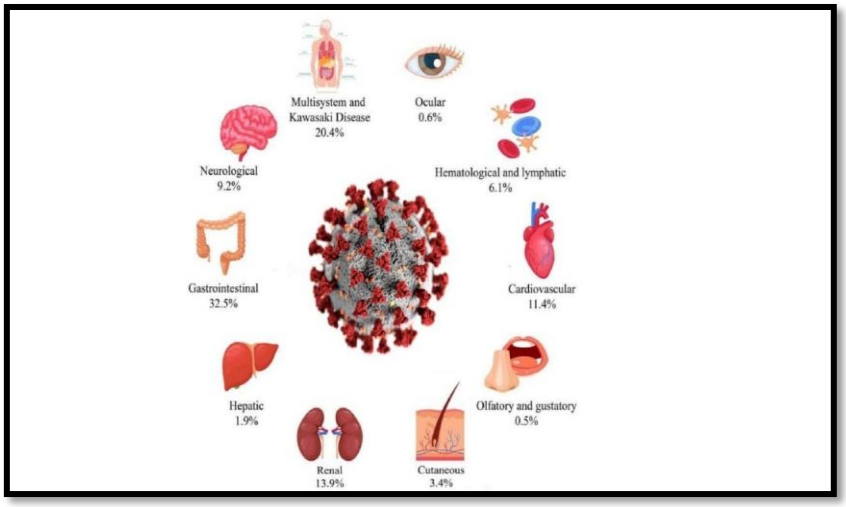
Ministery of Higher Education
And Scientific Research
University of Diyala
College of Medicine

Extrapulmonary Manifestation in COVID-19



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ABSTRACT

Although COVID-19 is maximum widely known for causing huge respiration pathology, it could additionally bring about numerous extrapulmonary manifestations. These situations consist of thrombotic complications, myocardial disorder and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications. Given that ACE2, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in multiple extrapulmonary tissues, direct viral tissue harm is a attainable mechanism of injury. In addition, endothelial harm and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-associated pathways may all make a contribution to those extrapulmonary manifestations of COVID-19. Here we overview the extrapulmonary organ-specific pathophysiology, shows and control concerns for sufferers with COVID-19 to aid clinicians and scientists in spotting and tracking the spectrum of manifestations, and in growing studies priorities and healing techniques for all organ systems involved (1)

INTRODUCTION

In December 2019, the SARS-CoV-2 epidemic emerged in Wuhan and quickly covered the entire world, becoming a pandemic. This new viral infection may lead to severe viral pneumonia in some cases, causing respiratory failure, multiple organ dysfunction due to sepsis, septic shock, and consequently death. The first stage of SARS-CoV-2 infection is the entry of the virus into the host cells. This process occurs, at least in part, by the interaction between the virus' spiny protein (S) and the receptor for angiotensin-converting enzyme 2 (ACE2). In theory, any organ with cells expressing angiotensin converting enzyme 2 is likely to be susceptible to SARS-CoV-2 infection. Besides direct viral infection, indirect mechanisms such as thrombophilia, immune system dysfunction, irregularity of the renin and angiotensin system, and therapeutic effects lead to impairment of multiple organ function. These manifestations must be carefully considered in clinical settings in diagnosing and monitoring manifestations to restrict further person-to-person transmission and expand treatment strategies for various system complications (1) (2)

SARS-CoV-2 PATHOGENESIS

Direct mechanism of viral infection:

The first step in infection is the introduction of the virus. The SARS-CoV-2 pathogen subunit binds to the receptor in the host cell. Spike protein includes two subunits, S1 and S2. S1 defines the host and cellular swelling and facilitates virus attachment to target cells. Also, the serine protease membrane protease, serine 2 (TMPRSS2) prepares SARS-CoV-2-S for entry. Moreover, according to a study by Wang et al., SARS-CoV-2-S binds to differentiation group (CD) 147 and is a trans-membrane protein of the immunoglobulin family. Therefore, the immune system itself could be an entry point for SARS-CoV-2.. These targets act on the initial phase of the SARS-CoV-2 infection (1)(2)

Indirect mechanisms of viral infection:

Besides the direct invasion of SARS-CoV-2 into the host cells, there are some indirect effects of the viral infection that lead to multiple organ failure, including thrombophilia, dysfunctional immune response, and dysregulation of the renin-angiotensin-aldosterone system (RAAS).

