

The spectrum of cardiovascular complications in COVID-19- A comprehensive literature review

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Abstract

A newly identified novel coronavirus named as severe acute respiratory syndrome-related coronavirus2 (SARS-CoV 2) has given rise to the global pandemic. SARS-CoV2 which causes coronavirus disease 2019 (COVID-19), is a positive-stranded RNA virus with nucleocapsid. It binds to host angiotensin-converting enzyme2 (ACE2) receptor through surface glycoprotein (S protein). These ACE 2 receptors are attached to the cell membranes of many organs. Thus, COVID-19 does not only result in acute respiratory distress syndrome but also affects multiple organ systems, requiring a multidisciplinary approach to manage this disease. COVID-19 can damage the myocardial cells and result in fulminant myocarditis, acute cardiac injury, cardiomyopathy, heart failure, cardiogenic shock, or arrhythmia. COVID-19 seeds harmful immune response through cytokine storm leading to indirect organ damage. In this literature review, the available data is comprehended regarding cardiovascular complications in COVID-19, and the correlation of biomarkers with the disease activity is discussed. This literature review also highlights the important treatment options and outcomes of the individual study.

Keywords: COVID-19; SARS-CoV2; Acute Cardiac Injury; Arrhythmia; Heart Failure; Cardiogenic Shock.

Background

At present, the world is suffering from a pandemic disease caused by novel coronavirus known as coronavirus disease 2019 (COVID-19). According to the Johns Hopkins University (JHU), the total number of cases as of 08th August 2020 is 19,193,661 cases, and total deaths recorded are 716,735 and affecting 227 countries (1) and 26 cruise ships (2). COVID-19 belongs to the Nidovirales order and Coronaviridae family and based on sequence analysis it belongs to beta-coronavirus sub-family and it is the seventh known human coronavirus (HCoV) (3). HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1, Severe acute respiratory syndrome-related coronavirus (SARS-CoV), and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) are the other six identified coronaviruses (4). COVID-19 is the third zoonotic coronavirus after SARS-CoV and MERS-CoV (5). COVID-19 was first discovered in Wuhan, China in November 2019 (6) resulting in severe pneumonia in the patients and later, it spread worldwide and WHO declared it a pandemic on 11th March 2020 (7).

COVID-19 is an enveloped positive-stranded RNA virus with nucleocapsid. The surface glycoprotein (S protein) comprises of two subunits (S1 and S2) producing the spikes of the virus, through which the virus binds to host angiotensin-converting enzyme2 (ACE2) receptor (8). The ACE2 receptors are attached to the cell membrane of the nasopharynx, lungs, arteries, heart, kidney, brain, and intestines (9). For this reason, COVID-19 does not cause only acute respiratory distress syndrome, but also affect multiple organ systems resulting in acute cardiac injury, cardiac arrhythmia, acute kidney injury, shock, and multiple organ dysfunction syndrome. On a cellular level, COVID-19 results in the production of early response pro-inflammatory cytokines (i.e. tumor necrosis factor [TNF],

interleukin (IL)-6, and IL-1 β). The overproduction of these cytokines may give rise to a phenomenon called cytokines storm which leads to increased vascular permeability, edema, multi-organ failure, and ultimately resulting in death (10). The serum levels of IL-2R and IL-6 in coronavirus patients are positively correlated with the severity of the disease (11).

Available studies have highlighted an increasing spectrum of cardiac manifestations secondary to COVID-19. These occur either directly through virus replication or indirectly due to harmful immune responses or myocardial oxygen demand-supply mismatch or acute coronary event or it could be iatrogenic. This literature review consolidates data regarding the potential effects of cardiac complications secondary to COVID-19, correlation with different cardiac biomarkers, and outcome.

Materials & Methods

A thorough literature search was done by availing online recourse: Medline database (PubMed). The following keywords and medical subject headings (MeSH) terms were used: "coronavirus," "coronavirus disease 2019", "COVID-19," "SARS-CoV2" "Acute Cardiac Injury," "Cardiac complications", "Arrhythmia", and "Heart Failure". We included articles from December 2019 onwards, covering the current COVID-19 outbreak. The search was further limited to articles related to human species and contained patients with cardiac complications secondary to COVID-19. The articles included in our systematic review were "Case Reports", "Case Series", "Retrospective Observational Studies" and "Prospective Studies" (Figure 1).

