Journal of Biosciences and Medicines, 2022, 10, 152-174
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

COVID-19 Pulmonary and Extrapulmonary Complications

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How to cite this paper: Li, L.L., Zhang, R.T., Li, F., Xiao, C.F., Zhong, B.W., Zhai, S.Y., Liu, C.Y., Hu, Q.Y., Lyu, J., Yang, M., Yang, C.M., Lyu, L., Li, Y. and Yu, D.M. (2022) COVID-19 Pulmonary and Extrapulmonary Complications. *Journal of Biosciences and Medicines*, **10**, 152-174.
https://doi.org/10.4236/jbm.2022.103016

Received: January 26, 2022
Accepted: March 11, 2022
Published: March 14, 2022

Abstract

To date, the coronavirus disease 2019 (COVID-19) outbreak has become a global pandemic and public health disaster. In addition to acute respiratory manifestations, patients with COVID-19 exhibit other non-respiratory manifestations, particularly in those with severe underlying disease. Few specific therapeutics are effective for COVID-19, and supportive care is the primary remedy. Here, we comprehensively surveyed the most recent reports on extrapulmonary complications of COVID-19 and their corresponding treatments, as well as the comparison of different clinical symptoms and complications of COVID-19, severe acute respiratory syndrome (SARS), and the Middle East respiratory syndrome (MERS) patients. We wish to provide a molecular and cellular understanding of the complications of COVID-19 and provide guidance for future diagnostics, therapeutics, and prognostics of COVID-19.

Keywords

COVID-19, SARS-CoV-2, Complications, Manifestations

1. Introduction

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has now become a global pandemic with a widespread impact on the health and economic sectors worldwide. SARS-CoV-2 belongs to the β-coronavirus genus and is structurally similar to SARS coronavirus 1 (SARS-CoV-1), which caused the SARS outbreak in 2003. The host entry receptor

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for both SARS-CoV-1 and SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) [1]. The viral Spike (S) protein binds to ACE2, leading to entry of the viral replication complex into the cytoplasm of the host cell [2]. All ACE2-expressing cells are susceptible to SARS-CoV-2 infection. In addition to the lungs, ACE2 receptors are highly expressed in the kidneys, heart, liver, gastrointestinal (GI) tract, neural cells and vascular epithelial cells. SARS-CoV-2 RNA was detected in the lungs, trachea, subcarinal lymph nodes, kidneys, large intestine and spleen (Figure 1). Therefore, besides the common respiratory symptoms such as severe shortness of breath, labored and abnormally rapid breathing, low blood pressure, and tiredness, patients with COVID-19 have symptoms in other organs and systems. Patients infected with COVID-19 have a lower mortality rate than SARS and MERS, and pulmonary and extrapulmonary complications can induce subsequent deterioration, possibly leading to a "cytokine storm" and causing multiple organ failure. People with underlying medical problems are more likely to develop serious complications. This review summarizes and distills current knowledge and understanding about the mechanism of pulmonary and extrapulmonary complications and their treatments as well as the differences among COVID-19, SARS and MERS.

2. Complications in the Neurological System

SARS-CoV-2 invades host cells, resulting in an inflammatory response and the pathophysiology of COVID-19. The various pathophysiological mechanisms

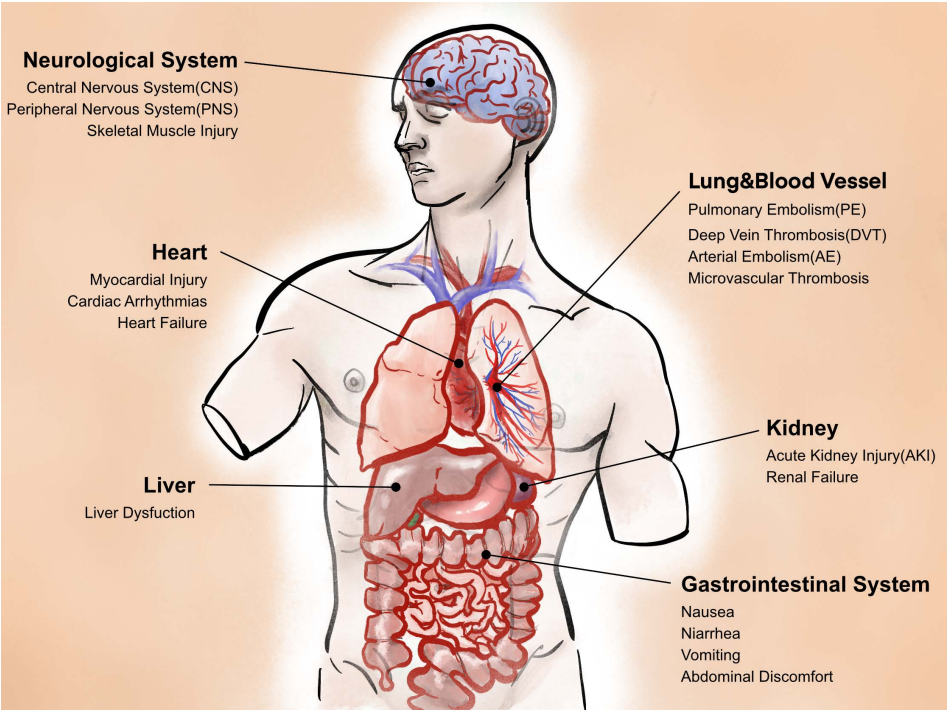

Figure 1. Classification of pulmonary and extrapulmonary complication. COVID-19 complications are related to multiple organs such neural system, kidney, liver, heart, GI system, blood vessel and nervous system.

associated with the neurological complications of SARS-CoV-2 are based on the previous epidemic coronavirus. SARS-CoV-2 is neurotropic and neuroinvasive. The virus takes a direct trans-synaptic route via the olfactory bulb upon inhalation [3]. Subsequently, the virus causes reactive astrogliosis and activation of microglia (MG), which leads to a massive neuroinflammatory cascade. Systemic inflammation associated with SARS-CoV-2 infection, especially platelets release interleukin-1β (IL-1β) in microparticles, compromises the permeability of the blood brain barrier (BBB) in the central nervous system (CNS), thereby severely disrupting brain homeostasis and leading to neuronal cell death. Chemosensory neural cells associated with respiratory and cardiovascular regulation might be affected by infection of the brainstem. The autonomic nervous system requires that the afferent and efferent limbs be in optimal hemostasis, the perturbation of which via COVID-19 damages the pulmonary ventilatory function, exacerbates respiratory failure, and eventually leads to profound hypoxia. Hypoxia, as well as existent neuro-inflammation, damages the hippocampal and cortical areas, inducing neuropsychiatric effects.

The neurogenic pathway for SARS-CoV-2 consists of the olfactory nerve (CNI), the trigeminal nerve (CNV), and the brainstem nuclei. Perivascular and interstitial encephalitis with neuronal cell loss and axon degeneration occurs in the dorsal motor nucleus of the vagus nerve, CNV, nucleus tractus solitarii, dorsal raphe nuclei, and medial longitudinal fasciculus [4]. The observed neuritis is most likely associated with axonal damage because olfactory fila lack myelin. Sustentacular cells maintain the integrity of olfactory sensory neurons, which express ACE2 and transmembrane protease, serine type 2 (TMPRSS2). Olfactory epithelial cells express neuropilin-1 (NRP1), which provides a direct route to the brain and binds spike (S) protein of SARS-CoV-2. TMPRSS2 participates in the priming of the S proteins on the cell surface, enabling entry of the viral genome [5]. The stimulation of nicotinic acetylcholine receptor by nicotine increases ACE2 expression in neural cells and alveolar epithelial cells, which may also increase mucus-secreting goblet cells and put smokers at higher risk of neurological complications [6].

Once the virus enters the CNS through the BBB, clearance is challenging because the nervous system lacks the major histocompatibility antigens and the immune response is restricted to cytotoxic T lymphocytes. The mechanism of simultaneous immune and hypoxic injury is responsible for neuropathology. Eventually, the patient develops either acute encephalitis, infectious toxic encephalopathy, or acute cerebrovascular attacks (CVAs).

