

Cardiovascular Diseases Burden in COVID-19: Systematic Review and Meta-analysis

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Abstract:

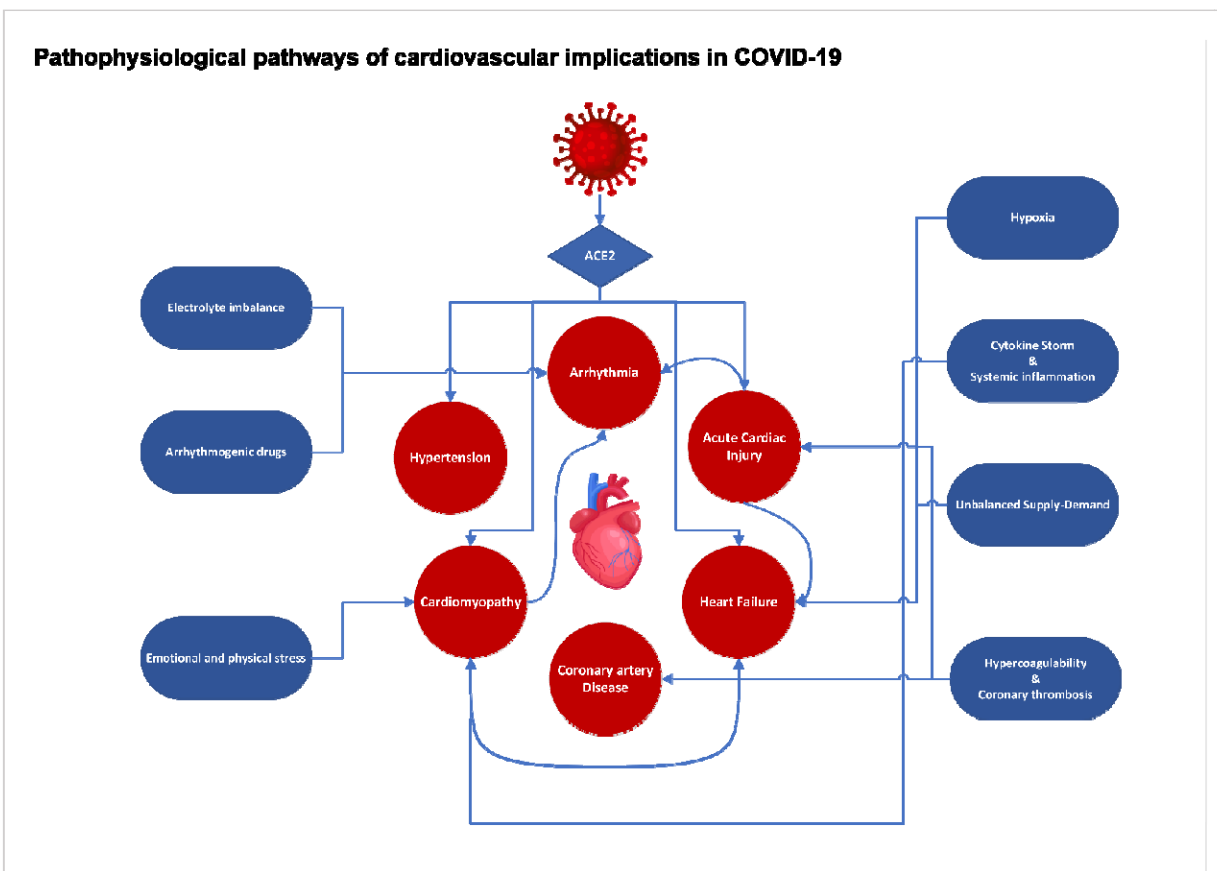
Background: High rate of cardiovascular disease (CVD) have been reported among patients with novel coronavirus disease (COVID-19). Meanwhile there were controversies among different studies about CVD burden in COVID-19 patients. Hence, we aimed to study CVD burden among COVID-19 patients, using a systematic review and meta-analysis.

Methods: We have systematically searched databases including PubMed, Embase, Cochrane Library, Scopus, Web of Science as well as medRxiv pre-print database. Hand searched was also conducted in journal websites and Google Scholar. Meta-analyses were carried out for Odds Ratio (OR) of mortality and Intensive Care Unit (ICU) admission for different CVDs. We have also performed a descriptive meta-analysis on different CVDs.

Results: Fifty-six studies entered into meta-analysis for ICU admission and mortality outcome and 198 papers for descriptive outcomes, including 159,698 COVID-19 patients. Results of meta-analysis indicated that acute cardiac injury, (OR: 13.29, 95% CI 7.35-24.03), hypertension (OR: 2.60, 95% CI 2.11-3.19), heart Failure (OR: 6.72, 95% CI 3.34-13.52), arrhythmia (OR: 2.75, 95% CI 1.43-5.25), coronary artery disease (OR: 3.78, 95% CI 2.42-5.90), and cardiovascular disease (OR: 2.61, 95% CI 1.89-3.62) were significantly associated with mortality. Arrhythmia (OR: 7.03, 95% CI 2.79-17.69), acute cardiac injury (OR: 15.58, 95% CI 5.15-47.12), coronary heart disease (OR: 2.61, 95% CI 1.09-6.26), cardiovascular disease (OR: 3.11, 95% CI 1.59-6.09), and hypertension (OR: 1.95, 95% CI 1.41-2.68) were also significantly associated with ICU admission in COVID-19 patients.

Conclusion: Findings of this study revealed a high burden of CVDs among COVID-19 patients, which was significantly associated with mortality and ICU admission. Proper management of CVD patients with COVID-19 and monitoring COVID-19 patients for acute cardiac conditions is highly recommended to prevent mortality and critical situations.

Keywords: COVID-19; Cardiovascular Disease; Meta-analysis



Graphical abstract

Introduction:

Coronaviruses are enveloped positive sense single stranded RNA viruses which cause respiratory infections in human and animals (1-3). There were six coronaviruses known to cause infection in humans (4), including Severe Acute Respiratory Syndrome (SARS), China, 2002 (5) and Middle Eastern Respiratory Syndrome (MERS), Saudi Arabia, 2012 (6, 7). The World Health Organization (WHO) reported cases of pneumonia with unknown source in Wuhan, China, December 2019 (8). Further investigations in samples of patients with respiratory infection, who were in contact with a seafood markets in Wuhan revealed a novel virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (9). On 11th March, 2020 WHO declared the SARS-CoV-2 outbreak as a pandemic (10). It has been estimated that 1.7 billion people (22% world population) have at least one underlying condition, including cardiovascular diseases (CVD), which increases the risk of developing severe disease in case of coronavirus disease (COVID-19) (11).

There is a mutual relationships between CVD and infections (12, 13), while the viral respiratory infectious diseases like influenza might increase the risk of myocardial infarction and cardiovascular events (13), underlying CVD might increase the risk of mortality among patients with infection (14).

Reports from COVID-19 disease including a large number of patients showed that fatality rate was 10.5% for CVD and 6.0% for hypertension among 72314 cases of COVID-19 (15). Studies indicated that there is an increased risk of mortality among hospitalized COVID-19 patients due to CVD (16-18).

Given the increasing number of COVID-19 patients besides from common clinical presentations of disease, CVD in COVID-19 infected patients are seems to be concerning (16). We aimed to assess the CVD burden of COVID-19, using a systematic review and meta-analysis method in this study.

Methods:

Search Strategy:

In this study, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline was used for study design, search strategy, screening and reporting. The research question has been developed using PECO; “P” stands for Patients, “E” as Exposure, “C” as Comparison and “O” as Outcome. PECO components were as follows: “P”; hospitalized COVID-19 patients, “E”; CVDs, “C”; no CVD, “O”; ICU admission/mortality. A systematic search was using all available MeSH terms and free keywords for “COVID-19”, “Cardiovascular Disease” “Myocardial Infarction”, “Heart Failure”, “Hypertension”, “Myocarditis”, “Arrhythmia”. Searched Databases included PubMed, Embase, Scopus, Web of Science, Cochrane Library, medRxiv pre-print database as well as Science Direct search engine. Hand search was done in publishers and journals databases including: Center for Disease Control and Prevention (CDC), The Journal of the American Medical Association (JAMA), The Lancet, The British Medical Journal (BMJ), Nature, Wiley, New England Journal of Medicine, Cambridge and Oxford. Our search included papers in all languages and there was no time limitation for publications. All original Cohort, Case Control, Cross-Sectional and Case-Series studies until 27th May 2020 were included.

Criteria for Study Selection

Two members of our team (F.P and A.H) selected the study independently and in case of disagreement R.A made the final decision. Studies met the following criteria included into systematic review: 1) Studies reporting characteristics of hospitalized COVID-19 patients; 2) Studies which reported any CVD in COVID-19 patients; 3) COVID-19 confirmed by Chest CT Scan, RT-PCR and hallmarks of the disease. Criteria for including studies into meta-analysis were: 1) Studies that reported CVD in COVID-19 patients admitted to ICU; 2) Studies reported the mortality rate of COVID-19 patients with underlying CVD; 3) Studies reported CVD among COVID-19 hospitalized patients.

