



COVID-19 and multi-systemic diseases: A review

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ABSTRACT

Coronaviruses was discovered in the mid-1960s that affect humans. In 2019, Wuhan city of Hubei, China, there was an out-break of "coronavirus disease (COVID-19)" which is the result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is induced by a novel enveloped virus having single-stranded RNA. It transmitted rapidly affecting more than 200 countries globally, so, the World Health Organization has declared it as a pandemic. SARS-CoV-2 presently is a 7th amongst known coronaviruses that cause infection in people, after 229E and OC43 (earliest studied viruses in human patients suffering from a common cold). It has infected humans in all age groups, of all ethnicities, both males and females while spreading through communities at an alarming rate. Infected patients experience common cold-like symptoms along with raised temperature, non-productive coughing and difficulty to breathe. It is considered as a relative of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 is caused by a beta coronavirus named SARS-CoV-2, which affects the lower respiratory tract. Besides, SARS-CoV-2 also harms different organs. Till today, there is comprehensive knowledge about the extent and management of COVID-19-related disorders other than pulmonary system. The present review is an overview of systemic manifestations of COVID-19 that may affect gastrointestinal, cardiovascular, urinary, reproductive, hepatocellular or neurological systems.



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INTRODUCTION

In late December of 2019, Wuhan, China reported the first case of "Coronavirus disease (COVID-19)" (Zhou *et al.*, 2020b). Ever since it has rapidly

spread in the world almost affecting more than 200 countries, it becomes pandemic globally. It has affected not only public health but also economic and social activities. Infected patients with COVID-19 often experience common cold-like symptoms along with raised temperature, non-productive coughing and difficulty to breathe (Jagzape *et al.*, 2013), (Figure 1). However, the infection often leads to a state of pneumonia, failure of multiple organs, severe sudden respiratory distress that may often be fatal (Dhadse *et al.*, 2020). In the past six months, it has affected health-care systems of various countries worldwide as there is a rise in the number of COVID-19 patients.

Coronaviruses (CoVs) is categorized into four classes: β -CoV, α -CoV, δ -CoV and γ -CoV. In mammals, β -CoV and α -CoV are only seen. evere acute respiratory syndrome (SARS) and the Middle East

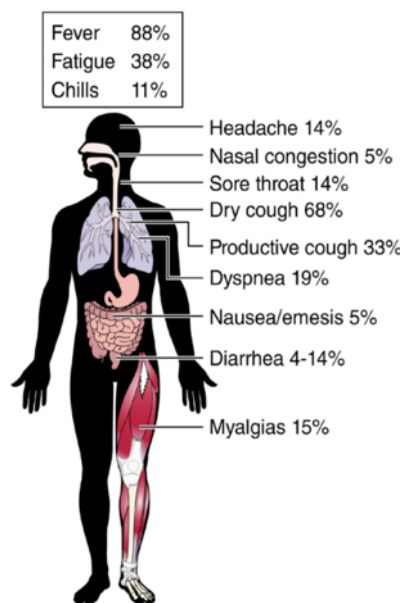


Figure 1: COVID-19 Symptoms

respiratory syndrome (MERS) are a result of β -CoVs, which is life-threatening respiratory disorders (Yin and Wunderink, 2018). SARS-CoV-2 is member of β -CoV which is responsible for COVID-19 (Zhu *et al.*, 2020). Genomic analysis of SARS-CoV-2 affirm 96% of similarity with Chinese chrysanthemum bat. Analysis of SARS-CoV-2 and its genomic sequence resembles 79.5% with SARS-CoV. Bats have been indicated as potential reservoirs for transfer for the virus in humans through an intermediate host which is unidentified. It was also detected that pangolin share 99% genome similarity with SARS-CoV-2, and it suggests that they also play a vital role in the transmission of the virus (Guo *et al.*, 2020) through respiratory droplets or zoonotic animals (Figure 2).

Analyzing clinical and epidemiological data of COVID-19, it proposed that specific comorbidity increase the risk of infection, causing death or lung injury. Most common comorbidities recorded are diabetes, hypertension and cardiovascular diseases (Zhou *et al.*, 2020a). A high number of patients with COVID-19 and other systemic diseases in admitted ICU indicate comorbidity as a potential risk factor for patients with COVID-19 (Wang *et al.*, 2020a). In the present review, we have linked COVID-19 with asthma, chronic obstructive pulmonary disease (COPD), hypertension, cardiovascular diseases (CVD), diabetes, renal diseases, liver diseases, obesity, human immunodeficiency viruses (HIV), malignancy, neurological disorder, psychological disorder and female and male reproductive system.

