Extra Pulmonary manifestations of COVID -19: Review of available literature

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ABSTRACT:

The Corona virus disease or Covid-19, which has started in Wuhan city of Hubei province, China during December 2019 is well known to affect respiratory system causing pneumonia and other symptoms. But studies from various countries have shown that it can also result in extra-pulmonary manifestations which include various organs. They are renal involvement, cardiac manifestations, gastrointestinal symptoms, hematological manifestations, liver dysfunction, neurological symptoms and dermatologic manifestations. The present article is based on the fact for early diagnosis and prompt treatment for Covid-19 to reduce or avoid various complications involving different organ systems of the body.

KEYWORDS: *SARS CoV-2, COVID-19, Extra Pulmonary Manifestations, Pandemic*

INTRODUCTION:

COVID-19 or Corona virus disease is caused by Severe Acute Respiratory Syndrome – Corona virus – 2 (SARS CoV-2) and has affected nearly 55064128 confirmed cases with 1328015 deaths worldwide affecting 220 countries[(1)] till 17th November 2020. In India 89,12,907 confirmed cases with 1,33,993 deaths by 18th November 2020[(2)] were reported.

This disease was first reported from Wuhan city of Hubei Province, China during a pneumonia outbreak in December 2019[(3)] and the causative agent was identified as a Novel Corona Virus (nCoV)[(4-6)]. Nucleic acid studies have revealed that this novel Corona virus have homology with SARS corona virus [(7)] of 2003, so it was named as Severe Acute Respiratory Syndrome Virus Corona Virus-2 (SARS CoV-2), and the disease was named as COVID-19. The virus was said to be originated from the bats as it has 95%homology with the bat corona virus[(8)]. The disease has spread across the world infecting 220 countries and was declared as pandemic by World Health Organisation on 11th March 2020.

SARS CoV-2 primarily affects the respiratory system which causes symptoms ranging from mild rhinitis to severe pneumonia, and some patients developed ARDS. But studies from various institutions and countries have shown that SARS CoV-2 is no longer a respiratory virus, but also affects other organ systems leading to extra pulmonary manifestations which include Gastrointestinal symptoms, Renal involvement, Neurological manifestations, endocrinal involvement and haematological manifestations. The present article discusses the extra pulmonary manifestations of Covid-19 from the available literature.

SARS CoV-2: MORPHOLOGY AND GENOME:

SARSCoV-2 belong to genus Corona virus, family Coronaviridae and the Order Nidovirales.[(10)] Corona viruses are a group of highly diverse, enveloped, single stranded positive-sense RNA viruses measuring from 60nm to 140 nm in diameter. They possess spike like projections on their surface giving a crown like appearance, hence the name Corona virus.[(11)]

Genome of Corona viruses is single stranded positive-sense RNA. Two-thirds of RNA encodes viral polymerase (RdRp), RNA synthesis materials, and two non structutal polyproteins that are not involved in host response modulation (ORF1a-ORF1b). The other one third of the genome encodes four structural proteins – spike (S), envelope (E), membrane (M) and nucleocapsid (N), and other helper proteins.[(12)]

The envelope spike (S) protein mediates receptor binding and membrane fusion and is crucial for determining host tropism and transmission capacity.[(13,14)] SARS-CoV2 uses Angiotensin-Converting Enzyme2 (ACE-2) as an entry receptor in ACE2 expressing cells[(6)]. Biophysical and structural analysis indicated that S protein of SARS-CoV-2 binds ACE-2 receptors with 10-20 fold higher affinity than S protein of SARS-CoV[(15)]. This might be the reason for higher infectivity rate of SARS-CoV-2 than SARS CoV.

PATHOPHYSIOLOGY:

The Spike (S) protein on the surface of the SARS CoV-2 virus facilitates the entry of the virus into the host cell. It uses Angiotensin Converting Enzyme 2(ACE2) as entry receptors.

Cell entry also requires priming spike protein by cellular serine protease TMPRSS2[16]. This imples co-expression of ACE-2 and TMPRSS2 is required to complete entry of the virus into the cell.

Main mechanisms that may have a key role in the pathophysiology of various organs involvement in COVID-19 are viral toxicity, endothelial cell damage, thromboinflammation, dysregulation of Immune system, but complete importance of these mechanisms in the pathophysiology of the infection is not fully understood yet.

