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Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcmCOVID-19 as a cardiovascular disease risk factor[☆]

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Coronavirus Disease 2019 (COVID-19) is a multisystem disease. It is characterized by endothelial dysfunction, microvascular injury, and thrombosis secondary to severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) infection and related systemic inflammatory and immune responses. Cardiovascular (CV) manifestations of COVID-19 have been investigated extensively since the pandemic's beginning [1]. The relationship between COVID-19 and CV disease (CVD) is bidirectional. Patients with CVD and cardiometabolic risk factors are at increased risk of severe COVID-19 illness and death. On the other hand, COVID-19 is a microvascular and macrovascular disease associated with various acute and potentially chronic CV complications [1].

The crucial role played by cardiologists in the care of COVID-19 patients has evolved. During earlier phases of the pandemic, cardiologists were predominantly involved in caring for acute cardiac complications of COVID-19 among hospitalized patients. However, in the post-vaccination era, this role appears to be replaced by the responsibility of caring for patients with chronic CV symptoms or complications after the resolution of acute COVID-19. Thus, it is paramount that the exponentially growing scientific data on the relationship between COVID-19 and CVD are concisely communicated to the cardiology community. Within this scope, the clinically-relevant review article authored by Mitrani et al. [2] published in this journal issue is an essential contribution to the liter-

ature. This well-written paper sets the stage with a brief introduction to acute CV complications of COVID-19 and data on myocarditis associated with vaccination. Unlike many prior publications on this topic, the authors have primarily focused on cardiac manifestations of COVID-19 during the early and late convalescent phases. Additionally, the authors have reviewed the available data on the manifestations of cardiac arrhythmias associated with COVID-19. The paper also includes essential practical tips for CV assessment strategies in athletes with a prior history of COVID-19. The authors' conclusions are well-balanced, and the authors have considered the available data's strengths and, more importantly, limitations.

The most common CV complication of COVID-19 is acute myocardial injury, defined by an elevation of cardiac troponin (cTn) concentration above the 99th percentile of the upper limit of normal. COVID-19-associated myocardial injury is often mild and correlates with the viral load and severity of illness [1,3]. Therefore, its frequency and reported severity vary depending on the population studied. Other cardiac complications associated with COVID-19 are acute heart failure, right ventricular dilatation/dysfunction, elevated pulmonary artery systolic pressure, cardiac arrhythmias, and conduction system abnormalities [1].

The underlying etiology of COVID-19-associated myocardial injury is broad and includes acute coronary syndrome (type-1 myocardial infarction), demand ischemia (type-2 myocardial infarction), myocarditis, acute heart failure, stress cardiomyopathy, and right ventricular strain due to respiratory failure or pulmonary emboli. In addition, it can be attributed to sepsis or exacerbation of preexisting chronic conditions such as cardiomyopathy [4,5]. Of note, more than one etiology may coexist in the same patient. A complex interplay of multiple mechanisms appears to underlie COVID-19-mediated myocardial injury. Emerging evidence has indicated a predominant role of indirect myocardial damage due to immune dysregulation and cytokine storm [6,7].

Myocarditis is characterized by cardiac symptoms, an elevated cTn, abnormal findings on ECG, echocardiography, cardiac magnetic resonance imaging (CMR), or histopathologic evidence (biopsy or

Abbreviations: CMR, cardiac magnetic resonance imaging; COVID-19, coronavirus disease 2019; CTN, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus-2.

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post-mortem evaluation) in the absence of obstructive coronary artery disease [5]. COVID-19 significantly increases the risk of myocarditis, with a reported prevalence varying depending on the definition and diagnostic evaluation [1]. However, despite the well-documented link, COVID-19-associated myocarditis appears to be relatively rare compared to the burden of myocardial injury in this patient population. A prospective, multicenter, observational cohort study involving 3018 young athletes who tested positive for COVID-19 reported the prevalence of CMR-based cardiac involvement as 0.5 to 3.0% [8]. Diagnostic workup and clinical significance of COVID-19-associated myocardial injury and myocarditis have been reviewed in detail by Mitrani et al. [2].

A recently published expert consensus document from the American College of Cardiology recommends triad testing with an ECG, cTn (preferably high sensitivity), and an echocardiogram when evaluating COVID-19 patients with cardiac symptoms or at least a moderate suspicion for cardiac involvement. Moreover, if the initial triad testing raises suspicion of myocardial involvement with COVID-19, CMR is recommended for further evaluation if the patient is hemodynamically stable and the results are likely to impact the management plan [5]. CMR is a highly sensitive diagnostic tool in evaluating COVID-19-associated myocardial involvement findings such as inflammation, late gadolinium enhancement, non-ischemic epicardial scar, and pericardial effusion [4,5].