Studies were excluded if they: 1) Reported outpatients or asymptomatic COVID-19 patients; 2) Not reported CVDs; 3) Review papers, case reports, *in vitro* studies and animal studies.

Data Extraction

Two investigators (F.P and A.H) have independently evaluated quality of publications and extracted data from included papers. In case of disagreement a supervisor (R.A) solved the issue and made the final decision. Data extraction included first author name, publication year, country and following data extracted for each group (Total Sample, ICU, Non-ICU, Mortality, Survival): Sample size, mean \pm standard deviation (SD) of age, number of females, number of males, heart failure, hypertension, other cardiovascular disease, acute cardiac injury, cardiomyopathy, myocardial damage, heart palpitation, coronary heart disease, arrhythmia and acute cardiac injury. In cases that data was presented as median (interquartile range), a method by *Wan et al.* (19) was used to calculate mean \pm SD.

Risk of Bias Assessment

Newcastle-Ottawa Scale tool was used for risk of bias assessment of studies included into meta-analysis (20). Risk of bias only assessed for studies entered into meta-analysis main outcomes (ICU and mortality) of the study (Figure 1).

Data Analysis

Odds Ratio (OR) and pooled estimate prevalence rate with 95% confidence interval (CI), were calculated using statistical analysis Comprehensive Meta-Analysis (CMA) V.2. In order to assess the heterogeneity, *I*-square (I^2) test was used. In case of high heterogeneity (more than 50%) random effect model was used for meta-analysis. Publication bias has been assessed using *Begg's* test.

Results:

Study selection process

Our search through databases resulted in 4658 records. Duplicate records, including 1695 studies, have been excluded and after title and abstract screening, full texts of 2963 papers were assessed for eligibility. Four studies were excluded due to unavailability of the full-text. Finally, 56 papers (21-76) entered into meta-analysis for primary outcomes (mortality and ICU admission) and 198 papers (16, 21-217) for descriptive outcomes. PRISMA flow diagram for the study selection process is presented in Figure 2.

Study characteristics

Out of 56 papers included into meta-analysis for primary outcomes, 2 studies were case-control, 1 case-cohort, 8 case series and 45 cohorts. The studies' sample size ranged from 13 to 11095 including 29,056 participants. One-hundred ninety-nine papers entered into meta-analysis for descriptive outcomes including 168 cohorts, 4 case-control, 4 cross-sectional, 21 case-series, 1 case-cohort. Studies sample size ranged from 10 to 27584 including 159698 patients.

Quality assessment

According to NOS tool for quality assessment, 56 studies earned the minimum eligibility score and entered into the meta-analysis for primary outcomes. Summary of risk of bias is presented in Figure 2. *Begg's* test showed that there was no publication bias ($P=0.7$).

Mortality

The meta-analysis showed that prevalence of CVDs among COVID-19 patients with mortality were as follows: Acute Cardiac Injury (52%), Hypertension (51%), Arrhythmia (37%), Heart Failure (27%), Coronary Heart Disease (23%) and Cardiovascular Diseases (23%) (Table 1).

Results of meta-analysis indicated that presence of Acute Cardiac Injury (OR: 13.29, 95% CI 7.35-24.03), Coronary Artery Disease (OR: 3.78 95% CI 2.42-5.90), Arrhythmia (OR: 2.75, 95% CI 1.43-5.25), Hypertension (OR: 2.60, 95% CI 2.11-3.19), Heart Failure (OR: 6.72, 95% CI 3.34-13.52), and Cardiovascular Disease (OR: 2.61, 95% CI 1.89-3.62) were significantly associated with mortality in COVID-19 patients (Table 2).

Intensive care unit admission

Pooled prevalence of cardiovascular implications including Acute Cardiac Injury, Arrhythmia, Heart Failure, Coronary Artery Disease, Hypertension and Cardiovascular Diseases were 33.6%, 33.0%, 20.4%, 20.6%, 43.6% and 25.0% in COVID-19 patients admitted to ICU respectively (Table 3).

The meta-analysis on ICU outcome showed that the odds of ICU admission in COVID-19 patients is significantly associated with Acute Cardiac Injury (OR: 15.58, 95% CI 5.15 - 47.12), Arrhythmia (OR: 7.03, 95% CI 2.79 - 17.69), Coronary Heart Disease (OR: 2.61, 95% CI 1.09 - 6.26), Cardiovascular Disease (OR: 3.11, 95% CI 1.59 - 6.09) and Hypertension (OR: 1.95, 95% CI 1.41 - 2.68). Heart Failure was not statistically significantly (OR: 2.44, 95% CI 0.67 - 8.79) associated with ICU admission in COVID-19 however, the effect size was considerable (Table 4).

Cardiovascular Complications

One-hundred ninety-eight studies have investigated for cardiovascular complications in the COVID-19 patients. Pooled prevalence of cardiovascular complications observed among patients with COVID-19 included hypertension (29%), cardiovascular and cerebrovascular disease (14%), heart failure (10%), acute cardiac injury (16%), coronary heart disease (10%), myocardial damage (20%), cardiovascular disease (11%), arrhythmia (11%), cardiomyopathy (7%), heart palpitation (6%) and heart valve disease (9%) (Table 5, Figure 3).

We have also analyzed pooled prevalence of cardiovascular disease in COVID-19 patient in different countries. Results of meta-analysis were as follows: Brazil (50.0%), China (7.8%), France (48.0%),

Germany (45.5%), Iran (4.4%), Italy (24.7%), Netherlands (44.0%), South Korea (11.2%), Spain (16.9%), Switzerland (71.4%), United Kingdom (15.1%), and United States (24.4%) (Figure 4).

Discussion:

The results of this meta-analysis indicated cardiovascular implications including acute cardiac injury, arrhythmia, coronary heart disease, hypertension and cardiovascular diseases were significantly associated with COVID-19 patient's admission to the ICU. Comparing pooled estimate of OR for CVDs showed odds of ICU admission was significantly higher in acute cardiac injury and arrhythmia than hypertension, but there was no significant difference between other cardiovascular implications. Investigations have shown that mortality in patients with acute cardiac injury was significantly higher than coronary artery disease, arrhythmia, and hypertension. Comparing estimated frequency of different cardiovascular complications including acute cardiac injury, arrhythmia, cardiomyopathy, coronary heart disease, heart palpitation, hypertension, myocardial damage, heart failure and other cardiovascular diseases did not show any significant difference among them.

Cardiovascular complications have been previously reported in previous respiratory infections with similar etiology and their condition affects severity of the disease (17, 218); so that even hospitalization for pneumonia is associated with long-term and short-term risk of CVD (12). Viral infections cause imbalance between cardiac supply and demand and increase in systemic inflammation. Therefore patients with pre-existing CVD have higher risks for acute cardiac conditions (219), infection, and develop severe conditions during the infection (220).

Acute myocardial injury was significantly associated with both ICU admission and mortality. There were several etiologies proposed for acute myocardial injury in these patients. The first possible mechanism is myocardial injury caused by cytokine storm as the results of systematic inflammation mediated by pathologic T-cells (221-223). Study by Chen *et al.* (25) showed elevated myocardial injury biomarkers including NT-proBNP, cTnI and hs-CRP were significantly correlated with COVID-19 severity. The second possible explanation is the imbalance between supply and demand caused by systemic infection along with hypoxia caused by respiratory infection, which lead to acute myocardial injury (221, 223). There are evidences that shows SARS-CoV-2 binds to human

angiotensin converting enzyme-2 (ACE2) to infect the cells (224), which being highly expressed in lungs and heart. The binding of SARS-CoV-2 to ACE2 in heart can result in acute myocardial injury (221, 225). COVID-19 has been associated with thrombotic events and coagulation disorders (226), which might lead to hypercoagulability and coronary thrombosis resulting in acute myocardial infarction (221, 223).

SARS-CoV-2 binding to ACE2 causes activation of the renin-angiotensin system and its complications including hypertension, heart failure, and atherosclerosis (220, 227, 228) as we resulted in our meta-analysis. These data could also suggest a reason for the high prevalence of hypertension in our pooled estimate. Underlying CVDs like hypertension could increase the risk of infection and developing more severe symptoms in COVID-19 patients (229). We showed in our meta-analysis that hypertension was significantly associated with ICU admission and mortality; therefore blood pressure control could be potentially beneficial to reduce disease burden (230). Using Angiotensin Receptor Blockers (ARBs) and ACE inhibitors in order to control hypertension have raised questions in the era of the COVID-19 pandemic. Studies suggested that using ARBs and ACE inhibitors could potentially be harmful as they can cause up-regulation of ACE2, SARS-CoV-2 receptor, and lung injury (230, 231); so, they should be carefully considered in COVID-19 patients (229). This meta-analysis also indicated that the mean age of COVID-19 patients admitted to ICU was significantly higher than non-ICU. An explanation to this condition by AlGhatrif *et al.* (232) suggested that elderly patients with hypertension are more likely to have down-regulation of ACE2 expression, due to viral binding, and up-regulated angiotensin II, which exaggerates the pro-inflammatory condition, predisposing them to severe conditions and mortality (233).

