

## REVIEW ARTICLE

# Unraveling the mystery of Covid-19 cytokine storm: From skin to organ systems

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**Abstract**

COVID-19 is a global pandemic that emerged from Wuhan, China. Besides pneumonia and acute respiratory distress syndrome, the disease leads to multisystem involvement in the form of myocarditis, arrhythmias, cardiac arrest, gastrointestinal symptoms, hypoxemic brain injury, acute liver, and renal function impairment. There are also reports of cutaneous lesions in form of urticarial and maculopapular rashes, chilblain like fingers and toes (covid feet), livedoid vasculopathy, and chicken-pox like or varicelliform vesicles. Clinically, many of these skin lesions are likely secondary to occlusion of small to medium blood vessels due to microthrombi formation or due to viral laden antigen-antibody immune complexes; and same explanation may hold true for possible hypoxemic injury simultaneously occurring in other vital organs like lungs, heart, brain, and kidneys. The histopathology, immunofluorescence and RT-PCR analysis of skin biopsies can provide useful insights for ascertaining the pathogenesis of this complex viral syndrome. Apparently, it is interplay of disarmed cellular immunity and over-activated humoral immunity that culminates in end-organ changes. The morbidity and mortality can be significantly reduced by upgrading the cellular immunity and downgrading the humoral response; along with prevention of hypoxemic and reperfusion injuries by using antivirals, immunomodulators, antioxidants, anti-platelets, and anticoagulants in judicious and phased manner.

**KEYWORDS**

Covid, cytokine storm, Covid feet

## 1 | INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) started from Wuhan, China in 2019 which is caused by severe acute respiratory syndrome-corona virus 2 (SARS-CoV-2). It has raised its head as an invincible pandemic spreading without any panacea, intriguing the commoner and the scientific community alike. Already there are more than 4.5 million cases worldwide with more than 300 000 mortalities, and the virus continues to spread and mutate with secondary attack rate of

30% to 40%.<sup>1</sup> There is no approved vaccine till date; however, several countries have initiated trials to explore potential vaccines. The current approach of social distancing, hand sanitization and wearing face mask seems very miniscule in preventing the community spread; and the development of herd immunity seems like a distant dream as of now!

Until few months back, COVID-19 was considered to just involve lungs causing severe pneumonia, eventually leading to cytokine storm and cardio-respiratory failure.<sup>2,3</sup> Gradually as more and more case reports started pouring in, there were evidence of involvement of heart, gastrointestinal system, liver, and kidneys.<sup>4</sup> Finally came the

Suruchi Garg and Mandeep Garg are co-first authors for their equal contribution.

reports of cutaneous involvement in the form of urticaria, chilblain like lesions on extremities and buttocks, livedoid vasculopathy, and varicella like vesicles.<sup>5,6</sup> Extensive review of literature based on epidemiology, pathogenesis, clinical presentation, histopathology, imaging, laboratory parameters, and treatment protocols was done by searching the following online databases: Google scholar, PubMed, web of science, bioRxiv, medRxiv, and researchgate.

## 1.1 | Genomic Structure of SARS-CoV-2

The genomic sequencing of SARS-CoV-2 indicates that it is genetically more identical to beta corona virus genera identified in bats.<sup>7</sup> There are structural differences compared to the earlier detected strains of SARS-CoV (about 79% sequence identity) and Middle East respiratory syndrome corona virus or MERS-CoV (nearly 50% sequence identity). On the contrary, it was more similar to two bat-derived SARS-like corona viruses - bat-SL-CoVZC45 (87.9% sequence identity) and bat-SL-CoVZXC21 (87.2% sequence identity).<sup>8</sup>

The virus has four major structural proteins: the spike surface glycoprotein, matrix protein, small envelope protein, and nucleocapsid protein. The spike protein targets the host receptors via the receptor-binding domains of angiotensin converting enzyme-2 (ACE2). The ACE2 protein is widely distributed in various human organs, including the respiratory system, gastrointestinal tract, blood vessels, bone marrow, spleen, thymus, lymph node, liver, kidney, and brain.<sup>9</sup>

## 1.2 | The origin of COVID-19

The origin of COVID-19 is still under investigation, but initial reports linked its origin to illegal trade of wild animals in Huanan seafood wholesale market located in Wuhan.<sup>3</sup> In the past as well, the origin of SARS virus has been traced to wet market and eventually to palm civets and wild bats in China.<sup>10-12</sup>

Another theory mentions that probably the virus leaked from one of the well reputed level 4 virology labs of Wuhan, located extremely near to the wet market. The lab is credited of isolating viruses from cave bats, understanding their genomic sequences and subsequently performing experiments on mice and primates to establish Koch's postulates in understanding the pathogenesis of SARS.<sup>10,13</sup> Though level 4 laboratories have highest level of bio-containment precautions, there is still a lot of controversy going on in possible leakage of this virus from the lab, but nothing substantial has been proven. The understanding of the actual nature of viral genome whether mammalian or synthetic is very essential in finding its cure and manufacturing a vaccine; as there are already multiple strains of mutated virus.

## 1.3 | Routes of transmission

There are three main established transmission routes for the COVID-19 namely, droplet transmission, contact transmission, and

aerosol transmission.<sup>14-16</sup> The duration of viral shedding extends upto 24 days, which is different from the studies from China; with biological difference or sampling technique cited as the possible reasons.<sup>17</sup> The duration of viral shedding for COVID-19 is not certain yet, but SARS-CoV-2 data indicate that 53% of cases achieved viral clearance in nasopharyngeal samples 21 days after symptom onset.<sup>18</sup>

In a Chinese study, ACE2 was highly expressed in absorptive enterocytes from ileum and colon in the patients who presented with abdominal discomfort and diarrhea.<sup>18</sup> Based on this finding, there is a possibility of enteric route as another portal of entry. Considering that the virus is transmitted via this route and if it retains its pathogenic potential; authors propose that eventually there is a remote possibility of COVID-19 turning into water borne disease as well. In that scenario, it may pose a potential danger to close nit communities and slum dwellers but this hypothesis needs further validation and research.

## 1.4 | Clinical presentation

The common clinical presentation of COVID-19 in the first week of illness is sore throat which is sometimes associated with loss of taste and loss of smell. Other symptoms like fever, fatigue, difficulty in breathing, cough (dry or with phlegm), diarrhea, bloating sensation, and abdominal discomfort are usually seen with start of the second week of illness. By the end of second week, there are reports of systemic presentations like hemoptysis, hematuria, cardiac complications (like myocarditis, arrhythmias, and shock), deranged hepatic, and renal functions.<sup>19,20</sup> Cutaneous presentations like urticarial skin lesions; chilblain like painful papulo-nodular lesions in fingers, toes, and buttocks; livedoid vasculopathy like lesions in legs; and chicken pox like blisters were reported in occasional cases.<sup>5,6</sup>

The articles from different parts of world had some common attributes that the mortality was higher in elderly population and especially the ones who had underlying coexisting disorders like hypertension, cardiovascular disease, diabetes, chronic pulmonary obstructive disease, malignancy, and so on. In a Chinese study, the complications observed in deceased patients included acute respiratory distress syndrome (ARDS) (100%), sepsis (100%), acute cardiac injury (77%), type I respiratory failure (51%), heart failure (49%), alkalosis (40%), hyperkalaemia (37%), acute kidney injury (25%), and hypoxic encephalopathy (20%).<sup>21</sup> Acute cardiac injury and heart failure were the most common features in deceased individuals which were unrelated to any underlying cardiovascular disease.

