



## Review article

## Immunopathological changes, complications, sequelae and immunological memory in COVID-19 patients

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## ABSTRACT

Confirmed SARS-CoV-2-caused disease (COVID-19) cases have reached 275.65 million worldwide. Although the majority of COVID-19 patients present mild to moderate symptoms, some have severe complications including death. We first reviewed the pathogenesis on ACE2, a binding receptor of SARS-CoV-2 expressed in multiple organs, and prevalent multinucleate syncytia in the lung tissues of COVID-19 patients. Then, we evaluated the pathological, immunological changes and sequelae in the major organs. Finally, we reviewed the immunological memory after SARS-CoV-2 infection and vaccination. The binding of SARS-CoV-2 to ACE2 receptor results in reduced ACE2 protein levels, which may lead to elevated susceptibility to inflammation, cell death, organ failure, and potentially severe illness. These damages increase the risk of health problems over a long period, which result in many complications. The complications in multiple organs lead to the increased risk of long-term health problems that require additional attention. A multidisciplinary care team is necessary for further management and recovery of the COVID-19 survivors. Many COVID-19 patients will probably make antibodies against SARS-CoV-2 virus for most of their lives, and the immunity against reinfection would last for 3–61 months.

## 1. Introduction

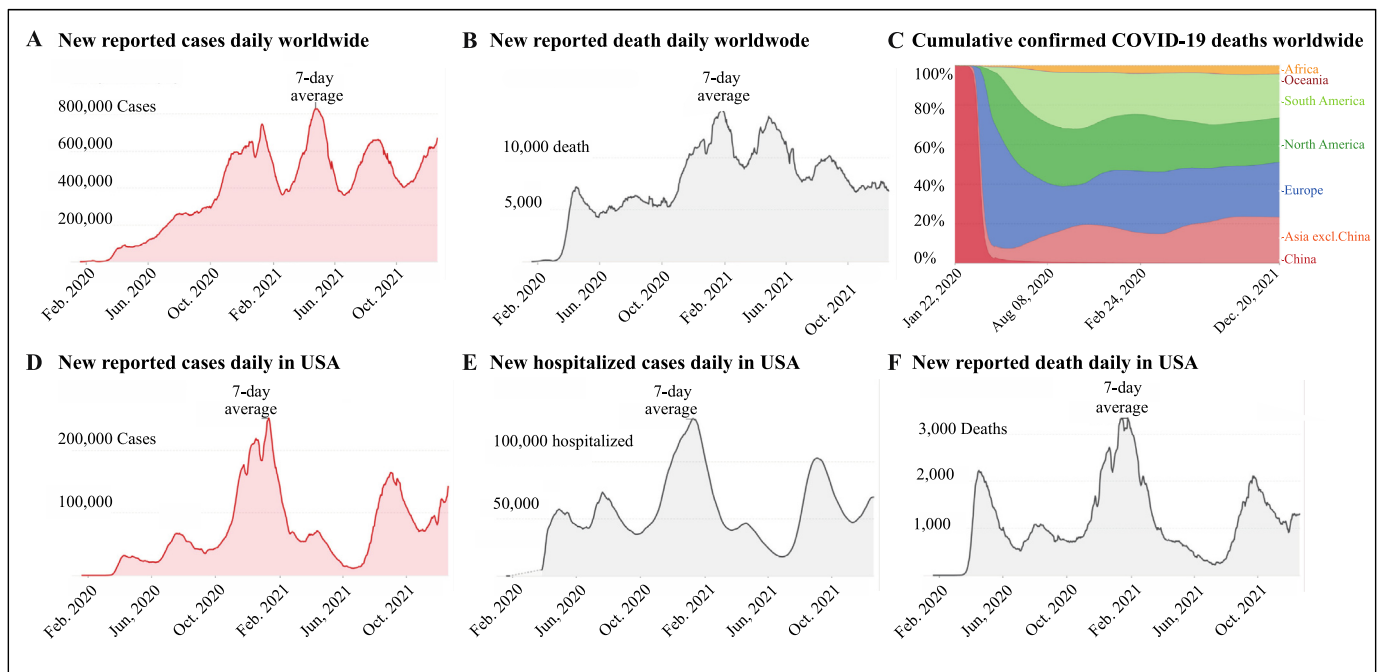
Highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus, which has spread worldwide and caused over 275.65 million infections (Figure 1) since its outbreak in Wuhan, China in Dec. 2019 [1]. The SARS-CoV-2-caused infection is named as COVID-19. Although different measurements, such as lockdown, social distance, masking, and recent roll-out of vaccines, have been executed and decreased the initial spread of infection, low vaccination rates, the emergence of COVID-19 virus variants, and the release of control measurements such as re-opening and unmasking has led to the resurgence of COVID-19, which was driven predominantly by the Omicron (B.1.1.529) variant of SARS-CoV-2 [2].

By binding to angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 virus particles are fused with membrane of human epithelial cells mainly in lung and then enter the cells for flu-like systemic replication [3]. ACE2 is ubiquitously expressed in different tissues and organs (e.g., lung, heart, kidney), which catalyzes hepatocytes-generated angiotensin, playing an important role in regulating blood pressure. Approximately one third of

patients with COVID-19 are asymptomatic [4]. COVID-19 typically presents with flu-like systemic and/or respiratory symptoms, which include cough, fever higher than 38 °C (100.4 °F), myalgia, headache, dyspnea, sore throat, diarrhea, nausea/vomiting, anosmia, ageusia, dysgeusia, abdominal pain, runny nose, loss of smell and taste. Severe cases demonstrate acute respiratory distress syndrome (ARDS) complications with multiple organ injury and failure, and even death [5, 6]. Isolation of symptomatic and asymptomatic cases and tracing of contacts have been used in many countries, with additional physical distancing measures [7]. Specific and effective treatments have not been developed before COVID-19 vaccines are available, and the standard of care for COVID-19 is focused on the alleviation of symptoms (e.g., oxygen supply, prevention of dehydration, etc.). Although monoclonal antibodies (e.g., Tocilizumab, a monoclonal antibody binding to human interleukin-6 receptors) have been used to the patients who are at the high risk of progressing to severe COVID-19 or being hospitalized [8]. According to The Centers for Disease Control and Prevention (CDC) and Mayo Clinic, most of patients with mild symptoms recover from COVID-19 with a minimal standard of care at home and are back to normal life. Some,

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**Figure 1.** Reported COVID-19 cases and death daily worldwide and in the US in the past two weeks. These data are from the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. A. New reported COVID-19 cases globally by day, this number is decreased by 10%. B. New reported death globally by day, this number is decreased by 8%. C. Cumulative confirmed COVID-19 death worldwide. D. The confirmed new cases increased by 20% daily in USA. E. New hospitalized cases daily increased by 14% in USA. F. New death increased by 3% daily in USA.

however, have post-viral symptoms (termed as sequelae), such as fatigue, loss of sense of smell or taste, and brain fog, after recovery [9]. These sequelae can sometimes last for months or longer and are becoming other critical health issues of post COVID-19 [10]. These symptoms are the barriers preventing individuals from returning to work [11].

Over the past 2 years, accumulating knowledge in COVID-19 is very helpful in beating COVID-19 and containing the pandemic. But we still need to be on alert for this virus to come back at any time. This review aims to comprehensively summarize the complications and sequelae of COVID-19 from the perspectives of its pathogenesis, pathological and immunological characteristics.

## 2. Pathogenesis

COVID-19 is a systemic disease with the major involvement of the lungs, showing diffuse alveolar damage (DAD) and pulmonary thrombotic microangiopathy [12, 13]. Inflammation and vascular damage were also observed in other organs such as heart, liver, kidney, and brain [4, 14]. Multi-organ failure is the major cause of COVID-19-related death [15]. However, the exact pathogenesis of COVID-19 related deaths remains poorly understood [16, 17].

ACE2 is a pivotal cell membrane receptor for the entry of SARS-CoV-2. Under normal circumstances, ACE2 protein plays an important role in regulating physiological and biological processes including wound healing, blood pressure, and inflammation, via the renin-angiotensin system (RAS) pathway [18]. ACE2 enzyme converts angiotensin I into angiotensin II (ANG II) [19]. ANG II, causing vasoconstriction and an increase in blood pressure, inflammation, increasing damage to the lining of blood vessels and various types of tissue injury [20]. ANG II can be broken down by ACE2 into the molecules that counteract the harmful effects of ANG II, whereas its role is blunted if the virus occupies the ACE2 receptor on the surface of cells [21]. ACE2 is found in a variety of human organs [3, 6, 7], which is highly abundant on type 2 pneumocytes in the respiratory system [22]. Once SARS-CoV-2 spike protein binds to ACE2 receptor, the complex is cleaved by transmembrane serine protease 2 (TMPRSS2), leading to membrane fusion, and the virus consequently

enters the cells [23]. Because patients with hypertension, diabetes and coronary heart disease have higher levels of ACE2 protein, it is not surprising that these health conditions are at risk for COVID-19 [9]. A study has shown that COVID-19 patients with these conditions have higher viral load and relatively more loss of epithelial cells with ACE2 expression [10]. On the other hand, the binding of SARS-CoV-2 spike proteins to ACE2 receptor can block the breakdown of ANG II proteins by ACE2, consequently leading to cell damage and inflammation [21]. Kuba et al. demonstrated that reduction of ACE2 expression by the injection of SARS-CoV spike protein into mice worsened acute lung failure *in vivo*, which could be attenuated by interrupting the renin-angiotensin pathway [24]. However, it is unclear whether the prevalent phenomenon exists in SARS-CoV-2 infection, although both SARS-CoV and SARS-CoV-2 are the members of coronavirus family.

In addition to ACE2, another potential molecular mechanism was recently reported. Zhang et al. demonstrated that generation of multinucleate syncytia was prevalently in the lung tissues of COVID-19 patients [25]. The authors further demonstrated that a few of human CD45<sup>+</sup> cells were enclosed in the special structure of multinucleate syncytia. They also found a negative correlation between the number of both syncytia and syncytia containing CD45<sup>+</sup> cells and the number of peripheral blood lymphocytes. Their findings confirmed that the multinucleate syncytia internalize human CD45<sup>+</sup> cells [25]. Consequently, internalization of human CD45<sup>+</sup> cells in the multinucleate syncytia in COVID-19 patients may be responsible for lymphocytopenia [25].

Microthrombosis is an exclusive clinical feature of COVID-19, and it was found in 91.3% of dead patients [26]. Microthrombi formation occurs mainly in the pulmonary vasculature but can also occur in other organs [27]. The disruption of the local renin-angiotensin system, endothelial injury (mostly DAD), the complement cascade activation and powerful thromboinflammatory reactions can profoundly result from entry of the SARS-CoV-2 into microvessels [28]. Particularly, microvascular plugging, ischemia and ultimately organ failure might be led by the induction of von Willebrand factor [28]. The production of membrane attack complex (MAC) and culminating in acquired ARDS attribute to the activation of three complement pathways [29]. Through either direct

action on platelets and the endothelium or indirect effects of inflammation and coagulopathy, COVID-19 can lead to increased thrombus formation, emboli and hemorrhage [11]. Zhang et al. demonstrated that platelets can be directly activated by the binding of SARS-CoV-2 spike protein to ACE2 receptor [30]. Thus, thrombus formation and inflammatory responses can be further promoted in COVID-19 patients [30]. In addition, neutrophil extracellular traps trigger thromboinflammation in patients with COVID-19 [12], which leads to vascular thrombosis and then death.

Aggressive inflammatory response and its related hypercoagulability was found in association with disease severity in patients with COVID-19 and poor outcomes [31]. The exact relationship between the levels of ACE2, infectivity of SARS-CoV-2, and severity of infection, however, are not well illustrated [12]. Burki et al. also pointed out that when COVID-19 cases progress to severe disease and death, men are at a substantial disadvantage [32]. Evidence from a large study shows that men have higher concentrations of ACE2 in the blood than women [33, 34]. Other factors may include gender behavior (i.e., higher rates of drinking and smoking among males compared to females), and attitude (i.e., more females are responsible and more cautious regarding the pandemic than males) [35]. In addition, sex chromosome genes and hormones (i.e., estrogens, progesterone and androgens) contribute to the differential regulation of immune responses between the sexes [36]. Females have 2 copies of X chromosomes that contain genes related to immune response and gene silencing, while males only have 1 copy [37]. These genes can influence the immune system through regulating many other proteins (e.g., TLR8, CD40L and CXCR3) that are overexpressed in females, as well as influence the response to viral infections and vaccinations [37].

In summary, the characteristics of COVID-19 pathogenesis include damage of endothelial cells, activation of platelet, thrombogenesis, blood coagulation disorder, and failure of multiple organs [38, 39]. Besides the respiratory system, cardiovascular, gastrointestinal and renal abnormalities have also been injured [40]. These changes are summarized in Figure 2.

### 3. Immunological features of COVID-19

The role of innate and adaptive immunities has not been fully explored in COVID-19. To date, scientists have mainly focused on adaptive immunity that are carried out by lymphocytes [41]. Among patients who died of COVID-19-related respiratory failure, it was found that DAD with perivascular T-cell infiltration was the typical histological pattern in the peripheral lung [42]. T cell infiltration is characterized by CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, which are predominantly distributed in interstitial spaces, larger bronchioles, and perivascular areas [14]. In addition to these T cells, CD61<sup>+</sup> megakaryocytes were also notably found, which were located within alveolar capillaries, actively producing platelets [43].

A common feature in severe COVID-19 patients is lymphopenia, but not in mild cases, which are characterized by drastic reduction of immune cells including CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, natural killer (NK) cells, and a decreased proportion of monocytes, eosinophils, and basophils [44, 45]. In contrast, a gain in neutrophil cell count and the ratio of neutrophil to lymphocyte are found in association with more severe disease and poorer clinical outcome [46]. These abnormal changes are restored in the recovered patients [47].

Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome caused by a sudden and acute increase of different pro-inflammatory cytokines including IL-6, IL-1, TNF $\alpha$ , and interferon in circulation [48]. The increased levels of cytokines result in converging of immune cells from circulation to the infection sites, lead to destructive effects on human tissues, which include instability of the interactions among endothelial cells, damages of diffuse alveoli, vascular barrier, capillaries, and multi-organ failure [49]. Lung injury is one of the consequences of cytokine storm, which can progress to acute lung injury or more severe ARDS [50]. In general, severely CRS is life threatening,

while mild patients with CRS have the symptoms of fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and difficulty in breathing [51]. Cytokine storm induced-vascular endothelial injury mediates hypercoagulability in blood vessels and disseminated intravascular coagulation (DIC) [52].

