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COVID-19 and Multiorgan Dysfunction Syndrome

Jitendra D. Lakhani, Sajni Kapadia, Rohit Choradiya, Roop Preet Gill and Som J. Lakhani

Abstract

Severe acute respiratory syndrome (SARS) is the leading cause of death in COVID-19 infection, however, multi-organ dysfunction due to COVID-19 and/or because of co-morbidities is a usual accompaniment causing unfavorable outcome. Early detection of organ failure and giving appropriate organ support may improve the chances of survival. Arterial Blood Gas (ABG) analysis; electrolytes coupled with clinical picture and with organ related laboratory investigations may help in diagnosis of MODS and sepsis in COVID-19 SEVERE SYNDROME. Acute kidney injury (AKI), myocarditis, thromboembolism, acute liver de-compensation, hospital acquired infections, cardiac arrest, glycemic variability, thyroid dysfunction and other organ failure may lead to MODS.As patients having multiple organ syndrome requires ICU admission and interventions like intubation, hemodialysis and other extracorporeal treatment support knowing holistically about "COVID-19 MODS" is important for treating physicians.

Keywords: COVID-19, SARS-CoV-2, Multi-organ dysfunction, cytokine storm, sepsis

1. Introduction

Corona viruses (CoVs) are a group of spherical/pleomorphic, enveloped, single stranded RNA viruses having club shaped glycoprotein projections, having four genera: alpha, beta, gamma and delta. Alpha and beta corona viruses infect many mammalian species ranging from bats to humans. Gamma and Delta Corona viruses affecting mainly birds known as Avian corona viruses [1]. First corona virus was isolated in chick embryo in 1937 and is known as Avian infectious bronchitis virus. The virus affects various organs as it is replicating in epithelial tissues of respiratory, genitourinary and enteric tracts of birds [1, 2].Evolution of corona virus as etiological agent of avian bronchitis to present COVID-19 pandemic is known to cause involvement of various organs like lung, intestine, liver and brain of animals and humans [2].

SARS-CoV-1, human beta-corona virus was first identified in 2003 as a causative agent of Severe Acute Respiratory Syndrome (SARS) outbreak of China which spread to four other countries [3, 4]. Number of corona viruses were identified then after which included Middle East Respiratory Syndrome (MERS) named MERS-CoV-2 which had features of acute respiratory distress with acute renal failure which was reported in large number of severe MERS cases [5, 6].

Corona Virus	Genera	Year of isolation	Organ involved/syndrome manifested
Avian infectious bronchitis virus	Gamma and Delta Corona viruses	1937	Chick Embryo / infectious bronchitis
Further evolution of Avian corona virus	Gamma and Delta Corona viruses	Poultry outbreaks	Epithelial tissues of respiratory, genito-urinary and enteric tracts of birds.
SARS-CoV-1	Beta	2003	Severe Acute respiratory syndrome (SARS)
MERS	Beta	2012	SARS with Kidney involvement
SARS-CoV-2	Beta	2019	SARS/Multi-organ involvement
SARS-CoV-2Variants: B.1.1.7, B.1.351P.1,B.1.427 B.1.429,B.1.617(delta Variant)	Beta	2020-2021	Variants of concern(VOC) having increased transmissibility, more severe disease

Table 1.
Evolution of corona viruses and their relation to organ involvement [1–10].

In December 2019, cases of pneumonia of unknown etiology were reported from Wuhan, China, which was identified to be caused by virus referred as "novel corona virus (NCV)-2019"/"2019-nCoV"and lung manifestation as "novel corona virus pneumonia (NCP)". WHO declared disease caused by new corona virus as COVID-19 (Corona Virus Disease) which appeared in 2019. [7]. As main manifestations of COVID-19 causing virus is Severe Acute Respiratory Syndrome, SARS-CoV-2 was the accepted name of the virus causing COVID-19.This new corona virus, had genetic and phylogenetic similarity to SARS-CoV-1 and MERS-CoV. All these three new corona viruses; SARS-CoV-1, MERS-CoV and SARS-CoV-2 are Beta corona virus causing human disease have some similarity and also having some dissimilarities, which is important to be noted as to understand pathogenicity and manifestations [8].

Though severe respiratory distress is an important feature of COVID-19 infection, it also causes acute kidney injury (AKI) like MERS virus and leads to multi-organ dysfunction syndrome (MODS). Multiple organ dysfunction in SARS-CoV-2 can be designated as MODS-CoV-2 which can represent multi-organ involvement of COVID-19 infection [9]. Like other viruses, genomic sequence of SARS-CoV-2 (COVID-19 virus) is changing over time and such variants are of concern (VOC); as it may cause rapid transmission, more severe disease and insufficient host response (**Table 1**) [10].

2. Pathogenesis and profile of various organ involvement in COVID-19

COVID-19 disease affects all organs of the body, predominantly lung, manifesting in form of severe acute respiratory syndrome (SARS) [11–14]. Multiple organ dysfunction is reported in severe manifestation of COVID-19 infection and is considered as late manifestation, while loss of sense of smell and of taste; a neurological manifestation, is reported as an early sign [11]. Mechanisms of COVID-19 induced multi-organ dysfunction is multi factorial.