Involvement of both central and peripheral nervous systems has been reported in COVID-19 patients. The commonly noted central nervous system manifestations include headache, dizziness, altered consciousness, seizures, and acute cerebrovascular disease. Dysfunction of both taste and smell, injury to skeletal muscles with an elevation of serum creatine kinase has also been described.<sup>22</sup> Acute stroke has been described in both old and young patients suffering from COVID-19.<sup>23</sup>

## 1.5 | Laboratory parameters

The patients who test positive for COVID-19 on real time RT-PCR show lymphopenia, leukocytosis, fall in hemoglobin levels, increased inflammatory markers like CRP, D-dimer, serum ferritin levels, fibrin degradation products, and prolonged prothrombin time. With involvement of different systems, there is elevation of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatinine, creatine kinase, cardiac troponin I, N-terminal pro-brain natriuretic peptide. There is detectable increase in inflammatory cytokines and chemokines like TNF- $\alpha$ , IFN- $\gamma$ , IL2, IL6, IL8, and IL10 pointing toward interplay of both cell mediated and humoral type response. Though CD4 and CD8 count is significantly depressed, there is evidence of hyperactivity of these markers.<sup>4,17-19</sup> There is evidence of high proportion of HLA-DR (CD4 3.4%) and CD38 (CD8 39.4%), over activation of T cells and increased level of Th17 and increased cytotoxicity of CD8 T cells; which points toward severe immune injury.<sup>24</sup>

Positive RT-PCR results have been obtained from samples taken from nasopharyngeal swabs, bronchoalveolar lavage, blood, stool, and urine. Secondary bacterial infections were also found in some deceased patients and persistent lymphopenia or deranged cellular immunity was a bad prognostic sign.<sup>25</sup>

## 1.6 | Role of imaging and its histopathological correlation

Chest radiographs and the computed tomography have demonstrated hallmark peripheral ground glass opacities (GGOs) and lung consolidations which are typically bilateral, peripheral and posterior.<sup>26</sup> The sensitivity of the CT scan has been found to be higher than routine nasopharyngeal swab in appropriate clinical settings, though the specificity is less. The Dutch study has also described venous congestion and venous thrombosis on CT scan surrounding the areas of GGO, which points toward the vascular injury besides the injury on lung parenchyma.<sup>26</sup> Chest X-ray and CT scan can be used to monitor disease severity and progression also. Severely ill patients who require ICU admission tend to show bilateral areas of multi lobular and subsegmental consolidation. On the other hand, patients with lesser symptoms who do not need ICU admission, usually have bilateral GGO and subsegmental consolidation on CT. GGO increase in size with disease progression. Consolidation and crazy paving pattern may also be seen. Resolution of the lesions with disappearance of the crazy paving will be seen during recovery. Larger areas of consolidation also suggest disease progression.<sup>27</sup> Lung ultrasonography has come up as another useful, cost effective and noninvasive modality in evaluation and monitoring of patients.<sup>28</sup>

Histopathological correlation of these GGO obtained from post-mortem core biopsies suggest that there is exudation of fluids into the alveoli due to attachment of viral proteins, endocytosis, and subsequent injury to the alveolar surface. Consolidation is a sequential feature where there is fibrosis in interstitial spaces following fibroblast stimulation, hyalinisation and matrix formation.<sup>27</sup> Previously, the

biopsies performed on SARS patients revealed multinucleated syncytial cells with atypical enlarged pneumocytes in the intra-alveolar spaces, showing viral cytopathic-like changes. Some cases showed neutrophilic infiltration with suspected superadded bacterial infection; fibrinoid necrosis of vessel wall, fibrin plugs, and pulmonary infarcts were also seen in cases beyond 14 days.<sup>29</sup>

