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Review Article

Insight into the Clinical Manifestations of COVID-19

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ABSTRACT:
Coronavirus disease (COVID-19) caused by SARS-CoV-2 has spread worldwide claiming many lives and has emerged as a global threat. It has an average incubation period of 6.4 days. Although majority of the patients present with common manifestations like fever and respiratory tract involvement, however SARS-CoV-2 has been found to have multisystem involvement affecting various other organs like gastrointestinal tract, renal, hepatic, cardiac, neurological, ocular, endocrine, skin manifestations etc. A knowledge of the wide range of clinical manifestations in COVID-19 will help clinicians in early diagnosis of the disease as often these extra-respiratory symptoms are the initial or the only manifestations of the disease. It will also help clinicians to have a high index of suspicion to identify patients who are more likely to develop complications.
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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which has become a global pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in Wuhan city of China in December 2019.[1] The incubation period of COVID-19 averages at 6.4 days ranging from 2-24 days.[2] Majority of the patients with COVID-19 present with respiratory tract symptoms. However it has also been found to involve other systems like gastrointestinal, hepatic, cardiac, renal, neurological, ocular, cutaneous, haematological symptoms etc and they may be the initial manifestation of COVID-19.[1] Therefore in this article we aim to throw light on the entire spectrum of manifestations of COVID-19 for the better understanding of the disease process and diagnosis.

RESPIRATORY SYMPTOMS

Majority of patients with COVID-19 present with respiratory tract involvement and the common symptoms experienced are fever (83–98%), shortness of breath (19–55%) and cough (59–82%).[3] Other features include sore throat, rhinorrhea, headache and confusion that may precede the onset of fever. Few patients were found to present with hemoptysis as well.[4] Patients presenting with dyspnea and hypoxemia can rapidly progress into acute respiratory distress syndrome (ARDS), multiple organ dysfunction, sepsis and shock within 1 week of presentation and carries very poor prognosis.[4] The time from onset of symptoms to development of ARDS averages at around 8-12 days.[5] A major difference between the seasonal influenza pneumonia and COVID-19 is the severity of the disease- rate of mechanical ventilation and ARDS was found to be higher in the COVD-19 patients with pneumonia.[6] Risk factors for severe illness and development of ARDS are mentioned in table 1. Other factors associated with severe disease include raised D-dimer, lactate dehydrogenase, aspartate aminotransferase etc.[7]

RISK FACTORS OF SEVERE PNEUMONIA IN COVID 19		
Age>60 yrs	Comorbidities – Diabetes, Hypertension, Cardiovascular,Malignancy,Chronic pulmonary disease	Elevated leucocytes, creatinine kinase levels

Table 1[7]

GASTROINTESTINAL AND HEPATIC SYMPTOMS

SARS-CoV-2 attacks host cells via angiotensin-converting enzyme 2 (ACE2) which is abundantly expressed on the alveolar cells of lung as well as the glandular cells of gastric, duodenal, rectal epithelia and enterocytes of the small intestine.[8] Therefore gastrointestinal symptoms are common in COVID-19 patients. Moreover, the virus is also known to cause direct viral infection of liver cells.[4] Results from a meta-analysis showed that gastrointestinal symptoms were most likely to be present in severe COVID-19 cases compared to non-severe cases (17.1% vs. 11.8%).[9] The common gastrointestinal manifestations seen in COVID-19 patients include diarrhoea, nausea/vomiting, anorexia and abdominal pain/discomfort.[1] Many reports have shown that the SARS-CoV-2 can be isolated from fecal specimens, hence one must keep in mind the possibitiy of feco-oral transmission of the virus and importance of hygiene and sanitation.[10] The most common hepatic manifestations in COVID-19 affected patients include abnormal elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.[9] However data on the incidence of liver failure in COVID-19 patients with pre-existing chronic liver diseases is insufficient and needs further studies.

RENAL MANIFESTATIONS

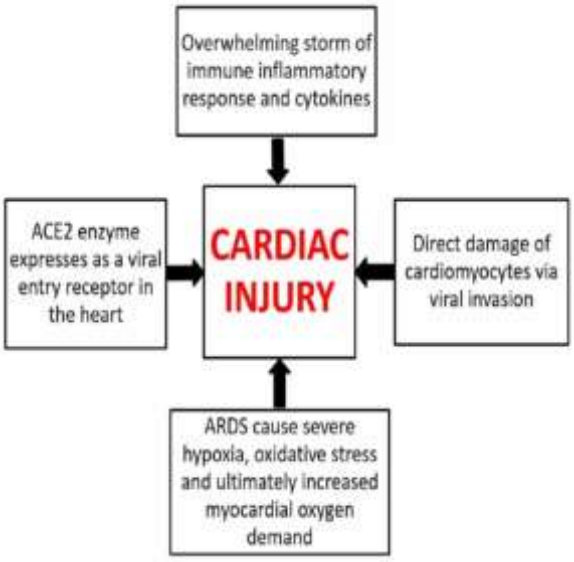
SARS-CoV-2 is found to adversely affect the kidneys by causing acute kidney injury (AKI) that is associated with severe COVID-19 disease and increased mortality.[11] Studies also suggest that pre-existing CKD is an independent risk factor for AKI in COVID-19 patients.[12] Moreover, pre-existing CKD is also associated with severe illness and death in COVID-19 patients.[13] Although studies have found that the prevalence of AKI in COVID-19 is low[1] but monitoring of kidney functions in affected patients is important. Multiple mechanisms may be involved in causing renal injury in COVID-19 (table-2)

