

COVID-19: More Than A Lung Infection

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1. Abstract

COVID-19 is a new strain of Coronaviruses virus declared by the World Health Organization (WHO) as a pandemic on March 11th, 2020. While the majority of patients with COVID-19 typically have characteristic respiratory presentations subsequently, a large number of patients were presented with multi-system affection, particularly digestive system, liver, cardiovascular, cutaneous, coagulopathy, vascular, endothelial, central nervous, oral cavity and renal systems. Of note the mortality and the need for mechanical ventilation were higher in old age and patients with comorbidities especially obesity, which can shift the risk of COVID-19 to a younger age. This review article will attain to summarize the literature published to date concerning different body system affection of COVID-19.

2. Introduction

It wasn't until the end of December of 2019 that the World Health Organization (WHO) was notified of the affection of a large num-

ber of patients with an obscure form of unidentified pneumonia in the Chinese city of Wuhan and the Hubei region [1]. This severe acute respiratory syndrome was later attributed to an original coronavirus named SARS-CoV-2, [2] defined by its extensively high communicability leading to its very rapid worldwide spread [3, 4]. Due to these factors WHO on March 11th, 2020, declared SARS-CoV-2 as a pandemic of global proportion for only the second time in the past century after the H1N1 influenza pandemic [5].

Coronaviruses (CoVs) receive their name due to the presence of surface crown-like spikes. These viruses form part of the Coronavirinae subfamily, subdivided by phylogenetic clustering into α , β , γ , and δ groups; human infection is caused by group α and β CoVs [6]. Coronaviruses are single-stranded positive-sense RNA viruses [7], that consist of major proteins specified as the S, or spike protein responsible for connecting to the host receptor allowing union between the cell membrane and virus, the N (nucleocapsid) protein, the M (membrane) protein, and the E (envelope) protein [8]. Isolation of coronaviruses can occur from a number of different

species including, birds, livestock various mammals such as cats, mice, and dogs [9].

While pathogenic CoV subtypes that affect humans generally cause mild clinical features, severe respiratory manifestations are the hallmark of two CoV exceptions, namely Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome-related coronavirus (SARS-CoV). MERS-CoV was first identified in the Arabian Peninsula in 2012 with 2,494 infected cases and 858 fatalities, while earlier in 2002, what began as an outbreak of the β CoV subtype in Guangdong province in China ultimately resulted in just over 8,000 confirmed infections with 774 fatalities across 37 countries [9]. The more recently described outbreak in Wuhan, China, in 2020 presented a type of pneumonia of unknown origin that was later identified by deep sequencing studies to be a novel strain of CoV [10]. Originally designated as 2019-nCoV, the virus was renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses [11], and the resultant disease subsequently labeled coronavirus disease-2019 (COVID-19) by the WHO on February 11, 2020.

2.1. Modes of Transmission of the COVID-19 Virus

While animal-to-human transmission by direct contact with infected animals at the Wuhan seafood market in China probably accounts for the first cases of COVID-19, the appearance of clinical cases with a variable history of virus introduction has increased, so much so that the primary type of transmission is currently human-to-human transmission, even from asymptomatic patients. Respiratory droplets and contact routes are currently evidenced as the principle methods of transmission of COVID-19 infection [12,13,14].

Close contact of less than 1m between an individual and a patient with respiratory symptoms, such as coughing or sneezing, subjects that individual to risk of exposure to COVID-19 infection through potentially infectious respiratory droplets. Similarly, fomites within the direct vicinity of an infected patient also have the potential to act as a source of infection [15]. Therefore, COVID-19 virus transmission is possible either by direct contact with an infected patient or by contact with objects contaminated by that patient, such as with stethoscopes or thermometers.

While some evidence supports the occurrence of COVID-19 intestinal infection with the presence of the virus in feces [16], feco-oral route has not been reported as means of transmission of COVID-19 virus.

2.2. Clinical Features

The wide range of clinical findings presenting with COVID-19 extends from simple asymptomatic infection to multiorgan failure with septic shock, forming the basis for characterization of COVID-19 based on the severity of manifestations into mild, mod-

erate, severe, and critical. Typically, 98.6% of patients exhibit symptoms of fever and 69.6% have fatigue, while dry cough and diarrhea are also commonly presented [11,17].