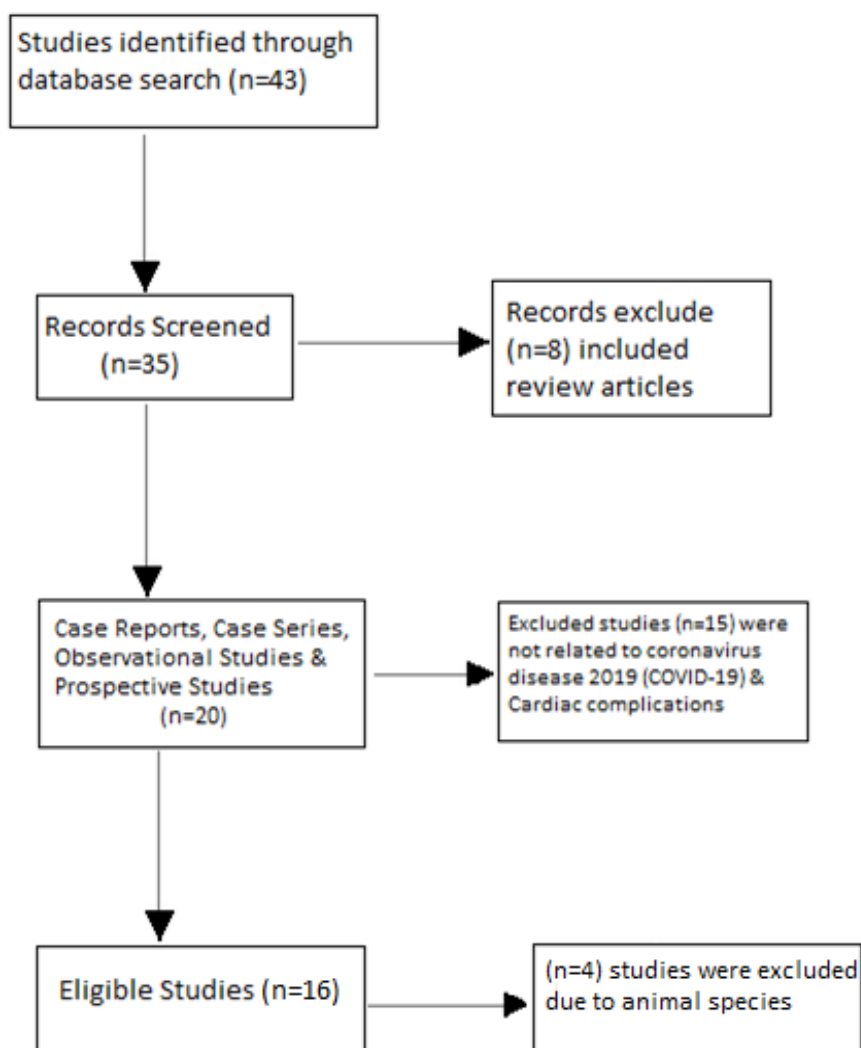


FIGURE 1: Material and Methods: Criteria for the selection of the articles.

