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Extra Respiratory Manifestations of COVID- 19- A Review

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ABSTRACT

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has become a global health threat. It has GIT as well as extra respiratory manifestations. The present review article highlights extra respiratory manifestations of COVID- 19.

Keywords: Coronavirus disease, extra respiratory, GIT.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global health threat, infecting 1 844 863 people and resulting in 117 021 deaths. SARS- CoV- 2 is similar to severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus in that these coronavirus infections are responsible for severe and potentially life- threatening acute respiratory syndromes in humans.[1]

An infected person's lungs are the organs most affected because the virus accesses host cells via angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells. The virus uses a surface glycoprotein, called a 'spike' (peplomer), to bind to ACE2 and enter the host cell. The ACE2 receptor is highly expressed in the lungs, kidneys, gastrointestinal (GI) tract, liver, vascular endothelial cells, and arterial smooth muscle cells.6 Thus, all of these organs and systems with high expression of ACE2 receptors might be speculated targets for SARS- CoV- 2 infection.[2]

Thus, respiratory manifestations such as cough, sputum production and shortness of breath remain the most common symptoms, following fever. In addition, upper airway manifestations, including nasal congestion and sore throat, are observed in patients exhibiting mild disease.[3]

COVID-19-related mortality has affected more individuals than its antecedents, SARS and MERS, combined. The number of identified cases is steadily growing, and the outbreak has rapidly spread to many different areas in China and more than 200 other countries in a short period of time.[4]

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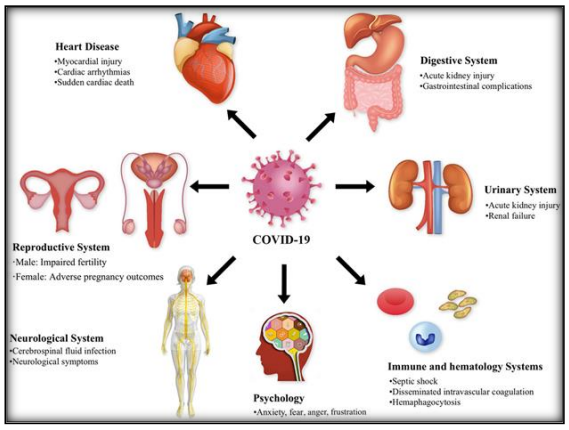
Organ-specific manifestations of COVID- 19



Gastrointestinal manifestations

SARS-CoV-2 also affects gastrointestinal organs because ACE2 is abundantly expressed on glandular cells of the gastric, duodenal and rectal epithelia as well as on endothelial cells and enterocytes of the small intestine. In addition, many reports show that SARS-CoV-2 can be detected in fecal specimens as well as in oesophageal, stomach, duodenal and rectal samples.[5]

Jin et al,[6] recorded either diarrhea, nausea, or vomiting in 74 of the 651 infected patients reviewed in their study. Interestingly, patients who experienced GI symptoms were more likely than those without GI symptoms to have a more severe disease course, characterized by greater degrees of liver insult (17.57 vs. 8.84%), development of ARDS (6.76 vs. 2.08%), and ICU admission requiring mechanical ventilation (6.76 vs. 2.08%) (32). Further, nearly a quarter (22.97%) of the study population who experienced critical illness reported GI symptoms at the initial presentation.

A recent meta-analysis including 4234 COVID-19 patients from 60 studies reporting gastrointestinal symptoms showed that the prevalence of all gastrointestinal symptoms was 17.6% and that severe COVID-19 cases were more likely to have

gastrointestinal symptoms than non-severe cases (17.1% vs. 11.8%).[7]

Cardiac manifestations

COVID-19-associated cardiac complications have been reported frequently and the mechanisms appear complicated, including direct viral injury, hypoxemia, unstable hemodynamic status with hypoperfusion, enhanced systematic inflammation, ACE2 receptor downregulation, increased endogenous catecholamine production and medication toxicity.

