac biomarkers and showed that higher levels of CK-MB and CK were associated with increased severity and poor prognosis in COVID-19 patients.⁴⁹

In a study conducted by Smadja et al., it was demonstrated that increased levels of proBNP and D-dimers were associated with a worse prognosis in COVID-19.⁵⁰ This was assessed by the need for life-sustaining treatments (LSTs).⁵¹ It was found that, in patients who needed LSTs, the average levels of proBNP were significantly increased compared to the group that didn't require LST (5115.92 \pm 10,865.93 g/mL; 3421.19 \pm 6433.58 g/mL; $p = 0.037$).⁵¹ In this study, patients with lower levels of D-dimers were more likely to not require LSTs wherein out of 135 patients who had D-dimers <1000 μ g/L, only 49 required the use of LSTs, which is significantly less than the level in those who didn't require LSTs which was 86.⁵¹ Stavileci et al. show that troponin I value of ≥ 16.05 pg/mL on the seventh day were related to the need for intensive care ($p < 0.001$).⁵² Troponin I value ≥ 30.25 pg/mL on the ninth day were related to mortality ($p < 0.001$) in patients with COVID-19.⁵² The association of D-dimers with disease severity and mortality in COVID-19 was assessed, and it showed that D-dimer values ≥ 878 hg/mL on the second day were associated with intensive care need ($p < 0.001$). D-dimer values ≥ 1106 hg/mL on the 10th day were associated with mortality ($p < 0.001$).⁵²

In order to assess the value of troponin I in predicting COVID-19-induced myocardial damage, Abdul Rehman et al. studied the relation of troponin I levels with the risk of myocarditis and COVID-19-induced myocardial injury in 104 patients.⁵³ In this study, cardiac Tn-I (cTn-I) and CRP were significantly higher in patients with myocarditis ($p < 0.01$). All patients who died secondary to COVID-19-induced myocardial injury had elevated serum cTn-I.⁵³ Additionally, Liu et al. evaluated the role of high-sensitivity cardiac Troponin T (hs-cTnT) in predicting mortality related to COVID-19.⁵⁴ In this study, on a per-patient level, a normal hs-cTnT had a negative predictive value of 94% (95% CI: 85–98) for ruling out mortality, while an elevated hs-cTnT had a low positive predictive value of 38% (95% CI: 39–47) for ruling in mortality.⁵⁴

Mukhopadhyay et al. studied the sex difference in the prognostic value of troponin and D-dimer in COVID-19 illness.⁵⁵ The initial and peak troponin levels were significantly associated with higher odds of severe COVID-19 (initial: OR = 1.16 per ng/mL, 95% CI = 1.08–1.25; peak: OR = 1.66 per ng/mL, 95% CI = 1.56–1.78,