Dysfunction of the immune response:

The ensuing cytokine storm triggers a violent inflammatory immune response by high secretion of cytokines and chemokines, such as interleukin (IL) -1, IL-6, IL-8, IL-17, IL-17, and chronic lymphocytic leukemia (CLL) 2 , Tumor necrosis factor alpha (TNF-), agranulocyte colony stimulating factor (G-CSF), gamma-antiviral protein (IP) -10, single-cell chemical attraction protein 1 (MCP1), and flammable protein (MIP). In the serum of COVID-19 patients requiring intensive care unit (ICU) admission, there is a high concentration of G-CSF, C-X-C ligand 10, MCP1, MIP1A, and TNF-α. Moreover, these cytokines are responsible for attracting neutrophils to sites of inflammation. Increased cytokine levels, particularly IL-6, appear to be associated with a worsening of patients' condition (3) (4) (5).

Thromboinflammation:

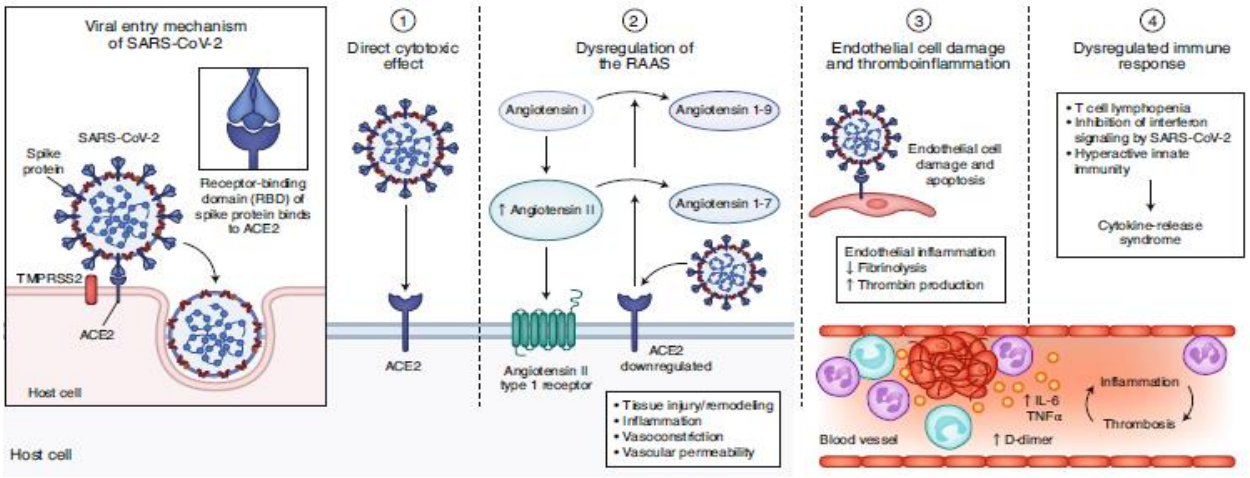
Angiotensin-converting enzyme 2 expression has been demonstrated in atrial and venous endothelium of different organs.[6] Therefore, the invasion of SARS-CoV-2 to these cells results in infection-mediated endothelial injury which triggers thrombin production, inhibits fibrinolysis, and activates complement pathways.

Dysregulation of RAAS:

Dysregulation of RAAS due to increased angiotensin II and decreased ACE2 can lead to a harmful inflammatory response. The abnormal functions of RAAS lead to another pathophysiological mechanism of SARS-CoV-2 infection–related, tissue damage. Angiotensin-converting enzyme 2 acts as a regulator of the RAAS pathway. Angiotensin-converting enzyme 2 also cleaves angiotensin I into inactive angiotensin 1–9 and cleaves angiotensin II into angiotensin 1–7, which has vasodilator, antiproliferative, and antifibrotic properties (6)

Cardiovascular manifestations

Epidemiology and clinical presentation: SARS-CoV-2 can cause both direct cardiovascular sequelae and indirect cardiovascular sequelae, including myocardial injury, acute coronary syndromes (ACS), cardiomyopathy, acute cor pulmonale, arrhythmias, and cardiogenic shock, as well as the aforementioned thrombotic complications105,106. Myocardial injury, with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit, occurred in 20–30% of



hospitalized patients with COVID-19, with higher rates (55%) among those with pre-existing cardiovascular disease3,107. A greater frequency and magnitude of troponin elevations in

hospitalized patients has been associated with more-severe disease and worse outcomes3,107. Biventricular cardiomyopathy has been reported in 7–33% of critically ill patients with COVID-19