2.3. Extra-Pulmonary Symptoms

2.3.1. 1-Gastrointestinal Symptoms of COVID-19

A-Enteric Manifestations of SAR-CoV2

Gastrointestinal symptoms have been reported in 2-40% of patients in case series [18, 19], but meta-analysis studies approximate the prevalence of GI manifestations at 17.6%, with anorexia being the most common complaint described by 26.8% of patients. Diarrhea presented in 12.5% of cases, followed by nausea and vomiting in 10.2% and abdominal pain in 9.2% of patients. Severe disease was characterized by 17.1% prevalence of GI symptoms whereas patients with the non-severe disease had GI symptoms in only 11.8%. Furthermore, adults, children, and pregnant women exhibited a similar prevalence of this clinical picture. Viral RNA was detectable in stool and respiratory samples at a rate of 48%, but studies on serial testing reported stool RNA positivity in 70% of patients, even after negativity of respiratory results [20].

Pathogenesis of SARS-CoV-2 infection of the gastrointestinal tract remains unknown, but it has been suggested that the virus may cause a functional disturbance in cell receptors of angiotensin-converting enzyme 2 (ACE2) present in large numbers in enterocytes of the proximal and distal small intestine, consequently resulting in diarrhea.

In SARS-CoV-2 infection, a metalloproteinase, ACE II (ACE2) has been proven to be the cell receptor [21,22,23].

This role of ACE2 receptors as the point of entry of SARS-CoV-2 virus into the GIT is evidenced by staining of viral nucleocapsid protein and ACE2 protein expression inside epithelial cells of the stomach, duodenum, and rectum [24,25].

B- Hepato-Biliary Manifestations

Liver comorbidities manifest in 2-11% of infected COVID-19 patients, of whom 14-53% demonstrate abnormally elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during the progressive course of the disease [26,27,28]. However, a number of factors regarding the liver remain unclear, including whether pre- and post-transplant patients undergoing immunosuppressive therapy and those with autoimmune hepatitis are more susceptible for severe COVID-19 infection [29], whether patients suffering from chronic hepatic diseases including infections with viral hepatitis C and B have increased risk of developing liver damage with COVID-19 [30], and whether COVID-19 infection in patients with underlying cirrhosis or cholestatic liver disease experience exacerbation of the cholestasis condition [31].

AST elevation was a characteristic finding in 62% of intensive care

patients compared to only 25% of non-ICU patients in a study by Huang et al., while a large cohort comprising cases from 552 hospitals showed that patients with more severe disease had more disturbance of aminotransferase levels when compared to patients with milder forms of the disease. [26] Furthermore, patients with CT-confirmed diagnosis of COVID-19 before the presentation of symptoms exhibited much lower AST irregularities than those diagnosed after becoming symptomatic. These observations indicate more apparent liver injury with increasing severity of COVID-19 disease [28].

Hospitalized COVID-19 patients also present with other hepatic enzymes abnormalities such as Gamma-Glutamyl Transferase (GGT), a biomarker indicative of cholangiocyte injury, that was found to be elevated in 54% of patients, and alkaline phosphatase that was increased in one in every 54 patients. [32] However, despite these enzymatic level disturbances, post-mortem liver tissue specimens taken from a patient with fatal COVID-19 infections did not demonstrate viral inclusions on pathological examination [33].

The liver is potentially a target for COVID-19 infection due to the presence of ACE2 receptors in hepatic and biliary epithelial cells that may provide a possible pathogenic mechanism for the liver damage occurring with this infection. [32] In addition, elevated liver enzymes seen in these patients may be indicative of a direct cytopathic effect by the virus and/or immune damage induced by the host inflammatory response to the virus [34]. Therefore, hepatic dysfunction may be due to direct binding of SARS-CoV-2 to ACE2-positive cholangiocytes propagated by inflammation which is mediated by an immune reaction in the form of cytokine storm leading to possible progression to hepatic failure in critically ill COVID-19 patients. This is in contrast to transient liver damage associated with milder COVID-19 infection where liver affection is typically normalized without therapy.