Table 2. Characteristics of included studies

Title	Methods	Results
The impact of daily troponin I and D-dimer serum levels on mortality in COVID-19 pneumonia patients (Stavileci et al., 2023) ⁵³	Retrospective observational study. Serum troponin I and D-dimer levels were recorded for at least 10 days after admission.	<ul style="list-style-type: none"> • Troponin I values ≥ 16.05 pg/mL were related to the need for intensive care ($p < 0.001$). • Troponin I values ≥ 30.25 pg/mL were related to mortality ($p < 0.001$). • D-dimer values ≥ 878 ng/mL were associated with intensive care need ($p < 0.001$). • D-dimer values ≥ 1106 ng/mL were associated with mortality ($p < 0.001$).
Cardiac Troponin-I, A Biomarker for Predicting COVID-Induced Myocardial Damage Prognosis (Rehman et al., 2023) ⁵⁴	Descriptive study. Levels of cardiac troponin I (cTn-I) were categorized (normal/raised/markedly raised) based on serial monitoring over a duration of 6–8 hours.	<ul style="list-style-type: none"> • Cardiac Tn-I and CRP were significantly higher in patients with myocarditis ($p < 0.01$). • Six out of 104 patients (5.7%) died due to COVID-19-induced myocardial injury all having raised cTn-I.
Normal high-sensitivity cardiac troponin for ruling-out inpatient mortality in acute COVID-19 (Liu et al., 2023) ⁵⁵	Retrospective diagnostic study. Aimed to test the diagnostic value of hs-cTnT in confirmed COVID-19 patients. A normal hs-cTnT was defined as ≤ 14 ng/L, and an elevated hs-cTnT was defined as > 14 ng/L.	<ul style="list-style-type: none"> • Patients with elevated hs-cTnT had worse inpatient survival ($p = 0.0014$) and higher risk of inpatient mortality (HR 5.84 [95% CI: 1.29–26.4]; $p = 0.02$). • Normal hs-cTnT had a negative predictive value of 94% (95% CI: 85–98). • Elevated hs-cTnT had a low positive predictive value of 38% (95% CI: 39–47).
The Evaluation of Troponin I Levels and Myocarditis in Children with COVID-19: A Pediatric Single-Center Experience (Ozenen et al., 2023) ⁵⁹	Single-centre retrospective study. Evaluated hospitalized children (available troponin I levels and with no known cardiac disease) diagnosed with COVID-19.	<ul style="list-style-type: none"> • All seven children with elevated troponin I levels had tachycardia. • Out of seven patients with elevated troponin levels, three (42.9%) of them were admitted to paediatric ICU, two (28.6%) required oxygen support, and one (14.3%) required mechanical ventilator support.
Echocardiographic assessment of COVID19 sequelae in survivors with elevated cardiac biomarkers (Ródenas-Alesina et al., 2022) ⁷	Retrospective case-control study. Patients with hs-TnI > 45 ng/L, NT-proBNP > 300 pg/mL, and D-dimer > 8000 ng/mL were matched with COVID-19 controls based on intensive care requirements and age and separately analysed.	<ul style="list-style-type: none"> • Increased Hs-TnI patients had lower myocardial work and longitudinal strain. • The presence of an abnormal echocardiogram was more frequent in the elevated cardiovascular biomarker group compared to controls (23.8 versus 10.3%, $p = 0.123$) but mainly associated with mild abnormalities in deformation parameters.
Sex differences in the prognostic value of troponin and D-dimer in COVID-19 illness (Mukhopadhyay et al., 2022) ⁵⁶	Retrospective cohort study to assess associations between sex, troponin, D-dimer, and severe COVID-19 illness.	<ul style="list-style-type: none"> • Among 4,574 patients hospitalized with COVID-19, the male sex was associated with higher levels of troponin and greater odds of severe COVID-19 illness but lower levels of initial D-dimer when compared with the female sex. • Peak D-dimer level was more strongly associated with severe COVID-19 illness in male patients compared with female patients (males: OR = 2.91, 95% CI = 2.63–2.34, $p < 0.001$; females: OR = 2.31, 95% CI = 2.04–2.63, $p < 0.001$; p-interaction = 0.005).
Admission High-Sensitive Cardiac Troponin T Level Increase Is Independently Associated with Higher Mortality in Critically Ill Patients with COVID-19: A Multicenter Study (Larcher et al., 2021) ³⁸	Observational study. Investigators on each site collected prospectively clinical and biological data for all critically ill patients diagnosed with COVID-19. Patients were followed up until hospital discharge or death and three months later by phone call.	<ul style="list-style-type: none"> • In-hospital mortality was 29% (32/111) and was independently associated with lower PaO₂/FIO₂ and higher hs-cTnT serum levels.
Characterization of NT-proBNP in a large cohort of COVID-19 patients (Caro-Codón et al., 2021) ⁴⁰	Retrospective study. Patients with confirmed SARS-CoV-2 infection and available NT-proBNP determinations who completed at least one-month follow-up or died	<ul style="list-style-type: none"> • Patients with higher NT-proBNP during admission experienced more frequent bleeding, arrhythmias, and HF decompensations. • NT-proBNP was associated with mortality both in the whole study population and after excluding patients with HF.