Chen et al,[8] reported that approximately 20% of these patients had signs of myocardial injury as reflected by increases in plasma N- terminal pro- B- type natriuretic peptide (NT- proBNP) and cardiac troponin I (cTnI) levels. Also, in a retrospective study of 52 critically ill COVID- 19 patients, 15 (29%) of these patients had increased cTnI levels (ie, >28 pg/mL). There is an estimated 12% of COVID- 19 patients without pre- existing or known ischemic heart disease had elevated troponin levels or cardiac arrest during the hospitalization.39 Particularly, cTnI levels were shown to be above the 99th centile upper normal limit in 46% of nonsurvivors, as compared to 1% of survivors.

Zou et al,[9] performed mapping of cells in various organ systems expressing ACE-2 with the use of single-cell RNA sequencing. Cells expressing similar or more ACE-2 than lung type II alveolar cells (AT2) were deemed as having the potential for increased vulnerability to SARS-CoV-2 (64). In their study, >7.5% of myocardial cells displayed ACE-2 expression suggesting that the heart may be at high risk for direct cellular toxicity by SARS-CoV-2 entry and replication. This ability to infiltrate cardiac tissues appears to be similar to MERS-CoV and SARS-CoV-1.

Hepatic Manifestations

The liver is another organ that can be affected by SARS-CoV-2. Commonly reported hepatic manifestations of COVID-19 to include elevations in serum levels of alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin, while levels of albumin are decreased.

Shi et al,[10] in a single-center retrospective study (n = 99) in patients with reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19, nearly half (43%) of patients demonstrated abnormal liver chemistries. Decreased albumin was noted in 98% of patients, while serum levels of AST, ALT, and bilirubin were elevated in 35, 28, and 18% of patients, respectively. Similarly, in an analysis of 1,099 patients, increased levels of AST were observed in 18.2% of patients with the non-severe disease and 39.4% of patients with severe disease, while increased ALT levels were observed in 19.8% of patients with the non-severe disease and 28.1% of patients with severe disease.

Huang et al,[11] first reported that circulating levels of liver function tests, such as serum transaminases, bilirubin, LDH, and prothrombin time (PT), were significantly higher in COVID- 19 patients admitted to ICU than in non- ICU patients. Management of liver transplant recipients has remained a challenge for physicians during the COVID- 19 outbreak. It is recognized that transplant recipients are more susceptible to SARS- CoV2 infection, are more likely to have increased severity of illness, and prolonged viral shedding.

Renal manifestations

The kidneys are one of the most frequently affected extrapulmonary organs in patients infected with SARS- CoV- 2; especially, in those patients who are severely ill. Previous studies of patients affected by the 2013 SARS outbreak have shown that kidney damage is mainly characterized by tubular injury (as reflected by abnormal urine test results) and increased serum creatinine and urea nitrogen concentrations. The mechanisms of acute kidney injury (AKI) in COVID-19 could be multifactorial, such as cytokine damage, cardiorenal crosstalk, hypoxia, intra-abdominal hypertension, fluid imbalance, hypoperfusion, rhabdomyolysis-related tubular toxicity and endotoxins.[12]

Yang et al,[13] in their study of 710 COVID- 19 patients reported that 44% of these patients had combined proteinuria and hematuria, 26.9% had hematuria alone, 15.5% had elevated serum creatinine, and 14.1% had elevated urea nitrogen levels. In a study performed by Chu et al,[14] 6.7% of 537 patients with SARS developed an AKI in the setting of normal Cr on admission. Additionally, Chu et al. revealed a significantly higher mortality rate (91.7%) associated with those having evidence of renal impairment compared to those with normal renal function in the setting of SARS (8.8%).