Cardiac arrhythmias,including new-onset atrial fibrillation, heart block, and ventricular arrhythmias, are also prevalent, occurring in 17% of hospitalized patients and 44% of patients in the ICU setting in a study of 138 patients from Wuhan, China. In a multicenter NewYork City cohort, 6% of 4,250 patients with COVID-19 had prolongedQTc (corrected QT; >500 ms) at the time of admission

Reports from Lombardi, Italy, show an increase of nearly 60% in the rate of out-of-hospital cardiac arrest during the 2020 COVID-19 pandemic relative to a similar time period in 2019, which suggests the etiology to be either COVID-19 or other untreated pathology due to patients' reluctance to seek care(7)

Pathophysiology:

The pathophysiology underlying cardiovascular manifestations is probably multifactorial. ACE2 has high expression in cardiovascular tissue, including cardiac myocytes, fibroblasts, endothelial cells, and smooth-muscle cells in support of a possible mechanism of direct viral injury. Myocarditis is a presumedetiology of cardiac dysfunction, and the development of myocarditis may relate to viral load. While isolation of the virus from myocardial tissue has been reported in a few autopsy studies other pathological reports have described inflammatory infiltrates without myocardial evidence of SARS-CoV-2

Additionally ,the finding of direct viral infection of the endothelium and accompanying inflammation, as reported in a patient with circulatory failure and MI, lends credence to the possibility of virus-mediated endothelial-cell damage as an underlying mechanism

Systemic inflammatory response syndrome (cytokine storm) is another putative mechanism of myocardial injury17. Furthermore, patients with pre-existing cardiovascular disease may have higher levels of ACE2, which would potentially predispose them to more-severe COVID-19

Other potential etiologies of myocardial damage not specificto COVID-19 include severe ischemia or MI in patients with pre-existing coronary artery disease, stress-mediated myocardial

dysfunction, tachycardia-induced cardiomyopathy, and myocardial stunning after resuscitation or prolonged hypotension(7)(8)

Management considerations:

Whether upregulation of ACE2 by ACE inhibitors or angiotensin-receptor blockers (ARBs) is lung protective or increases susceptibility to infection with SARS-CoV-2has been intensely debated within the cardiovascular community. This has implications for patients with hypertension ,heart failure, and/or diabetes, who are over represented among critically ill patients with COVID-19. There is no evidence to support an association between the use of ACE inhibitor and ARBs and more-severe disease; some large studies indicate no relationship between the use of these agents and the severity of COVID-19

Additionally, point-of-care echocardiography may be used to assess regional wall-motion abnormalities to guide decisions about cardiac catheterization. Less-urgent or elective procedures should be deferred in an effort to minimize the risk of viral transmission(8)(9)

DIGESTIVE SYSTEM MANIFESTATIONS

- **Gastrointestinal (GI) tract**

Prevalence and incidence:

Gastrointestinal symptoms may be the main evidence of COVID-19 in a certain subgroup of COVID-19 cases

According to the collected data from COVID-19 patients with or without GI symptoms, it has been revealed that GI symptoms during disease progression widely appear

The latest data from Wuhan showed that up to 79% of COVID-19 patients manifest GI symptoms such as diarrhea, loss of appetite, nausea, vomiting, abdominal pain, and GI bleeding during the onset of the disease and subsequent hospitalization. It is concluded that anorexia is the most frequent digestive symptom presented by adults (39.9–50.2%), whereas diarrhea is the most common symptom in adult patients and pediatric patients combined (2–49.5%), whereas vomiting is more common in children ,3.6–15.9% of adult patients and 6.5–66.7% of pediatric patients manifest vomiting. Nausea is present in 1–29.4% of cases and GI bleeding in 4–13.7% of patients. Also, abdominal pain (2.2–6.0%) is more frequent in severe cases

