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Review Article

Prevalence of Cardiovascular Complications in Coronavirus Disease 2019 adult Patients: A Systematic Review and Meta-Analysis

Camellia Torabizadeh[1], PhD; Raziyeh Iloonkashkooli[2], PhD candidate; Hajar Haghshenas[2], PhD candidate; Mohammad Fararouei[3], PhD

[1]Community Based Psychiatric Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;
[3]HIV/AIDs Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Hajar Haghshenas, PhD Candidate;
Shiraz University of Medical Sciences,
Zand Blvd., Namazi sq.,
Postal code: 13119-71936,
Shiraz, Iran
Tel: +98 71 36474254-8
Fax: +98 71 36474252
Email: haghshenah@gmail.com
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Abstract

Background: It has been found that the new coronavirus can affect various parts of the cardiovascular system. Cardiovascular complications caused by coronavirus disease 2019 (COVID-19) are often serious and can increase the mortality rate among infected patients. This study aimed to investigate the prevalence of cardiovascular complications in COVID-19 adult patients.

Methods: A systematic review and meta-analysis of observational studies published in English were conducted between December 2019 and February 2021. A complete search was performed in PubMed (PubMed Central and MEDLINE), Google Scholar, Cochrane Library, Science Direct, Ovid, Embase, Scopus, CINAHL, Web of Science, and WILEY, as well as BioRXiv, MedRXiv, and gray literature. A random effect model was used to examine the prevalence of cardiovascular complications among COVID-19 patients. The I^2 test was used to measure heterogeneity across the included studies.

Results: A total of 74 studies involving 34,379 COVID-19 patients were included for meta-analysis. The mean age of the participants was 61.30±14.75 years. The overall pooled prevalence of cardiovascular complications was 23.45%. The most prevalent complications were acute myocardial injury (AMI) (19.38%, 95% CI=13.62-26.81, test for heterogeneity I^2=97.5%, P<0.001), arrhythmia (11.16%, 95% CI=8.23-14.96, test for heterogeneity I^2=91.5%, P<0.001), heart failure (HF) (7.56%, 95% CI=4.50-12.45, test for heterogeneity I^2=96.3%, P<0.001), and cardiomyopathy (2.78%, 95% CI=0.34-9.68). The highest pooled prevalence of cardiac enzymes was lactate dehydrogenase (61.45%), troponin (23.10%), and creatine kinase-myocardial band or creatine kinase (14.52%).

Conclusion: The high prevalence of serious cardiovascular complications in COVID-19 patients (AMI, arrhythmia, and HF) necessitates increased awareness by healthcare administrators.

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Keywords • COVID-19 • Prevalence • Cardiovascular system • Biomarkers

What's Known

- There are no large-scale review studies investigating the pooled prevalence of cardiovascular complications associated with coronavirus disease 2019 (COVID-19), including underlying medical conditions and common cardiovascular signs and symptoms.
- The reported common cardiovascular consequences of infection with the new coronavirus vary depending on the number and types of reviewed articles.

What's New

- The overall pooled prevalence of cardiovascular complications was about 23.45%.
- The most prevalent cardiovascular complications in COVID-19 patients were, in descending order, acute cardiac/myocardial injury, cardiac arrhythmia, and heart failure. Cardiomyopathy and myocarditis have rarely been reported.

Introduction

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the predominance of clinical symptoms of the respiratory system led to the belief that the coronavirus was targeting its victims' lungs.[1] Later, it was established that the virus can spread throughout the body and directly attack other organs, including the heart. Cardiac and pulmonary cells are covered by a protein molecule called angiotensin II enzyme convertor (ACE2), through which the virus can enter the cells. In addition, as the heart and the lungs are closely related, the occurrence of pneumonia puts extra pressure on the heart, which may lead to cardiac injury with the signs and symptoms of cardiac disorders.[2-4] Previous viral epidemics, e.g., severe acute respiratory syndrome (SARS), were accompanied by cardiac complications, including arrhythmia, myocardial injury, and cardiomegaly.[5, 6] Likewise, the consequences of Middle East respiratory syndrome (MERS) were reported to include cardiac disorders, myocarditis, cardiomegaly, heart tissue damage, and heart failure (HF).[7-9] Compared to COVID-19, both SARS and MERS have been less infectious but had higher mortality rates.[10, 11] SARS-coronaviruses (SARS-CoV-2) and MERS-coronaviruses (MERS-CoV-2) have similar pathogenicity and can lead to myocardial damage which complicates the treatment of patients.[12]

Several studies showed that, as a result of their systemic inflammatory response and immune system disorders, COVID-19 patients are more prone to cardiovascular complications.[4, 13, 14] Arrhythmia and cardiomyopathy (CMP) are among the cardiac complications associated with COVID-19.[15-17] It appears that older individuals with underlying medical conditions, including hypertension (HTN), diabetes mellitus (DM), liver diseases, kidney diseases, malignancies, and cardiovascular diseases (CVD) are at greater risk of mortality.[18-20] In a study of 274 patients with COVID-19, 89 had suffered acute heart injury, 43 suffered acute heart failure, 83 had increased levels of cardiac troponin (cTn), and 116 had increased levels of lactate dehydrogenase.[21] Heart injury is a dominant complication that affects 20% to 30% of hospitalized patients and accounts for 40% of the mortality rate.[22] The prevalence of acute myocardial injury in COVID-19 patients were reported to range from 17% to 37.54%.[23, 24] The findings of several studies showed that there is an association between mortality and patients suffering from both cardiac injury and COVID-19.[13, 16]

According to official reports, acute myocardial injury, HF, cardiomegaly, various types of arrhythmias, blood pressure disorders, thromboembolism, inflammation of small and large vessels, circulatory collapse, and elevated rate of biomarkers indicative of cardiovascular injury are prevalent disorders in patients with COVID-19.[17, 22, 25] In a study by Xie and colleagues, of the 733 patients infected with the coronavirus, 357 suffered heart injury, and an increase in their cTn levels was observed.[26] Approximately, 45% of COVID-19 patients had above-normal levels of cTn.[27] Similarly, in another study, 107 of the 463 patients with COVID-19 had above-normal levels of cTn.[28] In a systematic review of 22 studies, the total incidence of HF, myocardial injury, and arrhythmia in COVID-19 patients was 22.24%, 17.85%, and 10.14%, respectively.[29] In a retrospective study, of the 339 patients infected with the new coronavirus, 70, 58, and 35 patients were found to have experienced acute heart injury, HF, and arrhythmia, respectively.[30] These patients were also at risk of complications such as myocarditis and reduced ejection fraction.[4, 31-35] Cases of cardiac tamponade were also reported.[4, 36, 37]

The cardiovascular consequences of COVID-19 are often serious, and increased awareness can significantly aid the treatment and care of those infected. Several studies have addressed cardiovascular complications in COVID-19 patients.[16, 17, 21, 28, 30, 32, 34-41] Organized presentation of the findings of these studies in the form of a systematic review and meta-analysis can be helpful in raising awareness of the complications, and early diagnosis and treatment. Therefore, the present study aimed to investigate the prevalence of different types of cardiovascular complications in COVID-19 adult patients through a systematic review and meta-analysis.

Materials and Methods

Search Strategy

A systematic review and meta-analysis were conducted using observational studies published in English between December 2019 and February 2021. A complete search was performed in PubMed (PubMed Central and MEDLINE), Google Scholar, Cochrane Library, Science Direct, Ovid, Embase, Scopus, CINAHL, Web of Science, and WILEY, as well as BioRXiv, MedRXiv, and gray literature. The sources were managed to remove duplicates using Mendeley reference management software version 1.19.8 (Elsevier, Amsterdam, The Netherlands). Using the syntax of various databases, the authors searched for medical subject headings (MeSH), keywords, and phrases in English: "COVID 19 virus OR COVID-19 virus OR coronavirus disease 2019 virus OR SARS-CoV-2 OR 2019 novel coronavirus OR 2019-nCoV AND comorbidities OR cardiovascular complications

OR cardiovascular diseases OR cardiac injury OR myocardial damage OR myocarditis OR Cardiovascular outcome OR cardiac arrhythmias (dysrhythmia) OR heart failure OR troponin, lactate dehydrogenase (LDH), creatine kinase (CK) OR creatine kinase-myocardial band (CK-MB), etc." An example of a search syntax for Scopus has been provided in appendix 1.

Two of the authors (HH and RI) reviewed the articles independently. Any inconsistencies were resolved by the third author (CT). The articles underwent full-text screening according to the inclusion and exclusion criteria. Moreover, the reference lists of the included articles were reviewed manually for other relevant articles that may have been overlooked in the electronic search. All observational studies, published in English, with a retrospective, prospective, and cross-sectional designs focusing on the clinical characteristics and laboratory outcomes of COVID-19-induced cardiovascular complications were used for analysis. Repeated and irrelevant studies and studies of animals and children were excluded. Besides, studies in which the target variables were measured using methods such as biopsy/autopsy were excluded from the analysis.

Data Extraction

Two of the authors independently extracted data from the included studies. To minimize selection bias, the articles were verified by the second and fourth authors. The extracted data included the name of the first author, year and month of publication, research site, research method, sample size, average age, male-to-female ratio, underlying medical condition (healthy, CVD, kidney and liver disorders, DM, chronic pulmonary diseases [CPD]), signs and symptoms, cardiovascular complications (tachycardia, bradycardia, hypotension, chest pain, acute myocardial injury, myocarditis, HF, cardiac tamponade, CMP, cardiac dysrhythmia), and cardiac markers (cTn, LDH, CK, CK-MB). The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[42] and was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran, (code: IR.SUMS.REC.1399.763).

