ISSN 2379-4046

EMERGENCY MEDICINE
OpenJournal

Openventio
PUBLISHERS

Retrospective Study

Extra-Pulmonary Manifestations of Coronavirus Disease 2019: A Multi System Disease

Vijayasree Biruduraju, DEM, MEM; Ankita R. Chawla, MEM, FACEE, FICM, PGCPHM, MBA*

Department of Emergency Medicine, Star Hospitals, Banjara Hills, Hyderabad, Telangana State, India

Corresponding author
Ankita R. Chawla, MEM, FACEE, FICM, PGCPHM, MBA
Consultant and Head, Department of Emergency Medicine, Star Hospitals, Banjara Hills, Hyderabad, Telangana State, India; E-mail: ankitarchawla@gmail.com

Article information
Received: March 4th, 2021; **Revised:** July 30th, 2021; **Accepted:** July 30th, 2021; **Published:** July 30th, 2021

Cite this article
Biruduraju V, Chawla AR. Extra-pulmonary manifestations of coronavirus disease 2019: A multi system disease. *Emerg Med Open J.* 2021; 7(1): 14-20.
doi: 10.17140/EMOJ-7-161

ABSTRACT

Introduction
The outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV- 2), has been recently declared a pandemic by the World Health Organization. Apart from acute respiratory manifestations, SARS-CoV-2 may also adversely affect other organ systems. To date, however, there is a very limited understanding of the manifestations and management of COVID-19 related conditions outside of the pulmonary system. This study provides an overview of the current literature about the extra pulmonary manifestations of COVID-19 that may affect the renal, cardiovascular, gastrointestinal, hematological, hematopoietic, neurological, or reproductive systems. This study also describes the current understanding of the extra pulmonary manifestations caused by COVID-19 to improve the management and prognosis of patients with COVID-19.

Materials and Methods
A total number of 200 hospitalized patients with COVID-19 disease were retrospectively evaluated for extra-pulmonary manifestations findings or complications. These patients had undergone various imaging studies, blood examinations during the course of hospital stay. The data reviewed using the institutional PACS, database system over a period of four months (August to November 2020).

Results
Among the 200 patients (males and females), 175 of them had extra-pulmonary complications. Various extra-pulmonary findings such as acute kidney injury, renal failure, cytokinase strome, acute myocardial injury, congestive cardiac failure, pulmonary thromboembolism, gastrointestinal, neurological complications were observed.

Inclusion and Exclusion Criteria
All retrospective clinical studies, case series, and case reports with data on extra-pulmonary manifestations in COVID-19 that were published from the end of December 2019 till the end of February 2021 were included. Studies that did not mention extra-pulmonary manifestations were excluded.

Literature Search
The review was based on publications available on PubMed and data collected by the World Health Organization (WHO). Search terms used were 'novel coronavirus 2019 (2019-nCoV)', 'SARS- CoV-2', or 'COVID-19' combined with 'asymptomatic', 'gastrointestinal', 'cardiac', 'neurological', 'hepatic', 'hematological', 'renal', 'psychiatric', 'hematological', and 'atypical'.

Keywords
COVID-19; SARS-CoV-2; 2019-nCoV.

INTRODUCTION

The spread of corona virus disease started in 2019 causing severe acute respiratory distress syndrome. It has recently become a global pandemic and public health problem in almost all countries. similar to severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) is SARS) and Middle-East respiratory syndrome (MERS). Coronavirus infections are responsible for severe and potentially life-threatening acute respiratory syndromes.

As of 17th June 2020, a total of more than 8,044,178 confirmed cases and approximately 440,413 total deaths for coronavirus disease 2019 (COVID-19) had been reported globally. In India, a total of more than 354,065 confirmed cases and approximately 11,903 total deaths for COVID-19 had been reported (Figure 1).

SARS-CoV-2 is thought to use cell receptor angiotensin converting enzyme 2 (ACE-2) to gain cellular access in humans. The ACE-2 receptor is highly expressed in lungs, kidneys, gastrointestinal (GI) tract, liver, vascular endothelial cells, and arterial smooth muscle cells. Thus, all these organs and systems with high expression of ACE-2 receptors might be speculated targets for SARS-CoV-2 infection.

The main purpose of this retrospective study is to provide an overview of the current literature on the extrapulmonary manifestations and complications of COVID-19 to improve the management and prognosis of these patients.

COVID- 19: DIAGNOSIS, TREATMENT AND OUTCOMES

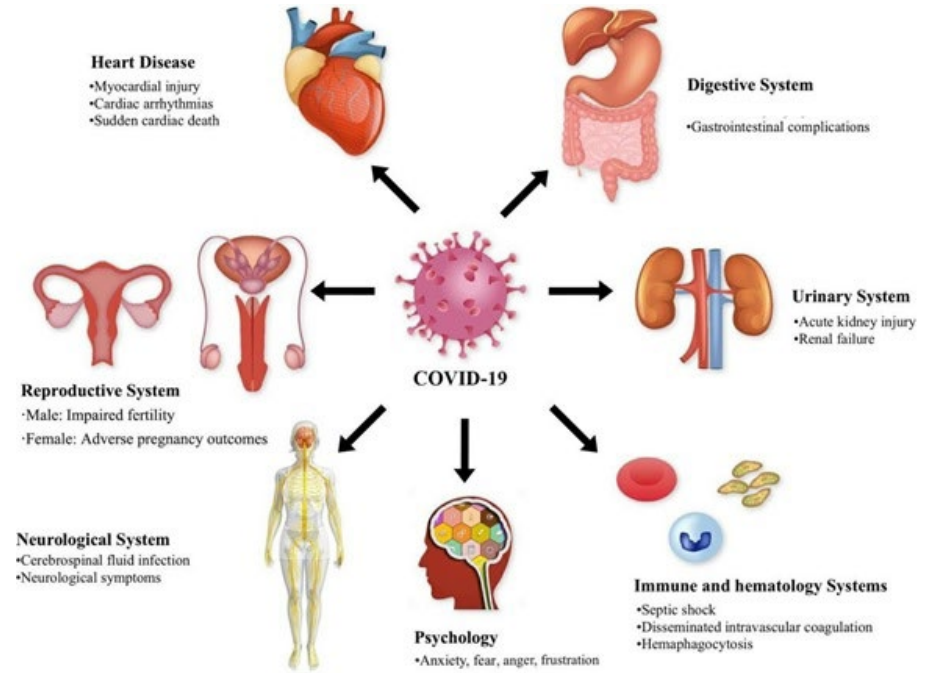
The diagnosis of SARS-CoV-2 infection is currently established with nucleic acid (RNA) testing of suspected patients using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) techniques by oropharyngeal and nasopharyngeal swabs. Initially, a patient was suspected of SARS-CoV-2 infection if he/she had symptoms of cough, fever and/or dyspnea, and a history of travel to endemic regions affected by the SARS-CoV-2 outbreak; or have had close contact(s) with individuals with an a forementioned travel history.

However, due to the ever-increasing number of COVID-19 cases, physicians are now recommending RT-PCR testing only in all patients showing any evidence of viral pneumonia on chest X-ray or computed tomography (CT) (e.g., ground-glass opacities and exudative lesions). In some cases, absence of fever and typical symptoms in the early stages of viral infection hinders the identification of infection in at risk individuals. To date, the treatment options are scarce mostly due to the fact that no targeted therapy for SARS-CoV-2 is available.

The mainstay of COVID-19 management is the patient's isolation and supportive medical care, as recommended by World Health Organization (WHO), which includes the use of antiviral, antibacterial medications, and oxygenation therapy as appropriate. Initially, corticosteroids were not recommended for routine use as their usage may be associated with delayed viral clearance. However, the latest trial data demonstrated that low to moderate dosage of dexamethasone may reduce mortality among critically ill patients, especially for patients requiring ventilation therapy. Patients on mechanical ventilator support or on oxygen support has shown better results by improving in PaO_2/FiO_2 ratio (P/F ratio) and SpO_2 levels in prone/awake prone ventilation. There is currently no drug for COVID-19, but it has been revealed that some commercially available drugs are promising, at least for treating symptoms in early stages. Among them, remdesivir, which can block the activity of RNA-dependent RNA polymerase (RdRp) in old SARS-CoV-2 and Middle-East respiratory syndrome corona virus (MERS-CoV) viruses, has been prescribed to COVID-19 patients in many countries.

The incidence of acute respiratory distress syndrome (ARDS) in COVID-19 patients is reported to be 15 to 30%. Compared to survivors, patients dying with COVID-19 are more likely to be older, have more severe viral infection, be admitted to

Figure 1. *Schematic Figure Showing the Potential Complications of COVID-19 Affecting Organ Systems*



intensive care unit (ICU), and are more likely to have comorbidities or develop ARDS. For survivors, the median recovery time from hospital admission to discharge is approximately 12 to 14 days; the median duration from ICU admission to death for nonsurvivors is approximately 7-days. The discharge criteria for COVID-19 patients after in-hospital treatment varied across the globe, while specific criteria can be quickly evolving.[1-7]

COVID-19: ACUTE KIDNEY INJURY AND RENAL FAILURE

The kidneys are one of the most frequently affected extrapulmonary organs in patients infected with SARS-CoV-2; especially, in those patients who are severely ill. Previous studies of patients affected by the 2013 SARS outbreak have shown that kidney damage is mainly characterized by tubular injury and increased serum creatinine and urea nitrogen concentrations. A recent study of 70 patients infected with SARS-CoV-2 showed that mild proteinuria was the commonest kidney abnormality in these patients. In addition, nearly 30 of these patients also had elevated urea nitrogen levels and approximately 20 had increased serum creatinine levels. Currently, the occurrence of acute kidney injury (AKI) among patients with COVID-19 is not consistent, ranging from 0.1 to 29%.

These patients had combined proteinuria and hematuria, hematuria alone, elevated serum creatinine, and elevated urea nitrogen levels. The occurrence of AKI in critically ill COVID-19 patients was high, and AKI was also found to be an important risk factor for increased hospital mortality. There are studies that showed that after a post-mortem analysis of patients revealed the presence of severe acute tubular necrosis with accumulation of SARS-CoV-2 nucleocapsid protein antigens. This finding suggests that the SARS-CoV-2 might directly infect kidney tubules.

Although the underlying virologic mechanisms are not completely understood, it is plausible to speculate that there is binding by the virus to the ACE-2 receptor, which is highly expressed in kidney tubules, causing glomerulopathy, acute tubular necrosis, and protein leakage in the Bowman's capsule. However, it is also possible to speculate that AKI could be an epiphenomenon of both respiratory distress syndrome-induced hypoxia and septic shock caused by the SARS-CoV-2. Other studies suggested that the endothelium is affected in the kidneys and is responsible for the proteinuria. SARS-CoV-2 particles in renal endothelial cells may suggest viremia as a possible cause of renal endothelial damage resulting in AKI. More recently, some case studies have reported the occurrence of subclinical AKI as reflected by increased urinary levels of β2-microglobulin, α1-microglobulin, N-acetyl-β-D-glucosaminidase, and retinol binding proteins.

In confirmed COVID-19 cases without prior chronic kidney disease acute kidney injury was seen. In addition, the severity of kidney tubular damage was also greater in severe COVID-19 patients than in less severely affected patients. Based on the available evidence, we can draw the following considerations: (a) AKI is not uncommon in patients with COVID-19, especially in those with severe COVID-19; while AKI often develops in later stages of the viral disease and is understood as an early sign of multiple organ dysfunction; (b) AKI could be related to direct effects of the virus, and to other concomitant virus-related complications, such as hypoxia and shock; (c) the precise incidence of AKI in SARS-CoV-2 infected patients is not known; however, it is reasonable to assume that AKI is more common in critically ill patients than in those with mild COVID-19 disease; and (d) COVID-19 patients with a prior history of chronic kidney disease are more likely to develop AKI; and (e) COVID-19 patients with AKI have a poorer prognosis.

Therefore, it is recommended that physicians who treat COVID-19 patients should be aware of acute changes in patients' kidney function. Volume depletion at hospital admission might be suggestive of subsequent occurrence of AKI, especially when COVID-19 patients are infrequently given prehospital fluid resuscitation. In the absence of targeted treatment strategies for SARS-CoV-2 infection, supportive care is the main strategy in managing COVID-19, for example, lung-protective ventilation may be used to reduce the risk of AKI by limiting ventilator-induced hemodynamic effects and the cytokine burden on the kidneys. In patients with early signs of hyperinflammation and "cytokine storm," possible strategies such as dexamethasone treatment or cytokine removal need to be considered further. However, large clinical trials are needed to test the risks and benefits of rigorous interventions in COVID-19 patients specifically at risk of AKI.[8-14]

COVID-19: HEART DISEASE

Myocardial Injury

Patients had signs of myocardial injury as reflected by increases in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) levels. Also, in a retrospective study of 200 critically ill COVID-19 patients, 50 patients had increased cTnI levels (i.e., >14 pg/mL). There is an estimated 16% of COVID-19 patients without pre-existing or known ischemic heart disease had elevated troponin levels.

The rise in cTnI levels together with proinflammatory markers, such as interleukin-6, lactate dehydrogenase (LDH), and D-dimer, might be indicative of cytokine storm or secondary hemophagocytic lymphohistiocytosis, in addition to isolated myocardial injury. However, based on preliminary data, the probability of fulminant myocarditis and cardiogenic shock is low. Some investigators have also suggested a potential mechanism of myocardial injury due to COVID-19-induced cytokine storm that is mediated by a mixed T-helper cell response in combination to hypoxia-induced excess of intracellular calcium causing cardiac myocyte cell death.

Although, it is uncertain whether SARS-CoV-2 may directly damage myocardial tissue and induce a major cardiovascular event, it is currently recommended that physicians should regularly monitor plasma cTnI and NT-proBNP levels in all COVID-19 patients. However, longer-term follow-up studies of cardiac function parameters of these infected patients are needed.[15]

Cardiac Arrhythmias

In addition to myocardial injury, arrhythmia is another facet of the

cardiac involvement in COVID-19 that ranges from tachycardia to bradycardia and asystole. A study of 200 COVID-19 patients showed that most of these patients had some type of arrhythmia, including sinus tachycardia unrelated to fever, bradycardia, and few patients with paroxysmal atrial fibrillation, ventricular tachycardia and supra ventricular tachycardia. Critically ill COVID-19 patients/nonsurvivors had increased blood pressure values, which might contribute to arrhythmia, potentially explaining the pathological activity of SARS-CoV-2 infection.

However, due to the retrospective nature of these data, it is difficult to explain whether the cause of this observed hypertension is due to physiological reactions to the viral illness, or it is a consequence of virus-induced derangements in ACE-2 expression. Overall, this suggests that arrhythmia may be an important complication among patients with SARS-CoV-2 infection. However, due to the very limited data available, arrhythmia type and corresponding electrocardiogram changes in patients with SARS-CoV-2 infection remain poorly defined.

Therefore, these findings suggest that especially in patients with severe COVID-19, routine electrocardiogram monitoring is needed to closely monitor patients for paroxysmal tachycardias and electrocardiography that do not match the patient's condition.

Sudden Cardiac Death

In a study involving 200 SARS-CoV-2 infected patients there were deaths due to sudden cardiac arrest among patients without a prior history of ischemic heart disease. These results suggest that the cause of death might be caused mainly by an imbalance of pulmonary ventilation-perfusion ratio and a decrease in capacity of the pulmonary vasculature. While acute myocarditis might contribute to heart failure and depressed left ventricular ejection fraction due to COVID-19, majority of COVID-19 patients with uncomplicated lymphocytic myocarditis had normal cardiac function.

The pathophysiologic factors possibly involved include occlusion of microvasculature and reduction of the amount of functional residual gas, which could lead to increased resistance of pulmonary vessels, resulting in subsequent pulmonary hypertension and corpulmonale. Cardiac dysfunction due to direct virus infection or systemic inflammation might potentially cause coronary microcirculation disruption and myocardial ischemic sequalae, but the relationship between SARS-CoV-2 infection and heart failure remains unclear. Although there is limited understanding of the pathophysiology of sudden cardiac death in patients infected with SARS-CoV-2, it is important to be aware of this condition to try and prevent cardiac arrest (especially in patients with a previous history of ischemic heart disease or multiple cardiovascular risk factors), so that appropriate measures may be taken to reduce the risk of death.[11-13,15-22]

COVID-19: LIVER DYSFUNCTION AND OTHER GI COMPLICATIONS

Liver Dysfunction

The circulating levels of liver function tests, such as serum glutamic oxaloacetic transaminase (sgot), serum glutamic pyruvic transaminase (sgpt), bilirubin, LDH, and prothrombin time (PT), were significantly higher in COVID-19 patients admitted to ICU than in non-ICU patients. Similar results were also seen in critically ill COVID-19 patients without pre-existing chronic liver diseases, who were admitted to ICU. Also, mild to moderate elevations of serum liver enzymes (mostly increased serum transaminases) were reported. In clinical practice, the liver function test results of patients with mild SARS- CoV-2 infection were relatively unremarkable and patients with severe (but noncritically ill) SARS-CoV-2 infection had mild to moderate sgot, sgpt, LDH levels. Jaundice is less common and was observed only in a few SARS-CoV-2 infected patients, who died during hospital admission with multi organ failure; however, deranged PT was also observed amongst patients who subsequently died. Liver failure has also been observed with other organ failures in nonsurvivors of SARS-CoV-2 infection and thus, it is not easy at this time to quantify the excess risk of death attributable to liver failure alone.

The current data suggests that liver injury occurs more frequently among critically ill patients with COVID-19, who have other coexisting causes of liver damage, such as the use of potentially hepatotoxic therapies and the coexistence of systemic inflammatory response, lung injury-causing hypoxia, and multiple organ dysfunction. Currently, there is little information on the effect of SARS-CoV-2 infection on GI functions. A retrospective study showed that GI symptoms were generally uncommon among SARS-CoV-2 infected patients who had nausea, vomiting and diarrhea. However, among SARS-CoV-2 infected patients who had developed atypical clinical presentations, a substantial portion of these patients had GI symptoms. Recently, negative fecal nucleic acid testing has been also added to the criteria for hospital discharge in COVID-19 patients.[10,12,13,17]

COVID-19: IMMUNOLOGICAL AND HEMATOLOGICAL COMPLICATIONS

Blood Leukocyte Abnormalities

At hospital admission, SARS-CoV-2 infected patients often have leucopenia, lymphopenia, or elevated levels of peripheral neutrophils. In a 14-day comparison of the biochemical profiles of survivors and nonsurvivors with SARS-CoV-2 infection, most of these patients had lymphopenia, but nonsurvivors developed more severe lymphopenia from day 7 to 14 with a lymphocyte count ranging from 0.5 to 0.3×10^9/L. In contrast, higher white blood cell (ranging from 4.2 to 15.0×10^9/L) and neutrophil counts from days 5 to 14, were reported in nonsurvivors compared to survivors.

Septic Shock and Disseminated Intravascular Coagulation

Multiple organ failure due to diffuse microvascular damage is an important cause of death in critically ill SARS-CoV-2 infected patients and is associated with cytokine release syndrome caused by an acute immune response. In a retrospective study of confirmed COVID-19 cases, the risk of septic shock was nearly 30-fold higher among ICU patients than among non-ICU patients. COVID-19 patients reported that septic shock was observed although not

severely affected and were severely ill; disseminated intravascular coagulation (DIC) was also observed in one nonsurvivors. It is also important to note that the occurrence of septic shock among nonsurvivors often led to multiple organ dysfunction syndrome and death.

