

Systematic Review



Cardiac Complications in COVID-19: A Systematic Review and Meta-analysis

Mehrdad Sahranavard, PharmD¹; Arash Akhavan Rezayat, MD^{2,3}; Mohammad Zamiri Bidary, MD³; Alireza Omranzadeh, MD³; Farahnaz Rohani, MD³; Ramin Hamidi Farahani, MD²; Ebrahim Hazrati, MD⁴; Seyyed Hossein Mousavi, MD⁵; Mohamed Afshar Ardalan, MD⁶; Saeed Soleiman-Meigooni, MD²; Seyyed-Javad Hosseini-Shokouh, MD²; Zia Hejripour, MD⁷; Ehsan Nassireslami, PharmD^{8,9}; Reza Laripour, MD^{10,11}; Amirahmad Salarian, PharmD⁸; Abbas Nourmohammadi, MD¹²; Reza Mosaed, PharmD^{13,14*}

¹Student Research Committee, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

²Infectious Disease Research Center, AJA University of Medical Sciences, Tehran, Iran

³Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁴Department Anesthesiology and Critical Care, AJA University of Medical Sciences, Tehran, Iran

⁵Department of Cardiology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

⁶Internal Medicine Department, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

⁷Department of Emergency Medicine, AJA University of Medical Sciences, Tehran, Iran

⁸Toxin Research center, AJA University of Medical Sciences, Tehran, Iran

⁹Department of Pharmacology and Toxicology, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran

¹⁰Education Development Center, AJA University of Medical Sciences, Tehran, Iran

¹¹Center for Educational Research in Medical Sciences, Iran University of Medical Sciences, Tehran, Iran

¹²Faculty of Aerospace and Diving Medicine, AJA University of Medical Sciences, Tehran, Iran

¹³Department of Clinical Pharmacy, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

¹⁴Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: The newly emerged coronavirus disease 2019 (COVID-19) seems to involve different organs, including the cardiovascular system. We systematically reviewed COVID-19 cardiac complications and calculated their pooled incidences. Secondly, we compared the cardiac troponin I (cTnI) level between the surviving and expired patients.

Methods: A systematic search was conducted for manuscripts published from December 1, 2019 to April 16, 2020. Cardiovascular complications, along with the levels of cTnI, creatine kinase (CK), and creatine kinase MB (CK-MB) in hospitalized PCR-confirmed COVID-19 patients were extracted. The pooled incidences of the extracted data were calculated, and the unadjusted cTnI level was compared between the surviving and expired patients.

Results: Out of 1094 obtained records, 22 studies on a total of 4,157 patients were included. The pooled incidence rate of arrhythmia was 10.11%. Furthermore, myocardial injury had a pooled incidence of 17.85%, and finally, the pooled incidence for heart failure was 22.34%. The pooled incidence rates of cTnI, CK-MB, and CK elevations were also reported at 15.16%, 10.92%, and 12.99%, respectively. Moreover, the pooled level of unadjusted cTnI was significantly higher in expired cases compared with the surviving (mean difference = 31.818, 95% CI = 17.923-45.713, *P* value <0.001).

Conclusion: COVID-19 can affect different parts of the heart; however, the myocardium is more involved.

Keywords: Cardiac complications, COVID-19, Creatine kinase MB form, Myocardial injury

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Introduction

On December 31, 2019, an atypical form of pneumonia was found in Wuhan city of China.¹ On January 8, 2020, the Chinese Center for Disease Control and Prevention declared that the culprit pathogen for this atypical type of pneumonia was a new type of coronavirus.² This coronavirus was subsequently named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) causing “coronavirus disease 2019” (COVID-19).³ Although the pathogen emerged in 2019, it quickly spread

all around the world and caused a pandemic in 2020.⁴

It is estimated that around 25% to 35% of COVID-19 patients are at risk for deterioration who develop complications such as acute respiratory distress syndrome, arrhythmia, and shock. These patients may need admission to the intensive care unit (ICU).⁵⁻⁷ It seems that the older population with underlying diseases such as hypertension, diabetes, liver diseases, kidney diseases, malignancies, and cardiovascular diseases are at higher risk of mortality.⁷⁻⁹

Although COVID-19 mainly presents with pneumonia,

*Corresponding Author: Reza Mosaed, PharmD; School of Medicine, AJA University of Medical Sciences, Etemadzadeh St., West Fatemi St., Tehran, Iran. Tel: +98-21-43822401; Fax: +98-71-32355936; Email: reza.mosaed@ajauoms.ac.ir

some complications result from this virus. Damage due to this virus occurs in different organs, including kidneys, liver, immune system, and also the heart and circulation systems.^{5,10} These injuries result in multiple organ failure, acute respiratory distress syndrome, arrhythmias, heart failure, and renal injuries that finally lead to death.^{10,11}