MECHANISMS OF RENAL INJURY			
1. Cytokine induced damage	2. Fluid imbalance	3. Direct cellular injury	4.Hypoxia and hypoperfusion

(TABLE 2)[14]

CARDIAC MANIFESTATIONS

COVID-19 like pneumonia infections are associated with six-fold increase in cardiac events like acute myocardial injury.[15] Acute cardiac injury was a common complication reported in patients of COVID-19. Study by Zeng et al. reported a male patient aged 63 years with COVID-19 who developed fulminant myocarditis as a complication.[16] Inciardi et al. reported a case of a 63 year old female who developed acute myocardial inflammation subsequent to COVID-19 and signs of heart failure one week after respiratory symptoms.[17]



(TABLE 3)[18]

Therefore careful cardiac monitoring needs to be done in patients with underlying co-morbidities and critically ill patients with COVID-19 to prevent life threatening complications.

NEUROLOGICAL

SARS-CoV-2 related neuromuscular injury could be caused by the presence of ACE2 receptors in the nervous system and skeletal system[19], direct viral injury, hypoxia and immune responses.[20] The commonly reported symptoms were headache,

dizziness, loss of taste (hypogeusia) and smell sensation(hyposmia).[21]

Other less commonly reported neurological symptoms include impaired consciousness, ataxia, seizures, impaired vision, neuralgia and acute cerebrovascular disease.[1] The various other neurological complications involving the central nervous system that were reported in COVID-19 patients included transverse myelitis, acute hemorrhagic necrotising encephalopathy, encephalitis, epilepsy, ataxia and various PNS manifestation include, skeletal muscle injury, Guillian Barre syndrome.[22] Skeletal muscle injury in COVID-19 patients was higher in the group with severe illness compared to the non-severe group.[23] Previous studies reported that COVID-19 patient had a sensorineural hearing loss.[24]

HEMATOLOGICAL MANIFESTATION

Lymphopenia is a common finding in COVID19 patients as in other viral illness.[1] Thrombocytopenia is frequently observed in critically-ill patients compared to non-critically ill [25] Previous studies also observed coagulation disorder in COVID19 patients.[1] Moreover studies have also found that thrombotic complications like arterial and venous thrombo-embolism are common among patients in critically-ill COVID-19 patients.[26-28] Patients with coagulopathy in COVID-19 had increased D-dimer levels, activated partial thromboplastin times and prothrombin times.[29] Patients of COVID-19 with thrombotic and coagulation disorders are associated with poor prognosis.

OCULAR MANIFESTATION

Ocular manifestations are not commonly reported in COVID-19 affected patients.[30] A series of cases showed that COVID-19 patients developed symtoms and signs of acute conjunctivitis like conjunctiva hyperaemia, epiphora, chemosis and increased secretions.[31] Therefore one must adopt eye protective measures to prevent spread of SARS-CoV-2 via ocular route when in contact with affected individuals.[32]

DERMATOLOGICAL MANIFESTATIONS

Dermatological manifestations are also rarely reported in COVID-19 patients.[33]

A study in Italy showed that around 20.4% of the confirmed COVID-19 patients (18/88) developed cutaneous manifestations.[33] The most common cutaneous presentation noted in this study were erythematous rash followed by few cases of vesicular lesions and urticaria. As COVID-19 may result in asymptomatic cases, therefore knowledge of the cutaneous manifestations may help in early diagnosis of the infection.[34]

ENDOCRINE ABNORMALITIES

SARS-CoV is found to express various amino acids that may mimic the host adrenocorticotropic hormone (ACTH) and form antibodies to it which creates a relative cortisol insufficiency in the host.[35] The hypothalamic–pituitary–adrenal (HPA) axis may be affected by SARS viruses by causing hypophysitis or direct damage to hypothalamus.[35]

CONCLUSION

COVID-19 caused by SARS-CoV-2 primarily affects the respiratory tract but has multisystem involvement affecting all organs. Therefore it can lead to complications like acute kidney injury, acute myocardial injury, seizures, increased incidence of acute cerebrovascular disease, conjunctivitis etc. Hence one must be aware of the wide spectrum of manifestations of COVID-19 to aid in early diagnosis.

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