Diabetes and COVID-19

Due to impaired capability of phagocytic cell, diabetes patients are prone to infections. In diabetic patients, various factors elevate the risk of COVID-19. Raised level of ACE-2 receptors was found to be related to diabetes by Mendelian randomization analysis; this prejudice diabetic patients to SARS-CoV-2 infection (Rao *et al.*, 2020). High levels of furin are expressed that is type 1 membrane-bound protease in patients with diabetes (Fernandez *et al.*, 2018). The proprotein convertase is required for entry of the virus inside the cell of a host by reducing the dependency of SARS-CoV-2 on human proteases. Furin levels are activated by SARS-CoV-2 spike (S) protein attached to ACE-2 receptors. The S protein pre-activation permits entry of the virus into the cell and elude immune system in humans (Shang *et al.*, 2020). Thus, an irregular immune response with raised furin expression and ACE-2 receptors results in lower insulin levels and inflammation of the lung. Thus virus entry leads induce life-threatening condition for patients with diabetes (Rao *et al.*, 2020; Fernandez *et al.*, 2018). Also, raised levels of interleukin-6 (IL-6) and impaired T-cell function plays a conclusive role in the development of COVID-19 disease in patients with diabetes (Kulcsar *et al.*, 2019). Data indicates that 11–58% of COVID-19 patients have diabetes, and 8% of diabetic patients have COVID-19 fatality rate (Bhatraju *et al.*, 2020). There is a high risk for ICU admissions in 14.2% of individuals with diabetic comorbidity in COVID-19 individuals than without diabetes (Zhou *et al.*, 2020a).

