

Pathogenesis, Clinical Manifestations and Laboratory Findings of the COVID-19

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Since the beginning of the pandemic of new coronavirus, scientists are trying to elucidate the mechanisms of SARS-CoV-2 replication in the human body, its genome, and the behavior of the virus into cells. Also, at the beginning of the outbreak, they found that the unique problem of the virus is the severe acute respiratory syndrome pneumonia, however, new discoveries revealed that the virus affects major organ systems in the human body, causing injuries and lethal damages. In addition, the tests for diagnosing the virus has become a priority. So, based on the literature review, we showed in this article the mechanisms of the virus into cells, the symptoms, the clinical course of the disease, and the main injuries caused in the human body's systems by the SARS-CoV-2, and the laboratory findings. We based our research in the articles of the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Excerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews and original articles in this order. We reviewed more than 317 articles and used 235 from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-Sars-2, COVID-19, corona virus, coronaviruses, pathogenesis, clinical manifestations, symptoms, body systems, damage, injuries, laboratory, diagnosis, with the tools MeSH (Medical Subject Headings), AND, OR, and characters [“,; /., to ensure the best review topics. We concluded that the virus could affect and damage the respiratory system, cardiovascular system, digestive system, urogenital system, and central nervous system. It makes the treatment harder than the physicians found at the beginning of the pandemic. We are initiating our understanding of this new virus and the effect in patients during the symptoms and after them. A deeper understanding of this virus from biomedical research and epidemiological observation will provide important clues to etiologic research, diagnosis, differential diagnosis, treatment, and prognostic assessment against COVID-19.

Keywords: COVID-19. SARS-CoV-2. Pathogenesis. Injuries. Laboratory Findings.

Introduction

In March 2020, the World Health Organization (WHO) declares a new pandemic that began in Wuhan, Hubei Province, China, and spreads worldwide. The disease, called COVID-19, causes severe acute respiratory syndrome by an RNA-virus of the Family Coronaviridae, named SARS-CoV-2 [1-4]. However, in addition to affecting the

pulmonary system, there are many other clinical features of the disease and other affected organs that were not known at the beginning of the pandemic. Now, studies reveal that this new virus compromises lungs, kidneys, liver, and central nervous system. In this article, we present the pathogenesis of the COVID-19 infection, clinical features, and laboratory findings about COVID-19 through reviewed studies, systematic review, and meta-analysis.

Pathophysiology of COVID-19

ACE2 (angiotensin-converting enzyme 2) is the receptor that allows SARS-CoV-2 to enter into the cells to trigger infection [5, 6]. ACE2

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is a multifunctional protein whose primary physiological role is the enzymatic conversion of angiotensin (Ang) II to Ang-(1-7), and Ang I to Ang-(1-9) [7]. The involvement of ACE2 in severe acute respiratory syndrome (SARS) infection occurs due to the binding in the coronavirus receptor [8]. This bond between SARS-CoV-2 spike protein and ACE2 promotes the virus to infiltrate the lung's alveolar epithelial cells, where it is overexpressed, by processes involving cell surface-associated transmembrane protein serine 2 (TMPRSS2) [9] (Figure 1). Inside the host cell, the RNA virus begins its replication conducting to newly formed genomic RNA, which is processed into virion-containing vesicles that join with the cell membrane to release the virus [9].

According to Wu and colleagues [11], SARS-CoV-2 is sprayed principally through the respiratory tract by droplets and respiratory secretions. The RAS/ACE2 appears to be interrupted by SARS-CoV-2 infection, which likely has a pathogenic role in critical lung injury and respiratory failure in COVID-19. Nevertheless, ACE2 is not only expressed in the lungs' cells, it also highly expressed in the human heart, vessels, gastrointestinal tract, and other human tissues, which can cause severe damage to the body system (Figure 2) [12-14].

Cytokine Storm and Inflammation

Previous studies have confirmed that the immune abnormality is related to the pathogenesis of SARS-CoV infection [15]. Several studies suggested that an overexpression of the immunological system, called cytokine storm, is the main contributor to the severity of the disease. Cytokine storm syndrome (CSS) is a systemic inflammatory response usually caused by viral infections. It is also called cytokine release syndrome (CRS) and characterized by an overexpression of the immunologic system with excessive numbers of pro-inflammatory cytokines (e.g., interleukin-1 β (IL-1 β), IL-6, interferon- γ (IFN- γ), IFN γ inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1),

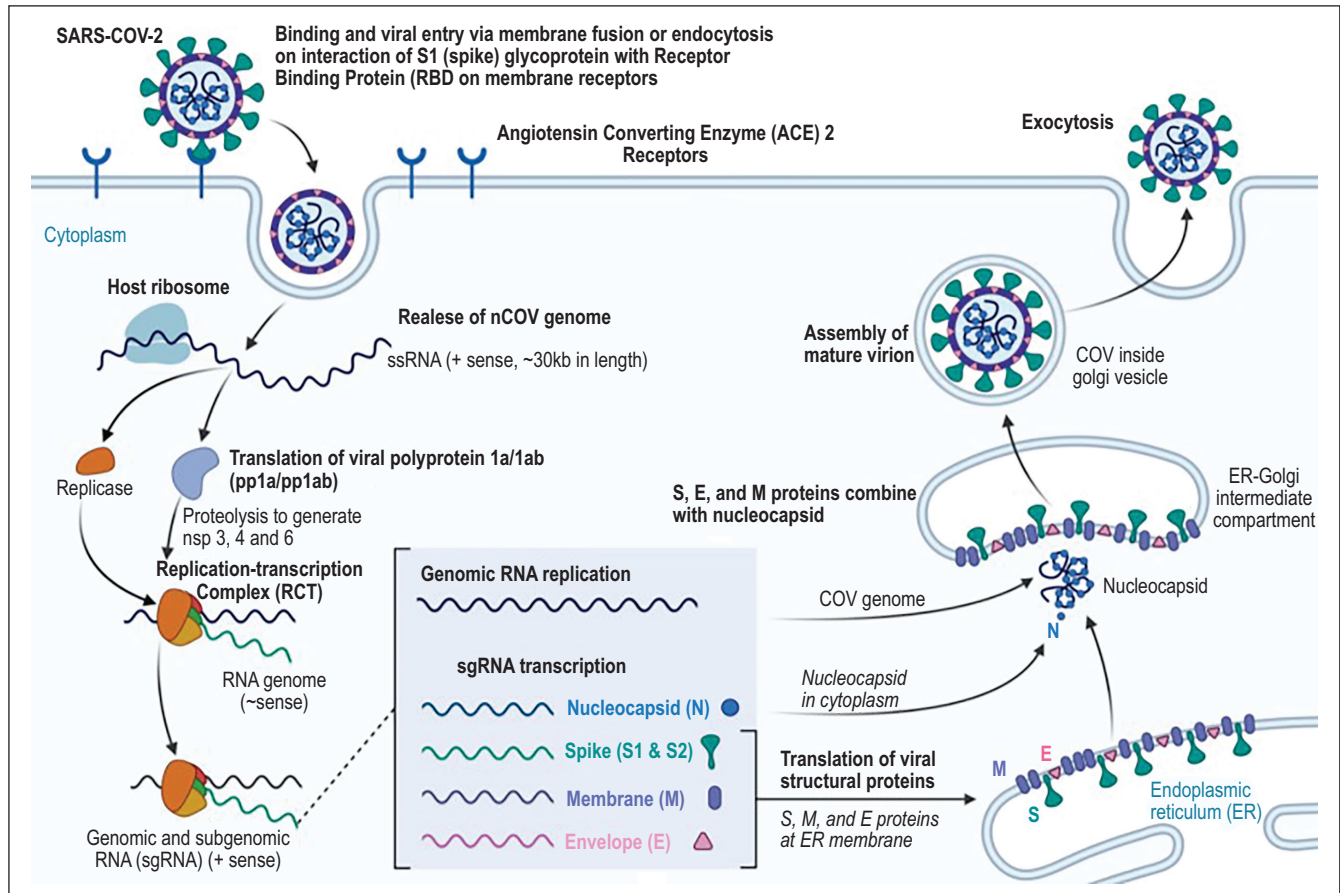
granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1 α (MIP-1 α), tumor necrosis factor- α (TNF- α). CSS is significantly raised in COVID-19 patients [16, 17].

The protagonist in the CSS is the interleukin 6 (IL-6), which is produced and delivered by activated leukocytes and acts on plenty of cells and tissues. Cytokine IL-6 seems to be the core of cytokine storm due to its ability not only to amplify cytokine storm by stimulating the production of other pro-inflammatory cytokines but also results in vascular leakage, interstitial edema [18]. Moreover, IL-6 has also been shown to weaken papillary muscle contraction, which causes myocardial dysfunction, as well as promoting the differentiation and activation of B lymphocytes, and stimulating production of acute-phase proteins. [19]. IFN γ is also another cytokine regarded as a marker of cytokine storm, causing cell apoptosis through regulating the JAK/STAT1 axis and p38-MAPK1 [20]. Nevertheless, anti-inflammatory cytokines such as IL-4 and IL-10 are also increased in COVID-19 patients, and their levels are also related to disease severity [16, 17], demonstrating the close relation between pro- and anti-inflammation. Uncontrolled inflammatory process caused by the cytokine storm has the potential to lead to injury multi-organs, septic shock, and organ failure [21].

In COVID-19 disease, SARS-CoV-2 invades host cells, replicates, and releases viruses via a process in which programmed cell death is triggered off by inflammation (pyroptosis). This process activates the innate and adaptive immune systems.

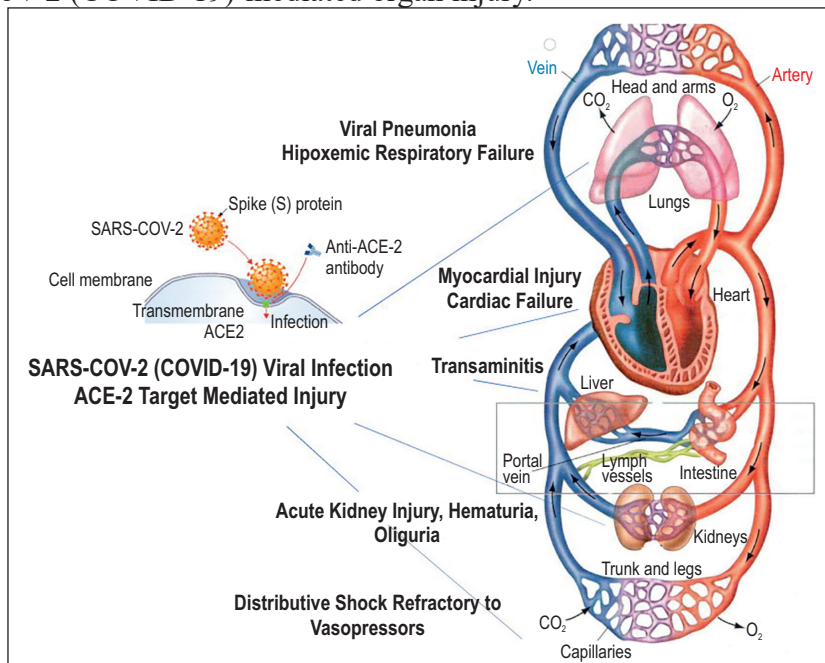
The viral infection leads epithelial cells and alveolar macrophages into the lungs to generate a large number of inflammatory cytokines and chemokines (Figures 3 and 4), which attract monocytes, macrophages, and T cells to the infection site, producing more inflammatory cytokines, which creates a feedback loop. The accumulation of T-cells in the lungs also provokes a reduction in the blood levels of lymphocytes (i.e.,

Figure 1. The machinery of SARS-CoV-2 getting into the human cell.



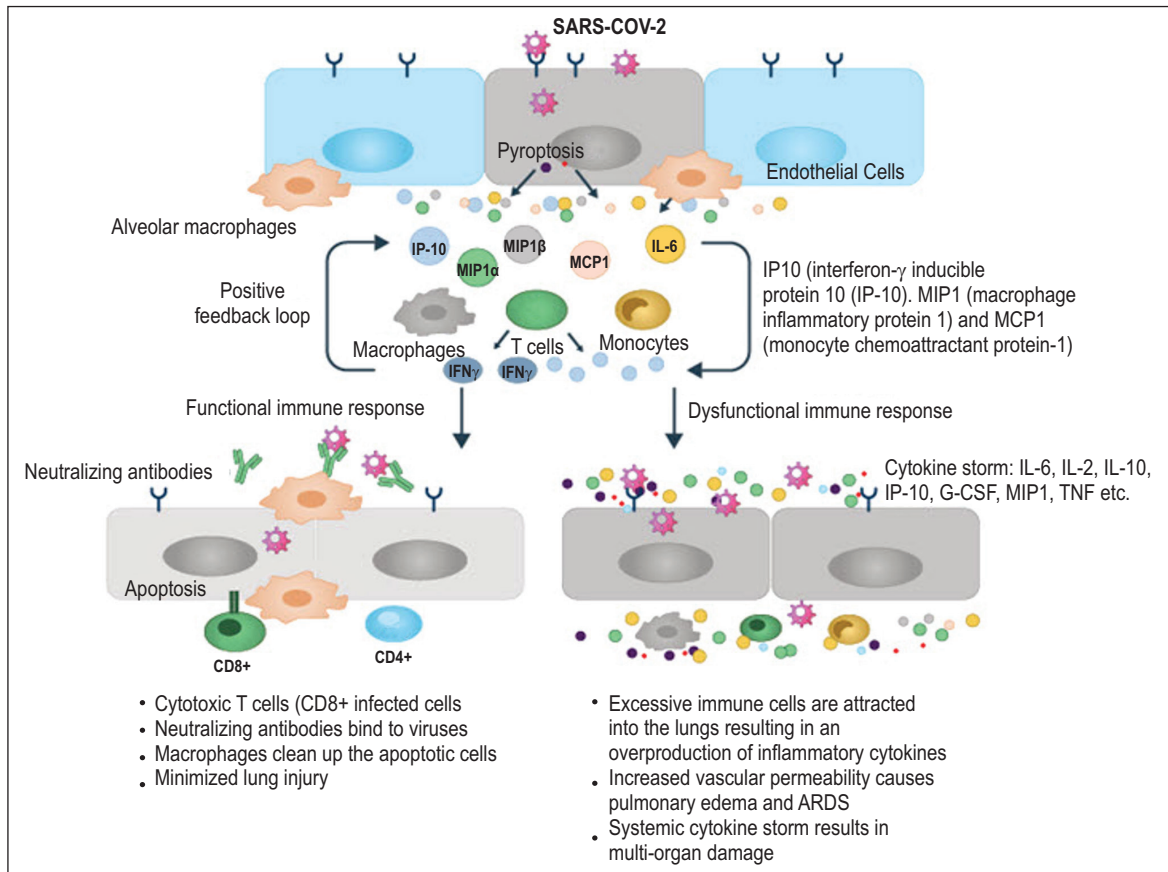
Source/Credit: Reproduced from the original work here [link to <https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance>] Permission obtained from © The European Society of Cardiology 2020. All rights reserved. [10].

Figure 2. SARS-CoV-2 (COVID-19)-mediated organ injury.