According to the Chinese population study by Tian et al., anorexia was the most frequent digestive symptom in adults (30–50%), whereas the prevalence of diarrhea ranged from 2% to 50%. Some adults also presented vomiting, whereas GI bleeding and abdominal pain were found in more severely ill patients(11)

Pathophysiology:

The single-cell RNA-sequencing data obtained from the digestive system explain the presence of ACE2 expressing cells in the esophagus, ileum, stomach, and liver

Angiotensin-converting enzyme 2 staining is rarely seen in esophageal mucosa because the esophageal epithelium is mainly made of squamous epithelial cells, which express less ACE2 than glandular epithelial cells

Accordingly, it is demonstrated that ACE2 is highly expressed in the small intestine, particularly in proximal and distal enterocytes. Because enterocytes are directly exposed to the food and pathogens, they are highly susceptible to SARS-CoV-2 infection

It has been reported that ACE2 controls intestinal inflammation and diarrhea; therefore, the interaction between SARS-CoV-2 and ACE2 receptor might disrupt the ACE2 function, leading to diarrhea and other GI symptoms

However, the active viral replication and induction of type III interferons and inflammatory mediators in human enteroids might contribute to the development of GI symptoms in patients

- ***The liver and gallbladder:***

Prevalence and incidence:

- Regarding the research on 417 COVID-19 patients, 76.3% had abnormal liver tests and 21.5% had a liver injury during hospitalization Studies have shown abnormal levels of alanine aminotransferase, aspartate aminotransferase (AST), and bilirubin in 14.8–53% of COVID-19 patients. Elevated levels of gamma-glutamyl transferase (GGT) and alkaline phosphatase have been observed in these patients
- However, even in severe cases, significant liver injury is uncommon and liver dysfunction is mild, with only microvesicular steatosis in biopsy

- It is known that elevated levels of aminotransferases are not specific to liver injuries. These elevations can result from the myositis induced by COVID-19 (11)

Pathophysiology : COVID-19 can induce liver damage through direct and indirect interactions

Direct damage:

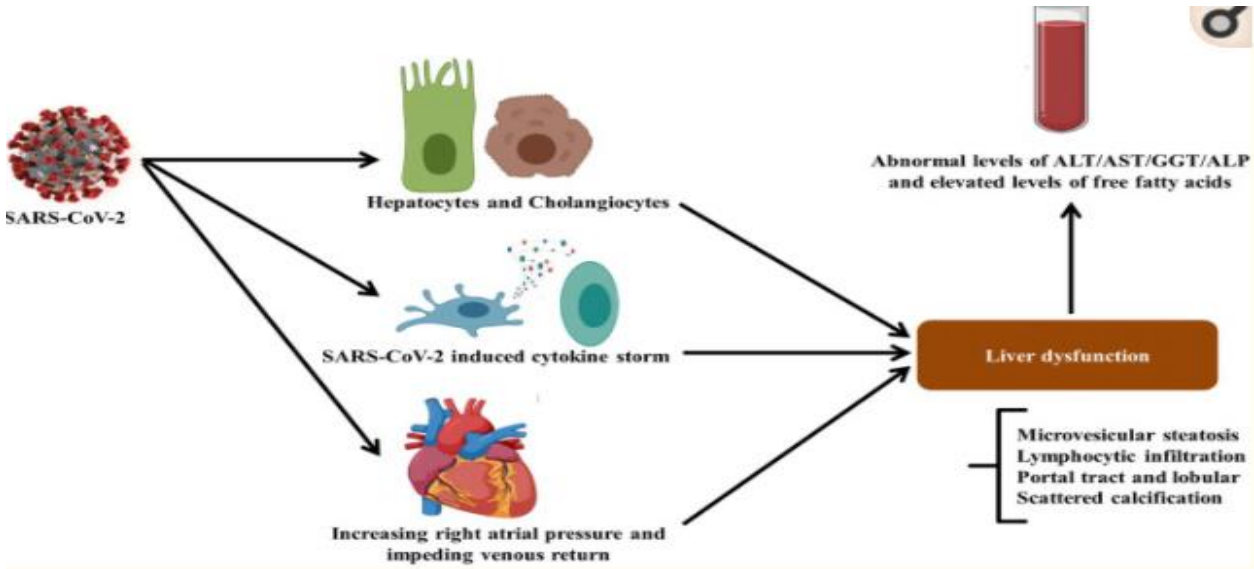
According to the single-cell–sequencing analysis, ACE2 receptor expression in liver tissue is only approximately 0.3%, and the specific expression of ACE2 in epithelial cells of the bile duct is 20 times higher than that in hepatocytes. Regarding the low expression of ACE2 by hepatocytes, direct liver damage requires further investigations