3. Myocarditis in COVID-19

Cardiac injury in patients with COVID-19 infection was associated with increased development of ARDS and a higher mortality rate when compared to non-cardiac patients. Interstitial mononuclear inflammatory cell infiltration of the myocardium has been suggested from sporadic autopsy findings [33], while severe myocarditis with diminished systolic function has been described as a post-COVID-19 infection [35,36]. Increased incidence of cardiac injury has been detected in cardiac biomarker studies conducted on hospitalized COVID-19 patients [37,38], most likely due to infection-associated myocarditis and/or ischemia, the latter being a powerful determinant of prognosis in COVID-19 infection. The importance of cardiac affection on mortality of hospitalized COVID-19 patients was demonstrated by the death of 57 of 416 patients who had either coronary heart disease (10.6%), heart failure

(4.1%), or cerebrovascular disease (5.3%).

Cardiac injury in about 20% of patients was characterized by the presence of increased blood levels of the cardiac biomarker hs-TnI (high-sensitivity troponin I) irrespective of electrocardiography (ECG) and echocardiography (ECHO) detection of recent anomalies. These patients were typically older with more comorbidities, and exhibited increased leukocyte but decreased lymphocyte counts, and higher levels of N-terminal pro-brain natriuretic peptides, C-reactive protein, and procalcitonin [37].

Utilization of medications such as ACE inhibitors and angiotensin II receptor blockers are more regularly being used by patients with elevated TnT, but have no effect on the mortality rate of these patients [38].

4. Nervous System Involvement in COVID-19

The neurotropic features of SARS-CoV-2 account for the detrimental effects of this virus on the Central Nervous System (CNS). This was initially evidenced by reports from Beijing Ditan Hospital of the first case of viral encephalitis due to a new coronavirus on March 4, 2020, subsequently confirming the causative pathogen to be SARS-CoV-2 via genome sequencing of cerebrospinal fluid [39]. Further support was provided by another published article also regarding cases of acute viral necrotizing encephalitis related to SARS-CoV-2 infection. The patient verified hemorrhagic rim-enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions on brain MRI. Noncontrast CT images demonstrated symmetric hypoattenuation within the bilateral medial thalami with a normal CT angiogram and CT venogram. [40] In addition, a study by Mao et al found that neurological symptoms such as headache, altered conscious state, and paresthesia developed in 36.4% of COVID-19 infected patients, these symptoms being more manifest in critically ill patients compared to those with milder forms of the disease [41]. Moreover, Guillain Barre syndrome was reported in an infected patient with COVID-19. The patient presented with acute progressive symmetric ascending quadriparesis. The electrodiagnostic test revealed that, the patient is an AMSAN variant of GBS [42].

Neurotropism of SARS-CoV-2 in the current COVID-19 pandemic is suggested to be attributed to its furin-like cleavage site. Furin and furin-like proteases resulted in cleavage of viral S protein, thereby influencing invasion and virulence properties as well as determining host specificity and tissue tropism of SARS-CoV and MERS-CoV [43]. These features may support membrane fusion, possibly enabling nervous system infection by the coronavirus. However, it is not yet clear whether the furin-like cleavage site on SARS-CoV-2 spike protein functions in any specific capacity towards nervous system invasion, an issue requiring further studies. Nevertheless, the lack of pathological evidence supporting viral infection of nervous tissue despite the presence of these isolated cases necessitates

clinical consideration of brain affection by SARS-CoV-2.

5. Cutaneous Manifestations in COVID-19.

Approximately 20% of COVID-19 patients (18 of 88 patients) at the Alessandro Manzoni Hospital in the northern Italian city of Lecco developed skin manifestations, of whom 44% (8 patients) had skin lesions at the onset of symptoms before admission while the remaining patients developed skin eruptions after hospitalization. A red rash developed in fourteen patients (78%), widespread urticaria was present in three cases, and chickenpox-like vesicles appeared in one patient, all most commonly affecting the trunk. Not correlating with disease severity, lesions typically subsided after a few days of mild or absent itching [44].

