



# Histopathological and molecular links of COVID-19 with novel clinical manifestations for the management of coronavirus-like complications

Ankita Sood<sup>1</sup> · Onkar Bedi<sup>1</sup>

Received: 31 March 2022 / Accepted: 12 April 2022 / Published online: 30 May 2022  
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

## Abstract

Coronavirus disease 2019 (COVID-19) causes transmissible viral illness of the respiratory tract prompted by the SARS-CoV-2 virus. COVID-19 is one of the worst global pandemics affecting a large population worldwide and causing catastrophic loss of life. Patients having pre-existing chronic disorders are more susceptible to contracting this viral infection. This pandemic virus is known to cause notable respiratory pathology. Besides, it can also cause extra-pulmonary manifestations. Multiple extra-pulmonary tissues express the SARS-CoV-2 entry receptor, hence causing direct viral tissue damage. This insightful review gives a brief description of the impact of coronavirus on the pulmonary system, extra-pulmonary systems, histopathology, multiorgan consequences, the possible mechanisms associated with the disease, and various potential therapeutic approaches to tackle the manifestations.

**Keywords** COVID-19 · SARS-CoV-2 · Pulmonary disorders · Systemic manifestations · Viral infection · Histopathology

## Introduction

The coronavirus of the family *Coronaviridae* caused corona-related diseases and devastating complications of COVID-19 which are characterized by signs and symptoms including fever, cough, fatigue, sore throat and respiratory distress (Gupta et al. 2020; Almaghaslah et al. 2020; Singhal 2020) as summarised in Table 1. This debilitating disorder upsurges the more pathological causes throughout the world as per the various scientific epidemiological reports. On March 11, 2020, the World Health Organization (WHO) pronounced SARS-CoV-2 a pandemic (Bulut and Kato 2020) which caused disease outbreak, and initial epidemiological data reported with a mortality rate of 9.56% with the involvement of 8098 patients and 774 deaths globally (Ganesh et al. 2021). In the end of 2021, the same data showed to produce a significant upsurge in the global cases, which revealed that there was 274,628,461 confirmed cases and 5,358,978 deaths. The recent reports revealed that the number of new COVID-19 cases and deaths continues to decline with over 4.1 million cases and 45,000 mortalities,

with a drop rate of 9% in weekly death incidence (World Health Organization 2021a).

These pandemic cases lead to the progression of respiratory-related complications, with symptoms ranging from mild flu-like condition, acute respiratory distress syndrome (ARDS) to a life-threatening complications (Pereira, 2020). However, vital systems of our body, such as cardiovascular, gastrointestinal, hepato-biliary, renal, endocrine and neurological system, are also considered as a key pathological consideration in the COVID-19 etiopathogenesis (Mahajan et al. 2020). The pathogenesis of COVID-19 virus involves various molecular pathological outcomes which lead to the progression of metabolic and other complications of respiratory burden. The molecular and enzymatic involvement of ACE-2 (angiotensin-converting enzyme 2), IL-6 (interleukin-6), MMP (matrix metalloproteinases), peroxidase radicals, cytokines, macrophages, chemokines like CCL<sub>2</sub> (C–C motif chemokine ligand 2) and CXCL<sub>10</sub> (C–X–C motif chemokine 10) is demonstrated to have a role in the progression of coronavirus-like symptoms. The structural elucidation of coronavirus is concerned with the glycoprotein envelope, which has an affinity to bind with ACE-2 for efficient transmission of the virus into the alveolar region of the lungs, causing inflammatory and oxidative burden. Later on, it might spread in the other vital organs of the body. Similarly, in the same direction it causes endothelial damage,

✉ Onkar Bedi  
Onkar.bedi@chitkara.edu.in

<sup>1</sup> Chitkara College of Pharmacy, Chitkara University, Punjab, India

**Table 1** Illustration of various signs and symptoms of COVID-19

Signs and symptoms	Prevalence (%)	References
Fever	Upto 90	Wiersinga et al. (2020)
Dry cough	60–86	Harapan et al. (2020)
Fatigue	38	Mao et al. (2020)
Sputum	33.4	Guan et al. (2019)
Breathlessness	53–80	Garg et al. (2020)
Sore throat	13.9	Richardson et al. (2020)
Myalgia	15–44	Docherty et al. (2020)
Arthralgia	14.8	Grasselli et al. (2020)
Chills	11.4	Huang et al. (2020)
Headache	13.6	Larsen et al. (2020)
Nausea/vomiting/diarrhoea	15–39	Varga et al. (2020)
Olfactory/gustatory dysfunctions	64–80	Lechien et al. (2020)
Anosmia/ageusia	3	Spinato et al. (2020)

thrombo-inflammation, immune system dysregulation and dysfunction of ACE-2 pathways contributing towards the extra-pulmonary manifestations, leading to more worsening outcomes of the disease (Papa et al. 2020; Gupta et al. 2020). It was also illustrated by histopathological examination that coronavirus causes tissue damage with reference to hepatocyte injury, alveolar damage, mesangial cell expansion, pancreatic tissue degradation, stenosis of small intestine, edema in alveolar capillaries and brain lesions (Deshmukh et al. 2021).

The major emphasis of the current review is based upon the pathological, histopathological, molecular exploration concerned with COVID-19 virus. However, the other target of present review is also dedicated towards the clinical and therapeutic evidences for the management of COVID-19 complications. It was clinically reported that numerous interventions were proved to be beneficial including antivirals and anti-inflammatory agents, antimicrobials and anti-protozoals for the management of devastating respiratory distress induced by pandemic virus (Ruckmani et al. 2021).

## History of COVID-19

Coronaviruses in humans were initially identified in 1960s and were attributed for a large number of upper respiratory tract infections in children and other age related subjects. Later on in 2003, the other novel human coronaviruses strains have been discovered, including, the SARS, NL63, representing a group of NL, the New Haven coronavirus and a newly established HKU group II coronavirus. Previously, the researchers had expressed little interest in inculcating new research gaps to study the coronavirus. However, the

spotlight was highlighted in 2019 which generates a new direction for evaluating novel pathological and physiological interventions for the better understanding of SARS-CoV-2 virus. Scientists worldwide are working to produce new methods and techniques for clearing the gap and hindrance for the development of vaccines. With the continuous hard work, the Pfizer and BioNTech pharmaceutical companies were successfully able to find out the vaccine for management of COVID-19 globally (Kahn and McIntosh 2005). Within the same context, the other historical views of the coronavirus are summarized in Table 2.

## Pathobiological and molecular links associated with COVID-19

The coronavirus spike protein promotes the virus entrance into the target cells via direct or indirect respiratory tract exposure through ACE2, which is engaged as an entry receptor by SARS-CoV-2 spike subunit inducing interstitial lung damage initially and parenchymal lesions later on. This protein proceeds with the priming process via transmembrane serine protease 2 (TMPRSS2) for the cell entry inside the lungs (Gupta et al. 2020). In the presence of TMPRSS2, SARS-CoV-2 enters host cells by interaction with the ACE2 entry receptor through its spike protein. The interaction between spike protein and TMPRSS2 causes downregulation of anti-inflammatory function and elevation of angiotensin II effects. Virus invades to the different cells and tissues of various vital organs leading to the progression of inflammatory changes including oedema and necrosis. These changes are associated with the release of proinflammatory cytokines which produce a situation of cytokine storm (Azer 2020). Cytokine storm can be defined as activation cascade of cytokine production due to uncontrolled host immune response with the upsurge of different causative triggers (Tong et al. 2020). The systemic inflammatory response syndrome or cytokine storm is activated by SARS-CoV-2, which thereby increases the pro-inflammatory cytokine load including, interferon  $\gamma$ , IL-1 $\beta$  (Interleukin 1 beta), IL-6 (Interleukin-6), IL-12 (Interleukin-12) and chemokines, such as CCL<sub>2</sub>, CXCL<sub>8</sub>, CCL<sub>5</sub>, CXCL<sub>10</sub> and CXCL<sub>9</sub>. Infiltrations of pro-inflammatory cells including macrophages and T helper 17 cells were reported in lung tissues of the infected patients during post-mortem investigations (Gupta et al. 2020). Tong et al. (2020) revealed that coronavirus affected patients have higher levels of white blood cells, neutrophils, procalcitonin, C-reactive protein, endothelial and epithelial cell apoptosis, vascular leakage followed by ARDS which indicate that there is generation of inflammatory and molecular pathways. These molecular and pathological triggers lead to symptomatic

**Table 2** The Historical journey of COVID-19 and their related developments since 1920 to 2021

Year	Inventions	References
1920	An acute respiratory infection of domesticated chickens came to light in North America	Kahn and McIntosh (2005)
1931	Arthur Schalk and M.C. Hawn made the first detailed report describing a new respiratory infection of chickens in North Dakota	Williams (2021)
1933	Leland David Bushnell and Carl Alfred Brandly isolated the virus that caused the infection and it was then termed as infectious bronchitis virus	Broadbent (2021)
1937	Charles D. Hudson and Fred Robert Beaudette cultivated the virus for the first time and specimen came to be known as Beaudette strain	Henry (2020)
1940	Two more animal coronaviruses, JHM that causes brain disease, murine encephalitis and mouse hepatitis virus that causes hepatitis in mice were discovered	Körner et al. (2020)
1965	Researchers at the Common Cold Research Unit in Wiltshire, UK, reported cultivating a virus, B814, from a boy with a cold and the pathogen was recognised as virtually unrelated to any other known virus of the human respiratory tract	Kapikian (1975)
1966	Dorothy Hamre and John Procknow described a virus, which they named 229E, isolated from a medical student with a cold. It was distinct from other known respiratory viruses	Singh et al. (2020)
1967	Scientists at the National Institute of Allergy and Infectious Diseases reported using the same methods used to culture B814 to grow another new human virus with a similar morphology. They named it OC43	Monto et al. (2014)
2003	An international group of researchers reported the outbreak of severe acute respiratory syndrome (SARS), which began in late 2002 in southern China and was caused by a newly emerged human coronavirus	Drosten et al. (2003)
2004	Researchers at Erasmus Medical Center in the Netherlands report isolating a coronavirus, later named NL63, from a child with pneumonia	van der Hoek et al. (2004)
2005	A group of researchers based at the University of Hong Kong discovers another coronavirus, HKU1, in samples from two patients with pneumonia	Woo et al. (2005)
2012	Researchers at Erasmus Medical Center and their colleagues identify a new coronavirus, later named MERS-CoV, which was isolated from a man in Saudi Arabia with pneumonia and kidney failure	Zhang et al. (2021)
2020	A team of researchers in China identify the cause of a disease outbreak in Wuhan as a novel coronavirus, now known as SARS-CoV-2	Bulut and Kato (2020)
2021	18 vaccines are authorized by at least one national regulatory authority for public use: two RNA vaccines (Pfizer–BioNTech and Moderna), nine conventional inactivated vaccines (BBIBP-CorV, Chinese Academy of Medical Sciences, CoronaVac, Covaxin, CoviVac, COVIran Barakat, Minhai-Kangtai, QazVac, and WIBP-CorV), five viral vector vaccines (Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, and Johnson & Johnson), and two protein subunit vaccines (EpiVacCorona and RBD-Dimer)	Kyriakidis et al. (2021)

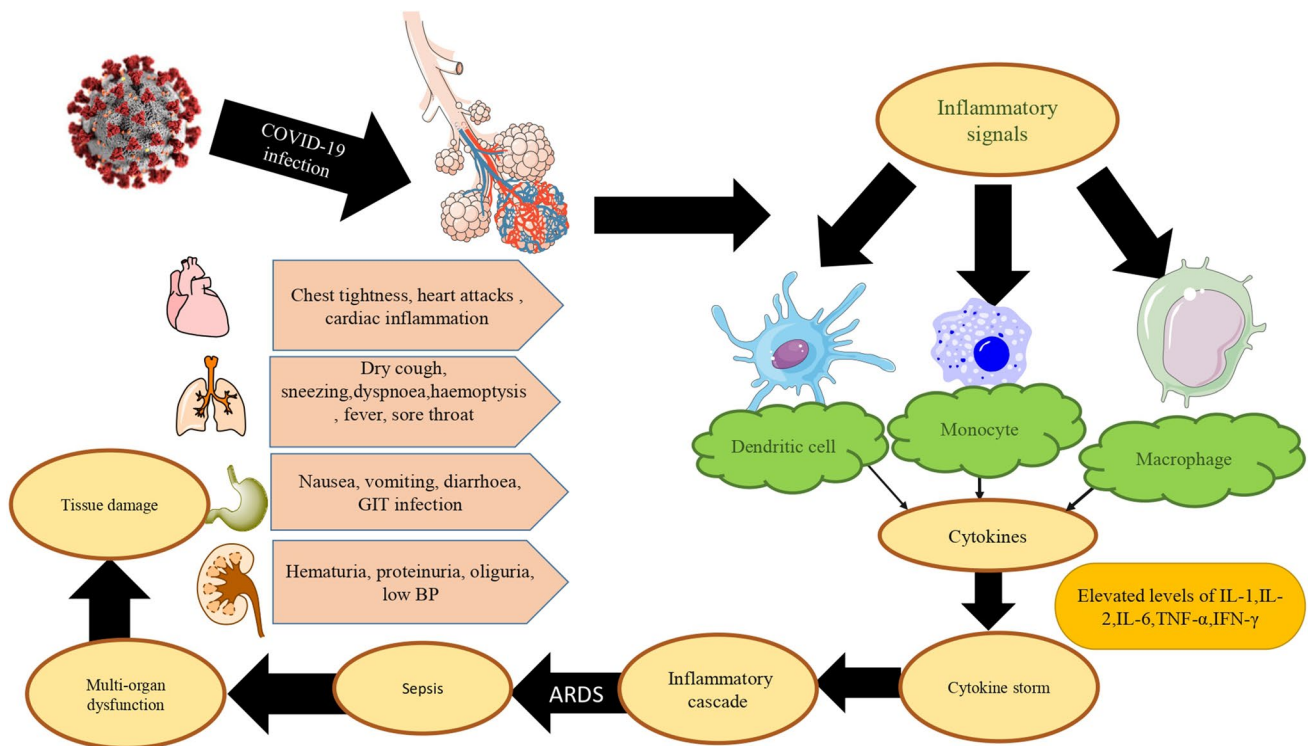
changes including cough, fatigue, fever, breathlessness, hypoxia, sore throat, chills and headache. Hypoxaemia, which is a leading symptom of coronavirus infection leads to accumulation of free radicals and lactic acid, alterations in intracellular pH and electrolytes imbalance finally causing cellular damage. Host immune response to coronavirus has a major involvement in disease progression, pathogenesis and clinical manifestations as depicted in Fig. 1 (Yang et al. 2020). In stage 1 or the asymptomatic phase, mechanisms related to innate immunity play a role consisting of NK cells, interferon production, and some cytokines whereas during stage 2 (mild symptomatic period), adaptive immune response is essential to eradicate the virus. Lung inflammation occurs in stage 3 (severe respiratory stage) with high viral load. Immune responses should be suppressed and symptoms need to be controlled with the help of pharmacological and non-pharmacological approaches (Velikova et al. 2020).

## Molecular observations associated with inflammatory mediators and immune cell activation involved in COVID-19 infection

### Inflammatory mediators correlation with COVID-19 infection

#### Molecular observations associated with type 1 interferon (IFN)

Innate immunity is the first line of defence against infections caused by viruses, and it has both a preventative and a harmful response to infections. Type 1 interferons have an essential role in host defence against the virus by inducing antiviral effector molecules which are encoded by IFN-stimulated genes (McNab et al. 2015). During the



**Fig. 1** Diagrammatic illustration of immune host response and pathogenesis of COVID-19

occurrence of viral infections, adaptive immune response is induced by type I interferon (IFN) responses, which further controls viral replication. The virus regulates antiviral IFN responses in SARS-CoV and MERS infections by interfering with IFN production. Type 1 IFN response was found to be decreased in a deceased patient of MERS-CoV in comparison to the recovered patient. The phosphorylation and stimulation of IFN regulatory factor 3 (IRF3) become necessary for IFN production, which is however suppressed during SARS-CoV infection. The ORF4a, ORF4b, and ORF5 proteins of the virus block IRF3 nuclear translocation and subsequent activation of IFN  $\beta$  production. SARS-CoV-2, SARS-CoV and MERS-CoV have a similar genomics which likely proves that SARS-CoV-2 adopts a similar strategy in regulating type 1 IFN response. SARS-CoV-2, on the other hand, appears to be more responsive to type I IFNs, as demonstrated by sequence analysis (Alipoor et al. 2021). Choi and Shin documented that trivial levels of IFN- $\beta$ , IFN- $\lambda$  and ISG expression were identified in serum of coronavirus affected patients along with strong expression of the chemokines indicating that COVID patients possess impaired type 1 IFN response. This can be described by the reduction of pDC, which are type 1 IFNs producers (Choi and Shin 2021). In another study, Yoshikawa et al. (2010) revealed that induction of IFN might be delayed rather than becoming impaired as detected in infected bronchial epithelial

cells. Channappanavar and Perlman carried out the studies in SARS-CoV- and MERS-CoV-infected animal models and defined the possible role of IFN as a novel therapy for COVID-19. Also, the viral replication of SARS-CoV-2 was decreased following treatment with type 1 IFN (Channappanavar and Perlman 2017). In contradiction, Choi et al. demonstrated that increased IFN generation and ISG expression are related with poor outcomes in coronavirus, and also related to atypical innate and adaptive immune responses. Increased transcriptional levels of IFNA2, IFNB1, IFNL2, and IFNL3 were observed in bronchoalveolar lavage fluid samples from COVID-19 patients. The severity of COVID-19 has been linked to high levels of IFN in serum of patients obtained 5–10 days after symptom onset. Severe patients of COVID-19 had increased IFN- $\alpha$  production in comparison to the patients with moderate severity (Choi and Shin 2021).

