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Infection and Viral Pathogenesis of SARS-CoV-2: A Review

Ilyes Zatla[1,*], Lamia Boublenza[2], Hafida Hassaine[3]

Abstract

COVID-19 is a highly infectious disease, posing a massive challenge to global health, with non-specific symptoms, the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and acute respiratory distress syndrome (ARDS). This review summarizes the current evidence on the major adverse pathological outcomes of COVID-19, which were found to affect different body systems like the respiratory system, cardiovascular system, and neurological system, as well as impaired hepatic and renal function. SARS-CoV-2 is highly transmissible and COVID-19 lethality is extremely versatile in the world, while some patients experience mild to moderate symptoms, others, suffer from severe ones. Even if recovery from the infection is assured, one must not forget the possible long-term effects of the disease.

Keywords: SARS-CoV-2, COVID-19, infection, pathology, pandemic

INTRODUCTION

This novel coronavirus scientifically named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the similarity of its structure to severe acute respiratory syndrome related coronaviruses [1], previously known by the provisional name of 2019 novel coronavirus (2019-nCoV), which causes the Coronavirus Disease COVID-19, a highly contagious and progressive infectious disease [2]. The beginning of the disease starts with flu-like symptoms, then it causes fever, headache, dry cough, nausea without vomiting, abdominal discomfort with some diarrhea, loss of smell and taste, after that, symptoms can worsen leading to shortness of breath and dyspnoea due to bilateral viral pneumonia from direct viral damage to lung parenchyma. Then henceforth day 10, the cytokine storm kicks in, subsequently, ARDS and multi-organ failure ensues [2, 3], septic shock and diarrhea were only noted in a small part of the patients, but severe cases rapidly showed metabolic acidosis, bleeding, and coagulation dysfunction [3]. SARS-CoV-2 infection can be divided into three stages, an asymptomatic incubation period, a non-severe symptomatic period, and a severe respiratory symptomatic stage with high viral load [4]. However, most of infected individuals can limit the infection from progression and recover by their immune system [5], the recovery is accompanied with a disappearance of symptoms and signs, consistent clearance of the virus, and absorption of lung inflammations [6], but still, due to the probability of COVID-19 virus recurrence after recovery, a follow-up should be considered regularly [7]. Severity seems to disproportionately affect those of advanced age and those with pre-existing chronic medical conditions [3], deducing,

*Author for Correspondence
Ilyes Zatla
E-mail: ilyes.zatla@aol.com

[1]PhD Student, Laboratory of Microbiology applied to the Food industry, Biomedical and the Environment, Faculty of Natural Sciences of Life, Earth and Universe, University of Tlemcen, Algeria, Africa
[2]Lecturer, Laboratory of Microbiology applied to the Food industry, Biomedical and the Environment, Faculty of Natural Sciences of Life, Earth and Universe, University of Tlemcen, Algeria, Africa
[3]Professor, Laboratory of Microbiology applied to the Food industry, Biomedical and the Environment, Faculty of Natural Sciences of Life, Earth and Universe, University of Tlemcen, Algeria, Africa

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that the most vulnerable group includes the elderly, malnourished, asthmatic, hypertensive, diabetic, immune compromised, cancer and cardiovascular patients, as well as pregnant women [8], excluding autoimmune thyroid disease (AITD) and rheumatoid arthritis (RA) patients from that high-risk group of COVID-19 [9]. Medications for Diabetes and conditions like hypertension, increase ACE2 expression, which facilitates viral uptake that can lead to a severe infection [10]. The same way, diabetes mellitus (DM) inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes, making the groups with this disease more and more vulnerable [11], as well as active smoking, which has adverse effects on both cardio and pulmonary systems, was also associated with worse composite outcomes [12]. In contrast to adults, most infected children appear to have a milder clinical course [13], probably due to the different immune responses to the virus, since aging is associated with a progressive decline in the normal functioning of the immune system, or the different regulation of ACE2 receptors, also probably to some COVID-19-cross-reactive antigens, or maybe because of the variety of interactions of other simultaneous viruses present in the mucosa of our lungs [5].

THE PATHOPHYSIOLOGY OF SARS-COV-2 INFECTION

ACE2 tissue distribution in organs like the lungs, heart, kidney, liver, endothelium, and intestine, and even on the surface of neurons of the brain, in addition to its vital role in the cardiovascular and immune systems, could explain the multi-organ dysfunction observed in patients [8, 14, 15].

Pulmonary Pathology

While replication in the lower respiratory tract is consistent with the onset of lung illness, replication in the upper respiratory tract is consistent with effective transmission between hosts. SARS-CoV-2 replicates effectively in respiratory epithelial cells in the nasal cavity, bronchi, bronchioles, and alveoli throughout the respiratory tract [16], and virus particles have also been found in type 2 alveolar and bronchial epithelial cells [17].

Bilateral diffuse alveolar damage (DAD), pulmonary edema, hyaline membrane formation, prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multi-nucleated giant cells, indicative of an acute respiratory distress syndrome, as well as typical syncytial cells in the alveolar lumen, were seen during histological examination and pathologic findings of the lungs [16].

