

# Cardiovascular Implications of Coronavirus Disease 2019 (COVID-19): A Systematic Review

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## Systematic Review

**Keywords:** Coronavirus disease-2019, COVID-19, Cardiovascular implications, Acute cardiac injury, Death

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## Abstract

**Background:** World Health Organization has declared Coronavirus disease (COVID-19) as a Public Health Emergency of International Concern. It has killed thousands and millions are infected worldwide. Though COVID-19 is supposed to be primarily a disease of respiratory system, it also has widespread implications on other systems as well. The aim of this systematic review is to summarize the cardiovascular implications of COVID-19.

**Methods:** PubMed, PubMed Central, EMBASE, and Google Scholar were searched for peer-reviewed articles which aimed to delineate the cardiovascular implications of COVID-19.

**Results:** A total of six articles (five original articles and one case report) were included. We found diverse cardiovascular implications of COVID-19 ranging from acute cardiac injury to death. New onset abnormalities in electrocardiogram or echocardiogram, elevated plasma levels of cardiac troponin, NT-proBNP, and D-dimer have role in early identification of acute cardiac injury in such patients. Additionally, cardiac troponin and NT-proBNP can be used to evaluate prognosis and possible need for intensive care in these patients.

**Conclusion:** Acute cardiac injury is common in patients with COVID-19. Aggressive supportive management based on prognostic indicators along with management of heart failure, arrhythmias, acute coronary syndrome and thrombosis can improve clinical outcomes in such patients.

## Introduction

In late 2019, a cluster of cases of 'pneumonia of unknown origin' emerged which was linked to seafood wholesale and wet market in Wuhan, China (1), that heralded the onset of Coronavirus disease (COVID-19). The disease has now spread rapidly to several countries around the globe and has already been declared a pandemic by WHO (2). Till April 8, 2020, a total of 1,441,589 confirmed cases of COVID-19 with mortality of 82,933 have been reported (2). COVID-19 is probably the greatest threat to mankind of 21<sup>st</sup> century that has not only challenged the current medical practices, but also has imposed a huge psychological and socio-economic burden to the entire world.

Coronavirus is one of the major pathogens that primarily target the human respiratory system (3). However, previous outbreaks of coronaviruses i.e. severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) have already shown multisystem involvement including cardiovascular system as well (4-6). Given that, with increasing number of confirmed cases and death due to COVID-19, it is important to be acquainted with cardiovascular manifestations induced by this viral infection. However, there is only limited published data pertaining to cardiovascular presentations of COVID-19. The present systematic review aims to describe the cardiovascular implications of COVID-19 and fill the gap in the knowledge regarding understanding of varied cardiovascular manifestations of COVID-19.

## Methods

### Protocol and registration

We followed the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (7). The systematic review protocol was not registered due to the urgency of the matter and very limited available evidence on the topic.

### Eligibility criteria

Published peer-reviewed articles from January 1, 2020 until March 30, 2020 which aimed to assess cardiovascular implications in patients with COVID-19 were included. Article language restrictions were not imposed. In addition to original articles; case reports, and case series were also included. Editorials, letters to editor, and correspondences were excluded.

### Search strategy

We searched standard relevant publications indexed in PubMed, PubMed Central (PMC), EMBASE, and Google Scholar. For COVID-19, we used "Novel coronavirus", "Novel coronavirus 2019", "2019 nCoV", "Coronavirus Disease 2019", "COVID-19", "Wuhan coronavirus," "Wuhan pneumonia," and "SARS-CoV-2." For cardiovascular implications, we used "Cardiovascular implications", "Acute myocardial injury", "Acute cardiac injury", "Arrhythmias", "Heart failure", and "Myocardial infarction". A thorough review of the references revealed further relevant articles.

### Study selection and data abstraction

First of all, we screened articles by title and abstract. Then, we examined full texts of relevant articles for inclusion and exclusion criteria. The data abstraction spreadsheet using Microsoft Excel version 2013 was developed; which included the following information: author, year of publication, journal, and country where the study was done, study design, sample size, baseline characteristics and laboratory parameters of the patients and cardiovascular implications of COVID-19. Any duplicated article was counted as a single article.