ARDS is a major complication of severe COVID-19 patients [53]. Some studies have showed that the overall mortality rate from ARDS in COVID-19 patients was 39% (95% CI: 23–56%) [54], it was 69% (95% CI: 67–72%) in China, 73% in Poland (95% CI: 58–86%), while it was 13% (95% CI: 2–29%) in Germany [6, 54]. Risk factors such as older age, increased neutrophils, elevated lactate dehydrogenase and D-dimer levels increase the risk of ARDS and death in those patients hospitalized with COVID-19 [6,55].

ARDS is the prominent immunopathological feature [6, 46]. Among the patients with SARS-CoV-2 infection, severe inflammation in lung may lead to dysregulation of the renin-angiotensin pathway, which then progressed to ARDS [56]. Cytokine storm is an essential mechanism of ARDS along with unregulated systemic inflammatory stimulus [57]. Nearly 20% of COVID-19 patients experiencing acute kidney injury (AKI) and ARDS are related to the cytokine storm [52].

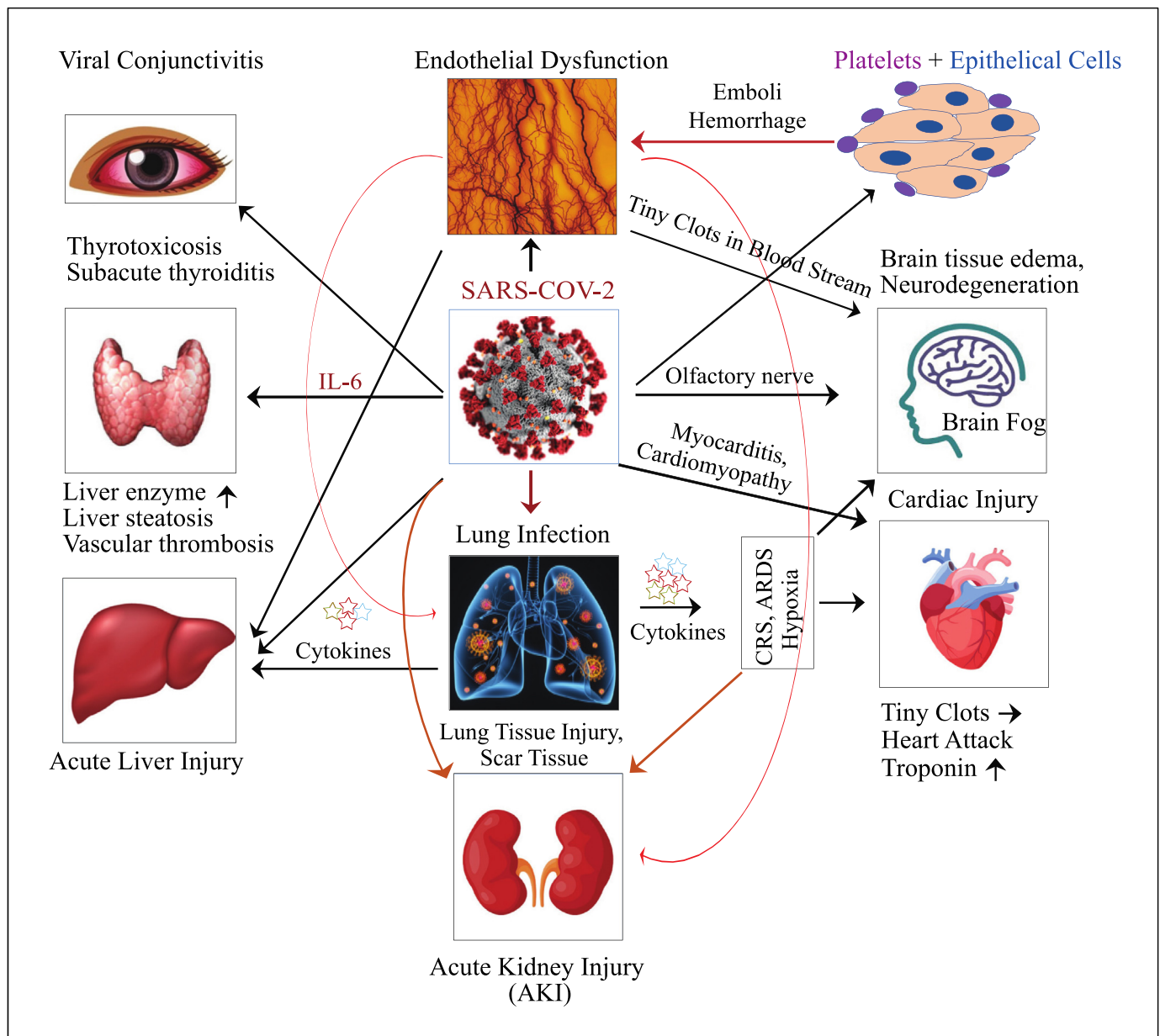
A distinct difference of cytokines, chemokines, and additional immune markers has been found between healthy adults and COVID-19 patients at levels from moderate to severe [58]. Several studies have indicated that the increased levels of serum proinflammatory cytokines were associated with pulmonary inflammation, and lung and organ failure in COVID-19 disease. It was reported that serum levels of IL-1Ra, IL-1 $\beta$ , IL-7, IL-8, IL-9, IL-10, FGF $\beta$ , G-CSF, GM-CSF, IFN $\gamma$ , IP10, MCP1, MIP1A, MIP1B, PDGF, TNF $\alpha$ , and VEGF concentration were higher in the COVID-19 patients at both intensive care unit (ICU) and non-ICU than it in healthy adults [59, 60, 61]. In contrast, the serum levels of IL-5, IL-12p70, IL15, Eotaxin, and RANTES (a chemokine, also known as CCL5) are similar between COVID-19 patients and healthy adults [59, 62]. Further study showed that plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNF $\alpha$  in the ICU patients with COVID-19 are higher than those in non-ICU COVID-19 patients [57]. To investigate the difference in cytokines, chemokines, and other immune markers between the COVID-19 patients with moderate and severe disease, Lucas et al. conducted a longitudinal study to determine the correlation of these soluble proteins in the patients [63]. The results showed that patients in the groups of both moderate and severe COVID-19 shared a “core COVID-19 signature” defined by the inflammatory cytokines, which positively correlated with each other, including IL-1 $\alpha$ , IL-1 $\beta$ , IL-17A, IL-12 p70, and IFN $\alpha$ . In the severe patients with COVID-19, other inflammatory factors were observed and defined, which are thrombopoietin (TPO), IL-33, IL-16, IL-21, IL-23, IFN $\lambda$ , eotaxin and eotaxin 3. These CRS-associated cytokines (e.g., IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-10, IL-18, and TNF) are positively correlated with severe disease in patients [63]. Overall, cytokine storm contributes to a poor prognosis [64].

