**This is an accepted, pre-copyedit version of a chapter published in Clinical, Biological and Molecular Aspects of COVID-19. The final authenticated version is available online at: http://dx.doi.org/10.1007/978-3-030-59261-5_29**

# Chapter

# The Cardiac Injury in COVID-19: A Systematic Review

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**Running title** Cardiac Injury in COVID-19

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**Abstract**

**Background**
Coronavirus 2019 (COVID-19) is responsible for the current pandemic, which has already resulted in considerable mortality worldwide. This systematic review was conducted to summarize the results of the published articles assessing the incidence of heart diseases in patients infected with COVID-19.
**Methods**
The electronic databases Scopus, Web of Science, Pubmed, Science Direct, and ProQuest were used to search for potentially relevant articles. Articles published from Dec 2019 to 20 April 2020 were included in this systematic review. All cross-sectional, retrospective or prospective observational cohort and case-control studies were selected which had reported the incidence or prevalence of myocardial injury, myocardial infarction, or cardiovascular disease in patients with confirmed COVID-19 infection.
**Results**
Based on the inclusion criteria, 12 articles were selected. The incidence of cardiac injury was reported in 8 articles and 8 articles focused on the cardiovascular outcomes of COVID-19 infection. The incidence of new cardiac injury was reported to be 7.2-77% in live and dead patients, respectively. The results showed that patients with cardiac injury had worse outcomes than other infected patients. Patients with cardiac injury had higher mortality than those without cardiac injury. The most common cardiac injury outcomes were shock and malignant arrhythmias. The commonest radiographic findings in patients with cardiac injury were multiple mottling and ground-glass opacity (64.6%). A significant number of patients required with cardiac injury required noninvasive mechanical ventilation (46.3%) or invasive mechanical ventilation (22.0%). Acute respiratory distress syndrome was seen in 58.5%, acute kidney injury in 8.5%, electrolyte disturbances in 15.9%, hypoproteinemia in13.4%, and coagulation disorders in 7.3% of patients with a cardiac injury. In addition, the survival days were negatively correlated with the high sensitivity-TnI level (r=-0.42, 95%, p=0.005).
**Conclusions:** The results of this review showed that myocardial injury in patients with COVID 19 has a poor prognosis. Hence, cardiac investigation and management in these patients are crucial.

**Keywords:** COVID-19, Cardiac Injury, Mortality, Cardiovascular, prognosis

## 1 Introduction

Coronavirus 2019 (COVID-19) is the pathogen responsible for the current pandemic causing severe pneumonia worldwide [**1, 2**]. Cardiovascular complications can occur in patients with COVID-19 infection. One of the major cause of death among patients hospitalized with COVID-19 is viral myocarditis or myocardial injury [**3**].

The studies done during the previous historical coronavirus outbreaks (SARS, MERS) shows that one of the important cause of mortality is the development of cardiovascular complications including acute myocardial infarction (AMI) and myocarditis [**4,5**]. Various mechanisms including systemic inflammation, relative ischemia, and pathogen-mediated have been attributed to cardiovascular complications with coronavirus infection [**6**]. Studies have shown that arrhythmia, bradycardia, tachycardia, hypotension, and sudden cardiac death are common in SARS pneumonia. Various investigations including electrocardiographic changes, troponin elevation, and echocardiography or invasive diagnostics methods were used to demonstrate myocarditis, cardiac injury, myocardial infarction, or other sub-clinical left ventricular diastolic impairment in these studies [**7-10**].

The level of cardiac Troponin I (cTnI) increase is an independent determinant of clinical disease in COVID-19 patients in the recent coronavirus pandemic [**3,6**]. The presence of cardiovascular diseases is a risk factor for mortality in patients with Covid-19 pneumonia [**11**]. It is noteworthy that there are still challenges in laboratory diagnostics as well as in the clinical treatment of COVID-19 disease [**12**].

Heart complications were reported in the various COVID-19 studies. One study showed that16.7% of confirmed patients with COVID-19 disease had myocardial damages [**13**]. In a clinical cohort study of COVID-19 to date, 7.2% of the infected patients hadacute myocardial injury (AMI), shock in 8.7%, and 16.7% of patients had arrhythmia [**14**]. Also, in another cohort with a follow-up study, a total of 82 patients (19.7%) had a cardiac injury. In one study, 27.8% of patients with COVID-19 disease had elevated cardiac troponin T (cTnT) levels which is a marker of myocardial injury [**15**].