Arrhythmia was significantly associated with ICU admission and mortality in our meta-analysis. There are pathophysiological mechanisms suggested for arrhythmia among COVID-19 patients; however, whether these patients had pre-existing arrhythmia or secondary to COVID-19 remains unknown (234). First, as any systemic infection COVID-19 can cause electrolyte imbalance, especially

hypokalemia (235), which might contribute to arrhythmia in susceptible patients (221). Second, as we have discussed earlier myocardial injury has been an important subject in COVID-19 patients. It has been suggested that myocardial damage can be potentially triggers arrhythmia (236, 237). Third, pharmacological therapies prescribed for these patients can be potential risk factors for arrhythmia. Hydroxychloroquine, as one the most common drugs which had been used in COVID-19, can triggers QT prolongation (237, 238). Fourth, arrhythmia could also occur secondary to myocarditis by disrupting cardiomyocyte membrane and electrolyte imbalance, myocardial fibrosis, proinflammatory cytokines and edema of pericardium (234).

In our meta-analysis the prevalence of heart palpitation was relatively high and it has been reported as one the initial symptoms of the disease (239). National Health Commission of China (NHC) reported that some patients have presented with heart palpitations and chest tightness instead of cough and fever as initial symptoms of COVID-19 (229); so, heart palpitations in outpatients setting needs to carefully considered as potential symptom of COVID-19.

Heart failure was significantly associated with mortality in our meta-analysis, ranked after acute cardiac injury. The incidence of heart failure might be as the consequence of myocardial injury or myocarditis (240), which has been previously discussed. Increasing systemic metabolic demand as the results of systemic infection could also exacerbate previous stable heart failure (221). Right heart failure and pulmonary hypertension should be also carefully considered in patients with acute respiratory distress syndrome (ARDS) and parenchymal lung disease (236).

Cardiomyopathy has been also observed in COVID-19 patients in various forms. Takotsubo syndrome (TTS) or stress cardiomyopathy, characterized by transient left ventricular dysfunction, is triggered by emotional and physical stresses following to natural disasters (241), like COVID-19 pandemic. There were number of studies reported TTS in COVID-19 patients (242-246). Mechanism of stress cardiomyopathy in COVID-19 patients might be due to emotional distress caused by pandemic along with inflammatory and metabolic distress (244). Inflammatory cardiomyopathy or myocarditis was

previously described in viral infections (247) as well as COVID-19 (248, 249). Cardiomyocytes expresses ACE2 which is the receptor for SARS-CoV-2, so this virus could infects human heart which can even exacerbate in case of heart failure (234).

Coronary artery disease was significantly associated with mortality of COVID-19 patients in our study. In patients with previous coronary artery disease, inflammatory state and hemodynamic changes in infection can potentially increase the risk of plaque rupture (163, 236, 250). Coagulopathy in COVID-19 patients (226) can also cause acute coronary syndrome in these patients.

We have discussed cardiovascular implications among COVID-19 patients. Cardiovascular diseases have significant role in the outcome of COVID-19 patients. Therefore, careful consideration and management of cardiovascular disease, from diagnosis to bedside, among COVID-19 patients are necessary. Results of this study could help policy makers, physicians and healthcare workers in front line to make evidence-based decisions and reduce the mortality and morbidity of this 21st century pandemic.

Limitation of this study was high heterogeneity of studies in population. Compounding effects of other co-morbidities in ICU admission and mortality was not being considered. It is possible that other co-morbidities related to respiratory system, renal system and gastrointestinal system affects patient's condition. Cardiovascular implications could be pre-existing in patients or either developed by the infection; so, we could not determine the casual relationship. However, given the burden and vital role of CVDs the importance does not differ. We only included studies of hospitalized adult COVID-19 patients and asymptomatic and outpatients are excluded. Data regarding to cardiovascular diseases in COVID-19 patients in some countries were missing.

Conclusion:

In conclusion, CVD have a significant role in disease severity and mortality of COVID-19 patients. Hypertension, acute cardiac injury, coronary heart diseases in COVID-19 patient needs to be carefully monitored and managed in case of acute conditions. Other cardiovascular implications, including arrhythmia and heart failure also need to be considered since they can be fatal. Therefore, careful consideration and management of cardiovascular disease among these patients are necessary. Results of this study could help policy makers, physicians and healthcare workers in front line to make evidence-based decisions and reduce the mortality and morbidity of this 21st century pandemic.

Conflicts of interests:

None of authors have declared any conflicts of interest.

Supplementary Material:

Forest Plots and characteristics of studies included into meta-analyses are presented in supplementary material.