Obesity and COVID-19

Obesity is associated with decreased saturation of

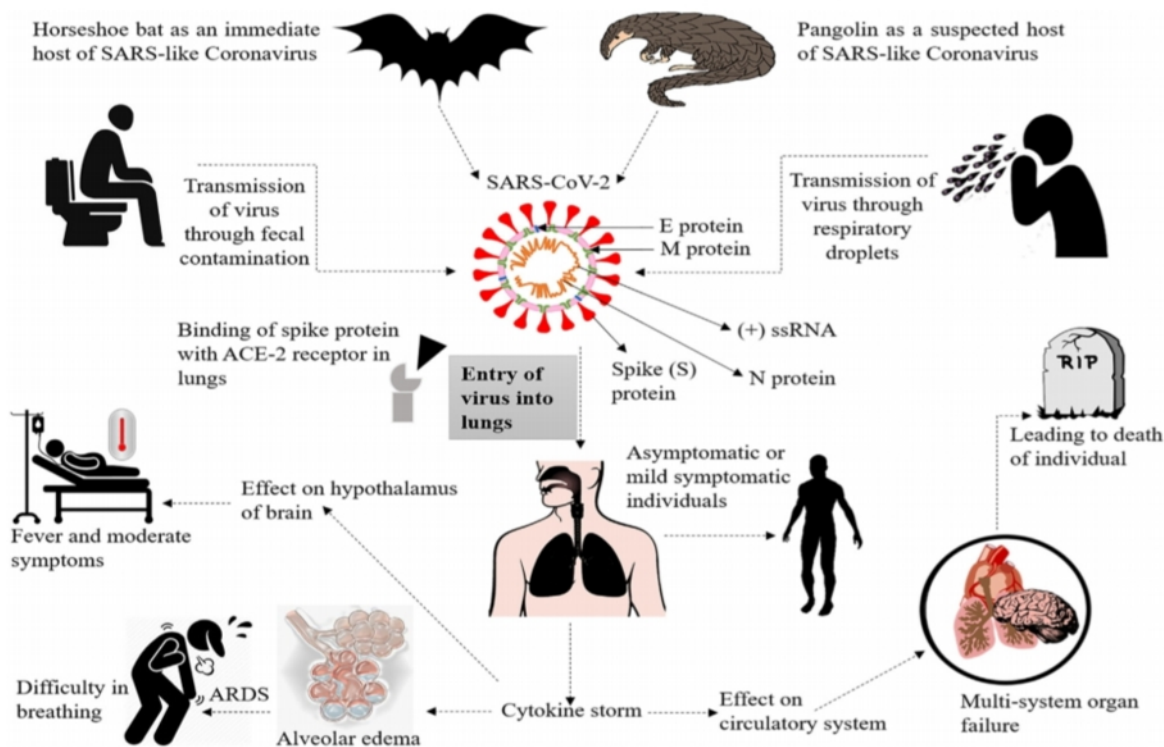


Figure 2: SARS-CoV-2 pathogenesis, transmission and its effect on various organs of the body

oxygen in the blood and compromised ventilation to the lungs. Due to obesity, other features such as abnormal secretions of interferon, cytokines, and adipokines results in immune response compromisation (Zhang *et al.*, 2017). Early reports from Italy, United States and China, obesity is not considered as a risk factor for COVID-19 (Bhatraju *et al.*, 2020; Grasselli *et al.*, 2020; Li *et al.*, 2020a). However, reports from North America and Europe showed more elevated cases of COVID-19 in obese people (Ryan *et al.*, 2020). Therefore, the survey is required to know the correlation between obesity and COVID-19 frequency. A study reported that 47.6% of COVID-19 infected were obese, while 68.6% of cases required ventilation in severe condition (World Health Organization, 2020). Thus, high body mass index (BMI) is considered as a risk factor for COVID-19, and in this pandemic, obese peoples to prevent themselves should take extra care.

COPD and COVID-19

COVID-19 infection in 15–20% of patients results in hypoxemia which in adverse conditions requires the support of ventilator (Qiu *et al.*, 2020). Transition in the inflammatory response, continual mucus production, microbiome imbalance, structural damages, use of respiratory corticosteroids, and weak immunity are necessary for developing COPD. COPD and other chronic disease are linked with MERS and SARS infections (Jagzape *et al.*, 2013). Early stud-

ies have not reported COPD in high cases COVID-19. Still, there was an increase in ACE-2 receptors expression, which contributes to cause severe symptoms such as hyper mucous production, structural damage to lungs and weak immunity (Wan *et al.*, 2020). In 50–52.3%, COVID-19 cases admitted in ICU reported COPD, which showed a high mortality rate with air passages blockage and an increase in mucous production (Liu *et al.*, 2020a).

Asthma and COVID-19

Individuals with asthma are prone to develop viral infections. If left untreated, they develop severe symptoms. Asthmatic people have impaired secretion of IFN- λ and delayed innate immune response, which makes individual susceptible to cause severe complications (Contoli *et al.*, 2006). Asthma is also linked with MERS and SARS (Jagzape *et al.*, 2013). It is assumed based on history that asthma might be a potent risk factor for COVID-19. A comparative analysis in Wuhan of patients with COVID-19 observed no significant link between SARS-CoV-2 with asthma and other allergies, such as allergic rhinitis, food allergy and atopic dermatitis. Therefore, the more severe disease could develop in cases of COVID-19 is linked with geriatric individuals, mostly asthmatic smoker (Zhao *et al.*, 2020). As there is no direct linked with asthma and COVID-19 infections, individuals with other respiratory diseases and complications are likely to intertwined.

Hypertension and COVID-19

High case fatality rate (CFR) is caused due to uncontrolled blood pressure in individuals with COVID-19. Chen et al. in their study noted that 23% of cases of COVID-19 and hypertension has 6% of CFR, and due to anxiety there were continuous inclined cases (Chen et al., 2020b). Treatment protocol for hypertensive patients is mainly angiotensin receptor blockers (ARBs) and ACE-2 inhibitors. When these drugs are used in high amount, there is upregulation of ACE-2 receptor, which results in high susceptibility to SARS-CoV-2 infection (Fang et al., 2020). When receptor cells have higher expression, it makes infection at more risk and may result in respiratory failure or lung injury. Besides, ACE-2 has a potent anti-inflammatory action which protects against respiratory distress syndrome, kidney and lung injury, which causes severe complications in patients with COVID-19. ARBs and ACE inhibitors elevate ACE 2, which lessens angiotensin II inflammatory action (Schiffrin et al., 2020). Use of ARB or ACE inhibitors is helpful or harmful is not yet clear, but to use these molecules is recommended for maintaining normal blood pressure. It is essential to control blood pressure and lessen disease burden in COVID-19 patients (Figure 3).