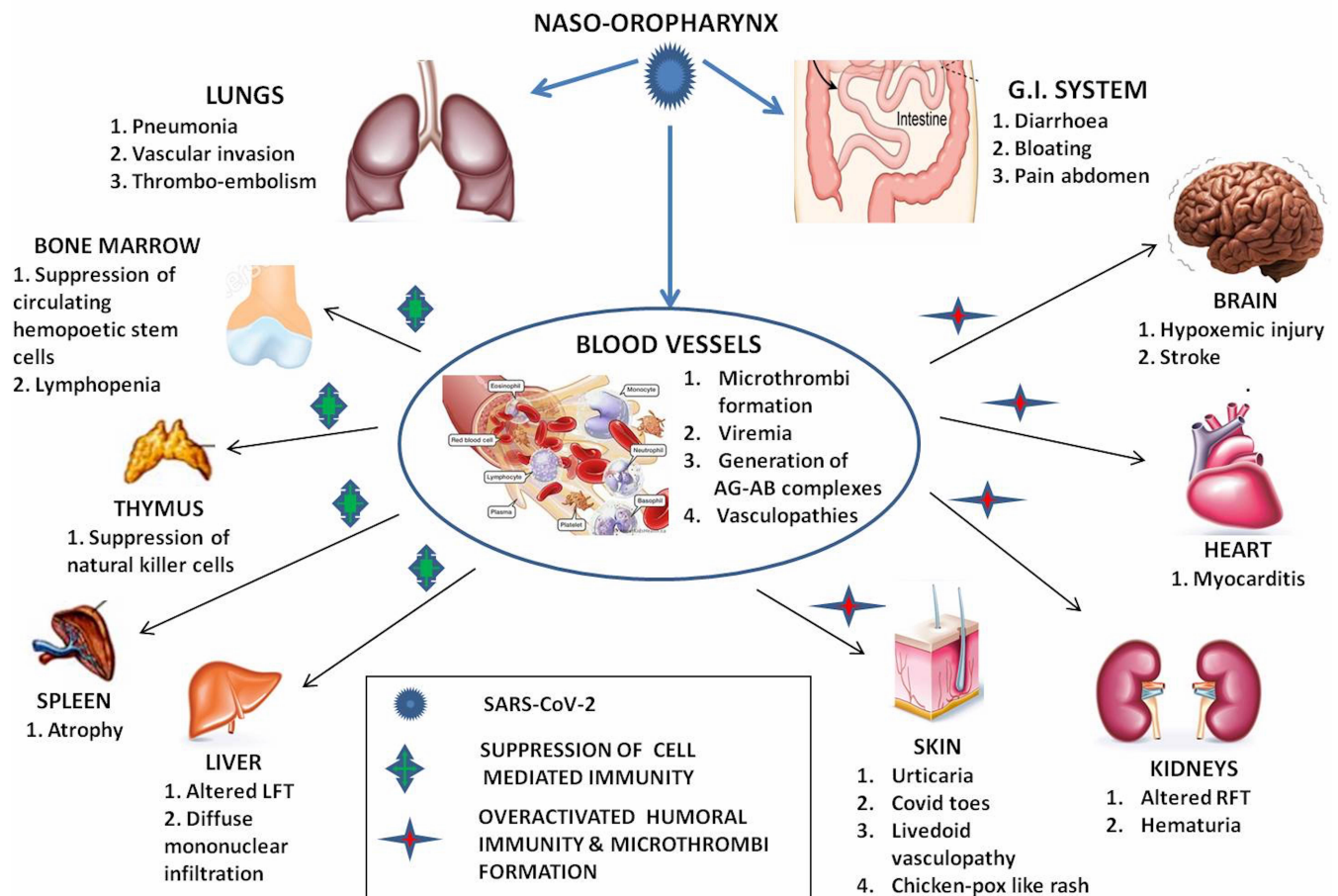
Patients with COVID induced ARDS have much higher rates of mortality as compared to those without ARDS. Critically ill COVID patients show reduced fibrinolysis. Fibrin deposition and microvascular thrombi are known to occur in the pulmonary vasculature of severely ill COVID-19 patients and may contribute to the ARDS.<sup>30</sup>