Statistical Analysis

The distribution of target variables, as reported by the included studies, were presented in the form of descriptive variables and expressed as percentages and mean±SD. A random effect analysis was performed to examine the prevalence of cardiovascular complications in COVID-19 patients using the package meta (R version 4.0.2, 2020-06-22, Copyright 2020, The R Foundation for Statistical Computing Platform). The I^2 test was used to evaluate heterogeneity across the included studies. A value of 0% indicated no observed heterogeneity, and larger values showed increasing heterogeneity (low: 0-25%, moderate: 25-50%, high: 50-75%). To explain the heterogeneity of the sources, meta-regression was applied based on the country, sex, and age of the patients. Linear regression test of funnel plot asymmetry was used to examine publication bias. The cut-off for type I error (statistically significant results) was set at 0.05.

Results

Description of Studies

In total, 3,873 records were screened through Web of Science (n=978), Scopus (n=579), PubMed (n=196), Google Scholar, and other sources (n=2,120). A total of 228 publications were identified in the search after duplicates, and unrelated titles were removed. Out of these, 74 studies involving a total of 34,379 participants were found to be eligible for the systematic review and meta-analysis (figure 1). The analysis included all the studies published from December 2019 until February 2021. All studies were observational, of which 67 were retrospective cohorts. As shown in table 1, the majority of the studies were conducted in China (n=50, 67.56%) followed by the USA (n=9, 12.16%), Italy (n=7, 9.45%), Spain (n=2, 2.70%), Germany (n=1, 1.35%), South Korea (n=1, 1.35%), UK (n=1, 1.35%), Mexico (n=1, 1.35%), Iran (n=1, 1.35%), and a multi-country study (n=1, 1.35%). The mean age of the participants in these studies was 61.30±14.75 years. A summary of the reviewed studies is presented in table 1.

Prevalence of Comorbidities

Meta-analysis of the included studies showed that the most prevalent comorbidities in COVID-19 patients were HTN (39.50%), DM (19.67%), CVD (15.07%), coronary artery disease (CAD) (12.98%), cardiac dysrhythmia (7.84%), HF (7.11%), CPD (6.88%), chronic kidney diseases (CKD) (5.62%), CMP (4.85%), and chronic liver diseases (CLD) (3.09%).

The highest and lowest rates of HTN among patients with COVID-19 were in Italy (89.29%, 95% CI=71.77-97.73)[65] and China (9.49%, 95% CI=5.15-15.68),[19] respectively. Based on the results of a random effect model, the pooled prevalence of HTN was 39.85% (95% CI=34.17-45.83). The Chi square test result for heterogeneity was

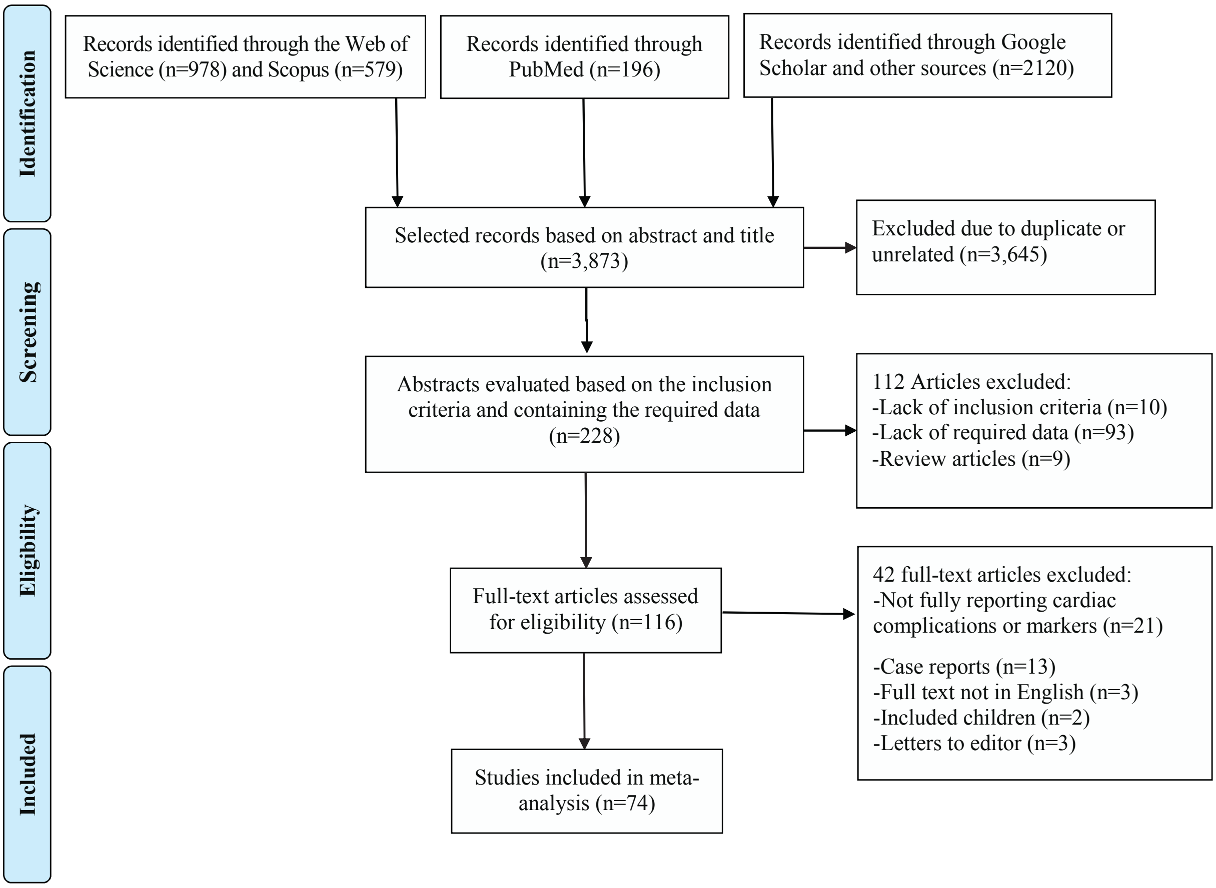

Figure 1: The flow diagram shows the study selection strategies according to the PRISMA guidelines.

significant for the reported prevalence of HTN (I^2=97.4%, P<0.001). The highest and lowest rates of DM among patients with COVID-19 were in the USA (52.63%, 95% CI=43.79-61.35)[69] and China (4.88%, 95% CI=0.60-16.53),[46] respectively. Based on the results of a random effect model, the pooled prevalence of DM was 19.88% (95% CI=17-23.11). The Chi square test result for heterogeneity was significant for the reported prevalence of DM (I^2=94.3%, P<0.001).

The highest and lowest rates of CVD among patients with COVID-19 were in Italy (66.17%, 95% CI=61.34-70.77)[64] and China (1.08%, 95% CI=0.03-5.85),[60] respectively. The results of a random effect model showed that the pooled prevalence of CVD was 15.07% (95% CI=12.05-18.68). The Chi square test result for heterogeneity was significant for the reported prevalence of CVD (I^2=96.3%, P<0.001).

The highest and lowest rates of CAD among patients with COVID-19 were in the USA (26.32%, 95% CI=19.06-34.65)[69] and China (4.43%, 95% CI=2.05-8.25),[89] respectively. Based on the results of a random effect model, the pooled prevalence of CAD was 12.98% (95% CI=10.74-15.61). The Chi square test result for heterogeneity was significant for the reported prevalence of CAD (I^2=91.2%, P<0.001).

The highest and lowest rates of cardiac arrhythmia among patients with COVID-19 were in Spain (33.95%, 95% CI=30.46-37.57)[88] and China (0.69%, 95% CI=0.08-2.46),[45] respectively. Based on the results of a random effect model, the pooled prevalence of cardiac arrhythmia was 7.84% (95% CI=3.79-15.50). The Chi square test result for heterogeneity was significant for the reported prevalence of cardiac arrhythmia (I^2=98.3%, P<0.001).

The highest and lowest rates of HF among patients with COVID-19 were in Spain (41.02%, 95% CI=37.37-44.75),[88] and China (0.34%, 95% CI=0.01-1.90),[45] respectively. Based on the results of a random effect model, the pooled prevalence of HF was 7.11% (95% CI=4.34-11.45). The Chi square test result for heterogeneity was significant for the reported prevalence of HF (I^2=98.2%, P<0.001).

The highest and lowest rates of CPD among patients with COVID-19 were in the USA (28.48%, 95% CI=23.51-33.86)[24] and China (0.74%, 95% CI=0.02-4.06),[51] respectively. Based on the results of a random effect model, the pooled prevalence of CPD was 6.88% (95% CI=5.23-8.99). The Chi square test result for heterogeneity was significant for the reported prevalence of CPD (I^2=94.8%, P<0.001).

