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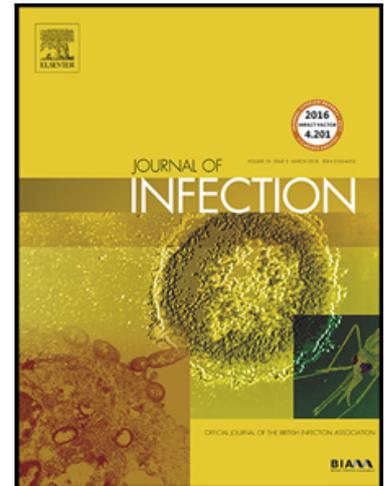
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Letter to the Editor

Cardiovascular complications in COVID-19: A systematic review and meta-analysis

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To the Editor

The coronavirus disease 2019 (COVID-19) pandemic poses the most significant modern-day public health challenge since the Spanish flu of 1918, causing substantial morbidity and mortality worldwide.(1) Coronavirus disease 2019 predominantly affects the respiratory system, causing severe pneumonia and respiratory distress syndrome. There is also involvement of multiple organs, and the cardiovascular system has been implicated. In a recent study to investigate characteristics and prognostic factors in 339 elderly patients with COVID-19, Wang and colleagues observed a high proportion of severe and critical cases as well as high fatality rates.(2) The cardiovascular complications recorded were acute cardiac injury (21%), arrhythmia (10.4%) and cardiac insufficiency (17.4%). However, not all cardiovascular manifestations of COVID-19 are clearly defined by published studies and it is also not clear if these conditions are directly caused by COVID-19 or are just unspecific complications.(3) There is a need to understand the interplay between COVID-19 and its cardiovascular manifestations to assist in the optimum management of patients. In this context, we conducted a systematic meta-analysis to attempt to address the following questions: (i) what are the cardiovascular complications associated with COVID-19?; (ii) what is the incidence of these complications?; and (iii) are patients with pre-existing cardiovascular morbidities more susceptible to these cardiovascular complications?

The protocol for this review was registered in the PROSPERO International prospective register of systematic reviews (CRD42020184851). The review was conducted in accordance with PRISMA and MOOSE guidelines (4, 5) (**Supplementary Materials 1-2**). We searched MEDLINE, Embase, and The Cochrane library from 2019 to 27 May 2020 for published studies reporting on cardiovascular outcomes in patients with COVID-19. Details of the search strategy are reported in **Supplementary Material 3**. The prevalence of comorbidities (pre-existing hypertension and cardiovascular disease, CVD) and incidence of cardiovascular complications across studies with their 95% confidence intervals (CIs) were pooled using Freeman-Tukey variance stabilising double arcsine transformation and random-effects models. STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Seventeen retrospective cohort studies comprising of 5,815 patients with COVID-19 were included (**Table 1; Supplementary Materials 4-5**). Eleven studies were based in China, four in the USA, one in South Korea and one in the Netherlands. The average age at baseline ranged from 47 to 71 years.

Across 15 studies, the pooled prevalence of pre-existing hypertension (95% CI) in COVID-19 patients was 29.3% (25.5-33.4; $I^2=87%$; 95% CI 79, 91%; p for heterogeneity<0.01) (**Supplementary Material 6**). The prevalence (95% CI) of pre-existing CVD across 16 studies was 14.6% (11.0-18.4; $I^2=91%$; 95% CI 87, 94%; p for heterogeneity<0.01) (**Supplementary Material 7**).

Over hospital stays ranging from 2 to 28 days, the pooled incidence was 17.6% (14.2-21.2; $I^2=32%$; 95% CI 0, 76%; p for heterogeneity=0.20) for heart failure (HF) (n=4 studies); 16.3% (11.8-21.3; $I^2=87%$; 95% CI 79, 92%; p for heterogeneity<0.01) for myocardial injury (n=11 studies); 9.3% (5.1-14.6; $I^2=78%$; 95% CI 52, 90%; p for heterogeneity<0.01) for cardiac arrhythmia (n=6 studies); 6.2% (1.8-12.3) for acute coronary syndrome (ACS) (n=2 studies); 5.7% (2.7-9.6) for cardiac arrest (n=2 studies); and 5.6% (3.4-8.3) for disseminated intravascular dissemination (DIC) (n=2 studies) (**Figure 1A**). Subgroup analyses suggested that the incidence of myocardial injury was higher in older age groups and groups with a higher prevalence of pre-existing hypertension; however, the incidence of myocardial injury was similar in groups with high or low prevalence of pre-existing CVD (**Figure 1B**). Over hospital stays ranging from 2 to 28 days following admission, mortality rate ranged from 0.7% to 52.4%, with a pooled rate of 15.3% (10.7-20.5).