## Results

A total of 315 articles were retrieved using the search strategy. After screening by abstract and title, 52 articles were selected for full-text assessment. Of these, 46 articles were excluded as they were not relevant to research aims and objectives [Figure 1].

### *Study characteristics*

All the studies were conducted in China in 2020 and all of them were original articles except for one case report of Cui, et al. (8). Among the original articles, all were retrospective studies except study by Huang, et al. (9) which was prospective, observational study. All the studies have categorized patients into two groups: non-ICU/non-critical/without myocardial injury/with normal cardiac Troponin group and ICU/critical/with myocardial injury/with elevated cardiac Troponin group. Wang, et al.(10) and Huang, et al. (9) defined acute cardiac injury as blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (>28 pg/mL) or new abnormalities shown on electrocardiography and echocardiography. Xingwei, et al. (11) defined myocardial injury as blood levels of myocardial troponin  $\geq 3$  times the upper reference limit (34.2 ng / L). However, Chen, et al.(12) and Guo, et al. (13) defined myocardial injury as serum levels of troponin above the 99th percentile upper reference limit [Table 1].

## **Baseline characteristics and co-morbidities of the patients**

The median age of the patients in all the studies was above 50 years, except in studies of Huang, et al.(9) (median age; 49 years) and Cui, et al. (8) (patient's age; 55 days). In all studies, patients requiring ICU/critical care or patients with myocardial injury/elevated cardiac Troponin were older comparatively, except in study conducted by Huang, et al.(9) (median ages of patients in non-ICU and ICU groups were same). Male predominance was seen in all studies except studies of Cui, et al. (8) and Guo, et al. (13). All the studies have included the underlying co-morbidities of the patients [Table 2].

## **Cardiovascular complications associated with COVID–19**

Wang, et al. (10) established that among the 138 patients, acute cardiac injury was seen in 10 (7.2%), shock in 12 (8.7%), and arrhythmia in 23 (16.7%) patients. ICU patients were more likely to have one of these complications than non-ICU patients ( $p < 0.001$ ) [Table 3]. ICU patients demonstrated significantly high levels of creatine phosphokinase myocardial band (CPK-MB), cardiac troponin I (cTnI) and D-dimer. Similarly, number of patients who had procalcitonin levels >0.05 ng/mL were more in ICU group compared with non-ICU group (27 [75%] vs 22 [21.6%]) [Table 4].

Study conducted by Huang, et al. (9) found that among the 41 patients, acute cardiac injury was seen in five (12%) and shock in three (7%) patients. Acute cardiac injury (4 [31%] vs 1 [4%]) and shock (3 [23%] vs zero [0%]) were seen more commonly in ICU patients compared with non-ICU patients [Table 3]. Besides, ICU patients demonstrated significantly high levels of creatine phosphokinase (CPK), and D-dimer. Number of patients who had procalcitonin levels >0.05 ng/mL and cTnI >28 pg/mL (99th percentile) were more in ICU group compared with non-ICU group [Table 4].

Similarly, Chen, et al. (12) discovered that among the 150 patients, 22 (7.1%) patients had acute cardiac injury. In the same study, out of 24 patients in critical group, 15 (62.5%) had acute cardiac injury and 7 (5.6%) out of 126 patients in non-critical group had acute cardiac injury and the difference was statistically significant ( $p$ -value <0.001) [Table 3]. Hypersensitive C-reactive protein (hs-CRP), N-terminal-pro brain natriuretic peptide (NT-proBNP) and cTnI levels of the patients were significantly higher in critical care cases than in mild cases ( $p$ -value <0.001) [Table 4]. On univariate logistic regression analysis, critical disease status had a significant correlation with age, male gender, elevated NT-proBNP, elevated cTnI, elevated hs-CRP, hypertension, and coronary artery disease (all  $p < 0.05$ ). Multivariate logistic regression analysis revealed that elevated cTnI (OR = 26.909, 95%CI 4.086–177.226,  $p = 0.001$ ) and coronary artery disease (OR = 16.609, 95%CI 2.288–120.577,  $p = 0.005$ ) were the independent risk factors of critical disease status.