Neurological manifestations

The presence of ACE2 receptors in the nervous system and in skeletal muscle is suggesting a mechanism for SARS-CoV-2-related neuromuscular injury. Apart from ACE2, COVID-19-associated nervous system damage may also be caused by direct infection injury, hypoxic injury and immune responses. A retrospective clinical study of 214 laboratory-confirmed COVID-19 cases reported that 78 patients (36.4%) had neurological manifestations, including 53 (24.8%) with central nervous system (CNS) injuries, 19 (8.9%) with peripheral nervous system (PNS) injuries and 23 (10.7%) with skeletal muscle injuries.[15] Dizziness (36 patients; 16.8%) and headache (28 patients; 13.1%) were the most commonly reported CNS symptoms; impairments of taste (12 patients; 5.6%) and smell (11 patients; 5.1%) were the most common PNS symptoms. In

addition, impaired consciousness, acute cerebrovascular disease, ataxia, seizures, vision impairment and nerve pain were reported in <10% of patients.

Magnetic resonance imaging (MRI) of the brain showed hyperintensity along the right lateral ventricle wall and hyperintense signal changes in the right mesial temporal lobe and hippocampus, indicating meningitis; SARS-CoV-2 RNA was detected in the cerebral spinal fluid (CSF).[16]

Psychological manifestations

Several factors may induce psychological disorders during the quarantine. History of psychiatric illness was found to be closely associated with anxiety and anger within 2 to 6 months for patients who were subject to release from quarantine. Interestingly, healthcare workers reported more severe symptoms of post- traumatic stress when compared to controls (nonhealthcare workers) after being quarantined. Unsurprisingly, after quarantine, healthcare workers also felt increased levels of stigmatization, having had more avoidance behaviors, reported a higher loss in income, and felt more negatively affected psychologically. Among the various psychological effects include increased worry, anger, fear, frustration, guilt, isolation, loneliness, and nervousness.[17]

Cutaneous manifestations

Although many viral infections can be associated with skin manifestations cutaneous symptoms have rarely been reported in association with COVID-19. In China, 0.2–1.2% of 1099 COVID-19 patients had a rash.[18] In a series of 88 patients infected with SARS-CoV-2 in Italy, Recalcati showed that 18 patients (20.5%) developed cutaneous lesions, including 8 who developed lesions at disease onset. Furthermore, erythematous rashes were the most common manifestation (n = 14), followed by hives rash (n = 3) and chickenpox-like vesicles (n = 1). In addition, acro-ischemia presented with finger/toe cyanosis, skin bullae and dry gangrene in seven critically ill patients with COVID-19 in China and in a child in Brazil.[19]

Hematological manifestations

As for other viral infections, lymphopenia is common in patients with COVID-19. One meta-analysis of 24 studies comprising 2507 patients showed the prevalence of lymphopenia to be 56.5% (95% CI 46.5–66.4%). In addition, decreased platelet counts were observed in 32.3% and 16.4% of critically and non-critically ill COVID-19 patients, respectively. Coagulation disorders are another common complication.[20] Chen et al,[8] showed that patients with COVID-19 pneumonia have increased D-dimer levels (36% of patients), activated partial thromboplastin times (6%) and prothrombin times (5%). Thrombotic complications have been observed in patients with COVID-19, especially in those who are critically ill. The incidence of thrombotic complications among 148 patients with COVID-19 in an ICU was 31%, including a venous thromboembolism incidence of 27% and an arterial thrombotic event incidence of 3.7%.

Ocular manifestations

Ocular manifestations such as conjunctivitis, retinitis, anterior uveitis, and optic neuritis have been reported due to infections from the coronaviruses in the past. However, there is a paucity of literature regarding the ocular manifestations of COVID-19, possibly because these manifestations are under-recognized and under-reported.[21]

In a case series of 36 patients with confirmed COVID-19, nearly one third (31.6%) of patients developed ocular manifestations such as chemosis, epiphora, and conjunctival congestion. Interestingly patients with ocular manifestations experienced a severe disease course. Loon et al,[22] published a case series of patients with suspected and probable SARS infection who had tear samples collected and analyzed by PCR. Using WHO case definitions of suspected and probable cases, eight patients were classified as probable SARS (based on chest imaging suggestive of pneumonia or ARDS) and 28 were classified as suspects of SARS (anyone experiencing fever >100.4°F, respiratory symptoms and known contact with a confirmed case of SARS).

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CONCLUSION

The authors suggested that his disease has manifested all over the world. Its manifestations have been observed in many systems of the body.

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