#### Molecular observations associated with IL-6

IL-6 is a cytokine that regulates cell proliferation and differentiation as well as the immune response. T cells, fibroblasts, macrophages, endothelial cells, and monocytes secrete IL-6. After a viral infection occurs, viral products stimulate the transcription or translation of IL-6 in fibroblasts, mesenchymal cells and endothelial cells. Increased IL-6 levels were found in SARS-CoV-2 patients, and these levels were linked

to pulmonary inflammation and significant lung damage. Decreased levels of cytokine signaling-3 suppressor, which modulates and enhances the negative feedback mechanism of IL-6, were observed in infected patients. In a critical COVID-19 group of patients, greater IL-6, IL-10 levels and C-reactive protein were more prominent in comparison to other cytokines (Vatansever and Becer 2020). Diao et al. (2020) observed that coronavirus affected people admitted in intensive care showed decreased CD8+ T cell counts, and total CD4+ and CD8+ count was inversely linked with TNF- and IL-6 levels.

### **Molecular observations associated with TNF- $\alpha$**

Tumor necrosis factor or TNF- $\alpha$  is the most important cytokines in the host defense system, and it plays a role in COVID-19 patients' pathogenesis. Ahmed et al. demonstrated that in COVID-19 patients, TNF- $\alpha$  allele A is significantly expressed when compared to controls. This suggests that people with the TNF-AA genotype are more likely to develop the condition. The TNF-AA genotype has been linked to a more severe disease pattern (Saleh et al. 2020).

### **Immune responses based upon antibody mediated immunity and their correlation with coronavirus infection**

Lymphocyte infection plays an essential role in viral-induced pathogenicity in coronavirus disease. During the virus entrance, immunogenic peptides are released to T cells along with human leukocyte antigen (HLA). HLA polymorphism may affect SARS-CoV infection susceptibility and outcome. Some HLA alleles, such as HLA-B\*4601, HLA-B\*0703, and HLA-Cw\*0801 and polymorphisms in the mannose-binding lectin gene, are linked to coronavirus infection susceptibility and risk. HLA-DRB1\*11:01 and HLA-DQB1\*02:0 alleles impose a risk for MERS-CoV infection and should be assessed in coronavirus patients. SARS-CoV-2-specific antibodies can be developed to neutralise the virus (Alipoor et al. 2021). It was documented that COVID-19 showed cross-reactivity with SARS-CoV and the serum of five patients had the ability to neutralise the coronavirus (Zhou et al. 2020). The patients had acquired IgG or IgM seroconversion within 20 days after the onset of symptoms. Asymptomatic patients who experienced no symptoms and had negative nucleic acid results were positive for IgG and IgM tests. Hence, this highlights the need for serological testing along with RT-PCR especially in case of asymptomatic patients (Liu and Li 2020). T helper (Th) cells have an essential role in adaptive immunity during viral infection. In SARS-CoV infection, the mild-to-moderate group had a substantial Th1 cell response and increased levels of neutralising antibodies, but the fatal group had a higher level of Th2

cytokines including IL-4, IL-5, and IL-10 and hence Th1 response becomes essential for controlling SARS-CoV-2. Controlling infection requires a balance of naive and memory T cells. The generation of cytokines by naive T cells is important for the defence against new, previously undetected infections. Memory T cells, on the other hand, stimulate antigen-specific immune responses. COVID-19 relapse may occur due to decreased memory T cells. In severe patients of coronavirus, CD8+ T cell responses were more frequent than CD4+ T cell responses. Cytotoxic granules are present in CD8+ T cell which can induce severe immune injury in patients. T cell depletion occurs as a result of T cell dysregulation during viral infections. Elevated levels of PD-1 and Tim-3, present in peripheral blood T cells of coronavirus patients are induced by T cell exhaustion due to IL-10 (Alipoor et al. 2021).

### **Histopathological links associated with COVID-19 with reference to major vital organs**

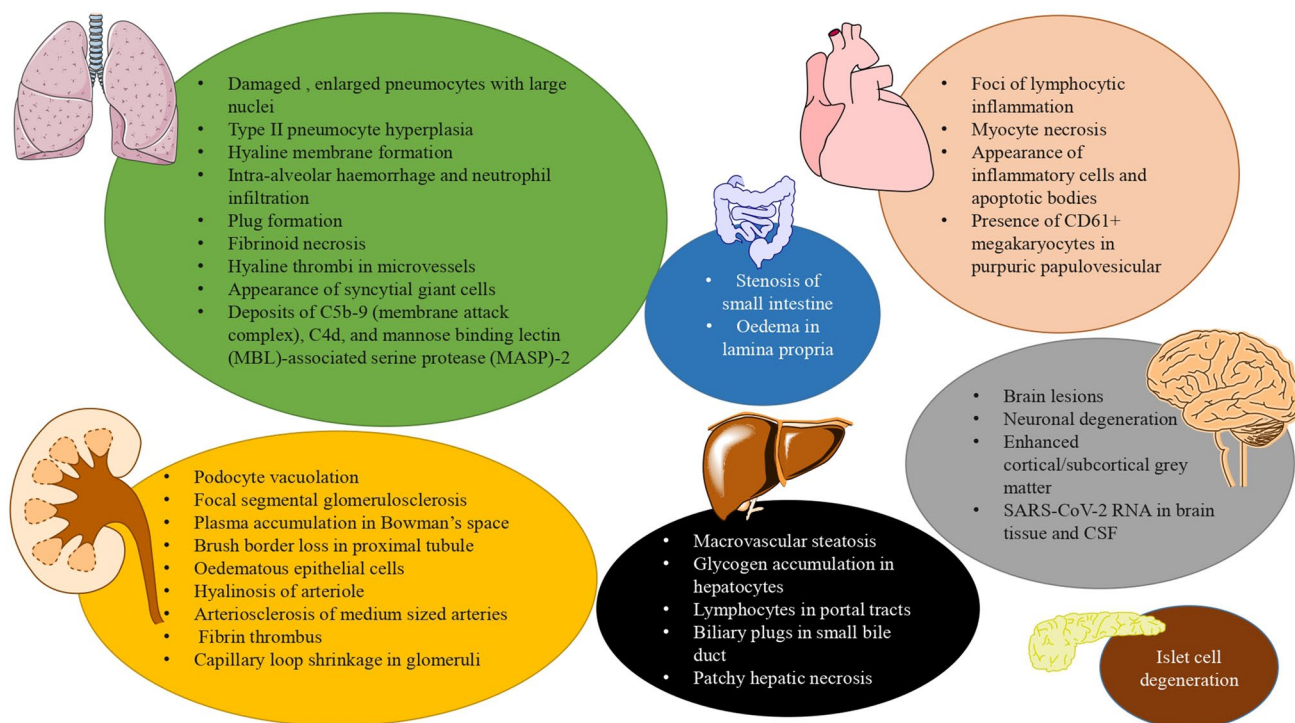
Early pathological findings indicate that coronavirus is broadly disseminated in the epithelial lining of the respiratory tract, digestive tract, distal convoluted tubules (DCT), sweat glands, and epithelium of the testes which is discussed in detail as follows (Vasquez-Bonilla et al. 2020; Deshmukh et al. 2021). The overall histopathological changes associated with various organ systems of the body is summarized with the help of pictorial representation (Fig. 2).

### **Histopathological evidences of brain tissues with references to COVID-19 progression**

Neurological symptoms like headache, dizziness, seizures and altered sensorium were frequently reported in COVID-19 indicating that the virus might be neurotropic. Neurotropic respiratory viruses invade into the CNS via hematogenous and neuronal retrograde routes. Brain lesions were observed along with oedema, neuronal degeneration followed by acute hypoxic ischaemic injury (Deshmukh et al. 2021). CT scan and MRI revealed enhanced subcortical and cortical grey matter followed by appearance of fibre tracts in the brain. Dotted subarachnoid haemorrhages were present in brain as reported by Vasquez-Bonilla et al. Other findings included cyanotic and edematous meninges (Stoyanov et al. 2020; Vasquez-Bonilla et al. 2020).

### **Histopathological evidences of pulmonary tissues with references to COVID-19 progression**

Upper respiratory tract infections often cause mild-to-moderate symptoms, whereas lower respiratory tract infections



**Fig. 2** Pictorial depiction of histopathological changes of various vital organ systems including the respiratory system, renal system, gastrointestinal system, neurological system and cardiovascular system with reference to COVID-19

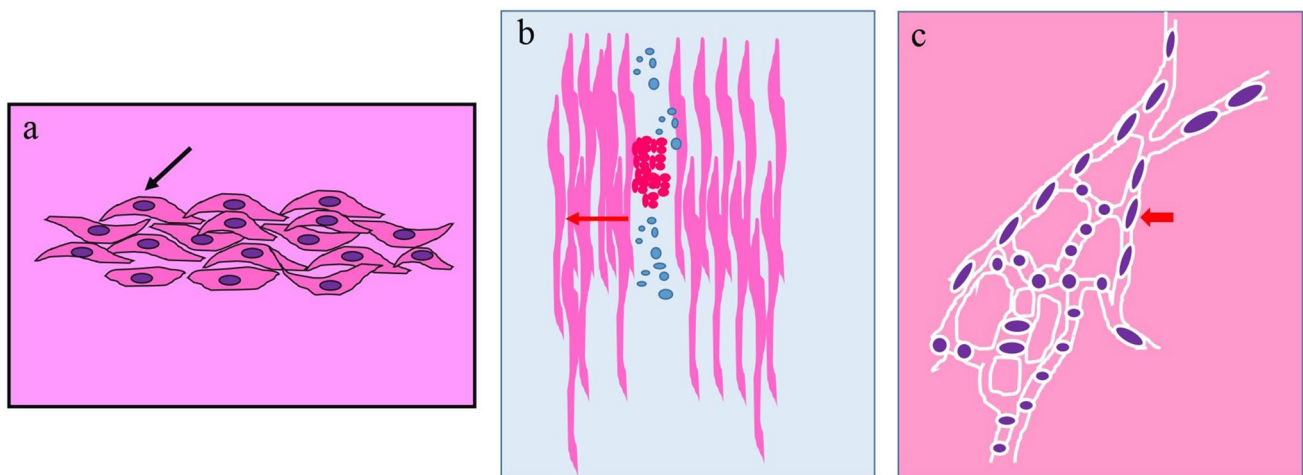
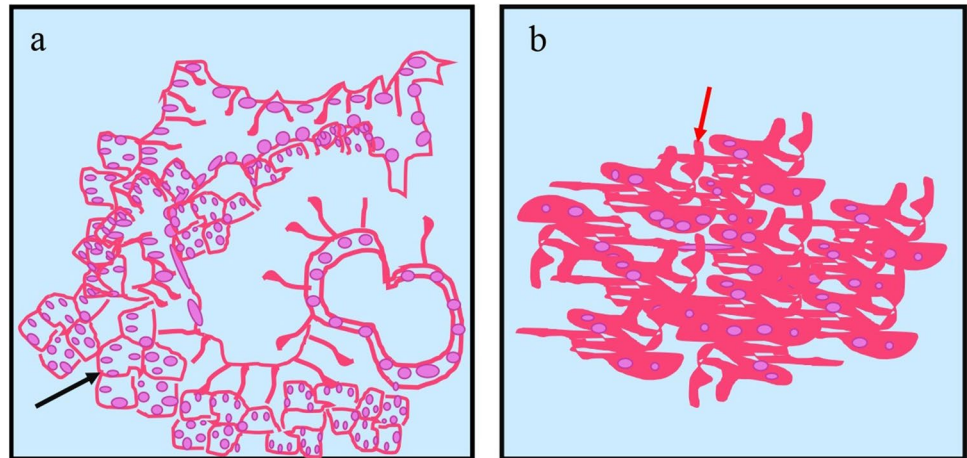
cause pneumonia-like symptoms and can lead to organ failure. Comorbidities including hypertension, chronic renal disease, obstructive sleep apnea, diabetes and obesity enhance the severity and pathological alterations might differ between the right and left lung. It was documented that coronavirus majorly affects the lungs causing alveolar damage, formation of hyaline membrane, presence of intra-alveolar fibrin, macroscopic diffusely consolidated lungs, loosely organized connective tissue in alveolar septal wells, macrophage and lymphocytic infiltration (Bradley et al. 2020; Vasquez-Bonilla et al. 2020; Stoyanov et al. 2020; Bryce et al. 2020). Vasquez-Bonilla et al. (2020) documented that intra-nuclear inclusions were suggestive of acute and necrotizing pneumonia, intravascular fibrin thrombi, and interstitial inflammatory infiltrate (Vasquez-Bonilla et al. 2020). It was revealed that the lungs were congestive, consisting of patches of haemorrhagic necrosis during macroscopic examination. Olfactory bulbs were found to be edematous with a pronounced oval shape (Stoyanov et al. 2020). Deshmukh et al. (2021) revealed that the microscopic features comprising alveolitis were observed along with vacuolar degradation, proliferation, atrophy and metaplasia of epithelial cells. Multinucleate giant cells, viral inclusion bodies, massive fibrinous exudate and epithelial cells in lumen were also present indicative of necrotic changes. Pneumocytes were observed to be damaged with immune cells infiltration. Further findings were indicative

of intra-alveolar haemorrhages and intra-alveolar neutrophil infiltration suggestive of superimposed bacterial infection. Presence of CD3+, CD4+ T cells, CD20+ B-lymphocytes and CD68+ macrophages was suggestive of inflammatory oedema in the respiratory mucosa. In conclusion, the major findings were observed to be pneumocyte hyperplasia, hyaline membrane formation, necrosis, hemorrhage and plug formation in alveoli (Deshmukh et al. 2021). Figure 3a shows the normal histology of lung alveolar septa and bronchiolar epithelium, whereas Fig. 3b demonstrates the lung histology of a COVID-compromised patient.

### Histopathological evidences of cardiac tissues and blood cells with references to COVID-19 progression

Viral infections are a major cause of myocarditis. ACE-2 receptors are present in vascular endothelial cells and can easily be targeted by the coronavirus. It was revealed that there was an inflammation of the myocardium, endocarditis, presence of viral particles, CD4+ T cells and other inflammatory infiltrates in the myocardial interstitial cells and myocardium (Bradley et al. 2020). Deshmukh et al. documented the presence of apoptotic bodies in endothelial cells, edema in alveolar capillaries and small vessels and appearance of fibrin thrombi, neutrophils and CD61+ megakaryocytes. Hence, the major histopathological findings

**Fig. 3** Diagrammatic depiction of various histological changes in the lung tissues. **a** Black arrow in figure a depicts the normal histology of lung alveolar septa lined by flattened epithelial cells (pneumocytes). **b** Red arrow depicts the lung histology of a COVID-compromised patient characterised by infiltration of tissue by mononuclear inflammatory cells, presence of hyaline membrane along with desquamation of alveolar epithelium



**Fig. 4** Diagrammatic depiction of various histological changes in the cardiac tissues. **a** Black arrow depicts the cardiomyocytes along with the presence of dense connective tissue with elastic fibers. **b** Red

arrow demonstrates the lymphocytic myocarditis. **c** Red arrow in figure c demonstrate the necrotic myocyte

were ruled out to be inflammation, presence of infiltrates and edema (Deshmukh et al. 2021). Figure 4a demonstrates the normal histology of heart Fig. 4b and c show the cardiac histology of COVID patients.