Neurological symptoms due to SARS-CoV-2 infection are demonstrated by CNS, peripheral nervous system (PNS), and skeletal muscle injury [7]. A cohort study [8] with 214 hospitalized COVID-19 patients showed that 78 patients (36.4%) had nervous system manifestations: CNS (53, 24.8%), PNS (19, 8.9%) and skeletal muscle injury (23, 10.7%). The most common CNS complications are dizziness (6.7% - 16.8%) and headache (8% - 27.6%). Other CNS symptoms include altered mental status (AMS), acute encephalitis, impaired consciousness,

infectious toxic encephalopathy, acute cerebrovascular disease (CVA), ataxia, seizures, and epilepsy [9]. SARS-CoV-2 appears in the cerebrospinal fluid of patients with COVID-19. Acute encephalitis is an inflammatory lesion in the brain parenchyma due to systemic symptoms of toxemia, metabolic disorders, cerebral edema and hypoxia, which may result in delirium and coma. Severe patients show CNS complications such as disorientation, loss of consciousness, coma and paralysis in the early stage of infection, with the exception of AMS and CVA [10], which also show lower lymphocyte counts, lower platelets count, and higher blood urea nitrogen in their laboratory test than those without CNS symptoms. The virus-mediated cytokine storm and coagulation abnormalities, as evidenced by abnormal d-dimer and platelets, increase the likelihood of acute CVA occurrence after SARS-CoV-2 infection [11]. Both ischemic and hemorrhagic CVA exist, with the former being more common. Clinical or subclinical acute and epileptic seizures occurred in severely ill patients [12].

PNS symptoms include dysgeusia, dysosmia, visual disturbances, neuralgia, anosmia, and ageusia (**Table 1**). A report [13] showed that the PNS of dysgeusia (5.6%), dysosmia (5.1%), visual disturbances (1.4%), and neuralgia (2.3%) with biochemical assays were indistinguishable between patients with or without PNS symptoms. A cross-sectional study [14] found that 33.9% of patients had taste or olfactory disorder, and 18.6% of patients had both anosmia and ageusia. Females showed a higher percentage of taste or smell loss (52.6% vs 25%) [15]. Patients

Table 1. Observational case series, retrospective studies and systemic reviews related to neurologic complications.

Reference	Sample Size	CNS	PNS	Skeletal Muscle Injury
Mao L *et al.* [18]	214	Total: 24.8% Dizziness: 16.8% Headache: 13.1%	Total: 8.9% Dysgeusia: 5.6% Dysosmia: 5.1% Visual disturbances: 1.4% Neuralgia: 2.3%	Total: 10.7%
Li Y *et al.* [19]	219	Acute ischaemic stroke: 4.6% Intracerebral haemorrhage: 0.5%	NA	NA
Huang C *et al.* [20]	42	Headache: 8%	Myalgia or Fatigue: 44%	NA
Chen N *et al.* [21]	99	Headache: 8%	Confusion: 9%	Muscle ache: 11%
Lu L *et al.* [22]	304	Seizures: 39% Hypoxia: 25% Encephalopathy: 2.6% Hypokalemia: 13% Hyponatremia: 11% Hypocalcemia: 7%	NA	NA
Giacomelli A *et al.* [14]	59	NA	NA	Anosmia or Ageusia: 33.9% Anosmia and Ageusia: 18.6%
Guan W *et al.* [23]	1099	NA	Nausea or Vomiting: 5% Diarrhea: 3.8%	NA

with anosmia are more likely to have dysgeusia but without symptoms of fever/cough/dyspnea [16].

Musculoskeletal symptoms vary from paresis to atonia. Patients with muscle injury have higher levels of creatine kinase regardless of its severity. They also have higher neutrophil counts, lower lymphocyte counts, higher levels of C-reactive protein and higher D-dimer levels, which indicates an increased inflammatory response and blood coagulation. In addition, patients with muscle injury also suffer from multi-organ damage, including liver (elevated levels of lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels) and kidney (elevated blood urea nitrogen and creatinine levels) abnormalities [17].

3. Cardiac Complications

SARS-CoV-1, MERS-CoV, and influenza viruses all cause cardiovascular complications, including myocardial injury, cardiac arrhythmias and heart failure and even sudden cardiac death (SCD) (**Table 2**). SARS-CoV-2 has a similar structure to SARS-CoV-1 and similar pathogenicity to MERS-CoV [24]. Patients with underlying cardiovascular diseases (CVDs) may experience higher mortality with a relatively unfavorable prognosis. Thus, cardiovascular protection is critical for COVID-19 treatment [25].

The exact mechanism by which COVID-19 induces heart diseases remains unknown. ACE2 is highly expressed in the heart, which is part of rennin-aldosterone-angiotensin system (RAAS) and involved in the development of diabetes, hypertension and heart failure. SARS-CoV-2 infection induces cytotoxic and proapoptotic effects associated with abolished cardiomyocyte beating in an ACE2 and cathepsins-dependent manner [26]. SARS-CoV-2 infection could result in the downregulation of ACE2, thereby leading to cardiac dysfunction and progression of atherosclerosis, as well as exacerbated lung damage [27]. Cytokine storms can play an important role in heart damage and increase vascular wall

Table 2. Observational case series, retrospective studies and systemic reviews related to cardiac disease.

Reference	Sample Size	Myocardial injury	Arrhythmias	Heart failure	Virus
Huang C *et al.* [29]	41	12.2%	n/a	n/a	SARS-CoV-2
Chen N *et al.* [53]	99	n/a	n/a	11%	SARS-CoV-2
Wang D *et al.*	138	n/a	16.7%	n/a	SARS-CoV-2
Shi S *et al.* [30]	460	19.7%	n/a	4.1%	SARS-CoV-2
Si D *et al.* [17]	1159	14.7%	3.8%	n/a	SARS-CoV-2
Du *et al.* [33]	85	44.7%	60%	n/a	SARS-CoV-2
Pan SF *et al.* [54]	15	n/a	33.3%	n/a	SARS-CoV
Saad M *et al.* [55]	70	n/a	15.7%	n/a	MERS-Cov
Chen T *et al.* [39]	113	63.7%	n/a	36.3%	SARS-CoV-2

permeability and myocardial edema. The functions of vascular endothelial cells include maintaining vascular integrity and barrier function, as well as preventing inflammation by limiting their interactions with immune cells and platelets. Endothelial dysfunction is emerging as an important pathological feature of COVID-19. Endothelial dysfunction, leading to arteriopathy and thrombosis, is a major contributor to the pathophysiology of thrombotic complications associated with COVID-19, including myocardial infarction and stroke.

Myocardial injury caused by SARS-CoV-2 may directly damage cardiomyocytes, myocardial interstitial fibrosis, interferon-mediated immune response, increased cytokine response by Type 1 and 2 helper T cells, interferon-mediated immunopathological events, and coronary plaque destabilization [28]. SARS-CoV-2 infection may induce endoplasmic reticulum (ER) stress, leading to a prolonged unfolded protein response and subsequent alterations in calcium homeostasis and cardiomyocyte cell death. Myocardial injury seems to be largely attributed to advanced systemic inflammation. Acute myocardial injury would be one of the most severe complications of COVID-19 [29]. A study of 138 hospitalized patients reported complications of acute cardiac injury (10 [7.2%]), shock (12 [8.7%]), and arrhythmias (23 [16.7%]) [1]. Patients with underlying CVD exhibited severe myocardial cell damage. Autopsies of post-COVID-19 heart tissue have revealed inflammation in the heart's blood vessels rather than its muscle cells. Pre-existing cardiovascular disease may be an important factor for myocardial injury, as approximately 30% and 60% of patients with cardiac injury have previously had coronary heart disease and hypertension [30]. Systemic pro-inflammatory cytokine responses contribute to local inflammation, which involves plaque rupture, induction of procoagulant factors, and formation of ischaemia and thrombosis. In addition, pharmacologic interventions may lead to cardiac issues, as antiviral drugs can cause cardiac insufficiency, arrhythmias and other cardiovascular disorders [31].

Myocardial injury can lead to atrial or ventricular fibrosis, which may subsequently lead to cardiac arrhythmias. Cardiac arrhythmias in COVID-19 include tachycardia, bradycardia, and asystole. The most observed symptom is palpitations. Other symptoms may occur, such as weakness, shortness of breath, dizziness, lightheadedness, syncope and chest pain. Symptoms would be worse for patients with tachycardia [32]. The most common factor triggering fatal arrhythmias is acute myocardial ischemia, which interacts with other stimulating conditions (e.g., structural heart anomalies) to produce sudden arrhythmic death. A study of 85 fatal cases of COVID-19 reported 51 (60%) patients had arrhythmias, indicating that arrhythmias are an important marker that manifests the deterioration [33]. Among 170 patients with COVID-19 and cardiac injury, 44 (25.9%) had arrhythmias, and 6 of them died of ventricular tachycardia or fibrillation [17]. Some patients showed arrhythmias with SARS-CoV and MERS-CoV infections, but unlike COVID-19, arrhythmia was not a major complication in these two coronaviruses [34]. A sufficiently rapid and long-lasting tachyarrhythmia can result in cardiomyopathy and congestive heart failure [32]. Acute

ventricular tachyarrhythmias are present in the majority of sudden deaths due to cardiac causes [35]. Awareness of this complication is vital, especially when the patient has a history of ischemic heart disease or manifold high-risk factors that trigger cardiovascular problems. Treatment options for cardiac arrhythmias include antiarrhythmic drugs, heart rate control drugs, anticoagulant or antiplatelet therapy, and therapeutic devices, such as pacing, synchronised direct current cardioversion, catheter ablation, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronisation therapy (CRT) [36].

Cardiac dysfunction and heart failure (HF) are common cardiovascular complications associated with COVID-19. Patients without chronic HF could develop HF after SARS-CoV-2 infection and eventually die of sudden cardiac death [37]. The HF complication may be due to lung disease, oxygen deficit, high pulmonary vascular resistance, or pulmonary hypertension (PH), which causes acute right ventricular (RV) overload and failure. Hypoxia can induce inchoate and massive inflammatory responses and cell damage, which ultimately leads to heart impairment [38]. In one study, HF was the most common cause of death, with 113 deaths in patients with COVID-19 followed by acute respiratory distress syndrome (ARDS) and sepsis [39]. The pathology at this stage reflects an uncontrolled feedforward loop, where inflammation causes tissue damage that triggers more inflammation, and so on. This hyperinflammatory state known as cytokine storm manifests itself as ARDS, sepsis and, eventually, organ failure, triggering neutrophil and monocyte recruitment, vascular leakage and tissue damage [40]. Myocarditis is an inflammation of cardiac muscle tissue, which is caused by infiltration of immunocompetent cells following cardiac injuries. COVID-19 patients with congestive heart failure, especially elderly patients with cardiovascular disease, show a greater severity of the disease, and thus are more likely to develop acute coronary syndromes, cardiac arrhythmias, and HF [41] [38].

Thrombosis is one of the most common complications for COVID-19 patients, especially in critically ill patients [42]. The average occurrence rate of both arterial and venous thromboembolic disease was 17.8% (9.9 - 27.4) [43]. D-dimer is a critical index of the coagulation pathway linked with thrombogenesis, which increases dramatically [44], especially in severely ill patients, and rises with increasing inflammation factors [45]. Thrombus is intensely associated with complex systemic inflammatory responses induced by virus infection. Inflammatory factors, such as IL-2R, IL-6, IL-10, and TNF-α are much higher in severe cases [46]. The virus released from endothelial cells induces the accumulation of inflammatory cells, leading to apoptosis and pyroptosis, which subsequently cause endotheliitis and endothelial cell injury [47]. Cytokines produced by activated inflammatory pathway can cause endothelial activation and injury with a higher risk of thrombogenesis [48]. Excessive release of inflammatory factors may cause a cytokine storm, leading to thrombogenesis. Activated platelets lead to thrombosis in the inflamed region and endothelial cell dysfunction. Activation of complement and neutrophils causes a poor inflammatory response,

leading to hyper-inflammation and thrombotic microangiopathy [49]. In addition, obesity and smoking are highly pathogenic factors for thrombosis generation [50]. Prophylactic anticoagulation drugs ameliorate thromboembolic complications in severe cases [51].

Patients are advised to undergo electrocardiography, imaging, and laboratory tests for proper clinical diagnosis, as current biomarkers of myocardial injury fail to identify myocardial impairment and acute coronary syndrome (ACS) [52]. The mechanisms underlying COVID-19-induced ACS might involve plaque rupture, coronary spasm or microthrombi due to systemic inflammation or cytokine storm. Activated macrophages secrete tissue factor, which triggers thrombus formation when plaque rupture occurs.

Certain therapeutics for COVID-19 induce QT interval prolongation, accompanied by potential arrhythmic effects, such as chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin, and lopinavir/ritonavir. Patients receiving HCQ + azithromycin were more likely to experience cardiac arrest and abnormal ECG compared to the group receiving HCQ and azithromycin alone [44]. Arrhythmias patients with COVID-19 should be placed on bed rest to maintain water and electrolyte balance, febrile patients should be kept cool, and patients with hypoxia or dyspnea should receive supplemental oxygen. Diltiazem or ivabradine can be used for patients with sinus tachycardia, and it is recommended not to use β-blockers when experiencing sinus or atrial tachycardia.

4. Vascular and Pulmonary Complications

SARS-CoV-2 can attack pulmonary capillary endothelial cells, resulting in the exudation of a large amount of plasma components in the alveolar cavity. Alveolar epithelial type II cells produce surfactant proteins, which can reduce surface tension and prevent the alveoli from collapsing. Alveolar macrophages or epithelial cells can produce various proinflammatory cytokines and chemokines. The monocytes and neutrophils are then chemotactic at the infection site to clear these exudates with viral particles and infected cells, resulting in uncontrolled inflammation, which further leads to acute respiratory distress syndrome (ARDS). Pulmonary pathology in severe disease differs from previous pneumonitis, with progressive loss of epithelial-endothelial integrity, septal capillary injury, and marked neutrophil infiltration through complement deposition, intravascular viral antigen deposition, and localized intravascular coagulation. SARS-CoV-2 undergoes haematogenous dissemination via infected pulmonary epithelium and then pulmonary endothelium. During this process, endothelial injury, inducing the coagulation cascade, and subsequent microvascular permeability occur [56] (**Table 3**).

The probability of coincidence of venous thromboembolism (VTE) increases with the hospitalization extension [57]. The occurrence rate of pulmonary embolism (PE) is high among patients with VTE, which is more likely to occur in critically ill patients [58]. An autopsy investigation of 12 cases demonstrated that

Table 3. Observational case series, retrospective studies and systemic reviews related to thrombosis.

Reference	Sample Size	VTE	PE	DVT	AE	Microvascular thrombosis	Virus
Ding YQ *et al.* [67]	NA	one third of critically ill SARS patients: VTE	NA	NA	NA	NA	SARS-CoV-1
Ren B *et al.* [63]	48	NA	NA	85.4%	NA	NA	SARS-CoV-2
Zhang L *et al.* [74]	143	NA	NA	46.1%	NA	NA	SARS-CoV-2
Santoliquido *et al.* [75]	84	NA	NA	11.9%	NA	NA	SARS-CoV-2
Wichmann D *et al.* [76]	12 (death)	58%	33%	NA	NA	NA	SARS-CoV-2
Fauvel C *et al.* [60]	1240	NA	8.3%	NA	NA	NA	SARS-CoV-2
Leonard-Lorant I *et al.* [77]	106	NA	30%	NA	NA	NA	SARS-CoV-2
Klok FA *et al.* [64]	184	NA	NA	NA	1.6%	NA	SARS-CoV-2
Marisa D *et al.* [67]	10 (death)	NA	NA	NA	NA	80%	SARS-CoV-2

one-third of patients died directly from PE with elevated D-dimer, lactate dehydrogenase, and C-reactive protein [39]. Therefore, risk stratification and understanding of PE development are helpful for its therapy. Low molecular weight heparin (LMWH) and heparin are effective for antithrombotic therapy and heparin assists the surgical prognosis of revascularization, limb salvage, and overall survival. PE patients receiving anticoagulation show better therapeutic effects [60]. There are many other promising drugs that interfere with the coagulation pathway directly or indirectly, including thrombolytic, antiplatelet, hemostatic modulating, and anti-inflammatory agents [61].

The occurrence of deep vein thrombosis (DVT) is 11.9% for non-ICU patients, with distal DVT being more frequent than proximal DVT [62]. Medications should pay more attention to distal DVT, although the risk of PE caused by proximal DVT is higher because embolus loss may obstruct the pulmonary vessel [63]. Therefore, DVT prophylaxis is vital to decrease mortality. Arterial Embolism (AE) is rarely reported, being present in 3 (3.4%) patients among 184 ICU cases [64]. The formation of small-vessel pulmonary thrombi correlates with the activation of megakaryocytes and neutrophil extracellular traps (NETs). Megakaryocytes and/or platelets may be able to take up intact virus via ACE2-independent mechanisms, such as endocytosis. NETs are important mediators of tissue damage in inflammatory diseases. SARS-CoV-2 could induce the release of NETs by healthy neutrophils, thereby promoting lung epithelial cell death in vitro [65]. The COVID-19 pathology found active endotheliitis and endothelial cells containing coronavirus-like particles, which support the claim of microvascular damage during infection. The presence of microvascular thrombosis is often overlooked by physicians due to limited diagnostic techniques and the lack of available cadavers during the early epidemic outbreak of SRAS-CoV-1 [66]. An autopsy report has found a large number of small fibrinous thrombi in the lungs rather than glomeruli and superficial dermal vessels

[67].

