Cardiovascular Diseases and COVID-19 Mortality and Intensive Care Unit Admission: A Systematic Review and Meta-analysis

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Key Points:

***Question*:** Are cardiovascular disease associated with mortality and Intensive Care Unit admission (ICU) of COVID-19 patients?

***Findings*:** In this systematic review and meta-analysis, acute cardiac injury, hypertension, heart failure and overall cardiovascular diseases were significantly associated with mortality in COVID-19 patients. Arrhythmia, coronary heart disease, hypertension, acute cardiac injury and other cardiovascular disease were significantly associated with ICU admission of COVID-19 patients.

***Meaning*:** Cardiovascular diseases have significant role in mortality and disease severity of COVID-19 patients. COVID-19 patients need to be carefully monitored for cardiovascular diseases and managed properly in case of acute cardiac conditions.

Abstract:

Importance: On 11th March, the World Health Organization declared a pandemic of COVID-19. There are over 1 million cases around the world with this disease and it continues to raise. Studies on COVID-19 patients have reported high rate of cardiovascular disease (CVD) among them and patients with CVD had higher mortality rate.

Objectives: Since there were controversies between different studies about CVD burden in COVID-19 patients, we aimed to study cardiovascular disease burden among COVID-19 patients using a systematic review and meta-analysis.

Data Sources: 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.

Study Selection: Studies reported cardiovascular disease among hospitalized adult COVID-19 patients with mortality or ICU admission (primary outcomes) were included into meta-analysis. In addition, all of studies which reported any cardiovascular implication were included for descriptive meta-analysis. Cohort studies, case-control, cross-sectional, case-cohort and case series studies included into the study. Finally, 16 studies met the inclusion criteria for primary outcome and 59 studies for descriptive outcome.

Data Extraction and Synthesis: Two investigators have independently evaluated quality of publications and extracted data from included papers. In case of disagreement a supervisor solved the issue and made the final decision. Quality assessment of studies was done using Newcastle-Ottawa Scale tool. Heterogeneity was assessed using *I*-squared test and in case of high heterogeneity (>%50) random effect model was used.

Main Outcomes and Measures: Meta-analyses were carried out for Odds Ratio (OR) of mortality and Intensive Care Unit (ICU) admission for different CVDs and Standardized Mean Difference (SMD) was calculated for Cardiac Troponin I. We have also performed a descriptive meta-analysis on different CVDs.

Results: Sixteen papers including 3473 patients entered into meta-analysis for ICU admission and mortality outcome and fifty-nine papers including 9509 patients for descriptive outcomes. Results of meta-analysis indicated that acute cardiac injury, (OR: 15.94, 95% CI 2.31-110.14), hypertension (OR: 1.92, 95% CI 1.92-2.74), heart Failure (OR: 11.73, 95% CI 5.17-26.60), other cardiovascular disease (OR: 1.95, 95% CI 1.17-3.24) and overall CVDs (OR: 3.37, 95% CI 2.06-5.52) were significantly associated with mortality in COVID-19 patients. Arrhythmia (OR: 22.17, 95%CI 4.47-110.04), acute cardiac injury (OR: 19.83, 95%CI 7.85-50.13), coronary heart disease (OR: 4.19, 95%CI 1.27-13.80), cardiovascular disease (OR: 4.17, 95%CI 2.52-6.88) and hypertension (OR: 2.69, 95%CI 1.55-4.67) were also significantly associated with ICU admission in COVID-19 patients.

Conclusion: Our findings showed 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

Introduction:

Coronaviruses are enveloped positive sense single stranded RNA viruses which cause respiratory infections in human and animals (1, 2). There were six coronaviruses known to cause infection in humans (3) including Sever Acute Respiratory Syndrome (SARS), China, 2002 (4) and Middle Eastern Respiratory Syndrome (MERS), Saudi Arabia, 2012 (5). The World Health Organization (WHO) reported cases of pneumonia with unknown source in Wuhan, China, December 2019 (6). Further investigations in samples of patients with respiratory infection, who were in contact with a seafood markets in Wuhan revealed a novel virus named 2019-nCoV (7). On 11th March, 2020 WHO declared the 2019-nCoV outbreak as a pandemic (8). According to Worldometer *info*, over 1 million confirmed cases and 61718 deaths due to COVID-19 have been reported throughout the world up to April 4th 2020 (9).