Angiotensin-converting enzyme-2 (ACE 2) receptors, inflammatory mediators, rouge antibodies (autoantibodies), and dysregulated host response play important role in pathogenesis of COVID-19 organ involvement [12]. COVID-19 can also regarded as

autoimmune disorder in which auto-antibodies formation leads to organ dysfunction and severe disease and are called Rouge antibodies". They are auto- antibodies which is non-protective and may play part in targeted longer term organ demage [12].

SARS-CoV-2 virus enters human respiratory epithelial cells through attachment of its spike (S) protein to the human angiotensin converting enzyme-2(h-ACE2). Angiotensin-converting enzyme 2 (ACE2) is a key player in pathogenesis of lung involvement leading to SARS. ACE-2 also works as a receptor site and entry point of virus to host cells. Disruption of ACE/ACE2 balance and RAAS activation is responsible for COVID-19 progression which can lead to severe disease and result in multi organ dysfunction especially in patients having co-morbidities like diabetes mellitus, hypertension, and cardiovascular disease [13]. Massive cytokine release, immune depression, cytopathic effect of virus are other mechanisms by which severe COVID-19 disease develops which can result in multi-organ dysfunction [14].

3. Various organ involvement in COVID-19

Various organ and systems are involved in COVID-19 infection. Lung can be entry site, can cause atypical pneumonia and may results in ARDS. Liver, Kidney, Blood, Heart, Brain, Endocrine glands, Gastro-intestinal tract, and Skin are involved which is discussed in sections 4 to 11 of this chapter. **Table 2** summarizes manifestations of various organ involvement and their surrogate markers.

4. Hepatobiliary involvement

The hepatic injury has been found in increasing number in COVID-19 patients [15–18]. It has been evident from altered liver enzymes and total bilirubin. It ranges from mild to severe hepato-cellular damage. It was observed and reported by American college of gastroenterology News Team, that 20-30% individuals with COVID-19 infection had raised transaminases on admission [15]. Liver injury can be attributed to multi-organ dysfunction or the disease process itself causing viral induced hepatitis. The mechanism underlying the liver injury is yet not clear, but few theories might explain the patho-physiology. Firstly, critical illness and immune mediated injury and secondly ACE2 mediated direct hepatocyte injury by the virus itself [16]. The role of ACE2 receptor in infecting the cells by COVID-19 virus has been well established and these receptors are highly expressed in gastrointestinal epithelial cells which can infect cholangiocytes as well [17]. With severe COVID-19 infection, severe hepatic injury has been observed [18]. In severe infection, liver failure can occur due to hypotension and immune mediated mechanisms. Liver dysfunction is heightened in COVID-19 infection due to cytokine storm. Patients who already have underlying chronic liver disease like hepatitis B infection, alcohol induced hepatitis, primary biliary cholangitis may get decompensated during COVID-19 infection. As these patients are at increased risk of acquiring infection due to their immuno-compromised status, liver enzymes should be carefully monitored [18].

5. Renal system involvement and electrolyte imbalance in COVID-19 infection

COVID-19 infection and kidney injury has been well observed and reported. In one study by Chen et al., in 710 patients, 15.5% had raised creatinine on admission and 44% had hematuria and proteinuria [19–24]. It implies that kidney involvement

	Organ.	Clinical manifestations	Clinical marker	Investigatory marker	Evidence of organ involvement	Possible Management/ intervention
1.	Lung	Cough, Fever, Shortness of breath, chest pain, dyspnea and fatigue	ARDS	Nasal and throat swab, Chest X-Ray, HRCT Thorax, Arterial Blood Gas (ABG) analysis	Pneumonia, Atelectasis, Peripheral ground glass opacities, consolidative pulmonary opacities, crazy paving pattern on HRCT Thorax. Hypoxemia with acute respiratory alkalosis on ABG	Oxygenation, hemodynamic resuscitation and awake prone positioning. Steroids in patients who need supplemental oxygen. Non-invasive ventilation like BiPap/CPAP and mechanical ventilation.
2.	GIT	Nausea, Vomiting, Diarrhea, Abdominal pain and loss of appetite	Low Volume pulse, Hypotension, Tenderness on palpation of abdomen	Stool samples	Detection of SARS-CoV-2 RNA in stool samples of infected patients,suggest that ACE2 receptors are highly expressed in the GI tract.	Intravenous fluids, proton pump inhibitors, anti-emetics, anti-spasmodic and other supportive treatment.
3.	Kidney	Hematuria, and proteinuria	AKI, Sepsis, multi-organ failure, shock	Renal function test, Urine routine and microscopy, ABG analysis	Albuminuria, Proteinuria, hematuria, raised levels of serum creatinine and blood urea nitrogen, and eGFR<60ml/min in per 1.73 m^2, Metabolic acidosis on ABG.	Renal Replacement Therapy
4.	Hematopoietic system	Thrombosis and bleeding	Clots, pulmonary embolism, DVT and hemorrhage	Complete blood picture, PT INR, APTT, D-Dimer levels, ferritin, Procalcitonin, Serum LDH, ESR.	Lymphopenia, Leukopenia, thrombocytopenia, raised neutrophil/lymphocyte and platelet/ lymphocyte ratios and raised PT INR, APTT, D-Dimer, Serum LDH, Ferritin Procalcitonin and ESR.	LMWH or Unfractionated Heparin