Platelets and fibrin accumulate in blood capillaries with degraded neutrophils and megakaryocytes [68]. Platelets form a bridge between the immune system and thrombosis via platelet activation and the release of haemostatic and inflammatory mediators. Platelet dysfunction and apoptosis contribute to excessive thrombosis and a dysfunctional immune response. Platelet apoptosis leads to the release of a wide variety of pro-inflammatory and procoagulant factors and highly thrombogenic apoptotic bodies. SARS-CoV-2-induced production of autoantibodies targeting platelet surface antigens leads to increased platelet destruction. Activated platelets regulate leukocyte activity during infections and allergic reactions, further contributing to the leukocyte cytokine release. Activated platelets express P-selectin and CD40L on the cell surface, can interact with neutrophils, and can release α-granules and complement C3, as well as various cytokines, which are significantly increased in COVID-19 patients compared to healthy individuals. The binding of activated platelets to neutrophils facilitates the transmigration of platelets to the alveolar lumen and contributes to the formation of oedematous lungs, which in turn leads to further platelet activation [68]. Hypoxia, inflammation, immune system activation, and endothelial activation and dysfunction can further induce platelet activation and apoptosis, thereby leading to increased thrombosis.

Complement activation induces platelet activation and aggregation, which may cause severe inflammation that destroys cells and tissues, leading to fibrin deposition to promote thrombosis [69]. Blockade of the C5a–C5aR1 axis limits the infiltration of myeloid cells in damaged organs and prevents the excessive lung inflammation and endothelialitis that are associated with ARDS in patients with COVID-19 [70]. Coronavirus N protein: Mannan-binding lectin-associated serine protease-2 (MASP-2) interaction leads to uncontrolled activation of the complement lectin pathway, which may be caused by antibody production, continuous viral load with subsequent endothelial, and tissue damage that keeps the complement system activated and inflammation prolonged [71]. Endothelial damage is a principal determinant of microvascular dysfunction due to shifting of the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state [72]. In severe or critical cases of COVID-19, the integrity of the epithelial–endothelial (air–blood) barrier is disrupted. Uncontrolled viral infection leads to more macrophage infiltration and further aggravates lung injury [73]. The formation of immune complexes is another potential mechanism for platelet hyperactivation and thrombocytopenia in COVID-19.

5. Liver and Kidney Dysfunction

Myocardial, lung and hepatorenal injury in COVID-19 patients can be due to cytokine storm, hypoxic injury, or/and direct endothelial/vascular injury [78]. Viral infection increases C-reactive protein and procalcitonin levels in patients,

which triggers an immune response to liver damage [79]. SARS-CoV-2 may infect cholangiocytes directly due to ACE2 expression, but not hepatocytes due to its low ACE2 expression [80] [81].

Patients with liver diseases are more likely to be infected with coronavirus and develop severe hepatitis [82]. The biomarkers of liver dysfunction are alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase, alkaline phosphatase, and bilirubin [83]. ALT and AST are abnormal in 18.2%/19.8% of mild cases and 39.4%/28.1% of severe cases, indicating that severe patients are more likely to have liver dysfunction as an indicator for disease progression [84]. Antiviral and antipyretic drugs may have hepatotoxic effects, such as acetaminophen, oseltamivir, lopinavir (LPV), and ritonavir (RPV) [85]. The prevalence of hepatic injury in patients receiving LPV/r is four folds for patients without LPV/r [86]. The plasma concentration of LPV/r positively correlated with C-reaction protein and inflammatory response [87], thereby leading to drug metabolism disorders and liver injury. RPV attacks liver cell directly by activating pregnane X receptor and disturbing CYP3A metabolic pathways, leading to hepatotoxicity. Gender, age and obesity are also potential pathogenic factors associated with liver dysfunction [88]. Glycyrrhizin is a non-toxic Chinese herb for the treatment of chronic hepatitis. However, the glycyrrhizin should be used cautiously in patients with acute liver damage, where blood routine, liver function, and blood oxygen saturation need to be timely monitored to prevent liver damage.

The kidney is one of the most frequently affected extrapulmonary organs in COVID-19 patients, especially in critically ill patients [89]. The predominant feature of kidney damage is tubular injury, which was known only after the SARS outbreak [5]. Tubular epithelial cells, endothelial cells and podocytes express ACE2, making the kidney a candidate target for SARS-CoV-2 infection [90]. The kidneys show mild to severe arterionephrosclerosis and diabetic nephropathy. SARS-CoV-2 immunohistochemical testing shows plaque-like renal tubular epithelial cells with granular cytoplasmic staining. Centrilobular necrosis is consistent with hypoperfusion injury [91]. Acute kidney injury (AKI) can be an epiphenomenon of both the hypoxia induced by respiratory distress syndrome and septic shock caused by SARS-CoV-2 infection. AKI is an important risk factor for increased hospital mortality. Avoiding hypervolemia, which may alleviate the patient's respiratory status, can prevent prerenal AKI. The Surviving Sepsis Campaign guidelines for critically ill patients with COVID-19 recommend a conservative fluid resuscitation strategy [92].

Diabetes is a common comorbidity associated with poorer outcomes in COVID-19 patients, and these patients often have hypertension. Diabetes is associated with immune dysregulation, which is potentially equivalent to accelerated aging and thus possibly explains the poor prognosis in patients with diabetes mellitus and COVID-19. The use of RAAS inhibitors halves the risk of adverse outcomes in diabetic patients with COVID-19, which may confer protective effects against complications and death in patients with COVID-19 [93].

ACE2 is involved in the association between COVID-19 and diabetes mellitus due to correlation between ACE2 and glucose regulation. ACE2 is also an important regulator of blood pressure. High expression of ACE2 in the circulatory system after SARS-CoV-2 infection could partly contribute to sepsis-induced hypotension [73]. Microvascular and macrovascular complications of diabetes mellitus are significantly associated with an increased risk of mortality in patients with COVID-19. The molecular pathogenesis of SARS-CoV-2 is related to oxidative stress and inflammation, which can contribute to the progression of sepsis. Thus, glycaemic deterioration is a typical complication of COVID-19 in patients with impaired glucose regulation or diabetes mellitus. Elevated glucose levels directly increase SARS-CoV-2 replication, whereas glycolysis sustains SARS-CoV-2 replication by producing mitochondrial reactive oxygen species and activating hypoxia-inducible factor 1*α*. In COVID-19 patients with or without diabetes mellitus, optimal glucose control using insulin infusion statistically significantly reduced IL-6 and D-dimer levels and improved severity [55].

6. Gastrointestinal (GI) Complications

COVID-19 patients have GI manifestations such as nausea, diarrhea, vomiting, anorexia and abdominal discomfort. Gastrointestinal symptoms from 4243 patients with COVID-19 show the morbidity of nausea/vomiting (10.2%), diarrhea (12.5%), and abdominal pain/discomfort (9.2%). Mechanisms that can cause GI damage include direct infection of GI cells, indirect damage by lung infection, and GI symptoms caused by drug side effects [94]. SARS-CoV-2 virus can be detected in the stool of 30% COVID-19 patients. Lung-derived CD4+ T cells are increased after infection and enter small intestine promoted by CCL25 [95], which lead to intestinal immune damage and disrupt the homeostasis of the intestinal flora. Diarrhea is the most common gastrointestinal symptom, manifesting itself earlier than pyrexia or respiratory symptoms in some cases [96]. Diarrhea may be associated with the use of antibacterial and antiviral drugs, which is shown from the previous experience of COVID1-9 treatment [36]. However, observations in a 22-year-old male showed complete disappearance of diarrhea after antiviral therapy following mitigation [97]. Therefore, further studies are necessary to find out the correlation between diarrhea and the use of antibacterial/antiviral drugs.

In comparison with SARS and MERS, GI symptoms in COVID-19 patients are less common, which may manifest differences in viral tropism. Antiviral and immunomodulatory drugs for COVID-19 patients can be the main treatment currently, but other therapies for patients with GI symptoms are also important to promote GI health, including performing microecological preparations and maintaining intestinal microecological balance, using ACE2 Inhibitors and paying more attention to enteral nutrition and digestive tract function [47]. Since the virus damages intestinal flora and gut function, probiotic treatment using antiviral drugs or antibacterial drugs can maintain intestinal flora balance and

prevent bacterial infections. In addition, enteral nutrition provides energy and maintains the normal function of intestinal microecology and mucosal immunity. Gut microbial products leakage and subsequent inflammasome activation may have an effect on cardiac involvement in COVID-19 patients [29], which indicates a potential gut-heart axis in COVID-19.