The current data based on up-to-date evidence suggests that the most common cardiovascular complications of COVID-19 are HF, myocardial injury and cardiac arrhythmias. Though the mechanisms for cardiovascular complications are still yet to be elucidated, the following multiple pathways have been proposed: (i) direct cardiotoxicity; (ii) systemic inflammation; (iii) myocardial demand-supply mismatch; (iv) plaque rupture and coronary thrombosis; (v) adverse effects of therapies during hospitalization; (vi) sepsis leading to DIC; (vii) increased systemic thrombogenesis; and (viii) electrolyte imbalances.(6, 7) Myocardial injury is reported to mainly result from direct viral involvement of cardiomyocytes and the effects of systemic inflammation.(6) Though venous

thromboembolism incidence was based on a single report, patients with COVID-19 are at increased risk of hypercoagulable states due to prolonged immobilisation, systemic inflammation and risk for DIC.(7)

In addition to pre-existing comorbidities including CVD being associated with worse outcomes in patients with COVID-19,(8, 9) cardiovascular complications such as myocardial injury have also been shown to be associated with increased risk of severe COVID-19 and fatal outcomes.(10) Myocardial injury is commonly defined as substantial elevation of high-sensitivity cardiac troponin levels and it has been reported that elevated troponin levels are associated with greater risk of severe disease and mortality. (10) Monitoring of markers of cardiac damage such as troponin, N-terminal pro B-type natriuretic peptide and creatine kinase during hospitalisation for COVID-19 could help in the identification of patients with possible cardiac manifestations, to enable early and more aggressive intervention.

The inherent limitations included the low sample sizes and methodological design of some of the studies, which was expected given the urgency to report and gain a better understanding of COVID-19; limited number of studies available, hence some of the findings were based on single reports; assays for cardiac injury and their time of assessment during hospitalisation may vary between studies, hence estimates may be biased; and the possibility of patient overlap given that the majority of studies were conducted from China and reports of duplicate publication of study participants in articles.(9)

Aggregate analysis of the literature suggests that the most frequent cardiovascular complications among patients hospitalised with COVID-19 are HF, myocardial injury, cardiac arrhythmias and ACS. Early identification and monitoring of cardiac complications could help in the prediction of more favourable outcomes. The causes of these cardiovascular manifestations warrant further investigation as more data becomes available.

Conflict of interest

None.

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Table 1. Characteristics of included studies

Author, year of publication	Source of data	Country	Dates of data collection	Mean/median age (years)	Male %	Hospitalisation (days)	No. of patients	CVD complications	NO
Guo, 2020	Seventh Hospital of Wuhan City	China	Jan - Feb 2020	58.5	48.7	16.3	187	Myocardial injury; ventricular arrhythmia	5
Wang, 2020	Zhongnan Hospital of Wuhan University	China	Jan, 2020	56.0	54.3	7.0	138	Myocardial injury; cardiac arrhythmia	4
Huang, 2020	Jin Yintan Hospital, Wuhan	China	Dec - Jan 2020	49.0	73.0	7.0	41	Myocardial injury	4
Zhou, 2020	Jinyintan Hospital & Wuhan Pulmonary Hospital	China	Dec - Jan 2020	56.0	62.0	11.0	191	Myocardial injury; HF	5
Shi, 2020	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	64.0	49.3	NR	416	Myocardial injury	6
Arentz, 2020	Evergreen Hospital in Kirkland, Washington	USA	Feb - March 2020	70.0	52.0	5.2	21	Cardiomyopathy	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62.0	13.0	274	Myocardial injury; HF; DIC	4
Du, 2020	Hannan Hospital and Wuhan Union Hospital	China	Jan - Feb 2020	65.8	72.9	10.1	85	Cardiac arrest; ACS; arrhythmia; DIC	4
Wang, 2020b	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	71.0	49.0	28.0	339	Myocardial injury, arrhythmia HF	4
Cao, 2020	Zhongnan Hospital of Wuhan University	China	Jan - Feb 2020	54.0	52.0	11.0	102	Myocardial injury; arrhythmia; cardiac arrest	4
Klok, 2020	Dutch Univesity Hospitals	Netherlands	March - April 2020	64.0	76.0	7.0	184	PE; VTE; stroke	4
Aggarwal, 2020	UnityPoint Clinic	USA	March - April 2020	67.0	75.0	2.0	16	ACS; cardiac arrhythmia; HF	4
Wang, 2020c	Zhongnan Hospital of Wuhan University and Xishui People's Hospital	China	Up to Feb, 2020	51.0	53.3	11.0	107	Myocardial injury	5
Hong, 2020	Yeungnam University Medical Center	South Korea	Up to March, 2020	55.4	38.8	7.7	98	Myocardial injury	4
Wan, 2020	Northeast Chongqing	China	Jan - Feb 2020	47.0	53.3	5.0	135	Myocardial injury	4
Price-Haywood, 2020	Ochsner Health in Louisiana	Asia	March - April, 2020	55.5	45.7	7.0	1,030	Cardiomyopathy/HF	6
Price-Haywood, 2020	Ochsner Health in Louisiana	Asia	March - April, 2020	53.6	37.7	6.0	2,451	Cardiomyopathy/HF	6

ACS, acute coronary syndrome; DIC, disseminated intravascular coagulation; HF, heart failure; NOS, Newcastle Ottawa Scale; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism