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Review Article

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Impact of COVID−19 on different organ systems and prognosis: A scoping review

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel virus SARS-CoV-2, has swept across the globe, affecting almost every country. The death toll resulting from COVID-19 continues to rise as it is highly contagious, and currently, there is no definite treatment available. As SARS-CoV-2 is transmitted mainly through droplets, the lungs are the primary organ to be damaged with diffuse alveolar involvement. Moreover, failure of other organ systems leading to myositis, disseminated intravascular coagulation and acute kidney injury has also been reported. Besides, cytokine storm has been hypothesized as a potentially life-threatening complication of COVID-19. In this review, we aim to compile the current knowledge about the impact of SARS-CoV-2 on various organ systems and the prognosis. This will help in early identification of complications and appropriate intervention of COVID-19 cases to increase the survival rate.

KEYWORDS: ARDS; Complications; Cytokine storm; Dissiminated intravascular coagulation; Myositis

1. Introduction

Coronavirus refers to a group of related viruses belonging to family Coronaviridae and subfamily Orthocoronavirinae. Its name is derived from the Latin word “corona”, meaning crown, based on the electron microscopic appearance of small spiky bulbar projections called peplomers. As an RNA virus, coronavirus is also a positive single-stranded enveloped virus known to be infective for birds and mammals. Although the virus is known to be able to invade various tissues in other mammals, for humans the preferring target site of invasion is the respiratory system. Seven coronaviruses are identified to cause disease in humans and most of these viruses belong to one of the following two groups, *i.e.* alpha coronaviruses (229E and NL63) and beta coronaviruses (OC43 and HKU1)[1]. Experience told us the coronaviruses may cause mild to moderate symptoms in common. Worse still, they have caused two pandemics known as severe acute respiratory syndrome (SARS) in 2002-2004 and Middle East respiratory syndrome (MERS) in 2012. As per World Health Organization report, SARS affected 29 countries with over 8000 confirmed cases and 774 deaths, whereas MERS affected 27 countries with about 2500 confirmed cases and 866 deaths[2,3]. In December 2019, a new coronavirus (later named SARS-CoV-2) emerged and engulfed almost every country across the globe very rapidly. By 14th December 2020, a total of 72.8 million population were affected world-wide leaving over 1.62 million dead with this new pandemic called coronavirus disease 2019 (COVID-19). With exponentially increasing cases being reported daily, no prediction seems to be enough to forecast the total devastation this disease will have in terms of morbidity and mortality. Fever, cough, dyspnoea and altered sense of taste and smell are the common symptoms of COVID-19 whereas arthralgia, myalgia, chest tightness, sore throat, anorexia and diarrhoea are some of the lesser common symptoms. However, the classical triad of fever, cough, and dyspnoea are seen in 15% of the patients[4].

COVID-19 is similar to seasonal flu in terms of symptoms, spread pattern, as it transmits mainly through droplets and its predilection for lung tissues. However, with a worldwide prevalence of about

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9 343 infections per million population and the mortality as high as 2.3%, COVID-19 has poised a major health concern to humanity[5]. Compared to seasonal flu, COVID-19 has a longer incubation period and is more contagious[6]. Though the symptoms may appear by the 5th day, the incubation period varies from 2 to 15 days. Patients with COVID-19 can be contagious 2 days before the development of the first symptom and continue to be infective up to 10 days. Lack of a definite treatment, unavailability of vaccines, possible mutation of the virus, and an unpredictable progression of the disease further aggravates the concern. Although some patients may have minimal symptoms and even be asymptomatic, some may present with severe pneumonia or complication such as ARDS, myocarditis, septic shock, venous thromboembolism, and multi-organ failure. Diffuse alveolar damage of the lungs leading to ARDS has been considered as the most common cause for mortality, but there are reports suggestive of SARS-CoV-2 affecting other organs either by aggravating a pre-existing disease or by independently affecting other organs.

Being a novel disease, COVID-19 was first reported in December 2019, and not much is known regarding its pathophysiological basis and progression yet. However, experience from SARS and MERS told us that understanding the pathological basis and progression of the virus' predecessors can help figure out its effect on various systems and events leading to multi-organ failure and death. Hence this review article highlights the effect of COVID-19 on various systems based on the literature currently available.

2. Data collection

For this qualitative review, PubMed, Scopus, and Google Scholar were searched and screened using different combinations of keywords, COVID-19/SARS-CoV-2 and ARDS, ACE2, comorbidities, myositis, disseminated intravascular coagulation (DIC), gastrointestinal tract, central nervous system (CNS), kidneys till 10th July 2020. The titles and abstracts of the articles were screened, and suitable articles were selected. Both review articles and original articles written in English language were included. Articles whose full text could not be accessed were excluded. EndNote X6 was used for citing the article.

3. Effect on respiratory system

Although it has been reported that all organ systems can be affected by SARS-CoV-2, the respiratory system is no doubt the primarily affected one. The entry of the virus is through the upper respiratory tract by attaching to angiotensin-converting enzyme 2 (ACE2) 'receptor' present in the nasal and pharyngeal mucosa. The mucosa of the respiratory tract also contains a protease-transmembrane serine protease 2 that primes the spike or S protein and facilitates the viral attachment to the receptors[7]. Although this mechanism is similar to that of SARS-CoV and MERS-CoV, presence of a 'furin cleavage site' at the priming site of S protein is postulated to make SARS-CoV-2 highly pathogenic, which can explain its high infectivity[8]. The pneumocytes in the alveolar spaces are rich in ACE2 thus making them the common sites for viral infiltration and immune-mediated destruction[9,10].

The attachment or binding of the virus to ACE2 is followed by viral penetration through membrane infusion or endocytosis. Once internalized into the host cells, the viral RNA begins to replicate, resulting in the biosynthesis of viral proteins. These viral proteins then undergo maturation and are released into the circulation (Figure 1)[8]. Once infected, the symptoms may either be very mild (fever, myalgia) or very severe such as dyspnea and even ARDS based on the person's immune response which involves activation of both innate and adaptive immune response[11,12].

The antigen-presenting cells (APCs): dendritic cells (DC) and alveolar macrophages present around the epithelial cells play a central role in innate immune response[13]. Although the exact mechanism of the SARS-CoV-2 entry into the APCs still warrants further research, various mechanisms have been hypothesized, and one of which is the phagocytosis of infected cells by the DC and macrophages. Perhaps there could be a direct infection of these cells by the SARS-CoV-2 virus but the fact that there is limited expression of ACE2 on the DC and macrophages, which limits this hypothesis. Or maybe there are other receptors or proteins involved. It has been reported that in addition to ACE2 receptors, the SAR-CoV binds to dendrite cell-specific intracellular adhesion molecule 3 grabbing nonintegrin (DC-SIGN) and DC-SIGN related proteins. The DC and alveolar macrophages are found to be rich in DC-SIGN. Once the APCs internalizes the infected cells, these are then presented to the CD4+ and CD8+ T cells initiating the adaptive immunity[14,15]. Initially, the immune response is well-coordinated followed by an innate response releasing disproportionate inflammatory mediators. This is then followed by a poorly regulated adaptive immune response releasing enormous amounts of cytokines resulting in a 'cytokine storm' causing acute lung injury and acute respiratory distress syndrome (ARDS)[12,16,17].

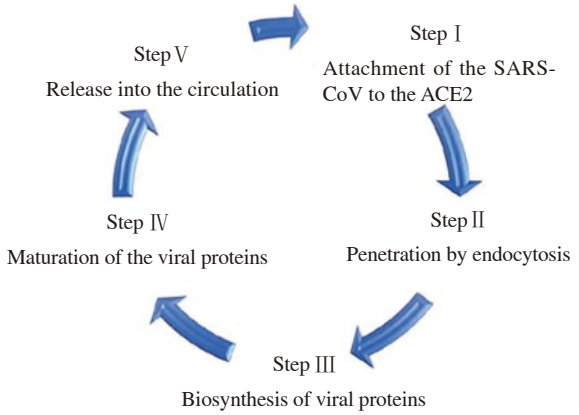

Figure 1. A diagrammatic presentation of the mode of entry of SARS-CoV in a host.