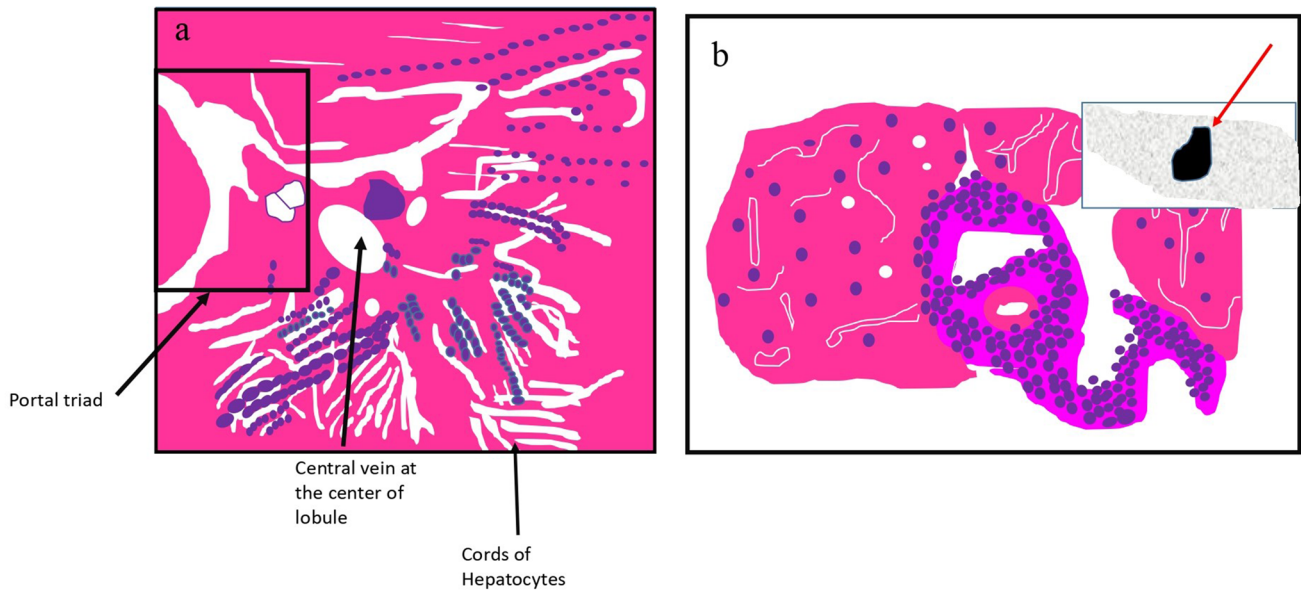
### Histopathological evidences of hepatological tissues with references to COVID-19 progression

The coronavirus can replicate and might be present in the digestive system as well. The hepatobiliary system has also been found to contain ACE-2 receptors. Coronavirus infection can be associated with liver injury as observed by a tremendous increase in liver function impairment and elevated enzyme levels (Ma et al. 2020). Vasquez-Bonilla et al. demonstrated hepatocyte degeneration, focal necrosis and presence of biliary plugs in small bile duct along with sinusoidal congestion (Vasquez-Bonilla et al. 2020). Li

et al. revealed that the liver might be indicative of cirrhosis, macro-vesicular steatosis, glycogen accumulation, lymphocytic infiltration and sinusoidal dilatation. The major findings were hence found to be degeneration of hepatocytes, necrosis, and stenosis along with tissue degradation (Li and Xiao 2020). Figure 5a is indicative of normal liver histology, whereas Fig. 5b shows the liver histology of COVID-affected patient.

### Histopathological evidences of renal tissues with references to COVID-19 progression

ACE-2 is highly expressed in COVID-19-infected people and it has been indicated by positive result of tubule immunostaining with the virus nucleoprotein antibody. Apart from the SARS-CoV-2 direct virulence, other major factors that contribute to progression towards acute kidney

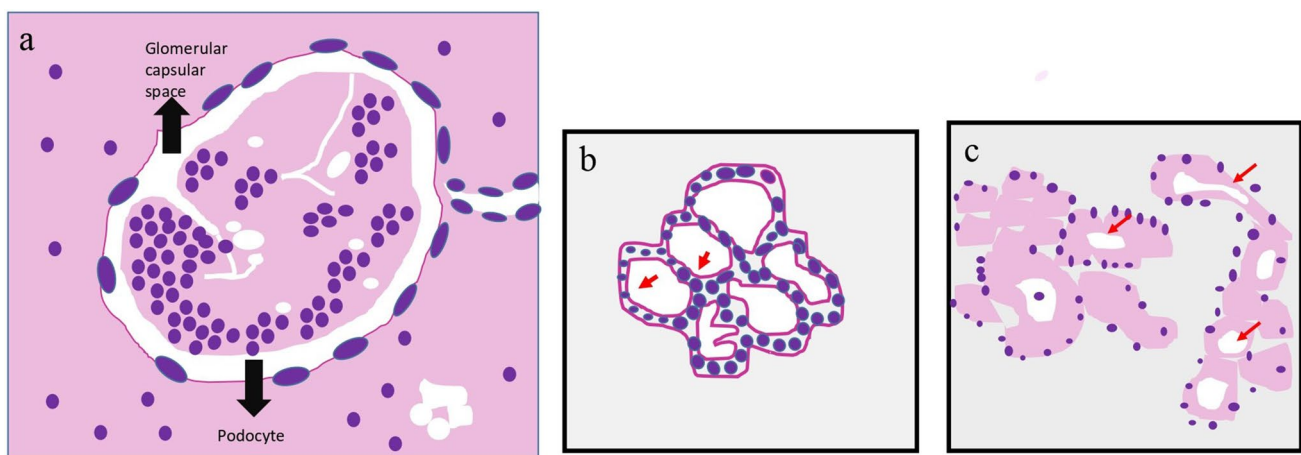


**Fig. 5** Diagrammatic depiction of various histological changes in the liver tissues. **a** Black arrow demonstrates the normal liver histology characterized by the presence of portal triad, hepatocytes, and center

of the lobule. **b** Red arrow indicates the presence of glycogenated nuclei in hepatocytes, atypical small lymphocytes infiltrating the portal triad area and exhibiting CD20 positivity

injury include abnormal coagulation, systemic hypoxia and potential drug or hyperventilation-related rhabdomyolysis. It was documented that microscopic changes consisted of necrosis, loss of brush border, diffuse proximal tubule injury and vacuolar degeneration. Besides, other observations included inflamed glomerular endothelial cells, presence of protein exudates and thrombus in the capillaries, tubular epithelial cells edema, accumulation of plasma in bowman's space, oedematous expansion in interstitial spaces of DCT and collecting ducts (Deshmukh et al. 2021; Stoyanov et al.

2020). It was revealed that fibrosis and lymphocytic infiltrates were present beneath renal capsule and arterionephrosclerosis was demonstrated (Vasquez-Bonilla et al. 2020; Bradley et al. 2020). Deshmukh et al. revealed the presence of viral particles with distinctive spikes in podocytes and tubular epithelium as observed in electronic microscopic examination (Deshmukh et al. 2021). The major findings from the above discussion were documented to be podocyte vacuolation, glomerulosclerosis, edematous epithelial cells and arteriosclerosis of arteries. Figure 6a is suggestive of



**Fig. 6** Diagrammatic depiction of various histological changes in the kidney tissues. **a** Depiction of normal kidney histology characterised by parietal and visceral layers bounded by glomerular capsular space, podocytes present in inner visceral layer and outer parietal layer of

simple squamous epithelium. **b** Red arrow indicates the loss of brush border in PCT (proximal convoluted tubule). **c** Red arrow shows vacuolar degeneration in tubular epithelial cells forming necrotic debris



normal kidney histology, whereas Fig. 6b and c demonstrate the renal histology of COVID patients.

### Histopathological evidences of gastrointestinal tissues with references to COVID-19 progression

Caramaschi et al. revealed that inflammation, shock and ischemia were observed in the small bowel along with endothelialitis and apoptotic bodies in small intestine (Caramaschi et al. 2021). Deshmukh et al. documented that stenosis occurred in the small intestine followed by necrosis, epithelial degeneration, shedding in gastrointestinal mucosa and gastric tissues along with the appearance of congested blood vessels presence in lamina propria and submucosa. Tissue degradation was observed in pancreas (Deshmukh et al. 2021).

### Histopathological evidences of reproductive tissues with references to COVID-19 progression

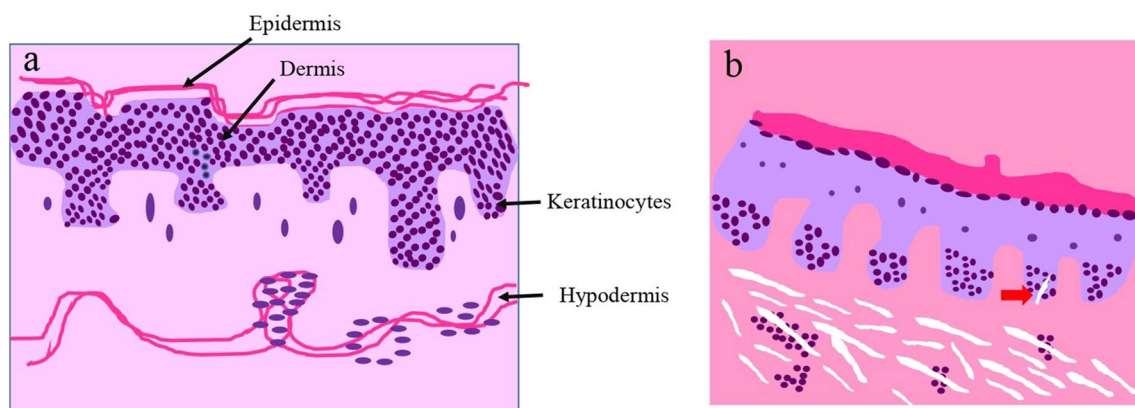
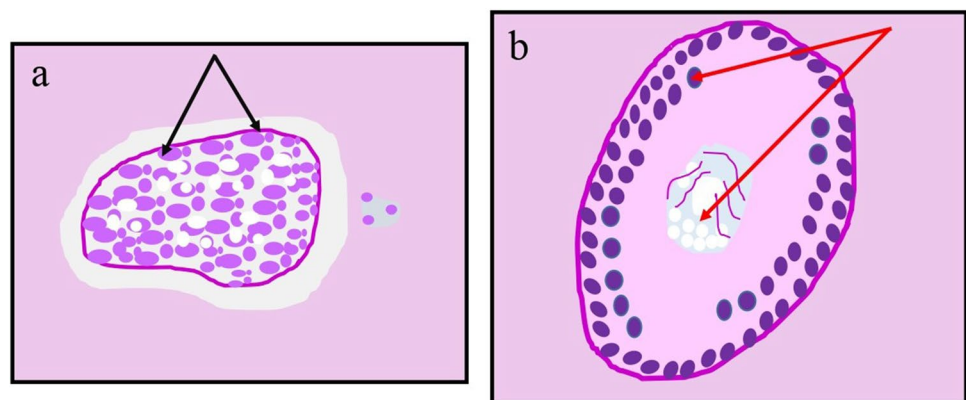
The histopathological changes observed in the reproductive system included basement membrane thickness with

peritubular fibrosis, vascular congestion, leucocyte infiltration, extensive germ cell destruction and increased apoptotic spermatogonic cells. Swelling, vacuolation and cytoplasmic rarefaction were observed in sertoli cells (Deshmukh et al. 2021). Figure 7a shows the normal histology of testes, Fig. 7b indicate the pathological changes in testes of patients with COVID.

### Histopathological evidences of skin with references to COVID-19 progression

Caramaschi et al. demonstrated that perivascular inflammatory cells and intraluminal thrombi were found in skin vessels. Parakeratosis, acanthosis, dyskeratotic keratinocytes and necrotic keratinocytes were found in epidermis (Caramaschi et al. 2021). Figure 8a demonstrates the normal histology of skin, whereas Fig. 8b shows the histology of skin in COVID-affected patients.

**Fig. 7** Diagrammatic depiction of various histological changes in testes. **a** Black arrows depict the normal histology of testes comprised of seminiferous tubules and Leydig cells. **b** Red arrows indicate the pathological changes in testes of patients with COVID consisting of defoliated and oedematous Sertoli cells along with vacuoles and scattered Leydig cells



**Fig. 8** Diagrammatic depiction of various histological changes in the skin. **a** Depiction of normal skin characterised by the presence of epidermis, dermis hypodermis and keratinocytes. **b** Red arrow demonstrates acanthosis with cleft presence

## Clinical evidences for the management of COVID-19

### Clinical approaches with reference to pulmonary compromised subjects

#### Acute respiratory distress syndrome (ARDS)

The management of ARDS seems to be challenging. It is essential to monitor the respiratory drive for detection of initial phases of respiratory fatigue. Non-invasive ventilation is being used for COVID patients, in which mask is the main interface in patient's respiratory tract (Nasibova and Pashayev 2020). When a patient has mild-to-moderate dyspnea and hypoxemia and does not react to normal low-flow cannula, a high-flow nasal cannula is advised (Calligaro et al. 2020). High-flow nasal cannula has bio-aerosol dispersion system and it is recommended that the patient be placed in a negative pressure room. Apparently, when high-flow nasal cannula fails to work, NIV support and Bi-level positive airway pressure are used and they are appropriate for patients having co-morbidities including chronic obstructive pulmonary disease and heart failure. Continuous positive airway pressure is reported to be advantageous pneumonia patients affected with coronavirus as it leads to effective alveolar recruitment (Gattinoni et al. 2020). The demonstration of different phenotype of ARDS with their novel characteristics is summarised in Table 3. Severe hypoxemia can be relieved via prone positioning by reducing overinflated lungs, re-expanding previously collapsed lung areas and decreasing ventilation/perfusion imbalance (Navas-Blanco and Dudaryk 2020). Evidently, prone positioning was known to decrease mortality of 28 and 90 days as documented in the clinical trial NCT00527813 (Guérin et al. 2013).

Use of nitric oxide and prostaglandins as pulmonary vasodilators is not proven yet and is still controversial because many questions arise like if NO can be self-administered safely to the patients at home or not, if the

benefit is unique to NO and if other therapies could also increase signalling along NO axis. The studies regarding use of NO in COVID-19 patients are being conducted under clinical trials and it might have potential as a useful therapy. Another strategy is the use of extracorporeal membrane oxygenation (ECMO) for patients with severe ARDS due to reversible conditions that are not responding to the standard therapy and has also been recommended by Extracorporeal Life Support Organization (ELSO) for younger group of patients with lesser or no morbidities, healthcare providers. Besides, ELSO has given algorithm for COVID-19-associated ARDS in furnishing conservative management consisting of prone positioning, pulmonary vasodilators, high PEEP, recruitment maneuvers in affected patients who have  $\text{PaO}_2/\text{FiO}_2$  ratio lesser than 150 mmHg along with worsening refractory hypoxemia and  $\text{PaO}_2/\text{FiO}_2$  ratio greater than 150 mmHg but having poor tissue perfusion signs and hypercarbia. However, EOLIA trial shows that 60-day mortality did not improve in ECMO group patients. ELSO (Bartlett et al. 2020; Navas-Blanco and Dudaryk 2020). Tocilizumab, a potential recombinant monoclonal antibody against IL-6, has the potential for treating COVID-associated ARDS and has been widely used in patients with inflammatory diseases. However, there is a need for data from more large and randomized clinical trials to confirm its efficacy and safety (Khiali et al. 2020). In ARDS, fibrin and platelet thrombotic microclots can accumulate in the air spaces and parenchyma of lungs progressing towards respiratory failure, additionally increasing the clot activation and mobilisation, furthermore activating the coagulation system. Plasminogen activators can attenuate the severity of ARDS as it has been observed that mortality rate was reduced from 100 to 70% in ARDS patients who were administered urokinase or streptokinase. Tissue plasminogen activator (tPA) is highly efficient, decreased mortality, increased arterial  $p\text{O}_2$  and decreased  $p\text{CO}_2$ . tPA is a recommended treatment in the absence of ECMO for ARDS patients affected with coronavirus having  $\text{PO}_2/\text{FiO}_2$  ratio  $< 50$  and  $p\text{CO}_2 > 60$  mmHg. However, there is a

**Table 3** The demonstration of different phenotype of ARDS with their novel characteristics

Phenotype of ARDS	Type 1 (non-ARDS)	Type 2 (ARDS)	References
Features	Severe hypoxemia Respiratory system compliance $> 50$ ml/cmH <sub>2</sub> O	Bilateral infiltrates Decreased respiratory system compliance Increased lung weight Respiratory system compliance $< 40$ ml/cm H <sub>2</sub> O	Gattinoni et al. (2020)
Gas volume	High	Lower	Maiolo et al. (2018)
Recruitability	Minimal	Increased	Maiolo et al. (2018)
Tidal volume	7–8 ml/kg ideal body weight	6 ml/kg ideal body weight	Gattinoni et al. (2020)
PEEP levels	8–10 cm H <sub>2</sub> O	14–15 cm H <sub>2</sub> O	Gattinoni et al. (2013)

limitation in using this therapy in patients with thrombocytopenia as tPA might cause platelet dysfunction (Lechowicz et al. 2020). Valproate is an HDAC (Histone deacetylases) inhibitor and a modulator of epigenetic changes and its inhibition results in acetylation of histones, modifies the gene expression regulating cell cycle, cell differentiation and apoptosis. It also inhibits the production of NF- $\kappa$ B, TNF- $\alpha$ , and IL-6 in lipopolysaccharide stimulated human cells, decreases nitric oxide expression along with downregulation of macrophage response and blocks NF- $\kappa$ B signalling. As a result, acute lung edema reduces and lung injury attenuates. Moreover, the metabolite of this drug, valproic acid Co-A, forms a stable interaction with nsp12 of coronavirus and inhibits viral replication (Bhargava et al. 2020).