Table 1: Summary of studies included in the review. All studies were published in the year 2020

No	Author	Country	Study method	N	Sex (M/F ratio)	Comorbidities (N)	Cardiovascular symptoms (N)	Cardiovascular complications (N)	Cardiac markers rise (N)
1	Chen et al.[43]	China	Retrospective cohort	99	2.09	CVD: 40, CPD: 1	CP: 2	HF: 1	LDH: 75, CK-MB: 13
2	Zhang et al.[44]	China	Retrospective cohort	82	1.60	HTN: 46, HD: 17, CKD: 4, CLD: 2, DM: 15, CPD: 12	CP: 36	ACI: 73	Tn: 52, LDH: 68, CK-MB: 21
3	Wang et al.[18]	China	Retrospective cohort	138	1.19	CVD: 20, HTN: 43, CKD: 4, CLD: 4, DM: 14, CPD: 4	HR: 88, MAP: 90	AMI: 10, Arrhythmia: 23	NR
4	Liu et al.[45]	China	Retrospective cohort	291	0.84	HTN: 54, CHD: 12, HF: 1, Arrhythmia: 2, DM: 22	CP: 1, HR: 84, SBP: 124, Palpitation: 3	ACI: 15	Tn: 15
5	Hui et al.[46]	China	Retrospective cohort	41	0.86	Arrhythmia: 1, CAD: 3, HTN: 5, DM: 2	Tachycardia: 3	Arrhythmia: 2, ACI: 4	Tn: 4
6	Huang et al.[12]	China	Prospective cohort	41	2.72	HTN: 6, CVD: 6, CLD: 1, DM: 8, CPD: 1	SBP: 125	ACI: 5	Tn: 5, LDH: 29, CK-MB: 13
7	Yang et al.[47]	China	Retrospective cohort	52	2.05	CHD: 5, DM: 9, CPD: 4	CP: 1, HR: 89	ACI: 12	NR
8	Ma et al.[32]	China	Retrospective Cohort	84	1.33	HTN: 12, Cardiopathy: 5, CKD: 1, CLD: 11, DM: 10, CPD: 5	CP: 1, Bradycardia: 3, Tachycardia: 3	Myocarditis: 4, Arrhythmia: 4, AMI: 13	Tn: 9
9	Wang et al.[30]	China	Retrospective cohort	339	0.95	HTN: 133, CVD: 53, CKD: 13, CLD: 2, DM: 54, CPD: 21	CP: 88, HR: 82, MAP: 94	ACI: 70, HF: 58 Arrhythmia: 35	NR
10	Liu et al.[19]	China	Retrospective cohort	137	0.80	HTN: 13, CVD: 10, DM: 14, CPD: 2	Palpitation: 10	NR	NR
11	Zhou et al.[41]	China	Retrospective cohort	191	1.65	HTN: 58, CHD: 15, CKD: 2, DM: 36, CPD: 6	NR	HF: 44, ACI: 33	Tn: 24, LDH: 123, CK-MB: 22
12	Wei et al.[48]	China	Prospective cohort	101	1.14	HTN: 21, CAD: 5, DM: 14, CPD: 1	CP: 11	AMI: 16	Tn: 16
13	Shi et al.[49]	China	Retrospective cohort	671	0.92	HTN: 199, CHD: 60, CHF: 22, Arrhythmia: 7, CKD: 28, DM: 97, CPD: 23	NR	AMI: 20, HF: 12	NR
14	Zheng et al.[14]	China	Retrospective cohort	34	2.09	HTN: 22, CVD: 4, CKD: 2, CLD: 4, DM: 8, CPD: 2	HR: 79, MAP: 89	ACI: 13	NR
15	Chen et al.[21]	China	Retrospective cohort	274	1.66	HTN: 93, CVD: 23, CHF: 1, CKD: 4, CLD: 11, DM: 47, CPD: 18	CP: 103, HR: 94, MAP: 129	ACI: 89, HF: 43	Tn: 83, LDH: 116
16	Hong et al.[38]	Korea	Retrospective cohort	98	0.63	CVD: 11, HTN: 30, CLD: 1, DM: 9, CPD: 3	HR: 84.7, MAP: 96.1	ACI: 11	LDH: 47, CK-MB: 11
17	Zhang et al.[50]	China	Retrospective cohort	221	0.95	HTN: 54, CVD: 22, CKD: 6, CLD: 7, DM: 22, CPD: 6	HR: 84, MAP: 90	ACI: 17, Arrhythmia: 24	NR

No	Author	Country	Study method	N	Sex (M/F ratio)	Comorbidities (N)	Cardiovascular symptoms (N)	Cardiovascular complications (N)	Cardiac markers rise (N)
18	Wan et al.[51]	China	Retrospective cohort	135	1.14	HTN: 13, CVD: 7, CLD: 2, DM: 12, CPD: 1	CP: 12, BP: 120/76, MAP: 90.66	ACI: 10	LDH: 58, CK-MB: 10
19	Zhang et al.[52]	China	Retrospective cohort	19	1.37	HTN: 11, CHD: 3, DM: 4, CPD: 3	NR	ACI: 9	Tn: 9
20	Li et al.[53]	China	Retrospective cohort	54	1.70	HTN: 15, CAD: 7, DM: 7, CPD: 4	NR	ACI: 23	Tn: 23
21	Shi et al.[54]	China	Retrospective cohort	416	0.97	HTN: 127, CHD: 44, CHF: 17, CKD: 14, CLD: 4, DM: 60, CPD: 12	CP: 14	AMI: 82	Tn: 82
22	Aggarwal et al.[55]	USA	Retrospective cohort	16	3	HTN: 9, CAD: 3, CHF: 4, CKD: 6, DM: 5, CPD: 2	CP: 1, HR: 94, MAP: 94, Hypotension: 5, Tachycardia: 5	AMI: 3, HF: 2, ACS: 4, Arrhythmia: 1	LDH: 13
23	Suleyman et al.[28]	USA	Retrospective cohort	463	0.78	HTN: 295, CAD: 59, HF: 49, CKD: 208, DM: 178, CPD: 122	HR: 96	NR	Tn: 107
24	Yang et al.[56]	China	Retrospective cohort	114	0.96	CVD: 12, CKD: 1, CPD:1	NR	NR	Tn: 114, CK-MB: 8
25	Richardson et al.[57]	USA	Retrospective cohort	5,700	1.51	HTN: 3026, CAD: 595, HF: 371, CKD: 454, CLD: 30, DM: 1,808, CPD: 766	HR: 97, Tachycardia: 2,457	NR	Tn: 801
26	Feng et al.[58]	China	Retrospective cohort	476	1.32	HTN: 113, CVD: 38, CKD: 4, DM: 49, CPD: 22	CP: 21	NR	Tn: 86
27	Yang et al.[59]	China	Retrospective cohort	200	0.96	HTN: 45, HD: 11, CKD: 3, CLD: 2, DM: 21, CPD: 7	NR	ACI: 20	LDH: 74, CK-MB: 5
28	Jin et al.[60]	China	Retrospective cohort	93	0.78	HTN: 16, CVD: 1, DM: 7, CPD: 3	CP: 5	ACI: 9	Tn: 9
29	Wang et al.[27]	China	Retrospective cohort	77	1.96	HTN: 33, HD: 18, CKD: 7, CLD: 4, DM: 18, CPD: 8	NR	AMI: 34	Tn: 34, LDH: 68, CK-MB: 14
30	Liu et al.[61]	China	Retrospective cohort	1,190	1.14	HTN: 308, CHD: 86, CKD: 30, CLD: 40, DM: 144, CPD: 22	NR	ACI: 82	NR
31	Lombardi et al.[62]	Italy	Cross-sectional	614	2.43	HTN: 350, HF: 87, Arrhythmia:100, CAD: 137, CKD: 110, DM: 148, CPD:58	HR: 86.5, MAP: 92.33	HF: 51, AMI: 17	Tn: 278
32	Li et al.[63]	China	Retrospective cohort	100	1.27	HTN: 40, CVD: 15, CLD: 3, DM: 21, CPD: 12	CP: 2, HR: 92.5, MAP: 99.3	ACI: 25	Tn: 10
33	Ghio et al.[64]	Italy	Retrospective cohort	405	2.18	CVD: 268, CKD: 38, DM: 79, CPD: 58	CP: 16, HR: 88, MAP: 98.33	AMI: 74, Arrhythmia: 29	Tn: 74
34	Lazzeri et al.[65]	Italy	Cross-sectional	28	3.66	HTN: 25, HD: 8, CKD: 1, DM: 11, CPD: 2	NR	AMI: 11	Tn: 11
35	Fan et al.[66]	China	Retrospective cohort	73	2.04	HTN: 24, CVD: 7	NR	ACI: 16	Tn: 16