	Organ.	Clinical manifestations	Clinical marker	Investigatory marker	Evidence of organ involvement	Possible Management/ intervention
5.	Immune System	Unremitting fever along with other cardinal features, ARDS, ACS	Hyperthermia, Hyper inflammatory state, shock	Complete Blood Picture, ESR, CRP, Serum Ferritin, IL-6 levels	Hyperferriteinemia, cytopenia, surge in inflammatory biomarkers and IL-6 levels can lead to cytokine storm resulting in ARDS, MODS and other severe syndromes, and even death.	Corticosteroids, Hydroxychloroquine, chloroquine and Tocilizumab.
6.	Cardio-Vascular System	Palpitations, dyspnea, chest tightness	Sinus tachycardia, DVT, thromboembolic complications	ECG, 2D-Echo, Troponin and creatine kinase levels, TTE, and Cardiac MRI	Acute cardiac injury, Reduced ejection fraction, increased levels of troponin and creatine kinase. Acute myocarditis, myocardial infarction and chronic DCMP.	Continuation of ACE inhibitors and ARBs. Statins, and antiplatelets.
7.	Nervous system	Loss of smell (Anosmia) and taste (dysgeusia), headache, dizziness, myalgia, neuralgia, fatigue, delirium, seizures.	Impaired consciousness, acute flaccid paralysis, seizure, ataxia	CT SCAN, MRI, ABG	Hypoxemia on ABG can detect hypoxic ischemic encephalopathy, CT SCAN can detect symmetric hypoattenuation of bilateral medial thalami and hemorrhagic rim lesions of bilateral thalami and medial temporal lobes can be evident on MRI.	Oxygenation, anticoagulation for stroke, mechanical ventilation in view of poor outcomes.
8.	Liver	Abdominal pain, loss of appetite, vomiting	Icterus (Acute Viral Hepatitis)	Liver function tests, GGT, Alkaline phosphatase, Serum LDH, USG Abdomen and pelvis, CT Abdomen and pelvis	Elevated levels of LDH, Bilirubin and ALT and AST, GGT and ALP levels suggestive of acute liver injury. USG may suggest fatty liver and portal venous gas on CT SCAN. Can be drug induced.	Avoidance of Hepato toxic drugs

	Organ.	Clinical manifestations	Clinical marker	Investigatory marker	Evidence of organ involvement	Possible Management/intervention
9.	Pancreas	Acute pancreatitis	Pancreatic injury, Prolonged hyperglycemia	Serum amylase and lipase levels, USG abdomen and pelvis.	Elevated levels of serum amylase and lipase	Use of high doses of insulin
10.	Thyroid	Palpitations, subacute thyroiditis, thyrotoxicosis	Swelling of thyroid gland	Thyroid function test	Low T3 levels with normal or low TSH	Continuation of thyroid medications.
11.	Skin.	Pseudo-chilblains (COVID-19 toes), Vesicular and maculo-papular eruptions, urticaria	COVID-19 heel	Clinical and local examination	Urticarial rash, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthema, chilblain-like acral pattern, livedoreticularis/racemose-like pattern, purpuric "vasculitic" pattern.	

Table 2.
Manifestations and markers of organ involvement

can be direct; perhaps in the form of glomerulonephritis that can be immune complex mediated or secondary to hypotension and multi organ dysfunction. The mechanism of injury can be multi-factorial. The presence of co-morbidities also play role in pathogenesis, as underlying renal injury in patients with diabetic nephropathy can get exacerbated due to decreased renal perfusion owing to shock. It has been found that this virus can have direct cytopathic effect on renal cells, as ACE2 is highly expressed in kidneys as well [20]. As cytokine storm can affect other organs due to increased pro-inflammatory markers like IL10, IL7, TNF alpha etc., which can result in injury to kidneys [21].

The electrolyte imbalances have also been found in form of hyponatremia and hypokalemia. In patients requiring ICU care, the strong association of electrolyte imbalance with severity of illness has been found [22]. In one multicenter case-control study in adult patients presenting in emergency department conducted in France, they found that 20.4% patients with infection had hyponatremia whereas it was found only in 12.3% controls [23]. Again, the possible role of ACE2, which is an important enzyme of RAS system can be postulated. As many patients have co-morbid conditions like hypertension and heart failure and are on diuretics, their water excretion is already disturbed and above that the severe COVID-19 infection with severe acute respiratory illness requiring ventilatory support renders these patients more dehydrated with fluid and electrolyte imbalance. In above mentioned French study, they found that hyponatremia was associated with most severe presentation of the disease and that it can be linked to increased ADH secretion in response to dehydration and volume depletion. Also, the syndrome of inappropriate ADH secretion occurs secondary to ARDS in such patients. The urinary loss of potassium was the primary cause of hypokalemia in these patients [24].