### 4. Pathological changes and damages

Although COVID-19 mainly affects the respiratory systems, other systems are also affected, which include cardiovascular, urinary, nervous system and gastrointestinal tract, etc. [65]. Pathological analyses play a crucial role in elucidating the pathogenesis of COVID-19, and autopsies have provided many valuable direct insights of pathological changes [66].

#### 4.1. Lung

The lung is the main site of injury for SARS-CoV-2 infection [67]. Bilaterally infected lungs show edema and maroon in color, weighing 2–3 times as much as normal lungs (1939 vs. 685–1050 g [68, 69, 70]). All the severely infected lungs showed varying degrees of consolidation, predominantly located at the borders of lobes [70, 71]. Many viscous secretions are seen in the section of lung in response to SARS-CoV-2 [43].



**Figure 2.** Organs affected by COVID-19. When SARS-CoV-2 particles enter human body through the respiratory tract, they bind to the ACE2 receptors that are expressed in multiple organs. With the activation of the immune system, inflammation occurs leading to endothelial cell injury, especially the damage of DAD, resulting in the formation of microthrombosis, ARDS and multiple organ failure via virus, cytokine storm, hypoxia and microthrombosis. IL-6 causes subacute thyroiditis. SARS-CoV-2 can also cause brain lesions and eye conjunctivitis. In addition to ACE2, individual factors including genetics, immune response, healthy status, and age also need to be considered in the disparity of COVID-19, and the heterogeneity of COVID-19 manifestations.

Pulmonary pathological examination revealed thrombus and microangiopathy in pulmonary small vessels and capillaries, accompanied by hemorrhage [72]. Other studies also showed severe endothelial injury, disrupted cell membranes and microthrombi, as well as lymphocytic interstitial inflammation and reactive pneumocyte hyperplasia in the lung [73]. Thrombosis in pulmonary arteries is associated with hemorrhagic lung infarction, and it is found in 20–30% of lethal courses [74]. However, venous thromboembolism is more common than arterial thromboembolism in hospitalized COVID-19 patients [75].

Acute pulmonary infection caused by COVID-19 has distinct characteristics of acute interstitial pneumonia with DAD components, microvascular involvement of fibrin deposition and intravascular capture of neutrophils, as well as microthrombus formation in arterioles [4, 13]. Severe patients presented with ventilation/perfusion imbalance and respiratory failure emerge [76]. Some patients with respiratory

insufficiency present with exudative DAD, accompanied by hyaline membrane formation [13] and pneumocyte type 2 hyperplasia, which can progress to DAD at the stage of organization/fibrosis [72, 77]. Firm thrombi in the peripheral pulmonary vessels along with DAD, have been the most consistent feature of COVID-19-related lung pathology [78].

Pulmonary fibrosis, a symptom of ARDS, is the most severe change in the lung [79]. Some patients develop fibrosis [74], which is usually associated with severe lung injury, permanent pulmonary structural distortion, and irreversible pulmonary dysfunction [80]. The potential mechanism underlying SARS-CoV-2-induced pulmonary fibrosis include (i) pulmonary fibrosis is a known sequela to ARDS, 40% of COVID-19 patients develop ARDS, 20% of ARDS cases are severe, (ii) the levels of TGF- $\beta$ , TNF- $\alpha$ , IL-6, etc. in peripheral blood of severe patients were increased [81].

#### 4.2. Kidney damage

Acute kidney injury (AKI) is one of the most common and most severe organ complications of COVID-19, which seriously affects the mortality of patients [82]. Approximately 30% of COVID-19-related deaths had AKI [83]. Another study showed that 27% of the COVID-19 patients exhibited AKI [84]. COVID-19 patients with AKI had a three-fold higher death risk than those without AKI [85]. The ICU/severe patients had about 30 times higher risk of AKI compared to the non-ICU/severe cases [86]. Chronic diseases, including hypertension and diabetes, are another risk factors for kidney damage associated with COVID-19 [87]. SARS-CoV-2 particles has been identified in renal tissue [88, 89, 90], this discovery suggested that human kidneys were directly infected by SARS-CoV-2, leading to pathogenesis of renal tubules and AKI [84]. Nearly 20% of patients experiencing AKI are caused by cytokine storm [52]. In most cases, the kidneys display acute tubular injury, with the characteristics of lymphocyte depletion in the lymph nodes spleen, and hyperplastic adrenal glands [74], while CD68<sup>+</sup> macrophages infiltration into the tubule-interstitium are observed [84]. The patients present abnormal renal functions such as increased serum creatinine (sCr), blood urea nitrogen (BUN), D-dimer, proteinuria, and hematuria [86].

Renal changes include fine granular kidneys and focal cortical scars [91]. These changes were caused by arteriolosclerosis, mesangial sclerosis, hypercellularity, and focal global glomerulosclerosis [91]. However, no inflammatory or ischemic changes were found in the medulla section [91]. An occasional adrenal cortical nodule and a papillary thyroid adenocarcinoma were also detected [91]. COVID-19 patients develop extensive glomerular and tubular diseases [92]. Acute renal tubular injury is the most common type of injury in both live kidney biopsies and autopsy [93].

In summary, current evidences suggest that the causes of renal injury in patients with COVID-19 include hypovolemia, ARDS associated cytokine storm, and direct viral invasion as seen on renal autopsy findings [94]. COVID-19 may leave people with lasting damage to their kidneys, among many other organs. The possibilities are the most likely due to: (1) presence of ACE2 receptors in kidney cells allowing SARS-CoV-2 to bind them, invade, potentially damaging kidney tissues; (2) too little oxygen in blood causes kidneys to malfunction, (3) cytokine storms destroy kidney tissue; and (4) tiny clots form in the bloodstream, blocking the smallest blood vessels in the kidney and impairing renal function.

#### 4.3. Neurologic disorder

Some COVID-19 patients may develop cerebral edema, neuronal degeneration, encephalitis, meningoencephalitis, acute disseminated encephalomyelitis, Guillain-Barré Syndrome, Bickerstaff's brainstem encephalitis, Miller Fisher syndrome, polyneuritis, myositis/rhabdomyolysis, toxic encephalopathy, and stroke [95].

An autopsy report revealed the presence of SARS-CoV2 particles in the brain tissues of a COVID-19 patient [96]. SARS-CoV-2 has been detected in both the cerebrospinal fluid (CSF) and brain parenchyma of many patients [97]. Brain tissue oedema and partial neurodegeneration have also been observed [98], showing increased weight (~1221 g) and hydrocephalus ex vacuo [91]. The pathological changes in brain probably show the consequence of both direct cytopathic effects due to SARS-CoV-2 replication and indirect effects such as respiratory failure, injurious cytokine reaction, reduced immune response and cerebrovascular accidents caused by viral infection [99].

The brainstem is another part infected by SARS-CoV2 in CNS. Autopsy studies provide evidence for the presence of SARS-CoV-2 RNA and proteins in the brainstem [100]. ACE2 receptor expression is relatively higher in the brainstem than in other brain regions [100]. In addition, another receptor of SARS-CoV-2 named neuropilin-1 is also expressed in the brainstem [101]. Moreover, the brainstem is susceptible to damages derived from either pathological immune or vascular activation [100].

Therefore, patients with encephalitis, encephalomyelitis, and brainstem encephalitis recover slowly and have a high mortality rate [102].