Table 1: Characteristics of the selected studies

S.No.	Author, Year	Country	Study Population (Age, Gender)	Type of study	SARS-CoV-2 (COVID 19) status/ Sampling	Outcome
1.	J.H. Zeng et al (12), March 2020,	China	63 years old, Male	Case Report	Positive	Recovered
2.	R. M. Inciardi et al (13), March 2020,	Italy	53-years old, Female	Case Report	Positive (RT-PCR) Nasopharyngeal swab	Recovered
3.	H. Hu et al (14), April 2020,	China	37 years old, Male	Case Report	Positive (NAT)	Recovered
4.	Y. Cui et al (15), March 2020	China	55 days old female infant	Case Report	Positive (RT-PCR) Nasopharyngeal swab	Recovered
5.	G. Tavazzi et al (16), April 2020	Italy	69-year-old, male	Case Report	Positive (RT-PCR) Nasopharyngeal Swab & Endomyocardial Biopsy	Died
6.	M. Arentz et al (17), March 2020,	USA	n=21; A: median 70 (43-92); M: 52%	Case Series	Positive (RT-PCR) Nasopharyngeal sample	67% Mortality
7.	D. Wang et al (18), February 2020,	China	n=138; A: 56 (42-68); M: 75 (54.3%)	Case series	Positive (RT-PCR) Throat swab samples	4.3% Mortality
8.	T. Chen et al (19), February 2020	China	n= 799; A: 62.0 (44.0-70.0); M: 171 (62%)	Case Series	Positive (RT-PCR) Throat Swabs	14.1% Mortality
9.	T. Guo et al (20), March 2020,	China	n=187; A: 58.5; M: 91 (48.7%)	Case Series	Positive (RT PCR)	23% Mortality
10.	X. Yang, et al (21),	China	n= 52; A: 59.7;	Retrospective observational	Positive	61.52% Mortality

	February 2020,		M: 21 (40%)	study		
11.	S. Shi, et al (22), February 2020,	China	n= 416; A: 64 (21-95); F: 211 (50.7%)	Cohort study	Positive (RT PCR)	13.7% Mortality
12.	C Chen et al (23), February 2020,	China	n= 150; A: 59 (\pm 16); M: 84 (56%)	Retrospective observational study	Positive (NAT) Pharyngeal/throat swab	7.3% Mortality
13.	H Hui et al (24), February 2020,	China	n=41; A:47; M: 46.3%	Retrospective Study	Positive	4.87% Mortality (2 out of 41 patients died)
14.	F. Zhou et al (25), March 2020,	China	n=191; A: 56 (46–67); M: 119 (62%)	Cohort Study	Positive (RT-PCR) Throat Swab	28.27% Mortality (54 out of 191 patients died)
15.	C. Huang et al (26), February 2020	China	n=41; A: 49 (41.0–58.0); M: 30 (73%)	Prospective Cohort	Positive (RT-PCR) Lower respiratory tract specimens	15% Mortality
16.	Q. Deng et al (27), March 2020	China	n=112; A: 65.0 (49.0-70.8P); M: 57(50.9%)	Retrospective Observational Study	Positive (RT-PCR) Nasopharyngeal Swab	12.5% Mortality

Acronyms: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus2; COVID-19: Coronavirus Disease 2019; RT-PCR: Real-Time Reverse Transcription Polymerase Chain Reaction; NAT: Nucleic Acid Test; A: Age; M: Male; F: Female

Results

A total of 16 studies were included in this literature review after a thorough analysis of research articles. Five out of sixteen studies were case reports, four were case series, four were retrospective observational study, and three were prospective cohort studies. Out of 16 studies, 13 studies were carried out in China while two were from Italy and one was from the United States (US). A total of 2,112 patients were included in this systematic review. The most common method of testing severe acute respiratory syndrome coronavirus2 (SARS-CoV2) was real-time reverse transcriptase polymerase chain reaction technique (Real-time- RT- PCR). Five studies mentioned nasopharyngeal swab as the sampling technique, four studies stated throat/pharynx as the source of sampling extracted and one collected from lower respiratory tract specimen while remaining six studies did not comment on the source of specimen. Tavazzi et al (16) localized the viral particles within the interstitial cells of the myocardium of the patient. The common presenting complaints were dry cough, fever, fatigue and shortness of breath. The common co-morbidities observed were hypertension, coronary heart disease, and diabetes. We focused on cardiac consequence secondary to coronavirus in this article and we found acute cardiac injury as the most common complication

(13 out of 16 studies) while other complications were cardiac arrhythmia (3 out of 16 studies), fulminant myocarditis (2 out of 16 studies), cardiogenic shock (2 out of 16 studies) and heart failure (2 out of 16 studies). Demographic details and other characteristics are mentioned in Table 1 and a summary of the results of all 16 studies is given in table 2.