In the context of cardiac injury, the biochemical parameters were more consistent with myocardial injury. There was focal oedema, fibrosis, and myocardial hypertrophy in postmortem examination of heart tissue.<sup>24,27</sup> Brain tissue showed hypoxic injuries along with underlying electrolyte imbalance.<sup>21</sup> Liver demonstrated diffuse mononuclear and periportal and centrilobular hepatic necrosis. Infiltration was more toward cholangiocytes (presence of ACE2 receptors) rather than hepatocytes along with sinusoidal dilatation and focal hemorrhages and hepatic necrosis.<sup>24,27</sup> A Korean scoping study, mentioned that elevated liver enzymes and suppression of CD4 and CD8 count was directly correlated with disease severity. Though, it was also mentioned that it could be due to Lopinavir or Ritonavir and that these drugs should be used with caution as these may lead to injury in cholangiocytes.<sup>30</sup> Splenic tissue was shown to be atrophic; and there were areas of focal hemorrhagic necrosis, macrophage proliferation and phagocytosis. There was also lymph node atrophy and decrease in number of lymph nodes along with necrosis. Immunohistochemical staining demonstrated that CD4 +ve T cells and CD8 +ve T cells were decreased in spleen and lymph nodes.<sup>31,32</sup> Though there is extensive damage found in other organs, kidneys were relatively preserved. Acute renal impairment was unlikely as studied in a series of 116 patients and only 3 of 48 urine samples were found to be positive for SARS-Cov-2 who did not have previous renal disease.<sup>33</sup>

## 2 | UNDERSTANDING THE PATHOGENESIS BASED ON CLINICAL PRESENTATION AND HISTOPATHOLOGICAL PICTURE

Based on extensive review of literature and the histopathological picture created in different systems, the possible modus operandi of SARS-CoV-2 can be predicted and summarized here (Figure 1). The virus enters the throat through aerosol or droplet infection and enters the lung and gastro-intestinal system facilitated by abundant presence of ACE2 receptors.<sup>34</sup> The virus attacks these receptors through s-proteins present on its surface and enters the alveolar epithelial cells and enterocytes by the process of endocytosis through receptor binding proteins. The patient starts getting mild fever, cough, and abdominal discomfort, though many patients remain completely asymptomatic depending upon viral load and resistance posed by host immunity. Most of the patients with good immunity tide over the

## SARS-CoV-2: Disarming the cell mediated immunity and eventually causing cytokine storm by microthrombi formation, viral load and overactive humoral immunity



**FIGURE 1** Flowchart explaining how the SARS-CoV-2 virus attacks the nasopharynx and gains entry into lung, gastrointestinal system, and blood vessels due to abundant presence of ACE2 receptors. Cell mediated immunity is disarmed by atrophy and destruction of lymph nodes, thymus, spleen, and liver. Blood vessels in lung are easy target due to presence of ACE2 receptors initiating cascade of micro-thrombi formation, immune complex deposition, and exaggerated humoral immune response leading to subsequent hypoxic injury to various vital organs

infection at this stage. Initial response to the virus is by cell mediated immunity, generated in regional lymph nodes which involve activation of natural killer (NK) cells and helper T cells, also handled by thymus, spleen, and liver. The virus also shows vasotropism toward endothelial cells in the blood vessels. The blood vessels are the easy targets due to their close proximity in alveoli and abundant presence of ACE2 receptors.<sup>34-36</sup> Endothelium gets upregulated by the expression of selectin and other adhesion molecules released by respiratory epithelium and neighboring cells. Activated endothelium can also secrete pro-inflammatory cytokines like IL6, type 1 and 2 IFNs, and TNF- $\alpha$  in response to a virus infection.<sup>36</sup>

There are elevated D-dimer levels detected earlier in course of illness while IL6 levels start rising by 13th day of illness, by this time D-dimer is already 10 times elevated.<sup>21</sup> D-dimer is an important marker in disorders of coagulation; this leads to a possibility that the process of microthrombi formation starts early in alveolar vessels and IL6 is a late response secondary to humoral response. This discrepancy between D-dimer and IL 6 also suggests that early D-dimer elevation may represent

a true thrombotic state due to cellular activation triggered by the virus.<sup>26</sup> Elevated serum D-dimer may also lead to embolic vascular events like stroke.<sup>22</sup> Oudkerk et al highlighted that the sequential D-dimer levels and CT scans can be utilized in monitoring of patient for possible pulmonary thrombo-embolism and venous clots and delineated when to start the prophylactic anti-coagulant therapy.<sup>26</sup>