In study performed by Xingwei, et al. (11) among the 54 severe/critically severe patients, acute myocardial injury was discovered in 24 (44.4%) patients while 26 (48.1%) patients died during hospital stay. In-hospital mortality rate was significantly higher in myocardial injury group compared to the group without myocardial injury [75.0% (18/24) vs. 26.7% (8/30),  $p$ -value = 0.001]. In myocardial injury group, C-reactive protein (CRP) and NT-proBNP levels were also found to be significantly higher than those without myocardial injury (all  $p$ -value<0.01)

Cui, et al (8) has described a case report of acute cardiac injury in an infant infected with COVID–19 as suggested by elevated plasma levels of CPK-MB, and cTnI.

Guo, et al. (13) discovered that among the 187 patients, 52 (27.8%) exhibited acute cardiac injury as indicated by elevated cardiac troponin T (cTnT) levels. During hospitalization, arrhythmias were seen in 11 (5.9%) patients. Patient with elevated cTnT levels had more frequent malignant arrhythmias compared with normal cTnT [9[17.3%] vs 2[1.5%]]. The overall mortality was 23% (43 patients died) [Table 4]. The mortalities were 7.62% (8 of 105), 13.33% (4 of 30), 37.50% (6 of 16), 69.44% (25 of 36) for patients without underlying CVD and normal cTnT levels, with underlying cardiovascular disease (CVD) and normal cTnT levels, without underlying CVD but elevated cTnT levels, and with underlying CVD and elevated cTnT levels respectively. Elevated cTnT levels was seen more commonly in patients with underlying CVD compared with patients without CVD (36 [54.5%] vs 16 [13.2%]). A significant positive linear correlation of plasma cTnT levels with plasma hsCRP levels ( $\beta = 0.530$ ,  $p < .001$ ) and NT-proBNP levels ( $\beta = 0.613$ ,  $p < .001$ ) was also observed.

## **Discussion**

In previous outbreaks of influenza and coronavirus i.e. MERS and SARS coronavirus, cardiovascular implications like myocarditis, acute myocardial infarction, and acute exacerbation of heart failure (both systolic and diastolic) have been well-recognized (4, 14–17) [Table 5]. Based on the studies analyzed, we found that patients with COVID–19 too have a diverse cardiovascular implications ranging from acute cardiac injury to death. The incidence of acute cardiac injury ranges from 7% to 44 % in different studies and the incidence were higher in patients admitted to ICU compared with non-ICU patients [Table 3]. Additionally,

cardiovascular involvement was more commonly seen in elderly male. Patients with underlying coronary artery disease, hypertension, cardiomyopathy and other co-morbid illness are more prone to experience myocardial injury during the course of COVID-19. In these patients, superimposed viral illness damages the myocardial cells by enhancing the systemic inflammatory responses, aggravating hypoxia, and destabilizing coronary plaque. The exact pathophysiology of myocardial injury in previously healthy patients with COVID-19 infection is not fully understood. Cardiac injury can occur via direct or indirect mechanisms [Figure 2]. Direct mechanism is exhibited by infiltration of virus into myocardial cells and myocardial inflammation, resulting into cardiomyocyte death. Indirect mechanisms include respiratory failure and hypoxemia, multi-organ dysfunction, hyper-inflammation accompanied by cytokine storm, which ultimately lead to myocardial injury (18). Cytokine storm during infection possibly cause reduction in coronary blood flow, destabilization of coronary plaque and microthrombogenesis (19).