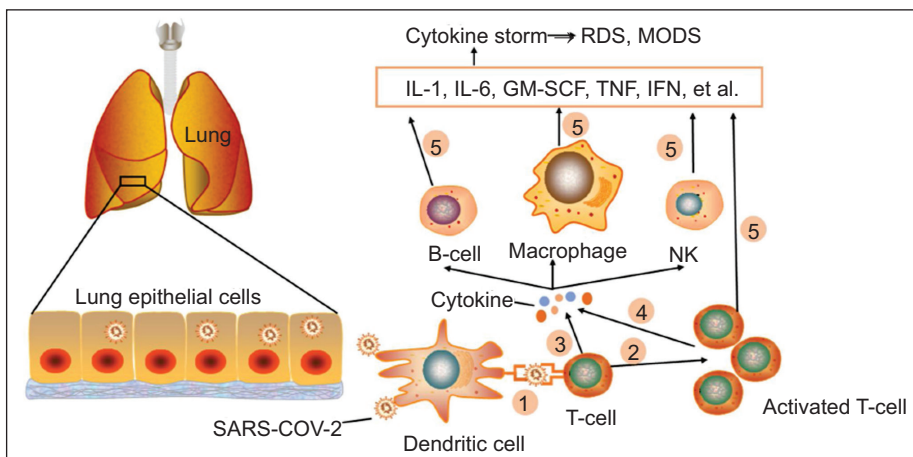
Source/Credit: Kazory and colleagues [14].

Figure 3. Immunopathogenesis of cytokine storm in COVID-19.



Source/Credit: Li [25].

Figure 4. Inflammatory storm mechanism.



1. Antigen presenting. 2. T cells activate and start reproducing. 3. A large amount of cytokine are secreted during T cell activation. B cells, macrophage and NK cells will be activated by these cytokine. 4. Activated T cells release cytokine and activate more B cells, macrophage and NK cells. 5. Cytokine secreted. The figure shows the mechanism of cytokine cascade, also known as an inflammatory cascade. Pathogen infection triggers an intense immune response and inflammatory response and rapid release of a large number of cytokines (such as tumor necrosis factor- α , interleukin (IL)-1, IL-6, and interferon- γ (IFN- γ)). In this context, patients with viral infection are particularly susceptible to acute respiratory distress syndrome and multiple organ failure. Cytokine cascades and low lymphocytes are also specific in other severe coronavirus diseases (such as SARS and MERS) and are positively related to disease progression and severity [26-28]. Recent studies have confirmed this conclusion, showing low lymphocytes and elevated inflammatory cytokines in most SARS-CoV-2 cases [29, 30]. Once triggered, the cytokine cascade may cause rapid failure of one or more organs with extremely adverse prognosis if not treated promptly.

Source/Credit: Zhang and colleagues [31].

lymphopenia) in severe COVID-19 patients [22, 23]. The intense immune response causes damage to the lungs and other vital organs. Li and colleagues [24] observed that, also in other body systems, the systemic cytokine storm and the microcirculation dysfunctions together lead to viral sepsis.

Hyperfibrinolysis

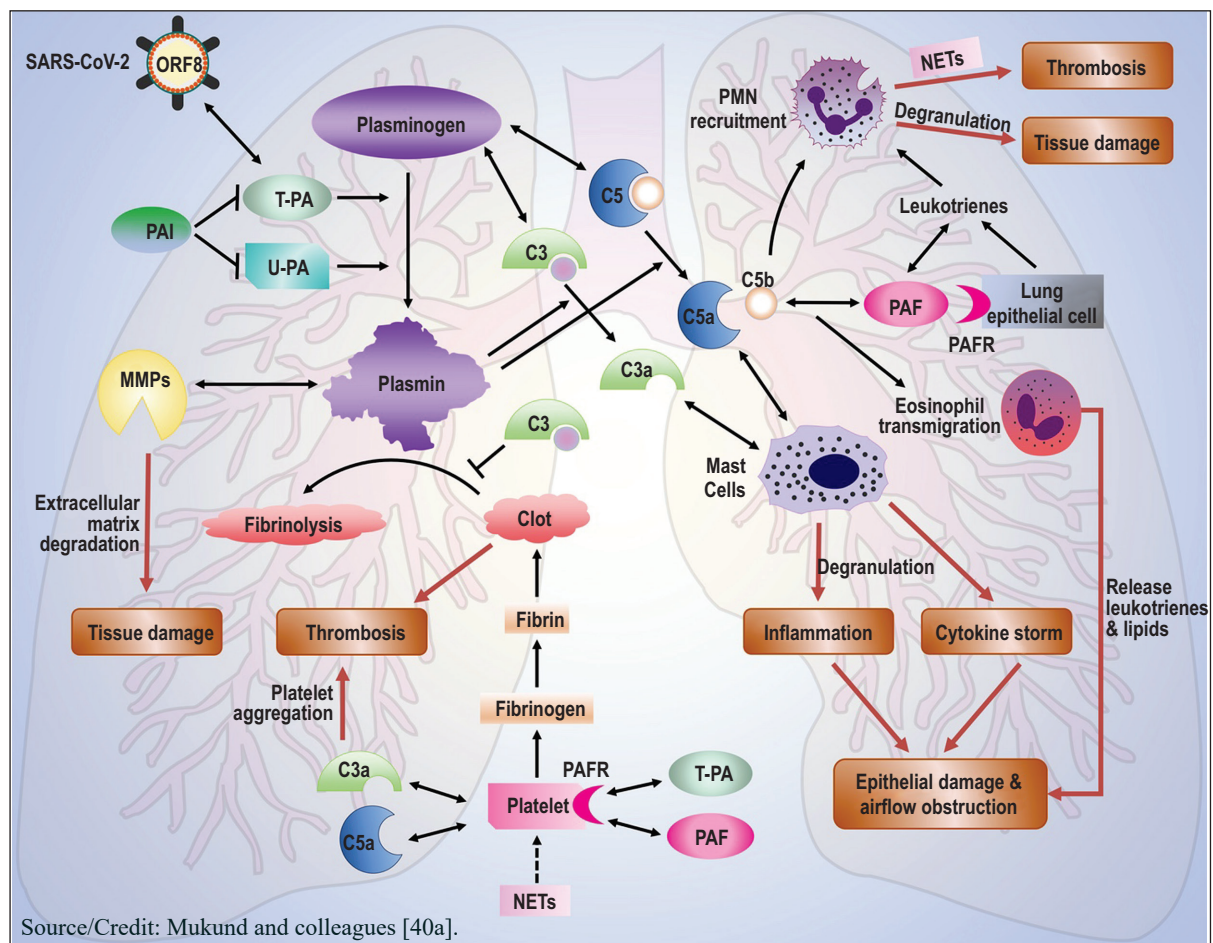
According to Ji and colleagues, four viral proteins are essential for the pathogenesis of COVID-19 [32]:

1. S proteins that bind to ACE2 receptors after being cleaved by furin-like proteases;
2. RNA-dependent RNA polymerase (RdRp, which is responsible for replicating SARS-CoV-2 RNA genome);

3. 3C-like and papain-like proteases that cleave two polyproteins, which are important for the packing new virions;
4. Plasmin and other host proteases cleave additional viral proteins that are not known.

The SARS-CoV-2 has a similar receptor-binding domain in the spike (S) protein for host ACE2 (angiotensin-converting enzyme 2) proteins [33-35]. So, the S protein of SARS-CoV-2 binds to human ACE2 receptors with higher affinity and this might be a furin-like cleavage site (682RRAR/S686) inserted in the S1/S2 protease (S1 region of the spike protein is responsible for binding to the host cell ACE2 receptor, where the S2 region is responsible for fusion of the viral RNA and cellular membranes) of the SARS-CoV-2 virus (Figure 5) [36]. The expression of furin-like proteases could increase SARS-CoV-2 cell and

Figure 5. The role of plasmin in the increase of SARS-CoV-2 cell and tissue tropism due to the expression of furin-like proteases.



tissue tropism and transmissibility, and enhance its pathogenicity, as well as possibly increasing the virus’ ability to attach and invade human cells expressing ACE2 and CD147 receptors [37-39].

The presence of significant increases in the fibrin degradation products (FDPs) elevates the serum D-dimer levels, prolongs prothrombin time, and decreases the platelets, which are consistent with the presence of hyperfibrinolysis and coagulation activation in patients with severe COVID-19 infection [29, 40-44].

The Role of Plasmin(ogen)

Plasmin is an important key in fibrinolysis, improving the virulence and pathogenicity of viruses carrying a furin-site such as SARS-CoV-2 [40]. According to Ji and colleagues [40], elevated plasmin(ogen) is a common characteristic in people with comorbidities such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic renal illness. These groups are especially susceptible to SARS-CoV-2 infection since the plasmin raises the virulence and infectivity of the SARS-CoV-2 virus by cleaving its spike proteins. And highly increased D-dimer in COVID-19 patients is the result of plasmin-associated hyperactive fibrinolysis. So, D-dimer and viral load are independent risk factors of disease severity and mortality.

Clinical Disease Course of COVID-19

Figure 6 summarizes the clinical course of COVID-19 infected patients according to survivors and non-survivors, related to the stage of the disease [45].

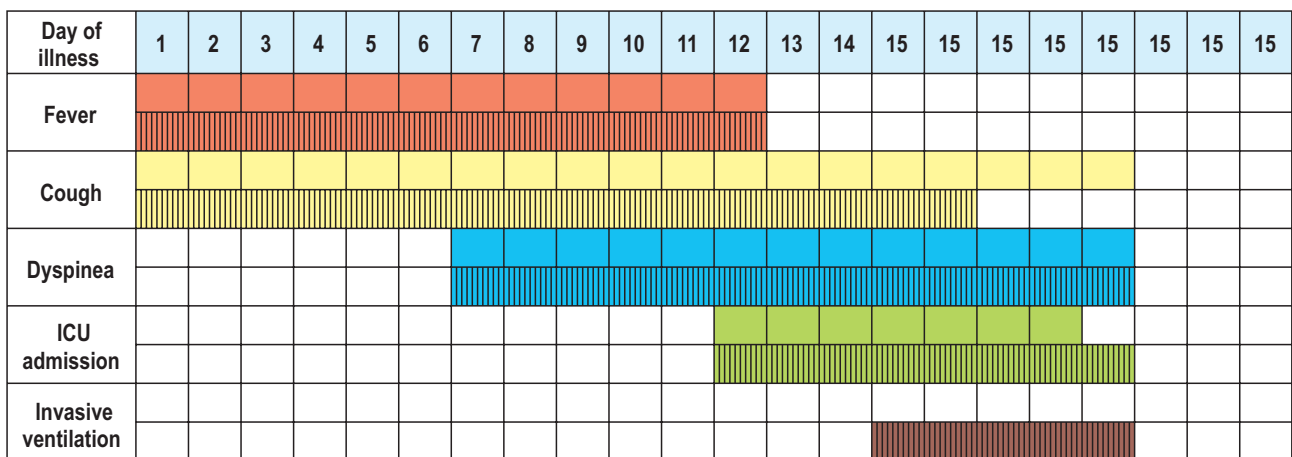
Clinical Manifestations and Symptoms of COVID-19 Infection