The patients with more severe disease present with rather complex pathogenesis. The cell mediated immunity is knocked off by the viral load in the initial phase of illness. The histopathological studies demonstrate that there is atrophy of spleen and thymus and widespread periportal and centrilobular destruction in liver along with depression of NK cells and T cells.<sup>27</sup> There is also evidence of depression of circulating hemopoetic stem cells released from bone marrow eventually leading to depression of cell mediating immunity.<sup>36</sup>

Apparently, the virus gains entry into vessels present in interstitial spaces and starts damaging the endothelial cells leading to the generation of nitric oxide and reactive oxygen species (ROS) in presence of leukocytes<sup>36</sup>; finally there are haemorrhagic exudates in lungs as detected



by postmortem core needle biopsy.<sup>25</sup> The injury produced on endothelial cells evokes a cascade of events involved in coagulation process. Body tries to repair it by depositing platelets and red blood cells and releasing various proinflammatory mediators. This in turn, leads to production of microthrombi in the blood vessels. When these virus laden microthrombi get dislodged and circulate in different organs of body; they lead to ischemic injuries as seen in heart, liver, brain and skin tissues, and occasionally kidneys. (Figure 1) The thrombocytopenia in circulation could be attributed either to impaired lung function leading to lesser production from megakaryocytes or due to consumption coagulopathy due to widespread thrombotic process going on in more severe cases, later presenting as disseminated intravascular coagulation (DIC).<sup>36</sup> Now, besides alveolar capillaries, whether the virus is able to gain entry into the small blood vessels of nose and nasopharynx is debatable; the anosmia and dysgeusia experienced in early phase of illness may possibly be justified by endocytosis and injury of tiny feeding blood vessels of olfactory bulb, facial and glossopharyngeal nerves.

Clinical viremia is actually detected in nearly 15% of patients in a Chinese study.<sup>37</sup> The virus laden antigen presenting cells and microthrombi start inducing B cells - the antibody forming cells, kick starting the humoral immunity. The circulating antigen-antibody complexes can further aggravate the cytokine storm leading to increased levels of TNF- $\alpha$ , interferon  $\gamma$ , IL2, IL6, IL8, IL10, IL17 and increased products of inflammation like CRP, D-dimer, serum ferritin, fibrin degradation products, erythrocyte sedimentation rate. The hypoxic injury in different organs along with underlying co-morbidities leads to multi organ dysfunction leading to more fatalities in elderly patients already compromised with associated co-morbidities.

Interestingly, the spectrum of cutaneous presentation is interplay of cellular and humoral immune response and can give a possible clue to the initial or late phase of illness and adjuvant supportive therapy required. Authors believe that while the viral exanthem like lesions, papulosquamous, and perifollicular lesions are more likely to be initial cell mediated response; chicken pox like and zosteriform blisters could be attributed secondary to viremia and cytopathic effect. Other cutaneous lesions like covid feet, livedoid, and vasculopathy are highly suggestive of small to medium vessel occlusion which could be attributed to either microthrombi formation or immune complex deposition and reperfusion injury reported in different articles.<sup>38,39</sup> On the other hand, Chilblain like lesions presenting on toes, feet and especially in buttock areas in supine patients is more suggestive of heavier immune complexes or microthrombi settling in dependent small to medium vessels. Though there is paucity of literature on histopathological picture of cutaneous lesions, the histopathology reports of early maculopapular truncal rashes were consistent with viral rash. Interestingly, there are reports of lymphocytic vasculitis with cutaneous vessels thrombi on one hand and the features of thrombophilic arteritis on the other.<sup>40</sup> While another study has described complement (C5b-9 and C4d) associated microvascular injury in skin and lung biopsies along with co-localisation of COVID-19 spike glycoproteins.<sup>41</sup> This is in concordance with our proposed virus-laden immune complex pathogenesis in more severe cases.

Immune complex mediated cascade of events needs to be stopped by use of immunosuppressants and anti-inflammatory drugs.