No	Author	Country	Study method	N	Sex (M/F ratio)	Comorbidities (N)	Cardiovascular symptoms (N)	Cardiovascular complications (N)	Cardiac markers rise (N)
36	Guo et al.[67]	China	Retrospective cohort	187	0.94	HTN: 61, CHD: 21, CMP: 8, CKD: 6, DM: 28, CPD: 4	NR	AMI: 52, Arrhythmia: 11	Tn: 52
37	Ferguson et al.[68]	USA	Retrospective cohort	72		CVD: 43, HTN: 26, DM: 20, CPD: 10	CP: 8, Bradycardia: 2	CMP: 2, ACI: 2, Arrhythmia: 4	Tn: 2
38	Abrams et al.[69]	USA	Retrospective cohort	133	1.25	HTN: 110, CHF: 31, CAD: 35, Arrhythmia: 31, CKD: 35, DM: 70, CPD: 28		ACI: 91, Arrhythmia: 17	Tn: 91
39	Chen et al.[70]	China	Retrospective cohort	21	4.25	HTN: 5, DM: 3	CP: 11, HR: 89	ACI: 2	Tn: 2, LDH: 11
40	Xie et al.[26]	China	Retrospective cohort	733	1.86	HTN: 308, CHD: 93, CHF: 15, CKD: 13, CLD: 11, DM: 138, CPD: 37	NR	ACI: 357	Tn: 357
41	Russo et al.[71]	Italy	Retrospective cohort	414	1.57	HTN: 263, HF: 46, CAD: 66, Arrhythmia: 72, CKD: 64, DM: 106, CPD: 88	NR	Arrhythmia: 50	NR
42	Xiong et al.[72]	China	Retrospective cohort	116	2.22	HTN: 45, CHD: 17, CVD: 8, CLD: 2, DM: 19, CPD: 1	CP: 50, HR: 86, MAP: 96.7, Palpitation: 13	ACI: 23, HF: 21	Tn: 16, LDH: 69, CK-MB: 19
43	Li et al.[73]	China	Retrospective cohort	312	1.49	HTN: 178, CVD: 93, CKD: 10, CLD: 11, DM: 121, CPD: 27	NR	Shock: 76, ACI: 103	NR
44	Guo et al.[74]	China	Retrospective cohort	105	0.84	HTN: 46, CD: 17, CKD: 5, CLD: 5, DM: 27, CPD: 9	NR	ACI: 5	LDH: 43, CK-MB: 12
45	He et al.[75]	China	Retrospective cohort	288	0.83	HTN: 84, CVD: 85, CKD: 8, CLD: 10, DM: 24, CPD: 5	NR	ACI: 22	Tn: 22
46	Li et al.[76]	China	Retrospective cohort	204	0.96	HTN: 74, CD: 44, CKD: 5, DM: 39, CPD: 21	CP: 33	ACI: 27	Tn: 60, CK-MB: 15
47	Du et al.[77]	China	Retrospective cohort	85	2.69	HTN: 32, CHD: 10, CKD: 3, CLD: 5, DM: 19, CPD: 2	CP: 2	AMI: 38, Arrhythmia: 51	LDH: 70, CK-MB: 31
48	Huang et al.[78]	China	Retrospective cohort	202	1.34	HTN: 29, CVD: 5, CLD: 4, DM: 19, CPD: 7	NR	AMI: 2	Tn: 2
49	Li et al.[79]	China	Retrospective cohort	25	0.66	HTN: 16, HD: 8, CKD: 5, CLD: 1, DM: 10, CPD: 2	NR		Tn: 11, LDH: 9
50	Palmieri et al.[80]	Italy	Retrospective cohort	3,032		HTN: 2,071, IHD: 856, HF: 490, Arrhythmia: 681, CKD: 618, CLD: 120, DM: 914, CPD: 498	NR	ACI: 314	NR
51	Mughal et al.[81]	USA	Retrospective cohort	129	1.68	HTN: 56, CAD: 10, HF: 12, CKD: 10, DM: 25, CPD: 12	MAP: 94	ACI: 9, Arrhythmia: 8	NR
52	Wang et al.[82]	China	Retrospective cohort	59	1.81	HTN: 31, CAD: 13, CLD: 4, DM: 15, CPD: 8	CP: 31	ACI: 38, Arrhythmia: 16	NR

No	Author	Country	Study method	N	Sex (M/F ratio)	Comorbidities (N)	Cardiovascular symptoms (N)	Cardiovascular complications (N)	Cardiac markers rise (N)
53	Stefanini et al.[83]	Italy	Retrospective cohort	397	2.05	HTN: 224, MI: 33, Arrhythmia: 39, CVD: 31, CKD: 85, CLD: 18, DM: 97, CPD: 35	Tachycardia: 72	ACI: 40	Tn: 40
54	Wang et al.[84]	China	Retrospective cohort	319	0.91	HTN: 139, CVD: 57, DM: 37	Tachycardia: 40, Bradycardia: 19	Arrhythmia: 20	Tn: 74
55	Heberto et al.[85]	Mexico	Prospective cohort	254	1.91	CHD: 14, HTN: 90, CKD: 2, DM: 80	NR	Arrhythmias: 20, AMI: 73	Tn: 73
56	Li et al.[86]	China	Retrospective cohort	2,068	0.94	HTN: 722, HF: 14, CAD: 182, ARRHY: 24, CKD: 31, DM: 292, CPD: 32	CP: 65, HR: 90, Palpitation: 45	ACI: 181, Arrhythmia: 151	Tn: 181, CK-MB: 40
57	Cao et al.[87]	China	Retrospective cohort	244	1.19	HTN: 75, DM: 36	CP: 3, HR: 87.26, MAP: 87.26	AMI: 45	Tn: 45, CK-MB: 153
58	Lorente-Ros et al.[88]	Spain	Retrospective cohort	707	1.68	HTN: 357, HF: 290, IHD: 66, Arrhythmia: 240, CKD: 79, DM: 143, CPD: 172	NR	AMI: 148	Tn: 148
59	Yang et al.[89]	China	Retrospective cohort	203	1.30	HTN: 80, CVD: 9, DM: 29, CPD: 6	NR	AMI: 38	NR
60	Qian et al.[90]	China	Retrospective cohort	77	2.20	HTN: 39, CVD: 18, CAD: 11, HF: 2, CKD: 4, DM: 17, CPD: 3	NR	AMI: 41, Arrhythmia: 19	NR
61	Shah et al.[24]	USA	Retrospective cohort	309	0.74	HTN: 261, HF: 65, CKD: 48, CLD: 5, DM: 143, CPD: 88	NR	AMI: 116	Tn: 116
62	Zhao et al.[91]	China	Retrospective cohort	83	2.32	HTN: 42, CVD: 13, CKD: 4, CLD: 5, DM: 30, CPD: 7	HR: 99, MAP: 93	AMI: 37	Tn: 37
63	Chen et al.[92]	China	Retrospective cohort	681	1.13	HTN: 293, CAD: 80, CKD: 27, DM: 114, CPD: 15	Palpitation: 17	AMI: 139	Tn: 139
64	Lala et al.[93]	USA	Retrospective cohort	2,736	1.47	HTN: 1,065, HF: 276, CAD: 453, Arrhythmia: 206, CKD: 273, DM: 719, CPD: 387	Tachycardia: 647, Hypotension: 228	AMI: 985	Tn: 985
65	Deng et al.[23]	China	Retrospective cohort	264	0.97	HTN: 100, CHD: 32, CKD: 9, CLD: 14, DM: 41, CPD: 8	NR	AMI: 45	Tn: 45
66	Karbalai Saleh et al.[94]	Iran	Prospective cohort	386	1.57	HTN: 142, CVD: 97, CKD: 16, DM: 133, CPD: 27	HR: 87.67	AMI: 115	Tn: 115
67	Xu et al.[95]	China	Retrospective cohort	53	1.12	HTN: 8, CVD: 6, DM: 8, CPD: 3	Tachycardia: 15, Angina: 8	AMI: 6, Arrhythmia: 4	NR
68	Argenziano et al.[96]	USA	Retrospective cohort	1,000	1.47	HTN: 601, CAD: 131, HF: 102, CKD: 137, CLD: 34, DM: 372, CPD: 179	NR	MI: 8, HF: 24, Arrhythmia: 79	NR

No	Author	Country	Study method	N	Sex (M/F ratio)	Comorbidities (N)	Cardiovascular symptoms (N)	Cardiovascular complications (N)	Cardiac markers rise (N)
69	Linschoten et al.[97]	Multi-country	Retrospective cohort	3,011	1.68	HTN: 1,317, CAD: 463, HF: 160, Arrhythmia: 453, CKD: 313, DM: 690, CPD: 373	NR	HF: 55, ACS: 15, Myocarditis: 3, Arrhythmia: 378	NR
70	Saleh et al.[98]	Germany	Prospective cohort	40	1.66	HTN: 19, HD: 10, DM: 11	Chest pain: 11	HF: 5, Arrhythmia: 13	Tn: 25, CK-MB: 17
71	Papageorgiou et al.[99]	UK	Retrospective Cohort	613	1.50	HTN: 288, HD: 86, DM: 199, CPD: 142	CP: 63	HF: 44, MI: 19, AMI: 287, Arrhythmia: 47	
72	Becerra-Muñoz et al.[100]	Spain	Retrospective Cohort	1,520	1.51	HTN: 1,047, HD: 562, Arrhythmia: 247, CKD: 164, CLD: 61, DM: 377, CPD: 380	NR	HF: 143	Tn: 150
73	Yan et al.[101]	China	Retrospective Cohort	119	0.80	HTN: 60, CHD: 19, CKD: 4, DM: 26, CPD: 2	Chest pain: 9	NR	Tn: 27
74	Arcari et al.[102]	Italy	Retrospective Cohort	111	0.85	HTN: 62, CVD: 35, Arrhythmia: 21, CAD: 12, HF: 8, CKD: 7, DM: 21, CPD: 26	NR	NR	Tn: 39

No: Number of studies; N: Number of patients; CVD: Cardiovascular diseases; IHD: Ischemic heart diseases; HTN: Hypertension; CHD: Chronic heart disease; HF: Heart failure; CAD: Coronary artery disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; DM: Diabetes mellitus; CPD: Chronic pulmonary disease; HR: Heart rate; SBP: Systolic blood pressure; MAP: Mean arterial pressure; CP: Chest pain; AC(M)I: Acute cardiac (myocardial) injury; CMP: Cardiomyopathy; MI: Myocardial infarction; ACS: Acute coronary syndrome; cTn: Cardiac troponin; LDH: Lactate dehydrogenase; CK-MB: Creatine kinase–myocardial band; CK: Creatine kinase; NR: Not reported, not reported by number, or incomplete

The highest and lowest rates of CKD among patients with COVID-19 were in the USA (44.92%, 95% CI=40.33-49.58)[28] and Mexico (0.79%, 95% CI=0.10-2.82),[85] respectively. Based on the results of a random effect model, the pooled prevalence of CKD was 5.62% (95% CI=4.79-6.59). The Chi square test result for heterogeneity was significant for the reported prevalence of CKD (I^2=96.6%, P<0.001).