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Table 1. Meta-analysis of pooled estimate prevalence of CVDs among COVID-19 patients with mortality

Complication	Number of Studies	Heterogeneity		Pooled Prevalence (95% CI)
		I-squared, %	P-value	
Acute Cardiac Injury	13	64.33	0.00	0.52 (0.46, 0.59)
Arrhythmia	4	89.08	0.00	0.37 (0.15, 0.67)
Coronary Heart Disease	18	78.84	0.00	0.23 (0.18, 0.30)
Heart Failure	11	96.21	0.00	0.27 (0.17, 0.38)
Hypertension	38	81.38	0.00	0.51 (0.47, 0.55)
Cardiovascular Disease	18	91.84	0.00	0.23 (0.17, 0.30)

Table 2. Meta-analysis of OR of mortality in COVID-19 patients for CVDs

Complication	Number of Studies	Heterogeneity		Pooled OR (95% CI)
		I-Squared, %	P-value	
Acute Cardiac Injury	12	74.26	0.00	13.29 (7.35, 24.03)
Heart Failure	8	86.78	0.00	6.72 (3.34, 13.52)
Arrhythmia	3	0.00	0.57	2.75 (1.43, 5.25)
Hypertension	31	73.92	0.00	2.60 (2.11, 3.19)
Cardiovascular Disease	14	55.49	0.00	2.61 (1.89, 3.62)
Coronary Heart Disease	16	76.20	0.00	3.78 (2.42, 5.90)

Table 3. Meta-analysis of pooled estimate prevalence of CVDs among COVID-19 patients admitted to ICU

Complication	Number of Studies	Heterogeneity		Pooled Prevalence (95% CI)
		I-squared, %	P-value	
Acute Cardiac Injury	8	51.15	0.04	0.33 (0.24, 0.43)
Arrhythmia	3	71.88	0.02	0.33 (0.18, 0.51)
Coronary Heart Disease	13	67.77	0.00	0.20 (0.15, 0.27)
Heart Failure	7	78.42	0.00	0.20 (0.09, 0.37)
Hypertension	31	88.89	0.00	0.43 (0.37, 0.50)
Cardiovascular Disease	19	91.54	0.00	0.25 (0.16, 0.35)

Table 4. Meta-analysis of OR for ICU admission outcome among COVID-19 patients

Complication	Number of studies	Heterogeneity		Prevalence (95% CI)
		I-Square (%)	P-value	
Coronary heart disease	60	93.92	0.00	0.10 (0.09, 0.12)
Cardiovascular and cerebrovascular disease	16	94.97	0.00	0.14 (0.09, 0.22)
Cardiovascular disease	87	95.73	0.00	0.11 (0.09, 0.12)
Arrhythmia	17	91.17	0.00	0.11 (0.07, 0.16)
Acute cardiac injury	28	92.35	0.00	0.16 (0.13, 0.19)
Cardiomyopathy	4	85.25	0.00	0.07 (0.01, 0.27)
Heart failure	31	99.11	0.00	0.10 (0.07, 0.13)
Myocardial damage	3	94.49	0.00	0.20 (0.06, 0.49)
Hypertension	158	97.97	0.00	0.29 (0.27, 0.31)
Heart palpation	6	85.06	0.00	0.06 (0.03, 0.13)
Heart Valve Disease	3	87.00	0.00	0.09 (0.02, 0.36)

Complication	Number of Studies	Heterogeneity		Pooled OR (CI 95%)
		I-squared, %	P-value	
Acute Cardiac Injury	6	61.73	0.02	15.58 (5.15, 47.12)
Arrhythmia	2	32.22	0.22	7.03 (2.79, 17.69)
Coronary Heart Disease	8	77.65	0.00	2.61 (1.09, 6.26)
Hypertension	21	67.62	0.00	1.95 (1.41, 2.68)
Cardiovascular Diseases	12	71.01	0.00	3.11 (1.59, 6.09)

Table 5. Pooled prevalence for cardiovascular complications among COVID-19 patients