Merely addressing the occlusive injuries caused by microthrombi may not halt the disease progress and end organ injuries. Presence of virus in skin tissue in itself is a more sinister sign for viremia; and when coupled with complement based deposits, it demands more extensive autoimmune work up including anti nuclear antibodies and anti phospholipid antibodies levels. Due to ease of access, authors recommend skin biopsy along with direct immunofluorescence examination within 48 hours of appearance of skin lesions to establish exact nature of deposits. It will also be worthwhile to perform RT-PCR on all skin biopsy specimens to ascertain viral presence. The nature of these occlusive lesions is likely to be microthrombi loaded with immune-complexes in more severe cases with possible widespread vasculitis phenomenon. It can help shaping the choice of therapy aimed to plan and treat hypoxemic injuries as well as underlying pathogenesis. The increase in free radical injuries due to ROS can be curbed by chelating action of antioxidants started early in course of illness.

The morbidity and mortality can be reduced by upgrading the cellular immunity in initial phase of illness and downgrading the humoral response by use of antivirals, immunomodulators, anti-inflammatory drugs, antioxidants, antiplatelets or anticoagulants in a judicious and phased manner.

### 3 | POSSIBLE TREATMENT SUGGESTIONS BASED ON CURRENT PATHOGENESIS

1. *To prevent the acquisition of infection:* There are multiple trials being conducted to develop effective vaccine against SARS-CoV-2 but there has been no major breakthrough so far. The present approach to prevent the infection is hand sanitization, wearing a mask and social distancing; and the measures to boost immunity by taking healthy balanced diet, anti-oxidants, vitamin C, sun exposure, and exercise.
2. *To counter the initial pathogenesis of virus:*
  - a. Antiviral drugs like Remdesivir, oseltavir, lopinavir, ritonavir, and so on.<sup>30</sup>
  - b. *Role of Chloroquin and hydroxychloroquin:* There are conflicting reports regarding efficacy of these drugs. Being weak bases, these drugs may help by altering the pH of alveolar mucosa, inhibiting the viral entry by altering glycosylation over ACE2 receptor and spike proteins and also acting as immunomodulators.<sup>42,43</sup>
  - c. To avoid superadded bacterial infection: moxifloxacin, macrolides.<sup>20</sup>
3. *To boost the cell mediated immunity:* There are no established studies in relation to COVID-19, but certain vaccines are proven to boost cell mediated immunity in leprosy and tuberculosis.<sup>44</sup> Theoretically speaking, these vaccines may help in diverting and controlling the cytokine storm by boosting cell mediated immunity which is otherwise depressed by COVID-19
  - a. Trials being taken up in Indian subcontinent for Mw vaccine primarily used for leprosy

b. BCG vaccine works well for protection against tuberculosis and hypothesized to be one of the reasons curbing the severity of COVID-19 in Indian subcontinent. A repeat booster may be advocated in adults for prevention on the same lines as it yields higher CMI as compared to Mw vaccine.<sup>44</sup>

c. Other immunomodulators: vitamin D,<sup>45</sup> oral zinc<sup>46</sup>

4. To depress over activated humoral response:

- a. By using anti-inflammatory drugs like glucocorticoids (conflicting reports but still recommended to be used only for short duration to avoid complications).<sup>47,48</sup>
- b. Immunosuppressants like mycophenolate mofetil, tacrolimus, cyclosporin (lack of clinical trials but interestingly severe COVID-19 disease course is conspicuously absent in rheumatic patients).<sup>47</sup>
- c. Inflammatory cytokine inhibitors under trials<sup>47</sup>:
  - I. Tocilizumab: IL-6R monoclonal antibody, Rituximab-CD20 monoclonal antibody.
  - II. Anakinra: IL-1 antagonist.
  - III. Baricitinib: a Janus kinase OR JAK inhibitor as well as an AAK1 inhibitor working on process of endocytosis on ACE2 receptors.
  - IV. Intravenous immunoglobulin (IVIg): can be used as it can confer anti-inflammatory response and antagonizes various inflammatory markers.<sup>49</sup>
  - V. Plasmapheresis or convalescent plasma therapy: Plasma component of blood is removed, cleaned and returned to body or

harvested from recovered patients to curb the inflammation process.<sup>50</sup>

- VI. Use of antioxidants like vitamin C, vitamin E, and superoxide dismutase to reduce free radical injuries<sup>51</sup> and to counter possible vasculitic cascade.<sup>52</sup>

5. To reduce hypoxemic injury:

- a. Vasodilators like pentoxifyllin, losartan.<sup>53</sup>
- b. Judicious use of anticoagulants like revaroxaban, low molecular weight heparin—enoxaparin, heparin, and antiplatelets like aspirin to minimize microthrombi formation.<sup>54</sup>

These treatment options are summarized in Table 1.