### Acute lung injury and pneumonia

The patients with COVID-19 pneumonia require treatment of efficacious antiviral and anti-inflammatory medications (Gallelli et al. 2020). In addition to hydroxychloroquine sulfate or tocilizumab, azithromycin use is recommended because it possesses immunomodulant effect (Gautret et al. 2020). Table 4 demonstrates the clinical status of azithromycin, alone or in combination with other drugs under clinical trials. Tocilizumab, a blocker of IL-6 signalling is used in treatment of cytokine release syndrome. Sarilumab and baricitinib, blockers of adaptor-associated protein kinase 1, are used in treating the cytokine storm. Corticosteroids exhibit anti-inflammation and immunomodulatory actions (Gallelli et al. 2020). However, the use of systemic corticosteroids is not recommended by WHO for treating viral pneumonia and ARDS as they can delay the viral clearance (World Health Organization Institutional Repository for Information Sharing 2021). Lianhuaqingwen capsule has been approved by the National Medical Products Administration of China for treating mild-to-moderate coronavirus pneumonia (Chen et al. 2021).

Escin, extracted from *Aesculus hippocastanum* L., *Aesculus wilsonii* possesses anti-inflammatory, antiviral effects and has the potential in treating COVID-19 patients by reducing the degree of lung injury. At 10  $\mu$ g/mL dose, it suppresses the secretion of nitric oxide, TNF- $\alpha$ , and IL-1 $\beta$ . The effect can be enhanced by combining escin and glucocorticoids because escin upregulates glucocorticoid receptor and increases antioxidant activity. The efficacy of escin is being studied under clinical trial NCT04322344 and it is under Phase 2/Phase3 of the study. However, it is being administered to COVID patients in Italy at dosage 40 mg three times daily orally or as a 20 mg IV injection (Gallelli et al. 2020).

### Pulmonary fibrosis

Interstitial lung disease consists of acute and chronic lung diseases which cause progressive scarring of the lung tissues. The most common one is pulmonary fibrosis (Antoniou et al. 2020). Patients affected with COVID-19 progress from atypical pneumonia to fibrosis, which causes interstitial matrix widening, compression, pulmonary parenchyma destruction and finally respiratory failure. Transforming growth factor beta 1 (TGF- $\beta$ 1) is responsible for causing fibrosis and is more prevalent in older people. The pulmonary fibroblast proliferation is increased due to overexpression of fibroblast growth factor and platelet-derived growth factor. The duration of COVID disease is correlated with the degree of pulmonary fibrosis. The cytokine profile of fibrosis and COVID-19 is similar and hence drugs used in treating fibrosis can also be used in COVID-19 (Lechowicz et al. 2020). In this condition, lung function deteriorates exigently causing respiratory failure and ultimately death. The disease can be idiopathic, genetically predisposed, fibroproliferative disease and chronic inflammation play a role in it. Pulmonary fibrosis can occur as a consequence of ARDS (Vasarmidi et al. 2020). Exacerbations of pulmonary fibrosis are triggered by viral infections of the respiratory tract. The evidence of using corticosteroids is limited. Some studies have reported that there is no influence of corticosteroids in improving survival and their use increases risk of mortality and secondary infections in influenza pneumonia. However, some studies are suggestive of decreased risk of death using methylprednisolone in COVID patients. Spironolactone is also effective in treating pulmonary fibrosis by attenuating the increased aldosterone levels due to mineralocorticoid activation which further causes elevation of extracellular matrix turnover. Besides, spironolactone is also known to possess antioxidant properties. Lung tissue of patients treated with spironolactone indicate lesser number of white blood cells and macrophages in the alveoli (Lechowicz et al. 2020; Yavas et al. 2019). Many anti-fibrotic drugs having antiviral and epithelial protective effects are available which are used in acute exacerbations of idiopathic pulmonary fibrosis and also enervate profibrotic pathways involved in coronavirus infection. The FDA approved drugs used include pirfenidone (suppressor of NLRP3 inflammatory activation) and nintedanib (tyrosine kinase inhibitor), which attenuate decline of lung function (Vitiello et al. 2020; Chaudhary et al. 2020). Pirfenidone decreases the concentration of IL-6, has anti-oxidant properties whereas, nintedanib decreases concentrations of IL-1 $\beta$ . Both these drugs are taken orally, hence it becomes very difficult to administer them to patients on ventilator and to be effective, they should be administered within the first week of ARDS (Vasarmidi et al. 2020; George et al. 2020). The approved anti-fibrotic drugs are meant for chronic disease management and do

**Table 4** Illustration of various clinical studies involving azithromycin alone or in combination with hydroxychloroquine and tocilizumab for the treatment and management of COVID-19

S. no.	Identifier	Study title	No. of subjects	Intervention /treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
1.	NCT04334382	Hydroxychloroquine vs. azithromycin for outpatients in Utah with COVID-19 (HyAzOUT)	1550	Hydroxychloroquine (400 mg po BID × 1 day, then 200 mg po BID × 4 days) and azithromycin (500 mg PO on day 1 plus 250 mg PO daily on days 2–5)	Hospitalization within 14 days of enrollment [time frame: from enrollment to 14 days after enrollment] Admitted to a hospital (not merely kept for emergency room observation)	Duration of COVID-19-attributable symptoms [time frame: from enrollment to 14 days after enrollment] Hospital-free days at 28 days [time frame: admission (day 1) to 28 days after admission (day 28)] Ventilator-free days at 28 days [time frame: admission (day 1) to 28 days after admission (day 28)] ICU-free days at 28 days [time frame: admission (day 1) to 28 days after admission (day 28)]	Recruiting	Phase 3
2.	NCT04349592	Hydroxychloroquine with or without azithromycin for virologic cure of COVID-19	456	Hydroxychloroquine (200 mg tablet oral, one tablet three times a day for 7 days) and Azithromycin (250 mg capsules oral, 2 capsules on day one, followed by 1 capsule once a day for days 2–5) Placebo tablet and capsules	Proportion of virologically cured (PCR-negative status) as assessed on day 6 [time frame: day 6] Days	Virologic cure on other study days [time frame: day 14 and day 21] Virologic semi-quantitative analysis of changing viral load [time frame: day 1 to day 21] Proportion of initially symptomatic subjects with disappearance of clinical symptoms [time frame: day 14 and day 21] Proportion of initially asymptomatic subjects with appearance of new clinical symptoms [time frame: day 14 and day 21] Proportions of subjects with potentially medication-related adverse events [time frame: 7 days]	Completed	N.A

**Table 4** (continued)

S. no.	Identifier	Study title	No. of subjects	Intervention /treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
3.	NCT04358081	Hydroxychloroquine monotherapy and in combination with azithromycin in patients with moderate and severe COVID-19 disease	20	Hydroxychloroquine Hydroxychloroquine + azithromycin Placebo	Number of participants who achieved clinical response by day 15 [time frame: 15 days] Clinical response was defined as (a) discharged alive; or (b) No need for mechanical ventilation in any participants and no need for supplemental oxygen requirement (SpO <sub>2</sub> ) in participants without pre-morbid O <sub>2</sub> requirement	Number of participants who achieved viral clearance [time frame: 6 days and 10 days] Number of participants discharged or ready for discharge [time frame: 15 days] Time to return to pre-morbid supplemental oxygen requirement in participants receiving hydrochloroquine or hydrochloroquine plus azithromycin relative to placebo [time frame: 15 days]	Completed	Phase 3
4.	NCT04332094	Clinical trial of combined use of hydroxychloroquine, azithromycin, and tocilizumab for the treatment of COVID-19 (TOCOVID)	276	Tocilizumab Hydroxychloroquine Azithromycin	In-hospital mortality [time frame: through hospitalization, an average of 2 weeks] Need for mechanical ventilation in the Intensive Care Unit [time frame: through hospitalization, an average of 2 weeks]		Recruiting	Phase 2

not reverse fibrosis. TGF- $\beta$  pathway is the main pathway or target for antifibrotic therapies including BG00011 ( $\alpha$ v $\beta$ 6 integrin), PLN-74809 and TD139 (galectins). Arg–Gly–Asp integrin-binding domain is present on spike protein of SARS-CoV-2. Hence, integrins or galectin inhibitors are beneficial in COVID-19. Combination of rapamycin (mTOR inhibitor) and oseltamivir is known to reduce viral replication. Inhibition of IL-1 prevents the development of post COVID-19 fibrosis. Anti-interleukin therapies may act as potential for treating COVID-19 (George et al. 2020). Table 5 demonstrates information on various clinical trials involving anti-interleukin therapies which could be beneficial in COVID-19.

Reduction of viral load is necessary in fibrosis. Antiviral drugs involve the use of chloroquine and hydroxychloroquine (cause disruption of coronavirus cell receptor glycosylation and modulation of immune system), teicoplanin (inhibitor of low-pH cleavage of the viral spike protein, preventing the release of genomic viral RNA with IC<sub>50</sub> value 1.66  $\mu$ M) (Baron et al. 2020) and remdesivir, favipiravir (RNA polymerase inhibitors) and lopinavir/ritonavir (viral protease inhibitors). Combination of lopinavir/ritonavir with interferon-1 $\beta$  or ribavirin might be effective against coronaviruses. Umifenovir inhibits virus binding to the cell membrane and is significant in improving clinical status of patients as compared to lopinavir/ritonavir (Nojomi et al. 2020), whereas, favipiravir inhibits virus reproduction in vitro (Ojo et al. 2020). Plasma therapy provides specific passive immunity and increased PaO<sub>2</sub>/FiO<sub>2</sub> and decreased viral load (Ray et al. 2020).

### COPD (chronic obstructive pulmonary disease)

Patients with underlying COPD might have excessive risk for contracting COVID-19. However, this topic is still in debate. Epidemiological studies indicate that there is a prevalence of 1.1–38% of COPD in coronavirus affected patients. Cleveland Clinic registry investigated that out of 15,586 patients having symptoms and tested for the virus, 9.2% had COPD (Sin 2020). ACE2 expression is also increased significantly in COPD patients and escalated by smoking. During coronavirus infection, patients may have commotions in the renin–angiotensin–aldosterone system, as well as upregulation and aggravation of ACE and angiotensin II, which can lead to pulmonary hypertension and edema. Inhaled corticosteroids decreases viral entry and their use is recommended (Leung et al. 2020). Patients with COPD are advised to use already prescribed inhalers, long acting bronchodilators. In case of COVID-associated exacerbations, patients are given dexamethasone systemically if they need supplemental oxygenation and mechanical ventilation (Sin 2020).

### Pulmonary embolism (PE)

A hypercoagulable state occurs in COVID-19 patients along with elevated levels of d-dimer, fibrinogen, fibrinogen degradation products, prolonged prothrombin time and international normalized ratio (Bompard et al. 2020; Osakwe and Hart 2020). Viral infections may lead to venous thromboembolism (VTE), thereby activating systemic inflammatory response. Prophylactic treatment with heparin improved survival in the patients having sepsis-induced coagulopathy and increased d-dimer. Low molecular weight heparins at a dose 40 mg qd and subcutaneous unfractionated heparin at a dose 5000 IU tid should be started in confirmed COVID-19 cases. Pneumatic compression is suggested in immobilized patients and in the patients in whom pharmacological prophylaxis is contraindicated. Enoxaparin at a dose of 4000 IU is considered in patients with multiple risk factors for VTE and obese patients are administered with a dose 40 mg twice daily. Direct oral anticoagulants are used after the acute phase in stable patients (Sakr et al. 2020).

### Other comorbid conditions and miscellaneous potential strategies for the management of pulmonary compromised situations in COVID subjects

Patients with conditions, such as lung carcinoma, autoimmune disease, pulmonary sarcoidosis, sick sinus syndrome and mild obstructive lung disease, are at a higher risk during coronavirus infection. Remdesivir is used in early stages but is restricted due to limited availability and potential toxicity (Yates et al. 2020). Patients treated with doxycycline show rapid clinical improvement. Metalloproteinases are responsible for viral entry into the cell and doxycycline is a metalloproteinase inhibitor. It is also an inhibitor of IL-6 and NF- $\kappa$ B (direct inhibition of DPP4 cell surface receptor) (Malek et al. 2020).

OATD-01 (chitotriosidase 1) aids in the treatment of pulmonary fibrosis in COVID-19 survivors. It exhibits anti-inflammatory actions and delays fibrosis development (OncoArendi Therapeutics 2020). Ivermectin (antiparasitic drug) reduces viral load by 99.98% after treating for 48 h. However, WHO recommends its use within clinical trials because current data on its use are inconclusive (World Health Organization, Newsroom 2021b). Ciclesonide, at an effective concentration of 6.3  $\mu$ M, is a blocker of SARS-CoV-2 RNA replication in vitro and is an inhibitor of its cytopathic activity (Iwabuchi et al. 2020). Tetrandrine is an alkaloid obtained from the plant *Stephania tetrandra* and at concentration 4.8  $\mu$ mol/L affects reactive oxygen species and caspase pathways associated with treating inflammation. It has the ability to suppress virus reproduction by blocking the two-pore channel 2 (TPC2) in host cells at low micro-molar concentrations and also inhibits proliferation of T cells and

**Table 5** Illustration of different clinical trials and their status with reference to anti-interleukin therapies for the management of COVID-19

S. no.	Identifier	Study title	No. of subjects	Intervention /treatment
1.	NCT04332913	Efficacy and safety of tocilizumab in the treatment of SARS-Cov-2 related pneumonia (TOSCA)	30	Tocilizumab
2.	NCT04322773	Anti-il6 treatment of serious COVID-19 disease with threatening respiratory failure (TOCIVID)	20	RoActemra iv, RoActemra sc, Kevzara sc
3.	NCT04331795	Tocilizumab to prevent clinical decompensation in hospitalized, non-critically ill patients with COVID-19 pneumonia (COVIDOSE)	32	Tocilizumab
4.	NCT04315298	Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19	1912	Sarilumab and placebo
5.	NCT04324021	Efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in patients with COVID-19 infection	16	Emapalumab and anakinra
S. no.	Primary outcomes	Secondary outcomes	Status	Phase
1.	Percentage of patients with complete recovery defined as fever disappearance and return to normal peripheral oxygen saturation values ( $SpO_2$ ) after 14 days from the end of treatment with tocilizumab. [time frame: 14 days] Fever normalization criteria: Temperature $< 36.6^\circ C$ for at least 72 h; $SpO_2$ normalization criterion: $SpO_2 > 94\%$ for at least 72 h	Percentage of patients achieving a score $< 3$ on the Brescia-COVID respiratory severity scale (BCRSS) after the last tocilizumab administration [time frame: 24 h] Percentage of patients with partial recovery defined as the disappearance of fever 14 days after the end of treatment with tocilizumab [time frame: 14 days] Fever normalization criteria: Temperature $< 36.6^\circ C$ for at least 72 h Duration of hospitalization [time frame: 14 days] Time to the first negative SARS-CoV-2 negative RT-PCR test [time frame: 14 days] Changes from the baseline in the white blood cell count [time frame: 7, 14 days] Number/microliter Changes from the baseline in the lymphocyte populations (cluster of differentiation (CD)3+ CD4+, CD3+ CD8+, CD19+, Th17) [time frame: 7, 14 days] Number/microliter Changes from the baseline of C-reactive protein (CRP) values [time frame: 7, 14 days] Changes from the baseline of Ferritin values [time frame: 7, 14 days] Changes from the baseline of BNP values [time frame: 7, 14 days] Changes from the baseline of CK-MB values [time frame: 7, 14 days] Changes from the baseline of troponin values [time frame: 7, 14 days]	Recruiting	N.A

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
2.	Time to independence from supplementary oxygen therapy [time frame: days from enrolment up to 28 days]	<p>Changes from the baseline of LDH values [time frame: 7, 14 days]</p> <p>Changes from the baseline of myoglobin values [time frame: 7, 14 days]</p> <p>Changes in myocardial ischemia signs at the electrocardiographic trace (YES or NO) [time frame: 7, 14 days] (ST segments elevation or depression, T-wave changes)</p> <p>Rate of adverse events report during and after tocilizumab [time frame: 14 days]</p> <p>Mortality (number of Participants, cause and timing) [time frame: 12 weeks]</p> <p>Percentage of patients who develop autoimmune diseases [time frame: 1 year]</p> <p>Number of deaths [time frame: 28 days from enrolment]</p> <p>Days out of hospital and alive [time frame: 28 days from enrolment]</p> <p>Ventilator-free days alive and out of hospital [time frame: 28 days from enrolment]</p> <p>C-reactive protein (CRP) level [time frame: baseline]</p> <p>Measured from standard blood test</p> <p>C-reactive protein (CRP) level [time frame: peak during hospitalisation, up to 28 days]</p> <p>Measured from standard blood test</p> <p>C-reactive protein (CRP) level [time frame: 14 days]</p> <p>Measured from standard blood test</p> <p>C-reactive protein (CRP) level [time frame: 28 days]</p> <p>Measured from standard blood test</p> <p>Number of participants with serious adverse events [time frame: during treatment, up to 28 days]</p> <p>Measured as occurrence of any serious adverse events</p>	Terminated	Phase 2



Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
3.	<p>Clinical response [time frame: assessed for the 24-h period after tocilizumab administration]</p> <p><math>T_{\max}</math> response: resolution of fever (from <math>T_{\max} &gt; 38^{\circ}\text{C}</math> in 24H period to <math>T_{\max} &lt; 38^{\circ}\text{C}</math> in following 24H period, with <math>T_{\max}</math> measured by commonly accepted clinical methods [forehead, tympanic, oral, axillary, rectal]). Maximum temperature within 24-h period of time (0:00–23:59) on the day prior to, day of, and every 24 h after tocilizumab administration. The primary endpoint is absence of <math>T_{\max}</math> greater than or equal to <math>38^{\circ}\text{C}</math> in the 24-h period following tocilizumab administration</p> <p>Biochemical response [Time frame: assessed every 24 h during patient's hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>CRP normalization rate: calculated as the ratio of the number of patients who achieve normal CRP value following tocilizumab administration and total number of patients who receive tocilizumab</p> <p>Time to CRP normalization: calculated as the number of hours between tocilizumab administration and first normal CRP value</p> <p>CRP response: defined as at least 25% decrease in CRP from baseline at least 16 h after administration of drug</p>	<p>Overall survival [time frame: 28 days]</p> <p>28-Day overall survival is defined as the status of the patient at the end of 28 days, beginning from the time of the first dose of tocilizumab</p> <p>Survival to hospital discharge [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be defined as the percentage of patients who are discharged in stable condition compared to the percentage of patients who die in the hospital. Patients who are discharged to hospice will be excluded from this calculation</p> <p>Progression of COVID-19 pneumonitis [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a binary outcome defined by worsening COVID-19 pneumonitis resulting in transition from clinical Group A or Group B COVID-19 pneumonitis to critical COVID-19 pneumonitis during the course of the patient's COVID-19 infection. This diagnosis will be determined by treating physicians on the basis of worsening pulmonary infiltrates on chest imaging as well as clinical deterioration marked by persistent fever, rising supplemental oxygen requirement, declining</p> <p><math>\text{PaO}_2/\text{FiO}_2</math> ratio, and the need for intensive care, such as mechanical ventilation or vasopressor/inotrope medication(s)</p> <p>Rate of non-elective mechanical ventilation [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a binary outcome defined as worsening COVID-19 disease resulting in the use of non-invasive (BiPap, heated high-flow nasal cannula) or invasive positive pressure ventilation during the course of the patient's COVID-19 infection. For patients admitted to the hospital using non-invasive mechanical ventilation, the utilization of mechanical ventilation will count toward this metric, as well. Calculated as the ratio of the number of patients who require non-invasive or invasive positive pressure ventilation during hospitalization and total number of patients who receive tocilizumab</p> <p>Duration of mechanical ventilation [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a continuous outcome defined by the amount of time between initiation and cessation of mechanical ventilation (invasive and non-invasive)</p> <p>Time to mechanical ventilation [time frame: assessed over hospitalization, up to 4 weeks after tocilizumab administration]</p>	Completed	Phase 2

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		<p>This will be a continuous outcome defined by the amount of time between tocilizumab dose administration and the initiation of mechanical ventilation. This will be treated as a time-to-event with possible censoring</p> <p>Rate of vasopressor/inotrope utilization [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a binary outcome defined as utilization of any vasopressor or inotropic medication during the course of the patient's COVID-19 infection</p> <p>Calculated as the ratio of the number of patients who require vasopressor or inotrope medication during hospitalization and total number of patients who receive tocilizumab</p> <p>Duration of vasopressor/inotrope utilization [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a continuous outcome defined by the amount of time between initiation of first and cessation of last vasopressor or inotrope medication(s)</p> <p>Time to vasopressor or inotropic utilization [time frame: assessed over hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>This will be a continuous outcome defined by the amount of time between first tocilizumab dose administration and the initiation of vasopressor or inotropic medication(s). This will be treated as a time-to-event with possible censoring</p> <p>Number of ICU days [time frame: hospitalization, up to 4 weeks after tocilizumab administration]</p> <p>Number of ICU days is defined as the time period when a patient is admitted to the ICU (defined as the timestamp on the first vital signs collected in an ICU) until they are transferred from the ICU to a non-ICU setting such as a general acute care bed (defined as the timestamp on the first vital signs collected outside an ICU, excepting any "off the floor" vital signs charted from operating rooms or procedure or imaging suites). Death in the ICU will be a competing risk</p> <p>Duration of increased supplemental oxygen requirement from baseline [time frame: assessed over hospitalization, up to 4 weeks after tocilizumab administration]</p>		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
4.	<p>Percent change in C-reactive protein (CRP) levels in patients with serum IL-6 level greater than the upper limit of normal [time frame: day 4]</p> <p>Phase 2</p> <p>Proportion of patients with at least 1-point improvement in clinical status using the 7-point ordinal scale in patients with critical COVID-19 receiving mechanical ventilation at baseline [time frame: up to day 22]</p> <p>Phase 3 Cohort 2</p>	<p>Duration of increased supplemental oxygen requirement from baseline is defined as the time period (number of days) during which the participant requires supplemental oxygen in excess of his/her baseline supplemental oxygen requirement. The supplemental oxygen requirement is defined as the highest liters-per-minute flow of supplemental oxygen required by the patient each day over the course of the hospitalization</p> <p>Time to improvement (2 points) in clinical status assessment on the 7-point ordinal scale in severe or critical patients with serum IL-6 levels greater than the upper limit of normal [time frame: up to day 29]</p> <p>Phase 2</p> <p>Time to improvement (2 points) in clinical status assessment on the 7-point ordinal scale reporting in severe or critical patients with all IL-6 levels [time frame: up to day 29]</p> <p>Phase 2</p> <p>Time to resolution of fever for at least 48 h without antipyretics in patients with documented fever [time frame: up to day 29]</p> <p>Phase 2</p> <p>Resolution of fever defined as post-baseline body temperature &lt; 37.2 °C (oral), or &lt; 37.6 °C (rectal or tympanic) or &lt; 36.8 °C (temporal or axillary)</p> <p>Documented fever defined as ≥ 38 °C (oral), ≥ 38.4 °C (rectal or tympanic), or ≥ 37.6 °C (temporal or axillary)</p> <p>Time to resolution of fever for at least 48 h without anti-pyretics by clinical severity [time frame: up to day 29]</p> <p>Phase 2</p> <p>Defined as post-baseline body temperature &lt; 37.2 °C (oral), or &lt; 37.6 °C (rectal or tympanic) or &lt; 36.8 °C (temporal or axillary)</p> <p>Time to resolution of fever for at least 48 h without antipyretics by baseline IL-6 levels [time frame: up to day 29]</p> <p>Phase 2</p> <p>Defined as post-baseline body temperature &lt; 37.2 °C (oral), or &lt; 37.6 °C (rectal or tympanic) or &lt; 36.8 °C (temporal or axillary)</p> <p>Time to improvement in oxygenation for at least 48 h [time frame: up to day 29]</p> <p>Phase 2</p> <p>Improvement in oxygenation defined as increase in SpO<sub>2</sub>/FiO<sub>2</sub> of 50 or greater compared to the nadir SpO<sub>2</sub>/FiO<sub>2</sub></p>	Completed	Phase 2/Phase 3

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Time to improvement in oxygenation for at least 48 h by clinical severity [time frame: up to day 29] Phase 2		
		Defined as increase in $SpO_2/FiO_2$ of 50 or greater compared to the nadir $SpO_2/FiO_2$		
		Time to improvement in oxygenation for at least 48 h by baseline IL-6 levels [time frame: up to day 29] Phase 2		
		Defined as increase in $SpO_2/FiO_2$ of 50 or greater compared to the nadir $SpO_2/FiO_2$		
		Time to resolution of fever and improvement in oxygenation for at least 48 h [time frame: up to day 29] Phase 2		
		Resolution of fever defined as post-baseline body temperature $< 37.2$ °C (oral), or $< 37.6$ °C (rectal or tympanic) or $< 36.8$ °C (temporal or axillary)		
		Improvement in oxygenation defined as increase in $SpO_2/FiO_2$ of 50 or greater compared to the nadir $SpO_2/FiO_2$		
		Mean change in the 7-point ordinal scale [time frame: up to day 29] Phase 2		
		Percentage of patients in each clinical status category using the 7-point ordinal scale [time frame: up to day 29] Phase 2		
		Time to discharge or to a National Early Warning Score 2 (NEWS2) of $\leq 2$ and maintained for 24 h [time frame: up to day 29] Phase 2		
		NEWS2 consists of: Physiological Parameters: Respiration rate (per minute), $SpO_2$ scale 1 (%), $SpO_2$ scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, temperature (°C)		
		Change from baseline in NEWS2 scoring system [time frame: up to day 29] Phase 2		
		Number of days with fever [time frame: up to day 29] Phase 2		
		Defined as $\geq 38$ °C (oral), $\geq 38.4$ °C (rectal or tympanic) or $\geq 37.6$ °C (temporal or axillary)		
		Proportion of patients alive, off oxygen [time frame: at day 29] Phase 2		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Number of days of resting respiratory rate > 24 breaths/min [time frame: up to day 29] Phase 2		
		Number of days with hypoxemia [time frame: up to day 29] Phase 2		
		Number of days of supplemental oxygen use [time frame: up to day 29] Phase 2		
		Time to saturation $\geq 94\%$ on room air [time frame: up to day 29] Phase 2		
		Number of ventilator free days in the first 28 days [time frame: baseline to day 29] Phase 2		
		Number of patients requiring initiation of mechanical ventilation [time frame: up to day 29] Phase 2		
		Number of patients requiring non-invasive ventilation [time frame: up to day 29] Phase 2		
		Number of patients requiring the use of high-flow nasal cannula [time frame: up to day 29] Phase 2		
		Number of patients admitted into an intensive care unit (ICU) [time frame: up to day 29] Phase 2		
		Number of days of hospitalization among survivors [time frame: up to day 29] Phase 2		
		Number of deaths due to any cause [time frame: up to day 60] Phase 2		
		Proportion of patients with at least 1-point improvement in clinical status using the 7-point ordinal scale [time frame: up to day 22] Phase 3		
		Proportion of patients who recover [time frame: up to day 22] Phase 3		
		Defined as discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use		
		Proportion of deaths [time frame: through day 29] Phase 3		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Proportion of patients alive not receiving mechanical ventilation [time frame: at day 22]		
		Phase 3		
		Proportion of patients alive not requiring extracorporeal membrane oxygenation (ECMO) [time frame: at day 22]		
		Phase 3		
		Proportion of patients with a 2-point improvement in clinical status on the 7-point ordinal scale [time frame: up to day 22]		
		Phase 3		
		Time to at least 1-point improvement in clinical status assessment on the 7-point ordinal scale [time frame: up to day 29]		
		Phase 3		
		Time to at least 2-point improvement in clinical status assessment on the 7-point ordinal scale [time frame: up to day 29]		
		Phase 3		
		Proportion of patients receiving mechanical ventilation [time frame: up to day 22]		
		Phase 3		
		Proportion of patients receiving ECMO [time frame: up to day 22]		
		Phase 3		
		Proportion of patients discharged and alive [time frame: at day 22]		
		Phase 3		
		Time to recovery [time frame: up to day 29]		
		Phase 3		
		Defined as discharged or alive without supplemental oxygen use or at pre-COVID oxygen use		
		Proportion of deaths [time frame: through day 60]		
		Phase 3		
		Time to death due to any cause [time frame: through day 60]		
		Phase 3		
		Number of ventilator free days [time frame: up to day 29]		
		Phase 3		
		Number of days of hospitalization among survivors [time frame: up to day 29]		
		Phase 3		
		Proportion of patients with serious adverse events [time frame: up to day 29]		
		Phase 2 and Phase 3		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Proportion of patients with Grade 4 neutropenia ( $ANC < 500/mm^3$ ) [time frame: up to day 29] Phase 2 and Phase 3		
		Proportion of patients with severe or life-threatening bacterial, invasive fungal, or opportunistic infection [time frame: up to day 29] Phase 2 and Phase 3		
		Proportion of patients with severe or life-threatening bacterial, invasive fungal, or opportunistic infection in patients with Grade 4 neutropenia ( $ANC < 500/mm^3$ ) [time frame: up to day 29] Phase 2 and Phase 3		
		Proportion of patients with hypersensitivity reactions [time frame: up to day 29] Phase 2 and Phase 3		
		Proportion of patients with infusion reactions [time frame: up to day 29] Phase 2 and Phase 3		
		Proportion of patients with gastrointestinal perforation [time frame: up to day 29] Phase 2 and Phase 3		
		White blood cell count [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Hemoglobin levels [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Platelet count [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Creatinine levels [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Total bilirubin level [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Alanine aminotransferase (ALT) level [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		
		Aspartate aminotransferase (AST) level [time frame: up to day 29 if still hospitalized] Phase 2 and Phase 3		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
5.	Treatment success [time frame: up to day 15] Defined as the proportion of patients not requiring invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO)	Time to mechanical ventilation [time frame: date of randomization to date of mechanical ventilation] Measured in days Change from baseline in modified early warning system score [time frame: baseline, day 15] Measured in total score Change from baseline in resting peripheral capillary oxygen saturation ( $SpO_2$ ) [time frame: baseline, 3 assessments every days 4, 7, 10, 13 and 15] Measured in percent (%) Change from baseline in partial pressure of oxygen/fraction of inspired oxygen ( $PaO_2/FiO_2$ ) [time frame: baseline, day 15] Measured in percent (%) Change of pH in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of carbon dioxide tension ( $pCO_2$ ) in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of oxygen tension ( $pO_2$ ) in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of potassium in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of sodium in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of chloride in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of lactic acid in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change of hemoglobin in hemogasanalysis from baseline [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units Change from baseline in oxygen supplementation [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in l/min	Terminated	Phase 2/Phase 3



Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Change of findings of high-resolution computed tomography (CT) scan of the chest [time frame: screening, day 15] Measured in scan evaluation: normal, abnormal but not clinically significant, abnormal clinical significant, not done Change from baseline in Ferritin [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in lactate dehydrogenase (LDH) [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in D-dimers [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in white blood cells with differential counts [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in red blood counts [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in hemoglobin [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in platelet count [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in fibrinogen [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in complement factors C3/C4 [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in Prothrombin time [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in Cardiac troponin [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in aspartate aminotransferase (AST) [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		

Table 5 (continued)

S. no.	Primary outcomes	Secondary outcomes	Status	Phase
		Change from baseline in alanine aminotransferase (ALT) [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in total bilirubin levels [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Change from baseline in C-reactive protein [time frame: baseline, days 4, 7, 10, 13 and 15] Measured in local units		
		Overall survival [time frame: weeks 6 and 10] Confirmation of death		
		Time to hospital discharge [time frame: weeks 6 and 10] Measured in days		

IFN $\gamma$  production. Tetrandrine has low and variable oral bioavailability which can be enhanced by making formulations of lipid nano-capsules, nanoparticles, ethosomes, and microspheres or by inhalation method (Heister and Poston 2020). Fuzheng Huayu formula and Anluohuaxian possess anti-fibrotic properties. Other treatment strategies include administrating mesenchymal stem cells and human purified amniotic fluid, having anti-inflammatory and antifibrotic properties (Lechowicz et al. 2020). Table 6 demonstrates the pharmacological therapy of coronavirus associated pulmonary fibrosis under clinical trials. Figure 9 describes the various therapeutic approaches in treating COVID-associated pulmonary fibrosis.