Once the virus enters the host, it stimulates the releases of specific inflammatory mediators which in turn stimulates and activates the macrophages. These activated macrophages then release cytokines such as IL-1, IL-6, and TNF-α, and the chemokines CXCL 10 and CCL 2 into the circulation. This results in increased capillary permeability and vasodilation causing the plasma to leak into the alveolar interstitial spaces. Accumulation and compression of the alveolar spaces cause decreased production and secretion of surfactant by the alveolar type Ⅱ cells leading to collapse of the alveoli and impairing gaseous exchange[18,19]. Moreover, activation of CD4+ T helper cells (Th 1 cells) releases the cytokines IL-17, IL-21, and IL-22 which enhances the production and accumulation of neutrophils and macrophages. This exaggerated response leads to cytokine storms which further damages the alveolar cells causing severe hypoxemia and ARDS[20-22]. In a case study reported by Xu *et al.*, histopathological autopsy finding of COVID-19 patients revealed bilateral diffuse alveolar damage with fibromyxoid exudates and lymphocytic dominated interstitial mononuclear inflammatory infiltrates. Evidence of ARDS was evident in both lungs. The right lung showed desquamation of pneumocytes along with formation of hyaline membrane, and the histopathology of the left lung showed pulmonary oedema and hyalinization indicating early phase of ARDS[23].

One aspect of COVID-19 which makes it different from other causes of ARDS is its non-uniformity in the progression. Three main factors are important *i.e.* severity of the infection (depends upon the viral load, hosts immune response, and comorbidities), patients' ventilatory support response to hypoxia, and the duration between onset of the disease and initiation of treatment[24]. As already mentioned, respiratory system may either present mild symptoms such as dry cough and sore throat or severe ones like chest pain and dyspnoea. In addition, COVID-19 may also be associated with silent hypoxia which refers to a state of severe hypoxia, characterized by rapidly falling oxygen saturation, with minimal or no symptoms of respiratory distress. The sudden and rapid deterioration in respiratory function within hours is observed in these patients. This is due to the concomitant presence of both hypoxia and hypocapnia resulting in the failure of stimulation of respiratory centers[25,26]. Hence, ARDS is a life-threatening complication of COVID-19. Based on the severity of ARDS and degree of hypoxia, COVID-19 pateints are catagorized into mild, moderate and severe. Those with moderate to severe ARDS require mechanical ventilation and are associated with poor prognosis[27].

4. Effect on cardiovascular system

Cardiovascular disease (CVD) is one of the most common comorbidities responsible for death in COVID-19 patients. Cardiovascular system complications or effects of a pre-existing CVD were also seen in SARS and MERS cases. Peiris *et al.* followed up 75 hospitalized SARS patients and reported 2 deaths out of 5 were caused by acute myocardial infarction[28]. In another study conducted by Li *et al.*, 46 SARS patients underwent echography for 30 consecutive days from the date of admission. They found that these patients had reversible subclinical diastolic dysfunction with minimal effect on systolic function. However, the extent of impairment was greater in critical cases[29]. In a cohort of 121 diagnosed SARS patients, Yu *et al.* studied the cardiovascular symptoms and found that tachycardia even without fever was the most common symptom presented in 72% of the patients. Other complications noted were hypotension in 50%, bradycardia in 15%, cardiomegaly in 11% and transient atrial fibrillation in 1%[30]. In a study on the autopsy finding of eight patients who succumbed to SARS, pulmonary thromboembolism was found in four patients and deep vein thrombosis in three. Subendocardial infarct was seen in one patient, and one patient had valvular vegetation in tricuspid, mitral and aortic valves with multiorgan infarcts[31]. Badawi *et al.* in their systemic review of 637 MERS patients found hypertension (50%) and diabetes mellitus (50%) to be the most prevalent condition followed by cardiac diseases (30%) and obesity (16%)[32].