6. Hematologic system and COVID-19 infection

The COVID-19 infection has significant impact on hematopoietic system like other viral infections such as varicella, dengue, MERS-CoV, etc [25–33]. The most common haematological changes observed are lymphopenia, neutrophilia and eosinopenia [25]. It has been found that lymphopenia, thrombocytopenia and leucocytosis have been associated with increased severity and fatality in COVID-19 cases [26]. The ACE2 receptor is expressed on lymphocytes and this virus directly infects lymphocytes causing cell lysis [27]. Also the cytokine storm promotes the lymphocyte apoptosis. It has been recommended that the serial assessment of lymphocyte count must be ensued as an indicator of prognostic outcome [28].

The changes in haemostasis tests like prolonged prothrombin time, activated partial thromboplastin time and elevated D-Dimer levels has been found during the COVID-19 infection[29]. Increasing D-dimer levels and formation of microthrombi in peripheral blood vessels have been associated with severe forms of COVID-19 infection [30]. Also increased ESR, CRP and Serum LDH has been found. Liu et al reported that the severity of COVID-19 infection can be predicted by lymphopenia, neutrophilia and high levels of CRP and Serum LDH [31]. These altered coagulation profiles also suggest that this virus stimulates a low grade DIC state and resulting thrombocytopenia due to consumption [32]. Few researchers also believe that virus infect bone marrow hematopoietic cells directly inducing growth inhibition and apoptosis [33].

7. Cardiovascular involvement

The epicenter of COVID-19 infection is pulmonary complication, however, accompanied cardiovascular complications contributes to mortality [34–45].

Cardiovascular complications commonly found to be associated with COVID-19 are myocardial injury, myocarditis, dysrhythmias, heart failure, acute myocardial infarction (AMI) and venous thromboembolic events (VTE). Myocarditis as the cause of death was reported in 7% of 68 fatal COVID-19 of total 150 cases studied [35]. Another study of 191 patients from Wuhan reported 54 deaths; of which 28 (52%) had heart failure, overall prevalence being 23% (44 of 191) [36].

Various mechanisms are postulated for CVS manifestations like destabilization of vascular plaques due to systemic inflammation, viral infection induced increase in cytokine activity leading to increased cardiac demand and direct damage to the heart by utilizing ACE2 receptors of cardiac tissue by virus [37, 38].

Many patients already may have pre-existing cardiovascular disease like coronary artery disease, hypertension and others which leads to greater severity of COVID-19 infection. A meta-analysis of 1527 patients of COVID-19 infection, showed that the prevalence of hypertension and cardiac disease was 17.1% and16.4% respectively, and all of them were more likely to develop more severe illness requiring ICU care [39]. Previous viral infections, including Middle East respiratory syndrome coronavirus (MERS-CoV), have been linked with myocardial injury and myocarditis with increased troponin concentration [40]. Acute cardiac injury can be recognised by increased troponin levels which were reported to be present in 7 to 17 % patients who are admitted with COVID-19. Cardiovascular complications are life threatening; proper monitoring by following trend of troponin level can be useful. Many such patients may require admission to intensive cardiac care unit. [30, 36, 41] Knowing such complication as part of multi-organ involvement is important for clinicians, as it may improve outcomes.[42] Palpitations may manifest as initial symptom in around 7% of patients with COVID-19 [43]. Patients with COVID-19 are also has increased risk of venous thrombo-embolisms (VTEs) [44, 45].

8. Nervous system involvement and COVID-19 infection

With dreadful presentation of SARS-CoV-2 infection with acute respiratory failure requiring ventilatory support, it also has been implicated in activation of pro-thrombotic pathways leading to cerebrovascular stroke and Central nervous system (CNS) affection in form of parenchymal and vascular inflammatory responses leading to various neurological manifestations [46–55]. The commonly found (80%) early symptom of anosmia and dysgeusia despite absence of nasal congestion and discharge, suggests the involvement of olfactory bulb and tract [47]. The virus may invade CNS through olfactory epithelium and neuro-mucosal interface [48]. There can be neurological dysfunction due to metabolic derangements due to organ failure and hypoxemia in the form of encephalopathy. In one multicenter study conducted in 69 ICUs across 14 countries, it was found that 55% patients with COVID-19 admitted in ICU had delirium [49]. The authors also found high prevalence of acute brain dysfunction in these patients [49]. Also, encephalopathy can be the primary symptom especially in elderly patients [50].

The direct injury to cerebral blood vessels due to invasion of virus into endothelial cells has also been reported in few autopsy findings, with similar findings in other organs – lungs, kidneys, heart and liver [51]. These findings are evidence suggesting direct invasion of nervous system. Patients with COVID-19 infection are at increased risk of cerebrovascular events. Cerebral venous sinus thrombosis, ischemic stroke, subarachnoid hemorrhage and intraparenchymal hemorrhage have been reported, among them ischemic stroke being the most common [52]. Besides the presence of traditional risk factors for vascular thrombosis, COVID-19infection per se is associated with a hypercoagulable state which is reflected by elevated levels of D-dimer [53].