Viral toxicity: SARS CoV-2 is transmitted by droplets from the infected person making the respiratory tract as the portal of entry either directly or indirectly. It has affinity for respiratory epithelial cells including alveolar epithelial cells which have high expression of ACE2 , the entry receptor.[17] Along with these cells ACE2 is attached to cell membranes of arteries, heart, kidney and intestines.[18] Single cell RNA sequencing studies have confirmed the expression of ACE2 and TMPRSS2 in lung alveolar epithelial cells, nasal goblet cells, cholangiocytes, colonocytes, GI epithelial cells, esophageal keratinocytes, pancreatic ß cells, renal proximal tubules and podocytes.[19,20,21] These findings suggest multiple organ involvement may occur due to direct viral toxicity due to attachment of the virus to these cells.

Endothelial cell damage and Thromboinflammation: ACE2 expression has been demonstrated in the arterial and venous endothelium, and histoplathological studies have found microscopic evidence of SARS CoV-2 viral particles on the endothelium of kidneys[22]. Endothelial injury found in multiple vascular beds of lungs, kidneys, heart, liver, etc in COVID-19 patients can trigger excessive thrombin production inhibit fibrinolysis and activate complement pathways, thus initiating thromboinflammation and leading to microthrombi formation and vascular dysfunction.[23,24,25] Cases have been reported demonstrating the presence of exudates and microthrombi in histopathological examinations of COVID-19 patients.[26]

Dysregulation of the Immune system: Prior studies with Corona viruses proposed rapid viral replication, interferon signaling antagonism and activation of neutrophils and macrophages as mediators of hyperinflammation. In COVID-19 patients, elevation of inflammatory markers like C-Reactive protein(CRP), Ferritin, ESR, D-Dimer, fibrinogen etc have been noticed[27-29], this indicates the role of dysregulation of immune system.

EXTRAPULMONARY MANIFESTATIONS:

Cardiac manifestations: ACE2 is expressed on cardiovascular tissue, including cardiac myocytes, fibroblasts, endothelial cells ad smooth muscle cells.[30] Studies have also reported isolation of virus from myocardial tissue[31]. Patients with pre-existing cardiovascular disease may have higher levels of ACE2, which would potentially predispose them to more severe COVID-19.[32] Also right ventricular dysfunction may occur as a result of elevated pulmonary vascular pressures secondary to ARDS(33) , pulmonary thromboembolism[34]. Studies have been reported of myocardial injury in COVID-19 patients. Myocardial injury is manifested as increased levels of markers like Cardiac troponin–I, Creatinine kinase, a-hydroxybutyrate dehydrogenase and lactate dehydrogenase(35). Clinical presentations in case of cardiac involvement are Myocardial ishchemia, Myocardial infarction, Myocarditis, Arrhythmias, Atrial fibrillation, Sinus tachycardia, QT prolongation, Cardiomyopathy etc.

Gastrointestinal manifestations: 12-61% of COVID-19 patients were shown to have gastrointestinal symptoms[36,37,38]. Studies have also reported only gastrointestinal manifestations without respiratory symptoms[39,40]. The commonest gastrointestinal presentation among COVID-19 patients was diarrhea, also other symptoms like nausea, vomiting, anorexia, abdominal pain were also reported.[38] Viral RNA was isolated from stools[37] and also live viral shedding of infectious virions in feces have also been reported[41].

Renal manifestations: ACE2 and TMPRSS are significantly expressed on podocytes and proximal convoluted tubules which makes them a potential host for SARS CoV-2. Acute kidney injury is a common complication of COVID-19, and is also associated with mortality[42, 43]. Other presentations include electrolyte imbalance (hyperkalemia, hypernatremia etc), proteinuria, hematuria, metabolic acidosis[43,44]. Collapsing glomerulopathy was also reported in few cases[45,46].

Neurological manifestations: SARS CoV-2 virus may access the central nervous system via the nasal mucosa, lamina cribrosa, olfactory route or by retrograde axonal transport. Nasal epithelial cells express highest expression of ACE2 in the whole respiratory system[47], this may account for the loss of smell or taste in majority of COVID-19 patients[48,49,50]. Other neurologic manifestatios include headache, dizziness, fatigue, malaise, encephalopathy, encephalitis, Gullian Barre syndrome etc. Neurovirulence of COVID-19 may reflect the proinflammatory and prothrombotic cascade in the wake of cytokine storm, as it affects the brain vasculature and blood brain barrier.