In our review, we found several studies with clinical manifestations of COVID-19. We then chose the major authors and discussions about the symptoms, the stage of the disease in which they occur, the laboratory abnormalities, and the implications for the patients (Table 1 and Figure 7).

In a meta-analysis, Nascimento, and colleagues [46] present the most common symptoms in patients with SARS-CoV-19 infection:

- Fever (82%);
- Dry cough (61%);
- Muscle aches (myalgia) and/or fatigue (36%); and
- Dyspnea (26%); and
- Chest images abnormalities: bilateral opacities, multiple ground-glass shadows/opacities, septal thickening, and parenchymal consolidation.

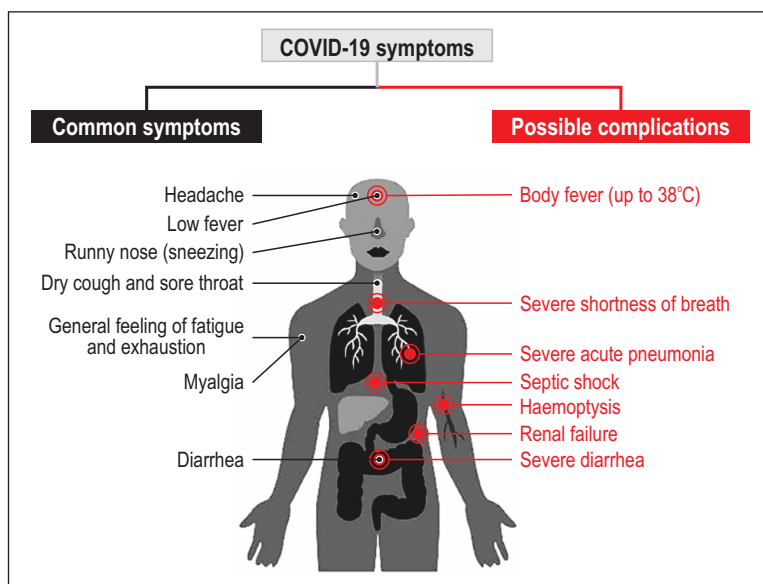
Figure 6. Summary of the clinical course and the main symptoms of COVID-19 patients.



The solid colors and cross-hatched patterns indicate the survivors (n = 137) and non-survivors (n = 54), respectively. Source/Credit: Kakodkar and colleagues [45].

Table 1. Clinical symptoms of patients with COVID-19 infection [66].

Study	Chen and colleagues [30]	Huang and colleagues [22]	Chung and colleagues [67]
Patient count	99	41	21
Age (mean, year)	55.5	49	51
Fever	83%	98%	67%
Cough	81%	76%	43%
Shortness of breath	31%	55%	-
Myalgia	11%	44%	3%
Haemoptysis	-	5%	-
Sputum production	-	28%	-
Confusion	9%	-	-
Sore throat	5%	-	-
Rhinorrhoea	4%	-	-
Chest pain	2%	-	-
Diarrhea	2%	1%	-

Figure 7. The most common symptoms of COVID-19 based on WHO.

McIntosh [47] and Wang and colleagues [29] also described the clinical features in COVID-19 infection:

- Pneumonia seems to be the most common and severe manifestations of COVID-19, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging]. Notwithstanding, there are no specific clinical features that can yet reliably distinguish pneumonia from COVID-19 to other viral pneumonia, the presence of dyspnea several days after the onset of initial symptoms is suggestive of COVID-19;
- Fever;
- Headache;
- Dry cough;
- Dyspnea;
- Sore throat, and rhinorrhea [30, 48];
- Myalgias and/or fatigue;
- Gastrointestinal symptoms (nausea and diarrhea, and abdominal pain in severe cases) [22, 29, 49-51];
- Smell or taste disorders (anosmia and dysgeusia) [52-54];
- Sputum production (uncommon; severity cases related the produce sputum due to the

opportunistic disease that could affect the severely ill patients) [22, 29, 55-57];

- Conjunctivitis (uncommon) [58];
- Dermatologic findings (more common in children) (maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis [59-61]; reddish-purple nodules on the distal digits similar in appearance to pernio (chilblains – also called “COVID toes”) have also been described, mainly in children and young adults [62-64].