#### 4.4. Heart damage

The heart is one of the most common organs affected by COVID-19; however, the nature and scope of cardiac pathology has been controversial [103]. A study reported that cardiac histopathological findings associated with COVID-19 are very common, but myocarditis is rare (<2%) [104]. Another study reported that the existence of SARS-CoV-2 in the myocardium was found in 47% of 316 deceased with COVID-19 [105], while cardiac pathological changes contributed to the death of 4.7% (15/316) cases [105]. Furthermore, postmortem examination demonstrated other pathological changes including cardiac dilatation (20%), acute ischemia (8%), intracardiac thrombi (2.5%), pericardial effusion (2.5%), and myocarditis (1.5%) [105]. Myocardial pathological examination revealed hypertrophy of myocardial cells with interstitial, and perivascular fibrous tissue, but no acute ischemic changes or inflammatory infiltration were observed [106]. Moreover, Zhou et al. reported that 48 % of the patients (91/191) with COVID-19 had comorbidities. Hypertension is the most common comorbidity (58/191, 30%), followed by diabetes (36/191, 19%) and coronary artery disease (15/191, 8%) [107].

Troponin is a marker of cardiomyocyte damage or injury. The majority of patients with an acute myocardial infarction have an elevated troponins within 2–3 h [108]. In the case of COVID-19, myocardial injury can occur, which is defined as elevated troponin level [109]. Among the patients in ICU, the levels of cardiac troponin are significantly higher in those with more severe infections [110]. Overall, the potential mechanisms of myocardial tissue damage include direct myocardial injury caused by SARS-CoV2 (i.e., viral myocarditis), systemic hyper-inflammatory response (i.e., CRS), hypoxemia, downregulation of ACE2, endothelialitis induced by systemic virus, and myocardial infarction [111].

#### 4.5. Liver damage

More than 1/3 patients with COVID-19 develop liver damage that is manifested by increased liver enzymes [112]. SARS-CoV-2 is mostly considered unlikely to cause liver infection because ACE2 expression is very low in liver cells. In the individuals with increased aminotransferases, autopsy liver biopsies were randomly obtained. Surprisingly, typical coronavirus particles with spike structures were found in the cytoplasm of liver cells in the patients with COVID-19 [113].

The distribution of ACE2 receptors is generally considered to be consistent with the distribution of infected organs [114]. However, the presence of ACE2 expression was significantly inconsistent with multiple organs targeted by SARS-CoV-2. Therefore, it is speculated that another Extra-ACE2 receptor or co-receptor may exists. Another possibility is that ACE2 expression in hepatocytes may be upregulated in response to viral invasion [115]. Analysis of ACE2 expression in post-SARS-CoV-2-infection hepatocytes will be interesting and helpful to untangle this inconsistency.

A meta-analysis of 18 studies from 7 countries showed that the combined prevalence of liver histopathological findings was: hepatic steatosis 55.1%, hepatic sinus congestion 34.7%, vascular thrombosis 29.4%, fibrosis 20.5%, Kupffer cell hyperplasia 13.5%, portal vein inflammation 13.2%, and lobular inflammation 11.6% [116]. In addition, venous outflow obstruction, portal vein sclerosis, portal vein herniation, abnormal periportal vessels, hemophagocytosis, and necrosis were also found [116]. In summary, the high prevalence of hepatic steatosis and vascular thrombosis are the major histological features of the liver in COVID-19 patients [116]. The liver steatosis, liver cell necrosis, portal inflammation, and proliferation of Kupffer cells are also very common [74].

During the clinic evaluation of COVID-19, liver injury has been observed in a large number of patients, especially in those who are in severe or critical conditions. The pathologic changes reported were a slight increase in sinusoidal lymphocytic infiltration, sinusoidal dilatation, steatosis and multifocal hepatic necrosis [117].

#### 4.6. Thyroid damage

SARS-CoV-2 infects host cells with ACE2-binding TMPRSS2 as the key molecular complex. Interestingly, ACE2 and TMPRSS2 were expressed at higher levels in the thyroid glands than in the lungs [118]. Subacute thyroiditis is a thyroid disease of viral or post-viral origin. A study reported that about two-thirds (66.7%) of COVID-19 patients developed subacute thyroiditis among 27 cases, including 11.1% of the COVID-19 patients required hospitalization, and 83.3% of the cases had subacute thyroiditis after COVID-19 [119]. Accordingly, patients who develop thyroid inflammation during acute COVID-19 may develop subacute thyroiditis months later, even after thyroid function has returned to normal.

COVID-19 may be associated with a high risk of hyperthyroidism associated with systemic immune activation caused by the SARS-CoV-2 infection, and thus plays a pivotal role in inducing hyperthyroidism of Graves' disease [120]. On this point, Lania et al. demonstrated that hyperthyroidism was significantly associated with higher IL-6 levels [121]. Similarly, another study showed that 75% of COVID-19 patients developed thyroid abnormalities and higher IL-6 levels ( $P < 0.01$ ) [122]. Thus, there are several potential thyroid outcomes in patients with COVID-19, such as thyrotoxicosis, low-T3 syndrome and subacute thyroiditis [123]. Taken together, COVID-19 are negatively impacting the thyroid. However, further investigations are required to validate the causal relationship between subacute thyroiditis and COVID-19.

#### 4.7. Gastrointestinal tract

Considering that gastrointestinal epithelial cells express ACE2, SARS-CoV-2 may also affect gastrointestinal tract. Mao and colleagues reported that 15% of the patients with COVID-19 had gastrointestinal symptoms, and the typical gastrointestinal symptoms were nausea, vomiting, diarrhea, and anorexia [124]. In addition, intestinal involvement of COVID-19 can be associated with intestinal ischemia, caused by shock or local thrombosis [74].

#### 4.8. Eyes

Conjunctivitis is the most common type of eye infection among COVID-19 patients [125]. SARS-CoV-2 particles were found from conjunctival swabs and tears of COVID-19 patients, additionally, SARS-CoV-2 RNA was detected in conjunctival, anterior corneal, posterior corneal, and vitreous from the deceased with COVID-19 [126]. In a case series report from the patients with COVID-19, some of them had ocular manifestations, including epiphora, conjunctival congestion, or chemosis [127]. This positive SARS-CoV-2 finding is common in severe COVID-19 patients. RT-PCR results of nasopharyngeal swabs and conjunctival swabs were positive for SARS-CoV-2, blood test results showed significant value changes among the COVID-19 patients with ocular abnormalities [128]. In addition, the presence of SARS-CoV-2 RNA on ocular surface suggests that the eye may be a site of viral replication [129]. SARS-CoV-2 proteins (e.g., spike and envelope proteins) were identified in the corneal epithelium undisinfecting with povidone-iodine (PVP-I) [126].

### 5. Complications

Most COVID-19 patients can recover within 2–6 weeks. But some of them still have symptoms after recovery. COVID-19 patients can experience multiple complications during infection. About 1 in 6 people with

COVID-19 will develop complications, which can be life-threatening. The result of a cohort demonstrated that COVID-19 survivors mainly had fatigue, muscle weakness, sleep difficulties, anxiety, depression, adjustment disorders, and tic disorders. During hospitalization, patients with severe COVID-19 had severely impaired pulmonary dispersion and abnormal chest imaging findings [130]. Another report indicated that 80% of the COVID-19 patients developed one or more long-term symptoms. The top five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) [131].