There is a knowledge gap in cardiac complications due to COVID-19 infection [**6**]. There are several articles looking into the effect of COVID-19 infection in the heart. Therefore the current systematic review was conducted to investigate the prevalence and outcome of cardiac injury in COVID-19 patients.

## 2 Methods

In the current systematic review, we selected the studies that reported prevalence of myocardial injury in the patients with confirmed COVID-19 or assessed the association between the cardiac injury in the patients infected with COVID- 19 and outcome in these patients.

This systematic review included all cross-sectional, retrospective or prospective observational cohorts, and case- control studies that assessed the prevalence and complication of cardiac injury in COVID-19 patients.

### Information Source

An extensive search was conducted on the electronic database PubMed, Scopus, Web of Science, Science Direct, and ProQuest for articles fulfilling the inclusion criteria. Publications from 2019 to 20 April 2020 were included in this systematic review. The elaborated syntax of each database is available in the additional file. Endnotes software (Thomson Reuters, X9, Bld 9325) was used to screen the studies. Related studies were screened by searching references of the screened studies.

**Data Collection Process**

After excluding the duplicated references of the 308 initial search publications, 206 articles remained based on PRISMA guideline. Two authors screened all of the abstracts and titles (Figure 1). Full texts for all potentially relevant articles were reviewed. Twelve articles had full text available and were included in this systematic review. A meta-analysis of the findings was not conducted due to high heterogeneity in these studies and most of the papers lacked a common set of attributes that could be combined. This review was done in a systematic review format.

**Ethical consideration**

The Ethics Committee of Baqiyatallah University of Medical Sciences approved this study with code IR.BMSU.REC.1399.116.

**3 Results**

In order to carry out this study, the electronic databases including Scopus, Web of Science, Pubmed, Science Direct, and ProQuest were searched for potentially relevant articles. Based on the inclusion criteria, 12 articles published from 2019 to 20 April 2020 were included in this systematic review. The entered studies in the systematic review were categorized into two separate groups. The prevalence of cardiac injury in COVID-19 infected patients was reported in the first group. The relationship between the cardiac injury in the COVID-19 patients and the outcome on these patients was analyzed in the second group.

Elevation in high sensitivity Troponin I (hs.TNI) or Troponin T levels were used as markers of myocardial injury in many studies. Also in some studies, the cardiac injury was confirmed by evaluating the level of α-Hydroxybutyrate dehydrogenase (HBDB), N-terminal pro-B-type natriuretic peptide, Creatine kinase (CK), Lactate dehydrogenase (LDH) in the plasma. The occurrence rate of new cardiac damage was reported between 7.2% [**14**] and 77%[**16**] in live or dead patients, respectively. 44.4% of COVID-19 patients developed a new cardiac injury during the length of hospital stay [**17**].

The results of the second group of publications showed that the patients with cardiac injury had worse outcomes than other infected patients; the mortality rate was reported 60.9% vs. 25.8%, (P=0.013) in He X et al. study[**17**]. There were also significant differences in mortality rate between patients with cardiac injury compared to patients who did not have any cardiac injury in both Wu C et al. (59.6% vs. 0.8%, P< 0.001)[**18**] and Shi S et al. (51.2%vs 4.5%) (P<0.001) [**19**] studies.

Wu C et al. showed that days of survival were negatively correlated with hs-TNI level and LDH on admission (r=-0.42, P=0.005) and (r= -0.35, P=0.022) respectively [**20**]. He X et al. demonstrated that the level of CRP [153.6 (80.3, 240.7) ng/L vs.(15.9, 101.9) ng/L] and NT-proBNP (852.0 (400.0, 2 315.3) ng/L vs. 197.0 (115.3, 63ng/L) were significantly higher in COVID-19 infected patients with myocardial damage than patients without myocardial damage [**17**]. Another study demonstrated that a higher level of hs-TNI of ≥6.126 pg/mL on admission was associated with an increase in the mortality rate of 50% compared with lower levels of hs-TNI with a mortality rate of 10.0% [**20**]. Also, Guo T et al. showed that in patients who died, TnT and NT-proBNP plasma levels within hospitalization and impending death increased significantly compared with admission values (0.0355; 796.90):(P = 0.001; P <0.001)[**15**].