Isolated cases of meningoencephalitis, acute hemorrhagic necrotizing encephalopathy, acute disseminated encephalomyelitis (ADEM) and GBS have also been reported. In one case report of meningoencephalitis in 24-year-old male who presented with seizures and altered mental status, virus was isolated from CSF [54]. There are increasing number of patients with hemorrhagic encephalomyelitis, with MRI features of hemorrhagic lesions in medial temporal lobes, bilateral thalami and sub insular regions [55].

9. COVID-19 and Pancreas; Diabetes

Diabetes is the most prevalent co-morbidity in COVID-19, second only to obesity. If those with diabetes do contract COVID-19, they are indeed likely to develop more severe form of the disease particularly if the diabetes is uncontrolled [56–68]. Data from Wuhan, China confirms that approximately 20% of severe cases of COVID-19 do show diabetes, as co morbidity [36]. According to reports from India, of the first 125 deaths on COVID-19, 56% had diabetes, 47% had hypertension, and over a third had both diabetes and hypertension [57]. An Indian study of 231 patients of COVID-19 infections, 21.2% had co-morbidities of which diabetes mellitus and hypertension was the most common.[58]. In some stable diabetic patients with COVID-19, there was rapid worsening of glycaemic control requiring high insulin dose. Possibility of pancreatic affection due to virus is postulated as high level of ACE2 was found in the pancreatic islet beta cells. [59–61].

Wang et al demonstrated that 9 of 52 admitted patients in Wuhan with COVID-19 pneumonia developed pancreatic injury as evidenced by abnormality in serum amylase or lipase levels [62]. After viral entry into the beta cells, there is a downregulation of ACE2 leading to increased angiotensin level, which also impairs insulin secretion [63]. Possible mechanisms on pancreatic injury include (i) direct cytopathic effect of SARS-CoV-2 replication, (ii) systemic response to respiratory failure, and (iii) harmful immune response induced by SARS-CoV-2 infection [62].

An important feature of type 2 diabetes is low grade inflammation. There is long term immune system imbalance, metabolic syndrome, or nutrient excess associated with obesity [64, 65]. Also, in individuals with diabetes, there is an exaggeration of pro-inflammatory responses, especially IL-1, IL-6 and TNF-alpha. This may be further worsened in those with severe COVID-19. Prolonged hyperglycaemia alters the host immune system. Dysfunctions in leukocytes, monocyte and macrophage chemotaxis and phagocytosis, and damaged specific immunity have also been reported in subjects with diabetes [66, 67]. Moreover, diabetes shares common features promoting disease progression with infectious disorders such as pro-inflammatory state and endothelial dysfunction [68].

10. COVID-19 and Gastro-intestinal involvement

Though pulmonary manifestations such as fever and cough are the commonly reported presenting symptoms in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the presenting symptoms in other organs such as the GI tract and hepatobiliary, including nausea/vomiting and diarrhoea, were also reported [69–77]. The entry of SARS-CoV-2 in human cell is through protein ACE-2 which is found on the surface of lung alveolar epithelial cells and also on enterocytes of the small intestine [70]. One of the study of 1099 patients with COVID-19 in retrospective analysis showed that the main presenting symptoms were fever (87.9%) and cough (67.7%), followed by diarrhoea (3.7%) and vomiting (5.0%) [69]. Out of

all the GI symptoms, there was higher incidence of diarrhoea and abdominal pain present in severe COVID-19 patients than that in patients with mild COVID-19 [69]. In one of the larger studies, systematic review and meta-analysis of 35 studies on GI manifestations, consisting of 6686 patients of COVID-19infection, the three commonest symptoms include nausea and/or vomiting, diarrhoea and loss of appetite with the pooled prevalence of all GI symptoms was 15%[71].

Currently, loss of appetite was reported, ranging from 1.0% to 79% [71]. It can be explained by taste dysfunction up to some extent, which was found in as high as 88.0% in group of 417 mild-to-moderate COVID-19 patients in Europe. Also taste dysfunction almost go hand in hand with olfactory dysfunction with a high prevalence of 85.6% and may further aggravate loss of appetite as identified in the study [47, 72].

Furthermore, SARS-CoV-2 RNA was first detected in a stool specimen from the first reported COVID-19 case in the United States (US) [73]. In a study of Chinese cohort with 73 COVID-19confirmed hospitalised patients, 53.42% of the patients had detected viral RNA in the stools, after the complete clearance from the respiratory tract with undetectable viral RNA but still it had been identified in the stool specimen [74]. SARS-CoV-2 has also been detected in stool samples of the patients in one of the studies without having GI symptoms [75].

Many a times diagnosis of COVID-19 has been missed as initial presenting symptom may be involving GI tract rather than respiratory tract. Many researchers proposed that patients with GI symptoms might have a bad prognosis than those without digestive symptoms, hence clinician had to give importance to patients presenting with GI symptoms such as diarrhoea for early diagnosis [76, 77]. In the same study, rate of severity of disease was also significantly increased in patients with GI symptoms as compared with those without GI symptoms [76]. Pan and colleagues also showed the same result that as the severity of the disease increased, there is worsening of GI symptoms [77].

