Cardiovascular system is at higher risk of affecting by COVID-19

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Summary. SARS-CoV-2 has shown its potential to cause severe manifestations among individuals with underlying cardiovascular disease (CVD). The patients infected with SARS-CoV-2 with pre-existing CVD are more likely to relapse. There are several reasons, including the prolonged hospitalization time as a consequence of their more severe illness and aberrant expression of angiotensin-converting enzyme 2 (ACE2) – the cell surface receptor of SARS-COV2 that is present on cardiac cells – and using drugs such as ACE inhibitors and angiotensin receptor blockers (ARBs) that alter the expression of ACE2. Besides, SARS-CoV-2 shares structural similarities with SARS-CoV-1, and that patients recovered from SARS-CoV1 have shown an increased risk of developing inflammatory, metabolic, and cardiac diseases. It makes some concerns that people who recovered from SARS-CoV2 are also liable to develop these chronic conditions later. Further studies should investigate the probability of recurrence of COVID-19 in patients with CVD and the development of approaches for the prevention of chronic inflammatory conditions in patients with CVD who recovered from COVID-19. (www.actabiomedica.it)

Key words: COVID-19, cardiovascular disease, recurrence, relapse, SARS-CoV-2, 2019-nCoV, angiotensin-converting enzyme 2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged human coronavirus (hCoV) that causes a highly infectious disease called novel coronavirus disease (COVID-19) with a long incubation period (2-14 days). For the first time, it was reported in December 2019, in the province of Hubei. Since then, the number of infected patients has

begun to increase worldwide (1). The World Health Organisation (WHO) declared the outbreak of COVID-19 on January 30, 2020 (2). Earlier, another strain of hCoVs known as the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) caused an outbreak of the viral respiratory disease in 2002. It also first happened in China. The Middle East respiratory syndrome (MERS) is another outbreak of respiratory infections caused by coronaviruses. It is known to be transmitted from camel to human. MERS mostly occurred in the Middle East, such as Saudi Arabia, Jordan, and Yemen (3).

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* indicates equal contributions

Does COVID-19 recure?

Some patients show fever and positive nucleic acid for the SARS-CoV-2 after recovery. There is a report of four patients who manifested no clinical symptoms and were without the abnormalities in their chest computed tomography (CT) scan and radiography images after recovery and tested positive for SARS-CoV2 5 to 13 days later (4). Also, Chen *et al.* published a report of a woman who showed the virus in oropharyngeal swab after recovery from respiratory symptoms and maintaining normal body temperature (5).

Risk of COVID-19 and its recurrence in patients with cardiovascular disease (CVD)

Most cases of SARS-CoV-2 demonstrate mild symptoms common to other respiratory infections. However, this virus has shown its potential to cause severe manifestations among certain groups, including older populations and individuals with underlying health problems interestingly CVD (6). Not only patients with CVD are at increased risk of COVID-19, but also they need to be admitted to hospitals more prolonged, and this, in turn, would make them more susceptible to recurrence because of more exposure to pathogens during hospitalization (7).

CVD is an inflammatory disease that causes changes in immune responses involved in infectious diseases. The association between CVD and recurrence of COVID-19 is consistent with previous findings showing that there is a bidirectional relationship between CVD and infections and that immune dysregulation mediates this relationship (8). Evidence indicates that as patients with CVD are at increased risk of re-infection, patients with re-infection are more liekly to develop acute and chronic cardiovascular events (9). Further, the role of inflammation has been well-elucidated in the pathogenesis of COVID-19. More precisely, patients with COVID-19 display immune dysregulation and that the more severe the COVID-19 is, the higher the degree of inflammation (10). Moreover, COVID-19 raises a cytokine storm as the dominant picture of organ failure and death. In this manner, it is most probable that COVID-19-associated immune

dysregulation acts in forming more frequent and more severe episodes of infection in patients with CVD.

The severity of COVID-19 and later development of complications in patients with CVD

SARS-CoV-2 and MERS-CoV have similarities in their pathogenicity (11). A meta-analysis has shown that MERS-CoV tends to cause a more severe lower respiratory tract infection and more serious complications like myocarditis and heart failure in patients who suffer from CVD (12,13). It has been true for COVID-19. As reported by the Center for Disease Control and Prevention (CDC) on April 05, 2020, among confirmed cases of COVID-19 who had at least a comorbid condition, those with CVD have shown the highest death rate of 13.2% compared with a range of 7.6 – 9.2% for other comorbid patient groups.

Both SARS-CoV-1 and SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2). Their Spike (S) proteins have 76% similarity in the full-length amino acid sequencing and 53.5% homology in the N-terminal domains (14). Wu et al. conducted a follow-up study on 25 patients infected with SARS-CoV-1 twelve years after the recovery. The study shows that the risk of cardiovascular disorders, hyperlipidemia, abnormal glucose metabolism, tumors, and inflammation are higher in recovered patients in comparison with healthy participants. They have also found that 44% of the recovered patients had cardiovascular abnormalities (15). There will be a possibility that patients with COVID-19 might be prone to later development of chronic cardiac conditions.

ACE2 and drugs that affect its expression a might mediate the particular action of COVID-19 on the cardiovascular system

ACE2 is a receptor of SARS-CoV-2. Molecular assessment of SARS-CoV-2 showed that antibodies against ACE2, an aminopeptidase, suppress the virus replication (11,16). Receptor binding domain (RBD) of the S protein of SARS-CoV-2 binds to ACE2 receptors that exist on alveolar lung cells, intestinal cells,

renal cells, and cardiac (16,17). Inflammatory pathways related to ACE2 signaling are one of the proposed mechanisms of myocardial injury caused by COVID-19 (11).

Since ACE2 acts as a gate that allows the SARS-CoV2 to enter the host cells, some authors suppose that increased expression of ACE2 contributes to COVID-19 virulence (18). Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and thiazolidinedione (19) upregulate the expression of ACE2. These drugs are often used in patients with hypertension and diabetes mellitus. Patients receiving these drugs account for the majority of severe cases with COVID-19 (20), and therefore, they might also be prone to relapse after recovery from COVID-19 (19). However, no completed studies exist about the recurrence of COVID-19 in patients using the abovementioned drugs compared with those who use other anti-hypertensive drugs like calcium channel blockers (CCBs) or diuretics.

Conclusions and recommendations

In conclusion, as the infectious rate of COVID-19 is higher in patients with CVD, the prevalence of recurrence might also be higher in these individuals versus the general population. Given the structural similarities of SARS-CoV-2 and SARS-CoV-1 and that the relation of SARS-CoV-1 with chronic cardiac diseases, infection with SARS-CoV-2 might also be associated with later development of CVD in recovered patients. Because they have reduced resistance to infections, patients with CVD recovered from COVID-19 should boost their immune system after discharge (7). ACE inhibitors or ARBs may confer susceptibility to COVID-19 and that due to related potential side effects like hypotension, dizziness, edema, nephrotoxicity, and cough, they are not suggested to be used for prevention from relapse in healthy individuals (21,22). Further studies should investigate the probability of recurrence of COVID-19 in patients with CVD and the development of approaches for the prevention of inflammation in patients with CVD who recovered from COVID-19. Cardiovascular complications need to be investigated in elderly people who are

the main target of COVID-19. However, the issue is also important to the pediatric population who suffer from congenital heart diseases (23). Finally, more research is necessary for the determination of all the potential drugs that can upregulate ACE2, especially for ACE inhibitors and ARBs.

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