Hematological manifestations: COVID-19 patients presented with various abnormalities in the laboratory investigations. It is believed that SARS CoV-2 induce hyperactive immune response, known as cytokine storm in COVID-19 patients, which leads to spilling of high levels of cytokines in the circulation. As a result of the overproduction of proinflammatory cytokines, multi organ failure may occur[51,52]. According to various studies, majority of the patients were reported to have lymphopenia- a marker of impaired cellular immunity [53,54]. In addition

thrombocytopenia[55], leukocytosis[56], were reported. Elevation in other inflammatory markers like C-reactive protein, D-Dimer, Ferritin, lactate dehydrogenase, ESR were reported in many COVID-19 patients[58,59,60]. Other complications may include Myocardial infarction, Ishchemic stroke, Deep vein thrombosis, pulmonary embolism etc.

Hepatobiliary manifestations: Histopathological studies have confirmed the presence of SARS CoV-2 in the liver tissue. The virus may directly damage the biliary ducts by binding to ACE-2 on cholangiocytes.[61] Hyperinflammation seen with cytokine storm and hypoxia associated metabolic derangements are other mechanisms of liver damage[62]. Elevated hepatic aminotransaminases, elevated bilirubin and low serum albumin were also observed in various studies[63,64].

Endocrinal Manifestations: A report from Centre for Disease Control (CDC, USA) stated that 24% of hospitalized patients and 32% of patients admitted in ICU due to COVID-19 had underlying diabetes. This implies patients with diabetes and obesity are at risk of developing more severe disease[65]. Another study from Newyork city reported, where out of 257 critically ill patients 36% had diabetes and 465 were obese[66]. Patients with COVID-19 exhibited abnormalities in glucose metabolism like increased hyperglycemia, euglycemic ketoacidosis, diabetic ketoacidosis. A study from China, which include 658 COVID-19 patients 6.45 of them presented with ketoacidosis[67]. The pathophysiology for this maybe due to elevated cytokine levels, which lead to impairments in the pancreatic ß-cell function and apoptosis[68] and as a result decreased insulin production and ketosis. ACE2 expression on pancreatic cells have also been reported[69], which may contribute to direct binding of SAS CoV-2 to ß-cells which may affect insulin deficiency and hyperglycemia.

Obesity is also a risk factor for COVID-19 severity[70], which may be related to effect lung functions like decreased lung volumes and compliance, increased airway resistance etc[71]. In addition increased adiposity has been linked with alterations in cytokines, chemokines and adipokines including proinflammatory cytokines like TNF-a∝, IL-6, IL-8, Leptin and adiponectin[72,73].

Dermatologic manifestations: A study from Italy first reported skin involvement in COVID-19, which showed nearly 44% of patients have shown skin lesions[74]. The dermatologic manifestations include erythematous rash, urticaria and chicken-pox like vesicles.

Pregnancy and COVID-19: Studies on clinical characteristics of pregnant women with COVID-19 showed that symptoms of the disease are similar in both pregnant and non-pregnant women and main symptoms were fever and cough[75]. Although currently there is no evidence of vertical transmission, mother to child transmission cannot be excluded[76]. Recent studies have shown that perinatal COVID-19 may cause severe effects on fetus which include fetal distress, premature labor, newborn respiratory distress, thrombocytopenia and even prenatal death[77].

CONCLUSION:

Although SARS CoV-2 mainly affects the respiratory system, it also causes extra pulmonary complications. But studies have shown that patients were also presented with other organ systems involvement with or without pulmonary symptoms. The present article summarizes the extra pulmonary manifestation of COVID-19 with the available literature. It is shown that COVID-19 may involve different organ systems with or without pulmonary manifestations and sometimes may lead to multiorgan failure. This implies that a COVID-19 patient can present with any of the symptoms discussed and a detailed history from the patient can give a clue about the exposure to SARS CoV-2. This is followed by investigations including RT-PCR along with other markers and prompt treatment. As trials for an effective vaccine are still under progress the only possibility to escape from the disease is to prevent it by following proper measures strictly as suggested.

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