Both the highest and lowest rates of CMP (as an underlying medical condition) among patients with COVID-19 were in China (5.95%, 95%CI=1.96-13.35[32] and 4.28%, 95% CI=1.86-8.26,[67] respectively). Based on the results of a random effect model, the pooled prevalence of CMP was 4.85% (95% CI=2.84-8.18). The Chi square test result for heterogeneity was not significant for the reported prevalence of CMP (I^2=0.0%, P=0.558%).

The highest and lowest rates of CLD among patients with COVID-19 were in China (13.10%, 95% CI=6.72-22.22)[32] and the USA (0.53%, 95% CI=0.36-0.75),[57] respectively. Based on the results of a random effect model, the pooled prevalence of CLD was 3.09% (95% CI=2.37-4.02). The Chi square test result for heterogeneity was significant for the reported prevalence of CLD (I^2=82.9%, P<0.001).

Prevalence of Cardiovascular Signs and Symptoms

Meta-analysis of the included studies indicated that the most prevalent signs and symptoms in COVID-19 patients were hypotension (14.42%), tachycardia (9.98%), chest pain (8.80%), and bradycardia (5.24%). The highest and lowest rates of hypotension among patients with COVID-19 were 31.25% (95% CI=11.02-58.66)[55] and 8.33% (95% CI=7.32-9.43),[93] respectively. Based on the results of a random effect model, the pooled prevalence of hypotension was 14.42% (95% CI=5.54-32.59). The Chi square test result for heterogeneity was significant for the reported prevalence of hypotension (I^2=88.6%, P=0.009). The highest and lowest rates of tachycardia among patients with COVID-19 were 43.11% (95% CI=41.81-44.40)[57] and 1.03% (95% CI=0.21-2.98),[45] respectively. Based on the results of a random effect model, the pooled prevalence of tachycardia was 9.98% (95% CI=5.32-17.93). The Chi square test result for heterogeneity was significant for the reported prevalence of tachycardia (I^2=99%, P<0.001).

The highest and lowest rates of chest pain among patients with COVID-19 were 52.54% (95% CI=39.12-65.70)[82] and 0.34% (95% CI=0.01-1.90),[45] respectively. Based on the results of a random effect model, the pooled prevalence of chest pain was 8.80% (95% CI=5.19-14.51). The Chi square test result for heterogeneity was significant for the reported prevalence of chest pain (I^2=96.4%, P<0.001). The highest and lowest rates of bradycardia among patients with COVID-19 were 5.96% (95% CI=3.62-9.15)[84] and 2.78% (95% CI=0.34-9.68),[68] respectively. Based on the results of a random effect model, the pooled prevalence of bradycardia was 5.24% (95% CI=3.53-7.69). The Chi square test result for heterogeneity was not significant for the reported prevalence of bradycardia (I^2=0.0%, P=0.394).

Prevalence of Cardiovascular Complications

The results of the present meta-analysis showed that the overall pooled prevalence of cardiovascular complications was 23.45% (95% CI=16.24-32.61). The Chi square test result for heterogeneity was significant for the reported prevalence of cardiovascular complications (I^2=97.8%, P<0.001) (figure 2). Since there were several articles on this type of complication, the available articles were divided into three groups according to sample size and subsequently presented in separate forest plots. The overall pooled prevalence of cardiovascular complications, based on analysis of the results of the studies, is presented in forest plots a, b, and c. The most prevalent cardiovascular complications in COVID-19 patients were, in descending order, acute cardiac (myocardial) injury (19.38%), cardiac arrhythmias (11.16%), HF (7.56%), CMP (2.78%), myocardial infarction (1.66%), and myocarditis (0.71%).

Both the highest and lowest rates of acute cardiac (myocardial) injury among patients with COVID-19 were in China (89.02%, 95% CI=80.18-94.86[44] and 0.99%, 95% CI=0.12-3.53,[78] respectively). Based on the results of a random effect model, the pooled prevalence of acute cardiac (myocardial) injury was 19.38% (95% CI=13.62-26.81). The Chi square test result for heterogeneity was significant for the reported prevalence of acute cardiac (myocardial) injury (I^2=97.5%, P<0.001) (figure 3). Since there were several articles on this type of complication, the available articles were divided into three groups according to sample size and subsequently presented in separate forest plots. The total pooled prevalence of acute cardiac (myocardial) injury, based on analysis of the results of the included studies, is presented in forest plots a, b, and c.

The highest and lowest rates of cardiac arrhythmia among patients with COVID-19 were both in China (60%, 95% CI=48.80-70.48[77] and 4.76%, 95% CI=1.31-11.75,[32] respectively).

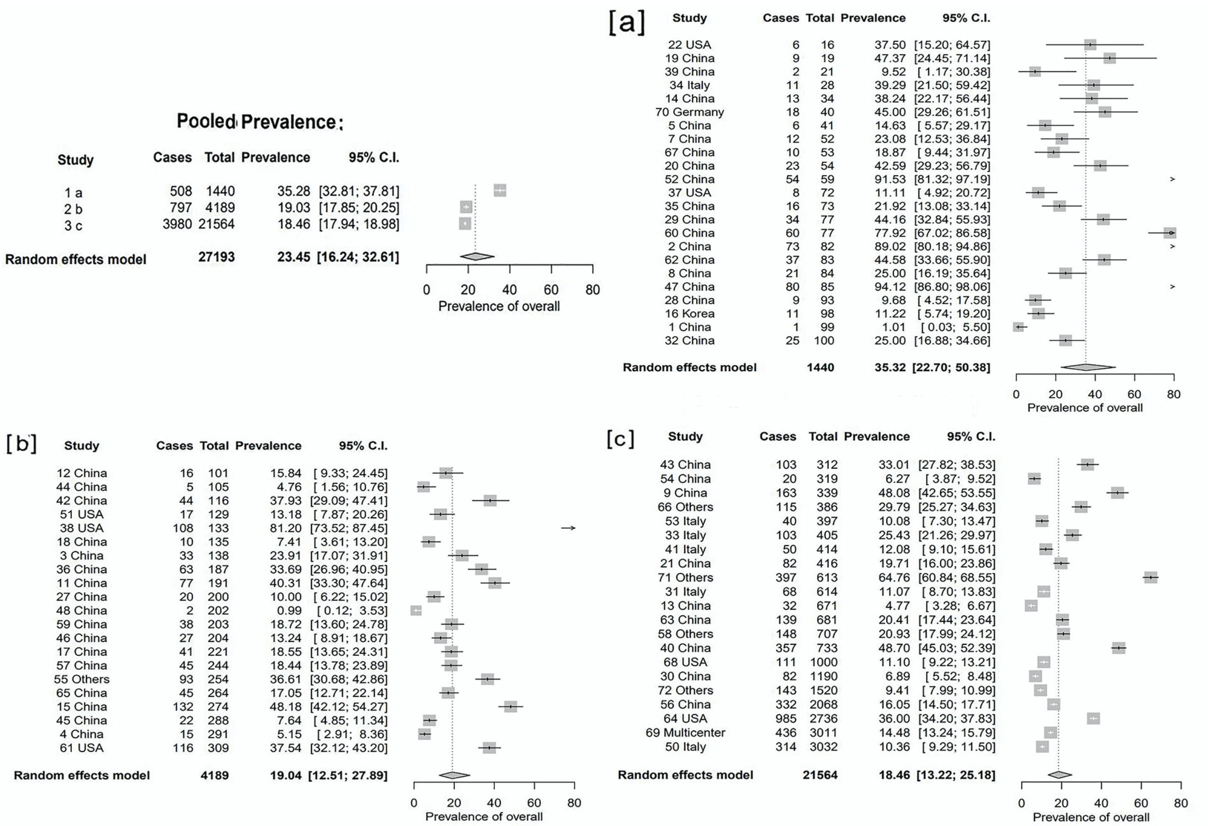

Figure 2: Forest plots show the overall prevalence of cardiovascular complications in patients with COVID-19 (pooled prevalence, as well as a, b, and c groups, are sorted by the sample size of the studies).