*Cytokine storm, hypoxia, and ischemia. :*Following SARS-CoV-2 infection, a large number of immune cells may be overactivated and secrete excessive cytokines, and chemokines such as TNF-α, IFN-γ, IL-6, and IL-8. These immune responses are similar to those of other viral respiratory infections and are related to the intrahepatic cytotoxic T cells and Kupffer cells *which leads to ischemia, hypoxia, ARDS, and systemic inflammatory response syndrome (SIRS). Because of ischemia and hypoxia, lipid accumulation, glycogen consumption, and adenosine triphosphate depletion of hepatocytes can inhibit cell survival signal transduction which rapidly leads to hepatocyte death (12)*

Drug hepatoxicity :

It is considered that hepatotoxicity can be induced following the use of some drugs. Lopinavir and ritonavir can cause abnormal levels of liver enzymes. Likewise, the combination of an overdose of lopinavir and ritonavir activates the endoplasmic reticulum stress pathway in the liver, inhibits the proliferation of hepatocytes, induces apoptosis of hepatocytes through the caspase cascade system, induces inflammatory reactions, and accelerates liver injury due to

aggravating oxidative stress(11)(12)



❖ *The pancreas:*

Prevalence and incidence:

Wang et al. showed that among 52 COVID-19 patients, 17% had a pancreatic injury. In this group, serum markers were mildly elevated (mean serum amylase 115 ± 25 U/L and serum lipase 71 ± 34 U/L). None of the patients had abdominal pain or clinically severe pancreatitis. Liu et al. also suggested 17% incidence of pancreatic injury among 67 severe COVID-19 cases. However, the injury was evident on computerized tomography (CT) scan in only 7.5% cases, mainly as focal pancreatic enlargement or pancreatic ductal dilatation. Incidence of pancreatic injury was low (1.9%) in patients with mild disease(13)

Pathophysiology:

- Studies demonstrate the potential mild pancreatic injury patterns with pneumonia. These injuries might directly be related to the cytopathic effect of local SARS-CoV-2 replication. Moreover, these symptoms indirectly occur because of the harmful immune response induced by the virus or from secondary enzyme abnormalities
- Acute pancreatitis can occur because of drug-induced injury either directly because of use of nonsteroidal anti-inflammatory drugs or glucocorticoids and indirectly through tocilizumab-induced hypertriglyceridemia (14

Renal manifestations

A substantial proportion of patients with severe COVID-19 may show signs of kidney damage

Clinical presentations:

• AKI

• Electrolyte abnormalities (hyperkalemia, hyponatremia, and hypernatremia, among others)

• Proteinuria

• Hematuria

• Metabolic acidosis

• Clotting of extracorporeal circuits used for RRT

COVID-19-specific considerations:

• Evaluate urine analysis and protein-to-creatinine ratio at admission, given the association of proteinuria and hematuria with outcomes

• Consider empiric low-dose systemic anticoagulation during the initiation and day-to-day management of extracorporeal circuits for RRT

• Consider co-localization of patients who require RRT and use shared RRT protocols

• Consider acute peritoneal dialysis in select patients to minimize personnel requirements

Epidemiology and clinical presentation.

Acute kidney injury (AKI) is a frequent complication of COVID-19 and is associated with mortality. In China, the reported incidence of AKI in hospitalized patients with COVID-19 ranged from 0.5% to 29% and occurred within a median of 7–14 days after admission .Studies from the USA have reported much higher rates of AKI. In a study of nearly 5,500 patients admitted with COVID-19 in a New York City hospital system, AKI occurred in 37%, with 14% of the patients requiring dialysis. About one third were diagnosed with AKI within 24 hours of admission in this study(15)