### Clinical approaches with reference to extra-pulmonary manifestations associated with other organ systems

SARS-CoV-2 is predominantly responsible for causing disorders of the respiratory tract but it can also cause extra-pulmonary manifestations including thrombotic complications, dysfunction of the myocardium, arrhythmias, coronary syndrome, kidney injury, gastrointestinal disorders, hepatocellular injury, neurological disorders, ocular disorders and ketosis (Gupta et al. 2020).

### Cardiovascular manifestations

SARS-COV-2 virus has major implications on cardiovascular system. Patients with cardiovascular risk factors including age above 60 years, obesity and comorbid conditions including diabetes and hypertension are at a higher mortality risk because of higher ACE 2 expression in myocytes, fibroblasts, endothelial cells, and smooth-muscle cells (Shafi et al. 2020). Cardiovascular diseases including heart failure, myocardial injury, myocarditis, arrhythmias, and acute coronary syndrome are correlated with COVID-19. Heart failure occurs as a response to infection and ARDS (Temgoua et al. 2020). Wang et al. reported that 44.4% COVID-19 patients admitted in a hospital had cardiac arrhythmias (Wang et al. 2020) and were mostly affected with *torsade de pointes*. Risk of QT prolongation can occur due to drugs like hydroxychloroquine, renal failure and hypokalaemia. Patients are at a risk of developing venous thromboembolism due to inflammation, hypoxia, immobilization, and diffused intravascular coagulation (Temgoua et al. 2020). ACE catalyses angiotensin II to angiotensin 1–7 conversion, exerting a protective effect on the cardiovascular system. SARS-CoV-2 and ACE2 binding can decrease this catalytic effect (Dou et al. 2020). Stimulation of macrophages and leucocyte adhesion molecule expression on endothelial cells of atherosclerotic lesions makes them prone to get disrupted and causing acute coronary syndrome (Gavriatopoulou et al. 2020). Current

treatment guidelines include the use of antiplatelet drugs,  $\beta$ -blockers, statins, and ACE inhibitors (Mahajan et al. 2020). In patients with ST segment elevation, percutaneous coronary intervention is recommended but fibrinolytic therapy can also be used. Obtaining baseline QTc interval is essential before administration of any drug (Gupta et al. 2020). Remdesivir 200 mg administered IV on day 1 followed by 100 mg for 9 days showed clinical improvement in the patients. Lopinavir and ritonavir show potential benefits. But the adverse effect associated with them include prolongation of QT and PR intervals and hyperlipidaemia (Nishiga et al. 2020). Other antiviral drugs consist of oseltamivir and favipiravir. But antiviral drugs might show interaction with antiplatelet agents and anticoagulants. So they should be monitored cautiously (Su et al. 2020). Chloroquine and hydroxychloroquine have antiviral and anti-inflammatory effects but they may cause QT prolongation and monitoring is essential when azithromycin is also used (Takla and Jeevaratnam 2020). Patients with cardiovascular diseases are prescribed statins. Statin shows therapeutic efficacy in hyper-inflammatory ARDS. Rosuvastatin is known to reduce pneumonia. Drug interactions between statins and protease inhibitors can occur. So, they should be cautiously used (Atri et al. 2020; Rossi et al. 2020). Amiodarone is used in treating cardiac arrhythmias and can inhibit in vitro spread of coronavirus. Colchicine reduces the release of interleukins IL-1 $\beta$  and IL-6. ACC/AHA recommends the use of ACE inhibitors and ARBs in patients who have been previously prescribed. But, there is still no evidence which supports their use. Mortality risk in COVID-19 patients with hypertension was reduced by administering them (Su et al. 2020; Kang et al. 2020). Camostat mesylate (inhibitor of cellular serine protease TMPRSS2) blocks SARS-CoV-2 entry, which is further dependent on ACE2 for its entry into the host cell (Madjid et al. 2020). Tranexamic acid reduces the conversion of plasminogen to plasmin and can reduce the pathogenicity and viral load. However, various adverse effects including venous and arterial thrombosis and thromboembolism are involved with its use. So, tranexamic acid must be cautiously used in patients with underlying cardiovascular diseases (Driggin et al. 2020).

### Renal manifestations

The brush border present in proximal tubular cells and podocytes highly expresses ACE 2 receptors. Chronic kidney disease and transplantation are considered as risk factors for contracting the infection. Renal manifestations include acute kidney injury, proteinuria, hematuria, increased kaliuresis, decreased glomerular filtration rate (GFR), increased blood urea nitrogen (BUN) and serum creatinine levels and the presence of SARS-CoV-2 in the urine (Gavriatopoulou et al. 2020; Temgoua et al. 2020). The mechanisms responsible for

acute kidney injury include dehydration, hypoxia followed by hypovolemia and ischemia, which further cause tubular necrosis, renal cell infection, cytokine storm syndrome, diabetes, hypertension, use of NSAIDs and rhabdomyolysis. Management consists of sufficient hydration and abstaining from using nephrotoxic medications and dialysis is required in second week of infection. Other options consist of haemodialysis, slow low-efficiency dialysis and continuous renal replacement therapy (Mahajan et al. 2020). Urine analysis and protein-to-creatinine ratio are evaluated at the time of patient admission. Patient can be given empiric low-dose systemic anticoagulation for renal replacement therapy. Fluid balance strategies should be applied to correct the levels of serum lactate and electrolytes. Renal replacement therapy should be considered in patients with acute kidney injury (Gupta et al. 2020).

### Immuno-hematological manifestations

Clinical manifestations occurring due to virally induced hyper-inflammation consist of enlargement of spleen, atrophy and lymphoid organ atrophy. Lymphopenia occurs due to direct viral cytotoxicity, followed by lymphocyte depletion due to apoptosis and inhibitory actions of lactic acid on proliferation of the lymphocytes. Spleen atrophy and lymphoid tissue destruction occur in COVID-19 (Gupta et al. 2020). Abnormalities in blood consist of anaemia, leucocytosis and neutrophilia, elevated levels of neutrophils/lymphocytes ratio, decreased count of eosinophil, monocytes, lymphocytes (CD4/CD8) and platelets, elevated D-dimer, and decreased fibrinogen levels (Joly et al. 2020; Al-Samkari et al. 2020). Antiphospholipid antibodies are observed in case of viral infections (Marietta et al. 2020). Hyper-inflammation causes anaemia, bacterial infections cause leucocytosis and increased neutrophils. Apoptosis induced by virus, elevated activation of lymphocytes and inhibition of lymphocyte proliferation lead to lymphopenia. Excess platelet consumption in micro-thrombosis site can cause thrombocytopenia. Inflammatory syndrome is followed by cytokine storm and changes in biochemical parameters including increased erythrocyte sedimentation rate (ESR), increased CRP, elevated levels of ferritin and procalcitonin (Temgoua et al. 2020). Coagulation activation occurs due to sepsis, cytokine storm, and multi-organ failure. Active bleeding requires transfusion. Routine risk assessment of developing VTE should be done in hospitalized COVID patients. Prophylactic treatment of anticoagulants should be considered in case of active bleeding and platelet count less than  $25 \times 10^9/L$  (Gupta et al. 2020; Kasinathan and Sathar, 2020). Low molecular weight heparin (4000–5000 kD) is used in treatment and it has a better prognosis in COVID-19 especially in cases of elevated d-dimer (Mahajan et al. 2020; Sathler 2020; Aggarwal

et al. 2020; Joly et al. 2020). Fondaparinux can reduce mortality in patients of pulmonary artery thromboembolism (Zabolotsky Dmitrii and Koryachkin Viktor 2020). Enoxaparin at a dose of 40 mg twice daily, enoxaparin 1 mg/kg daily, nadroparin 5700 IU daily and nadroparin 2850 IU twice daily are the proposed dosage regimens for prophylaxis (Orsi et al. 2020).

### Septic shock

60% of COVID-19 patients experience sepsis and nearly 20% experience further complications including septic shock. The organ dysfunction in sepsis can be evaluated using Sequential Organ Failure Assessment (SOFA) score. Clinical management involves the empirical use of antimicrobials with mechanical ventilation. US FDA has approved the emergency use authorisation for remdesivir. However, there is no solid evidence for the use of other category of drugs including antivirals, interferons, tocilizumab, immunoglobulins, and plasma therapy, chloroquine phosphate and hydroxychloroquine. FDA has abrogated the use of chloroquine and hydroxychloroquine due to cardiac complications. Apparently, hydroxychloroquine is being administered in severe patients at 400–600 mg daily for 5 days (Mahajan et al. 2020).

### Endocrine and metabolic manifestations

ACE2 receptors are expressed in various endocrine organs including pancreas, female ovaries, pituitary gland, thyroid and male testicles. The coronavirus infection in critical patients is followed by complications including pancreatitis, diabetes mellitus, hypogonadism and hypothyroidism (Temgoua et al. 2020). The binding of coronavirus to ACE2 receptors in the pancreas causes hyperglycemia and diabetes mellitus, followed by increased receptor expression, which enhances infection susceptibility and multi-organ failure. Glucose metabolism and blood pressure can be improved using antidiabetic medications such as glucagon-like peptide-1 agonists. Agonists of glucagon-like-peptide-1 are beneficial to enhance the metabolic activity and instigate protective ACE2 and Mas receptor pathways (Mahajan et al. 2020). Hemoglobin A1C needs to be checked in COVID-19 patients with hyperglycemia and ketoacidosis. Glucose monitoring is essential. Subcutaneous insulin should be considered in patients with mild-to-moderate diabetic ketoacidosis. Treatment of diabetic ketoacidosis should be initiated with standard protocols. Patients taking steroids should be given increased insulin (Gupta et al. 2020).

### Gastrointestinal manifestations

The epithelial cells present in the upper oesophagus and enterocytes in ileum and colon consist of ACE2 receptors. SARS-CoV-2 replication and high ACE2 expression causes direct cytopathic effect. Viral infections enhance the permeability of the gastrointestinal wall to pathogens (Mahajan et al. 2020). Moreover, liver function is dysregulated due to SARS-CoV-2 and ACE2 binding and it is reflected by low albumin. Liver injury may occur as a result of using lopinavir/ritonavir and hydroxychloroquine and biomarkers, such as serum transaminases and bilirubin levels, indicate the degree of injury (Temgoua et al. 2020). Gastrointestinal manifestations include nausea, vomiting, diarrhoea, abdominal pain, bleeding and anorexia. Diagnostic endoscopy should be avoided but should be reserved in patients in whom upper gastrointestinal bleeding is prominent. Regular monitoring of hepatic transaminases is necessary when giving interventions, such as remdesivir, lopinavir, and tocilizumab (Gupta et al. 2020).

### Neurological manifestations

When ACE2 becomes highly expressed in the nervous system, it gives rise to symptoms, such as headache, ataxia, unconsciousness, dizziness, cerebral haemorrhage and infarction, hypogeusia, epilepsy, hyposmia, hypopsia and neuralgia (Mahajan et al. 2020). Neurological complications occur due to various mechanisms including cytokine dysregulation and up regulation of cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-6, myeloid cells, transmigration and post-infectious autoimmunity (Temgoua et al. 2020). Virus can invade via neural parenchyma and nasal epithelial cells show the highest expression for ACE2 receptors. Patients with neurological disorders including Parkinson's and Alzheimer's disease should be taken care of properly and monitored regularly. Immunomodulatory therapies should be considered in patients with multiple sclerosis. Use of tPA and anticoagulants should be evaluated as they can increase risk for intracranial bleeding and haemorrhagic conversion of stroke. Practice of telemedicine can be executed in patients with cognitive impairment. Tele neurology can be used to provide treatment to dementia patients (Kim et al. 2017). Depression and anxiety can be reduced by doing mindfulness activities and through online interaction. Physical activities done at home can help in eradicating psychological stress and hence improve the symptoms (Helmich and Bloem, 2020).

**Table 6** Illustration of various Clinical trials of potential novel strategies in COVID-19-associated pulmonary fibrosis

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
1.	NCT04510233	Ivermectin nasal spray for COVID19 patients	60	Ivermectin nasal and ivermectin oral	<p>PCR of SARS-Cov2 RNA [time frame: 14 days]</p> <p>Negative PCR result of SARS-Cov2 RNA in COVID19 patients</p>	<p>Number of participants with clinical response [time frame: 10 days (5 days ivermectin therapy plus 5 days follow-up)]</p> <p>Mortality [time frame: through study completion, an average of 3 months]</p> <p>Changes in oxygen saturation (<math>SpO_2</math>) values [time frame: from 6th to the end of 10th day]</p> <p>Changes in the ratio of partial pressure of oxygen (<math>PaO_2</math>) to fraction of inspired oxygen (<math>FiO_2</math>) (<math>PaO_2/FiO_2</math>) [time frame: from 6th to the end of 10th day]</p> <p>Changes in serum lymphocyte counts [time frame: from 6th to the end of 10th day]</p> <p>Changes in the ratio of polymorphonuclear leukocyte count to lymphocyte count (PNL/L) [time frame: from 6th to the end of 10th day]</p> <p>Changes in serum ferritin levels [time frame: from 6th to the end of 10th day]</p> <p>Changes in serum D-dimer levels [time frame: from 6th to the end of 10th day]</p> <p>Rate of COVID-19 polymerase chain reaction (PCR) test negativity [time frame: at the end of 10th day]</p> <p>Treatment-related adverse events as assessed by CTCAE v4.0 [time frame: from the 6th day of study to the 10th day of study]</p>	Not yet recruiting	Phase 2
2.	NCT04646109	Ivermectin for severe COVID-19 management	66	Ivermectin	<p>Gender distribution of the patients [time frame: at the first day of the study]</p> <p>Age distribution of the patients [time frame: at the first day of the study]</p> <p>Percentage of patients with accompanying diseases [time frame: at the first day of the study]</p> <p>Percentage of patients with baseline clinical symptoms [time frame: at the first day of the study]</p> <p>Body temperature means of the patients [time frame: at the first day of the study]</p> <p>Heart rate means of the patients [time frame: at the first day of the study]</p> <p>Respiratory rate means of the patients [time frame: at the first day of the study]</p> <p>Systolic and diastolic pressure means of the patients [time frame: at the first day of the study]</p> <p>Number of participants with clinical response [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in oxygen saturation (<math>SpO_2</math>) values [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in the Ratio of partial pressure of oxygen (<math>PaO_2</math>) to fraction of inspired oxygen (<math>FiO_2</math>) (<math>PaO_2/FiO_2</math>) [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in serum lymphocyte counts [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in the ratio of polymorphonuclear leukocyte count to lymphocyte count (PNL/L) [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in serum ferritin levels [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Changes in serum D-dimer levels [time frame: from starting to the end of ivermectin therapy (0 to the end of 5th day)]</p> <p>Genetic examination of haplotypes and mutations that cause function losing for ivermectin metabolism [time frame: at the first day of ivermectin therapy (1st day)]</p> <p>Treatment-related adverse events as assessed by CTCAE v4.0 [time frame: at the first 5 days of study]</p>	Completed	Phase 3	

Table 6 (continued)

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
3.	NCT04681053	Inhaled ivermectin and COVID-19 (CCOVID-19)	80	Ivermectin Powder	Rate of virological cure by Rt-PCR for COVID-19 using ivermectin when compared to standard treatment [time frame: throughout the study completion up to 1 year (for every case must be done after 2 weeks from the start of treatment)] All PCR for COVID-19 must be negative	Resolution of pneumonia [time frame: throughout the study completion up to one year (for every case must be done after 2 weeks from the start of treatment)] The score severity index of pneumonia will be measured before and after receiving treatment by computed tomography (CT) (index from 0–20) increasing the index means increase severity	Recruiting	Phase 3
4.	NCT04330586	A trial of ciclesonide in adults with mild-to-moderate COVID-19	68	Ciclesonide Metered Dose Inhaler [Alvesco]	Rate of SARS-CoV-2 eradication at day 14 from study enrollment [time frame: hospital day 14] Viral load	Rate of SARS-CoV-2 eradication at day 7 from study enrollment [time frame: hospital day 7] Viral load Time to SARS-CoV-2 eradication (days) [time frame: hospital day 1, 4, 7, 10, 14, 21] Viral load Viral load area-under-the-curve (AUC) reduction versus control [time frame: hospital day 1, 4, 7, 10, 14, 21] Viral load change Time to clinical improvement (days) [time frame: up to 28 days] Resolution of all systemic and respiratory symptoms for $\geq 2$ consecutive days Proportion of clinical failure [time frame: up to 28 days] High-flow oxygen therapy or mechanical ventilation requiring salvage therapy	Completed	Phase 2