11. COVID-19 and Skin involvement

Skin manifestations of COVID-19 include a wide variety of skin disorders which may include specific COVID-19 related dermatoses and a variety of other skin disorders that may be worsened by COVID-19 infection [78–85]. Like other viral infections, skin rash is the most common manifestation, which is described as confluent, erythematous, morbilliform, maculopapular rash. Urticarial rash is found in one fifth of the skin manifested cases. Early lesions can be in form of vesicular eruptions which may appear before symptoms also. Pseudo-chilblain like lesions is described as late manifestation in which acral areas will have red vesicles or pustules. Livedo reticularis/racemose-like pattern can appear with COVID-19 symptoms. Purpuric "vasculitic" pattern is associated with severe COVID-19 infection [78, 79]. Acute urticaria is well known to be triggered by viral infections and COVID-19 is no exception [80]. Urticarial vasculitis has also been well demonstrated in a few patients. Urticarial vasculitis differs from urticaria and in that the lesions tend to persist beyond 24 hours and can be painful instead of pruritic [81]. Confluent maculopapular rash is also a well known manifestation of viral infections. Monomorphic vesicular exanthema is often considered an important clue to COVID-19infection. It differs from chicken pox in the fact that chicken pox rash tends to be polymorphic. Chilblain like acral pattern often manifests with cold sensitivity and purplish discoloration of the extremities. This is believed to be a manifestation of hypercoagulability and prothrombotic consequence of COVID-19. Livedo reticularis is believed to be often of similar aetiology. Purpuric lesions

are one of the most common manifestations of COVID-19. Purpuric lesions involving the heel known as "COVID-19 heel" is one the specific markers of COVID-19 infection [82–85].

The mutant strains of COVID-19 are believed to cause more extra pulmonary symptoms and thus skin manifestations of COVID-19 too could become more evident.

12. Lung involvement, ARDS and Multiorgan dysfunction

COVID-19 infection may start with influenza like illness with mild symptoms which can progress to severe acute respiratory distress in around 5.6–13.2% patients; a pooled estimate being around 9.4% [86–92]. A systematic review and meta-analysis reported risks of severity and mortality estimated from 18.0 and 3.2%, respectively. If we extrapolate the data of this meta-analysis, additional around 9% will have risk of severe disease other than ARDS [86]. ABG analysis data of critically ill COVID-19 patients showed mixed ABG picture, suggesting multi-organ involvement [87]. If only lung involvement was the cause of severe disease and/or death, ABG picture should have been of respiratory acidosis or in patients with hyperventilation and CO2 washout of respiratory alkalosis which was not the case in this study [87]. Accompanied metabolic acidosis in a mixed ABG pattern can be because of sepsis, AKI, lactic acidosis ketoacidosis which is reported in COVID-19 patients and in sepsis [87–89].

In lungs, diffuse alveolar damage (DAD), a pathological hallmark of ARDS, has been observed in direct viral invasion of cells and lytic effects [90]. In a systemic review by Bao et al. of 2700 patients of COVID-19, most common abnormalities found on HRCT Chest were ground glass opacifications (83%), ground glass opacification with mixed consolidation (58%) and adjacent pleural thickening (52%) followed by interlobular septal thickening (48%) and air bronchograms (46%) [91]. ARDS can be related to inflammatory markers and also to glycaemic variability, and thus ARDS can be one of the spectrums of MODS and may result in a vicious circle of metabolic derangements [92].

13. Cytokine storm as cause of mods

The cytokine storm caused by COVID-19 has been proposed to be associated with the severity of COVID-19 which is multisystem inflammatory syndrome [30, 93, 94]. The early symptomatic presentation of COVID-19 mainly include fever, cough, myalgia, fatigue, or may have dyspnoea. With the progression of disease in later course, dyspnoea may worsen in susceptible host to acute respiratory distress syndrome (ARDS) or multiple organ failure (MOF) [95]. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) is known to be associated with a cytokine storm like many other infectious diseases. [95, 96].

One of the major reasons for the deaths in this infection is suspected to be due to the "cytokine storm" [also called "cytokine storm syndrome"(CSS)]. Cron and Behrens bring the current knowledge of CSS. They define that "cytokine storm" is an activation cascade of auto-amplifying the production of cytokines due to dysregulated host immune response. The triggering factors for the host immune response may be due to infections, rheumatic disorders, malignancy, etc [97]. It is also thought that cytokine storm is a systemic inflammatory response to infections and drugs and leads to excessive activation of host immunity which further leads to activation of pro-inflammatory cytokines [98].