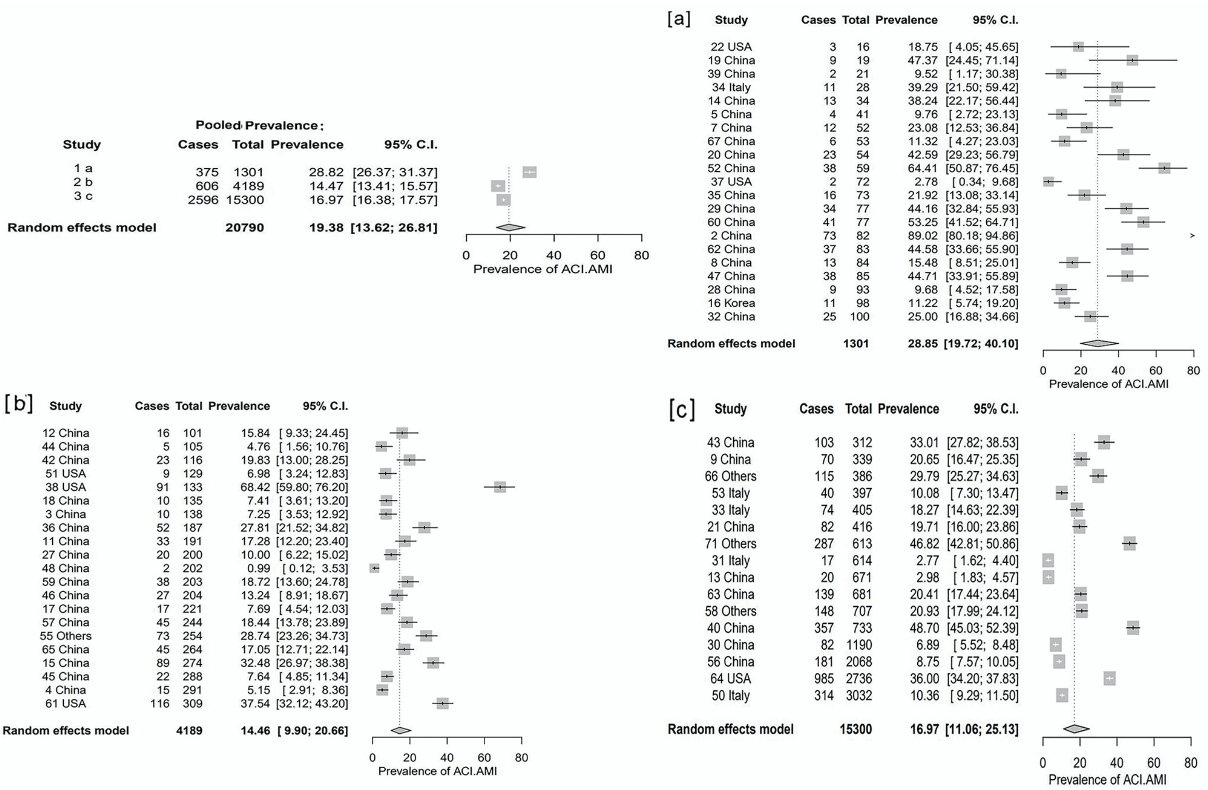

Figure 3: Forest plots show the prevalence of acute cardiac (myocardial) injury (ACI/AMI) in patients with COVID-19 (pooled prevalence, as well as a, b, and c groups, are sorted by the sample size of the studies).

Based on the results of a random effect model, the pooled prevalence of arrhythmia was 11.16% (95% CI=8.23-14.96). The Chi square test result for heterogeneity was significant for the reported prevalence of arrhythmia (I^2=91.5%, P<0.001) (figure 4).

Both the highest and lowest rates of HF among patients with COVID-19 were in China (23.04%, 95% CI=17.27-29.66[41] and 1.01%, 95% CI=0.03-5.50,[43] respectively). Based on the results of a random effect model, the pooled prevalence of HF was 7.56% (95% CI=4.50-12.45). The Chi square test result for heterogeneity was significant for the reported prevalence of HF (I^2=96.3%, P<0.001) (figure 5). The prevalence of CMP among patients with COVID-19 in one study that met the inclusion criteria was 2.78% (95% CI=0.34-9.68).[68]

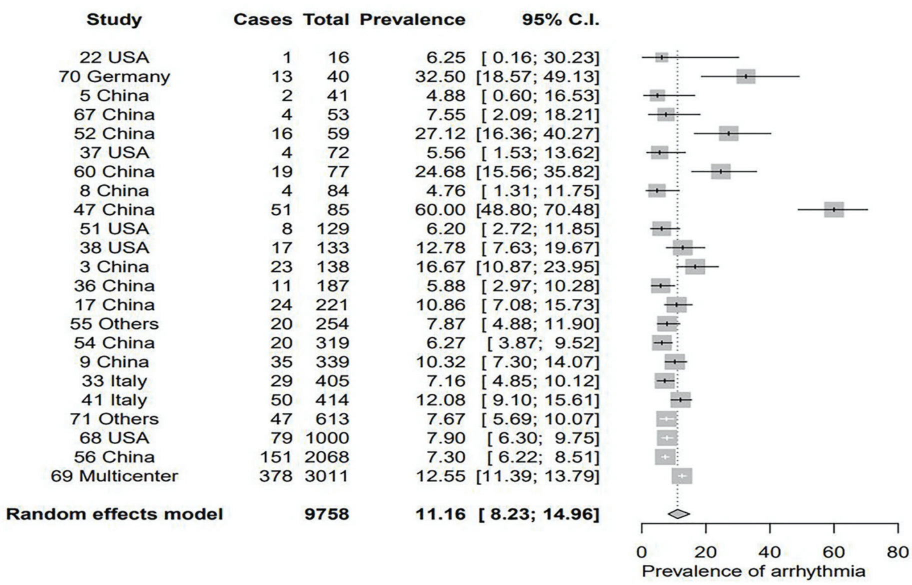

Figure 4: The forest plot shows the prevalence of cardiac arrhythmia in patients with COVID-19.

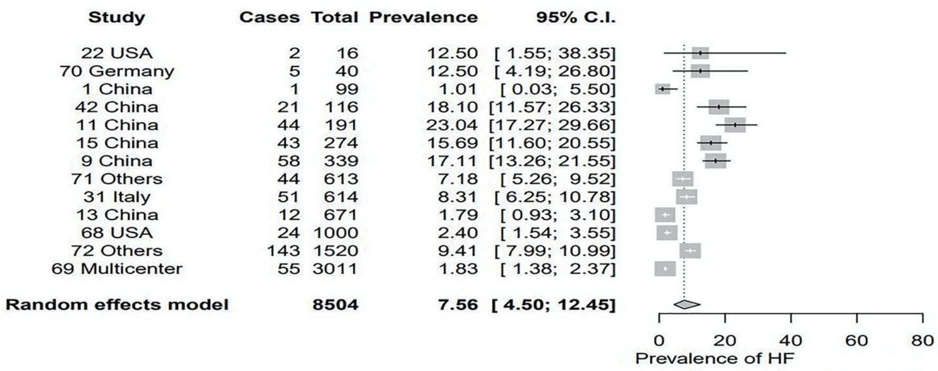

Figure 5: The forest plot shows the prevalence of heart failure in patients with COVID-19.

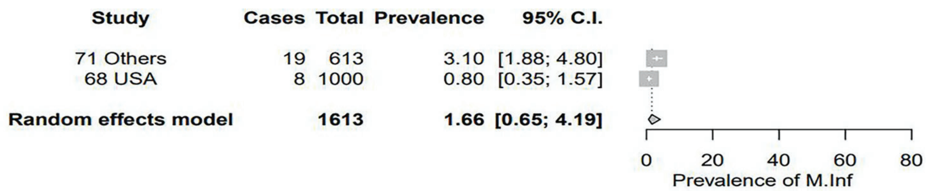

Figure 6: The forest plot shows the prevalence of myocardial infarction (M.Inf.) in patients with COVID-19.

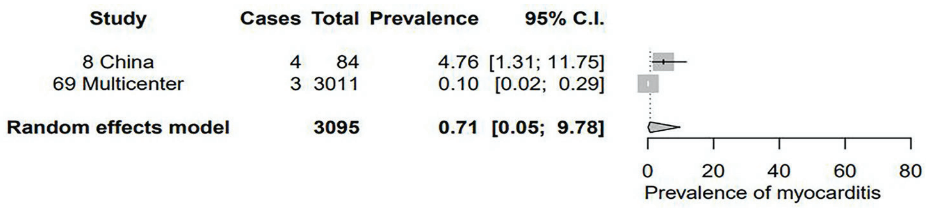

Figure 7: The forest plot shows the prevalence of myocarditis in patients with COVID-19.

The highest and lowest rates of myocardial infarction among patients with COVID-19 were in the UK (3.10%, 95% CI=1.88-4.80)[99] and the USA (0.80%, 95% CI=0.35-1.57),[96] respectively. Based on the results of a random effect model, the pooled prevalence of myocardial infarction was 1.66% (95% CI=0.65-4.19). The Chi square test result for heterogeneity was significant for the reported prevalence of myocardial infarction (I^2=90.5%, P<0.001) (figure 6).

The highest and lowest rates of myocarditis among patients with COVID-19 were in China (4.76%, 95% CI=1.31-11.75)[32] and a multi-country study (0.10%, 95% CI=0.02-0.29),[97] respectively. Based on the results of a random effect model, the pooled prevalence of myocarditis was 0.71% (95% CI=0.05-9.78). The Chi square test result for heterogeneity was significant for the reported prevalence of myocarditis (I^2=96.1%, P<0.001) (figure 7).

The meta-analysis of the included studies showed that the most prevalent elevated cardiac markers in COVID-19 patients were, in order of frequency, LDH (61.45%), cTnI(T) (23.10%), and CK or CK-MB (14.52%). Both the highest and lowest rates of increased LDH among patients with COVID-19 were in China (88.31%, 95% CI=78.97-94.51[27] and 36%, 95% CI=17.97-57.48,[79] respectively). Based on the results of a random effect model, the pooled prevalence of increased LDH was 61.45% (95% CI=51.11-70.85). The Chi square test result for heterogeneity was significant for the reported prevalence of increased LDH (I^2=91.5%, P<0.001) (figure 8).

The highest and lowest rates of increased cTnI(T) among patients with COVID-19 were both in China (100%, 95% CI=96.82-100.00[56] and 0.99%, 95% CI=0.12-3.53,[78] respectively). Based on the results of a random effect model, the pooled prevalence of increased TnI(T) was 23.10% (95% CI; 20.78-25.60). Chi square test result for heterogeneity was significant for the reported prevalence of increased cTnI(T) (I^2=97.4%, P<0.001) (figure 9). Since there were several articles for this variable, the available articles were divided into three groups according to sample size and subsequently presented in separate forest plots. The total pooled prevalence of cTnI(T), based on analysis of the results of the studies, is presented in forest plots a, b, and c.