At present, the occurrence of septic shock, organ dysfunction, or organ failure among SARS-CoV-2 infected patients appears to be higher than that of DIC. However, a retrospective study of deaths in SARS-CoV-2 infected patients recently reported that patients who died had DIC with a median time of 4 days from admission to presentation of DIC. These data suggest that acute coagulation disorders and DIC in severe cases of SARS-CoV-2 infection are common, and acute coagulation disorders and DIC are important risk factors for increased in-hospital mortality. Therefore, special attention should be paid to early diagnosis and treatment of these acute hematological conditions to improve patient survival.[14,17-19,22-24]

Management for Coagulopathy

Patients with moderate and severe COVID-19 illness are more likely to have a hyper-coagulable state placing them at high-risk for venous thromboembolism (VTE) than end stage DIC. Patients with a hypercoagulable state may exhibit normal or increased platelet count with a fairly normal activated partial thromboplastin time, a dramatic increase in fibrinogen and D-dimer levels, increased levels of C-reactive protein, protein C, factor VII, and von Willebrand factor, while antithrombin levels may be marginally decreased. VTE occurs in severe COVID-19 patients, while thrombotic complications occur in those requiring ICU. Elevations in D-dimer levels may be indicative of thrombosis and can be used as a predictor for VTE. The use of anticoagulants is associated with decreased mortality among severe COVID-19 patients. In a study of severe COVID-19 patients who used low molecular weight heparin (LMWH) for 7-days or longer, the 28-day mortality of heparin users was significantly lower, compared to non-users, especially amongst those with sepsi induced coagulopathy.

As per recommendations by the American College of Chest Physicians, in the absence of contra- indications, thrombotic prophylaxis is recommended in all moderate and severe COVID-19 patients, while LMWH is preferred over direct oral anticoagulants. In patients requiring ICU admission, therapeutic treatment of LMWH can be effective in reducing in-hospital mortality. There is a mixed recommendation for prolonged use of thromboprophylaxis after hospital discharge, although it is generally recommended in COVID-19 patients with proximal deep venous thrombosis or VTE (continued therapy for a minimum of 3-months). In those with recurrent VTE despite anticoagulation by LMWH, increasing the dosage is suggested.

COVID-19: NEUROLOGICAL COMPLICATIONS

Neurological Symptoms

Little information is available on the possible adverse effects of SARS-CoV-2 infection on the neurological system. The neurological signs and symptoms caused by the SARS-CoV-2 infection can be divided into three main clinical presentations: (a) central nervous system presentations, such as headache, dizziness, disturbance of consciousness, acute cerebrovascular disease, and epilepsy; (b) peripheral nervous system presentations, such as neuralgia and decreased taste, smell, and appetite; and (c) skeletal muscle injury presentations. A retrospective study of patients diagnosed with SARS-CoV-2 had neurological symptoms, accounting for 2.5% all confirmed COVID-19 patients. Patients with severe COVID-19 were more likely to develop neurologic symptoms, such as acute cerebrovascular disease, loss of smell and taste, giddiness, headache and seizures.[25]

COVID-19: PSYCHOLOGICAL DISORDERS

The common psychological effects of quarantine during infectious outbreak have been well-documented such as anger, stress, confusion and anxiety. During quarantine, alcohol abuse or dependency symptoms, depression, anxiety have been common symptoms. Post-quarantine, increased avoidance behaviors have been described to be common among healthcare workers.

Factors Influencing Psychological Disorders

Several factors may induce psychological disorders during quarantine. History of psychiatric illness was found to be closely associated with anxiety and anger issues for patients who were subject to release from quarantine. Interestingly, healthcare workers reported more severe symptoms of post-traumatic stress when compared to others (non-healthcare workers) after being quarantined. After quarantine, healthcare workers also felt increased levels of stigmatization, having had more avoidance behaviors, reported higher lost in income and felt more negatively affected psychologically.Among the various psychological effects include increased worry, anger, fear, frustration, guilt, isolation, loneliness, and nervousness. Other factors attributable to adverse psychological effects include fear of infection (directed at self-condition or transmitting to others), adverse reactions to confinement or isolation, lack of sufficient information from authorities, long work hours, hydration and fear of financial loss.[26-30]