Moreover, skin lesions may be categorized as acral areas of erythema with vesicles or pustules (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%) [45]. Many reports from Italy of acrocyanotic lesions earlier than skin rash onset had been reported in some patients. These patients have lesions on their feet and hands. The foot lesions mainly affect the toes and plantar aspect, however, may not affect all the toes. The lesions may appear red to blue, may become bullous or develop blackish crusts, be, but finally resolved [46]. The appearance of skin lesions before fever or respiratory symptoms suggests that, skin eruptions may be of COVID-19 origin [47]. One suggestion is that these skin manifestations may be due to the development of venous or arterial thrombosis occurring with COVID-19 infection.

6. Coagulopathy and Vascular Endothelial Dysfunction

It has been suggested that COVID-19 infection may be complicated by vascular endothelial dysfunction and coagulopathy [48]. Affection of the endothelium, leads to vasodilation, anti-aggregation abilities and fibrinolysis may lead to a systemic state of endothelial dysfunction [49].

The common respiratory symptoms associated with COVID-19 infection can be explained by the same pathophysiologic mechanisms of viral access of host cell-mediated by angiotensin-converting enzyme 2 (ACE2) was found extensively in the lungs [28]. Expression of ACE2 by endothelial cells (ECs) [50,51], along with clinical observations of thrombosis and occurrence of pulmonary embolism in COVID-19 patients [52,53], may suggest affection of the endothelium by SARS-CoV-2 [54].

Coagulopathy associated with organ dysfunction accounts for the higher mechanical ventilation requirement, ICU admission, and mortality rate evidenced in patients with COVID-19 infection [55,56]. Abnormalities in hemostasis most commonly include mild thrombocytopenia [57], elevated levels of D-dimer,58 and development of disseminated intravascular coagulation (DIC) in late in the course of disease [56].

7. Oral Cavity and COVID-19

Expression of ACE2 has been demonstrated in the mouth, particularly in epithelial cells of the tongue, thus explaining the fundamental part played by the oral cavity in allowing viral entry, thereby acting as a site for potentially increased host susceptibility to infectious SARS-CoV-2 [59].

Dentistry is considered one of the most hazardous profession regarding COVID-19 infection [60]. This increased risk arises from the close face-to-face contact with patients [61], with studies showing that infection with COVID-19 may be acquired directly through airborne dissemination of aerosols created during medical procedures or indirectly through saliva [62,63]. SARS-CoV-2 might be present in saliva from the upper or lower respiratory tract after gaining entry along with liquid droplets through the oral cavity [64,65]. Another route is via an exudate specific to the oral cavity called crevicular fluid containing regional proteins originating from extracellular matrix and serum [66]. In addition, salivary gland infection may result in subsequent release through salivary ducts of viral particles into saliva. SARS-CoV can infect salivary gland epithelial cells in rhesus macaques, so these glands might be a source of virus in saliva [67]. Moreover, studies have shown that SARS-CoV-specific secretory immunoglobulin. A (sIgA) was produced in saliva of immunized animal models [68], leading to the assumption that COVID-19 infection diagnosed by saliva can be achieved using antibodies specific to viral proteins.

8. Possible Links Between Diabetes and COVID-19 Infection

Diabetes, occurring in an estimated 20% of patients, acts as a risk factor for the occurrence of extreme pneumonia [69]. The Centers for Disease Control (CDC), reported that COVID-19 infection is associated with a higher risk of fatality in up to 50% of diabetic patients compared with non-diabetics [70]. Another study included a cohort of 339 patients with COVID-19 suggested that diabetes was associated with about 4-fold increased risk of having severe COVID-19 illness [71]. While defective innate immunity, manifested by altered phagocytic and neutrophil chemotactic functions, and cell-mediated immunity account for the increased risk of infection in all types of diabetic patients, the presence of increased incidence of type 2 diabetes in older patients may explain the higher frequency of diabetes with severe COVID-19 infections. In addition, the presence of cardiovascular disease in association with diabetes in older aged individuals may account for the increased death rate characteristic of COVID-19 [72]. Entry into the host of SARS-Cov-2 results in reduced expression of ACE2 leading to hyper inflammation, cellular damage, and respiratory failure associated with COVID-19 infection [73]. Upregulation of cell ACE2 expression with acute hyperglycemia might promote entry of the virus into the host, but downregulation of ACE2 expression in

chronic hyperglycemia subjects host cells to inflammatory and damaging consequences of viral effect. In addition, ACE2 expression on β cells of the pancreas can directly affect the function of these cells. These observations, not only suggest that diabetes may increase the risk to severe COVID-19 infection but may also be induced by infection [74,75,76].