The cardiac cells, cardiac fibroblasts, and endothelial cells of the coronary blood vessels are rich in ACE2[33]. Although the mechanism and extent of damage to cardiomyocytes following SARS-CoV-2 infection is still not clear, it is for sure that uncontrolled and unregulated immune response results in overload of inflammatory mediators and cytokines thus damaging the cardiomyocytes causing myositis. Moreover, damaging effects of hypoxia or a direct viral toxic effect of SARS-CoV-2 are also possible causes that need to be explored. It has been hypothesized that ACE2 regulates heart function and its overproduction has a cardioprotective action. Hence, SARS-CoV-2 infection reduces ACE2, which could deteriorate pre-existing cardiovascular diseases[34,35]. An epidemiological survey report from mainland China conducted on 44672 confirmed COVID-19 patients revealed that 17% of them were associated with cardiovascular complications including hypertension. Out of the reported 1023 deaths, 39.7% had hypertension and another 22.7% had other CVD. Also, the fatality ratio of CVD and hypertension was 10.5% and 6.0% respectively[36]. Similarly, Chen *et al.*, in an epidemiological study on 99 patients of COVID-19 found that 40% of the patients had an underlying CVD[4,37]. Another study by Huang *et al.* found 30% of COVID-19 patients to be associated with CVD and hypertension[12].

Though a pre-existing cardiac disease may be considered as a comorbid condition, damage to the myocardium induced by SARS-CoV-2 infection also causes mortality. Fan *et al.* in a retrospective study on 73 patients of COVID-19 admitted in ICU found that high sensitive troponin I (hs-TnI) was elevated among the non-survivors indicating its damage to cardiac cells. Moreover, this increased hs-TnI had a poor prognosis and was associated with a short duration between the onset of the symptom to death. It was also observed that for every one unit increase of hs-TnI levels, the risk of mortality increased by 20.8%[37]. In another study on 416 hospitalized patients, 19.7% of the patients had cardiovascular involvement with a mortality rate of 51.2% as compared to 4.5% among those without cardiac complications. Laboratory profile

of patients with cardiovascular involvement showed elevated hs-CRP, serum prolactin, hs-TnI, *N*-terminal pro-B-type natriuretic peptide indicating damage to myocardium[38]. In a case series study of 187 COVID-19 patients, Guo *et al.* reported that 35.3% had an underlying CVD condition such as hypertension, coronary artery disease, and cardiomyopathy and another 27.8% had elevated TnT levels indicating myocardial injury. They reported a mortality of 7.62% for patients with no pre-existing cardiac disorder and normal TnT levels, 13.33% for those with an underlying cardiac disease but normal TnT levels. The mortality rate of patients without an underlying cardiac disease but elevated TnT level was 37.50%. The highest mortality of 69.44% was observed in patients with an underlying cardiac disease and elevated TnT levels[39].

5. Effect on blood vessels

Patients with underlying coronary artery disease, ventricular dysfunction, or hypertension are at a high risk of developing acute coronary syndrome following SARS-CoV-2 infection. This could be due to the direct effect of the infection or increased oxygen demands of the myocardial cells. Moreover, the release of inflammatory mediators and abundant cytokines could rupture a pre-existing atherosclerotic plaque[40]. Inflammation of the blood vessels causes endothelial dysfunction, and platelet activation predisposes the patient to develop thrombosis. Impaired coagulation profile and DIC have been reported as a cause of death in COVID-19[41,42].

Xiong *et al.* in their meta-analysis reported that prothrombin time (PT) and D-dimer levels were significantly elevated in severe COVID-19 patients[43]. This increase in D-dimer and PT points towards DIC which was a common entity found in deceased COVID-19 patients. Fibrin clots are formed in response to viral infections which protects against the virus. Therefore, there is a possibility that a severe COVID-19 infection may induce fibrinolysis as a cause of DIC[43,44].

In a study of Tang *et al.*, among 183 COVID-19 positive patients, 71.4% of the non-survivor had overt DIC compared to 0.6% of the survivors. The D-dimer levels and fibrin degradation products in non-survivors were elevated on admission, and as their disease progressed fibrinogen levels were reduced[41]. In another study on 201 COVID-19 positive patients, high D-dimer and PT were observed in patients who developed ARDS. Besides, 52.8% who died had elevated D-dimer levels compared to those who recovered[45].