Inflammatory markers like CRP/ hs-CRP, and procalcitonin were found to be significantly elevated in patients with myocardial injury/critical patients/ICU patients; suggesting role of inflammation in COVID-19 mediated cardiac injury. Increased plasma levels of cardiac troponin, NT-proBNP, and D-dimer or new onset abnormalities in electrocardiogram or echocardiogram can be helpful in early identification of acute cardiac injury in patients of COVID-19. Besides, cardiac troponin and NT-proBNP may play role in prognostication and possible need for intensive care in such patients. Aggressive supportive management based on prognostic indicators can improve clinical outcomes in such patients. Management of heart failure, arrhythmias, acute coronary syndrome and thrombosis is important.

The present work is, to the best of our knowledge, the first systematic review of the latest published peer reviewed studies, addressing the cardiovascular implications of COVID-19.

## Limitations of the review

Our review has included limited number of available studies with small sample size. Hence, the result of our systematic review should be considered with caution. All studies included in our review were conducted in China and most of them were retrospective. Thus, our review lacks heterogeneous and diverse population. We recommend multicenter, multi-national, prospective studies be carried on cardiovascular implications of COVID-19. It is difficult to postulate myocardial injury as the sole cause of death as it may have occurred due to multi-organ dysfunction.

## Conclusion

Acute cardiac injury is common in patients with COVID-19 and when it occurs, has a poor prognosis. Monitoring of myocardial injury markers and cardiac function is of utmost importance, and attention should be paid to the early identification and comprehensive management of myocardial injury in such patients.

## Declarations

**Ethics approval and consent to participate:** Not applicable.

**Consent to publish:** Not applicable.

**Availability of data and materials:**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

Authors declare no competing interests.

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**Authors' contribution:**

RRP, AKY, and SM contributed to writing and reviewing data, data extraction, analysis of the results, and screening articles. RRP and AKY supervised and conceptualized the project. Specifically, all authors have (i) made substantial contributions to conception and design or acquisition of data or analysis and interpretation of data, (ii) been involved in drafting the manuscript or revising it critically for important intellectual content, (iii) given final approval of the version to be published, and (iv) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Tables

Table 1: Study characteristics

Author	Year	Country	Journal	Sample size	Study design	Objectives	Inclusion criteria	Exclusion criteria
Wang, et al. (10)	2020 Feb	China	JAMA	138; non-ICU group: 102, ICU group: 36	Retrospective	To describe the epidemiological and clinical characteristics of novel coronavirus-infected pneumonia.	Patients with novel coronavirus-infected pneumonia diagnosed according to WHO interim guidance. Acute cardiac injury was defined if blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (>28 pg/mL) or new abnormalities shown on electrocardiography and echocardiography.	NA
Huang, et al. (9)	2020 Feb	China	Lancet	41; non-ICU group: 28, ICU group: 13	Prospective, observational	To describe epidemiological, clinical, laboratory, and radiological characteristics, treatment, and outcomes of patients confirmed to have 2019-novel coronavirus infection, and to compare the clinical features between ICU and non-ICU patients.	Real-time RT-PCR confirmed cases of 2019-novel coronavirus. Acute cardiac injury was defined if blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (>28 pg/mL) or new abnormalities shown on electrocardiography and echocardiography.	NA
Chen, et al. (12)	2020 March	China	Chinese J Card Dis	150; non-critical group: 126, critical group: 24	Retrospective	Analysis of myocardial injury and cardiovascular disease in critically ill patients with new coronavirus pneumonia.	Patients of new Coronavirus pneumonia clinically typed according to the "Diagnosis and Treatment Scheme for New Coronavirus Infected Pneumonia (Trial Version 6)". Critically ill patients were defined by one of the following conditions: respiratory failure requiring mechanical ventilation, presence of shock, and multi-organ failure requiring ICU admission. Acute cardiac injury was defined if blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (>26.3 ng/L).	Patients of acute myocardial infarction diagnosed by clinical chest pain symptoms and ECG changes.
Xingwei, et al. (11)	2020 March	China	Chinese J Card Dis.	54; Group with myocardial injury: 24, Group without myocardial injury: 30	Retrospective	To know the impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients.	(1) 2019-nCoV nucleic acid test positive cases, and meeting the diagnostic criteria for severe / critically severe cases;  (3) Critical and severe COVID-19 is defined in accordance with any of the following: (a) respiratory failure requiring mechanical ventilation; (b) shock; (c) combined with other organ failure requiring ICU monitoring and treatment (2) Complete clinical data and at least two cardiac troponin test results.  3. Myocardial injury was defined as blood levels of myocardial troponin $\geq 3$ times the upper reference limit (34.2 ng / L).	(1) Non-2019-nCoV infection confirmed cases; (2) patients with acute myocardial infarction, decompensated heart failure, and chronic renal failure; (3) missing clinical data.
Cui, et al (8)	2020 March	China	J Inf Dis.	1	Case report	To highlight that child with COVID-19 can also present with multiple organ damage and rapid disease changes.	NA	NA
Guo, et al. (13)	2020 March	China	JAMA	187; Group normal cardiac troponin: 135, Group with elevated cardiac troponin: 52	Retrospective	To evaluate the association of underlying cardiovascular disease and myocardial injury with fatal outcomes in patients with COVID-19.	Patients with COVID-19 who were diagnosed as per WHO interim guideline, and who were either treated and discharged or died during hospitalization. Myocardial injury was defined by serum levels of troponin T were above the 99th percentile upper reference limit.	NA