7. Psychological Complications

During COVID-19 pandemic, people pay more attention on the physiological illness, but few persons focus on their mental problems. Especially for the people who are quarantined at home or in the hospital, they are more likely to occur negative stress responses, such as increasing stress level, anxiety, depression symptoms and unhappiness. Long-term stress is chronic that can influence the release of glucocorticoid hormones and inflammatory response. When a person is under high psychological pressure for a long period, the over-production of glucocorticoid hormones will reduce the occurrence probability of hyperinflammation. The chronic psychological stress is a potential significant risk factor for adverse COVID-19 related health outcomes.

10% hospital workers have high SARS-related posttraumatic stress (PTS) symptoms since they may feel stigmatized and rejected in their neighborhood because of their job nature. Although there are few reports about COVID-19 psychological trauma, it is absolutely worth intensive studies in the future. With the help of tele-medicine, it is urgent to find the risky population with psychological trauma and give them appropriate intervention at early stage.

8. Conclusion and Perspective

Coronaviruses share comparable viral structures and routes of infection, such as direct contact and respiratory droplets. With the successful replication and spread of SARS-CoV-2, the disease transits from mild to moderate stage arising from both virus-associated tissue damage in the respiratory tract and antiviral activity of the adaptive immune system [40]. Viral infection develops a suite of defense mechanisms, including memory B lymphocytes capable of producing neutralizing antibodies directed at a particular pathogen, and memory T lymphocytes that regulate immune responses and induce death of infected cells [98]. SARS-CoV-2-specific CD4+ and CD8+ T cells are both associated with milder disease [99]. $\gamma\delta$ T cells account for the majority of tissue-resident T cells and participate in the front line of host immune defense [100]. SARS-CoV-2 may be able to directly infect T cells. The pathogenesis of late severe COVID-19 pneumonia involves a dysregulated immune response, rather than direct viral damage. The diagnosis and treatment of the disease was complicated by the variety of symptoms and the severity of the disease.

The severe COVID-19 symptoms of hyperinflammation, catastrophic damage to the vascular endothelium, thrombotic complications, septic shock, brain damage, acute disseminated encephalomyelitis, and acute neurological and psy-

chiatric complications are unprecedented for coronaviral infection. Many COVID-19 deaths are a result of hyperinflammatory complications, termed "cytokine storm", endotheliitis and blood clotting, all with the potential to cause multiple organ dysfunction and sudden death [101]. SARS-CoV-2 triggers impaired and dysregulated immune responses and elevates the inflammatory response, which works in synergy with interferon production in the vicinity of infected cells, thereby driving a feed-forward loop to up-regulate ACE2 and further exacerbate infection [102]. Angiotensin II (Ang II) can promote immune response and inflammatory damage, which play a role similar to cytokine storm. ACE2 converts Ang I to Ang II, which is highly expressed in pulmonary vascular endothelial cells [4]. Reactive oxygen species (ROS) will accumulate under the cytokine storm, while elevated levels of Ang II lead to profound ROS production, which worsens the cardiovascular outcomes in COVID-19 patients. It provides possible explanations as to why patients with underlying diseases involving the RAAS system may have exacerbated the condition after COVID-19.

COVID-19 causes pulmonary and extrapulmonary complications. ACE2 is expressed in pancreatic islets, vascular endothelium and adipose tissue, and the SARS-CoV-2-ACE2 interaction, along with other factors, governs the spectrum and severity of clinical manifestations among COVID-19 patients. Splenic atrophy, hilar lymph node necrosis, focal haemorrhage in the kidney, enlarged liver with inflammatory cell infiltration, oedema, and scattered degeneration of neurons in the brain are present in COVID-19 patients. Ophthalmological changes have recently been associated with COVID-19 infection in humans [103]. Viral sepsis is crucial to the disease mechanism of COVID-19. Glomerular changes and nephritis-like histology have been described in postmortem samples from patients with COVID-19. Magnetic resonance imaging (MRI) showed symptoms of myocarditis, such as subepicardial late gadolinium enhancement of the apex and inferolateral wall.

Viral attack, host response and therapeutics interact and influence each other, complicating the situation. The use of antiviral drug can cause cardiovascular problems, such as arrhythmias, cardiac insufficiency, and cardiac arrest. The IFN I response is vital for viral killing. However, IFN I stimulates the expression of the ACE2 receptor. Children may benefit from a virtuous cycle with decreased ACE2 leading to a reduced induction of the IFN response, which subsequently further attenuates ACE2 expression [104]. IFN-I could play an important role in exacerbating TNF- and IL-1-driven inflammation in the progression to severe COVID-19 [100]. Suppression of the IFN response has recently emerged as a major clinical determinant of COVID-19 severity, with almost complete loss of secreted IFN being a feature of the most severe cases. TNF inhibition decreases adhesion molecules and vascular endothelial growth factor, known as vascular permeability factor. There is a concern that anti-TNF therapy might increase the risk of viral infections. Early treatment after infection is more effective. Therefore, it is essential to identify individuals with early SARS-CoV-2 infection to prevent viral entry and replication.

The impression that the COVID-19 is always mild in children is challenged by the report of the rare multisystem inflammatory syndrome in children (MIS-C) [4]. Children exhibit high fever and a variety of symptoms previously associated with Kawasaki disease, such as conjunctivitis, lymphadenopathy, mucocutaneous rash, and coronary artery dilation, in the most severe cases, cardiovascular shock, encephalitis, and multiple organ failure. Affected children were also diagnosed with Kawasaki disease at a mean age older than the normal age, and functional deficits in IFN-I response may account for up to 14% of severe COVID-19 cases [105]. Neutrophils infiltrate the arterial wall and, in severe cases, develop necrotizing arteritis, leading to connective tissue destruction and arterial dilation [106]. The pathogenesis suggests vasculitis and a possible autoimmune etiology, in which multiple autoantibodies may be involved in the pathogenesis of MIS-C. Antibody-dependent enhancement (ADE) of disease is an inducing mechanism in SARS-CoV-2-mediated immunopathogenesis of MIS-C [107].

Furthermore, obesity and aging are comorbidities of severe disease in the context of COVID-19. Obesity weakens immunity, chronic inflammation, blood that is prone to clotting, all of which can worsen COVID-19. Fat in the abdomen pushes up on the diaphragm, which impinges on the lungs and restricts airflow, resulting in collapse of the airways in the lower lobes of the lungs. Obese patients have weakened immunity, partly due to the infiltration of fat cells into the organs where immune cells are produced and stored. Individuals with obesity suffer from chronic low-grade inflammation [108]. Elderly people have a poorer immune response. Aging is associated with endothelial dysfunction, which contributes to vascular pathologies and cardiovascular diseases in the elderly. Senescent cells accumulate during the aging process and lead to increased baseline inflammation [109]. Senescent cells within adipose tissue or adipocytes themselves secrete pro-inflammatory mediators and amplify inflammatory events.

In summary, COVID-19 is a severe pulmonary disease, which not only causes psychological trauma, but also damages multiple organs and tissues including the brain, heart, liver, GI, kidneys, muscles, blood and bones. As the pandemic continually destroys the global economy and claim millions of lives, therapeutics and vaccines are vigorously being developed with unprecedented cooperation and collaboration. Understanding the pathogenic mechanisms of pulmonary and extrapulmonary complications of COVID-19 will facilitate the development of potent therapeutics and vaccination. In addition, with the aid of deep learning and wearable sensors, it is possible to detect the person's psychological and physiological complications accurately at earlier stage. We have significant progress in understanding of COVID-19 complications. However, there is still a long way to go. Viral pathogenesis, inflammation, glucotoxicity, inflammation-induced endothelial dysfunction, oxidative stress, cytokine production, platelets, obesity, aging, and gender all contribute to COVID-19 pulmonary and extrapulmonary complications in a network and systematic manner. As new viral mutations become more contagious and lethal, scientists from diverse discipline should col-

laborate to investigate the mechanisms of viral pathogenesis and corresponding diagnosis, therapeutics and vaccines, and to ensure that our cognition of viruses is faster than the rate of their evolution.

Author Contributions

All authors are involved in discussion and writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding Sources

This work is supported by National Natural Science Foundation of China (31970752), Science, Technology, and Innovation Commission of Shenzhen Municipality (JCYJ20190809180003689, JSGG20200225150707332, JSGG20191129110812), and Shenzhen Laboratory Open Funding (SZBL2020090501004).