The high prevalence of cardiac injury in the acute setting of COVID-19 has led to significant concern for long-term cardiac damage in patients who recover from acute illness. This concern was supported by the fact that observational studies revealed a high prevalence (26% to 60%) of CMR-identified cardiac abnormalities in patients with a history of COVID-19 hospitalization more than a month prior [4]. The reported abnormalities included ventricular systolic dysfunction, myocarditis, pericardial effusion, and enhancement. Of note, these studies had small sample sizes and often lacked matched control groups to confirm the true frequency of cardiac abnormalities attributable to COVID-19. Also, the long-term consequences of these mostly asymptomatic cardiac abnormalities are unknown. Reassuringly, a case-control study involving healthy adults (mean age 37 years) demonstrated that mild or asymptomatic COVID-19 infection was not associated with a higher risk of CMR abnormalities [9].

As the pandemic has evolved over the past two years, it has become clear that COVID-19 is not only characterized by acute morbidity and mortality but also associated with increased incidence of CVD and persistent cardiac symptoms. These observations led to the identification of a heterogeneous disorder called post-acute sequelae of SARS-CoV-2 infection (PASC) or "long-COVID." PASC is defined as a constellation of new, returning, or persistent health problems present beyond four weeks of SARS-CoV-2 infection [5,10]. PASC presents with a wide range of symptoms affecting multiple organ systems, and these patients often report fatigue, chest pain, dyspnea on exertion, exercise intolerance, or palpitations [11]. Affected patients may also experience tachycardia and elevated blood pressure. PASC-related persistent symptoms can significantly impair quality of life and cause heightened anxiety. The etiology of these cardiac complaints in the early post-acute or late-convalescent phases of COVID-19 can be due to underlying CVD (preexisting or COVID-19-associated) in a minority of individuals. However, most patients with PASC and persistent cardiac symptoms lack objective evidence of abnormalities on standard testing to explain symptoms [5].

The prevalence of PASC is highly variable depending on the description, study population and design, and duration of follow-up. The frequency of PASC appears to correlate with the severity of acute illness and the presence of comorbidities [11]. A recent longitudinal cohort study from China reported health outcomes in individuals two years after surviving COVID-19 hospitalization. In

this cohort, the burden of persistent symptoms and functional impairment declined over time. Nevertheless, even after two years, a high percentage of participants reported symptomatic sequelae (fatigue in 31%, palpitations in 15%, and chest pain in 8% of the participants) [12]. Interestingly, women are twice as likely to develop PASC compared to men, even though the male sex is associated with a higher risk of short-term complications of COVID-19 in most countries [13,14]. Potential mechanisms of CV manifestations of PASC remain under investigation. Because of the multifactorial nature of this condition, patients with PASC often require care by multidisciplinary teams, including primary care, cardiology, and other medical specialties. Cardiac testing should be guided based on the pre-test probability of CVD, functional status, and pattern of persistent symptoms. Ambulatory rhythm monitoring is recommended when there is a concern for arrhythmia as the cause of symptoms. Furthermore, stress testing or cardiopulmonary exercise testing are recommended when patients present with chest pain, dyspnea, or exercise intolerance [5].

The biological effects of COVID-19 on the CV system are not isolated from the other detrimental impacts of the pandemic. For example, the pandemic and social restrictions have led to an increased sedentary lifestyle, impaired access to health care for economic reasons, and disrupted routine and preventative health care services. In addition, social isolation has contributed to an increased burden of mental health issues in the general population, regardless of the individuals' SARS-CoV-2 infection status [13,15]. The pandemic's impact on these social, economic, and psychologic determinants of health is more pronounced in women and vulnerable populations [15,16]. Furthermore, this raises concern for the increased burden of CVD and worse CVD outcomes globally in the years to come.

We have witnessed remarkable advances in understanding the interplay between COVID-19 and heart disease. The comprehensive review by Mitrani et al. [2] summarizes these advances well. However, many unanswered questions remain. Future research is needed to better understand the CV effects of different strains of SARS-CoV-2 virus, recurrent COVID-19, and breakthrough infections in individuals vaccinated against SARS-CoV-2. In addition, long-term follow-up studies will hopefully help understand CV outcomes related to PASC and subclinical cardiac abnormalities detected with imaging studies among individuals recovered from COVID-19.

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