Previously, cardiac manifestations, including myocardial infarction, acute myocarditis, and even heart failure, were reported due to the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) viruses, which are also members of the coronavirus family.¹²⁻⁴ These cardiovascular complications may also accompany the newly emerged COVID 19.⁷ Similar to the SARS virus,^{14,15} patients with SARS-CoV-2 develop arrhythmias and cardiac injury.^{7,16} Furthermore, even patients with no past medical history of cardiovascular problems may develop heart failure and sudden cardiac arrest.³ COVID-19 can also cause myocardial injury which has been reported in some studies as elevated levels of serum cardiac troponin I (cTnI).^{5,16} It is also reported that elevated levels of cardiac markers such as cTnI are indicative of severe COVID-19 infection and also a marker of acute heart failure due to cardiac involvement in COVID-19 infection.¹⁷ No study has yet reviewed the cardiac complications of COVID-19 infection. Here, we aimed to systematically review the cardiac complications of the patients with COVID-19 and assess their incidence through a meta-analysis. Furthermore, we compared the unadjusted cTnI level between the surviving and expired patients.

Materials and Methods

A systematic review and meta-analysis were conducted and described according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹⁸ to assess possible cardiovascular involvement induced by COVID-19.

Search Strategy

On April 16, 2020, a comprehensive systematic search was performed using PubMed, Scopus and Web of Science electronic databases with no language restrictions. Since the first case of COVID-19 was identified at the end of 2019, we restricted the search to studies published after December 1, 2019. Our search strategy contained two parts joining with "AND". The first part included "OR" combination of "COVID-19", "severe acute respiratory syndrome coronavirus 2", "Coronavirus", "Coronavirus Infections" medical subject headings (MESH), and their related entry terms on COVID-19. Meanwhile, the second part was "OR" combination of MESH and entry terms of "Cardiovascular Diseases", "Cardiovascular System", and their relevance to possible cardiovascular symptoms subcategories. The detailed search strategy is outlined in the Supplementary Material. Also, a manual

search on references and the Google scholar database was performed to identify additional studies meeting our inclusion criteria. The EndNote X8 (Thomson Reuters, New York, NY, USA) reference manager software was used to aggregate the search results.

Inclusion and Exclusion Criteria

We did not apply any language restrictions. We included original studies conducted on polymerase chain reaction (PCR) confirmed hospitalized COVID-19 patients reporting cardiac involvements or elevation of at least one of cTnI, creatine kinase (CK), or creatine kinase MB (CK-MB) parameters. Review articles, clinical guidelines, and studies that included only a specific hospitalized group such as patients admitted to the ICU, severe pneumonia patients, or infected medical staff were excluded. In order not to miss newer results, gray-literature (i.e. in-press and preprint studies) were not excluded. In case of population overlap among studies, studies reporting different outcomes were included. Also, if studies on the same sample reported the same outcome, only the one with a lower score obtained by Quality assessment was included in the study or meta-analysis.

Study Selection

The literature search (A.A.R. and F.R.), study selection (M.S. and M.Z.B.), data extraction (A.O. and R.H.F.), and quality assessment (S.S.M. and S.J.H.S.) were each performed by two reviewers independently and carefully. Discrepancies were resolved by consensus through discussion or third reviewer (R.M.) consultation, if needed. Non-English articles were translated into the English language using Google Translate service, in order to avoid errors in translation, and Chinese language articles were double-checked with Fatemeh A. Jafari, who is fluent in Chinese.

Data Extraction

The following information was extracted from eligible articles: Title, first author, study design, publication date, city and hospital, sample size, age, gender, prescribed antiviral drugs, and their dose, cardiac complications, and cTnI, CK, and CK-MB elevation as cardiac biomarkers. The cTnI level was extracted when reported for expired and surviving patients, separately. Also, the prevalence of myocardial injury defined as the elevation of cTnI or CK-MB, or the presence of "cardiomyopathy" was extracted.

Quality Assessment

The studies were systematically assessed for quality and risk of bias using the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies¹⁹, or the Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies in meta-analyses²⁰, as appropriate. For the IHE checklist "yes" and "partial", and

for the NOS, each star was counted as one point, yielding a maximum score 20 and 9 for each checklist, respectively. Only studies with a score of at least twelve on IHE or four on NOS were included.

Statistical Analysis

Summary data from individual studies were pooled using a random-effect model. The pooled prevalence of cardiovascular complications is summarized as the frequency and 95% confidence interval (CI). Also, the mean difference, along with 95% CIs was reported to assess the difference between cTnI among expired and surviving patients. Heterogeneity was quantified using the inconsistency index. The Comprehensive Meta-Analysis (CMA) software version 3.3.070 (Biostat, Englewood, NJ, USA) was used to perform analyses with p-values <0.05 considered statistically significant. Furthermore, the publication bias of studies reporting myocardial injury was assessed using the Egger's test and trim and fill method. Also, a trim and fill analysis was carried out to eliminate the small studies from the positive side of the funnel plot and recalculate the effect size at each repetition of a process until the funnel plot was symmetric about the new effect size.