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Wang, D., *et al.* (2020) Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, **323**, 1061-1069. https://doi.org/10.1001/jama.2020.1585

[2] Huang, C., *et al.* (2020) Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *The Lancet*, **395**, 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[3] Steardo, L., *et al.* (2020) Neuroinfection May Contribute to Pathophysiology and Clinical Manifestations of COVID-19. *Acta Physiologica*, **229**, e13473. https://doi.org/10.1111/apha.13473

[4] Viner, R.M. and Whittaker, E. (2020) Kawasaki-Like Disease: Emerging Complication during the COVID-19 Pandemic. *The Lancet*, **395**, 1741-1743. https://doi.org/10.1016/S0140-6736(20)31129-6

[5] Joob, B. and Wiwanitkit, V. (2014) Novel Middle East Respiratory Syndrome and Renal Failure. *Renal Failure*, **36**, 147. https://doi.org/10.3109/0886022X.2013.832316

[6] Baig, A.M., *et al.* (2020) Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *Acs Chemical Neuroscience*, **11**, 995-998. https://doi.org/10.1021/acschemneuro.0c00122

[7] Herman, C., Mayer, K. and Sarwal, A. (2020) Scoping Review of Prevalence of Neurologic Comorbidities in Patients Hospitalized for COVID-19. *Neurology*, **95**, 77-84. https://doi.org/10.1212/WNL.0000000000009673

[8] Ronco, C. and Reis, T. (2020) Kidney Involvement in COVID-19 and Rationale for Extracorporeal Therapies. *Nature Reviews Nephrology*, **16**, 308-310. https://doi.org/10.1038/s41581-020-0284-7

[9] Campbell, V.K., *et al.* (2021) Midkine and Chronic Kidney Disease-Associated Multisystem Organ Dysfunctions. *Nephrology Dialysis Transplantation*, **36**, 1577-1584. https://doi.org/10.1093/ndt/gfaa084

[10] Dobbs, M.R. (2011) Toxic Encephalopathy. *Seminars in Neurology*, **31**, 184-193. https://doi.org/10.1055/s-0031-1277989

[11] Cheng, Y., *et al.* (2020) Kidney Disease Is Associated with In-Hospital Death of Patients with COVID-19. *Kidney International*, **97**, 829-838. https://doi.org/10.1016/j.kint.2020.03.005

[12] Asadi-Pooya, A.A. and Simani, L. (2020) Central Nervous System Manifestations of COVID-19: A Systematic Review. *Journal of the Neurological Sciences*, **413**, Article ID: 116832. https://doi.org/10.1016/j.jns.2020.116832

[13] Kochi, A.N., *et al.* (2020) Cardiac and Arrhythmic Complications in Patients with COVID-19. *Journal of Cardiovascular Electrophysiology*, **31**, 1003-1008. https://doi.org/10.1111/jce.14479

[14] Giacomelli, A., *et al.* (2020) Self-Reported Olfactory and Taste Disorders in Patients with Severe Acute Respiratory Coronavirus 2 Infection: A Cross-Sectional Study. *Clinical Infectious Diseases*, **71**, 889-890. https://doi.org/10.1093/cid/ciaa330

[15] Xydakis, M.S., *et al.* (2020) Smell and Taste Dysfunction in Patients with COVID-19. *The Lancet Infectious Diseases*, **20**, 1015-1016. https://doi.org/10.1016/S1473-3099(20)30293-0

[16] Benezit, F., *et al.* (2020) Utility of Hyposmia and Hypogeusia for the Diagnosis of COVID-19. *The Lancet Infectious Diseases*, **20**, 1014-1015. https://doi.org/10.1016/S1473-3099(20)30297-8

[17] Si, D., *et al.* (2020) Death, Discharge and Arrhythmias among Patients with COVID-19 and Cardiac Injury. *CMAJ*, **192**, E791-E798. https://doi.org/10.1503/cmaj.200879

[18] Assiri, A., *et al.* (2013) Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus. *The New England Journal of Medicine*, **369**, 407-416. https://doi.org/10.1056/NEJMoa1306742

[19] Fowler, R.A., *et al.* (2003) Critically Ill Patients with Severe Acute Respiratory Syndrome. *JAMA*, **290**, 367-373. https://doi.org/10.1001/jama.290.3.367

[20] Ingul, C.B., *et al.* (2022) Cardiac Dysfunction and Arrhythmias 3 Months after Hospitalization for COVID-19. *Journal of the American Heart Association*, **11**, e023473. https://doi.org/10.1161/JAHA.121.023473

[21] Du, Y., *et al.* (2020) Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. *American Journal of Respiratory and Critical Care Medicine*, **201**, 1372-1379. https://doi.org/10.1164/rccm.202003-0543OC

[22] Bhatla, A., *et al.* (2020) COVID-19 and Cardiac Arrhythmias. *Heart Rhythm*, **17**, 1439-1444. https://doi.org/10.1016/j.hrthm.2020.06.016

[23] Chen, N., *et al.* (2020) Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. *The Lancet*, **395**, 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

[24] Pan, S.F., *et al.* (2003) Cardiac Arrest in Severe Acute Respiratory Syndrome: Analysis of 15 Cases. *Chinese Journal of Tuberculosis and Respiratory Diseases*, **26**, 602-605.

[25] Zhang, B., *et al.* (2020) Treatment with Convalescent Plasma for Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest*, **158**, e9-e13. https://doi.org/10.1016/j.chest.2020.03.039

[26] Saad, M., *et al.* (2014) Clinical Aspects and Outcomes of 70 Patients with Middle East Respiratory Syndrome Coronavirus Infection: A Single-Center Experience in Saudi Arabia. *International Journal of Infectious Diseases*, **29**, 301-306.

https://doi.org/10.1016/j.ijid.2014.09.003

[27] Guo, T., *et al.* (2020) Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). *JAMA Cardiology*, **5**, 811-818. https://doi.org/10.1001/jamacardio.2020.1017

[28] Babapoor-Farrokhran, S., *et al.* (2020) Myocardial Injury and COVID-19: Possible Mechanisms. *Life Sciences*, **253**, Article ID: 117723. https://doi.org/10.1016/j.lfs.2020.117723

[29] Huang, C., Wang, Y. and Li, X. (2020) Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *The Lancet*, **395**, 496-496. https://doi.org/10.1016/S0140-6736(20)30183-5

[30] Shi, S., *et al.* (2020) Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiology*, **5**, 802-810. https://doi.org/10.1001/jamacardio.2020.0950

[31] Sakabe, M., Yoshioka, R. and Fujiki, A. (2013) Sick Sinus Syndrome Induced by Interferon and Ribavirin Therapy in a Patient with Chronic Hepatitis C. *Journal of Cardiology Cases*, **8**, 173-175. https://doi.org/10.1016/j.jccase.2013.08.002

[32] Kastor, J.A. and Saba, M.M. (2002) Cardiac Arrhythmias. eLS. https://doi.org/10.1038/npg.els.0002112

[33] Du, Y., *et al.* (2020) Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. *American Journal of Respiratory and Critical Care Medicine*, **201**, 1372-1379. https://doi.org/10.1164/rccm.202003-0543OC

[34] Holshue, M.L., *et al.* (2020) First Case of 2019 Novel Coronavirus in the United States. *The New England Journal of Medicine*, **382**, 929-936. https://doi.org/10.1056/NEJMoa2001191

[35] Huikuri, H.V., Castellanos, A. and Myerburg, R.J. (2001) Sudden Death Due to Cardiac Arrhythmias. *New England Journal of Medicine*, **345**, 1473-1482. https://doi.org/10.1056/NEJMra000650

[36] Leung, W.K., *et al.* (2003) Enteric Involvement of Severe Acute Respiratory Syndrome-Associated Coronavirus Infection. *Gastroenterology*, **125**, 1011-1017. https://doi.org/10.1016/j.gastro.2003.08.001

[37] Cameli, M., *et al.* (2020) Usefulness of Echocardiography to Detect Cardiac Involvement in COVID-19 Patients. *Echocardiography*, **37**, 1278-1286. https://doi.org/10.1111/echo.14779

[38] Nguyen, J.L., *et al.* (2016) Seasonal Influenza Infections and Cardiovascular Disease Mortality. *JAMA Cardiology*, **1**, 274-281. https://doi.org/10.1001/jamacardio.2016.0433

[39] Chen, T., *et al.* (2020) Clinical Characteristics of 113 Deceased Patients with Coronavirus Disease 2019: Retrospective Study. *BMJ*, **368**, m1295.