According to El-Aziza and colleagues in a review study, present [65] the most common symptoms of COVID-19 based on the World Health Organization (WHO) report:

- Fever (88%);
- Dry cough (72%);
- Sore throat (68%),
- Fatigue (38%); and
- Diarrhea (4%);
- Severe shortness of breath (20%) (severity cases);
- Severe headache (13%) (severity cases).

Less common symptoms include headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting [22, 29].

Pulmonary Manifestations

Gulati and colleagues [68] described the studies that researched the pulmonary manifestations caused by COVID-19 and showed the clinical features and important discoveries as follow:

- a. A dry cough is a common symptom, present in 68% of infected patients [29].
- b. Sore throat and sputum production are uncommon (<5%) [48].
- c. The presence of dyspnea is predictive of ICU admission [48].
- d. Hospitalized patients had an abnormal chest computed tomography: ground-glass opacities with a peripheral lung distribution, followed by

consolidation and interstitial abnormalities [22, 29, 48].

- e. Lung histopathology presents diffuse alveolar damage, denuded alveolar lining cells, and interstitial fibrosis [69].
- f. Higher incidence of thromboembolism with an association between elevated D-dimer levels and mortality [44].
- g. Studies speculated that cytokine storms are responsible for lung injury [70,71].
- h. COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptors to enter into cells [5, 72-74].

Specific Features of COVID-19-related SARS

According to the Task Force of Berlin definition, SARS is divided into three stages based on oxygenation index ($\text{PaO}_2/\text{FiO}_2$) on positive end-expiratory pressure (PEEP) ≥ 5 cmH₂O:

- a. Mild ($200\text{mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$);
- b. Moderate ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200\text{mmHg}$); and
- c. Severe ($\text{PaO}_2/\text{FiO}_2 \leq 100\text{mmHg}$) [75].

And also according to the same Task Force, there is a higher incidence of SARS-Cov-2 among hospitalized patients (29%) with higher mortality (15%) [75].

Nevertheless, although the presence of consolidation and exudation in SARS caused from many pathogens might be common, the image of SARS in COVID-19 is not as frequent as in other pneumonia since SARS is a condition associated with many disease processes, resulting in reduced lung compliance and severe hypoxemia (Box 1) [75, 76].

In the early exudative stage, the lungs present diffuse alveolar damage with the destruction of epithelial and endothelial cells, and present dry cough (59.4-82%) as the most common respiratory symptom [22, 29, 30, 44, 48, 76] The chest computed tomography (CT) scans usually showed multifocal bilateral patchy shadows and/or ground-glass opacities; and some patients showed a mixed pattern of ground-glass opacities and consolidation (Figures 8 and 9).

Pulmonary and Cardiac Injury Caused by COVID-19

SARS-CoV-2 is primarily a respiratory disease that causes fast pneumonia, and in severe cases can lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes [22]. Despite COVID-19 effecting primary the lungs, COVID-19 is being currently regarded as a systemic disease involving other vital organs, such as heart, liver, and kidneys [79]. We are aware of the role of ACE2 in the disease and how the ACE2 is expressed widely in many organs and tissues, including the cardiovascular, digestive, and urogenital systems besides the respiratory tract [80, 81]. However, it remains unclear if the organ and tissue injury in patients with COVID-19 is a direct or indirect consequence of the virus infection. Theoretically, the virus may target those organs and tissues with positive expression of ACE2. As we described in the cytokine storm, the viral

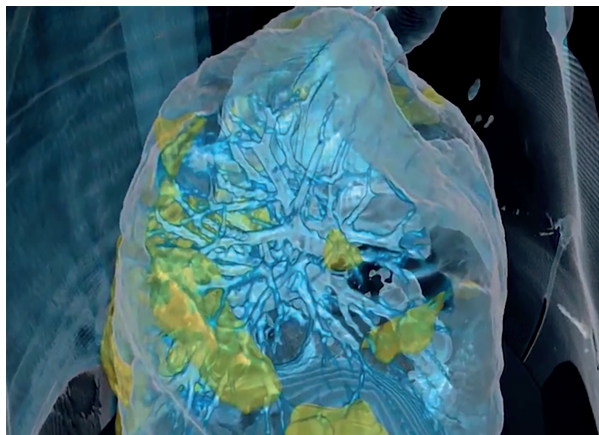
infection induces an excessive immune reaction in the host, which leads to damage in the organ. Nonetheless, the pulmonary events can trigger the “Lung-Heart” syndromes with a combination of the respiratory and cardiovascular adverse events and conditions (Figure 10) [82, 83]. Seeing as many severe patients have cardiovascular disease (CVD), including hypertension, acute cardiac injury, and myocarditis, the cardiac damage may be secondary to the lung disease, since acute lung injury itself leads to increased cardiac workload. That can be problematic especially in patients with pre-existing hypertension or CVD, which may also be the important (patho)physiological role of the RAS/ACE2 in the cardiovascular system since ACE2 is expressed in the human heart, vascular cells and pericytes [84-87]. For instance, SARS-CoV-2 infection injures the myocardium, leading to elevated levels of myocardial biomarkers (e.g., troponin I > 28 pg/mL) and certain abnormalities

Box 1. Summary of characteristics of COVID-19-related ARDS.