Several studies have examined the side effects and comorbidities of cardiac injury and the level of the cardiac biomarkers in COVID-19 patients [**15,21-23**]. High levels of cTnT were more frequently associated with mechanical ventilation 59.6% vs 10.4% and malignant arrhythmias 71.2% vs 51.1% [**15**]. An increased TnI level (46.8ng/L vs. 4.8ng/L), HBDB

(453U/L vs. 245U/L) and CK 199U/L vs. 88U/L are a common phenomenon in the severe or critically ill patients [**24**]. Hui H and et al. found that TnI is remarkably higher in the critical group 0.54 (0.05-5.90), P<0.001[**21**].
Results of a meta-analysis by Lippi G and et al. showed that the severity of disease in COVID-19 patients was correlated with higher levels of cTnT [**23**]. A meta-analysis has demonstrated a higher incidence of acute myocardial injury occurred in patients who were hospitalized in ICU in comparison to the non-ICU patients [RR = 13.48, Z = 3.86, P = 0.0001[**22**].
Shi S et al. demonstrated an increase in reports of ground-glass opacity and multiple mottling (64.6% vs 4.5%) radiographically in patients with cardiac involvement. More patients (46.3%) required noninvasive mechanical ventilation or invasive mechanical ventilation (22.0%), P <0.001[**15,19**] who had cardiac involvement compared to COVID-19 patients without cardiac involvement. In addition, ARDS(58.5% vs. 14.7%: P<0.001)[**14,19**], hypo-proteinemia (13.4% vs. 4.8%: P =0.01), coagulation disorders (7.3% vs 1.8%: P=0.02), electrolyte disturbances (15.9% vs. 5.1%: P=0.003) [**19**], tachycardia[**21**], shock (8.7%), and arrhythmia (16.7%)[**14**], shock (11.9% versus. 0: P 0< 0.001), and dissiminated intravascular coagulation (DIC) (6.4% versus 0, P = 0.006) were common in patients with cardiac involvement compared to patients without cardiac involvement [**18**].These results showed in Tables 1 and 2.

**4 Discussion**

The current systematic review was conducted to investigate the prevalence of cardiac injury in COVID-19 and its outcomes in COVID-19 patients. The result of this study showed that there is a significant cardiac injury in patients with COVID-19 infection. Some of the studies included in this review reported an increase in markers of cardiac injury associated with the worse outcome in COVID -19 patient. In this study, there was a cardiac injury in 7-77% of infected patients. In the other study, high level of cardiac injury marker, was found in 8–12% of COVID-19 infected cases[**26**]. Another study reported that 11.8% of patients with no history of cardiovascular disease had a significant myocardial injury, with raised markers of cardiac injury [**27**]. The studies demonstrated that cardiac injury with a higher level of cTnI was associated with an increase in mortality and other comorbidities. Severe disease, an increase in the severity of radiological findings in the lung on computed tomography, the requirement of invasive ventilation, acute kidney injury, electrolyte imbalance, hypo-proteinemia, and disorders of blood coagulation, increase in mortality, increased hospital stay were reported in COVID-19 patients with cardiac injury compared to patients without cardiac injury.
The response of the inflammatory system and the presence of a disorder in the immune system due to progression of COVID-19 lead to the development of cardiac damage in these patients (20). The results of the studies confirmed that infected COVID-19 patients with myocardial injury often had poor prognosis because of multi-organ failure. The increase in the incidence of shock and hemodynamic disorder resulting from cardiac injury due to myocardial ischemia or necrosis results in high mortality. In one study, 80% of patients with myocardial injury were admitted to the intensive-care unit [**27**]. Therefore, cardiac function monitoring in COVID-19 patients using cardiac biomarkers and their prompt management could be vital to reducing the mortality associated with COVID-19 [**21,27**].
Another study showed that MERS-CoV infection results in cardiac dysfunction and myocarditis in patients [**10**]. Patients with an increased level of cTnI had increased morbidity and mortality [**15,17,20,23,25**]. Some studies have reported a similar rate of complications between MERS and COVID-19 [**28,29**]. However, another study reported that COVID-19

infection was associated with more cardiac complications, hypotension, bradycardia and cardiac arrest; it seems that the etiology of these complications is complex [**30**].
Therefore, monitoring of cardiac biomarkers test as soon as COVID-19 patients are diagnosed and also continuous assessment during the hospitalization will help to identify some of the patients with potential for myocardial damage and therewith forestall the progression of COVID-19 mortality [**20,23**]. This monitoring is more significant for patients who have high risk factors including demographic characteristics such as age (older patients), presence of cardiovascular comorbidities such as hypertensive patients, male patients and current smokers [**20,31**]. The collaboration of several specialist teams including the cardiologist, emergency medicine, and infectious disease specialists, are needed for the prevention of complications in COVID-19 patients[**32**]. Health professionals should focus not only on respiratory parameters but also on cardiac parameters which are predictors of mortality [**33**].