## 4 | LESSONS LEARNT

COVID-19 is one unique pandemic where every section of society has lessons to learn from. Six months have gone by and there is no definitive cure to this deadly pandemic but surely the current scenario has taught us many lessons. Under the circumstances, the best approach will be to indulge in healthy eating habits, respecting the circadian rhythm, and building up own immunity against pathogens.<sup>55</sup>

Following section is purely based on opinion of authors:

1. The present scenario is a wake-up call for us “humans” to introspect ourselves. It is high time to respect the ecosystem and to

**TABLE 1** Summary of possible treatment options based on disease duration and progression

For all asymptomatic individuals	For SARS-CoV-2 positive patients	
	First week of illness	Second/third week of illness
1. Daily oral zinc supplementation (22.5 mg)	1. Low dose Aspirin (75 mg/d) with close monitoring of platelet count, coagulation profile, D-dimer levels, and by radiological imaging	1. Use of appropriate vasodilators (pentoxifyllin/losartan) when signs of hypoxemic injury in form of altered biochemical parameters signifying myocardial injury, deranged renal or liver function tests, electrolyte imbalance or appearance of acral/peripheral cutaneous lesions/covid feet in sick patients
2. Low levels of vitamin D: therapeutic weekly dose of 60 000 IU for 8 wks followed by monthly dose of 60 000 IU for 6 months	2. Oral remdesivir/ritonavir/lopinavir with or without hydroxychloroquin/chloroquin in symptomatic patients to reduce viral burden	2. Judicious use of oral anti-coagulants like enoxaparin, heparin, or revaroxaban based on elevating D-dimer levels and radiographical scans
3. Normal levels of vitamin D: Daily supplementation of 2000-4000 IU of vitamin D	3. Oral antioxidants like glutathione, superoxide dismutase, vitamin C or vitamin E to quench reactive oxygen species and counter possible immune complex injuries	3. Convalescent Plasma therapy from recovered patients or intravenous/subcutaneous IVIg (intravenous immunoglobulin) may be considered
4. BCG vaccination in nonimmunized population	4. Trials of Mw or BCG vaccine to boost cell mediated immunity. If useful, either of them may be routinely administered just at the start of initial symptoms to boost immune system in order to reduce viral burden and divert cytokine storm toward cell mediated immunity	4. Short course of oral or intravenous glucocorticoids may be lifesaving in selected patients with careful check on viral burden; rescuing multiple systems from acute cytokine and hypoxemic injury. Other option is to carefully select one of the inflammatory cytokine inhibitor like tocilizumab, cyclosporine, mycophenolate mofetil and tacrolimus

refrain from falling prey to nature's punishment of not following the rules of food chain. If we go by the concept of overcrowding in food chain, nature has its own rational ways of creating predators to curb uncontrolled population which unfortunately is happening with humans in the current scenario.

- The world politics need to understand that proving superiority of one nation over other using power, intimidation and manipulation tactics needs to be introspected and discouraged. On the contrary, world needs to learn empathy and tolerance and all possible actions should be taken up to save "mother earth" from physical, chemical, and biological assaults.
- The scientific community needs to understand the safe boundaries of experimentation they want to indulge in. The temptation to fiddle with what lies safe and hidden in the domains of nature needs to be curtailed and ethics of safe, productive, and progressive scientific temperament needs to be inculcated. It will help in giving a prudent lesson and a healthy and safe environment to the future generations rather than repentance and remorse of digging our own graves.

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## CONFLICT OF INTEREST

Authors have no conflict of interest or financial obligations to declare.

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