Results

Selection Process Results

Our search using the predefined search strategy yielded

in 464, 409 and 221 studies from the Scopus, PubMed and Web of Science databases, respectively; furthermore, 14 additional publications were added through searching the Google Scholar and three studies were added from reviewing the references list of the relevant studies. After excluding duplicates, 995 studies remained. Title and abstract screening excluded 932 studies. Subsequently, the full-text of the remaining 63 studies were assessed, and 41 publications were excluded (two studies due to population overlap, 27 because of irrelevant outcomes, four for lack of PCR confirmation, and eight due to the inclusion of only a specific group of hospitalized patients). Finally, 22 studies were eligible for the systematic review and meta-analysis. The selection process is detailed in Figure 1. Among the above-mentioned included publications, five studies were preprint manuscripts.^{15,16,21-23}

Characteristics of the Included Studies

All the included studies were from China. Thirteen studies were from Wuhan city.^{3,5,7,15,21,22,24-30} Other publications were from Beijing,²³ Chengdu,¹⁶ Chongqing,³¹ Guangzhou,³² Shanghai,³³ Shenzhen,³⁴ Wenzhou,³⁵ and Yueqing.³⁶ Furthermore, one large study was from 30 provinces in China.³⁷ All the studies were case-series except for four cohort studies.^{26,29,30,36} Furthermore, all included studies were in English, except for one Chinese article.²⁷ The total sample size summation of the studies was 4157 PCR-confirmed COVID-19 cases. The median or mean

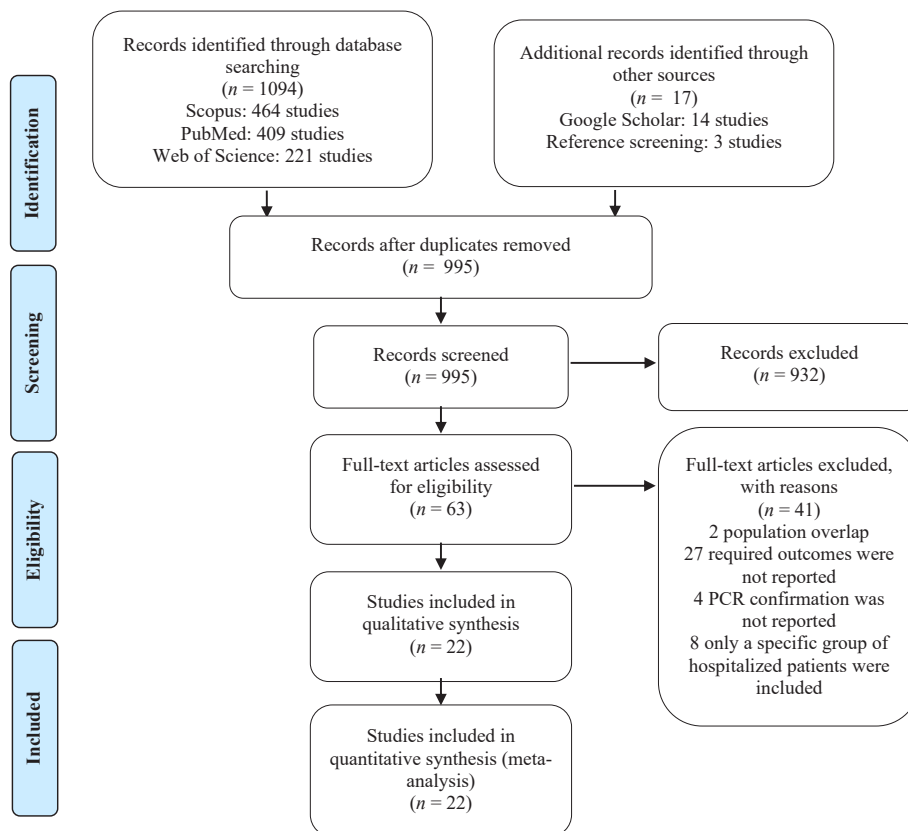


Figure 1. PRISMA flow diagram of the selection process.¹⁸

age range of the included patients was between 46 and 64 years. Also, 2,269 cases were males, and 1888 were females. Table 1 shows the characteristics of the included studies.

Quality Assessment

Assessment of the 18 case-series studies showed that most of the studies were retrospective (16 studies) and single-center (17 studies). No study was blinded, and also none of them had before/after (outcome) measurement pattern. All the case series had a quality scores of 12 to 16 and were above or equal to the eligible cutoff point for inclusion. The four included cohort studies had a score of 6^{26,30,36} and 9²⁹ out of 9. Figure 2 shows a schematic of quality assessment of the included studies.

Treatment of Coronavirus in the Studies

Fourteen studies mentioned that antiviral treatment was used for COVID-19 patients,^{3,5,7,15,16,22,24,26,29-31,34,36,37} however, eight studies only mentioned the use of antiviral therapy and did not specify the type of treatment.^{15,16,22,24,26} Oseltamivir was mentioned in five studies,^{3,5,7,34,37} lopinavir/ritonavir in three studies,^{3,29,31} interferon in two studies,^{31,34} ribavirin in one study (34), and ganciclovir in one study.³ The treatments mentioned above are listed in Table 1.

Cardiac Complications

The main cardiac complications in our review were categorized as myocardial injury, arrhythmia, valve involvement, pericardial effusion, and heart failure. PCR-confirmed COVID-19 patients observed with cardiac complications were 40 cases of arrhythmia out of 378 patients in three studies,^{7,16,24} 108 cases of heart failure out of 530 patients in four studies,^{16,22,29,34} 4 cases of pericardial effusion out of 141 patients in two studies,^{32,33} 9 cases of valve involvement out of 53 patients in one study,¹⁶ as well as 356 cases of myocardial injury (defined as cTnI or CK-Mb elevation, or cardiomyopathy) out of 1912 patients in thirteen studies.^{5,7,15,16,21-23,26,27,29,34-36} Table 1 demonstrates these complications.

Enzyme Elevation

Totally, cTnI elevation was reported in 274 cases out of 1617 patients in nine studies.^{5,15,22,23,25-27,29,34} This elevation was based on values of more than 28 ng/L in four studies,^{5,15,29,34} more than 40 ng/L in four studies,^{23,25-27} and more than 15.6 ng/L in one study.²²

Four studies had assessed the level of cTnI in surviving and expired patients. Chen et al.²² reported that 161 surviving patients (58.8%) had a median cTnI level of 3.3 ng/L and 113 expired patients (41.2%) had a median cTnI of 40.8 ng/L. A mean cTnI level of 3.5 ng/L was also reported in 82 (54.7%) surviving COVID-19 cases in the study by Ruan et al,³⁰ compared with a mean level of 30.3

ng/L in 68 expired cases (45.3%). Moreover, Wang *et al.* reported a median cTnI level of 6 ng/L in 169 (83.7%) surviving cases and cTnI level of 47 in 33 (16.3%) expired COVID-19 patients. Finally, in another study by Zhou et al, the median level of cTnI was 3 ng/L in 137 (71.7%) surviving cases, whereas it was 4.1 ng/L in 54 expired patients (28.3%).

Moreover, 221 cases out of 1701 patients in nine studies^{3,5,15,28,29,31,35-37} were observed with elevated levels of CK considering an upper limit of normal of 170 U/L in one study,³⁵ 185 U/L in two studies,^{5,29} 200 U/L in three studies,^{28,31,37} and 310 U/L in two studies.^{3,15} The upper limit of normal was not reported in the study by Hong.³⁶ Additionally, the CK-MB elevation of 5 ng/ml in two studies,^{25,34} 18 U/L in one study,³⁵ and 24 U/L in one study¹⁵ was observed in a total of 78 cases out of 723 patients in five studies.^{15,25,34-36} The upper limit of normal level was not reported in the study by Hong.³⁶ Table 2 presents the details of the above-mentioned data.

Data Synthesis of Different Cardiac Complications of COVID-19

Pooled analysis showed a pooled incidence rate of 10.11% (5.12-19.00) for arrhythmia and 22.34% (14.05-33.60) for heart failure. Furthermore, the pooled incidence of myocardial injury was 17.85% (13.18-23.72).

Enzyme Elevation Assessment

The pooled incidence of cTnI elevation was 15.16% (10.79–20.93). Also, the incidence rate of high levels of CK and CK-MB was 12.99% (10.61–15.82) and 10.92% (5.36–20.96), respectively. Table 3 represents the results mentioned above. Figures 3 and 4 show the forest and funnel plots of the myocardial injury meta-analysis.

Comparison of cTnI Level between the Expired and Surviving Patients

A comparison of unadjusted cTnI levels between expired and surviving patients was made in four studies.^{22,27,29,30} The results showed that expired patients had significantly higher levels of cTnI compared with surviving patients (mean difference = 31.818, 95% CI = 17.923–45.713, *P* value<0.001). Figure 5 shows the funnel plot of meta-analysis in expired and surviving patients.

Publication Bias Assessment

The result of Egger's test and trim and fill method for the quantitative assessment on myocardial injury studies demonstrated no significant publication bias for the findings of this study (*P* = 0.313).

Discussion

The results of our review showed that cardiac involvement by COVID-19 can affect all parts of the heart, especially the myocardium and conduction system. The pooled

Table 1. Characteristics of the Included Studies Including First Authors' Name, Symptoms, Hospitals of Study, Publication Date, Country and City of Origin, Sample Size, Gender and Mean Age of the Patients, Drug Dose, and Quality Assessment Score.