Two case reports (12,14), revealed fulminant myocarditis in COVID-19 patients. Zeng et al (12) reported the first case of COVID-19 infection complicated with fulminant myocarditis. The echocardiography of the patient showed diffuse myocardial dyskinesia and reduced left ventricular ejection fraction (LVEF) of 32% and the troponin I and NT-BNP were 11.37 g/L, 22,600pg/ml, respectively. Hu et al(14) reported fulminant myocarditis with cardiogenic shock in a 37-year-old male COVID-19 patient. The electrocardiogram (ECG) suspected the ST-segment elevation myocardial infarction and echocardiography revealed an enlarged heart with a markedly decrease in LVEF of 27%, and trace pericardial effusion. The Troponin T was >10,000 ng/ml and NT-BNP was up to 21,025 ng/L. Inciardi et al (13) noticed myopericarditis in a middle-aged female, the echocardiography showed diffuse biventricular hypokinesia, circumferential pericardial effusion, and LVEF of 40%. The troponin T level was 0.24 ng/ml and NT-BNP was 5647 pg/mL. In the latter two studies, coronary angiography was done but there was no evidence of obstructive coronary disease. Cui (15) et al stated the first case of acute cardiac injury in a 55-day old infant female with COVID-19 and troponin I level was up to 0.025 µg/l.

Tavazzi et al (16) found viral particles within the myocardial interstitial cells on myocardial biopsy of a 69-year-old patient, who already tested positive for COVID-19 on nasopharyngeal swab RT-PCR. The patient developed an acute cardiac injury, cardiogenic shock, and worsening hypotension. The echocardiography showed severe and diffused left ventricle (LV) hypokinesia and LVEF of 34% that dropped to 25% in a few hours while hs-TnI was elevated up to 4332 ng/l. Coronary angiography findings were unremarkable. The patient in this case report died of septic shock.

In a case series, Arentz et al (17) reported cardiomyopathy in 7 patients (33%) and mean Troponin I was 3 ng/ml and mean NT-BNP 4720pg/ml. The patients were managed on mechanical ventilators and vasopressors while the study reports a mortality rate of 67%. Three other case series (18–20), reported the acute cardiac injury as the potential cardiac complication in COVID-19 patients. Wang et al (18) reported acute cardiac injury in 7.2%, shock in 8.7%, and arrhythmia in 16.7% of the total population as the cardiac outcomes. The mean troponin I level was 11.0 (5.6-26.4) pg/ml in ICU patients and the mortality rate was recorded 4.3%. Chen et al (19) discussed that 113 deceased COVID-19 patients had an acute cardiac injury (77%) and heart failure (49%). The following biomarkers in deceased patients were higher as compared to recovered patients: NT-BNP was 800 (389.8-1817.5) pg/mL, hs-troponin was 40.8 (14.7-157.8) pg/mL and interleukin-6 was 72.0 (35.6-146.8) pg/mL. Patients with cardiovascular co-morbidities were prone to develop severe cardiac complications. Guo et al (20) narrated a case series study in which 27.8% of patients had myocardial injury marked by elevated TnT levels resulting in cardiac dysfunction and arrhythmias. Those with elevated TnT levels also had significantly higher levels of other biomarkers of cardiac injury, specifically CK-MB (median 3.34ng/ml) and NT-BNP (median 817.4pg/ml). The TnT levels demonstrated a positive linear correlation with NT-proBNP levels ($P < .001$). The overall mortality rate was 23.0% and it was markedly higher in elevated plasma TnT group (59.6%).