## 5 Conclusion

Acute cardiac injury is more common in deceased patients with COVID-19 infection causing damage to the myocardium, although the specific mechanisms are uncertain. COVID-19 infection patients with myocardial injury have a poor prognosis potentially increasing the mortality and several adverse outcomes, Therefore, particular attention should be given to cardiovascular monitoring while managing patients with COVID-19.

**Acknowledgments**
Thanks to financial support, guidance and advice from the "Clinical Research Development Unit of Baqiyatallah Hospital.

**Financial Disclosure:**
No conflict.

**Conflict of interests**
None.

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**Fig. 1** Screening and selecting the articles based on PRISMA guidelines

**Appendix**

**Scopus: 44** (TITLE-ABS-KEY ( "Novel coronavirus" OR "Novel coronavirus 2019" OR "2019 novel coronavirus" OR "2019 nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR covid-19 OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV") AND TITLE-ABSKEY ( cardiovascular OR myocardial OR myocarditis OR myocardium OR heart OR cardiac OR hypotension OR tachycardia OR bradycardia OR fibrillation OR ventricular OR arrhythmia OR hypertension OR "blood pressure" ) )

**EMBASE: 65** ('novel coronavirus':ti,ab,kw OR 'novel coronavirus 2019':ti,ab,kw OR '2019 novel coronavirus':ti,ab,kw OR 'wuhan coronavirus':ti,ab,kw OR 'wuhan pneumonia':ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars cov 2':ti,ab,kw OR 'coronavirus 2019':ti,ab,kw OR '2019 ncov':ti,ab,kw) AND (cardiovascular:ti,ab,kw OR myocardial:ti,ab,kw OR myocarditis:ti,ab,kw OR myocardium:ti,ab,kw OR heart:ti,ab,kw OR cardiac:ti,ab,kw OR hypotension:ti,ab,kw OR tachycardia:ti,ab,kw OR bradycardia:ti,ab,kw OR fibrillation:ti,ab,kw OR ventricular:ti,ab,kw OR arrhythmia:ti,ab,kw OR hypertension:ti,ab,kw OR 'blood pressure':ti,ab,kw)

**ProQuest: 94** ab("Novel coronavirus" OR "Novel coronavirus 2019" OR "2019 novel coronavirus" OR "2019 nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR covid-19 OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV" ) AND ab(cardiovascular OR myocardial OR myocarditis OR myocardium OR heart OR cardiac OR hypotension OR tachycardia OR bradycardia OR fibrillation OR ventricular OR arrhythmia OR hypertension OR "blood pressure" )

**Web of science: 12** ("Novel coronavirus" OR "Novel coronavirus 2019" OR "2019 novel coronavirus" OR "2019 nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR covid-19 OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV") AND **TOPIC:** (cardiovascular OR myocardial OR myocarditis OR myocardium OR heart OR cardiac OR hypotension OR tachycardia OR bradycardia OR fibrillation OR ventricular OR arrhythmia OR hypertension OR "blood pressure")

**PubMed: 105** (("Novel coronavirus" [Title/Abstract] OR "Novel coronavirus 2019" [Title/Abstract] OR "2019 novel coronavirus" [Title/Abstract] OR "2019 nCoV" [Title/Abstract] OR "Wuhan coronavirus" [Title/Abstract] OR "Wuhan pneumonia" [Title/Abstract] OR covid-19 [Title/Abstract] OR "2019-nCoV" [Title/Abstract] OR "SARS-CoV-2" [Title/Abstract] OR "coronavirus 2019" [Title/Abstract] OR "2019-nCoV"[Title/Abstract])) AND (cardiovascular [Title/Abstract] OR myocardial [Title/Abstract] OR myocarditis [Title/Abstract] OR myocardium [Title/Abstract] OR heart [Title/Abstract] OR cardiac [Title/Abstract] OR hypotension [Title/Abstract] OR tachycardia [Title/Abstract] OR bradycardia [Title/Abstract] OR fibrillation [Title/Abstract] OR ventricular [Title/Abstract] OR arrhythmia [Title/Abstract] OR hypertension [Title/Abstract] OR "blood pressure"[Title/Abstract])