CVD and COVID-19

It is noted that SARS and MERS have a strong relation with CVD (Chan et al., 2003; Badawi and Ryoo, 2016). Likewise, there was an increased prevalence of CVD noted in COVID-19 patients with severe symptoms and signs. A study of 191 patients with COVID-19 non-survivors noted 6.8% CVD, while other study noted COVID-19 non-survivors had 17% CVD (Guo et al., 2020; Zheng et al., 2020). Till now, the relationship between CVD and COVID-19 is direct or indirect is not confirmed, but it was reported that the immune system was compromised CVDs patients (Kulcsar et al., 2019). In patients with CVD, there is an increased risk of COVID-19 as ACE-2 receptors are present on cardiac muscle cells which involves the cardiovascular system. In acute infections of CVD patients, there is increased risk of the acute coronary syndrome. This syndrome intensifies myocardial action that results in myocardial infarction or injury. However, in COVID-19 cases, there is an elevated level of inflammatory cytokines which mediate hemodynamic instability, atherosclerosis and procoagulant activation resulting in thrombosis or ischemia (Bonow et al., 2020), to decrease the mortality and morbidity in CVD patients, immediate care is needed in COVID-19 infection (Figure 4).

Liver Diseases and COVID-19

Abnormal liver biochemistry and liver injuries are observed in COVID-19 infections. This suggests the relation between coronavirus infection and abnormal liver enzyme secretion. On liver cells, there is a presence of ACE-2 receptors which permits entry of SARS-CoV-2 within a cell (Uhlen et al., 2015). In COVID-19 cases, there was 43.4% abnormal secretion of aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and alanine aminotransferase (ALT) (Chen et al., 2020a). Yet hepatic failure or intrahepatic cholestasis was not seen in patient. Another study noted that patients with COVID-19 showed a 39.1% increase in levels of AST and ALT, and a 6% increase in the level of bilirubin (Jin et al., 2020). During the late stage of infection, COVID-19 individuals showed 29% of liver injury or severe complication (Cai et al., 2020). In SARS-CoV-2 infection, underlying mechanisms of liver damage could be a systemic inflammatory response, preceding hepatic diseases, psychological stress and drug toxicity (Liu et al., 2020b). Presently, there is no evidence that intrahepatic cholestasis pathophysiology or hepatocellular damage is linked with SARS-CoV-2.

Malignancy and COVID-19

As the immune system is weak in malignancy patients, there is an increase chance of COVID-19 infection. In these patients for the cause of SARS-CoV-2 infection, there is sufficient environment for replication. In lung carcinoma, 58.3% of patients had COVID-19, and 41.7% were taking radiotherapy, immunotherapy or chemotherapy, but during the stay in the hospital, no patients required ICU care (Chen et al., 2020a). The fatality rate of 2% was seen in individuals with malignancies and COVID-19 (Zhou et al., 2020a).

HIV and COVID-19

In 2003, CoV OC43 strain was found in patients with HIV positive, and there was a strong history of having CoVs in patients with HIV (Pene et al., 2003). As the immune system is compromised in individuals with HIV, there is increase chances of COVID-19 infection. It was assumed that individuals who are positive for HIV and SARS-CoV-2, there will be vulnerable comorbidity, but no significant correlation was reported (Yin and Wunderink, 2018). As out-break expanded, all patients had mild symptoms without the need for admission in ICU. Thus it indicates COVID-19 infection affects HIV cases as the patient undergoes antiretroviral therapy which has potent activity against SARS-CoV-2 (Martinez, 2020).