(Continued)

Table 2. (Continued)

Title	Methods	Results
N-Terminal Pro-B-Type Natriuretic Peptide as a Biomarker for the Severity and Outcomes With COVID-19 in a Nationwide Hospitalized Cohort (O'Donnell et al., 2021) ⁴³	Observational cohort study of the American Heart Association's COVID-19 Cardiovascular Disease Registry. 4675 patients hospitalized with COVID-19 were divided into normal and elevated NT-proBNP cohorts by standard age-adjusted heart failure (HF) thresholds, as well as separated by quintiles.	<ul style="list-style-type: none"> • Patients with elevated NT-proBNP were older, with more cardiovascular risk factors, and had a significantly higher rate of in-hospital mortality (37% versus 16%; $p < 0.001$) and shorter median time to death (7 versus 9 days; $p < 0.001$) than those with normal values. • Analysis by quintile of NT-proBNP revealed a steep graded relationship with mortality (7.1%–40.2%; $p < 0.001$). • NT-proBNP was associated with major adverse cardiac events, ICU admission, intubation, shock, and cardiac arrest ($p < 0.001$ for each).
B-Type Natriuretic Peptide Concentrations, COVID-19 Severity, and Mortality: A Systematic Review and Meta-Analysis With Meta-Regression (Zinellu et al., 2021) ⁴⁴	Systematic review and meta-analysis with meta-regression of studies reporting B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) plasma concentrations in COVID-19.	<ul style="list-style-type: none"> • In pooled results, BNP/NT-proBNP concentrations were significantly higher in patients with high severity or non-survivor status when compared to patients with low severity or survivor status during follow-up (SMD = 1.07; 95% CI: 0.89–1.24; $p < 0.001$).
Myoglobin and troponin as prognostic factors in patients with COVID-19 pneumonia (Zhu et al., 2021) ⁶⁰	Retrospective study of 499 severe/critical COVID-19 hospitalized patients at Leishenshan Hospital, Wuhan, China.	<ul style="list-style-type: none"> • Myoglobin was increased in the death group ($p < 0.001$). • Troponin was significantly elevated in the death group ($p < 0.001$).
High sensitivity Troponin-T for prediction of adverse events in patients with COVID-19 (Singh et al., 2020) ³⁶	Retrospective chart review. Initial and peak hs-TnT were recorded. Assessed primary composite endpoint of in-hospital death, intubation, need for critical care, or cardiac arrest.	<ul style="list-style-type: none"> • Initial hs-TnT above the median (≥ 17 ng/L) was associated with increased length of stay, need for vasoactive medications, and death, along with the composite endpoint (OR 3.92, $p < 0.001$).
Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis (Pranata et al., 2020) ⁴¹	Systematic review and meta-analysis. NT-proBNP data were in continuous variable (pg/mL), dichotomous data (elevated/non-elevated), and effect estimate adjusted to cardiac injury/elevated biomarkers of cardiac injury.	<ul style="list-style-type: none"> • NT-proBNP was higher in a non-survivor group ($p < 0.001$). • Elevated NT-proBNP was associated with increased mortality (RR 3.63 [92.21, 5.95], $p < 0.001$). • Elevated NT-proBNP was independently associated with mortality (HR 1.37 [1.19, 1.57], $p < 0.001$). • Elevated NT-proBNP likelihood ratio (LR) +6.4 and LR -0.3.
B-Type Natriuretic Peptide as Biomarker of COVID-19 Disease Severity-A Meta-Analysis (Sorrentino et al., 2020) ⁴²	Meta-analysis. Evidence on NT-proBNP in patients admitted for COVID-19. Pooled mean, mean differences (MD) and standardized mean difference (SMD) were the summary metrics.	<ul style="list-style-type: none"> • Mean NT-proBNP levels on admission were 790.57 pg in patients who experienced a severe clinical condition or died. • Mean NT-proBNP was 160.56 pg/mL in non-severe patients.