Pathophysiology: Several possible mechanisms specific to SARS-CoV-2 that distinguish this renal abnormality from the more general AKI that accompanies severe illness are noteworthy. First, SARS-CoV-2 may directly infect renal cells, a possibility supported by histopathology findings and the presence of ACE2 receptors.Histopathological findings include prominent acute tubular injury and diffuse erythrocyte aggregation and obstruction in peritubular and glomerular capillary loops. Viral inclusion particles with distinctive spikes in the tubular epithelium and podocytes, and endothelial cells of the glomerular capillary loops, have been visualized by electron microscopy. Second, the demonstration of lymphocytic endothelialitis in the kidney, in addition to viral inclusion particles in glomerular capillary endothelial cells, suggests that microvascular dysfunction is secondary to endothelial damage. Third, similar to severe infection with influenza virus, cytokine storm may have an important role in the immunopathology of AKI. (16)

Management considerations: Urine analysis and protein-to creatinine ratio may be obtained at admission for patients with COVID-19, as proteinuria and hematuria seem to be associated with a more severe clinical course and higher mortality, and this would provide an opportunity for early risk stratification. In patients with suspected or confirmed COVID-19, an emphasis should be placed on optimization of volume status to prevent prerenal AKI, particularly given the high prevalence of AKI at presentation, while avoiding hypervolemia, which may worsen the patient's respiratory status. The Surviving Sepsis guidelines for critical illness in COVID-19 recommend a conservative fluid-resuscitation strategy while acknowledging that the supporting evidence base is weak. A dramatic increase in the need for RRT in critically ill patients may require judicious resource planning, including the use of shared continuous RRT protocols, co-localization of patients, and the utilization of acute peritoneal dialysis in select patients(15)(16)

Neurologic and ophthalmologic manifestations

There is growing evidence of neurologic complications of COVID-19.

Clinical presentations:

• Headache, dizziness

• Anosmia, ageusia, anorexia, myalgias, fatigue

• Stroke

• Encephalopathy, encephalitis, Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalopathy

• Conjunctivitis

- COVID-19-specific considerations

• Continue adherence to established guidelines for acute ischemic stroke, including thrombolysis and thrombectomy209

• Adapt post-acute-care monitoring guidelines for pandemic constraints (most stable patients do not need to be monitored in an ICU for 24 hours)

• Use remote video evaluation, whenever possible, for hospitalized patients with COVID-19 who have symptoms that are of concern for a stroke

• Consider extended-interval or delayed dosing of chronic immunomodulatory therapies in conditions such as multiple sclerosis during COVID-19

Epidemiology and clinical presentation

Similar to SARS and Middle East respiratory syndrome193,194, multiple neurological manifestations of COVID-19 have been described. An analysis of 214 patients with severe COVID-19 found that neurologic symptoms occurred in 36% of the patients. A number of non-specific mild neurological symptoms are notable in hospitalized patients with COVID-19, including headache (8–42%), dizziness (12%), myalgia and/or fatigue (11–44%), anorexia (40%), anosmia (5%), and ageusia (5%), although the epidemiology may be different in milder outpatient presentations(17)

Pathophysiology

SARS-CoV and the coronavirus that causes Middle East respiratory syndrome have known neuroinvasive and neurotropic abilities. Direct viral invasion of neural parenchyma is a possibility; SARS-CoV-2 may access the central nervous system via the nasal mucosa, lamina cribrosa, and olfactory bulb or via retrograde axonal transport. Nasal epithelial cells display the

highest expression of ACE2 (the receptor for SARS-CoV-2) in the respiratory tree; this may account for the symptoms of altered sense of taste or smell frequently reported retrospectively in the majority of outpatients with COVID-19(18)

Management considerations

Provisional guidelines during theCOVID-19 crisis call for continued adherence to established guidelines for acute ischemic stroke, including providing access to thrombolysis and thrombectomy, while recognizing the need to minimize the use of personal protective equipment

Potent baseline immunomodulatory therapies may be considered for extended-interval or delayed dosing in conditions such as multiple sclerosis during COVID-19. Long-term considerations, such as post-infectious neurodegenerative and neuroinflammatory involvement, as well as the efficacy of an eventual vaccine in some immunosuppressed populations, are under investigation(17)(18)

Dermatologic manifestations

Epidemiology and clinical presentation:

The dermatologic manifestations of COVID-19 were first reported in a single-center observational study in Italy, with a frequency of 20% in hospitalized patients with no history of drug exposure in the previous 2 weeks. Approximately 44% of the patients had cutaneous findings at disease onset, while the remaining patients developed these during the course of their illness. No correlation with disease severity was noted in this small study. The cutaneous manifestations included erythematous rash, urticaria, and chickenpox-like vesicles. A preliminary systematic review of 46 studies (including case reports and series) found acro-cutaneous (pernio or chilblain-like) lesions to be the most commonly reported skin manifestation

Biopsy of acrocutaneous lesions has shown diffuseand dense lymphoid infiltrates, along with signs of endothelial inflammation(19)(20)

Management considerations:

Most cutaneous manifestations of COVID-19 have been self-resolving. It is not clearly understood whether patients with dermatologic diseases who receive biologic therapies are at

increased risk of complications from COVID-19221. In their interim guidelines, the American Academy of Dermatology recommends discontinuation of biologic therapy in COVID-19-positive patients (20)

REPRODUCTIVE SYSTEM MANIFESTATIONS

Prevalence and incidence:

According to a recent study, 81 COVID-19 male patients' total testosterone (T) was lower, whereas serum luteinizing hormone (LH) was significantly higher than that of 100 age-matched healthy men. The serum T:LH ratio was also significantly lower in COVID-19 patients and was negatively associated with disease severity(21)

Pathophysiology.

The existence of ACE2 receptors on the testicular cells including spermatogonia, Leydig, and Sertoli makes these cells a target for SARS-CoV-2 infection.To further characterize ACE2-positive cells in human testis, gene ontology (GO) enrichment analysis was performed to determine which biological processes are enriched within either spermatogonia or Leydig and Sertoli cells by comparing ACE2-positive cells with ACE2-negative cells. Twenty-four GO terms associated with viral reproduction and transmission were evaluated, which were positively enriched in ACE2-positive spermatogonia and include viral gene expression

A study on 12 COVID-19 patients demonstrated the absence of viral RNA in testicular biopsy tissues.It indicates that SARS-CoV-2 cannot directly infect testes or the male genital tract even in the acute phase; therefore, no evidence shows that the novel coronavirus can be sexually transmitted from males.Other studies indicated that serum LH in males with COVID-19 infection could be significantly increased; however, the ratio of T to LH and the ratio of follicle-stimulating hormone (FSH) to LH are dramatically decreased. Furthermore, regarding the serum analysis, elevated levels of prolactin (PRL) have been reported. Clearly, elevated levels of PRL lead to pituitary suppression. Hence, decreased levels of gonadotropins are expected. In COVID-19 patients, the level of LH in serum is reported to be increased as well. The elevated level of LH and decreased level of T (leading to low T/LH ratios) are more likely to be caused by testes dysfunctions such as the possible damage to Leydig cells(22)

Endocrinologic manifestations:

While patients with pre-existing endocrinologic disorders may be predisposed to more-severe presentations of COVID-19, observations of a range of endocrinologic manifestations in patients without pre-existing disease have also been made(23)

Clinical presentations:

• Hyperglycemia

• Ketoacidosis, including that in patients with previously undiagnosed diabetes or no diabetes

• Euglycemic ketosis

• Severe illness in patients with pre-existing diabetes and/or obesity (24)

COVID-19-specific considerations

• Consider checking serum ketones in patients with hyperglycemia who are on sodium–glucose transport protein inhibitors177

• Measure hemoglobin A1C in patients without known history of diabetes mellitus who present with hyperglycemia and/or ketoacidosis

• Consider alternative protocols for subcutaneous insulin in selected patients with mild to moderate diabetic ketoacidosis on an individual-patient-level basis(24)

Epidemiology and clinical manifestations.