Table 2: Summary of the results of all 16 studies

S.No.	Author	Presenting complaints	Co-Morbidities	Troponin Levels	(NT-BNP)	Cardiac complications	Treatment options
1.	J.H. Zeng et al (12)	Cough, fever, shortness of breath & chest tightness	None	TnI I- 11.37 g/L	22600 pg/ml	Fulminant myocarditis	Antiviral & Antibiotic therapy Interferon α -1b Corticosteroids & Immunoglobulin Mechanical Ventilation CRRT & ECMO
2.	R. M. Inciardi et al (13)	Fever, cough, & severe fatigue	None	TnT-0.24 ng/ml	5647 pg/mL	Acute cardiac injury (Myopericarditis)	Heart failure-related medicines HCQ, Antiviral therapy & Corticosteroids
3.	H. Hu et al (14)	Chest pain, dyspnea & diarrhea	None	TnT >10,000 ng/ml	21,025 pg/ml	Fulminant Myocarditis & cardiogenic shock	Corticosteroids & Immunoglobulin Vasopressors Diuretic Milrinone Antibiotics & PPIs
4.	Y. Cui et al (15)	Rhinorrhoea & dry cough	None	TnI-0.025 μ g/l	Not given	Acute cardiac injury	Oxygen Inhalation Ambroxol Antibiotics Interferon α -1b & IV sodium creatine phosphate
5.	G. Tavazzi et al (16)	Dyspnea, cough & weakness	Not Known	hs-TnI (4332 ng/L)	Not given	Acute cardiac injury, Cardiogenic Shock	Mechanical ventilation & VA-ECMO, Vasopressors & IABP
6.	M. Arentz et al (17)	Fever, cough, shortness of breath	CKD, CHF & Diabetes	Mean TnI- 3ng/ml	Mean 4720 pg/ml	Cardiomyopathy	Mechanical Ventilation & Vasopressors

7.	D. Wang et al (18)	Fever, fatigue & dry cough	HTN, CVD, Diabetes, Malignancy	Mean TnI- 11.0 pg/ml	Not given	Acute cardiac injury Arrhythmia & Shock	Antiviral & Antibiotics therapy Glucocorticoid therapy Oxygen Inhalation NIV, Mechanical Ventilation CRRT & ECMO
8.	T. Chen et al (19)	Fever, cough & fatigue	HTN, Diabetes & CVD	Median Hs-Tn I, 40.8 (14.7-157.8) pg/mL (In deceased pts)	Not Given	Acute cardiac Injury Heart Failure	Antiviral & Antibiotics therapy Glucocorticoid therapy & IVIG Interferon inhalation Oxygen Inhalation Mechanical ventilation CRRT & ECMO
9.	T. Guo et al (20)	Not given	HTN, CHD, and Diabetes	Not given	Mean 817.4 pg/mL	Acute Cardiac Injury Malignant Arrhythmia VT/VF	Antiviral & Antibiotics therapy Corticosteroids & Mechanical Ventilators
10.	X. Yang, et al (21)	Fever, cough & dyspnea	HTN, CHD, Diabetes & CVA	Median hs-Tn I- 161.0 pg/ml	Not given	Acute Cardiac injury	Antiviral & Antibacterial therapy Vasopressors Glucocorticoids & Immunoglobulin Mechanical ventilation ECMO & CRRT
11.	S. Shi, et al (22)	Fever, Cough & shortness of breath	HTN and Diabetes	Hs-Tn I 0.19 ug/L (In cardiac injury pts)	1689 pg/ml (In cardiac injury patients)	Acute Cardiac Injury	Antiviral & Antibiotics treatment Oxygen inhalation NIV & Invasive mechanical ventilation CRRT, Glucocorticoids & IVIG
12.	C Chen et al (23)	Not given	HTN, CHD & Diabetes	TnI 68.5 ng/l (In critical group)	1030 ng/l (In critical group)	Acute Cardiac Injury	CRRT & ECMO
13.	H Hui et al (24)	Respiratory symptoms	HTN, CAD, & DM-2 and tumor	TnI 0.54 ng/ml (In cardiac injury pts)	Not given	Arrhythmia (Atrial Fibrillation) Acute cardiac injury	Oxygen support NIV & Mechanical Ventilation

14.	F. Zhou et al (25)	Fever, Cough & malaise	HTN, Diabetes, and CHD	Median hs-TnI 22.2 pg/ml (In non-survivors group)	Not given	Heart Failure, Acute Cardiac Injury	Antibiotics & Antiviral treatment Corticosteroids, IVIG Oxygen therapy NIV & Invasive mechanical ventilation ECMO & CRRT
15.	C. Huang et al (26)	Fever, cough & myalgia /fatigue	Diabetes, HTN & CVD	Hs-TnI 3.3 (3.0–163.0) pg/ml in ICU pts	Not Given	Acute Cardiac Injury Shock	Anti-viral & Antibiotic therapy Corticosteroids NIV & Invasive Mechanical ventilation ECMO & CRRT
16.	Q. Deng et al (27)	Fever, cough & shortness of breath	HTN, CHD & diabetes	TnI 0.10 (0.01-0.77) ng/ml	1142.0(38 8.3-5956.5) ng/L	Acute cardiac injury (Myocarditis)	Mechanical ventilation & ECMO