Acute infections are associated with increased risk of cardiovascular diseases (CVD) (10) including respiratory infections (11, 12). There is a mutual relationships between CVD and infections; while the viral respiratory infectious diseases like influenza might increase the risk of myocardial infarction and cardiovascular events (12), underlying CVD might increase the risk of mortality among patients with infection (13). 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 (14). Studies indicated that there is an increased risk of mortality among hospitalized COVID-19 patients due to CVD (15-17).

Primary studies have been suggested high rate of mortality in COVID-19 patients with CVD, but there are still some controversies. Hence, we aimed to determine the mortality rate as well as Intensive Care Unit (ICU) admission associations in these patients using a systematic review and meta-analysis in order to overcome the controversies.

Methods:

Search Strategy:

In this study, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines 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 done by A.H 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 English and Chinese and there were no time limitation publications. All original Cohort, Case Control, Cross-Sectional and Case-Series studies until 31th March 2020 were included.

Criteria for Study Selection

Two members of our team (A.H and A.S) 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. Records have been entered into EndNote and duplications were removed.

Data Extraction

Two investigators (A.H and K.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 ± 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, acute cardiac injury and cardiac troponin I mean ± SD. In cases that data was presented as median (interquartile range), a method by *Wan et al.* (18) was used to calculate mean ± SD.

Risk of Bias Assessment

Newcastle-Ottawa Scale tool was used for risk of bias assessment of studies included into meta-analysis (19). Risk of bias only assessed for studies entered into meta-analysis main outcomes (ICU and mortality) of the study (Figure 2,3).

Data Analysis

Odds Ratio (OR), and Standardized Mean Difference (SMD) with 95% confidence interval (CI) and pooled estimate prevalence rate were calculated using statistical analysis STATA v.11. 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 have been assessed using *Begg*'s test.

Results:

Study selection process

Our search through databases resulted in 329 papers. Eighty-seven duplicated papers have been excluded and after title and abstract screening, full texts of 81 papers were assessed for eligibility. Finally, 60 papers entered into qualitative synthesis, 16 papers (20-35) have entered into meta-analysis for primary outcomes and 59 papers (15, 20, 23-25, 29, 33, 34, 36-86) for descriptive outcomes. PRISMA flow diagram for the study selection process presented in Figure 1.

Study characteristics

Out of 16 papers included into meta-analysis for primary outcomes, four studies were case-control and four and eight of them were cross-sectional and cohort studies, respectively. The studies' sample size ranged from 41 to 1099 including 3473 participants. Characteristics of studies entered into meta-analysis for ICU and mortality outcome are presented in eTable 1 and studies entered into meta-analysis for descriptive outcomes in eTable 2. Fifty-nine papers entered into meta-analysis for descriptive outcomes including 16 cohorts, five case-control, 28 cross-sectional, nine case-series, one case-cohort. Studies sample size ranged from 2 to 1590 including 9509 patients.

Quality assessment

According to NOS tool for quality assessment, 16 studies earned the minimum eligibility score and entered into the meta-analysis for primary outcomes. Summary of risk of bias presented in Figure 2 and 3. *Begg*'s test showed that there was no considerable publication bias (P=0.7).

Mortality

The meta-analysis showed mortality rate of acute cardiac injury and coronary heart disease were 74% (95% CI 0.30-1.18) and 48% (95% CI 0.10-0.86) among COVID-19 patients. However, results indicated that mortality in COVID-19 patients with other cardiovascular disease was 55% (95% CI -0.22-1.31) but it was not statistically significant (Table 1).