Pneumonia and ARDS are the common immune-pathological event for SARS-CoV-2 [17], since the virus mainly attacks the lungs at the beginning [18], they're characterized by the rapid onset of widespread inflammation in the lungs and subsequent short/rapid breathing, hypoxia and cyanosis, causing a respiratory failure [4, 14].

A scenario of multiple sites of pulmonary vascular thrombosis with progressive myocardial ischemia, in which it is thought that pulmonary intravascular coagulopathy is the best explanation for the COVID-19 pneumonia risk factors for poor survival and suggests an explanation for the increased cardiovascular mortality due to disseminated intravascular coagulation, indicates that lung inflammation was the primary cause of life-threatening respiratory disorders at the severe stage [4].

Cardiac Pathology

This novel virus disease might theoretically cause chronic damage to the cardiovascular system [19], where an acute myocardial injury was the most described cardiovascular complication, in addition to both tachycardia and bradycardia arrhythmia [20]. The elevated levels of ACE2 protein expression on cardiomyocytes have been linked to reports and small case series suggesting an increased risk of myocardial damage, coronary vascular involvement, and heart failure as a sequela to the disease [8, 12].

Nephropathology

Hematuria and proteinuria as albumin in the urine are the two common symptoms in COVID-19 patients with renal failure, meanwhile the major issue is impaired renal function [21].

Immunohistochemistry (IHC) results indicated that the expression level of the ACE2 protein is significantly higher in the kidney, especially in the renal tubular cells, subsequently, their injury causes renal tubular atrophy [21]. Along with, kidney histopathologic, ultrastructural, and immunostaining findings, that cited a range of abnormalities, like a significant acute tubular injury (ATI), the occlusion of microvascular lumens mainly by erythrocytes with ensuing endothelial damage, as well as glomerular and vascular changes indicative of underlying diabetic or hypertensive disease, while an observed diffuse acute proximal tubular injury with loss of brush border and non-isometric vacuolation, may be partially caused by the direct virulence of SARS-CoV-2 [22].

Acute kidney injury (AKI) is common among critically ill patients with COVID-19, likely to be multifactorial, with cardiovascular comorbidity, damage in the kidney or a dysregulated immune response [19].

Based on a meta-analysis, it was stated that Chronic Renal Pathology would appear to be associated with an increased risk of severe COVID-19 infection, but the viral infection would not aggravate pre-existing chronic renal failure [21].

Hematopathology

Indicators of liver damage in COVID-19 individuals include abnormally high levels of the enzymes Alanine transaminase (ALT), Aspartate transaminase (AST), and total bilirubin (TBIL), as well as abnormally low levels of albumin (ALB) [23].

An increased number of COVID-19 patients with liver injury have been reported [23], either by a direct virus infection, immune injury, drug-induced liver injury, ischemia, hypoxia, and recurrence or exacerbation of underlying liver disease [23, 24].

In severe COVID-19, hepatic dysfunction is associated by increased coagulative and fibrinolytic pathway activity, relatively low platelet counts, rising neutrophil counts, and elevated ferritin levels [25]. Additionally, liver biopsy samples from COVID-19 patients with severe disease exhibited moderate microvascular steatosis and mild lobular and portal activity, while autopsies revealed a mild dilatation of zone 3 sinusoids, patchy hepatic necrosis, and a mild increase in sinusoidal lymphocytes, suggesting that the injury may have been brought on by either SARS-CoV-2 infection or drug-induced liver injury [23, 24].

A focus of hepatic necrosis was examined in adjacent to terminal hepatic veins and periportal area, with no significant surrounding inflammatory cellular infiltration, surprisingly consistent with the pattern of acute liver injury, that may indicate a direct viral attack on the liver [25].

Gastrointestinal Pathology

Gastrointestinal involvement is present with diarrhea, abdominal pain, vomiting or nausea, these symptoms can exist independently of respiratory symptoms [26, 27]. Hemorrhagic colitis caused by a SARS-CoV-2 intestinal infection was seen endoscopically, and hemorrhagic enteritis was also reported [26, 28].

Neuropathology

The COVID-19 is not always restricted to the respiratory tract; it can also affect the central nervous system (CNS), where neurological illnesses can be brought on by invading peripheral neurons and entering the CNS through synapses [29]. Although it is obvious that pulmonary, renal, and cardiac damage are the main factors in patient deaths from COVID-19, cerebrovascular or neuronal damage that develops during the illness may also play a role [15]. The virus can penetrate and kill the medullary neurons during the latency phase [29].

It has been proposed that SARS-CoV-2 gains entry to the CNS in one of three ways: by systemic vascular dissemination through the hematogenous route, peripheral neurons and cerebrospinal fluid (CSF) via a synapse-connected route or more locally across the cribriform plate of the ethmoid bone [30], where the virus possibly attaches to the olfactory epithelium (OE) via ACE2 receptor and gains entry [31]. The majority of patients also reported impairments in their ability to smell and taste, which suggests that the digestive system may be a viable pathway for invasion and transmission to the enteric nervous system (ENS) [32].