**Table 6** (continued)

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
5.	NCT04377711	A study of the safety and efficacy of ciclesonide in the treatment of non-hospitalized COVID-19 patients	400	Ciclesonide and placebo	Time to alleviation of COVID-19-related symptoms by Day 30 [time frame: Day 30] Time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of more than 24 h (i.e., later than 3 AM/PM assessments) by day 30	Percentage of patients with hospital admission or death by day 30 [time frame: day 30] All-cause mortality by day 30 [time frame: day 30] COVID-19-related mortality by day 30 [time frame: day 30] Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30 [time frame: day 30] Percentage of patients with alleviation of COVID-19-related symptoms defined as symptom-free for a continuous period of more than 24 h (i.e., later than 3 AM/PM assessments) by day 7, by day 14, and by day 30 [time frame: by day 7, by day 14, and by day 30] Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of more than 24 h (i.e., later than 3 AM/PM assessments) by day 7, by day 14, and by day 30 Time to hospital admission or death [time frame: day 30] Change from baseline in oxygen saturation levels [time frame: day 30] Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30 [time frame: day 30]	Completed	Phase 3

Table 6 (continued)

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
6.	NCT04308317	Tetradrine tablets used in the treatment of COVID-19 (TT-NPC)	60	Tetradrine	Survival rate [time frame: 12 weeks] Death event	Body temperature [time frame: 2 weeks] Inflammatory indicator	Enrolling by invitation	Phase 4
7.	NCT04645407	Effects of fuzheng huayu tablets on COVID-19	66	Fuzheng Huayu tablet	The percentage of patients showing improvement in chest CT [time frame: week 2] Evaluation of the therapeutic effect of Fuzheng huayu tablet	Remission rate or progression rate of critical illness [time frame: week 2] Evaluation of pulmonary inflammation improvement clinical remission rate of respiratory symptoms [time frame: week 2] Evaluation of pulmonary inflammation improvement routine blood examination [time frame: week 2] Evaluation of pulmonary inflammation improvement C-reactive protein level [time frame: week 2] Evaluation of the therapeutic effect of Fuzheng huayu tablet procalcitonin level [Time frame: week 2] Evaluation of pulmonary inflammation improvement oxygen saturation [time frame: week 2] Evaluation of pulmonary inflammation improvement	Completed	Phase 4

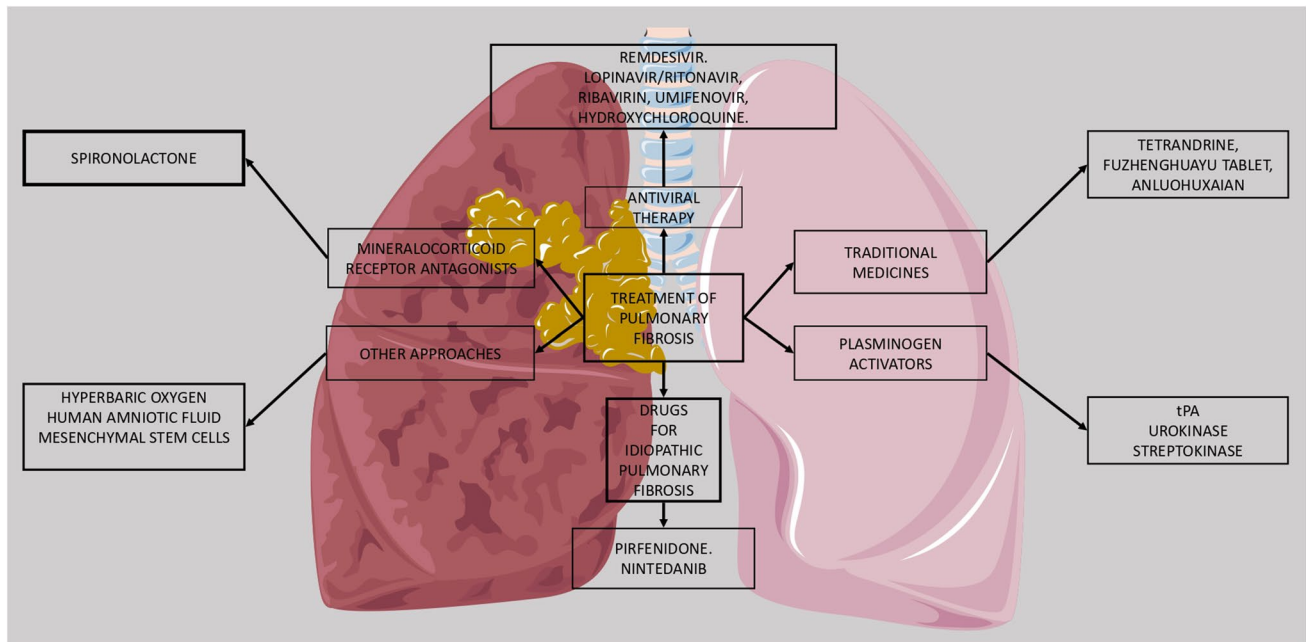


Table 6 (continued)

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
8.	NCT04279197	Treatment of pulmonary fibrosis due to COVID-19 with fuzheng huayu	160	Fuzheng Huayu Tablet, vitamin C and placebo	The improvement proportion of pulmonary fibrosis [time frame: week 24] Evaluation of pulmonary fibrosis Improvement. Pulmonary fibrosis judged by HRCT score. HRCT images are divided into four grades according to the score, and a reduction of one grade is an improvement	Blood oxygen saturation [time frame: week 24] Evaluation of lung function improvement Clinical symptom score [time frame: week 24] Discomfort symptoms include dyspnea, cough, exhausted, fatigue, insomnia, sweating, poor appetite, diarrhoea, etc., which are common manifestations of patients with COVID-19 Quality of Life-BREF (QOL-BREF) [time frame: week 24] This scale can reflect the quality of life of patients to some extent Patient Health Questionnaire-9(PHQ-9) [time frame: week 24] This scale can reflect the quality of life of patients to some extent Generalized anxiety disorder-7 (GAD-7) [time frame: week 24] This scale can reflect the quality of life of patients to some extent The 6-min walk distance [time frame: week 24] Evaluation of lung function improvement	Recruiting	Phase 2

Table 6 (continued)

S. no	Identifier	Study title	No. of subjects	Intervention/ treatment	Primary outcome measures	Secondary outcome measures	Status	Phase
9.	NCT04334265	Efficacy and safety of anluohuaxian in the treatment of rehabilitation patients with coronavirus disease 2019	750	Anluohuaxian	Changes in high-resolution computer tomography of the lung [time frame: 3 months] Changes in ground-glass shadows, interstitial or air nodules found on high-resolution computer tomography Change in 6-min walking distance [time frame: 3 months]	Changes in compound physiological index [time frame: 3 months] Changes in the scores of the St. George's Hospital Respiratory Questionnaire [time frame: 3 months] St. George's Hospital Respiratory Questionnaire range from 0 to 100. 0 stands for no impact on life and 100 stands for extreme impact on life Changes in modified British Medical Research Council Dyspnea Scale (mMRC) scores [time frame: 3 months] mMRC score range from 0 to 4. 0 stands for wheezing only when exercising hard and 4 stands for severe breathing difficulties Changes in vital capacity of the lung [time frame: 3 months] Adult male vital capacity is about 3500 ml and female is about 2500 ml	Recruiting	N.A



**Fig. 9** Illustration of various drugs for treating COVID-19-associated pulmonary fibrosis

## Lay summary

SARS-CoV-2-mediated manifestations have been reported in both pulmonary as well as extra-pulmonary tissues. Elderly groups of people are at higher risk because of the presence of comorbid conditions. It becomes very essential for the clinicians worldwide to understand the pathophysiological mechanisms and manifestations associated with organ systems. Various areas require attention for annotation of the mechanisms by which the coronavirus promulgates towards the extra-pulmonary tissues, viral properties which intensify the extra-pulmonary spread and effect of various pharmacological therapies. High binding affinity of the virus with the ACE2 receptors is the major mechanism for multi-systemic involvement. Mild-to-moderate cases can be resolved following precautionary measures, such as social distancing and hygiene. For severe cases, patients are admitted to ICU and are given drugs and treatment including chloroquine, hydroxychloroquine, corticosteroids, remdesivir, immunomodulatory agents, lopinavir/ritonavir, statins and prophylaxis with anticoagulants, mechanical ventilation and use of hyperbaric oxygen therapy. Many emerging therapeutic approaches, such as traditional drugs Fuzheng Huayu formula and anluohuaxian, ciclesonide, OATD-01, ivermectin and tetrandrine, have the potential in COVID-19 treatment. More large and well-designed trials are still required to evaluate the safety profile and efficacy of these emerging options. COVID-19 vaccines are available, majority of which neutralize antibodies against the spike protein and registration for the same has been started in various

countries. The anti-SARS-CoV-2 vaccination may not eradicate the disease completely but will surely decrease morbidity and mortality. But the major issue is the availability of the vaccine and its unbiased distribution worldwide. In the absence of a truly effective treatment to prevent and treat COVID-19, strict adherence to social distancing and hygiene precautions must be followed for an enduring future.

**Author contributions** AS and OB contributed to the study concept and design. Material preparation, data collection, and draft was written by AS. Review and final editing was performed by OB. All authors read and approved the final manuscript.

**Funding** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Data availability statement** On request, the data will be provided to the journal.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose. The authors declare no conflict of interest/competing interests.

**Ethical approval** This work does not involve animals or human subjects.

**Consent for publication** All the authors provided their consent for the publication of this study.

## References

- Aggarwal M, Dass J, Mahapatra M (2020) Hemostatic abnormalities in COVID-19: an update. *Indian J Hematol Blood Transfus*. <https://doi.org/10.1007/s12288-020-01328-2>
- Alipoor SD, Mortaz E, Jamaati H, Tabarsi P, Bayram H, Varahram M, Adcock IM (2021) COVID-19: molecular and cellular response. *Front Cell Infect Microbiol*. <https://doi.org/10.3389/fcimb.2021.563085>
- Almaghaslah D, Kandasamy G, Almanasef M, Vasudevan R, Chandramohan S (2020) Review on the coronavirus disease (COVID-19) pandemic: its outbreak and current status. *Int J Clin Pract* 74(11):e13637. <https://doi.org/10.1111/ijcp.13637>
- Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE et al (2020) COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood Am J Hematol* 136(4):489–500. <https://doi.org/10.1182/blood.202006520>
- Antoniou KM, Raghu G, Tzilas V, Bouros D (2020) Management of patients with interstitial lung disease in the midst of the COVID-19 pandemic. *Respiration*. <https://doi.org/10.1159/000509523>
- Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA (2020) COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. *Basic Transl Sci* 5(5):518–536. <https://doi.org/10.1016/j.jacbts.2020.04.002>
- Azer SA (2020) COVID-19: Pathophysiology, diagnosis, complications and Investigational therapeutics. *New Microbes New Infect*. <https://doi.org/10.1016/j.nmni.2020.100738>
- Baron SA, Devaux C, Colson P, Raoult D, Rolain JM (2020) Teicoplanin: an alternative drug for the treatment of COVID-19? *Int J Antimicrob Agents*. <https://doi.org/10.1016/j.ijantimicag.2020.105944>
- Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, Stead CM, Rycus P, Fraser JF, Belohlavek J, Salazar L (2020) Initial ELSO guidance document: ECMO for COVID-19 patients with severe cardiopulmonary failure. *Asaio J* 66(5):472. <https://doi.org/10.1097/MAT.0000000000001173>
- Bhargava P, Panda P, Ostwal V, Ramaswamy A (2020) Repurposing valproate to prevent acute respiratory distress syndrome/acute lung injury in COVID-19: a review of immunomodulatory action. *Cancer Res Stat Treat* 3(5):65. [https://doi.org/10.4103/CRST.CRST\\_156\\_20](https://doi.org/10.4103/CRST.CRST_156_20)
- Bompard F, Monnier H, Saab I, Tordjman M, Abdoul H, Fournier L, Sanchez O, Lorut C, Chassagnon G, Revel MP (2020) Pulmonary embolism in patients with Covid-19 pneumonia. *Eur Respir J* 1:2–58. <https://doi.org/10.1183/13993003.01365-2020>
- Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N (2020) Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington state: a case series. *Lancet* 396(10247):320–332. [https://doi.org/10.1016/S0140-6736\(20\)31305-2](https://doi.org/10.1016/S0140-6736(20)31305-2)
- Broadbent L (2021) Coronaviruses—a brief history. *The conversation* 2021. <https://theconversation.com/coronaviruses-a-brief-history-135506>. Accessed 3 Aug 2021
- Bryce C, Grimes Z, Pujada, E et al (2020) Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. *The Mount Sinai COVID-19 autopsy experience*. *MedRxiv*. <https://doi.org/10.1101/2020.05.18.20099960>
- Bulut C, Kato Y (2020) Epidemiology of COVID-19. *Turk J Med Sci* 50(SI-1):563–570
- Calligaro GL, Lalla U, Audley G et al (2020) The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study. *EClinicalMedicine* 28:100570. <https://doi.org/10.1016/j.eclinm.2020.100570>
- Caramaschi S, Kapp ME, Miller SE et al (2021) Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. *Mod Pathol*. <https://doi.org/10.1038/s41379-021-00814-w>
- Channappanavar R, Perlman S (2017) Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 39(5):529–539. <https://doi.org/10.1007/s00281-017-0629-x>
- Chaudhary S, Natt B, Bime C et al (2020) Antifibrotics in COVID-19 lung disease: let us stay focused. *Front Med* 7:539. <https://doi.org/10.3389/fmed.2020.00539>
- Chen X, Wu Y, Chen C et al (2021) Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. *Acta Pharm Sin B* 11(1):222–236. <https://doi.org/10.1016/j.apsb.2020.10.002>
- Choi H, Shin EC (2021) Roles of type I and III interferons in COVID-19. *Yonsei Med J* 62(5):381. <https://doi.org/10.3349/ymj.2021.62.5.381>
- Deshmukh V, Motwani R, Kumar A et al (2021) Histopathological observations in COVID-19: a systematic review. *J Clin Pathol* 74(2):76–83. <https://doi.org/10.1136/jclinpath-2020-206995>
- Diao B, Wang C, Tan Y et al (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol* 11:827. <https://doi.org/10.3389/fimmu.2020.00827>
- Docherty AB, Harrison EM, Green CA et al (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. <https://doi.org/10.1136/bmj.m1985>
- Dou Q, Wei X, Zhou K, Jia P (2020) Cardiovascular manifestations and mechanisms in patients with COVID-19. *Trends Endocrinol Metab* 31(12):893–904. <https://doi.org/10.1016/j.tem.2020.10.001>
- Driggin E, Madhavan MV, Bikdeli B et al (2020) Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol* 75(18):2352–2371. <https://doi.org/10.1016/j.jacc.2020.03.031>
- Drosten C, Günther S, Preiser W et al (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 348(20):1967–1976. <https://doi.org/10.1056/NEJMoA030747>
- Gallelli L, Zhang L, Wang T, Fu F (2020) severe acute lung injury related to COVID-19 infection: a review and the possible role for escin. *J Clin Pharmacol* 60(7):815–825. <https://doi.org/10.1002/jcph.1644>
- Ganesh B, Rajakumar T, Malathi M et al (2021) Epidemiology and pathobiology of SARS-CoV-2 (COVID-19) in comparison with SARS, MERS: an updated overview of current knowledge and future perspectives. *Clin Epidemiol Glob Health* 10:100694. <https://doi.org/10.1016/j.cegh.2020.100694>
- Garg S, Kim L, Whitaker M et al (2020) Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. *Morb Mortal Wkly Rep* 69(15):458. <https://doi.org/10.15585/mmwr.mm6915e3>
- Gattinoni L, Taccone P, Carlesso E, Marini JJ (2013) Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. *Am J Respir Crit Care Med* 188(11):1286–1293. <https://doi.org/10.1164/rccm.201308-1532CI>
- Gattinoni L, Chiumello D, Rossi S (2020) COVID-19 pneumonia: ARDS or not? *Crit Care* 24:154. <https://doi.org/10.1186/s13054-020-02880-z>