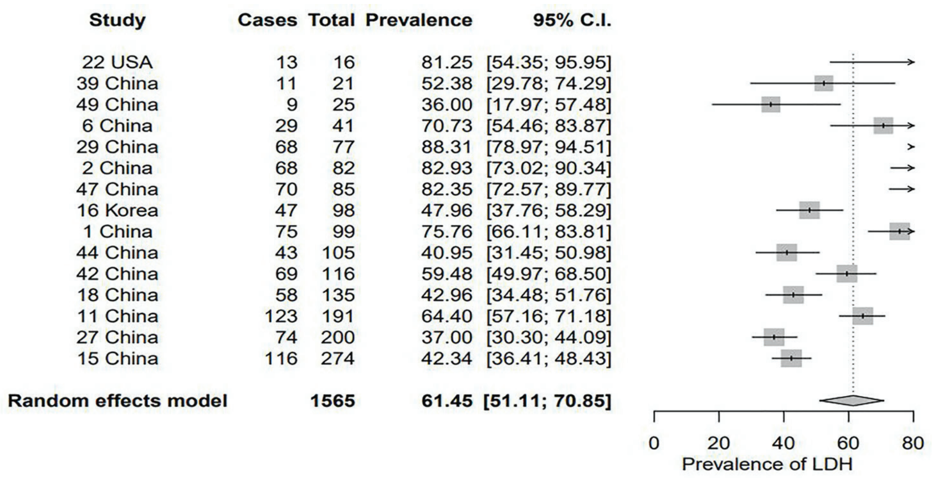

Figure 8: The forest plot shows the prevalence of increased lactate dehydrogenase levels in patients with COVID-19.

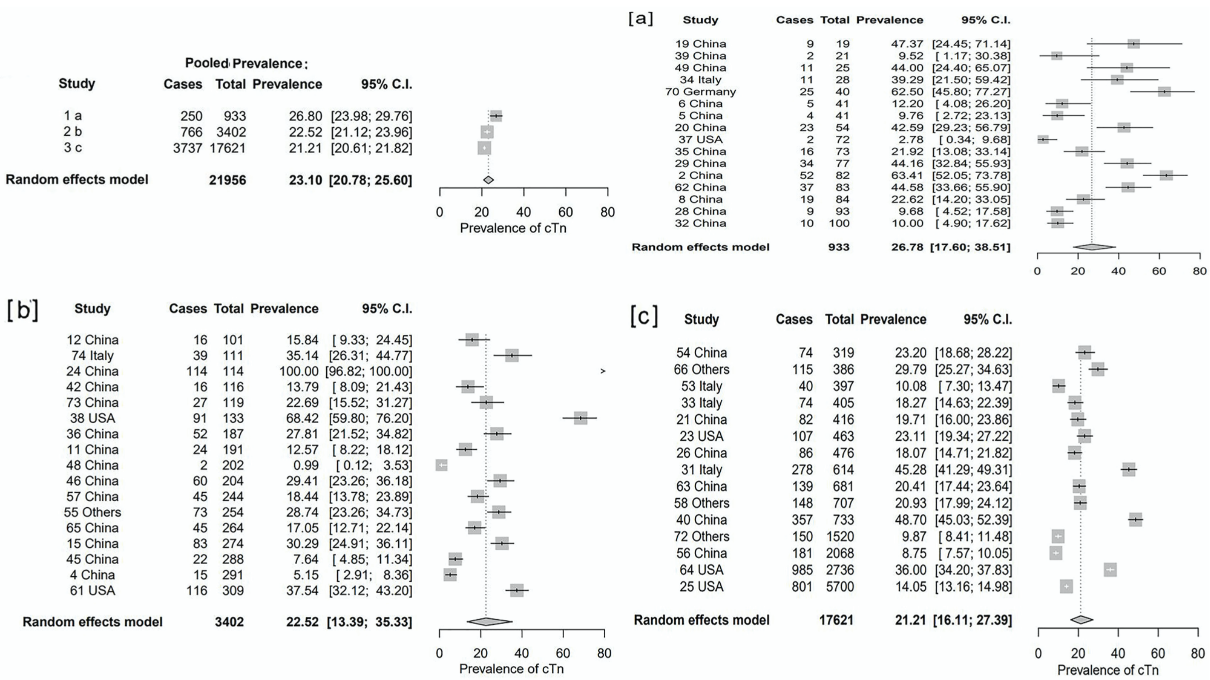

Figure 9: Forest plots show the prevalence of increased cTnI(T) level in patients with COVID-19 (pooled prevalence, as well as a, b, and c groups, were sorted by the sample size of the studies).

Both the highest and lowest rates of increased CK and/or CK-MB among patients with COVID-19 were in China (62.70%, 95% CI=56.31-68.79[87] and 1.93%, 95% CI=1.39-2.62,[86] respectively). Based on the results of a random effect model, the pooled prevalence of increased CK or CK-MB was 14.52% (95% CI=8.82-22.98). The Chi square test result for heterogeneity was significant for the reported prevalence of increased CK and/or CK-MB (I^2=97.4%, P<0.001) (figure 10).

Publication Bias and Heterogeneity of the Study Results

Linear regression test of funnel plot asymmetry suggested no statistically significant publication bias for HR (t=-1.93, P=0.075). However, the heterogeneity of the results of the included studies was highly significant (I^2=98%, P<0.001). Regarding the MAP level in the participants, the test of funnel plot asymmetry suggested no statistically significant publication bias (t=-0.55, P=0.594). Again, the heterogeneity of the results of the included studies was highly significant (I^2=99%, P<0.001). Evaluation of the effect of country, sex, and age of the participants on the results of the included studies, using meta-regression, revealed no significant contribution of these variables on the prevalence of cardiovascular comorbidities and the observed heterogeneity (P>0.05 for all) (tables 2 and 3).

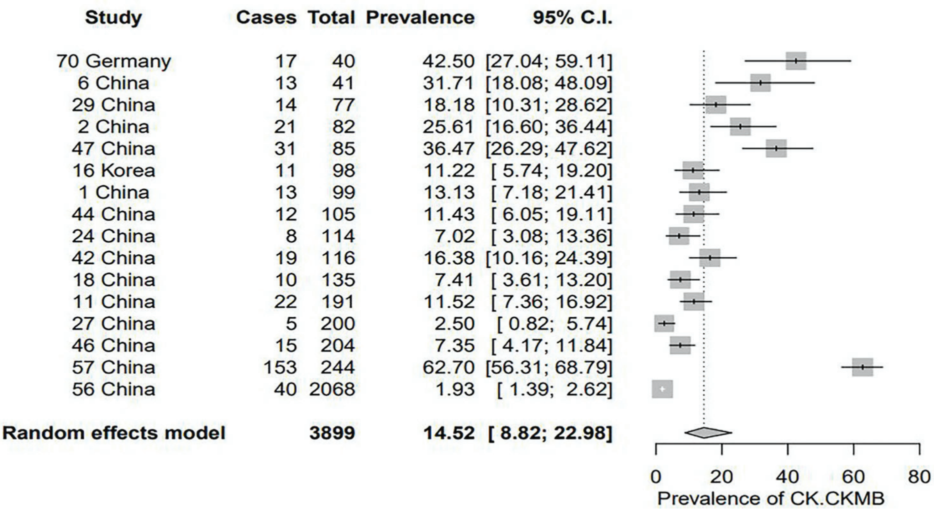

Figure 10: The forest plot shows the prevalence of increased creatine kinase or creatine kinase-myocardial band level in patients with COVID-19.

Table 2: Results of meta-regression for cardiovascular diseases

Estimate		B	SE	Z-value	95% CI	P value
Intercept		-5.44	0.74	-7.2893	-6.91 to -3.98	<0.001
Country	Korea	0.24	0.66	0.3610	-1.07 to 1.55	0.718
	Italy	0.76	0.35	2.1976	0.08 to 1.45	0.028
	Germany	0.39	0.69	0.5757	-0.95 to 1.74	0.564
	Others	-0.07	0.28	-0.2687	-0.64 to 0.48	0.788
Mean age (years)		0.05	0.01	4.5849	0.03 to 0.08	<0.001
Sex ratio		0.19	0.16	1.2138	-0.11 to 0.49	0.224

B: Regression coefficient; SE: Standard error; CI: Confidence interval; Amount of heterogeneity accounted for (R2=15.63%); Estimated amount of residual heterogeneity (tau^2=23.37); Test for residual heterogeneity (QE=220.55, P<0.001); Test of moderators (QM=8.49, P=0.20)

Table 3: Results of meta-regression for cardiac arrhythmia

Estimate		B	SE	Z-value	95% CI	P value
Intercept		-5.43	0.98	-5.5307	-7.35 to -3.50	<0.001
Country	USA	-0.94	0.28	-3.3093	-1.50 to -0.39	0.0009
	Italy	-1.14	0.33	-3.4644	-1.79 to -0.50	0.0005
	Germany	0.63	0.51	1.2208	-0.38 to 1.63	0.222
	Others	-0.99	0.31	-3.1178	-1.61 to -0.37	0.001
	Multicenter	-0.57	0.38	-1.4800	-1.33 to 0.18	0.138
Mean age (years)		0.03	0.01	2.2105	0.00 to 0.06	0.027
Sex ratio		1.04	0.19	5.3994	0.66 to 1.41	<0.001

B: Regression coefficient; SE: Standard error; CI: Confidence interval; Amount of heterogeneity accounted for (R2=15.63%); Estimated amount of residual heterogeneity (tau^2=23.37); Test for residual heterogeneity based on Likelihood-ratio test (I^2=89.219, P<0.001); Test of moderators based on Chi square test (QM=40.59, P=0.20)