[40] Cain, D.W. and Cidlowski, J.A. (2020) After 62 Years of Regulating Immunity, Dexamethasone Meets COVID-19. *Nature Reviews Immunology*, **20**, 587-588. https://doi.org/10.1038/s41577-020-00421-x

[41] Aghagoli, G., *et al.* (2020) Cardiac Involvement in COVID-19 Patients: Risk Factors, Predictors, and Complications: A Review. *Journal of Cardiac Surgery*, **35**, 1302-1305. https://doi.org/10.1111/jocs.14538

[42] Zhang, J.J., *et al.* (2020) Clinical Characteristics of 140 Patients Infected with SARS-CoV-2 in Wuhan, China. *Allergy*, **75**, 1730-1741. https://doi.org/10.1111/all.14238

[43] Kunutsor, S.K. and Laukkanen, J.A. (2020) Incidence of Venous and Arterial

Thromboembolic Complications in COVID-19: A Systematic Review and Meta-Analysis. *Thrombosis Research*, **196**, 27-30. https://doi.org/10.1016/j.thromres.2020.08.022

[44] Rosenberg, E.S., *et al.* (2020) Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State. *JAMA*, **323**, 2493-2502. https://doi.org/10.1001/jama.2020.8630

[45] Rydyznski Moderbacher, C., *et al.* (2020) Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell*, **183**, 996-1012e19. https://doi.org/10.1016/j.cell.2020.09.038

[46] Beck, D.B. and Aksentijevich, I. (2020) Susceptibility to Severe COVID-19. *Science*, **370**, 404-405. https://doi.org/10.1126/science.abe7591

[47] Ye, Q., *et al.* (2020) The Mechanism and Treatment of Gastrointestinal Symptoms in Patients with COVID-19. *The American Journal of Physiology-Gastrointestinal and Liver Physiology*, **319**, G245-G252. https://doi.org/10.1152/ajpgi.00148.2020

[48] Iba, T. and Levy, J.H. (2019) Derangement of the Endothelial Glycocalyx in Sepsis. *Journal of Thrombosis and Haemostasis*, **17**, 283-294. https://doi.org/10.1111/jth.14371

[49] Wang, J., *et al.* (2014) Respiratory Influenza virus Infection Induces Intestinal Immune Injury via Microbiota-Mediated Th17 Cell-Dependent Inflammation. *Journal of Experimental Medicine*, **211**, 2397-2410. https://doi.org/10.1084/jem.20140625

[50] Xie, C., *et al.* (2020) The Evidence of Indirect Transmission of SARS-CoV-2 Reported in Guangzhou, China. *BMC Public Health*, **20**, Article No. 1202. https://doi.org/10.1186/s12889-020-09296-y

[51] Wan, Y., *et al.* (2020) Enteric Involvement in Hospitalised Patients with COVID-19 outside Wuhan. *The Lancet Gastroenterology and Hepatology*, **5**, 534-535. https://doi.org/10.1016/S2468-1253(20)30118-7

[52] Takahashi, T., *et al.* (2020) Sex Differences in Immune Responses That Underlie COVID-19 Disease Outcomes. *Nature*, **588**, 315-320. https://doi.org/10.1038/s41586-020-2700-3

[53] Nishiga, M., *et al.* (2020) COVID-19 and Cardiovascular Disease: From Basic Mechanisms to Clinical Perspectives. *Nature Reviews Cardiology*, **17**, 543-558. https://doi.org/10.1038/s41569-020-0413-9

[54] Gu, S.X., *et al.* (2021) Thrombocytopathy and Endotheliopathy: Crucial Contributors to COVID-19 Thromboinflammation. *Nature Reviews Cardiology*, **18**, 194-209. https://doi.org/10.1038/s41569-020-00469-1

[55] Lim, S., *et al.* (2021) COVID-19 and Diabetes Mellitus: From Pathophysiology to Clinical Management. *Nature Reviews Endocrinology*, **17**, 11-30. https://doi.org/10.1038/s41574-020-00435-4

[56] Schubert, K., *et al.* (2020) SARS-CoV-2 Nsp1 Binds the Ribosomal mRNA Channel to Inhibit Translation. *Nature Structural & Molecular Biology*, **27**, 959-966. https://doi.org/10.1038/s41594-020-0511-8

[57] Carter, M.J., *et al.* (2020) Peripheral Immunophenotypes in Children with Multisystem Inflammatory Syndrome Associated with SARS-CoV-2 Infection. *Nature Medicine*, **26**, 1701-1707. https://doi.org/10.1038/s41591-020-1054-6

[58] Buchrieser, J., *et al.* (2020) Syncytia Formation by SARS-CoV-2-Infected Cells. *EMBO Journal*, **39**, e106267. https://doi.org/10.15252/embj.2020106267

[59] Wichmann, D., *et al.* (2020) Autopsy Findings and Venous Thromboembolism in Patients with COVID-19: A Prospective Cohort Study. *Annals of Internal Medicine*,

173, 268-277. https://doi.org/10.7326/M20-2003

[60] Fauvel, C., Trimaille, A., *et al.* (2020) Pulmonary Embolism in COVID-19 Patients: A French Multicentre Cohort Study. *European Heart Journal*, **41**, 3058-3068. https://doi.org/10.1093/eurheartj/ehaa500

[61] Paar, V., *et al.* (2021) Anti-Coagulation for COVID-19 Treatment: Both Anti-Thrombotic and Anti-Inflammatory? *Journal of Thrombosis and Thrombolysis*, **51**, 226-231. https://doi.org/10.1007/s11239-020-02212-6

[62] Zhang, L., *et al.* (2020) Deep Vein Thrombosis in Hospitalized Patients with COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*, **142**, 114-128. https://doi.org/10.1161/CIRCULATIONAHA.120.046702

[63] Ren, B., *et al.* (2020) Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan. *Circulation*, **142**, 181-183. https://doi.org/10.1161/CIRCULATIONAHA.120.047407

[64] Klok, F.A., *et al.* (2020) Incidence of Thrombotic Complications in Critically Ill ICU Patients with COVID-19. *Thrombosis Research*, **191**, 145-147. https://doi.org/10.1016/j.thromres.2020.04.013

[65] Szturmowicz, M. and Demkow, U. (2021) Neutrophil Extracellular Traps (NETs) in Severe SARS-CoV-2 Lung Disease. *International Journal of Molecular Sciences*, **22**, 8854. https://doi.org/10.3390/ijms22168854

[66] Ding, Y.Q., *et al.* (2003) The Clinical Pathology of Severe Acute Respiratory Syndrome (SARS): A Report from China. *Journal of Pathology*, **200**, 282-289. https://doi.org/10.1002/path.1440

[67] Dolhnikoff, M., *et al.* (2020) Pathological Evidence of Pulmonary Thrombotic Phenomena in Severe COVID-19. *Journal of Thrombosis and Haemostasis*, **18**, 1517-1519. https://doi.org/10.1111/jth.14844

[68] Gu, S.X., *et al.* (2020) Thrombocytopathy and Endotheliopathy: Crucial Contributors to COVID-19 Thromboinflammation. *Nature Reviews Cardiology*, **18**, 194-209. https://doi.org/10.1038/s41569-020-00469-1

[69] Campbell, C.M. and Kahwash, R. (2020) Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? *Circulation*, **141**, 1739-1741. https://doi.org/10.1161/CIRCULATIONAHA.120.047419

[70] Carvelli, J., *et al.* (2020) Association of COVID-19 Inflammation with Activation of the C5a-C5aR1 Axis. *Nature*, **588**, 146-150. https://doi.org/10.1038/s41586-020-2600-6

[71] Flude, B.M., *et al.* (2021) Targeting the Complement Serine Protease MASP-2 as a Therapeutic Strategy for Coronavirus Infections. *Viruses*, **13**, 312. https://doi.org/10.3390/v13020312

[72] Varga, Z., *et al.* (2020) Endothelial Cell Infection and Endotheliitis in COVID-19. *The Lancet*, **395**, 1417-1418. https://doi.org/10.1016/S0140-6736(20)30937-5

[73] Yousefi, B., *et al.* (2020) A Global Treatments for Coronaviruses Including COVID-19. *Journal of Cellular Physiology*, **235**, 9133-9142. https://doi.org/10.1002/jcp.29785

[74] Zhang, L., *et al.* (2020) Deep Vein Thrombosis in Hospitalized Patients with COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*, **142**, E33. https://doi.org/10.1161/CIR.0000000000000887

[75] Pieralli, F., *et al.* (2021) Incidence of Deep Vein Thrombosis through an Ultrasound Surveillance Protocol in Patients with COVID-19 Pneumonia in Non-ICU Setting: A Multicenter Prospective Study. *PLoS ONE*, **16**, e0251966.