ICU: Intensive Care Unit

NA: Not available

nCoV: novel coronavirus

RT-PCR: Reverse Transcriptase- Polymerase Chain Reaction

WHO: World Health Organization

Table 2: Baseline characteristics and co-morbidities of the patients

Author	Age (years)	Male percentage	Hypertension (%)	Cardiovascular disease (%)	Diabetes (%)	Malignancy (%)	Cerebrovascular disease (%)	COPD (%)	CKD (%)	CLD (%)	HIV infec (%)
Wang, et al. (10)	Median: 56; non-ICU group: 51, ICU group: 66	54.3	31.2	14.5	10.1	7.2	5.1	2.9	2.9	2.9	1.4
Huang, et al.(9)	Median: 49; non-ICU group:49 , ICU group:49	73	15	15	20	2	NA	2	NA	2	NA
Chen, et al.(12)	Mean: 59; non-critical group:57.1 , critical group:68.5	56	32.6	6	13.3	2	NA	NA	1.3	NA	NA
Xingwei, et al. (11)	Median: 68; Group without myocardial injury:67 , Group with myocardial injury:69.5	63	44.4	14.8	24.1	3.7	5.6	3.7	NA	NA	NA
Cui, et al (8)	55 days	Female	NA	NA	NA	NA	NA	NA	NA	NA	NA
Guo, et al. (13)	Mean: 58.5; Group normal cardiac troponin:53.53 , Group with elevated cardiac troponin: 71.4	48.7	32.6	15.5	15	7	NA	2.1	3.2	NA	NA

ICU: Intensive Care Unit

NA: Not available

Table 3: Cardiovascular complications associated with COVID-19

Author	Complications	All patients (%)	ICU patients (%)	Non-ICU patients (%)	p-value
Wang, et al. (10)	Shock	8.7	30.6	1	< 0.001
	Acute cardiac injury	7.2	22.2	2	< 0.001
	Arrhythmia	16.7	44.4	6.9	< 0.001
	Death	4.3	NA	NA	NA
Huang, et al. (9)	Shock	7	23	0	0.027
	Acute cardiac injury	12	31	4	0.017
	Death	15	38	4	NA
Chen, et al. (12)	Acute cardiac injury	7.1	62.5	5.6	<0.001
	Death	7.3	41.7	0.8	<0.001
Xingwei, et al. (11)	Acute cardiac injury	44.4	NA	NA	NA
	Death	48.1	75 <sup>a</sup>	26.7 <sup>b</sup>	0.001
Cui, et al (8)	Death	Patient recovered	NA	NA	NA
Guo, et al. (13)	Acute cardiac injury	27.8	NA	NA	NA
	Arrhythmia	5.9	17.3 <sup>c</sup>	1.5 <sup>d</sup>	<0.001
	Death	23	59.6 <sup>c</sup>	8.9 <sup>d</sup>	<0.001