Cytokine Release Syndrome (CRS) is a similar entity which is mainly due to acute systemic inflammatory syndrome characterized by multiple-organ dysfunction (MOD). It has been said that chimeric antigen receptor (CAR)-T-cell therapy would be helpful to differentiate CRS from a cytokine storm [98]. For patients with COVID-19, C-reactive protein (CRP), and other inflammatory cytokines and chemokines are markedly elevated in the intensive care unit (ICU) patients [99, 100]. Many studies showed link between pro-inflammatory cytokines, especially interleukin 6 (IL-6), with the severity of illness in COVID-19 [30,101-103.].Increased D-dimer levels are also found in severe disease [104]. The higher concentration of cytokines also has a poor prognosis in COVID-19 [102, 105]. Activation of both innate and adaptive immune responses by SARS-CoV-2 infection can lead to dysregulated inflammatory responses which ultimately results into the cytokine storm [106]. Furthermore, the cytokine storm leads to apoptosis of epithelial cells and endothelial cells, and dysfunction of endothelial cells causing vascular leakage and, finally, result in ARDS, MODS and other severe syndromes, and even death [107].

Many therapies are targeted to reduce the cytokine storm which can results in one of the life-saving measures in severely ill COVID-19 infection. Out of many therapies, Corticosteroids, Hydroxychloroquine (HCQ) and chloroquine (CQ) and Tocilizumab (TCZ) (IL-6 Inhibitor) are widely used in the recent past. Corticosteroids inhibit the host inflammatory response and suppress the immune response and pathogen clearance [108]. In a retrospective study of 401 patients infected with SARS-CoV, the rational use of corticosteroids shortened hospital stays and reduced the mortality of seriously ill patients without complications [109]. In view of their in vitro antiviral effects and anti-inflammatory properties, CQ and its analogue HCQ are most potential therapies against COVID-19. CQ and HCQ can reduce CD154 expression in T cells and suppress the release of IL-6 and TNF53 [110]. TCZ, an IL- 6 receptor (IL-6R) antagonist, can inhibit cytokine storms by blocking the IL-6 signal transduction pathway [111].

14. Sepsis and Multi-Organ Dysfunction Syndrome (MODS) in COVID-19

Patho-physiology of SARS-CoV-2 infection is complex and is known to involve activation of the immune and hematologic systems [112–118]. Endotoxin and tumor necrosis factor-alpha (TNF-alpha) trigger the production of interleukin-6 (IL-6) and IL-8, which is followed by the cytokine storm. Further events lead to activation of the coagulation cascade through endothelial and tissue factor (TF) pathways, as well as systemic inflammatory activation [94, 112]. Moreover, SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE-2) receptors, which are widely distributed. not only in lung alveolar epithelial cells and oro-nasopharyngeal mucosa but also in the endothelium as well as vascular smooth muscle cells, in the brain, in the gut and in peripheral organs such as liver and kidney [113]. This suggests that the clinical spectrum of COVID-19 is not limited to local pneumonia, but rather represents a multisystem illness with involvement of different organs and potential for systemic complications [113]. It seems that the highly pathogenic SARS-CoV-2 is associated with rapid virus replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress.

Most SARS-CoV-2 infected patients admitted to ICU showed a dysregulated host response characterized by hyperinflammation, alterations in coagulation, and dysregulation in the immune response that further contribute to MODS, like occurs in sepsis [114, 115]. Due to virus infection and to MODS in some cases, many patients with severe COVID-19 meet the Third International Consensus Definitions for Sepsis (SEPSIS-3), which define sepsis as "a life-threatening condition that

arises when the body's immune response to infection damages the host's own tissues" [116]. Also, when performing specimen cultures in septic patients from a COVID-19 cohort, about 80% of patients had no bacterial or fungal infection and so viral infection would seem to be the only reason for sepsis which was reported in 50% of their 191 COVID-19 patients. This retrospective study from Wuhan reported Sequential Organ Failure Assessment (SOFA) score of 5·65 on admission. [36].SOFA score may increase on day 3 to 7as reported in one series of 50 patients of bacterial and malarial sepsis [117]. It may be due to release of mediators that there may be upward trend of SOFA score, development MODS and in mortality in sepsis patients who has unfavourable outcome. COVID-19 sepsis which can be called as viral sepsis or secondary sepsis which can be hospital acquired; may worsen the clinical phenotypes of these critically ill COVID-19 patients [118].

15. Co-morbidities, MODS and COVID-19

Co-morbidities like hypertension, diabetes, cardiovascular diseases and respiratory disorders are associated with COVID-19 infection and they serve as additional risk factors for severity and can have deleterious effect [119–122]. Significant difference was noted in COVID-19 outcomes in those who had co-morbidities and those without it [87, 121]. Multi-organ dysfunction could be due to COVID-19 or may be because of resultant deterioration of co-morbidities associated end–organ acute injury [87]. Drugs used for co-morbidities and for COVID-19 can also lead to multi-organ dysfunction [122]. **Table 3** shows list of co-morbidities commonly encountered in COVID-19 patients leading to organ/multi-organ involvement.