Renal Diseases and COVID-19

SARS-CoV-2 influences its action on the kidney by

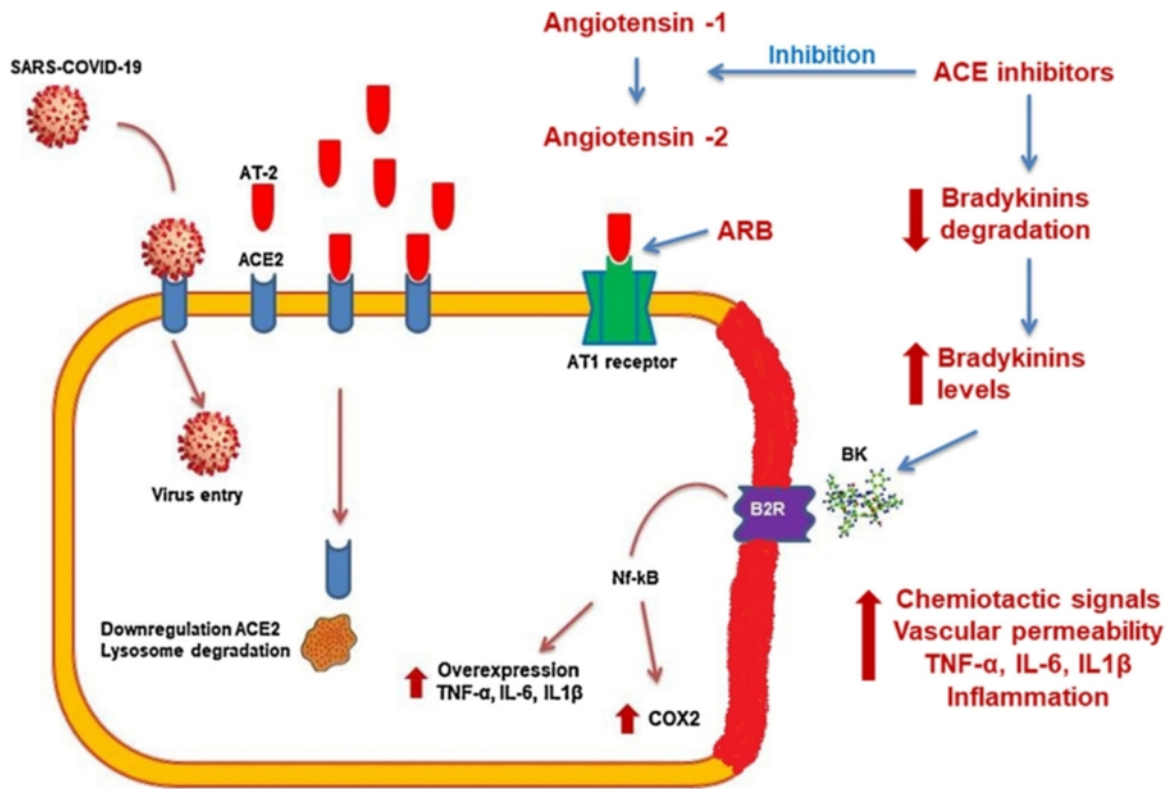


Figure 3: Potential mechanisms linking the ACE system and COVID-19

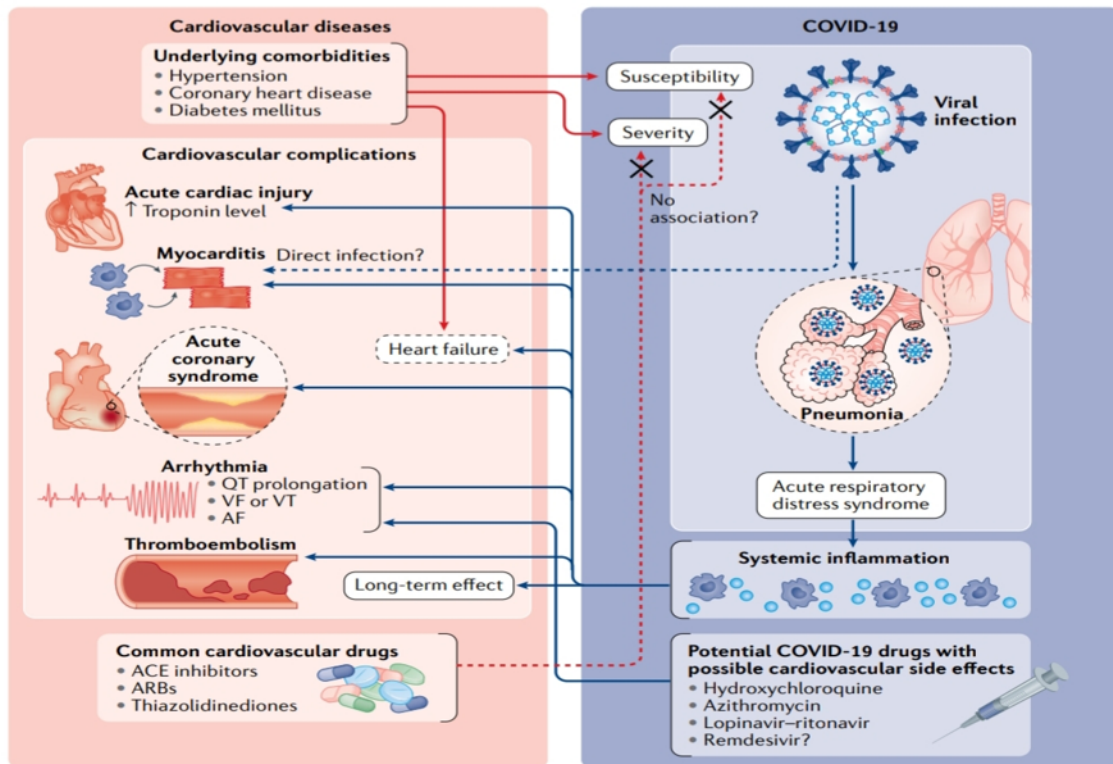


Figure 4: Bidirectional interaction between cardiovascular diseases and COVID-19

direct cellular sepsis or injury, which results in a cytokine storm. Sun et al., in their study, collected urine samples from SARS-CoV-2 patients and concluded that kidneys have potential effect from infected patients (Sun et al., 2020). Acute kidney injury (AKI) was seen 3–9% in patients with COVID-19 while 15% in MERS and 5% in SARS patients with a mortality rate of 60%–90% (Sun et al., 2020; Chen et al., 2020c). Studies observed that proteinuria was seen in 63%, hematuria in 26.7% and albuminuria in 34% (Cheng et al., 2020; Li et al., 2020b). As there is an increase expression of ACE-2 in individuals with renal diseases, they are at risk to COVID-19.

Neurological System and COVID-19

Significantly less literature is available about the effects of COVID-19 on the neurological system. Neurological signs and symptoms are divided into three clinical presentations as a result of SARS-CoV-2 :

1. The central nervous system includes acute cerebrovascular disease, epilepsy, dizziness, headache and disturbance of consciousness;
2. The peripheral nervous system includes decreased smell, appetite, taste and neuralgia;
3. Skeletal muscle injury.

Mao et al., in their study of 214 COVID-19 cases, 78 individuals (36.4%) showed neurological symptoms (Mao et al., 2019). Severe COVID-19 patients develop impaired consciousness, acute cerebrovascular disease and skeletal muscle injury (Mao et al., 2019; Herman et al., 2020).

Psychological Disorders and COVID-19