<sup>a</sup> Group with myocardial injury

<sup>b</sup> Group without myocardial injury

<sup>c</sup> Group with elevated cardiac troponin T

<sup>d</sup> Group without elevated cardiac troponin T

NA: Not available

Table 4: Inflammatory and cardiac biomarkers of the patients



Author	Parameters,	Normal range	All patients	Patients with severe disease or non-ICU patients	Patients with very severe disease or ICU patients	p-value
Wang, et al.(10)	CPK-MB (U/L)	< 25	14	13	18	< 0.001
	Procalcitonin (ng/mL) $\geq$ 0.05, No. (%)	< 0.05	49 (35.5)	22 (21.6)	27 (75)	< 0.001
	Troponin I (pg/mL)	< 26.2	6.4	5.1	11	0.004
	D-dimer (mg/L)	0-500	203	166	414	<0.001
Huang, et al. (9)	CPK (U/L)	$\leq$ 185	132.5	0.31	133	0.31
	Procalcitonin (ng/mL) $\geq$ 0.05, No. (%)	<0.05	3 (8)	0	3 (25)	NA
	Troponin I (pg/mL), >28 (99th percentile)	NA	5/41 (12%)	1/28 (4%)	4/13 (31%)	0.017
	D-dimer (mg/L)	NA	0.5	0.5	2.4	0.0042
Chen, et al. (12)	hsCRP (mg/L)	NA	NA	30.9	84.9	<0.001
	NT-proBNP (ng / L)	NA	NA	83	1030	<0.001
	Troponin I (ng/L)	NA	NA	4.5	68.5	<0.001
Xingwei, et al. (11)	CRP (mg/L)	10	NA	62.9 <sup>b</sup>	135 <sup>a</sup>	0.007
	NT-proBNP (ng/L)	<486	NA	201 <sup>b</sup>	971 <sup>a</sup>	<0.001
Cui, et al (8)	CRP (mg/L)	0–5	0.56	NA	NA	NA
	Procalcitonin (ng/mL)	0-0.046	0.15	NA	NA	NA
	CPK-MB (U/L)	0-25	46	NA	NA	NA
	Troponin I (ugm/L)	0-0.0156	0.025	NA	NA	NA
Guo, et al. (13)	hsCRP (mg/dL)	NA	4.04	3.13 <sup>d</sup>	8.55 <sup>c</sup>	<0.001
	Procalcitonin (ng/mL)	NA	0.08	0.05 <sup>d</sup>	0.21 <sup>c</sup>	<0.001
	Globulin (g/L)	NA	27.7	27.4 <sup>d</sup>	29.7 <sup>c</sup>	<0.001
	CPK-MB (ng/mL)	NA	1.14	0.81 <sup>d</sup>	3.34 <sup>c</sup>	<0.001
	Myoglobin (ug/L)	NA	38.5	27.2 <sup>d</sup>	128.7 <sup>c</sup>	<0.001
	NT-proBNP (pg/mL)	NA	268.4	141.4 <sup>d</sup>	817.4 <sup>c</sup>	<0.001
	d-dimer (ugm/mL)	NA	0.43	0.29 <sup>d</sup>	3.85 <sup>c</sup>	<0.001

CPK-MB: Creatine phosphokinase myocardial band

CPK: Creatine phosphokinase

hsCRP: Hypersensitive C-reactive protein

NT-proBNP: N-terminal-pro brain natriuretic peptide

<sup>a</sup> Group with myocardial injury

<sup>b</sup> Group without myocardial injury

<sup>c</sup> Group with elevated cardiac troponin T

<sup>d</sup> Group without elevated cardiac troponin T

Table 5: Cardiovascular implications of SARS-CoV and MERS-CoV

Outbreak	Author	Journal	Sample size	Cardiovascular implications
SARS	Yu, et al. (4)	BMJ	121	Hypotension, tachycardia, bradycardia, cardiomegaly, and arrhythmia
	Pan, et al. (15)	Chinese J Tuberculosis and Respiratory Dis	15	Cardiac arrest
	Li, et al (16)	Circulation	46	Sub-clinical diastolic impairment without systolic involvement on echocardiography
MERS	Alhogbani (17)	Annals Saudi Med.	1	Acute myocarditis and acute-onset heart failure