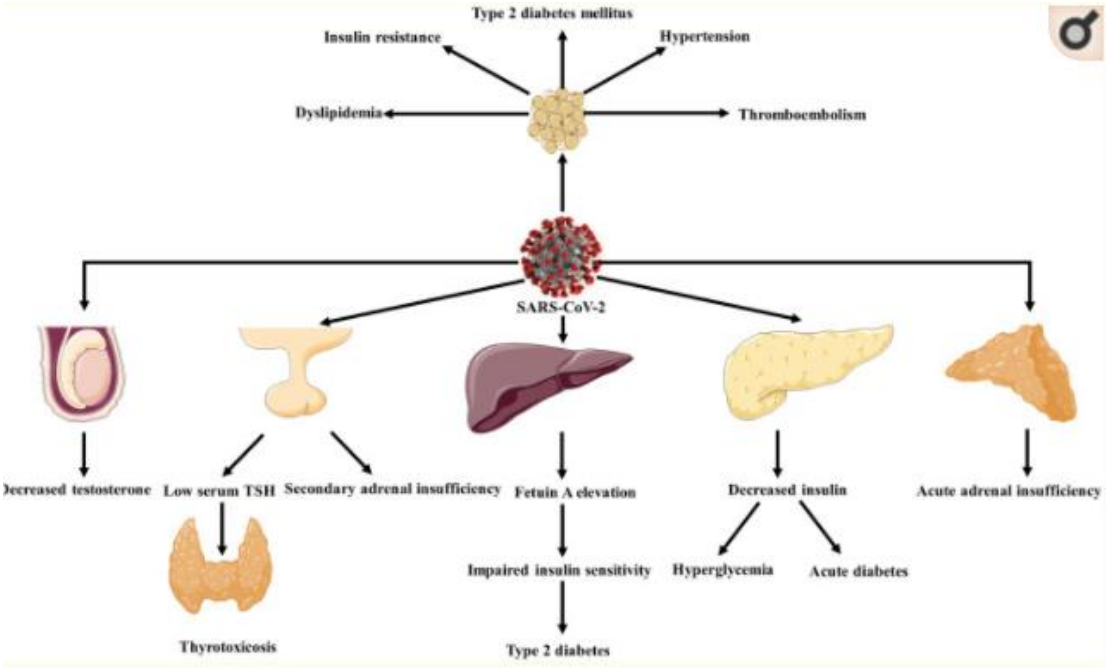
Patients with diabetes mellitus and/or obesity are at risk of developing more-severe COVID-19 illness. In a report from the US Centers for Disease Control, 24% of hospitalized patients and 32% of patients admitted to the ICU had underlying diabetes125. In an initial experience with 257 critically ill patients hospitalized in a tertiary-care hospital in New York City, 36% had diabetes and 46% were obese. Similar observations were made in studies from China and Italy that demonstrated an association of underlying diabetes with severe illness and death(24)

Pathophysiology.

Several mechanisms may account for the more severe disease course, including worsened hyperglycemia and ketosis, observed in patients with COVID-19 and diabetes. Factors related to SARS-CoV-2 include substantially elevated cytokine levels, which may lead to impairments in pancreatic β-cell function and apoptosis178 and, consequently, decreased insulin production and ketosis. In addition, ACE2 expression has been reported in the endocrine pancreas albeit inconsistently(23)

Management considerations:

Hemoglobin A1C should be assessed in patients with COVID-19 who present with hyperglycemia and/or ketoacidosis, to identify possibly undiagnosed diabetes. Logistically, the management of diabetic ketoacidosis poses an increased risk to medical personnel, due to the need for hourly glucose checks while patients are on an insulin drip. There may be a role for remote glucose monitoring via continuous glucose monitors to alleviate this problem and reduce demands on nursing staff. Alternative protocols for subcutaneous insulin in selected groups of patients with mild to moderate diabetic ketoacidosis may be considered on an individual patient-level basis(23)(24)



Conclusions and future directions:

Beyond the life-threatening pulmonary complications of SARS-CoV-2, the widespread organ-specific manifestations of COVID-19 are increasingly being appreciated. As clinicians around the world brace themselves to care for patients with COVID-19 for the foreseeable future, the development of a comprehensive understanding of the common and organ-specific pathophysiologies and clinical manifestations of this multi-system disease is imperative. It is also important that scientists identify and pursue clear research priorities that will help elucidate several aspects of what remains a poorly understood disease. Some examples of areas that require further attention include elucidation of the mechanism by which SARS-CoV-2 is disseminated to extrapulmonary tissues, understanding of the viral properties that may enhance extrapulmonary spread, the contribution of immunopathology and effect of anti-inflammatory therapies, anticipation of the long-term effects of multi-organ injury, the identification of factors that account for the variability in presentation and severity of illness, and the biological and social mechanisms that underlie disparities in outcomes. Aand data standards for research relating to COVID-19. Regional, national, and international collaborations of clinicians and scientists focused on high-quality, transparent, ethical, and evidence-based research practices would help propel the global community toward achieving success against this pandemic.

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