Discussion

In this meta-analysis, 74 studies involving 34,379 COVID-19 patients were analyzed. Meta-analysis of the included studies showed that the most prevalent comorbidities in COVID-19 patients were HTN, DM, CVD, CAD, cardiac dysrhythmia, HF, CPD, CKD, CMP, and CLD. The most prevalent signs and symptoms in COVID-19 patients were hypotension, tachycardia, chest pain, and bradycardia. The results showed that the overall pooled prevalence of cardiovascular complications was 23.45%. The most prevalent cardiovascular complications in COVID-19 patients were, in descending order, acute cardiac (myocardial) injury, cardiac arrhythmias, HF, CMP, myocardial infarction, and myocarditis. In addition, the most prevalent underlying medical condition in COVID-19 patients was HTN. According to previous studies on SARS-CoV-2, the presence of comorbidities increases the risk of mortality, with cardiac diseases and DM being the most important predictors of adverse outcomes.[103] A large-scale study of 44,672 patients reported that CVD was a major risk factor for mortality in COVID-19 patients.[104]

According to previous systematic reviews and meta-analyses, HTN was the most prevalent underlying disease in hospitalized COVID-19 patients.[105-107] Moreover, the severity and mortality of COVID-19 were found to be higher in patients with HTN. HTN was even reported to increase the mortality rate associated with COVID-19 by a factor of 2.5.[105] Research findings also show that, in addition to HTN, CVD is among the prevalent underlying medical conditions in COVID-19 patients. Several studies reported a correlation between the severity/mortality of the infection and the above-mentioned underlying diseases.[47, 67, 106-112]

DM was found to be the second most prevalent underlying medical condition in COVID-19 patients. In the present meta-analysis, the third and fourth most prevalent underlying conditions were CVD and CAD, respectively. CVD and HTN in COVID-19 patients were associated with ACE2 receptors.[113] The entry of the new coronavirus into cells through membrane fusion results in a significant decrease in the efficacy of ACE2 receptors and loss of their catalytic function on the outer membrane. Elevated pulmonary inflammation and vasoconstriction were reported as undesirable consequences of an increase and lack of response to angiotensin II in COVID-19. Clinical reports of COVID-19 patients showed that several factors associated with infection severity (old age, HTN, DM, and cardiac disease) correlated with some degree of ACE2 deficiency.[114]

A meta-analysis of 1,527 patients with COVID-19, conducted to determine the prevalence and impact of cardiovascular metabolic diseases on COVID-19 patients in China, showed that the frequency of HTN and cardiac disease was 17.1% and 16.4%, respectively, and also patients with these conditions were more likely to require critical care.[115] HTN, DM, and ischemic heart disease are prevalent in people hospitalized for infection with the new coronavirus and correlate with an increased risk of disease progression and death.[116]

The fifth most prevalent underlying condition was cardiac dysrhythmias. In a study of 700 patients with COVID-19, Bhatla and colleagues reported that 6% of the infected patients had a history of atrial fibrillation.[117] In the present review, the sixth most prevalent underlying disease was HF, which is in line with other studies that refer to HF as a major underlying condition and risk factor in COVID-19 patients.[21, 39, 54, 117, 118] Other underlying conditions identified in the present study were, in descending order, a positive history of CPD, CKD, CMP, and CLD. Edler and colleagues reported that 5% of their patients with COVID-19 had CMP.[36]

In the present meta-analysis, we also included the reported cardiac signs and symptoms. The most prevalent symptom in the infected patients was hypotension followed by tachycardia, chest pain, and bradycardia. Liu and colleagues studied 133 patients with COVID-19 and reported that 7.3% of the patients complained of tachycardia at the time of admission.[19] The results of the present review study showed that the most prevalent complication in COVID-19 patients was cardiac injury. Based on our review, 19.38% of COVID-19 patients suffered from an acute cardiac (myocardial) injury as a result of the infection. Some studies showed that SARS-CoV-2 can both directly and indirectly lead to cardiovascular sequelae, including myocardial injury, acute coronary syndromes (ACS), CMP, acute cor pulmonale, arrhythmias, and cardiogenic shock, as well as thrombotic complications.[2, 119] ACE2 is regarded as one of the primary receptors leading to cardiac injury.[115, 120] Being tissue-specific, ACE2 is found on the pulmonary, cardiovascular, gastrointestinal, and renal cells. This phenomenon results in intracellular acidosis and the production of oxygen-free radicals, in addition to the influx of calcium, which eventually leads to myocyte injury and death.[115] Thus, the close resemblance of SARS to the COVID-19 genome, alongside similarities between their receptor binding areas, can lead to myocardial damage. Another possible mechanism may be associated with the cytokine storm. Lack of balance between T-helper (Th) 1 and Th2 cells causes the overproduction of inflammatory cytokines, which may be one of the contributory factors in the pathogenesis of cardiac injury.[12] Myocardial injury, with elevated cardiac biomarkers above the 99th percentile of the upper reference limit, was reported in 20%-30% of hospitalized COVID-19 patients; those with pre-existing CVD were more prone to the injury (55%).[54, 67] A systematic review of 22 articles showed the pooled incidence of myocardial injury to be 17.85%,[29] and that of cardiac arrhythmia was 11.16% (the second most prevalent complication). In a study by Zhang and others, 24 of the 221 observed patients had experienced cardiac arrhythmia.[50] It was reported that about 16% of patients with MERS experienced cardiac arrhythmia.[9] The results of a study by Li and colleagues showed that patients with emerging arrhythmia were at higher risk of contracting severe diseases and requiring intensive care.[121] In another review, the pooled incidence of cardiac arrhythmia was reported to be 10.14%.[29] In a study by Chen and colleagues, 1.3% of the patients had cardiac arrhythmia at the time of admission; yet, 44% indicated signs of atrial fibrillation during hospitalization.[122]

In the present review, the third most prevalent complication in COVID-19 patients was HF. In a study by Zhou and colleagues, 23% of the patients experienced HF following infection with the new coronavirus.[41] In a previous systematic review of 22 articles, HF was the most prevalent complication among COVID-19 patients with an incidence rate of 22%.[29]

Our findings showed that other prevalent cardiovascular complications associated with COVID-19 are, in descending order, CMP, myocardial infarction, and myocarditis. A previous study reported that five out of 76 patients with SARS had cardiac arrhythmia and CMP.[123] Because of extensive inflammation and hypercoagulability, patients with COVID-19 are at risk of acute myocardial infarction.[119, 124] In a study of 75 inpatients with SARS, acute myocardial infarction was found to account for two out of five deaths.[125] Viral myocarditis can cause various cardiac complications, from subclinical myocarditis, with only enzyme elevation due to local myocyte necrosis, to sudden cardiac death due to arrhythmia.[126, 127] Among ten professional athletes with SARS-CoV-2 infection, 2.3% had signs of clinical or subclinical myocarditis.[128]

In the present meta-analysis, the most prevalent elevated cardiac markers in COVID-19 patients were LDH (61.45%), cTnI(T) (23.10%), and CK or CK-MB (14.52%). CK, CK-MB, and LDH were indicators associated with cardiac injury.[129, 130] Elevated TnI and CK-MB levels showed cardiac injuries, such as viral myocarditis or myocardial infarction, as well as multiple organ injuries.[131] High-sensitivity cTnI and cTnT are the gold standard biomarkers for the diagnosis of acute myocardial infarction.[132] TnI has a very good prognostic value not only for patients with COVID-19 but also for patients with other types of influenza virus infection.[125] LDH, on the other hand, is not highly specific to the heart.[133] The results of a study of 76 patients with SARS showed that 73 and 34 patients had elevated levels of serum LDH and CK, respectively.[123] According to a systematic review and meta-analysis, patients with elevated cTnI(T), CK, CK-MB, and LDH levels were at higher risk of developing a serious illness requiring intensive care. However, LDH levels have predictive value for mortality.[121] An increase in the frequency and extent of troponin elevations in hospitalized patients was associated with greater disease severity and more serious consequences.[54, 67]

Our meta-analysis revealed significant heterogeneities in the results of the included studies regarding CVD and cardiac arrhythmia. We attempted to clarify the effect of the patients' country, age, and sex to the heterogeneity of the results by conducting a meta-regression analysis. However, the residual heterogeneity remained significant even after the above factors were included in the meta-regression. This may suggest the impact of hidden factors (e.g., differences between studies in diagnosis, reporting, and hospital admission strategies). No publication bias was detected in the present study.

As the main limitation of the present study, we only included observational studies on adult patients. Furthermore, vascular complications (e.g., venous thrombosis) were not addressed. Therefore, it is recommended to include a review of clinical trials and thrombotic disorders for a better understanding of the cardiovascular complications caused by COVID-19.

Conclusion

The most prevalent cardiovascular complications in patients with COVID-19 were, in descending order, acute cardiac (myocardial) injury, cardiac arrhythmias, HF, and CMP. Healthcare administrators should pay closer attention to viral infection-related cardiovascular complications when treating those infected. Since the occurrence of cardiovascular complications has a negative impact on the mortality rate in patients with COVID-19, clinicians and nurses should be aware of the various types of cardiovascular complications associated with COVID-19 and include them in their patient care and treatment plan.

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Authors' Contribution

CT, HH, and RI were responsible for the study conception and performed data collection; MF, HH, and RI performed the data analysis; HH and RI led the writing of the manuscript. CT, MF, and HH made critical revisions to the paper. CT and HH supervised the study. All the authors helped to conceptualize ideas, interpret findings, and review drafts of the manuscript. All authors read and approved the final manuscript and responsible 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.

Conflict of Interest: None declared.

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