SARS: Severe Acute Respiratory Syndrome

MERS: Middle East Respiratory Syndrome

BMJ: British Medical Journal

## Figures

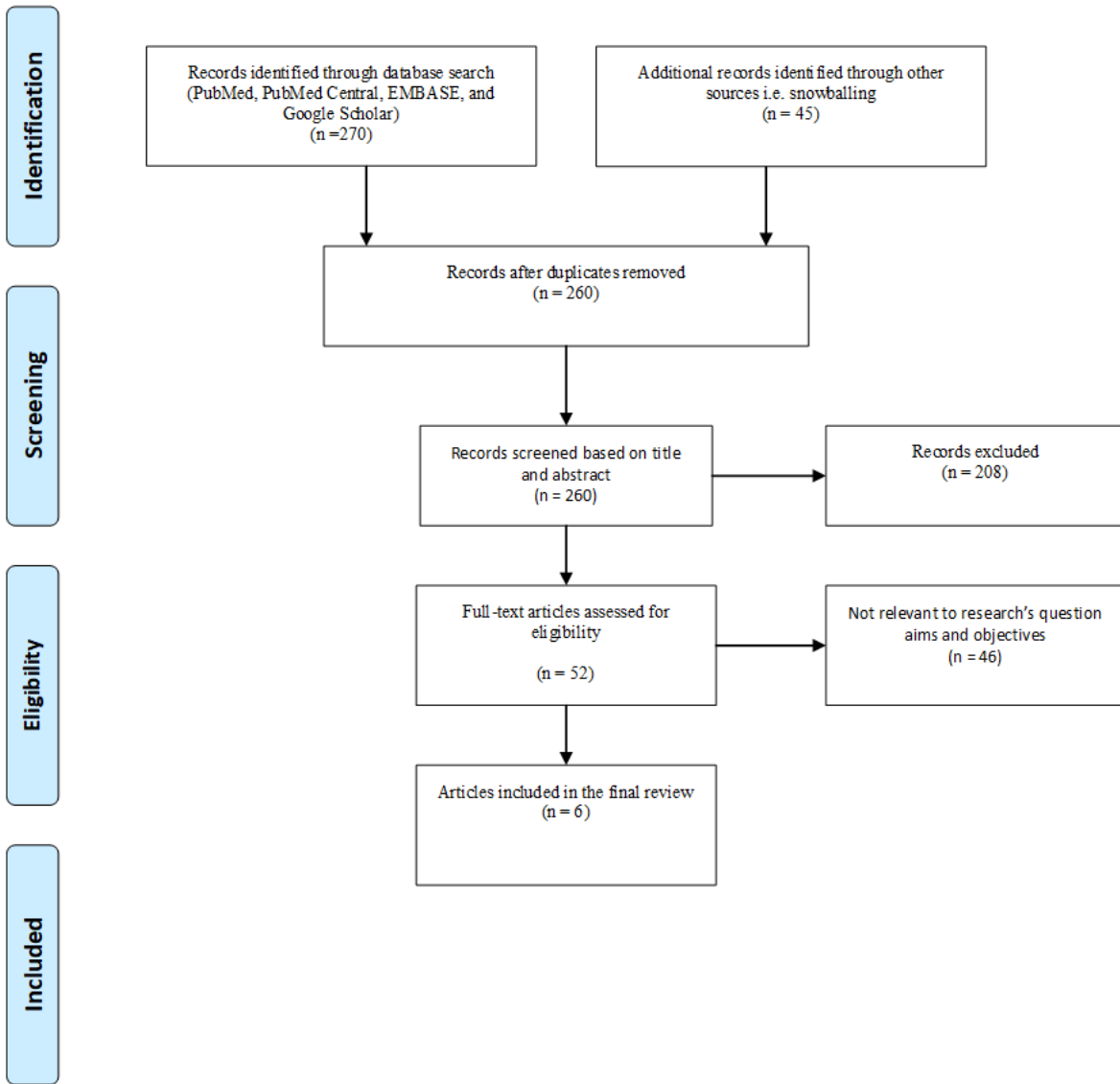


Figure 1