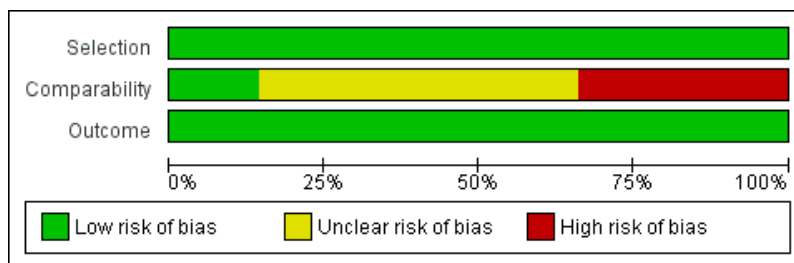


Figure 1. Summary of Risk of Bias

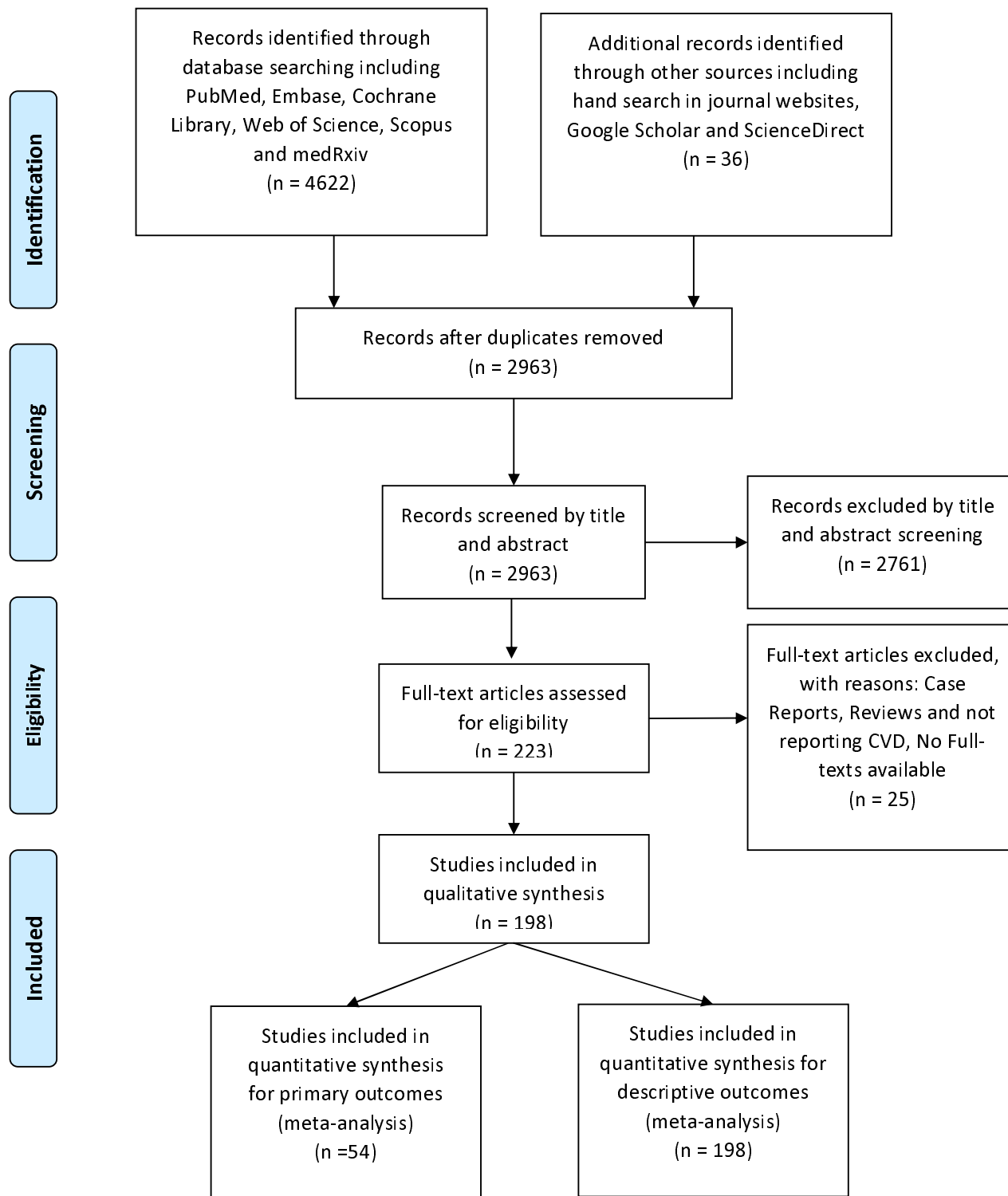


Figure 2. PRISMA Flow Diagram

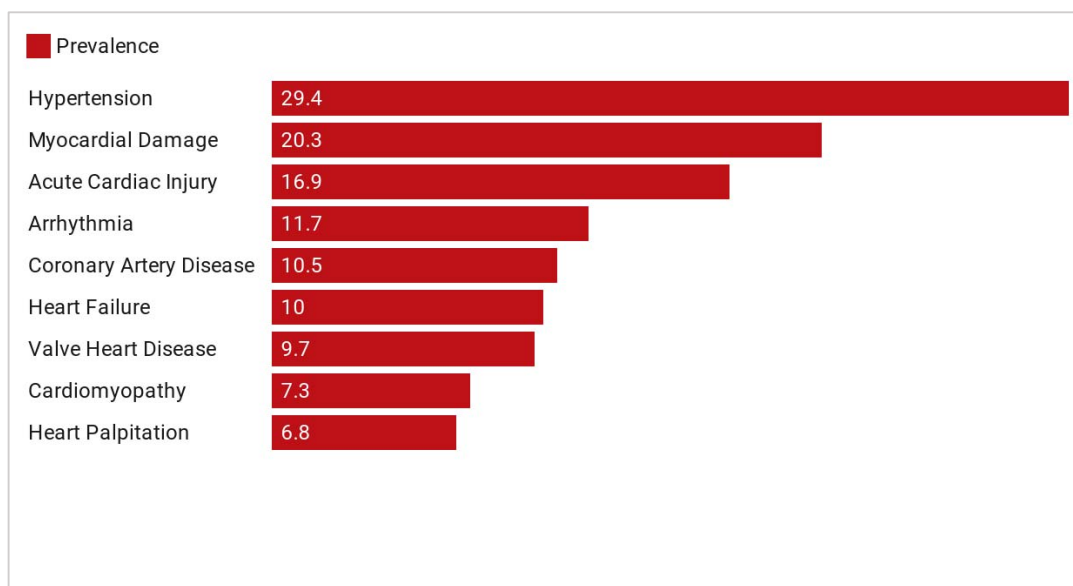