Acronyms: NT-BNP: N-terminal Brain Natriuretic Peptide [or NT-proBNP: N-terminal Pro hormone Brain Natriuretic Peptide(NT-proBNP)]; TnI: Troponin I; TnT: Troponin T; CRRT: Continuous Renal Replacement Therapy; ECMO; Extracorporeal Membrane Oxygenation; HCQ: Hydroxychloroquine; PPIs: Proton Pump Inhibitors; IV: Intravenous; hs-TnI: high-sensitivity Troponin I; VA-ECMO: Venous-Arterial Extracorporeal Membrane Oxygenation; IABP: Intra-Aortic Balloon Pump; CKD: Chronic Kidney Disease; CHF: Congestive Heart Failure; HTN: Hypertension; NIV: Non-Invasive Ventilation; CVD: Cardiovascular disease; IVIG: Intravenous Immunoglobulin; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; CVA: Cerebrovascular accident; CHD: Coronary Heart Disease; CAD: Coronary Artery Disease; DM-2: Diabetes Mellitus Type 2; pts: patients

Acute cardiac injury remained a frequent cardiac complication in COVID-19 patients in other studies as well. Yang et al (21) reported acute cardiac injury in 23% of the patients and median hs-TnI: 161.0pg/ml while the overall mortality rate was 61.5%. The cardiac injury was more common in non-survivors than survivors. Shi et al (22) analyzed that 19.7% of the patients had a cardiac injury and median hs-Troponin I was 0.19 ug/L and NT-proBNP was 1689pg/ml. Cardiac injury in this study was more prevalent in older patients with co-morbidities and requiring either noninvasive ventilation or mechanical ventilation. The overall mortality rate was 13.7% and it was very high in patients with cardiac injury (51.2%). Chen et al (23) stated the levels of NT-BNP 1030ng/l and cTnI 68.5ng/l in critical group indicating cardiac injury and levels were significantly higher than those in the non-critically ill patients. The multivariate logistic regression results showed that increased cTnI (OR = 26.909, 95% CI 4.086-177.226, P = 0.001), and previous coronary heart disease history (OR = 16.609, 95 % CI 2.288-120.577, P = 0.005) are an independent related factor of COVID-19 severity. Hui et al (24) reported troponin I 0.54ng/ml level in critically ill patients and the increased TnI was statistically significant compared with the light group (p<0.05), the mild group (p<0.01), and the severe group (p<0.01). The number of severe and critical cases were significantly larger in the cardiac-related chronic diseases group (P<0.01) and old age patients group (P<0.01).

Zhou et al(25) reported acute cardiac injury in 17% and heart failure in 23% of the population and both were reported higher in the non-survivor group than in the survivor group (p <0.0001). The median hs-Troponin I was 22.2pg/ml in non-survivor higher than the survivor group. The overall mortality rate recorded was 28.27%. Huang et al (26) mentioned acute cardiac injury in 12% and shock in 7% of the total population and both complications were more common in ICU care patients. The level of hs-troponin I noted was 3.3 (3.0–163.0) pg/mL in the ICU care group and the overall mortality rate was up to 15%. Deng et al (27) analyzed that 12.5% of COVID-19 patients had myocarditis (cardiac injury) Cardiac troponin I was elevated up to > 0.04ng/mL and increased up to the thrice times (over 0.12ng/mL) patients during hospitalization and NT-BNP levels were 1142.0(388.3-5956.5) ng/L. Both cardiac biomarkers were significantly higher in the severe group (p<0.01). The typical signs of myocarditis were absent on echocardiography and electrocardiogram except there were 6 (5.4%) patients with LVEF <50% and no patients had LVEF <40%, whereas, the pericardial effusion was noticed in patients in the severe group.