First Author and Reported Involvements	Involvement Prevalence n (%)	Hospital	Publication Date	Origin	Sample Size	Study Type	Mean Age (SD)/Median (25, 75)	Gender (Male/Female)	Drug Dose	Quality Assessment Score
^a Bai T. ²¹ Myocardial injury	21 (16.5)	Jinyintan Hospital	Preprint (3/5/2020)	Wuhan, China	127	Case Series	55 (44, 67)	80/47	N/A	14/20
Chen D. ³⁵ Myocardial injury	39 (22.3)	Hospital for Infectious Diseases	Preprint (2/29/2020)	Wenzhou, China	175	Case Series	46 (34, 54)	83/92	N/A	12/20
^a Chen N. ³		Jinyintan Hospital	2/15/2020	Wuhan, China	99	Case Series	55.5 (13.1)	67/32	Oseltamivir, 75mg BID, ganciclovir, 250mg BID, lopinavir/ritonavir 500mg BID	15/20
Chen T. ²² Heart failure	43 (15.7)	Tongji Hospital	3/26/2020	Wuhan, China	274	Case Series	62 (44, 77)	171/103	Antiviral therapy	15/20
Myocardial injury	83 (30.3)	552 hospitals in 30 provinces	2/28/2020	China	1099	Case Series	47 (35, 58)	639/460	Oseltamivir therapy	16/20
Guan W. ³⁷		Seventh Hospital of Wuhan	3/27/2020	Wuhan, China	187	Case Series	58.5 (14.7)	91/96	Antiviral therapy	15/20
Guo T. ²⁴ Arrhythmia	13 (7.0)	Renmin Hospital of Wuhan	3/31/2020	Wuhan, China	273	Case Series	58.9 (11.9)	97/176	N/A	12/20
^b Han H. ²⁵		Yueqing People's Hospital	3/27/2020	Yueqing, China	75	Cohort	46.3 (13.3)	41/34	Antiviral therapy	6/9
Hong Y. ³⁶ Myocardial injury	9 (12.0)	Jinyintan Hospital	2/15/2020	Wuhan, China	41	Case Series	49 (41, 58)	30/11	Oseltamivir, 75mg BID	16/20
^a Huang C. ⁵ Myocardial injury	5 (12.2)	Yuan Hospital	Preprint (2/27/2020)	Beijing, China	41	Case Series	47 (35.5, 64)	19/22	N/A	13/20
Hui H. ²³ Myocardial injury	4 (20)	Shenzhen Third People's Hospital	9/2/2020	Shenzhen, China	12	Case Series	53.6	8/4	Oseltamivir, Ribavirin, Interferon	16/20
^b Liu Y. ²⁴ Heart failure	1 (8.3)	Jin Yin-tan Hospital and Tongji Hospital	3/3/2020	Wuhan, China	150	Cohort	N/A	102/48	Antiviral therapy	6/9
Myocardial injury	1 (8.3)									
Ruan Q. ³⁰	—									

Table 1. Continued

First Author and Reported Involvements	Involvement Prevalence n (%)	Hospital	Publication Date	Origin	Sample Size	Study Type	Mean Age (SD)/ Median (25, 75)	Gender (Male/Female)	Drug, Dose	Quality Assessment Score
¹⁵ Shi S. ²⁶ Myocardial injury	82 (19.7)	Renmin Hospital of Wuhan	3/25/2020	Wuhan, China	416	Cohort	64 (N/A, N/A)	205/211	Antiviral therapy	6/9
Song F. ³³ Pericardial effusion	3 (5.9)	The Shanghai Public Health Clinical Center	2/6/2020	Shanghai, China	51	Case Series	49 (16)	25/26	N/A	12/20
Wan S. ³¹	—	Chongqing University Three Gorges Hospital	3/21/2020	Chongqing, China	135	Case Series	47 (36, 55)	72/63	Lopinavir/ritonavir and interferon	15/20
Wang D. ⁷ Arrhythmia	23 (16.7)	Zhongnan Hospital	2/7/2020	Wuhan, China	138	Case Series	56 (42, 68)	75/63	Oseltamivir therapy	15/20
Wang L. ²⁷ Myocardial injury	27 (13.4)	People's Hospital of Wuhan	4/14/2020	Wuhan, China	202	Case Series	63 (51, 70)	88/114	N/A	12/20
^a Wu C. ¹⁵ Myocardial injury	21 (11.2)	Jinyintan Hospital	Preprint (2/29/2020)	Wuhan, China	188	Case Series	51.9 (14.3)	119/69	Antiviral Therapy	14/20
Xu H. ¹⁶ Arrhythmia	4 (7.55)	West China Hospital	Preprint (3/5/2020)	Chengdu, China	53	Case Series	^c N/A	28/25	Antiviral therapy	14/20
Heart failure	20 (37.7)									
Myocardial injury	30 (56.6)									
Valve involvement	9 (17.0)									
Xu X. ³² Pericardial effusion	1 (1.1)	Guangzhou Eighth People's Hospital	2/28/2020	Guangzhou, China	90	Case Series	50 (N/A, N/A)	39/51	N/A	12/20
Zhang J. J. ²⁸		Wuhan No. 7 Hospital	2/19/2020	Wuhan, China	140	Case Series	57 (25, 87)	71/69	N/A	12/20
^a Zhou F. ²⁹ Heart failure	44 (23)	Jinyintan Hospital (135)	3/28/2020	Wuhan, China	191	Cohort	56 (46, 67)	119/72	Lopinavir/ritonavir	9/9
Myocardial injury	24 (12.6)	Wuhan Pulmonary Hospital (56)								

^a There might be population overlap among Bai T.²¹ Chen N.³ Huang C.⁵ Wu C.¹⁵ and Zhou F.²⁹ as all of them have recruited all or part of their study population from the Jinyintan Hospital, Wuhan, China.

^b There might be population overlap between Han H.²⁵ and Shi S.³⁶ since the study population of these studies were recruited from the Renmin Hospital of Wuhan University, Wuhan, China.