Figure 1. Prevalence of Cardiovascular Complications Among COVID-19 Patients

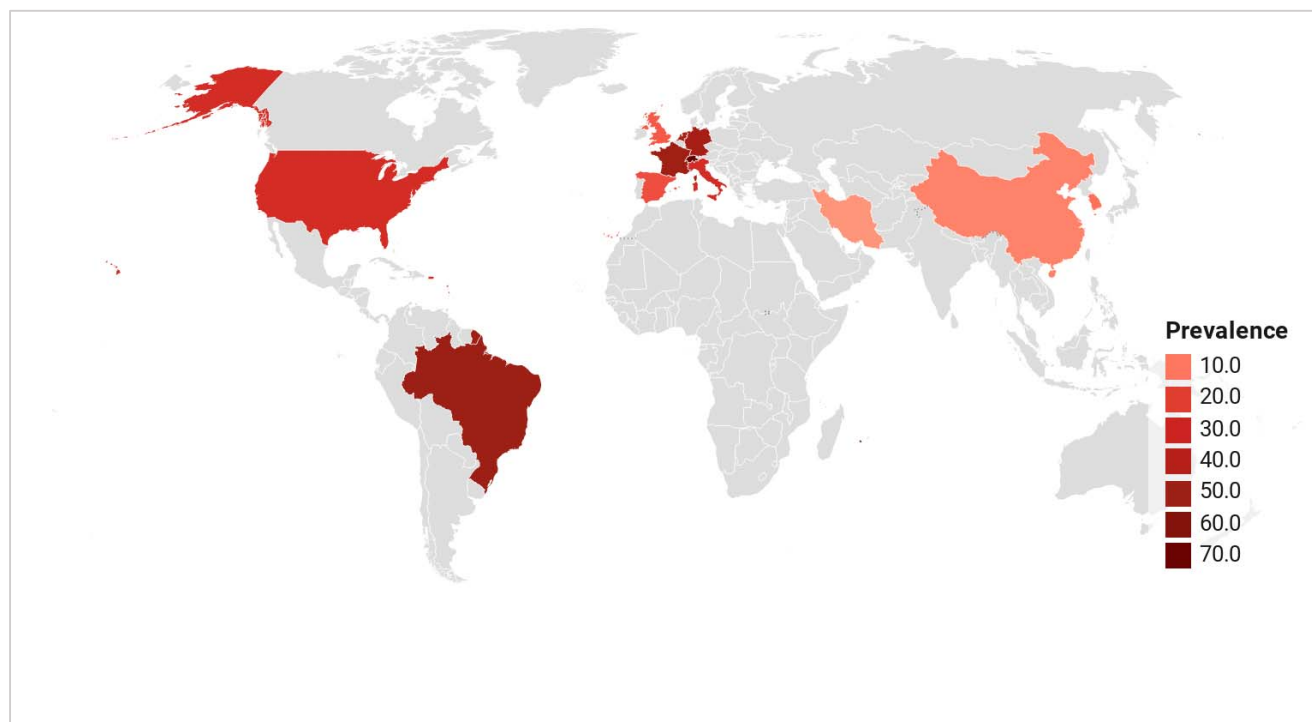


Figure 4. Cardiovascular Disease Burden among COVID-19 Patients in different countries

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