Complications in Patients With COVID-19

To the Editor Madjid et al1 recently reviewed the association between the cardiovascular system and infection with coronavirus disease 2019 (COVID-19). They point out the association between cardiovascular risk factors and the outcome of patients with COVID-19. However, the underlying risk associated with obesity was not listed among the risk factors. There are several lines of evidence that being overweight or obese is associated with risk of poor outcome (ie, admission to an intensive care unit or death) after infection with COVID-19. Recently, 72% of 775 patients with COVID-19 admitted to an intensive care unit in the UK were reported to have a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 25 and 38% had a BMI greater than 30,2 a proportion higher than in the standard intensive care population. Obesity is also reported as a risk factor of poor outcome by the US Centers for Disease Control and Prevention.3

A potential pathophysiological background exists linking the increasing severity of COVID-19 among patients with obesity. COVID-19 binds to angiotensin-converting enzyme 2 (ACE2), a surface molecule that allow the virus to enter the host cell. In this line, the role of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) in the pathogenicity of COVID-19 has been intensively debated.4 The level of ACE2 expression has been reported to be high in adipose tissue, therefore likely making the adipose tissue a reservoir for severe acute respiratory syndrome coronavirus 2. In turn, the adipose tissue can trigger an increased inflammatory response to infection, potentially affecting all organs. Finally, patients with obesity can be at higher risk of hypoxemia due to altered thoracic compliance and the risk of lung atelectasis.5

I suggest that both BMI and treatment with ACEi or ARB be systematically reported in case series of patients with COVID-19 to further appreciate their interaction and association with outcome. Further research should then explore the impact of adipose tissue on the viral load, the systemic inflammatory response, and the outcome of patients with COVID-19. In the meantime, the potential risk of future deterioration should probably be appreciated in overweight patients developing COVID-19–related symptoms.

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To the Editor In their excellent article, Madjid et al provide a comprehensive overview of all the latest data regarding coronaviruses, with a focus on their effects on the cardiovascular system. The authors present several reports suggesting evidence of myocardial injury in patients with coronavirus disease 2019 (COVID-19) infection, manifested by elevation of high-sensitivity troponin T and I. They propose that myocardial injury in these patients is likely associated with infection-related myocarditis, based on sporadic autopsy cases as well as 2 cases of severe myocarditis with reduced systolic function. Nonetheless, the autopsy study by Xu et al that is cited1 reports no obvious histological changes seen in heart tissue, suggesting that severe acute respiratory syndrome coronavirus 2 might directly affect the heart. Additionally, the 2 definite myocarditis case reports by Inciardi et al and Hu et al that are also cited1 did not show any respiratory involvement during the clinical course, which is a quite different clinical presentation from most critically ill patients. During the previous 2003 severe acute respiratory syndrome and Middle East respiratory syndrome epidemic, myocarditis was not documented as a proven complication of coronavirus infection, and only subclinical reversible diastolic impairment without any systolic involvement was observed in most patients.2 Troponin elevation in the context of COVID-19 infection may as well be related to various other mechanisms,3 including acute myocardial infarction type I (ie, plaque rupture induced by arterial wall inflammation), acute myocardial infarction type II (supply-demand mismatch) triggered by infection, or even Takotsubo stress cardiomyopathy, which is observed with increasing frequency in patients with sepsis.4 Furthermore, troponin elevation may originate from right ventricle injury related to respiratory failure or pulmonary thromboembolic phenomena, which have also been reported as a common feature of this disease, or from transient cytosolic leakage of cardiac troponin T due to increased myocardial membrane permeability induced by systemic inflammatory response. Finally, multiple pathways may cooperate in some cases, with myocarditis remaining a challenging diagnosis, especially when echocardiography or electrocardiographic data are limited due to conditions in the isolation ward. From this perspective, troponin elevation should not be regarded as equivalent to myocarditis or, even worse, to left ventricle impairment, which could potentially mislead clinical judgment in severely ill patients, but rather as a significant prognosticator. This is also supported by data suggesting that patients with elevated troponin T levels but without any underlying cardiovascular disease may experience a more dismal outcome compared with patients with preexisting cardiac disease but with normal troponin T levels during the course of COVID-19 infection.5
Letters

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In Reply Our knowledge of coronavirus disease 2019 (COVID-19) has extensively evolved and expanded since the publication of our article.1 We agree with Legrand regarding the importance of obesity in COVID-19. While initial epidemiologic reports did not identify obesity as a risk factor for COVID-19, later studies demonstrated that obesity is a risk factor for the severity of COVID-19. In 482 patients admitted with COVID-19 in Italy,2 patients with a body mass index (calculated as weight in kilograms divided by height in meters squared) between 30 and 34.9 had higher odds of respiratory failure (odds ratio, 2.32; 95% CI, 1.31-4.09) and admission to the intensive care unit (odds ratio, 4.96; 95% CI, 2.53-9.74), while patients with a BMI of 35 or greater had an increased risk of death (odds ratio, 12.1; 95% CI, 3.3-45.1; P < .001).

Obesity may aggravate the severity of COVID-19 through multiple mechanisms. (1) Obesity is often associated with multiple comorbidities, including hypertension, diabetes, chronic kidney disease, cardiovascular diseases, obstructive sleep apnea, and obesity-hypoventilation syndrome, which can further contribute to increased COVID-19 severity; (2) obesity leads to accumulation of fat in the mediastinum and abdominal cavities, which may cause mechanical effects with increased pulmonary resistance, decreased total respiratory system compliance, and decreased respiratory muscle strength; (3) excess adipose tissues contribute to a chronic inflammatory state through increased production of multiple proinflammatory cytokines, including tumor necrosis factor-α, interleukin 1β, and interleukin 6, which could play a role in hyperinflammation and cytokine storm in COVID-19; and (4) angiotensin-converting enzyme 2 is highly expressed in adipose tissues.

We also agree with Stavroulakis and colleagues regarding the important role of cardiac injury in COVID-19. Myocardial injury is generally defined as troponin elevation above the 99th percentile of the upper reference limit and is rather common in patients hospitalized with COVID-19. In most cases, troponin is only mildly elevated and yet is still associated with a modest increase in adverse outcomes.3 Higher troponin levels are associated with up to 3-fold higher risk of mortality.3

As expected, patients with a cardiac history are more likely to show signs of myocardial injury. Multiple pathways can lead to elevated troponin levels3,4: (1) some conditions, such as heart failure, myocardial hypertrophy, cardiomyopathies, atrial fibrillation, hypertension, and chronic kidney disease, can lead to elevated troponin levels at baseline; (2) acute myocardial infarction and ischemia can increase troponins; COVID-19 has been associated with either type 1 myocardial infarction due to plaque rupture and coronary thrombosis or type 2 myocardial infarction due to increased demand and/or concomitant hypoxia; (3) myocarditis with or without direct viral infection can increase troponins; and (4) troponin can be released from cardiomyocytes due to the indirect effect of systemic infection and cytokine storm in a hyperinflammatory state or due to pulmonary embolism.4 These mechanisms are not exclusive of each other and can overlap. Elevated troponin levels have important prognostic implications, can be useful in patients’ risk stratification and triaging both in inpatient and outpatient settings, and could potentially be used to identify high-risk patients in future targeted clinical trials.

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