SYSTEMATIC REVIEW

Cardiovascular implications of coronavirus disease 2019: a systematic review [version 1; peer review: 2 not approved]

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V1 First published: 04 Aug 2020, 9:899
<https://doi.org/10.12688/f1000research.25211.1>
 Latest published: 04 Aug 2020, 9:899
<https://doi.org/10.12688/f1000research.25211.1>

Abstract

Background: World Health Organization has declared coronavirus disease 2019 (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 the 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.

Conclusions: 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.

Keywords

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

This article is included in the **Emerging Diseases and Outbreaks** gateway.

Open Peer Review

Approval Status **XX**

	1	2
version 1	X	X
04 Aug 2020	view	view

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This article is included in the **Coronavirus** collection.

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Author roles: **Pradhan RR:** Conceptualization, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Yadav AK:** Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Mandal S:** Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Pradhan RR, Yadav AK and Mandal S. **Cardiovascular implications of coronavirus disease 2019: a systematic review [version 1; peer review: 2 not approved]** F1000Research 2020, 9:899 <https://doi.org/10.12688/f1000research.25211.1>

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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, China¹, that heralded the onset of coronavirus disease (COVID-19). The disease has now spread rapidly to several countries around the globe and has been declared a pandemic by WHO². By April 8, 2020, a total of 1,441,589 confirmed cases of COVID-19 with mortality of 82,933 were reported². COVID-19 is probably the greatest threat to mankind of 21st century; it has not only challenged the current medical practices, but also imposed a huge psychological and socio-economic burden to the entire world.

Coronaviruses are a group of pathogen that primarily target the human respiratory system³. 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 of the cardiovascular system, as well^{4–6}. Given the 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^{7,8}. The systematic review protocol was not registered due to the urgency of the matter and very limited available evidence on the topic.

Assessment of methodological quality and risk of bias

For quality assessment, we used the Newcastle-Ottawa scale (NOS). The total score was found to be 9 and all the studies are of high quality⁹.

Eligibility criteria

Published peer-reviewed articles from January 1, 2020 until June 15, 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. Databases were searched using the search terms under the two search themes below, combined using the Boolean operator “AND”. 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. A 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. A third researcher checked the article list and data abstraction spreadsheet to ensure there were no duplicate articles. Any duplicated article was counted as a single article.

Results

Study selection

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, by Cui *et al.*¹⁰. Among the original articles, all were retrospective studies except study by Huang *et al.*¹¹, which was a 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 and severe/with myocardial injury/with elevated cardiac Troponin group. Critical and severe COVID-19 was defined as presence of one of the following conditions: respiratory failure requiring mechanical ventilation; shock; failure of other organs that requires treatment in ICU. Wang *et al.*¹² and Huang *et al.*¹¹ 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.*¹³ defined myocardial injury as blood levels of myocardial troponin ≥ 3 times the upper reference limit (34.2 ng/L). However, Chen *et al.*¹⁴ and Guo *et al.*¹⁵ 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 the studies by Huang *et al.*¹¹ (median age, 49 years) and Cui *et al.*¹⁰ (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.*¹¹ (median ages of patients in non-ICU and ICU groups were same). Male predominance was seen in all studies except those by Cui *et al.*¹⁰ and Guo *et al.*¹⁵. All the studies have included the underlying co-morbidities of the patients (Table 2).

Figure 1. PRISMA diagram detailing the study identification and selection process.

Cardiovascular complications associated with COVID-19

Wang *et al.*¹² established that among the 138 patients, acute cardiac injury was seen in $n=10$ (7.2%), shock in $n=12$ (8.7%), and arrhythmia in $n=23$ (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, the number of patients who had procalcitonin levels >0.05 ng/mL was higher in the ICU group compared with the non-ICU group ($n=27$ [75%] vs $n=22$ [21.6%]) (Table 4).

The study conducted by Huang *et al.*¹¹ found that among the 41 patients, acute cardiac injury was seen in $n=5$ (12%) and

shock in $n=3$ (7%) patients. Acute cardiac injury $n=4$ ([31%] vs $n=1$ [4%]) and shock ($n=3$ [23%] vs $n=0$ [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.*¹⁴ observed that among the $n=150$ patients, $n=22$ (7.1%) had acute cardiac injury. In the same study, out of $n=24$ patients in the critical group, $n=15$ (62.5%) had acute cardiac injury and $n=7$ (5.6%) out of 126 patients in non-critical group had acute cardiac injury and the difference was

Table 1. Study characteristics.

Author	Year	Country	Journal	Sample size	Study design	Objectives	Inclusion criteria	Exclusion criteria
Wang, <i>et al.</i> ¹²	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, <i>et al.</i> ¹¹	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, <i>et al.</i> ¹⁴	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.

Author	Year	Country	Journal	Sample size	Study design	Objectives	Inclusion criteria	Exclusion criteria
Xingwei, <i>et al.</i> ¹³	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; (2) 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 (3) Complete clinical data and at least two cardiac troponin test results. (4) Myocardial injury was defined as blood levels of myocardial troponin ≥ 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, <i>et al.</i> ¹⁰	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, <i>et al.</i> ¹⁵	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 infection (%)
Wang, <i>et al.</i> ¹²	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, <i>et al.</i> ¹¹	Median: 49; non-ICU group: 49, ICU group: 49	73	15	15	20	2	NA	2	NA	2	NA
Chen, <i>et al.</i> ¹⁴	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, <i>et al.</i> ¹³	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, <i>et al.</i> ¹⁰	55 days	Female	NA	NA	NA	NA	NA	NA	NA	NA	NA
Guo, <i>et al.</i> ¹⁵	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, <i>et al.</i> ¹²	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, <i>et al.</i> ¹¹	Shock	7	23	0	0.027
	Acute cardiac injury	12	31	4	0.017
	Death	15	38	4	NA
Chen, <i>et al.</i> ¹⁴	Acute cardiac injury	7.1	62.5	5.6	<0.001
	Death	7.3	41.7	0.8	<0.001
Xingwei, <i>et al.</i> ¹³	Acute cardiac injury	44.4	NA	NA	NA
	Death	48.1	75 ^a	26.7 ^b	0.001
Cui, <i>et al.</i> ¹⁰	Death	Patient recovered	NA	NA	NA
Guo, <i>et al.</i> ¹⁵	Acute cardiac injury	27.8	NA	NA	NA
	Arrhythmia	5.9	17.3 ^c	1.5 ^d	<0.001
	Death	23	59.6 ^c	8.9 ^d	<0.001

^a Group with myocardial injury^b Group without myocardial injury^c Group with elevated cardiac troponin T^d 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, <i>et al.</i> ¹²	CPK-MB (U/L)	< 25	14	13	18	< 0.001
	Procalcitonin (ng/mL) ≥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, <i>et al.</i> ¹¹	CPK (U/L)	≤185	132.5	133	132	0.31
	Procalcitonin (ng/mL) ≥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, <i>et al.</i> ¹⁴	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, <i>et al.</i> ¹³	CRP (mg/L)	10	NA	62.9 ^b	135 ^a	0.007
	NT-proBNP (ng/L)	<486	NA	201 ^b	971 ^a	<0.001
Cui, <i>et al.</i> ¹⁰	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

Author	Parameters	Normal range	All patients	Patients with severe disease or non-ICU patients	Patients with very severe disease or ICU patients	p-value
Guo, <i>et al.</i> ¹⁵	hsCRP (mg/dL)	NA	4.04	3.13 ^a	8.55 ^c	<0.001
	Procalcitonin (ng/mL)	NA	0.08	0.05 ^a	0.21 ^c	<0.001
	Globulin (g/L)	NA	27.7	27.4 ^a	29.7 ^c	<0.001
	CPK-MB (ng/mL)	NA	1.14	0.81 ^a	3.34 ^c	<0.001
	Myoglobin (ug/L)	NA	38.5	27.2 ^a	128.7 ^c	<0.001
	NT-proBNP (pg/mL)	NA	268.4	141.4 ^a	817.4 ^c	<0.001
	d-dimer (ugm/mL)	NA	0.43	0.29 ^a	3.85 ^c	<0.001

CPK-MB: Creatine phosphokinase myocardial band; CPK: Creatine phosphokinase; hsCRP: Hypersensitive C-reactive protein; NT-proBNP: N-terminal-pro brain natriuretic peptide.

^a Group with myocardial injury

^b Group without myocardial injury

^c Group with elevated cardiac troponin T

^d Group without elevated cardiac troponin T

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.*¹³, among the n=54 severe/critically severe patients, acute myocardial injury was discovered in 24 (44.4%) patients while 26 (48.1%) patients died during hospital stay. The in-hospital mortality rate was significantly higher in the 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.*¹⁰ 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.*¹⁵ observed that among the n=187 patients, n=52 (27.8%) exhibited acute cardiac injury as indicated by elevated cardiac troponin T (cTnT) levels. During hospitalization, arrhythmias were seen in n=11 (5.9%) patients. Patient with elevated cTnT levels had more frequent malignant arrhythmias compared with normal cTnT (n=9 [17.3%] vs n=2 [1.5%]). The overall mortality was 23% (43 patients died) (Table 4). The mortality rates 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

cardiovascular disease (CVD) and normal cTnT levels, with underlying 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 ($\beta = 0.530$, $p < 0.001$) and NT-proBNP levels ($\beta = 0.613$, $p < 0.001$) 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) are well-recognized^{4,16–19} (Table 5). Based on the studies analyzed, we found that patients with COVID-19 have 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 males. Patients with underlying coronary artery disease, hypertension, cardiomyopathy and other co-morbidities 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 injury²⁰.