https://doi.org/10.1371/journal.pone.0251966

[76] Epelbaum, O. (2020) Autopsy Findings and Venous Thromboembolism in Patients with COVID-19. *Annals of Internal Medicine*, **173**, 1029-1030. https://doi.org/10.7326/L20-1205

[77] Grillet, F., *et al.* (2020) Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected with Pulmonary CT Angiography. *Radiology*, **296**, E186-E188. https://doi.org/10.1148/radiol.2020201544

[78] Yalcin, A.D. and Yalcin, A.N. (2021) Future Perspective: Biologic Agents in Patients with Severe COVID-19. *Immunopharmacology and Immunotoxicology*, **43**, 1-7. https://doi.org/10.1080/08923973.2020.1818770

[79] Pink, I., *et al.* (2021) C-Reactive Protein and Procalcitonin for Antimicrobial Stewardship in COVID-19. *Infection*, **49**, 935-943. https://doi.org/10.1007/s15010-021-01615-8

[80] Ni, W., *et al.* (2020) Role of Angiotensin-Converting Enzyme 2 (ACE2) in COVID-19. *Critical Care*, **24**, 422. https://doi.org/10.1186/s13054-020-03120-0

[81] Vieira, C., *et al.* (2021) Downregulation of Membrane-Bound Angiotensin Converting Enzyme 2 (ACE2) Receptor Has a Pivotal Role in COVID-19 Immunopathology. *Current Drug Targets*, **22**, 254-281. https://doi.org/10.2174/1389450121666201020154033

[82] Martinez, M.A. and Franco, S. (2021) Impact of COVID-19 in Liver Disease Progression. *Hepatology Communications*, **5**, 1138-1150. https://doi.org/10.1002/hep4.1745

[83] Lv, Y., *et al.* (2021) Abnormal Liver Function Tests Were Associated with Adverse Clinical Outcomes: An Observational Cohort Study of 2,912 Patients with COVID-19. *Frontiers in Medicine* (*Lausanne*), **8**, Article ID: 639855. https://doi.org/10.3389/fmed.2021.639855

[84] Ali, N. (2020) Relationship between COVID-19 Infection and Liver Injury: A Review of Recent Data. *Frontiers in Medicine* (*Lausanne*), **7**, Article No. 458. https://doi.org/10.3389/fmed.2020.00458

[85] Wu, R., *et al.* (2020) An Update on Current Therapeutic Drugs Treating COVID-19. *Current Pharmacology Reports*, **6**, 56-70. https://doi.org/10.1007/s40495-020-00216-7

[86] Micheli, V., *et al.* (2008) Lopinavir/Ritonavir Pharmacokinetics in HIV/HCV-Coinfected Patients with or without Cirrhosis. *Therapeutic Drug Monitoring*, **30**, 306-313. https://doi.org/10.1097/FTD.0b013e318177209e

[87] Marzolini, C., *et al.* (2020) Effect of Systemic Inflammatory Response to SARS-CoV-2 on Lopinavir and Hydroxychloroquine Plasma Concentrations. *Antimicrobial Agents and Chemotherapy*, **64**, e01177-20. https://doi.org/10.1128/AAC.01177-20

[88] Medeiros, A.K., *et al.* (2020) Higher Frequency of Hepatic Steatosis at CT among COVID-19-Positive Patients. *Abdominal Radiology* (*NY*), **45**, 2748-2754. https://doi.org/10.1007/s00261-020-02648-7

[89] Zheng, K.I., *et al.* (2021) Extrapulmonary Complications of COVID-19: A Multisystem Disease? *Journal of Medical Virology*, **93**, 323-335. https://doi.org/10.1002/jmv.26294

[90] Nascimento Conde, J., *et al.* (2020) Recombinant ACE2 Expression Is Required for SARS-CoV-2 to Infect Primary Human Endothelial Cells and Induce Inflammatory and Procoagulative Responses. *mBio*, **11**, e03185-20. https://doi.org/10.1128/mBio.03185-20

[91] Massoth, L.R., *et al.* (2021) Comparison of RNA *in Situ* Hybridization and Immunohistochemistry Techniques for the Detection and Localization of SARS-CoV-2 in Human Tissues. *The American Journal of Surgical Pathology*, **45**, 14-24. https://doi.org/10.1097/PAS.0000000000001563

[92] Alhazzani, W., *et al.* (2020) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Critical Care Medicine*, **48**, e440-e469. https://doi.org/10.21608/bjas.2021.168301

[93] Zhang, G., *et al.* (2021) Effects of Renin-Angiotensin-Aldosterone System Inhibitors on Disease Severity and Mortality in Patients with COVID-19: A Meta-Analysis. *Journal of Medical Virology*, **93**, 2287-2300. https://doi.org/10.1002/jmv.26695

[94] Delgado-Gonzalez, P., *et al.* (2021) Inflammatory Effect on the Gastrointestinal System Associated with COVID-19. *World Journal of Gastroenterology*, **27**, 4160-4171. https://doi.org/10.3748/wjg.v27.i26.4160

[95] Soy, M., *et al.* (2020) Cytokine Storm in COVID-19: Pathogenesis and Overview of Anti-Inflammatory Agents Used in Treatment. *Clinical Rheumatology*, **39**, 2085-2094. https://doi.org/10.1007/s10067-020-05190-5

[96] Borriello, G., *et al.* (2021) Case Report: COVID-19 Infection with Gastrointestinal Symptoms and Mood Disorder: Criticalities in Differential Diagnosis, Therapy and Management of Complications. *Frontiers in Psychiatry*, **12**, Article ID: 568553. https://doi.org/10.3389/fpsyt.2021.568553

[97] Duan, K., *et al.* (2020) Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients. *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 9490-9496. https://doi.org/10.1073/pnas.2004168117

[98] Peng, Y., *et al.* (2020) Broad and Strong Memory CD4(+) and CD8(+) T Cells Induced by SARS-CoV-2 in UK Convalescent Individuals Following COVID-19. *Nature Immunology*, **21**, 1336-1345. https://doi.org/10.1038/s41590-020-0782-6

[99] Peng, Y., *et al.* (2020) Broad and Strong Memory CD4 (+) and CD8 (+) T Cells Induced by SARS-CoV-2 in UK Convalescent COVID-19 Patients.

[100] Lee, J.S. and Shin, E.C. (2020) The Type I interferon Response in COVID-19: Implications for Treatment. *Nature Reviews Immunology*, **20**, 585-586. https://doi.org/10.1038/s41577-020-00429-3

[101] McGowan, E.M., *et al.* (2020) Targeting the SphK-S1P-SIPR Pathway as a Potential Therapeutic Approach for COVID-19. *International Journal of Molecular Sciences*, **21**, 7189. https://doi.org/10.3390/ijms21197189

[102] Zamai, L. (2021) Upregulation of the Renin-Angiotensin System Pathways and SARS-CoV-2 Infection: The Rationale for the Administration of Zinc-Chelating Agents in COVID-19 Patients. *Cells*, **10**, 506. https://doi.org/10.3390/cells10030506

[103] Hu, K., *et al.* (2022) Ophthalmic Manifestations of Coronavirus (COVID-19). StatPearls, Treasure Island.

[104] Zamorano Cuervo, N. and Grandvaux, N. (2020) ACE2: Evidence of Role as Entry Receptor for SARS-CoV-2 and Implications in Comorbidities. *Elife*, **9**, e61390. https://doi.org/10.7554/eLife.61390

[105] Bhattacharyya, P. (2020) Multisystem Inflammatory Syndrome of Children Related to SARS-CoV-2: A Novel Experience in Children with a Novel Virus. *Indian Journal of Critical Care Medicine*, **24**, 1010-1011. https://doi.org/10.5005/jp-journals-10071-23652

[106] Consiglio, C.R., *et al.* (2020) The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell*, **183**, 968-981e7.

https://doi.org/10.1016/j.cell.2020.09.016

[107] Ricke, D.O. (2021) Two Different Antibody-Dependent Enhancement (ADE) Risks for SARS-CoV-2 Antibodies. *Frontiers in Immunology*, **12**, Article ID: 640093. https://doi.org/10.3389/fimmu.2021.640093

[108] Wadman, M. (2020) Why Obesity Worsens COVID-19. *Science*, **369**, 1280-1281. https://doi.org/10.1126/science.369.6509.1280

[109] Akbar, A.N. and Gilroy, D.W. (2020) Aging Immunity May Exacerbate COVID-19. *Science*, **369**, 256-257. https://doi.org/10.1126/science.abb0762