^c Age was not reported for population all together: AMI (6): 78.5(60.5, 81.75), Cardiac marker abnormalities (24): 48.50 (37, 62.75), Without cardiac marker abnormalities (23): 40 (32, 51).

IHE ^a (Used for case series studies)	Study objective			Study design			Study population			Intervention and co-intervention		Outcome measure			Statistical analysis	Results and Conclusions				Competing interests and sources of support
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
First Author																				
Bai T. ²¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen D. ³⁵	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen N. ³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen T. ²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Guan W. ³⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Guo T. ²⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han H. ²⁵	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Huang C. ⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hui H. ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu Y. ³⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Song F. ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wan S. ³¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang D. ⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang L. ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wu C. ¹⁵	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xu H. ¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xu X. ³²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang J. J. ²⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NOS^b (Used for Cohort Studies)	Selection				Comparability			Outcome			Total Score									
First Author	1	2	3	4	5	6	7	8												
Hong Y. ³⁶	*	*	*	*	-	*	*	-	6/9											
Ruan Q. ³⁰	*	*	*	*	-	*	*	-	6/9											
Shi S. ²⁶	*	*	*	*	-	*	*	*	6/9											
Zhou F. ²⁹	*	*	*	*	**	*	*	*	9/9											

Yes No Unclear Partial

Figure 2. Quality assessment of the included studies. ^aThe Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies.¹⁹ ^bThe Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies in meta-analyses.²⁰

incidence of arrhythmia was 10.14%. Cardiac involvement may result in heart failure in 22.24% of the patients, as our meta-analysis showed. The most prominent part of cardiac involvement was myocardial injury, with a pooled incidence of 17.85%. This involvement was evident as enzyme elevation with the cTnI elevation in 15.16% and CK-MB elevation in 10.92% of the patients. In addition to cTnI and CK-MB elevation as signs of myocardial injury, CK was raised in 12.99% of COVID-19 patients. All these analyses were mainly based on the data obtained from hospitalized patients.

Initially, cardiac complications can be assumed as part of all types of pneumonia. Pneumonia may exacerbate pre-existing symptomless heart failure and even cause myocardial infarction in patients with pre-existing coronary artery disease. Furthermore, it can worsen arrhythmia. However, new-onset heart failure, arrhythmia, or even myocardial infarction may happen as a result of pneumonia. These cardiac complications had been reported with some other respiratory viral infections such as influenza,³⁸ SARS,^{14,39,40} and MERS.⁴¹ In this regard, COVID-19 pneumonia can cause ventilation/perfusion mismatch that subsequently causes microvascular occlusion and, eventually, pulmonary hypertension. It seems that all these events may lead to heart failure.⁴²

Cardiac manifestations of COVID-19 can be also attributed to the underlying myocarditis. This myocarditis can cause a variety of cardiac manifestations from subclinical myocarditis, with only enzyme elevation due

to local myocyte necrosis, to sudden cardiac death because of arrhythmia.^{43,44} This hypothesis has been proposed in other viral infections like influenza.⁴³ Other cardiac markers, including CK and CK-MB, are also reported to be elevated in COVID-19 infected cases, suggesting myocardial injury in these patients.¹⁵ Our pooled analysis showed incidence rates of 12.99% and 10.92% for high levels of CK and CK-MB, respectively. These elevated cardiac markers imply an underlying myocardial injury due to myocarditis.⁴⁵

This myocarditis is believed to happen due to the systemic inflammation caused by COVID-19.^{46,7} It is reported that the number of white blood cells and neutrophils and also levels of interleukin-6 and C-reactive protein are elevated due to COVID-19 infection, subsequently causing myocardial injury.⁴⁸ Furthermore, pathology assessments have shown monocytes in the myocardial interstitium.⁴⁹ Other cytokines such as interleukin 1B, interferon γ , Interferon γ -Inducible Protein-10 (IP-10), and monocyte chemoattractant protein 1 were also increased in patients with COVID-19.⁵

This inflammation may also cause myocardial infarction due to the cytokine storm.⁴⁸ Also, it was found that patients with COVID-19 infection had higher levels of D-dimer concentrations. This hypercoagulable state is present in about 90% of pneumonia cases.⁵⁰ Zhou et al reported that D-dimer levels of higher than 1 $\mu\text{g/mL}$ are related to higher mortality of inpatient COVID-19 cases.⁵¹ It is hypothesized that the systemic inflammation

Table 2. Data Regarding Cardiac Injury, Troponin, Creatine Kinase, and Creatine Kinase MB Levels