The inability of air to enter the lungs, which may truly be a defect in respiration under the control of the neurological system, is said to be the cause of the symptoms that might be attributed to respiratory disease [29].Reports of neurological manifestations of SARS-CoV-2 are still emerging, ranging from milder presentations such as headache, nausea, and vomiting, to severe complications such as acute cerebrovascular diseases, impaired consciousness, epilepsy, seizures, and strokes [15, 29–32], consistent with the cases of encephalitis that have been officially reported to be a clinical manifestation in patients with COVID-19 [15]. Therefore, these reports show that SARS-CoV-2 have the potency of being neuroinvasive [28, 29]. Confirmed cases, also reported Guillain-Barre syndrome (GBS) and multi-system inflammatory syndrome in children (MIS-C), altered mental status (AMS) & cardiorespiratory failure as being a significant neurological sequel of SARS-CoV-2 [33].

Hemopathology

Scientists' findings suggest that SARS-CoV-2 can bind to the human hemoglobin (Hb) beta chain, damaging the Heme (composed of iron and porphyrin) structure of erythrocytes, rendering the human Hb deoxygenated [34], and suggest also, that red blood cells can probably be infected by Spike-CD147 pathway [35].

Autopsy of COVID-19 patients, found that spleens were significantly reduced in size, suggesting that there might be an impact of SARS-CoV-2 targeting the Hb [35], in addition to the mild anemia and decreased Hb content that have been reported [14].

Through molecular docking, certain proteins of the novel coronavirus 'ORFs' showed binding to porphyrin [34], predicting that these ORF proteins can interact with hemoglobin to reduce both oxygen (O_2) affinity and total hemoglobin content [14].

A genetic study showed that there was the detection of a novel locus, indicating a susceptibility in the involvement of the ABO blood-group system, favoring the platform for the SARS-CoV-2 infection, confirming that blood group O is associated with a lower risk of acquiring COVID-19, whereas blood group A was associated with a higher risk [36].

Viral Sepsis

Patients with severe COVID-19 who met the diagnostic standards for sepsis and septic shock also displayed clinical signs of shock, cold extremities, weak peripheral pulses, and severe metabolic acidosis, which may be an indication of microcirculation dysfunction. In addition to significant lung damage and dispersed neuronal degeneration in the brain, several individuals also exhibited compromised liver and renal function [33]. Some patients with COVID-19 pneumonia also exhibit the hypercytokinemia and severe hyperferritinemia that are commonly associated with hemophagocytic lymphohistiocytosis (HLH) and occur in 3,7–4,3 percent of sepsis cases [19]. The cultures of blood and lower respiratory tract specimens were found to be devoid of the fungi and bacteria that cause sepsis. Patients with COVID-19 who showed signs of viral sepsis led researchers to hypothesize that viral sepsis is a key component of the disease's pathophysiology [37].

Kawasaki Disease

Kawasaki disease is an acute, self-limiting vasculitis, that exclusively affects children, mainly boys, it causes acute inflammation of the blood vessels [38–42] its etiology is unknown [43], but scientists generally associated it with viruses like Influenza and Epstein-Barr virus (EBV) [42].

A limited percentage of infants who experienced a more severe inflammatory syndrome linked to COVID-19 [37] displayed symptoms of Kawasaki disease (KD), including shock, multi-organ failure, conjunctivitis, erythema in the oral mucosa, cervical lymphadenopathy, and polymorphic rash [37, 38]; misdiagnosis of KD could drive over-treatment and heighten anxiety [40], and there was an increasing incidence and multiple reports of children who were diagnosed with KD from different countries like the USA, France, England and Italy at the early stage of the pandemic [39–41].

The Gut Microbiota

SARS-CoV-2-Gut interaction is a factor because the ecology of the gut and commensal microbiota can both regulate and be regulated by invasive viruses, promoting either stimulatory or suppressive effects, with roles in affecting the severity of the infection, either by direct or non-direct microbiome pathways, specifically, on its impacts on cytokines, and roles in affecting the degree of recovery too. However, no investigation has been published to date to identify the microbiota species interacting with the virus [44]. Of note, *Prevotella* has been abundantly identified in the clinical samples of SARS-CoV-2 infected individuals.

CONCLUSION

COVID-19 is a progressive illness that is still posing a challenge to our global health, although for most people it causes only mild illness, it can make others very ill, with an increase fatality for older people, and those with pre-existing medical conditions such as high blood pressure, heart problems, or diabetes. The virus continues to spread across the world with a hard to predict patterns. The health, humanitarian and socio-economic policies adopted/abandoned by countries will determine the speed and strength of the recovery. In recent years and still, a lot of diseases are being associated with the gut flora, where different interactions occur between the host and these gut microbes, to the point that it was considered to be the second brain of the human body, so is there a bacterial intervention? If there is, can it modulate the infectious process of SARS-CoV-2?

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