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

Outbreak	Author	Journal	Sample size	Cardiovascular implications
SARS	Yu, <i>et al.</i> ⁴	BMJ	121	Hypotension, tachycardia, bradycardia, cardiomegaly, and arrhythmia
	Pan, <i>et al.</i> ¹⁷	Chinese J Tuberculosis and Respiratory Dis	15	Cardiac arrest
	Li, <i>et al.</i> ¹⁸	Circulation	46	Sub-clinical diastolic impairment without systolic involvement on echocardiography
MERS	Alhagbani ¹⁹	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.

Figure 2. Pathophysiology of myocardial injury in patients with COVID-19.

Cytokine storm during infection possibly causes a reduction in coronary blood flow, destabilization of coronary plaque and microthrombogenesis²¹.

Inflammatory markers like CRP/hs-CRP, and procalcitonin were found to be significantly elevated in patients with myocardial injury/critical patients/ICU patients; suggesting a role for 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 have a 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.

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.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'Cardiovascular implications of coronavirus disease 2019: a systematic review'. <https://doi.org/10.6084/m9.figshare.12658409.v1>⁸.

The completed PRISMA checklist is available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Current Peer Review Status:

Version 1

Reviewer Report 11 August 2021

<https://doi.org/10.5256/f1000research.27822.r90989>

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Many thanks for the review. This was an interesting read but there are a few niggling issues.

Abstract:

- Reads well but I think 'global pandemic' would be an all encompassing term vs 'Public Health Emergency of International Concern'.

Introduction:

- The study is slightly dated in that C-19 has affected more than 7 Countries!
- The stats about deaths and mortality should be updated as well
- Coronaviruses are a group of PATHOGENS
- i.e. severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), have already shown multisystem involvement, including of the cardiovascular system, as well- the as well can be deleted as its use is improper
- The present systematic review aims to describe the cardiovascular implications of COVID-19 and fill the gap in the knowledge regarding THE understanding of varied cardiovascular manifestations of COVID-19.

Discussion:

- Management of heart failure, arrhythmias, acute coronary syndrome and thrombosis is important- this is a redundant statement. If the authors want to keep this, I would cite the reference.

The manuscript would a further grammatical check prior to submission as there are multiple grammatical errors.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiothoracic Surgery, Mechanical Circulatory Support

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 14 September 2020

<https://doi.org/10.5256/f1000research.27822.r70363>

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Pradhan *et al.* used six articles to review the idea that cardiovascular issues can predict the severity of a COVID-19 diagnosis, or that COVID-19 infection can lead to heart conditions. Major strengths of the this review is authors clearly said in discussion that very small number of papers to make clear conclusions. They also used several evidences to convenience readers. However, this manuscript has several weakness and need to be addressed.

1. On page four in the section “cardiovascular complications associated with COVID-19 patients”, it mentions that patients admitted to the ICU had a higher rate of cardiovascular complications but doesn’t give a number to that stat until the very end. Will be good to say it upfront.
2. Also in the same paragraph, authors mention lot of chemicals like “procalcitonin levels, NT-proBNP”. Would it make sense to describe in more detail?

3. In discussion, it would make more sense to have two separate sections detailing patients with COVID-19 who developed heart conditions vs patients with underlying heart conditions who became infected with COVID-19?
4. The article Cui *et al.* describing the infant with COVID-19 and myocardial injury, but it got missed and no further discussion on that and hardly referenced in the actual review.
5. It is bit misleading the first sentence of their conclusion is indicative of what they wrote about "Acute cardiac injury is common in patients with COVID-19 and when it occurs, has a poor prognosis". Because most of the paper was dedicated to people already suffering from cardiovascular issues before being infected with COVID-19
6. It will be good to mention section of myocardial injury in younger populations?
7. Adding more papers and including some mechanistic angle is needed in order to strengthen the review.
8. There are several papers published on this topic, therefore it is advised to include better key words and perform better systematic review.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: SARS-CoV-2; Cardiovascular diseases; COVID-19.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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