Results of meta-analysis indicated that acute cardiac injury (OR: 15.94, 95% CI 2.31-110.14), Hypertension (OR: 1.92, 95% CI 1.92-2.74), Heart Failure (OR: 11.73, 95% CI 5.17-26.60), other cardiovascular disease (OR: 1.95, 95% CI 1.17-3.24) and overall CVDs (OR: 3.37, 95% CI 2.06-5.52) were significantly associated with mortality in COVID-19 patients. Odds of mortality of COVID-19 patients with heart failure was significantly higher than hypertension and other cardiovascular diseases (Table 2).

Intensive care unit admission

Carrying meta-analysis between groups of patients who admitted/do not admitted to the ICU showed the higher chance of ICU admission for males in compare to females, which was also more probable in older ages (SMD: 0.61, 95%CI 0.26-0.95). There were no statistically significant differences between two groups regarding levels of cardiac troponin I, however the effect size was considerable (SMD: 1.12, 95% CI -0.90-1.34) (Table 3).

The meta-analysis showed that the odds of patients with arrhythmia (OR: 22.17, 95%CI 4.47-110.04), acute cardiac injury (OR: 19.83, 95%CI 7.85-50.13), coronary heart disease (OR: 4.19, 95%CI 1.27-13.80), cardiovascular disease (OR: 4.17, 95%CI 2.52-6.88) and hypertension (OR: 2.69, 95%CI 1.55-4.67) were higher to being admitted to the ICU in compare to other group. Besides, the mortality rate was 47.86 times higher in ICU admitted COVID-19 patients than those patients who did not required the intensive care (Table 3).

Cardiovascular Complications

Fifty-nine studies have investigated for cardiovascular complications in the COVID-19 patients. Pooled prevalence of cardiovascular complications observed among patients with COVID-19 included hypertension (27%), cardiovascular and cerebrovascular disease (23%), heart failure (21%), acute cardiac injury (20%), coronary heart disease (17%), myocardial damage (16%), cardiovascular disease (12%), arrhythmia (11%), cardiomyopathy (12%) and heart palpitation (6%) (Table 4).

Discussion:

The results of this meta-analysis indicated cardiovascular implications including acute cardiac injury, arrhythmia, coronary heart disease, hypertension and other cardiovascular diseases were significantly associated with COVID-19 patient's admission to the ICU. Comparing pooled estimate of OR for CVDs in ICU admission did not show any significant differences between different cardiovascular implications. SMD for cardiac troponin *I* and OR for mortality was significantly higher among ICU patients than non-ICU. Odds for ICU admission was significantly higher in males than females. Investigating mortality outcome showed that mortality in patients with acute cardiac injury and coronary heart disease was significantly high. Comparing estimated prevalence of different cardiovascular complications including acute cardiac injury, arrythmia, cardiomyopathy, coronary heart disease, heart palpitation, hypertension, myocardial damage, heart failure and other cardiovascular diseases did not show any significant difference between them. Arrythmia, cardiomyopathy, heart palpitation and myocardial damage were not significantly prevalent among COVID-19 patients.

Cardiovascular complications have been previously reported in previous respiratory infections with similar etiology and their condition affects severity of the disease (16, 87), so that even hospitalization for pneumonia is associated with long-term and short-term risk of CVD (11). 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 (88), infection and develop severe conditions during the infection (89). There are evidences that shows Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) binds to human angiotensin converting enzyme-2 (ACE2) to infect the cells (90) which being highly expressed in lungs and heart. Therefore, virus binding to ACE2 causes activation of renin-angiotensin system and its complications including hypertension, heart failure and atherosclerosis (89, 91, 92) as we resulted in our meta-analysis. These data could suggest a reason for high prevalence of hypertension in our pooled estimate.

This meta-analysis also indicated that mean age of COVID-19 patients admitted to ICU was significantly higher that non-ICU. An explanation to this condition by AlGhatrif *et al.* (93) suggested that elderly patients with hypertension are more likely to have downregulation of ACE2 expression, due to viral binding, and upregulated angiotensin *II* which exaggerates proinflammatory condition, predisposing them to severe conditions and mortality.

In our meta-analysis, acute cardiac injury was significantly higher in COVID-19 expired group, which was also in association with ICU admission. The pathophysiology of this condition is might be related to ACE2 and its related signaling pathways involved in heart function and other mechanisms including cytokines storm and hypoxemia caused by lung injuries (89). Cardiac troponin *I* can be an early biomarker for assessing risk of COVID-19 patients to perform an early intervention (15) as in our meta-analysis cardiac troponin *I* was significantly higher among ICU patients.

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. We only included studies of hospitalized adult COVID-19 patients and asymptomatic and outpatients are excluded. Most of studies entered into meta-analysis have been conducted in China, therefore, population genetic variation is possible.

Conclusion:

In conclusion, CVD might have a significant role in disease severity and mortality of COVID-19 patients. Hypertension, acute cardiac injury and coronary heart diseases in COVID-19 patients needs to be carefully monitored and managed in case of acute conditions. Other cardiovascular implications including arrythmia and heart failure also needs to be considered since they can be fatal.

Conflicts of interests:

None of authors have declared any conflicts of interest.

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

Complication	**Number of Studies**	**Heterogeneity**		**Pooled Prevalence (95% CI)**
		I-squared, %	**Q (P-value)**	
Acute Cardiac Injury	4	0.0	0.889	0.74 (0.30,1.18)
Coronary Heart Disease	5	0.0	0.811	0.48 (0.10, 0.86)
Other Cardiovascular Disease	2	0.0	0.517	0.55 (-0.22,1.31)

Table 2. Meta-analysis of Odd Ratio of CVDs for mortality outcome in COVID-19 patients

Complication	**Number of Studies**	**Heterogeneity**		**Pooled OR (95% CI)**
		I-Squared, %	**Q (P-value)**	
Acute Cardiac Injury	3	84.6	0.002	15.94 (2.31, 110.14)
Heart Failure	3	47.0	0.151	11.73 (5.17, 26.60)
Hypertension	7	34.1	0.168	1.92 (1.34, 2.74)
Other Cardiovascular Disease	4	23.5	0.270	1.95 (1.17, 3.24)
Overall	8	82.3	0.000	3.37 (2.06, 5.52)

Table 3. Meta-analysis of OR and SMD for ICU admission outcome among COVID-19 patients

Complication	**Number of Studies**	**Heterogeneity**		**Pooled OR (CI 95%)**
		I-squared, %	**Q (P-value)**	**/ SMD (CI 95%)**
Acute Cardiac Injury	4	22.6	0.275	19.83 (7.85, 50.13)
Arrhythmia	2	68.7	0.074	22.17 (4.47, 110.04)
Coronary Heart Disease	3	69	0.040	4.19 (1.27, 13.80)
Hypertension	9	69.5	0.001	2.69 (1.55,4.67)
Mortality	5	43.6	0.131	47.86 (20.72,110.53)
Other Cardiovascular Diseases	6	0.0	0.750	4.17 (2.52,6.88)
Male to Female	6	0.0	0.819	1.61 (1.16, 2.23)
Age	7	74.9	0.001	0.61 (0.26, 0.95)
Cardiac Troponin I	4	0.0	0.680	1.12 (0.90, 1.34)

Table 4. Pooled prevalence for cardiovascular complications among COVID-19 patients

Complication	**Number of studies**	**Heterogeneity**		**Prevalence (95% CI)**
		I-Square (%)	**Q (P-value)**	
Coronary heart disease	16	0.0	0.990	0.17 (0.04,0.31)
Cardiovascular and cerebrovascular disease	7	0.0	0.949	0.23 (0.06,0.41)
Cardiovascular disease	28	0.0	1.000	0.12 (0.01,0.22)
Arrhythmia	8	0.0	1.000	0.11 (-0.12,0.33)
Acute cardiac injury	11	0.0	0.997	0.20 (0.07,0.33)
Cardiomyopathy	2	0.00	0.021	0.12 (-0.41,0.21)
Heart failure	8	0.0	0.977	0.21 (0.05,0.37)
Myocardial damage	3	93.35	0.00	18 (-0.11,0.47)
Hypertension	45	95.39	0.00	27 (0.22, 0.33)
Heart palpation	4	75.44	0.01	0.06 (-0.26, 0.46)