Studies	Troponin Test Type	Elevated Cardiac Troponin I			Elevated Creatine Kinase			Elevated Creatine Kinase-MB			Cardiac Troponin I Level				
		Upper Limit (ng/L)	All n (%)	All n (%)	Upper limit (U/L)	All n (%)	Upper limit (U/L)	All n (%)	All n (%)	Upper limit (ng/L)	Dead n (%)	All Level (ng/L)	Survived n (%)	Dead Level (ng/L)	Survived Level (ng/L)
Chen et al ¹⁵	N/A	N/A	N/A	>170	24 (13.7)	>18 U/L	39 (22.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen et al ³	N/A	N/A	N/A	≥310	13 (13)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen et al ²²	Hypersensitive troponin I	>15.6	83 (40.9)	N/A	N/A	N/A	N/A	274 (100)	8.7 (2.9, 33.6)	113 (41.2)	40.8 (14.7, 157.8)	161 (58.8)	3.3 (1.9, 7.0)	N/A	
Guan et al ¹⁷	N/A	N/A	N/A	≥200	90 (13.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Han et al ¹⁵	ultrasensitive Troponin I	>40	27 (9.9)	N/A	N/A	>5 ng/ml	10 (3.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Hong et al ¹⁶	N/A	N/A	N/A	N/A	9 (12.0)	N/A	12 (16.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Huang et al ⁵	Hypersensitive troponin I	>28	5 (12.2)	>185	13 (17.8)	N/A	N/A	41 (100)	3.4 (1.1, 9.1)	N/A	N/A	N/A	N/A	N/A	
Hui et al ²³	Cardiac troponin I	>40	4 (20.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Liu et al ¹⁴	Cardiac troponin I	>28	1 (8.3)	N/A	N/A	>5 ng/ml	1 (8.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Ruan et al ¹⁰	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	68 (45.3)	30.3 (151.0)	82 (54.7)	3.5 (6.2)	N/A	
Shi et al ¹⁶	High-Sensitivity troponin I	>40	82 (19.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Wan et al ¹³	N/A	N/A	N/A	>200	10 (7.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Wang et al ⁷	Hypersensitive troponin I	N/A	N/A	N/A	N/A	N/A	N/A	138 (100)	6.4 (2.8, 18.5)	N/A	N/A	N/A	N/A	N/A	
Wang et al ²⁷	Hypersensitive troponin I	>40	27 (13.4)	N/A	N/A	N/A	N/A	202 (100)	6 (6, 16)	33 (16.3)	47 (14, 140)	169 (83.7)	6 (6, 11)	N/A	
Wu et al ¹⁵	High-Sensitivity troponin I	>28	21 (11.2)	>310	21 (11.2)	>24 U/L	19 (10.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Zhang et al ²⁸	N/A	N/A	N/A	≥200	16 (6.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Zhou et al ²⁹	High-sensitivity troponin I	>28	24 (16.6)	>185	22 (13.1)	N/A	N/A	191 (100)	4.1 (2.0, 14.1)	54 (28.3)	22.2 (5.6, 83.1)	137 (71.7)	3.0 (1.1, 5.5)	N/A	

Table 3. Meta-analysis Table of the Pooled Incidence of Different Cardiac Complications

Groups	No. of Studies	Effect size and 95% CI			Test of null (2-Tail)		Heterogeneity	
		Point Estimate	Lower Limit	Upper Limit	Z Value	P Value	P Value	I ²
Arrhythmia	3	10.11	5.12	19.00	-5.82	<0.001	0.02	75.21
Elevated Creatine kinase	9	12.99	10.61	15.82	-16.23	<0.001	0.03	52.01
Elevated Creatine kinase-MB	5	10.92	5.36	20.96	-5.33	<0.001	<0.001	87.85
Elevated cardiac Troponin I	9	15.16	10.76	20.93	-8.59	<0.001	<0.001	85.09
Heart failure	4	22.34	14.05	33.60	-4.32	<0.001	<0.001	79.44
Myocardial injury	13	17.85	13.18	23.72	-8.34	<0.001	<0.001	86.84

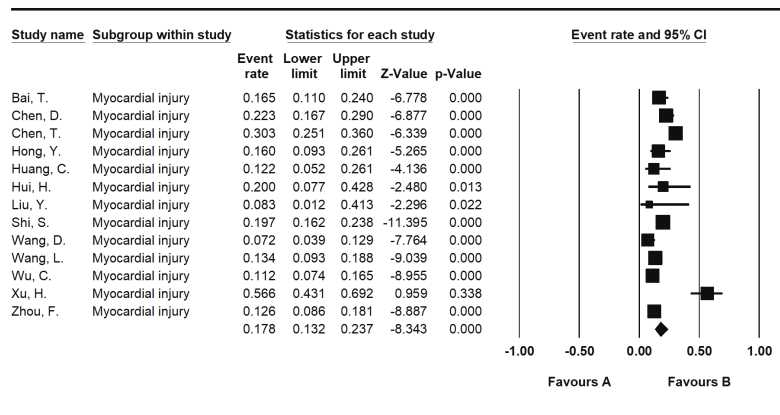


Figure 3. Forest Plot of Myocardial Injury in COVID-19 Infected Patients. The figure is created using Comprehensive Meta-Analysis (CMA) software.

along with hypercoagulable state make an arterial plaque unstable and even cause it to rupture.⁵²⁻⁵⁴ Thus, it can be predictable that COVID-19 causes myocardial infarction with subsequent enzyme elevation.¹⁶