Potential insulin deficiency resulting from β cell injury induced by viral infection is supported by Italian reports of frequent incidences of severe diabetic ketoacidosis (DKA) during hospitalization of COVID-19 patients and increased insulin demand by patients with severe COVID-19 infection. However, the exact role played by SARS-CoV-2 in promoting this enhanced insulin resistance remains unknown [72].

9. Kidney Involvement in COVID-19 Infection

Increased incidence of renal affection has been reported with COVID-19 infection, as evidenced by the development of albuminuria in 34% of 59 studied patients on initial hospital admission, with 63% subsequently developing proteinuria later during hospitalization. Two-thirds of fatalities demonstrated elevated blood urea nitrogen, as did 27% of overall patients, with signs suggestive of kidney inflammation and edema present on CT scan [77]. A recent study by Cheng et al also reported that 44% of 710 consecutive hospitalized COVID-19 patients had proteinuria and hematuria on admission while 26.7% had only hematuria, with increased serum creatinine and blood urea nitrogen found in 15.5% and 14.1% of patients, respectively. Prognosis of this infection was found to be dependent on the presence of acute kidney injury (AKI), proteinuria, hematuria, and elevated blood creatinine and urea nitrogen [78].

Studies reported SARS-CoV-2 viral entry via ACE2 receptors abundantly present in renal tissue, indicating effective targeting of renal cells in COVID-19 infection [78,79,80,81]. This is supported by the identification of viral RNA from tissue in infections of both the kidney and urinary tract [81,82], as well as by successful isolation of the virus from a urine sample of an infected individual in Guangzhou [83].

Moreover, quantification of the SARS-CoV-2 viral load in autopsy tissue samples obtained from 22 patients who had died from Covid-19 demonstrated that seventeen patients had more than two coexisting conditions, and the commonest coexisting conditions were associated with SARS-CoV-2 tropism for the kidneys, even in patients without a history of chronic kidney disease [84]. Depending on these findings, renal tropism is a potential explanation of frequently reported new clinical signs of kidney injury in patients with COVID-19 [85], even in patients with SARS-CoV-2 infection who are not critically ill.

10. Obesity & COVID-19

In COVID-19 the main risk factors are cardiovascular disease, clincisofoncology.com

diabetes mellitus, chronic respiratory diseases, hypertension, and cancer. Obesity is the main risk factor for these comorbidities. In the UK, a report suggested that, 2/3 of people presented by critically ill coronavirus infection were overweight or had obesity [86]. Meanwhile, a report from Italy suggests 99% of deaths have been in patients with pre-existing conditions, including those which are commonly seen in people with obesity such as hypertension, cancer, diabetes, and heart diseases [87].

Among 383 patients from Shenzhen with COVID-19, overweight was associated with an 86% higher, and obesity with 2.42-fold higher odds, risk of developing severe pneumonia compared with patients of normal weight in statistical models that controlled for potential confounders [88]. Moreover, among 4,103 patients with COVID-19 at an academic health system in New York City, BMI >40 kg/m² was the second strongest independent predictor of hospitalization, after old age [89]. Furthermore, in a study from France included 124 patients with COVID-19, the need for invasive mechanical ventilation was associated with a BMI of ≥ 35 kg/m², independently of other comorbidities [90]. So, obesity can shift the risk of COVID-19 to younger age raising the importance of obesity as a risk factor in patients with COVID-19.

The presence of metabolic Associated Fatty Liver Disease (MAFLD) was associated with a 4-fold increase in risk of severe COVID-19, independent of other metabolic risk factors [91]. Notably, MAFLD was also associated with increased risk among younger [92]. Furthermore, patients with MAFLD with increased fibrosis scores, such as FIB-4 or NFS were at higher risk of having severe COVID-19 illness, regardless of other metabolic comorbidities [93].

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