According to the pathogenesis, pathological and immunological changes, these complications may include acute respiratory failure, pneumonia, ARDS, acute liver injury, acute myocardial injury, acute kidney injury, secondary infection, septic shock, DIC, blood clots, multi-system inflammatory syndrome in children, chronic fatigue, and rhabdomyolysis may adversely affect the prognosis. Some complications may be unanticipated. In severe cases of COVID-19, cytokine storm-induced thrombotic complications including DIC are a prominent feature [78].

#### 5.1. Pulmonary complications

Reported complications of COVID-19 include long period damage to tiny air alveoli in the lungs and the resulting scar tissue, which can lead to long-term breathing problems. About 30–40% of COVID-19 hospitalization and nearly 70% of fatal cases develop ARDS [132]. ARDS occurs in 42% of COVID-19 patients, and 61–81% of the patients required intensive care [55].

#### 5.2. Cardiac concerns

Imaging tests taken months after recovery from COVID-19 showed that even people with only mild symptoms of COVID-19 suffered lasting damage to the heart muscle. This damage can be caused by the formation of blood clots in both large and tiny vessels. This could increase the risk of heart failure or other cardiac complications in the future. Data on long-term cardiovascular complications of COVID-19 are scarce. However, it can be learned from the experience of dealing with other types of myocardial injury. In a follow-up study of patients with acute myocarditis (mean age 40.2 years), the authors noted that the rate of hospitalization associated with heart failure ranged from 6% to 8% [133]. Patients with viral myocarditis may be associated with COVID-19 related myocarditis and/or fibrosis due to inflammation (regional or local) associated with acute disease.

#### 5.3. Brain

While SARS-CoV-2 virus mainly targets the respiratory system, patients and survivors of COVID-19 can also experience neurological changes and develop neurological and psychiatric symptoms. SARS-CoV-2 bind directly to the cells in neural tissue [95]. 73% of hospitalized COVID-19 patients had neurological symptoms, mainly headache, myalgias and impaired consciousness [134]. These symptoms including anosmia, hypogeusia, headache, nausea and altered consciousness are very common, but more severe and specific conditions have also been clinically reported, such as acute cerebrovascular accident, encephalitis, and demyelinating disease. Even in young people, COVID-19 can also cause strokes, seizures, and Guillain-Barre syndrome according to Mayo Clinic. Additionally, COVID-19 may also raise the risk of suffering Parkinson's disease and Alzheimer's disease.

The manifestation in central nervous system (CNS) is caused by direct viral invasion of CNS or by indirect mechanisms [99]. Studies have shown that SARS-CoV-2 can get access into CNS through olfactory nerves and even stretch to the medulla. The virus impairs CNS through either direct viral damage or immunopathological damage to nerve cells. Neurological symptoms involving the CNS can lead to acute or longer period consequences [135]. Wyss-Coray and colleagues compared

samples of the frontal cortex and choroid plexus from control and COVID-19 patients, they observed extensive cellular perturbations, with T cell infiltrating into the parenchyma. They identified subpopulations of microglia and astrocyte associated with COVID-19 disease that share genetic signatures with pathological cell states in human neurodegenerative disease, such as cognitive disorders, schizophrenia, and depression [136]. These findings may help to interpret the symptoms of brain fog, fatigue, and other neurological and psychiatric symptoms.

#### 5.4. Kidney

Kidney complications are relatively common. As above mentioned, AKI is a lethal complication in COVID-19 patients [137]. In addition, rhabdomyolysis is also a fatal syndrome caused by the breakdown of skeletal muscle fibers and leakage of muscle contents into the systemic circulation. However, this can lead to serious complications of renal failure. A study has reported rhabdomyolysis in 10 COVID-19 patients [138].

### 6. Sequelae or long-standing effects of COVID-19

Much remain unknown about the long period effects of COVID-19 on human health. Sequelae of SARS-CoV-2 infection include fatigue, dyspnea, chest pain, cognitive impairment, joint pain, and reduced quality of life [139]. Daugherty et al. reported that 14% of the adult patients ( $\leq 65$  years) with COVID-19 had at least one clinical sequelae. These sequelae including chronic respiratory failure, cardiac arrhythmia, hypercoagulability, encephalopathy, peripheral neuropathy, amnesia, diabetes, abnormal liver function tests, myocarditis, anxiety, and fatigue need medical care after passing through the acute phase of COVID-19 [140]. SARS-CoV-2 infection-induced cellular damage, a strong innate immune response that produces inflammatory cytokines, and a pro-coagulant state may contribute to these sequelae [141, 142]. COVID-19 infection can cause lasting damage to kidneys.

Close monitoring of the COVID-19 patients is recommended to understand the function of their organs after recovery. Many medical centers are going to set up and open specialist clinics to provide better cares for the individuals who have persistent symptoms or related illnesses after recovering from COVID-19. In general, most COVID-19 patients recover quickly; however, the potential long standing problems make it more important in addition to reduce the spread of COVID-19. Extreme fatigue with sleep changes, post-exercise nerve failure, multiregional cognitive dysfunction, persistent headache, demyelinating syndromes, peripheral neuropathy, and autonomic nervous instability are notable features of post-viral syndromes; similar concerns exist for people with persistent symptoms of COVID-19 [9]. Currently, there is no curative treatment for post-viral syndromes. The aim of treatment is symptomatic treatment to relieve symptoms.

#### 6.1. Problems with mood, fatigue, and chronic brain disorders

Patients with severe COVID-19 who are admitted to an ICU might experience mechanical assistance for breathing. The patients who had ventilator-aid experience are more likely to experience post-traumatic stress syndrome, depression, and anxiety. Early intervention should begin to reduce the risk for posttraumatic stress syndrome (PTSS) after hospitalization [143]. In addition, an extensive cellular perturbation was discovered in the brains of COVID-19 patients, may be due to inflammation caused by the infection. T cell infiltration was observed in the parenchyma, and these disturbances overlap with chronic cognitive impairment, schizophrenia, and depression [87].

#### 6.2. Clots in blood vessel

SARS-CoV-2 infection makes blood cells at high risk of clotting and forming blood clots in many organs (e.g., lungs, heart, legs, liver, and

kidneys, etc.). While large clots can cause heart attacks and strokes, smaller clots can damage heart by blocking capillaries in cardiac muscle. COVID-19 can also damage the lining of blood vessels, resulting in vessel leaking, and potentially long-term issues with both the liver and kidneys. A previous study reported that blood clots in the veins occurred in 20% of the COVID-19 patients, and in 31% patients in the ICU. Clots in vein or thrombosis in deep vein can circulate to the lungs and form pulmonary embolism, which consequently result in higher risk of death. An amputation may be needed if the clots are not treated timely with either a surgical or interventional treatment [144].

### 7. Prevention and immunological memory

Isolation and quarantine of infected individuals are effective approaches in controlling respiratory infectious diseases aside from vaccination of susceptible persons. Nevertheless, a key blind spot in the pandemic is asymptomatic infection in the community and pre-symptomatic viral transmission, which posed a major barrier in halting the spread of the virus. Although large-scale screening with RNA detection or rapid antibody detection are helpful in identifying these potential infection sources; however, society and economic costs are huge.

