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CARDIOVASCULAR DISEASE (R FORAKER, SECTION EDITOR)

Cardiovascular Disease and Coronavirus Disease 2019: Epidemiology, Management, and Prevention

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Abstract

Purpose of Review Coronavirus disease 2019 (COVID-19) has become a global pandemic associated with significant morbidity and mortality. This review summarizes findings up to date on the relationship between cardiovascular disease (CVD) and COVID-19.

Recent Findings Preexisting CVD is a common condition among patients with COVID-19 and is associated with increased disease severity and mortality. Conversely, COVID-19 has various clinical manifestations on cardiovascular system, including thrombotic events and cardiac dysfunction. The pandemic has impacted healthcare utilization among patients with CVD, which may have led to potential delay in access to the healthcare system during acute events not directly COVID-19-related.

Summary While COVID-19 vaccine is being developed and distributed, controlling CVD risk factors and adherence to recommendations of existing immunization (e.g., influenza vaccine) are key in protecting the health of individuals with CVD during the COVID-19 pandemic. Further research is needed to understand the epidemiological and pathophysiological basis for the interaction between CVD and COVID-19.

Keywords COVID-19 · Cardiovascular disease · Epidemiology · Risk factors · Management · Review

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first case report in December 2019, COVID-19 has rapidly grown to a global pandemic [1]. High contagiousness of SARS-CoV-2 is a major challenge to contain the disease spread [2•, 3]. The symptoms of COVID-19 are variable. The majority of patients have no symptom or mild respiratory symptoms [1]. However, some patients develop severe diseases including multi-organ failure and die due to COVID-19 [1]. Significant portions of morbidity and mortality have occurred in individuals with risk factors, such as older age and underlying chronic diseases [1].

Cardiovascular disease (CVD) has been shown as a key underlying disease leading to severe manifestation of COVID-19 [4, 5•]. Also, cardiovascular complications of COVID-19 have been recognized. This review summarizes recent literature on the bidirectional relationship between CVD and COVID-19. We also discuss the impact of COVID-19 on healthcare utilization for patients with CVD and how individuals with CVD should protect themselves from COVID-19.

The Prevalence of CVD Among COVID-19 Cases

Studies have consistently shown CVD as a common underlying condition among COVID-19 patients, although the prevalence substantially varied across countries and regions. The United States (US) Center for Disease Control and Prevention has reported that CVD was prevalent in 9.0% of patients with COVID-19, which was similar to the prevalence of chronic lung disease (9.2%) and diabetes (10.9%) [6]. Across different reports, the prevalence of different CVD subtypes among COVID-19 patients ranged from 2.5 to 17.7% for coronary

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heart disease, 0.8 to 21.0% for heart failure, and 1.0 to 19.0% for atrial fibrillation [7–12, 13•, 14, 15, 16•, 17–20].

CVD as a Potential Risk Factor of Severe COVID-19

In a systematic review and meta-analysis pooling estimates from 10 studies with nearly 30,000 patients with COVID-19, patients with prior CVD had an approximately 5 times higher risk of severe COVID-19 (i.e., mortality, intensive care unit [ICU] admission, acute respiratory distress syndrome, or the need for mechanical ventilation) compared to those without prior CVD [5•]. Similar associations have been reported across different definitions of severe COVID-19 such as ICU admission [17, 18, 21], acute respiratory distress syndrome [11, 22], and all-cause mortality [11, 23, 24].

We should recognize that most previous studies did not account for major confounders, such as hypertension and diabetes, when exploring prior CVD as a risk factor for severe COVID-19. Nonetheless, a few studies have reported an independent association of CVD with severe COVID-19 (Table 1). Also, given prior CVD as a potent prognostic factor in general, it is intuitive that prior CVD is associated with poor prognosis in patients with COVID-19 as well. An unanswered question is whether persons with prior CVD are more susceptible to SARS-CoV-2 infection compared to those without CVD.

Potential Mechanisms Linking CVD to Severe COVID-19

There are a few potential mechanisms that may explain the increased risk of severe COVID-19 in patients with prior CVD. First of all, as noted above, CVD is a potent prognostic factor regardless of COVID-19. Thus, risk factors of CVD such as older age, hypertension, and diabetes may also play a role in this regard [11, 21]. Indeed, a number of studies have reported that these CVD risk factors are associated with severe manifestation of COVID-19 [4, 5•, 25, 26].

In addition, the interplay between the immune system and CVD is known, which may be relevant to the increased risk of severe COVID-19. Epidemiological studies have shown a prospective association between CVD and subsequent risk of different types of infection [27–29]. Also, immune cells are broadly recruited to the myocardial tissue in response to cardiac injury to remove dying tissue, scavenge pathogens, and promote healing [30]. However, these immune cell activities may disrupt the local or systemic host immune response, increasing susceptibility to viral myocarditis and sepsis [31]. Although data on COVID-19 are sparse, a small Chinese cross-sectional study of 64 patients with COVID-19 found that levels of inflammatory markers, such as high sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor

Table 1 Representative studies assessing the independent association of CVD with severe COVID-19

First author	Country	CVD subtype	Severe COVID-19 definition	Key findings
Cummings MJ	USA	Chronic cardiac disease (coronary artery disease or congestive heart failure)	In-hospital death	Among 257 critically ill patients, preexisting chronic cardiac disease was associated with a higher risk of mortality (HR 1.76 [95% CI, 1.08–2.86])*
Bhatla A	USA	Atrial fibrillation	Admission to the ICU	Among 700 hospitalized patients, incident atrial fibrillation was associated with admission to the ICU (OR 4.68 [1.66–13.18])†
Shi S	China	Cardiac injury (blood levels of cardiac troponin I above the 99th percentile upper reference limit)	In-hospital death	Among 416 hospitalized patients, cardiac injury was associated with a higher risk of in-hospital death from symptom onset (HR 4.26 [1.92–9.49])‡
Song Y	China	Cardiac injury (an elevated cardiac troponin value above the 99th percentile of the upper reference limit)	In-hospital death	Among 64 critically ill patients, myocardial injury was an independent risk factor for mortality (HR 2.06 [1.10–3.83]) §
Wang L	China	CVD	In-hospital death	Among 339 patients, CVD was associated with in-hospital death (HR 2.06 [1.10–3.83])¶

*Adjusted for age, sex, symptom duration before hospital presentation, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, diabetes, interleukin-6, D-dimer

†Adjusted for age, sex, race, body mass index, heart failure, coronary heart disease, diabetes, hypertension, chronic kidney disease, and hydroxychloroquine treatment

‡Adjusted for age, cardiovascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, renal failure, cancer, acute respiratory distress syndrome, creatinine (≥ 1.50 mg/d or not) and N-terminal pro-B-type natriuretic peptide (≥ 900 pg/mL or not)

§Adjusted for age, smoking history and preexisting with CVD

¶Adjusted for age, CVD, chronic obstructive pulmonary disease, and cerebrovascular disease

CVD cardiovascular disease, HR hazard ratio, ICU intensive care unit, OR odds ratio

alpha, were higher among patients with myocardial injury than those without [32].

The Impact of COVID-19 on the Cardiovascular System

A number of studies have reported the impact of COVID-19 on the cardiovascular system. Its impact may vary from cardiac damage to thrombotic events. The bidirectional association between CVD and COVID-19 can create a vicious cycle and bring immense challenges in the care of patients with COVID-19. In this section, we summarize a few representative cardiovascular manifestations in patients with COVID-19.

Cardiac Damage

A few studies reported abnormal echocardiographic findings in approximately 60 to 70% of hospitalized COVID-19 patients [33••, 34]. An international study including 1272 COVID-19 patients from 69 countries showed that 39% of hospitalized COVID-19 patients had left ventricular abnormality (i.e., dilation, systolic dysfunction, and diastolic dysfunction), 33% had right ventricular abnormality, and 28% had biventricular failure [33••]. Furthermore, a case series autopsy study of patients with COVID-19 has shown that myocyte necrosis and mononuclear cell infiltrates were observed in cardiac muscle autopsy specimens [35]. Another case report has demonstrated that viral particles were found in cardiac tissues obtained from a patient with COVID-19 [36].

In addition to functional and structural abnormality of the heart, elevated levels of cardiac markers such as cardiac troponin T and I were observed in 7 to 36% of hospitalized patients with COVID-19 [7, 19, 20]. Higher levels of troponin were associated with a higher risk of ICU admission and mortality [7, 14, 19, 20]. Of note, this association was observed regardless of a history of CVD [20]. Thus, cardiac markers may be utilized in stratifying the risk of adverse events among hospitalized patients with COVID-19. Such a risk classification may be especially useful when resources for clinical management are limited.

Arrhythmias

A variety of arrhythmia, including atrial fibrillations, ventricular tachycardias, and ventricular fibrillations, have been reported in patients with COVID-19 [17, 18, 20]. A study from the USA including 700 patients with COVID-19 found that 53 (8%) patients developed arrhythmia-related events during hospitalization, including 9 cardiac arrests, 25 atrial fibrillations, 9 clinically significant bradyarrhythmias, and 10 non-sustained ventricular tachycardias [17]. These observations further support the potential pathophysiological impact of COVID-19 on the heart.

Thrombotic Events

COVID-19 may interfere with the coagulation system as well. The incidence of venous thrombosis and pulmonary embolism has been reported to be high in patients with COVID-19 [37–40]. In a systematic review of 20 studies with 1988 patients with COVID-19, on average, venous thromboembolism events were recognized in 31.3% of the patients [37]. Other types of thrombotic events including the arterial system have also been reported in patients with COVID-19, such as myocardial infarction [41] and stroke [42–44]. Thrombotic events were consistently associated with a higher risk of mortality [38, 40, 41]. In addition, a few studies have reported elevated levels of D-dimer among patients with COVID-19 and their association with an increased risk of thrombotic events and mortality [14, 40]. Accordingly, the International Society of Thrombosis and Hemostasis recommends using a prophylactic dose of low-molecular weight heparin for all hospitalized COVID-19 patients without contraindications [45].

The Management of CVD in the Context of COVID-19

The Impact of COVID-19 on the Management of CVD

A rapid surge in COVID-19 cases has strained healthcare systems and posed a great threat to the care for patients with CVD, especially in heavily hit areas such as the Hubei province in China, the state of New York in the USA, and the Lombardy region in Italy [46–48]. Several healthcare systems have observed a marked reduction (approximately 40%) in the number of diagnoses and hospitalizations for acute CVD events during the COVID-19 pandemic such as acute coronary syndrome [49, 50], decompensated heart failure [51], and stroke [52].

These observations have raised concerns about delays in access to healthcare systems and the initiation of treatment among patients with new-onset CVD [53]. A study from Italy showed that patients with acute coronary syndrome during the COVID-19 outbreak had a substantially delayed time from symptom onset to hospital admission compared to pre-outbreak (median of 15 hours versus 2 hours) [54]. Other studies have also shown a delay in treatment timelines and an increase in the rates of in-hospital mortality and out-of-hospital cardiac arrest [47, 55, 56].

Accordingly, some countries have modified clinical guidelines for the management of CVD. For example, experts from China recommend thrombolytic treatment as the first-line therapy for patients with ST-elevated myocardial infarction when COVID-19 is confirmed or suspected [57]. This recommendation is likely to reflect local resources and settings (e.g., the number of catheterization labs equipped for the adequate protection of healthcare professionals) [58].

Optimizing the Management of CVD and its Risk Factors

As we discussed earlier, prior CVD has been associated with an increased risk of severe COVID-19 in a number of studies. Thus, CVD patients need to be among the top priorities for the prevention of COVID-19. Also, the value of controlling CVD risk factors should be emphasized during the outbreak of COVID-19, although the management of CVD risk factors may not be prioritized when the healthcare system is stretched due to the outbreak.

In the early stages of the COVID-19 pandemic, several researchers raised concerns about the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) for patients with COVID-19 [59, 60]. The concern was mainly driven by experimental data on ACEI and ARB as potentially increasing the relative abundance of ACE-2, a receptor used for SARS-CoV-2 for entering into the cell [61, 62]. However, subsequent studies have shown that the use of ACEI/ARB was not associated with an increased risk of COVID-19 infection, severity, or mortality [63–65]. To date, all major clinical guidelines state that ACEI and ARB should not be discontinued because of COVID-19 [66–69].

Most patients with CVD and its risk factors require continuous medical management. In this regard, telemedicine has been attracting attention as a way to interact with patients without direct person-to-person contact [70, 71•]. Previous studies have demonstrated that telemedicine was feasibly implemented in the care of conditions related to CVD risk factors, such as hypertension and diabetes [72, 73]. Indeed, the COVID-19 pandemic has resulted in a dramatic increase in the utilization of telemedicine. The US Department of Health and Human Services has reported that 44% of Medicare primary care visits were provided via telehealth in April 2020, as compared to merely 0.1% before the pandemic in February 2020 [74]. Nonetheless, several challenges remain to be solved before telemedicine can be widely adopted, such as technological barriers, the potential for such an approach to widen disparities, and potentially adverse effects on the patient-provider relationship [75, 76].