CRP = C-reactive protein; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory coronavirus virus 2; CI = confidence interval; OR = odds ratio.

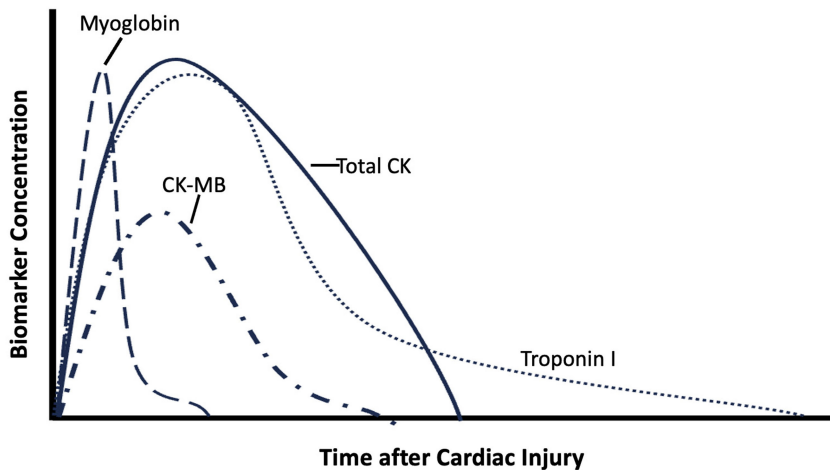
$p < 0.001$). Similarly, both initial and peak D-dimer levels were associated with higher odds of severe COVID-19 illness (initial: OR = 1.34 per 1000 ng/L, 95% CI = 1.23–1.45, $p < 0.001$; peak: OR = 2.67 per 1000 ng/mL, 95% CI = 2.46–2.90, $p < 0.001$).⁵⁵ These associations were not modified by sex; however, peak D-dimer level was more strongly associated with severe COVID-19 illness in males than females (male: OR = 2.91, 95% CI = 2.63–3.24 versus female: OR = 2.31, 95% CI = 2.04–2.63, p -interaction = 0.005).⁵⁵

Bayaz et al. assessed the correlation between cardiac troponin I (TPI) level and the in-hospital mortality in severely ill COVID-19 patients.⁵⁶ In this study, patients who died in the hospital had higher levels of TPI (2.27 ± 9.58 $\mu\text{g/L}$) than patients who survived until discharge (0.07 ± 0.06 $\mu\text{g/L}$), therefore suggesting a valuable role for TPI in early diagnosis of cardiac injury and decreasing mortality in patients with COVID-19.⁵⁶

Additionally, the association of right ventricular dysfunction in patients with COVID-19 pneumonitis whose lungs are mechanically ventilated was explored in a multicentre prospective cohort study.⁵⁷

The results of the study portray that patients with right ventricular dysfunction were more likely to have higher plasma N-terminal pro-B-type natriuretic peptide levels ($p = 0.006$) and elevated plasma troponin levels ($p = 0.048$).⁵⁷ In this study, the prevalence of right ventricular dysfunction of 6% was associated with increased mortality (86%).⁵⁷

Ultimately, to evaluate the role of cardiac biomarkers in COVID-19 in paediatric children, Ozenen et al. evaluated the troponin levels in 412 paediatric children that were hospitalized and were infected with COVID-19.⁵⁸ They found that troponin I levels were elevated in seven (1.7%) patients and that all of them experienced tachycardia. Out of the seven patients with elevated troponin levels, three (42.9%) required paediatric ICU admission, two (28.6%) required oxygen support, and one (14.3%) required invasive mechanical ventilator.⁵⁸ Out of the patients with normal troponin I levels, 94 (23.2%) had tachycardia, 10 (2.5%) were admitted to ICU, 12 (3%) required oxygen support, and 2 (0.5%) required mechanical ventilation.⁵⁸ Therefore, tachycardia, ICU admission, oxygen support, and



Graph 1. Trend of cardiac biomarkers concentration in time after cardiac injury⁶⁰.