Recommendations for the Current Infectious Outbreak

With the virus worrisome transmission rate and the threat to human health, negative emotions are spreading among the general public, and it is expected to be on the same trajectory similar to past experiences. For normal individuals, the outbreak of COVID-19 has been reported to cause anxiety and fear. It is also advisable for authorities to properly educate others on the necessary duration length, to keep a clear communication channel between those that are quarantined and actively address those experiencing psychological symptoms. Healthcare workers are often quarantined as they serve on the frontline, and thus, special attention should be paid to this group of individuals to reduce the negative psychosocial and mental impact during, and after, the infectious outbreak.[7]

COVID-19: PREGNANCY AND MALE REPRODUCTIVE COMPLICATIONS

Prior studies have shown that pregnant women with viral respiratory diseases have a higher-risk of obstetric complications and adverse perinatal outcomes compared to non-pregnant women, possibly due to concomitant changes in the immune response. According to a previous report on pregnant SARS-infected patients, COVID-19 may be associated with poorer perinatal outcomes, including spontaneous abortion, maternal death, and preterm birth.[31,32]

Until now there are no reports of the effects of COVID-19 on the male reproductive system. Previous studies have reported that SARS virus infection may cause orchitis, spermatogenic tubule destruction, or male infertility; indeed, viral orchitis can severely damage testicular spermatogenic function, causing oligospermia and even azoospermia. Whether the COVID-19 may also have similar adverse effects on the male reproductive system remains currently not known.

COVID-19: CUTANEOUS PRESENTATION

The patterns of cutaneous manifestations associated with SARS-CoV-2 infection could be classified into four categories: exanthema (varicella-like, papulo-vesicular and morbilliform rash), vascular (chilblain-like, purpuric/petechial and livedoid lesions), urticarial and acro-papular eruption. Lastly, other skin manifestations to be considered are the cutaneous adverse reactions to the drugs prescribed for the treatment of COVID-19. Whether SARS-CoV-2 infection can directly cause a worsening of chronic inflammatory diseases such as psoriasis or atopic dermatitis remains to be determined.[33-35]

CONCLUSION

The prevention and control of the COVID-19 outbreak is well-underway around the world and efforts must continue to target this virus. This retrospective study that more careful surveillance and management of extrapulmonary complications of COVID-19 patients are needed. Indeed, this viral infection appears to adversely affect not only the respiratory system but also several other organ systems, including the renal, cardiovascular, GI, and neurological systems. The COVID-19 pandemic has also caused tremendous anxiety and other psychological effects both in suspected and confirmed cases with SARS-CoV-2 infection, while it remains to be clarified if it also causes negative psychological effects on those who have been released from quarantine. However, further research is needed to better understand the underlying mechanisms linking SARS-CoV-2 with the occurrence of multiple extrapulmonary manifestations. In the meantime, we believe that the frontline team should carefully monitor multiorgan functions, which may also be the key to the survival of infected patients. We suggest an improved knowledge of COVID-19 related extrapulmonary manifestations will help to develop better medical management strategies for these patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed.* 2020; 91(1): 157-160. doi: 10.23750/abm.v91i1.9397

2. World Health Organizaion (WHO). Report of the WHO-China joint mission on corona virus disease 2019 (COVID-19). 2020. Web site. https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19). Accessed March 3, 2021.

3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* 2020; 20(5): 533-534. doi: 10.1016/S1473-3099(20)30120-1

4. Guan WJ, Ni Z-y, Hu Y, Liang W, He J-x, Liu L, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020; 382: 1708-1720. doi: 10.1056/NEJMoa2002032

5. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med.* 2020; 382: 2372-2374. doi: 10.1056/NEJMc2010419 Shi S,

6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395: 497-506. doi: 10.1016/S0140-6736(20)30183-5

7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet.* 2020; 395: 507-513. doi: 10.1016/S0140-6736(20)30211-7

8. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med.* 2020; 382: 1653-1659. doi: 10.1056/NEJMsr2005760

9. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. *J Am Soc Nephrol.* 2006; 17: 3067-3075. doi: 10.1681/ASN.2006050423

10. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: A peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther.* 2010; 128: 119-128. doi: 10.1016/j.pharmthera.2010.06.003

11. Strawn WB, Ferrario CM, Tallant EA. Angiotensin-(1-7) reduces smooth muscle growth after vascular injury. *Hypertension.* 1999; 33: 207-211. doi: 10.1161/01.hyp.33.1.207

12. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chonget M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *J Am Med Assoc.* 2020; 323: 1612-1614. doi: 10.1001/jama.2020.4326

13. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region — case series. *N Engl J Med.* 2020; 382: 2012-2022. doi: 10.1056/NEJMoa2004500

14. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta.* 2020; 506: 145- 148. doi: 10.1016/j.cca.2020.03.022

15. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-segment elevation in patients with Covid-19 — a case series. *N Engl J Med.* 2020; 382(25): 2478-2480. doi: 10.1056/NEJMc2009020

16. Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020; 5(7): 802-810. doi: 10.1001/jamacardio.2020.0950

17. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis.* 2020; 71(15): 762-768. doi: 10.1093/cid/ciaa248

18. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020; 135: 2033-2040. doi: 10.1182/blood.2020006000

19. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020; 18: 844-847. doi: 10.1111/jth.14768

20. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.* 2020; 18: 1421-1424. doi: 10.1111/jth.14830

21. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020; 191: 145-147. doi: 10.1016/j.thromres.2020.04.013

22. Robson SC, Shephard EG, Kirsch RE. Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1β, IL-6 and plasminogen activator inhibitors from monocytes in vitro. *Br J Haematol.* 1994; 86: 322-326. doi: 10.1111/j.1365-2141.1994.tb04733.x

23. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol.* 2020; 95: 834-847. doi: 10.1002/ajh.25829

24. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol.* 2020; 95(6): E131-E134. doi: 10.1002/ajh.25774

25. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* 2020; 382(23): 2268-2270. doi: 10.1056/NEJMc2008597

26. Sher L. COVID-19, anxiety, sleep disturbances and suicide. *Sleep Med.* 2020; 70: 124. doi: 10.1016/j.sleep.2020.04.019

27. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. *Lancet Psychiatry.* 2020; 7: 389-390. doi: 10.1016/S2215-0366(20)30141-3

28. Rajkumar RP. COVID-19 and mental health: A review of the existing literature. *Asian J Psychiatry.* 2020; 52: 102066. doi: 10.1016/j.ajp.2020.102066

29. Gunnell D, Appleby L, Arensman E, Hawton K, John A, Kapur N, et al. Suicide risk and prevention during the COVID-19 pandemic. *Lancet Psychiatry.* 2020; 7: 468-471. doi: 10.1016/S2215-0366(20)30171-1

30. World Health Organization (WHO). Occupational safety and health in public health emergencies: A manual for protecting health workers and responders. Web sites. https://www.who.int/publications/i/item/9789241514347. Accessed on 21 July 2020.

31. Wong SF, Chow KM, Leung TN. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol.* 2004; 191: 292-297. doi: 10.1016/j.ajog.2003.11.019

32. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: Report of two cases and review of the literature. *J Microbiol Immunol Infect.* 2019; 52: 501-503. doi: 10.1016/j.jmii.2018.04.005

33. Henry D, Ackerman M, Sancelme E, Finon A, Esteve E. Urticarial eruption in COVID-19 infection. *J Eur Acad Dermatol Venereol.* 2020; 34(6): e244-e245. doi: 10.1111/jdv.16472

34. Estebanez A, Perez-Santiago L, Silva E, Guillen-Climent S, García-Vázquez A, Ramón MD. Cutaneous manifestations in COVID-19: A new contribution. *J Eur Acad Dermatol Venereol.* 2020 doi: 10.1111/jdv.16474

35. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients. *J Am Acad Dermatol.* 2020; 34(6): e250-e251. doi: 10.1016/j.jaad.2020.04.044