Smoking cessation is critically important since current/former smoking was strongly associated with adverse outcomes of COVID-19 [5•]. Feelings of stress during the pandemic can drive an increase in the dose of smoking among current smokers [77, 78]; a survey has shown a dose-dependent association between stress and smoking in a positive direction [79]. Other health behaviors may also be relevant, since some evidence suggests increases in alcohol consumption [80] and decreases in daily physical activity [81] during the COVID-19 pandemic.

Optimizing Immunization in CVD Patients

Adherence to existing immunization recommendations is critical to mitigate morbidities associated with COVID-19 [82]. Influenza and pneumococcal vaccines are particularly relevant since they can reduce the risk of respiratory infection and subsequent complications [83–86]. Coinfection is common in COVID-19, reported in up to 20% of COVID-19 patients on samples from nasopharyngeal swabs [87]. Although data are limited in COVID-19, studies among hospitalized patients with infection have shown that coinfection with virus or bacteria was associated with an increased risk of developing acute respiratory distress syndrome [88], requiring ICU admission [89], and mortality [90, 91]. Of note, the US Advisory Committee on Immunization Practices recommends influenza vaccination for all adults and pneumococcal vaccination for older adults and those with risk conditions including heart disease [92].

Efforts are underway to develop, test, and distribute vaccines against SARS-CoV-2. For equitable allocation of vaccines, the World Health Organization proposes that healthcare workers, older adults, and those with high-risk conditions including CVD should be prioritized for vaccination [93]. A recent study of 19,793 US adults with CVD demonstrated that sociodemographic factors, such as lack of a usual source of care or health insurance and having a low income and education level, were major barriers to influenza vaccination [94••]. Thus, public support would be needed for fair distribution of forthcoming vaccines against SARS-CoV-2. Skepticism on vaccine safety and efficacy in some individuals would be another important issue relevant for effective and efficient prevention of COVID-19 [95, 96].

Potential Future Directions

Despite an unprecedented surge in the number of publications related to COVID-19 since the beginning of the pandemic, our understanding of the relationship between CVD and COVID-19 is still limited. Many observational studies did not account for major confounders of the association between CVD and COVID-19, and the magnitude of the association varied across countries and regions. Thus, further studies are needed to quantify the independent association of CVD with the risk of COVID-19. Also, rigorous evidence is needed to optimize the management of CVD and COVID-19. For example, cases of medication-induced arrhythmia, such as QT prolongation and sudden cardiac death, have been reported in patients with COVID-19 who received a compassionate drug use of hydroxychloroquine or azithromycin [97, 98].

To date, only short-term outcomes of COVID-19 are available. However, several studies have suggested the potential longer term impact of COVID-19, such as lingering symptoms following COVID-19 [99, 100] and reinfection of COVID-19 [101]. Thus, continued follow-up for patients with COVID-19 is needed to determine the long-term consequence of COVID-19 on the cardiovascular system. Finally, as COVID-19 will likely continue to pose challenges to our

healthcare system (e.g., optimization of telemedicine, dissemination of COVID-19 vaccine), comprehensive approaches that involve policy- and system-level interventions are needed to ensure equal and equitable healthcare delivery for individuals with CVD and its risk factors in this new era.

Conclusions

A body of evidence suggests that there is a bidirectional relationship between CVD and COVID-19, which may present challenges in the prevention and management of patients with CVD and COVID-19 during the course of this pandemic. A rapid surge in COVID-19 cases has strained the healthcare system and has complicated the management of CVD and its risk factors. While we are awaiting the wide availability of COVID-19 vaccine, the management of CVD risk factors and adherence to immunization recommendations are critically important for individuals with CVD. Telemedicine may be a promising tool to provide CVD care while minimizing in-person clinic visits. Further research is needed to understand the epidemiological and pathophysiological basis for the interaction between CVD and COVID-19.

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Compliance with Ethical Standards

Conflict of Interest Junichi Ishigami, Minghao Kou, and Ning Ding declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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