mechanical ventilation requirement were more common in children with elevated troponin I levels (p values were 0.020, < 0.001 , 0.050, and < 0.001 , respectively).⁵⁸

Furthermore, Zhu et al. assessed the levels of myoglobin in patients with COVID-19 by comparing the levels in patients who died and the survivors. Myoglobin and troponin levels were significantly elevated in the death group (134.4 [interquartile range (IQR) 24.80, 605] versus 38.02 [IQR 3.87, 11.73] ng/mL, $p < 0.001$), and (0.01 [IQR 0.01, 0.01] versus 0.04 [IQR 0.02, 0.15] ng/mL, $p < 0.001$),⁵⁹ respectively. Thus, they concluded that myoglobin levels can be used as a predictor of mortality in patients with COVID-19.⁵⁹

In addition, Zinellu et al. reviewed the literature on the role of CK-MB as a prognostic marker for COVID-19 by analysing 55 studies that included 11,791 COVID-19 patients. In this study, high levels of CK-MB were related to poor prognosis and increased mortality in COVID-19.⁴⁹

As it turned out of the 14 papers included in Table 2, 8 studies showed evidence of poor progression of the disease when there is increased troponin. The severity of the disease manifestation was evaluated differently; some studies evaluated the severity of the disease in terms of ICU admission, while others evaluated the severity in terms of mortality, need for ventilators, or myocardial work. This shows that troponin and other cardiac biomarkers may predict poor outcomes of COVID-19 in various aspects.

This shows that elevation in either troponin, proBNP, or D-dimers in the early phases of COVID-19 is a predictor of poor outcomes on various levels.

The worst outcome of COVID-19 is death; 6 studies out of the 14 mentioned in this review showed a positive correlation between mortality and elevation in cardiac biomarkers. This shows the significance of cardiac biomarkers in predicting mortality in patients with COVID-19.

Henceforth, cardiac biomarkers, including troponin, natriuretic peptides, myoglobin, CK, CK-MB, and inflammatory markers, play a crucial role in risk stratification, diagnosis, monitoring, and prognostication in individuals with COVID-19. These biomarkers provide valuable insights into cardiac injury, myocardial stress, inflammation, prediction of adverse cardiovascular outcomes, and optimize therapeutic interventions.

It is important to highlight the half-life and the origin of each cardiac biomarker, as seen in Table 1, in order to understand the

relationship between these cardiac biomarkers and the severity of the disease. Additionally, it is important to consider the natural trend of biomarkers levels because some biomarkers, such as myoglobin, peak early after the onset of cardiac injury and decrease directly afterwards, whereas others, for instance, troponin I, peak early after cardiac injury and take a longer period to drop. Each biomarker concentration follows a different trend after the onset of cardiac injury (Graph 1).⁶⁰ These trends allow us to track the onset of cardiac damage that occurred. In addition, the origin of each cardiac biomarker facilitates the process of determining the location of cardiac injury.

Conclusion

To sum up, COVID-19 is associated with a wide range of cardiovascular complications, which significantly contribute to the burden of the disease and its mortality. The mechanisms underlying the cardiovascular complications of COVID-19 involve direct viral invasion, immune response dysregulation, endothelial dysfunction, and thrombotic processes. Cardiac biomarkers such as troponin, natriuretic peptides, and inflammatory markers were proven to play a vital role in the pathogenesis of COVID-19 and are correlated with negative outcomes. Increased length of hospitalization, need for life-sustaining treatment, myocarditis, invasive and non-invasive respiratory support, and even death were linked to elevated cardiac biomarkers levels. Hence, this highlights the role of these biomarkers in predicting clinical outcomes. Further research is required to enhance our understanding of the relationship between cardiac biomarkers and COVID-19 and to guide their effective use in the clinical setting. This research should focus on the elevation timelines of these biomarkers with respect to the course of illness, the role of specific therapies such as remdesivir in the setting of cardiac biomarkers, and the value of their early use in the disease to stratify patients in terms of risks and outcome.

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for profit sectors.

Competing interests. None.

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