Three studies (18,20,24) found cardiac arrhythmia as the potential cardiac complication in COVID-19 patients. In a study conducted by Wang et al (18), 16.7% of the total population developed arrhythmia and this complication was seen more common in ICU care patients than non-ICU patients (44.4% vs 6.9%). Guo et al (20) reported malignant arrhythmia including VT/VF in 5.9% patients, described as rapid ventricular tachycardia lasting more than 30 seconds, causing hemodynamic instability and/or ventricular fibrillation. It was found in this study that NT-BNP elevation and malignant arrhythmias were significantly more common in patients with elevated TnT levels. In another study, Hui et al (24) mentioned that two patients in the critical group had the onset of atrial fibrillation. One patient had persistent atrial fibrillation before the infection of COVID-19 and another patient was not been diagnosed with any cardiac problem before. However, both of these patients died. Thus, it is very important to note the tachycardia in the severe and critical COVID-19 patients and look for underlying arrhythmia.

Three of the studies (12,19,25) mentioned interleukin-6 (IL-6) levels indicating underlying cytokine storm. Zeng et al (12) reported the highest level of Interleukin 6 was 272.40pg/ml in a patient with

fulminant myocarditis. After receiving the treatment, interleukin 6 reduced to 7.63pg/ml. Chen et al (19) also reported interleukin-6 72.0 (35.6-146.8) pg/mL higher than recovered patients. Zhou et al (25) stated that IL-6 in non-survivor patients 11.0 (7.5-14.4) pg/ml more than survivor group.

Discussion

COVID-19 can cause either direct damage to the myocardial cells by using ACE2 receptors as an entry point to the cells or a high level of cytokine cascade causing damage to cardiac myocytes or oxygen demand and supply mismatch (28). It can cause cardiac outcomes like fulminant myocarditis, acute cardiac injury, cardiomyopathy, heart failure, cardiogenic shock, or arrhythmia. Fulminant myocarditis is the sudden onset, severe myocardial injury with the rapid emergence of severe hemodynamic instability, and elevated cardiac biomarkers leading to a high mortality rate (29). Acute cardiac injury refers to acute myocardial involvement in COVID-19 and it is defined as blood levels of cardiac biomarkers [high-sensitivity troponin I (hs-TnI)] above the 99th-percentile upper reference limit (16,26). The acute cardiac damage could be either due to myocardial inflammation (myocarditis or myopericarditis), or necrosis (16).

Fulminant myocarditis associated with COVID-19 was first reported by Zeng et al (12). The patient cardiac biomarkers were significantly elevated but it was observed that interleukin-6 level was also increased (272.40pg/ml), suggesting the presence of cytokine storm. The cytokine cascade can cause vascular permeability, myocardial edema, and thickening of the interventricular septum in this patient. The extracorporeal membrane oxygenation (ECMO) was used to decrease the cardiopulmonary burden, played a pivotal role in improving LVEF of the patient to 68%, and reversing the left ventricle wall thickness to the normal range. The use of CRRT removed cytokines from the blood, reducing the further harmful immune response. Hu et al (14) reported fulminant myocarditis and cardiogenic shock in a patient accompanied by elevated cardiac biomarkers and cardiomegaly and decreased LVEF on echocardiography. Early corticosteroids were used to suppress inflammation and immunoglobulin therapy to regulate the immune status of the patient which resulted in the improvement of the patient.

Myopericarditis was reported by Inciardi et al (13) in a 53-year-old female based on echocardiography, cardiac magnetic resonance imaging (MRI), and cardiac biomarkers. The cardiac MRI findings showed marked biventricular myocardial interstitial edema and a circumferential pericardial effusion and the slow gadolinium washout was consistent with acute myocarditis. The patient was conservatively managed on inotropic support for hypotension and started on heart failure-directed medicines, hydroxychloroquine, antiviral agents, corticosteroids and the patient showed significant clinical improvement.

Cui et al (15) reported the first case of acute myocardial injury in a 55 days old female infant. IV sodium creatine phosphate was added to protect the heart. The patient was managed and later on improved on antibiotics, interferon α -1b, oxygen inhalation, and ambroxol (for mucus clearance). Tavazzi et al (16) for the first time reported biopsy-proven myocardial localization of coronavirus in COVID-19 patients. Thus, it demonstrates that COVID-19 can localize in other organs/tissues. Arentz et al (17) noticed cardiomyopathy in COVID-19 patients causing a globally decreased left ventricular systolic function and elevation in the level of cardiac biomarkers without a history of systolic dysfunction.