As the rate of transmission of the virus has increased, it becomes a threat to humans as there is a spread of negative emotions in the general public (Zhou, 2020). It has been reported that COVID-19 out-break has caused fear and anxiety in normal people (Yao et al., 2020; Park and Park, 2020). The negative effects of quarantine are numerous, which can be felt in individuals for months or years (Creanga et al., 2010). Therefore the authorities are commended for keeping a short quarantine period and also educating people. As health-care workers serve as front-line warriors, special attention should be provided with these people to decrease the chances of negative mental and psychosocial impact during this out-break. Limited literature exists regarding the effect of COVID-19 on mental health.

Female and Male Reproductive System and COVID-19

Wong et al. observed that there was a higher risk of adverse perinatal outcomes and obstetric complications in pregnant women compared to non-pregnant women (Wong et al., 2003). A study of 10 pregnant SARS-infected patients reported that COVID-19 was associated with preterm birth, spontaneous abortion and maternal death (Wang et al., 2020b). Yet, no proven evidence of COVID-19 affecting male reproductive system has found, but it can cause orchitis, spermatogenic tubule destruction or male infertility (Xu et al., 2006).

CONCLUSION

The present review article highlights on control, prevention and management of complications associated with COVID-19 patients. This virus affects not only the respiratory system but also gastrointestinal, cardiovascular, urinary, reproductive, hepatocellular or neurological systems. Further studies are required for underlying understanding mechanisms linked with SARS-CoV-2 with another organ system. For the time being, the front-line multidisciplinary team should carefully monitor multi-organ functions for the survival of COVID-19 individual.

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Conflict of Interest

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