Another proposed mechanism that has been previously described for the SARS-CoV-2 is direct action on the angiotensin-converting enzyme 2 receptor.⁵⁵ This

functional receptor for the SARS-CoV-2 is expressed on the surface of myocytes and vascular endothelial cells.^{56,57} It can imply direct cardiac involvement due to COVID-19; however, studies using virus detection methods have not been conducted.⁴⁹ A secondary finding of our study was the comparison of cTnI between surviving and expired patients. Our results showed that the unadjusted cTnI level was significantly higher in expired patients compared with the surviving. The autopsies of the patients who died of COVID-19 also showed that the underlying inflammation may be the cause of cardiac involvement and arrest.⁴⁹ It is believed that the elevated cardiac marker in expired patients may be due to the acute heart failure that subsequently leads to patients' death.¹⁷ We hypothesize

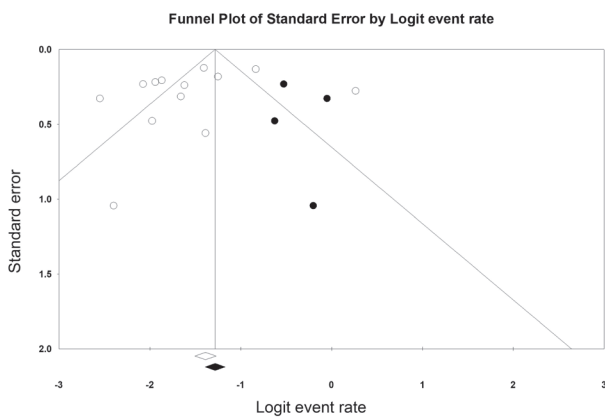


Figure 4. Funnel plot of Myocardial Injury in COVID-19 Infected Patients. Egger's test and trim and fill analysis showed no publication bias between studies (egger's intercept = -1.83, P value = 0.313; number of trim studies = 4, point estimate after trim = 0.21, change after trim = 0.02). The figure is created using Comprehensive Meta-Analysis (CMA) software.

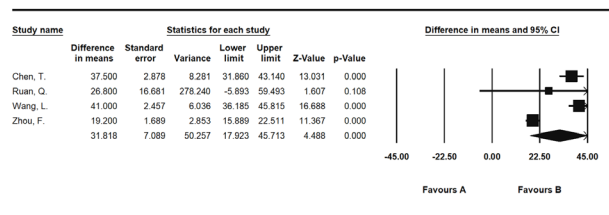


Figure 5. Forest Plot of Unadjusted cTnI Level Comparison between Expired and Surviving COVID-19 Patients. The figure is created using Comprehensive Meta-Analysis (CMA) software.

that cardiac markers not only show that myocardial injury may happen due to the coronavirus but also demonstrates the severity of injury in COVID-19 cases and may be even associated with prognosis.

Although our study suggests myocardial injury due to the coronavirus in inpatient COVID-19 cases, some limitations make the conclusion difficult. For example, patients who die of COVID-19 infection usually have underlying diseases such as cardiac problems, and the enzyme elevation may be a component of their previous cardiac disease. However, even in the absence of obvious cardiovascular problems, the expired patients developed more cardiac injury than other hospitalized COVID-19 cases.⁵ Also, most of the included studies were case series articles, and more studies with larger sample sizes may be needed. However, the quality of the included studies was acceptable. Also, elevated levels of heterogeneity were observed concerning a portion of our findings, which can be because of the heterogeneous characteristics of the included population and the differences in the timing of tests and cardiac evaluation and some patient demographics. Furthermore, angiography and tissue biopsy were not feasible in COVID-19 patients; thus, the exact etiology of cardiovascular complications was not defined. Another important limitation of our study was that to assess troponin levels in expired and surviving patients, unadjusted measures for individual studies were pooled. It is suggested that in future studies, troponin levels be adjusted based on known risk factors for the survival of patients with COVID-19. Finally, it should be emphasized that the included studies were mainly on inpatient cases, and outpatient COVID-19 patients may show different results. Besides all the shortcomings mentioned above, the pooled analysis was conducted with an appropriate sample size and an adequate number of studies. More pathology and echocardiography assessments are recommended to confirm the cardiac involvement in COVID-19.

In conclusion, this systematic review and meta-analysis showed that the hallmark of COVID-19 cardiac involvement is myocardial injury. This myocardial injury may be due to pro-inflammatory state, pro-coagulant state, or even direct invasion of the virus to the myocytes. All these involvements may result in a considerable rate of heart failure. Furthermore, it seems that expired patients present a higher cTnI level (as a marker of myocardial injury) compared with the surviving cases. However, further studies should be conducted to complete the results of this study. Also, researchers are recommended to control confounding factors and conduct pathology and echocardiography assessments to have a better understanding of cardiac injury due to the COVID-19 infection.

Authors' Contribution

RM and SHM designed study and were responsible for study conduct. AAR and FR conducted public database search based

on keywords developed by EH and MAA. AO and RHF conducted data extraction on studies selected by MS and MZB. SSM and SJHS performed quality assessment. ZH, EN and MS performed analysis. RL, AS, AN, AO and MZB drafted the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

Not Applicable.

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