The publication of SARS-CoV-2's genome sequence has accelerated the development of vaccines, particularly novel RNA vaccines [145]. As of Aug. 31, 2021, WHO has authorized the following COVID-19 vaccines for emergency use (EUA). All the vaccines under EUA (1–7) together with 2 more with rolling data submission (8–9) were summarized in Table 1. As of Nov. 23, 2021, 132 vaccines are still in clinical development and 194 vaccines are in pre-clinical development according to WHO (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>). Novel delivery systems are under developing, for example, exosomes-mediated mRNA delivery [146], and exosomes carrying immunogenic viral peptides from COVID-19 patients ([www.covidx.eu/exocovac](http://www.covidx.eu/exocovac)).

mRNA vaccine (e.g., BNT162b/Pfizer, or mRNA-1273/Moderna) uses genetically engineered mRNA derived from S-protein of SARS-CoV-2 and it is delivered through lipid nanoparticles. Once the mRNA vaccine is administered, the lipid nanoparticles encapsulated mRNA are taken up by cells. The mRNA is then translated into the S-protein within the recipient cell cytoplasm. S-protein are next transported to the cytoplasm and cell membrane of the host cells. The S-protein can be recognized by the innate immune cells including NK cells, eosinophils, etc. and phagocytic cells (macrophages, neutrophils, and dendritic cells) for antigen presentation; adaptive immune cells (T- and B cells) are then triggered to recognize and memorize how to attack the virus that causes COVID-19 if infected again in the future.

Protein vaccines (e.g., inactivated cronovac/Sinovac and Sinopharm) include harmless protein pieces, which are derived from SARS-CoV-2. After vaccination, the immune system recognizes the proteins. B cells produce antibodies and T-lymphocytes recognizes and memorize the proteins, and therefore attack the virus once invaded in the future.

Vector-based vaccines (e.g., Ad26.COV2. S/Johnson & Johnson) use a modified version of a different virus as a vector to deliver the nucleic acid coding S-protein to the recipient's host cells. Once administrated, the host will build immune responses including T- and B-lymphocytes.

Duration of immunological memory (memory B cells, memory T cells including CD4+ T cells, and/or memory CD8+ T cells, as well as antibodies) after SARS-CoV-2 infection is unclear. Many COVID-19 patients will probably make life time antibodies against SARS-CoV-2 [147]. Because Turner et al. recently reported that long-lived antibody-producing cells (plasma cells) were identified in the bone marrow from the patients who recovered from COVID-19 [148,149]. These people infected with SARS-CoV-2 induce robust antigen-specific, long-lived humoral immune memory [148]. Another study investigated immunological memory by measuring the titer of antibodies against SARS-CoV-2 specific antigens, and immune cells in the blood. The results demonstrated that 95% of subjects remained immunological memory for

**Table 1.** Status of COVID-19 vaccines within WHO EUA.

	Vaccine Brand	Vaccine Name	Vaccine Types/Platform	EOI Accepted	EUA Date	Age to get vaccines	Doses	Interval
1	Pfizer-BioNTech	BNT162b2	Nucleoside modified mRNA	Yes	Dec. 31, 2020	≥12 years	3 shots	3 weeks for the first 2 doses, 6 months for the booster
2	Moderna	mRNA-1273	mRNA encapsulated in lipid nanoparticle (LNP)	Yes	Apr. 30, 2021	≥18 years	3 shots	4 weeks for the first 2 doses, 6 months for the booster
3	Janssen	Ad26.COV2. S	Vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein	Yes	Mar. 12, 2021	≥18 years	2 shot	2 months after completing the primary vaccination
4	Astrazeneca-Oxford University	AZD1222	Adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	Yes	Apr. 16, 2021	≥18 years	2 shots	4 weeks
5	Serum Institute of India	Covishield (ChAdOx1_nCoV- 19)	Adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	Yes	Feb. 15, 2021	≥18 years	2 shots	8–12 weeks
6	Sinopharm	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	Inactivated, produced in Vero cells	Yes	May 7, 2021	≥18 years	2 shots	2–4 weeks
7	Sinovac	COVID-19 Vaccine (Vero Cell), Inactivated/ Coronavac	Inactivated, produced in Vero cells	Yes	Jun. 1, 2021	≥18 years	2 shots	2–4 weeks
8	The Gamaleya National Center	Sputnik V	Russian MRNA, Human Adenovirus Vector- based Covid-19 vaccine	Additional information submitted	Rolling submission of clinical and CMC data has started. Anticipated date will be set once all data is submitted, and follow-up of inspection observations completed.	≥18 years	2 shots	3 weeks
9	Bharat Biotech, India	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)/ COVAXIN	DCGI, Whole-Virion Inactivated Vero Cell	Yes	Rolling data started 06 July 2021. Decision date: To be confirmed.	≥12 years	2 shots	4–8 weeks

**Abbreviation:** WHO: The World Health Organization; EUA: Emergency Use Authorization; EOI: Expression of Interest; DCGI: the Drugs Controller General of India.

**Table 2.** SARS-CoV-2 variants of concern (VOC).

Bango Lineage Name	WHO Label	First Identified	Spike Protein Substitutions
B.1.1.7	Alpha	United Kingdom	69del, 70del, 144del, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)
B.1.351 B.1.351.2, B.1.351.3	Beta	South Africa	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V
B.1.617.2 AY.1, AY.2, AY.3, AY.4, AY.5, AY.6, AY.7, AY.8, AY.9, AY.10, AY.11, AY.12	Delta	India	T19R, (V70F*), T95I, G142D, E156-, F157-, R158G, (A222V*), (W258L*), (K417N*), L452R, T478K, D614G, P681R, D950N
P.1 P.1.1, P.1.2	Gamma	Japan/Brazil	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I
B.1.1.529	Omicron	South Africa and Botswana	A67V, Δ69–70, T95I, G142D, Δ143–145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

8 months since infection [150]. Another similar study showed specific immunological memory for 5 months after recovery [151]. In addition, a very recent study reported that unvaccinated people should have immunity against reinfection for 3–61 months after getting infected with COVID-19 [152]. A further study has demonstrated that SARS-CoV-2 antibodies remain stable for at least 7 months after an infection with the virus [153]. The relatively short immunological memory suggests that COVID-19 infection-induced immune memory will not last too long.

Similarly, COVID-19 vaccine-induced immune memory may have a similar situation, suggesting that people may need the fourth dose as a booster. Before the rollout of a large-scale of booster vaccination, it is a priority to understand who need the booster vaccination, how the booster vaccination affects long period health, and how long the immunological memory lasts for the booster vaccination.

Breakthrough and second infection of COVID-19 indicate that it is unknown what antibody levels are able to prevent reinfection and how



**Table 3.** SARS-CoV-2 variants of interest (VOI).

Pango Lineage Name	WHO Label	First Identified	Spike Protein Substitution
B.1.525	Eta	UK/Nigeria	A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L
B.1.526	Iota	USA/New York	L5F, (D80G*), T95I, (Y144-*), (F157S*), D253G, (L452R*), (S477N*), E484K, D614G, A701V, (T859N*), (D950H*), (Q957R*)
B.1.617.1	Kappa	India	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H
B.1.617.3	None	India	T19R, G142D, L452R, E484Q, D614G, P681R, D950N
B.1.621	Mu	Columbia	N/A
B.1.621.1			

long it can last against the virus, even if the neutralizing antibodies produced by the COVID-19 vaccines are protective, protecting vulnerable populations from severe disease, and limiting the spread of the virus.