6. Effect on renal system

The incidence of acute kidney injury (AKI) in COVID-19 positive patients is around 4% to 9% with a higher incidence reported from critical patients[46,47]. The extent of renal damage depends upon the severity of the infection and is usually associated with poor prognosis. Although the mechanism of renal damage is still not clear, other mechanisms such as a multi-organ dysfunction following viral septicaemia, effect of cytokine storm or direct infection of the kidneys following SARS-CoV-2 infection could play a role in the pathogenesis of AKI[46]. Loss of ACE2 enzymatic activity on the renal tubular cells affects the transportation of sodium. This causes an increased blood pressure along with acute and chronic detrimental effect on kidneys[33,48]. Patients with existing renal diseases are classified as high-risk patient with relevant high mortality. It is reported that AKI can occur anytime during COVID-19 therapy. For example, In one of the earliest reports of COVID-19 and renal diseases, 43.9% of patients presented with proteinuria and 26.7% had hematuria indicating a renal pathology out of the 701 admitted patients. During the treatment, 5.1% of the patients developed AKI. It was also found that the mortality increased by 4 times in patients with stage 3 AKI, confirming that advanced kidney disease is associated with a poor prognosis in COVID-19 patients[49].

7. Effect on CNS

Coronavirus affects the nervous system by invading the neurons directly or enters the CNS after infecting the respiratory system. Several manifestations such as loss of smell (anosmia) and taste (hypogeusia), seizures, convulsions, disorientation, and encephalitis have been reported[50].

Literature and studies regarding the effect of COVID-19 on CNS are scarce. However, it was reported that following the infection of SARS-CoV, the cerebrospinal fluid nalysis tested positive for the virus[51]. Li *et al.* in their study found that 12% of the 183 children admitted with encephalitis tested positive for anti-CoV IgM despite the absence of classical symptoms of COVID-19[52].

The sudden loss of smell and taste sensation has been identified as a marker of COVID-19 infection by the British Association of Otorhinolaryngology, and it is considered as a significant symptom by World Health Organization and Center for Disease Control even in the absence of any other symptoms. Numerous studies have reported that a sizable percentage of COVID-19 positive patients developed anosmia, hyposmia, and hypogeusia even in the absence of other respiratory symptoms[53]. It has been reported that about 80% of the patient could be having anosmia or hyposmia[53,54]. Animal studies have shown that ACE2 is abundantly expressed in the brain including the olfactory areas and motor cortex and also in the vagal complex of medulla[55,56]. This could imply that the SARS-CoV-2 may have a high affinity for the olfactory bulb thus exerting its neurotropic action and entering the CNS[55].

8. Effect on gastrointestinal (GI) systems

As mentioned earlier, the main target of COVID-19 is the respiratory system so that gastrointestinal manifestations are easily ignored. The epithelial lining in the oesophagus and the intestinal cell lining have high expression of ACE2 thus suggestive of a fecal-oral mode of the transmission of COVID-19. Data suggest GI

symptoms such as diarrhea, nausea, vomiting, loss of appetite, acute abdominal pain, and GI bleeding are usually presented at the time of admission or developed during treatment[57]. Diarrhea and loss of appetite were the most common symptoms reported by up to 50% of the patients. Initial studies reported the incidence of diarrhea to be about 3%. However, one of the latest studies from the same city has reported it to be around 79%. The reason could be that initially more emphasis was given to respiratory symptoms, and GI symptoms were ignored. In another meta-analysis study conducted in Hong Kong shows that 17.6% of COVID-19 patients had GI symptoms. Stool analysis shows RNA virus in 48.1% of patients even despite negative respiratory samples[58].

9. Conclusions

The pandemic COVID-19, caused by SARS-CoV-2, is a highly contagious viral pneumonia which has resulted in mass loss of lives. The virus enters the upper respiratory system by binding to ACE2 in the nasal and pharyngeal mucosa, following which an exaggerated immune response results in overproduction of inflammatory mediators and cytokines. This results in cytokine storm causing severe ARDS. Similar to elderly population, patients with coexisting comorbid conditions such as underlying heart disease, hypertension, diabetes mellitus, and renal pathologies have shown poor prognoses. Moreover, the virus may also have a direct cytotoxic effect on various systems leading to myositis, DIC, acute kidney injury, diarrhea, and nerve damage. Therefore, apart from evaluating comorbid conditions in high-risk patients, we have to vigilant regarding the complications to other organ systems while managing a case of COVID-19.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

The idea for the research was conceptualized by A.K.M. The literature search was done by A.K.M. and M.A. The manuscript was written by A.K.M. and critically reviewed and edited by M.A.

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