The majority of the studies described the acute cardiac injury as the major cardiac concern in COVID-19 patients. Wang et al(18) reported cardiac complications including acute cardiac injury, arrhythmia, and shock were more common in the ICU patients. The most critically ill patients were older and had more underlying co-morbidities than non-critical patients. Chen et al (19) mentioned that acute cardiac injury and heart failure were more frequent in deceased patients. This study specified that cardiac complications could be a major risk for mortality in COVID-19 regardless of the history of previous cardiovascular disease. Guo et al (20) reported malignant arrhythmia and acute cardiac injury in COVID-19 patients. The patients with elevated TnT levels were older, prevalently male population, and had co-morbidities. The patients in the elevated TnT level group had frequent malignant arrhythmias, the use of glucocorticoid therapy or mechanical ventilation, and a higher mortality rate. Yang et al (21) analyzed that non-survivor patients as compared to survivors were older, more likely to develop ARDS and acute cardiac injury resulting in more likely to receive mechanical ventilation. Shi et al (22) stated that patients with cardiac injury were older, had more co-morbidities, required noninvasive/invasive mechanical ventilation, and leading to a higher mortality rate. Chen et al (23) narrated that critical cases had more male patients with co-morbidities, elevated NT-proBNP, and cTnI causing myocardial injury than in mild cases. Hui et al (24) mentioned that the cardiac injury was common in severe and critical patients and atrial fibrillation was also seen in the critical group. It was proposed that the cardiac-related chronic diseases in COVID-19 patients could result in severe or critical cases, thus such patients should get more intense clinical care.

Zhou et al (25) discussed that acute cardiac injury and heart failure were more common in the non-survivor group and elevated levels of IL-6, hs-troponin I, and lactate dehydrogenase and lymphopenia were also seen commonly in severe COVID-19 illness. The cardiac consequences in COVID-19 patients in Huang et al (26) were shock and acute cardiac injury and both were more in the ICU care group. Hs-troponin I (hs-TnI) and elevated cytokines were recorded in the plasma of critically ill patients. The ICU care group witnessed more deaths than non-ICU care. Deng et al (27) analyzed that myocarditis was more common in severe disease group and cardiac biomarkers were also higher in those patients. The severely affected group had more old age patients than non-severe but there were no significant differences in co-morbidities between severe and non-severe groups. This study suggested that myocardial injury was more likely related to systemic consequences rather than direct damage by the 2019 nCoV.

Conclusion

This review study summarizes different aspects of cardiac complications secondary to COVID-19. This literature discusses the level of cardiac biomarkers and interleukin 6 levels related to the disease severity. The key points of cardiac imaging and electrocardiography linked with cardiac outcomes in COVID-19 patients are also described. We highlighted different treatment options which were pivotal in the management of these patients and stated mortality rate or recovery rate of different studies. We observed that cardiac complications were more common in old age, male patients, and those with chronic cardiac diseases. We also noticed that coronary angiography in such cases may yield non-obstructed coronary arteries. The study emphasizes that the spectrum of cardiovascular outcomes in COVID-19 patients should be evaluated carefully so that life-threatening complications could be avoided. To understand the pathophysiology of the disease and outline the management options such clinical studies are needed.

Limitations

There were few limitations while writing this systematic review. First, the data in various studies were not adjusted for confounding variables including age, gender, hypertension, coronary artery disease, or diabetes. Secondly, the population size of the different studies was small. Thirdly, the correlation between biomarkers (TnI/ TnT or NT-BNP or IL-6) was not present in all studies, thus it was difficult to quantify the direction and strength of the relationship between biomarkers. Fourthly, electrocardiographic and cardiac imaging including echocardiographic findings were missing in some studies which could help to understand disease characteristics. Therefore, we propose further clinical studies at a large scale to eliminate confounding bias and increase the statistical power of each study.

Additional Information

Disclosures: The authors have declared that no conflicts of interest exist.

Author did not receive any funding source for this article.

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