## 8. Conclusions

COVID-19 is a systemic disease that mainly affects the lungs, but often other organs as well. COVID-19 is a new virus infection disease, and nobody has adaptive immunity against it. Infected individuals were reported to have a broad range of symptoms ranging from mild to severe sicknesses. Minor symptoms include fever or chills, cough, shortness of breath, fatigue muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, joint pain, and chest pain. Other concerns include cognitive disorders, difficulty in focusing, depression, myalgia, headache, fast heartbeat, and sporadic fever. Severe illness include difficulty in breathing, constant pain or compression in the chest, and cyanosis caused by hypoxemia, etc. Organ damage caused by SARS-CoV-2 increase the risk of long period health problems, leading to complications and sequelae that require special attention to pay. 95% of the COVID-19 patients retained immunological memory for up to 8 months, a booster of COVID-19 vaccine may need eight months after being fully vaccinated.

## 9. Outlook

The complete eradication of SARS-CoV-2 remains challenging at least in a short term for a variety of reasons. SARS-CoV-2 is going to be present for a while, especially the emergence of the mutant viruses such as Delta and Omicron variants, etc. Even if we eventually eliminate SARS-CoV-2, there might be other novel coronavirus strains in nature waiting their turn. Given the large number of incident cases are diagnosed and a certain considerable number of COVID-19-related death occurring every day globally, the intellectual collaboration on SARS-CoV-2 and the variants must continue, requiring multidisciplinary knowledge collaboration not only between academia but also between industry.

Generally, herd immunity can be reached if over 80% of individuals are vaccinated. Vaccination coverage is still far below this level, particularly in undeveloped countries. Severe inequality exists in vaccine resources and supplies around the world. Even in the developed countries, although they have enriched vaccine resources with strong economic and treasure support, the goal of herd immunity has not been all reached. One of the potential reasons for those who are reluctant to get vaccinated is the concern for long-term effects of vaccines since all vaccines are EUA except recently FDA-approved Pfizer/BNT and Moderna vaccines. It is still debatable whether mRNA from the COVID-19 vaccines can be integrated into human genome DNA or not [154, 155]. A study demonstrated that chimeric transcription of SARS-CoV-2 and infected host cell RNA were observed, suggesting the ability of SARS-CoV-2 RNA to be reverse-transcribed and integrated into the genome of the infected host cells [156]. Another study showed no evidence that SARS-CoV-2 mRNA was able to be reverse transcribed and integrated into host cells [157]. Additional possibility is that some individuals doubt the transparency of vaccines. Injected lipid nanoparticles encapsulated mRNA vaccines invoke immune response when they are engulfed by antigen-presenting

cells (e.g., macrophage and dendritic cells). However, lipid nanoparticles are non-specific vesicles, which can be engulfed by other types of cells (e.g., cardiocytes, endothelial cells, etc.) even after the release of packaged mRNAs from macrophages and dendritic cells. Spike-protein expressed on cardiocytes and endothelial cells may lead to myocarditis and thrombosis. Thus, it is necessary to develop a relatively more specific vaccine. For example, by modifying proteins in lipid membrane, which can be engulfed by a certain type of cells through ligand-receptor mechanisms or targeting with certain antibodies. In addition, adjuvants are usually used in vaccine manufacture. Whereas AS03 (Adjuvant System 03), and MF59 (an oil-in-water emulsion of squalene oil) are squalene-based immunologic adjuvants that have been used in licensed vaccine products by GSK (GlaxoSmithKline) and Novartis, respectively [158], it is unknown what adjuvants are used in mRNA vaccines or other types of vaccines. Breakthroughs and the emergence of new variants remind the scientific communities that we still have much uncover and improve regarding future vaccines.

Lockdown is an effective measurement to suppress the spreading. However, lengthy period lockdown brings a heavy society and economic burden. Re-opening is necessary and on the way around the world. With new variants of SARS-CoV-2 emerging, e.g., Omicron (B.1.1.529) and Delta (B.1.617.2) variants, which can double hospitalization risk compared to the Alpha variant (B.1.1.7), however, new strategies are needed to re-open.

As a major target in controlling SARS-CoV-2, mutations in the receptor binding domain (RBD) are being of particular concern, which may substantially weaken RBD-binding antibodies. It is a gap to fill how much cross-protection exists against variant strains following the original vaccination or infection [159]. The Delta variant has 3 RBD mutations, 417, 452 and 478, respectively, which change the conformation of S protein, and may aid immune escape. Novel vaccines may be necessary, and mRNA vaccines may have some advantages by including the mutation containing ORFs. The SARS-CoV-2 variants of concern have been listed in Table 2.

SARS-CoV-2 may also infect other species besides human. Certain strains of wild type (i.e., non-hACE2 bearing) mice are vulnerable to the SARS-CoV-2 variants, e.g., B.1.1.7, B.1.351, and P.1 can infect mice via the endogenous mouse ACE2 receptor (<https://www.jax.org/jax-mice-and-services/sarscov2-test-kit>).

We still have some key unknown questions to be addressed: how soon after infection do T cells become activated to stop the spread of the virus? How long do T cells retain SARS-CoV-2 memory? These would be of concern to us because traditional vaccines focus on producing neutralizing antibodies. As our understanding of the interaction between the immune system and SARS-CoV-2 continues to grow, it is important to go beyond neutralizing antibodies to pursue T cell immunity.

Each newly emerging variant raises concerns: Will the disease course be changed? How will the immune system respond to new variants? Can the variant evade a pre-existing immune response from previous infection or vaccination, or pre-existing vaccines are still valid or not?

Apart from the above SARS-CoV-2 variants of concern, the variants of interest (VOI) have also caught the attention of scientists (Table 3). Among the VOI, Mu was just designated by the WHO on August 30, 2021. Outbreaks of the Mu variant has been reported in South America and

Europe, a descendent (B.1.621.1) of Mu has already been detected in 43 countries. Although this Mu belongs to VOI, but it has mutations that indicate a risk of resistance to the current COVID-19 vaccines. Table 3 summarized the VOI according to the previous information from the CDC. Currently, no SARS-CoV-2 variants are designated as VOI.

Scientific source-tracking of SARS-CoV-2 is another important issue in prevention and control of SARS-CoV-2 infection. With accumulating knowledges in this novel emerging virus, in addition to the first wave of COVID-19 cases reported in Wuhan, China in Dec. 2019 [57], COVID-19 was also spreading in other countries. Alteri, etc. described that the highest numbers of SARS-CoV-2 cases was found in Lombardy, Italy from February to April 2020. Over 16,000 deaths were reported in Lombardy in a couple of weeks during the time frame [160]. After analyzing 346 whole SARS-CoV-2 genomes, seven viral lineages were found; at least two were likely originated in Lombardy, Italy [160].

## Declarations

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