- Gautret P, Lagier JC, Parola P et al (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 56(1):105949. <https://doi.org/10.1016/j.ijantimicag.2020.105949>
- Gavriatopoulou M, Korompoki E, Fotiou D et al (2020) Organ-specific manifestations of COVID-19 infection. *Int J Clin Exp Med* 20(4):493–506. <https://doi.org/10.1007/s10238-020-00648-x>
- George PM, Wells AU, Jenkins RG (2020) Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir* 8(8):807–815. [https://doi.org/10.1016/S2213-2600\(20\)30225-3](https://doi.org/10.1016/S2213-2600(20)30225-3)
- Grasselli G, Zangrillo A, Zanella A et al (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 323(16):1574–1581. <https://doi.org/10.1001/jama.2020.5394>
- Guan WJ, Ni ZY, Hu Y et al (2019) China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease. *N Engl J Med* 382:1708–1720. <https://doi.org/10.1056/NEJMoa2002032>
- Guérin C, Reignier J, Richard JC et al (2013) Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 368(23):2159–2168. <https://doi.org/10.1056/NEJMoa1214103>
- Gupta A, Madhavan MV, Sehgal K et al (2020) Extrapulmonary manifestations of COVID-19. *Nat Med* 26(7):1017–1032. <https://doi.org/10.1038/s41591-020-0968-3>
- Harapan H, Itoh N, Yufika A et al (2020) Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health* 13(5):667–673. <https://doi.org/10.1016/j.jiph.2020.03.019>
- Heister PM, Poston RN (2020) Pharmacological hypothesis: TPC2 antagonist tetrandrine as a potential therapeutic agent for COVID-19. *Pharmacol Res Perspect* 8(5):e00653. <https://doi.org/10.1002/prp2.653>
- Helmich RC, Bloem BR (2020) The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis* 10(2):351. <https://doi.org/10.3233/JPD-202038>
- Henry R (2020) Etymologia: coronavirus. *Emerg Infect Dis* 26(5):1027. <https://doi.org/10.3201/eid2605.et2605>
- Huang C, Wang Y, Li X et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223):497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Iwabuchi K, Yoshie K, Kurakami Y et al (2020) Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: report of three cases. *J Infect Chemother* 26(6):625–632. <https://doi.org/10.1016/j.jiac.2020.04.007>
- Joly BS, Siguret V, Veyradier A (2020) Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. *Intensive Care Med* 46(8):1603–1606. <https://doi.org/10.1007/s00134-020-06088-1>
- Kahn JS, McIntosh K (2005) History and recent advances in coronavirus discovery. *Pediatr Infect Dis J* 24(11):S223–S227. <https://doi.org/10.1097/01.inf.0000188166.17324.60>
- Kang Y, Chen T, Mui D et al (2020) Cardiovascular manifestations and treatment considerations in covid-19. *Heart* 106(15):1132–1141. <https://doi.org/10.1136/heartjnl-2020-317056>
- Kapikian AZ (1975) The coronaviruses. *Dev Biol Stand* 28:42–64
- Kasinathan G, Sathar J (2020) Haematological manifestations, mechanisms of thrombosis and anti-coagulation in COVID-19 disease: a review. *Ann Med Surg* 56:173–177. <https://doi.org/10.1016/j.amsu.2020.06.035>
- Khiali S, Khani E, Entezari-Maleki T (2020) A comprehensive review of tocilizumab in COVID-19 acute respiratory distress syndrome. *J Clin Pharmacol* 60(9):1131–1146. <https://doi.org/10.1002/jcph.1693>
- Kim H, Jhoo JH, Jang JW (2017) The effect of telemedicine on cognitive decline in patients with dementia. *J Telemed Telecare* 23(1):149–154. <https://doi.org/10.1177/1357633X15615049>
- Körner RW, Majjouti M, Alcazar M, Mahabir E (2020) Of mice and men: the coronavirus MHV and mouse models as a translational approach to understand SARS-CoV-2. *Viruses* 12(8):880. <https://doi.org/10.3390/v12080880>
- Kyriakidis NC, López-Cortés A, González EV et al (2021) SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines* 6(1):1–17. <https://doi.org/10.1038/s41541-021-00292-w>
- Larsen JR, Martin MR, Martin JD et al (2020) Modeling the onset of symptoms of COVID-19. *Front Public Health* 8:473. <https://doi.org/10.3389/fpubh.2020.00473>
- Lechien JR, Chiesa-Estomba CM, De Siaty DR et al (2020) Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 277(8):2251–2261. <https://doi.org/10.1007/s00405-020-05965-1>
- Lechowitz K, Drożdżal S, Machaj F et al (2020) COVID-19: the potential treatment of pulmonary fibrosis associated with SARS-CoV-2 infection. *J Clin Med* 9(6):1917. <https://doi.org/10.3390/jcm9061917>
- Leung JM, Niikura M, Yang CWT, Sin DD (2020) COVID-19 and COPD. *Eur Respir J* 56(2):2002108. <https://doi.org/10.1183/13993003.02108-2020>
- Li Y, Xiao SY (2020) Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 92(9):1491–1494. <https://doi.org/10.1002/jmv.25973>
- Liu A, Li Y (2020) Antibody responses against SARS-CoV-2 in COVID-19 patients. *J Med Virol* 93(1):144–148. <https://doi.org/10.1002/jmv.26241>
- Ma C, Cong Y, Zhang H (2020) COVID-19 and the digestive system. *Am J Gastroenterol* 115(7):1003–1006. <https://doi.org/10.14309/ajg.0000000000000691>
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O (2020) Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 5(7):831–840. <https://doi.org/10.1001/jamacardio.2020.1286>
- Mahajan RK, Paul G, Mahajan R et al (2020) Systemic manifestations of COVID-19. *J Anaesthesiol Clin Pharmacol* 36(4):435. [https://doi.org/10.4103/joacp.JOACP\\_359\\_20](https://doi.org/10.4103/joacp.JOACP_359_20)
- Maiolo G, Collino F, Vasques F et al (2018) Reclassifying acute respiratory distress syndrome. *Am J Respir Crit Care Med* 197(12):1586–1595. <https://doi.org/10.1164/rccm.201709-1804OC>
- Malek AE, Granwehr B, Kontoyiannis DP (2020) Doxycycline as a potential partner of COVID-19 therapies. *Idcases* 21:e00864. <https://doi.org/10.1016/j.idcr.2020.e00864>
- Mao R, Qiu Y, He JS et al (2020) Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 5(7):667–678. [https://doi.org/10.1016/S2468-1253\(20\)30126-6](https://doi.org/10.1016/S2468-1253(20)30126-6)
- Marietta M, Coluccio V, Luppi M (2020) COVID-19, coagulopathy and venous thromboembolism: more questions than answers. *Intern Emerg Med* 15(8):1375–1387. <https://doi.org/10.1007/s11739-020-02432-x>
- McNab F, Mayer-Barber K, Sher A et al (2015) Type I interferons in infectious disease. *Nat Rev Immunol* 15(2):87–103. <https://doi.org/10.1038/nri3787>
- Monto AS, Cowling BJ, Peiris J (2014) Coronaviruses. *Viral Infect Hum Epidemiol Control*. [https://doi.org/10.1007/978-1-4899-7448-8\\_10](https://doi.org/10.1007/978-1-4899-7448-8_10)

- Nasibova EM, Pashayev CN (2020) The use of non-invasive ventilation (NIV) in the treatment of patients with COVID-19. *J Anesth and Surgery* 3(2):1–6. <https://doi.org/10.36648/2471-8505.6.2.5>
- Navas-Blanco JR, Dudaryk R (2020) Management of respiratory distress syndrome due to COVID-19 infection. *BMC Anesthesiol* 20(1):1–6. <https://doi.org/10.1186/s12871-020-01095-7>
- Nishiga M, Wang DW, Han Y et al (2020) COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 17(9):543–558. <https://doi.org/10.1038/s41569-020-0413-9>
- Nojomi M, Yassin Z, Keyvani H et al (2020) Effect of arbidol (umifenovir) on COVID-19: a randomized controlled trial. *BMC Infect Dis* 20(1):1–10. <https://doi.org/10.1186/s12879-020-05698-w>
- Ojo AS, Balogun SA, Williams OT, Ojo OS (2020) Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies. *Pulm Med* 2020:6175964. <https://doi.org/10.1155/2020/6175964>
- OncoArendi Therapeutics (2020) <https://oncoarendi.com/en/drug-candidate-oatd-01-may-find-use-in-treatment-of-pulmonary-fibrosis-in-patients-who-have-survived-a-new-coronavirus-infection-covid-19/>. Accessed 4 May 2021
- Orsi FA, De Paula EV, de Oliveira SF et al (2020) Guidance on diagnosis, prevention and treatment of thromboembolic complications in COVID-19: a position paper of the Brazilian Society of Thrombosis and Hemostasis and the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy. *Hematol Transfus Cell Ther* 42(4):300–308. <https://doi.org/10.1016/j.htct.2020.06.001>
- Osakwe N, Hart D (2020) Clinical presentation of acute pulmonary embolism in patients with coronavirus disease 2019 (COVID-19). *Case Rep Hematol* 2020:8855957. <https://doi.org/10.1155/2020/8855957>
- Papa SM, Brundin P, Fung VS et al (2020) Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. *Mov Disord Clin Pract* 7(4):357. <https://doi.org/10.1002/mds.28067>
- Pereira A (2020) Long-term neurological threats of COVID-19: a call to update the thinking about the outcomes of the coronavirus pandemic. *Front Neurol* 11:308. <https://doi.org/10.3389/fneur.2020.00308>
- Ray I, Sánchez DF, Robert CA, Robert MP (2020) Convalescent plasma therapy: an effective therapeutic option to treat COVID-19? a narrative review. *Int J Clin Transfus Med* 8:7. <https://doi.org/10.2147/IJCTM.S269691>
- Richardson S, Hirsch JS, Narasimhan M et al (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 323(20):2052–2059. <https://doi.org/10.1001/jama.2020.6775>
- Rossi R, Talarico M, Coppi F, Boriani G (2020) Protective role of statins in COVID 19 patients: importance of pharmacokinetic characteristics rather than intensity of action. *Intern Emerg Med* 15(8):1573–1576. <https://doi.org/10.1007/s11739-020-02504-y>
- Ruckmani A, Ilamathi KR, Kumar RA, Kumar PU (2021) COVID-19: a review of clinical trials and repurposed drugs. *Int J Nutr Pharmacol Neurol Dis* 11(1):27. [https://doi.org/10.4103/ijnpnd.ijnpnd\\_90\\_20](https://doi.org/10.4103/ijnpnd.ijnpnd_90_20)
- Sakr Y, Giovini M, Leone M et al (2020) Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. *Ann Intensive Care* 10(1):1–13. <https://doi.org/10.1186/s13613-020-00741-0>
- Saleh A, Sultan A, Elashry MA et al (2020) Association of TNF- $\alpha$  G-308 a promoter polymorphism with the course and outcome of COVID-19 patients. *Immunol Invest* 25:1–2. <https://doi.org/10.1080/08820139.2020.1851709>
- Sathler PC (2020) Hemostatic abnormalities in COVID-19: A guided review. *An Acad Bras Cienc* 92(4):e20200834. <https://doi.org/10.1590/0001-3765202020200834>
- Shafi AM, Shaikh SA, Shirke MM et al (2020) Cardiac manifestations in COVID-19 patients—a systematic review. *J Card Surg* 35(8):1988–2008. <https://doi.org/10.1111/jocs.14808>
- Sin DD (2020) COVID-19 in COPD: a growing concern. *EClinical-Medicine* 26:100546. <https://doi.org/10.1016/j.eclinm.2020.100546>
- Singh N, Suthar B, Mehta A et al (2020) Corona virus: an immunological perspective review. *Int J Immunol Immunother* 7:050. <https://doi.org/10.23937/2378-3672/1410050>
- Singhal T (2020) A review of coronavirus disease-2019 (COVID-19). *Indian J Pediatr* 87(4):281–286. <https://doi.org/10.1007/s12098-020-03263-6>
- Spinato G, Fabbris C, Polese J (2020) Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 323(20):2089–2090. <https://doi.org/10.1001/jama.2020.6771>
- Stoyanov GS, Petkova L, Dzhakov DL et al (2020) Gross and Histopathology of COVID-19 with First Histology Report of Olfactory Bulb Changes. *Cureus* 12(12):e11912. <https://doi.org/10.7759/cureus.11912>
- Su YB, Kuo MJ, Lin TY et al (2020) Cardiovascular manifestation and treatment in COVID-19. *J Chin Med Assoc* 83(8):704. <https://doi.org/10.1097/JCMA.0000000000000352>
- Takla M, Jeevaratnam K (2020) Chloroquine, hydroxychloroquine, and COVID-19: systematic review and narrative synthesis of efficacy and safety. *Saudi Pharm J* 28(12):1760–1776. <https://doi.org/10.1016/j.jsps.2020.11.003>
- Temgoua MN, Endomba FT, Nkeck JR et al (2020) Coronavirus disease 2019 (COVID-19) as a multi-systemic disease and its impact in low-and middle-income countries (LMICs). *SN Compr Clin Med* 20:1–11. <https://doi.org/10.1007/s42399-020-00417-7>
- Tong ZD, Tang A, Li KF et al (2020) Potential presymptomatic transmission of SARS-CoV-2, Zhejiang province, China, 2020. *Emerg Infect Dis* 26(5):1052. <https://doi.org/10.3201/eid2605.200198>
- Van Der Hoek L, Pyrc K, Jebbink MF et al (2004) Identification of a new human coronavirus. *Nat Med* 10(4):368–373. <https://doi.org/10.1038/nm1024>
- Varga Z, Flammer AJ, Steiger P et al (2020) Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395(10234):1417–1418. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5)
- Vasarmidi E, Tsitoura E, Spandidos DA et al (2020) Pulmonary fibrosis in the aftermath of the COVID-19 era. *Exp Ther Med* 20(3):2557–2560. <https://doi.org/10.3892/etm.2020.8980>
- Vasquez-Bonilla WO, Orozco R, Argueta V et al (2020) A review of the main histopathological findings in the coronavirus disease 2019 (COVID-19). *Hum Pathol* 105:74–83. <https://doi.org/10.1016/j.humpath.2020.07.023>
- Vatansever HS, Becer E (2020) Relationship between IL-6 and COVID-19: to be considered during treatment. *Future Virol* 15(12):817–822. <https://doi.org/10.2217/fvl-2020-0168>
- Velikova TV, Kotsev SV, Georgiev DS, Batselova HM (2020) Immunological aspects of COVID-19: What do we know? *World J Biol Chem* 11(2):14. <https://doi.org/10.4331/wjbc.v11.i2.14>
- Vitiello A, Pelliccia C, Ferrara F (2020) COVID-19 patients with pulmonary fibrotic tissue: clinical pharmacological rationale of anti-fibrotic therapy. *SN Compr Clin Med* 2(10):1709–1712. <https://doi.org/10.1007/s42399-020-00487-7>
- Wang D, Hu B, Hu C et al (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 323(11):1061–1069. <https://doi.org/10.1001/jama.2020.1585>

- Wiersinga WJ, Rhodes A, Cheng AC et al (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 324(8):782–793. <https://doi.org/10.1001/jama.2020.12839>
- Williams S (2021) A brief history of human coronaviruses. *The Scientist Magazine*. <https://www.the-scientist.com/news-opinion/a-brief-history-of-human-coronaviruses-67600>. Accessed 3 Aug 2021
- Woo PC, Lau SK, Chu CM et al (2005) Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol* 79(2):884–895. <https://doi.org/10.1128/JVI.79.2.884-895.2005>
- World Health Organization (2021a) <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19--21-december-2021a>. Accessed 22 Dec 2021a
- World Health Organization Institutional Repository for Information Sharing (2021) Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance. <https://apps.who.int/iris/handle/10665/330893>. Accessed 4 May 2021
- World Health Organization Newsroom (2021b) <https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials> Accessed 22 June 2021b
- Yang L, Liu S, Liu J et al (2020) COVID-19: immunopathogenesis and immunotherapeutics. *Signal Transduct Target Ther* 5(1):1–8. <https://doi.org/10.1038/s41392-020-00243-2>
- Yates PA, Newman SA, Oshry LJ et al (2020) Doxycycline treatment of high-risk COVID-19-positive patients with comorbid pulmonary disease. *Ther Adv Respir Dis*. <https://doi.org/10.1177/1753466620951053>
- Yavas G, Yavas C, Celik E et al (2019) The impact of spironolactone on the lung injury induced by concomitant trastuzumab and thoracic radiotherapy. *Int J Radiat Res* 17(1):87–95. <https://doi.org/10.18869/acadpub.ijrr.17.1.87>
- Yoshikawa T, Hill TE, Yoshikawa N et al (2010) Dynamic innate immune responses of human bronchial epithelial cells to severe acute respiratory syndrome-associated coronavirus infection. *PLoS ONE* 5(1):e8729. <https://doi.org/10.1371/journal.pone.0008729>
- Zabolotsky Dmitrii V, Koryachkin Viktor A (2020) Covid-19: effect on hemostasis. *Asian Pac J Cancer Prev* 3(S1):9–11. <https://doi.org/10.31557/APJEC.2020.3.S1.9-11>
- Zhang AR, Shi WQ, Liu K et al (2021) Epidemiology and evolution of Middle East respiratory syndrome coronavirus, 2012–2020. *Infect Dis Poverty* 10(1):1–3. <https://doi.org/10.1186/s40249-021-00853-0>
- Zhou P, Yang XL, Wang XG et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579(7798):270–273. <https://doi.org/10.1038/s41586-020-2012-7>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.