	Co-morbidity	Presenting features	Organ involved/ pathological feature	Consequences
1.	Sepsis/Hospital acquired Sepsis	Fever, Shock, Hypotension, decreased output, respiratory failure, Hospital/ventilator acquired pneumonia.	Lungs, Bloodstream infection, Cardiovascular and circulatory collapse, Renal shutdown.	ARDS, Septic shock, AKI, sudden cardiac arrest, and even death.
2.	Diabetes	Unaware of diabetes, Hyperglycemia, Hypoglycemia, Glycemic variability.	Multiorgan, Liver, Diabetic Ketoacidosis, Hospital acquired sepsis	Lactic acidosis, AKI, poor outcome
3	Hypertension	Unaware about hypertensive state, dyspnea, giddiness, headache, vomiting.	Kidneys, cardiovascular system, more chances of severe infection and SARS.	Hypertensive emergency, CVA (hypertensive bleed), AKI, Acute lung injury.
4	Cardiovascular Disease	Fever, palpitations, dyspnea, chest tightness, dry cough, nausea and vomiting.	Multiorgan-Heart, Kidneys, lungs, CNS	Coronary artery disease, Myocardial injury and myocarditis, dysrhythmias, heart failure, venous thromboembolic events (VTE), Cardioembolic stroke, renal infarction.

	Co-morbidity	Presenting features	Organ involved/ pathological feature	Consequences
5	Cerebrovascular disease	Loss of smell (Anosmia) and taste (dysgeusia), headache, dizziness, myalgia, neuralgia, fatigue, delirium, encephalopathy, seizures.	CNS, Spinal cord, Cranial and peripheral nerves.	Cerebral venous sinus thrombosis, ischemic stroke, subarachnoid hemorrhage and intraparenchymal hemorrhage, meningoencephalitis, acute hemorrhagic necrotizing encephalopathy, acute disseminated encephalomyelitis (ADEM) and GBS.
6	COPD/Other respiratory diseases	Fever, cough with expectoration, dyspnea, chest pain, shortness of breath, fatigue.	In lungs, diffuse alveolar damage (DAD), is a pathological hallmark of ARDS.	ARDS, poor prognosis, MODS.
7	Epilepsy	Seizures, fever, altered mental status, status epilepticus.	Hemorrhagic lesions in medial temporal lobes, bilateral thalami and sub insular regions.	Exacerbation of seizures.
8	Chronic Kidney Disease	Hematuria, proteinuria, vomiting.	Kidneys, cardiovascular system.	Metabolic acidosis, hypertension, decreased renal perfusion leading to shock,pulmonary odema,. heart failure.
9	Chronic Liver Disease	Diarrhea, abdominal pain, loss of appetite, vomiting.	In severe infection, liver failure can occur due to hypotension and immune mediated mechanisms which are heightened in COVID-19infection in the form cytokine storm.	Decompensation of hepatitis B infection, alcohol induced hepatitis, primary biliary cholangitis in COVID-19 infection can occur leading to liver failure.

Table 3.
Co-morbidities commonly encountered in COVID-19 patients leading to organ/multi-organ involvement.

16. Drugs used in COVID-19 and cause of MODS

Various drugs are used in COVID-19 which can alter immunity, can cause organ damage like acute liver and kidney injury, may lead to electrophysiological disturbances in heart and can contribute to pre-existing MODS or may become the risk factor [9]. Tocilizumab (TCZ), a monoclonal antibody which inhibits the interleukin-6 receptor may predispose COVID-19 patients to secondary infections [123]. Tocilizumab (TCZ) can cause liver dysfunction, lead to induction and reduction of cytochrome P450 enzyme and can cause allergic reaction apart from secondary infection [124, 125]. Use of HCQ and Azithromycin may be responsible for QT prolongation, which can in turn lead to torsades' de pointes [126]. Use of

corticosteroids in COVID-19 patients can also induce secondary bacterial and fungal infections and such patients may need more antibiotic coverage [127]. It is imperative to see the drug contribution in MODS of COVID-19 infections.

17. Fighting the COVID-19 pandemic; key messages

- Human Corona viruses can lead to Severe Acute Respiratory syndrome with other multiple organ involvement.

- Pathogenesis of COVID-19 MODS can be multi-factorial. Virus entry to the cell through human Angiotensin-converting enzyme-2 (ACE 2) receptor plays an important role in lung and in other organ affection. Inflammatory mediators, rouge antibodies, and dysregulated host response also play role in pathogenesis of COVID-19 organ involvement.

- Various organ and systems are involved in COVID-19 infection. Lung can be considered main but Liver, Kidney, Blood, Heart, Brain, Endocrine glands, Gastro-intestinal tract, and Skin are also involved.

- COVID-19 infection may start with influenza like illness, can lead to SARS with or without multiple organ involvement.

- Cytokine storm as cause of MODS which can lead to unfavourable outcome.

- COVID-19 per se is a sepsis syndrome as per recent definition of sepsis as there is dysregulated immune response. Secondary nosocomial sepsis is also not uncommon. Sepsis due to inflammatory mediators can cause MODS.

- Co-morbidities in patient having COVID-19 infection may serve as additional contributor to MODS.

- Drugs used in COVID-19 may be responsible for acute organ injury or predispose to infections which may be responsible for MODS.

- "FIGHTING THE COVID-19 PANDEMIC" is for better tomorrow.

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