PRISMA diagram detailing the study identification and selection process

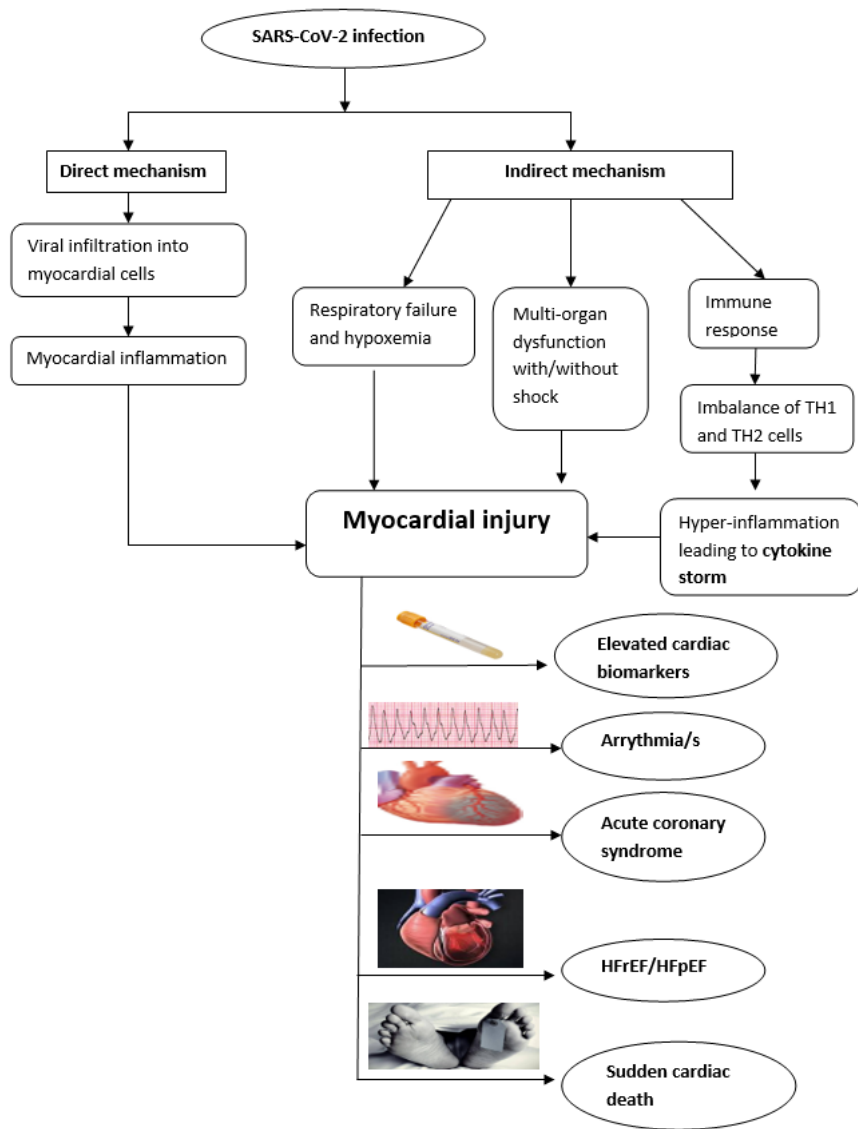


Figure 2

Pathophysiology of myocardial injury in patients with COVID-19