Specific features of COVID-19-related ARDS	Differences from ARDS caused by other factors
<ul style="list-style-type: none"> • Injury site <ul style="list-style-type: none"> • Mainly respiratory system • Alveolar epithelial cells • Specificity of clinical features <ul style="list-style-type: none"> • Clinical symptoms were inconsistent with the severity of laboratory and imaging findings • Clinical manifestations were relatively mild 	<ul style="list-style-type: none"> • Timing of onset <ul style="list-style-type: none"> • 8-12 days • Respiratory system compliance <ul style="list-style-type: none"> • Lung compliance might be relatively normal in some COVID-19-related ARDS patients • Severity based on oxygenation index <ul style="list-style-type: none"> • Three categories (PEEP ≥ 5cmH₂O) <ul style="list-style-type: none"> • Mild (200mmHg ≤ PaO₂/FiO₂ < 300mmHg) • Mild-moderate (150mmHg ≤ PaO₂/FiO₂ < 200mmHg) • Moderate-severe (PaO₂/FiO₂ < 150mmHg) • Management protocols <ul style="list-style-type: none"> • HFNO <ul style="list-style-type: none"> • HFNO can be safe even in some moderate-severe patients • The timing of invasive mechanical ventilation is very important • Corticosteroids <ul style="list-style-type: none"> • The effects of corticosteroids were uncertain

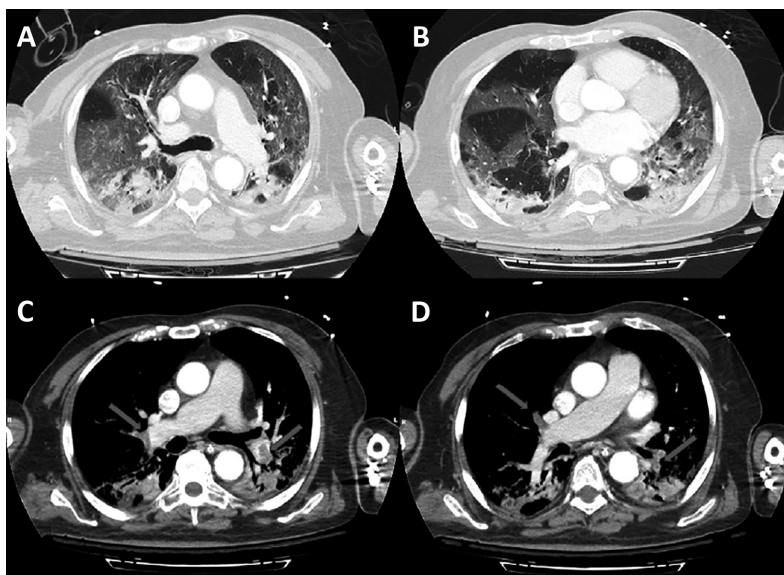
Source/Credit: Li and Ma [76].

Figure 8. 3D model based on computerized tomography scans presents extensive lung damage (yellow) in a patient with COVID-19.



Source/Credit: Wadman and colleagues [77].

Figure 9. Axial contrast-enhanced computer tomography (CT) of the chest.



A, B, Diffuse bilateral ground-glass opacities and small bibasilar consolidations compatible with COVID-19 pneumonia. C, D, Filling defects consistent with pulmonary emboli within the right upper lobe, right middle lobe, right lower lobe, and left lower lobe pulmonary arteries (arrows).
Source/Credit: Lushina and colleagues [78].

in electrocardiography and echocardiography, but the mechanisms still remain largely unclear (Figure 11).

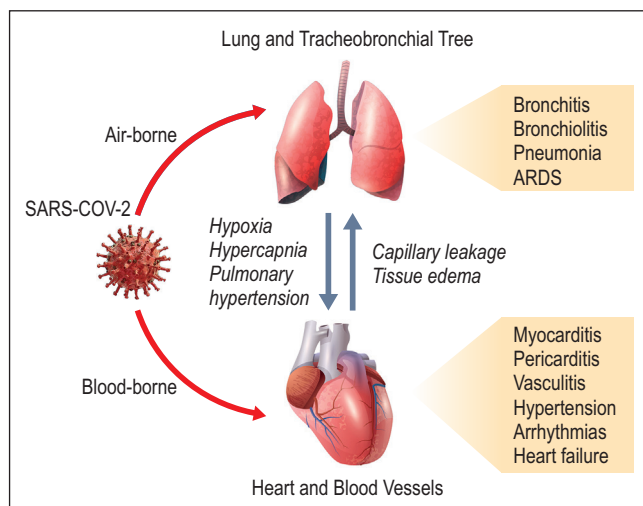
Wu and colleagues [88] showed that the lung and cardiac tissues contain significant amounts of inflammatory infiltrations, indicating the inflammatory nature of tissue damage by SARS-CoV-2 infection. In autopsy reports, COVID-19-induced pulmonary and myocardial injury, and the

lungs presented: edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells [88].

Cardiovascular Manifestations

Gulati and colleagues [68], as well as the European Society of Cardiology [10] summarized

Figure 10. Schematic demonstration of the viral injury to the lung and heart triggering the “Lung-Heart” syndromes.

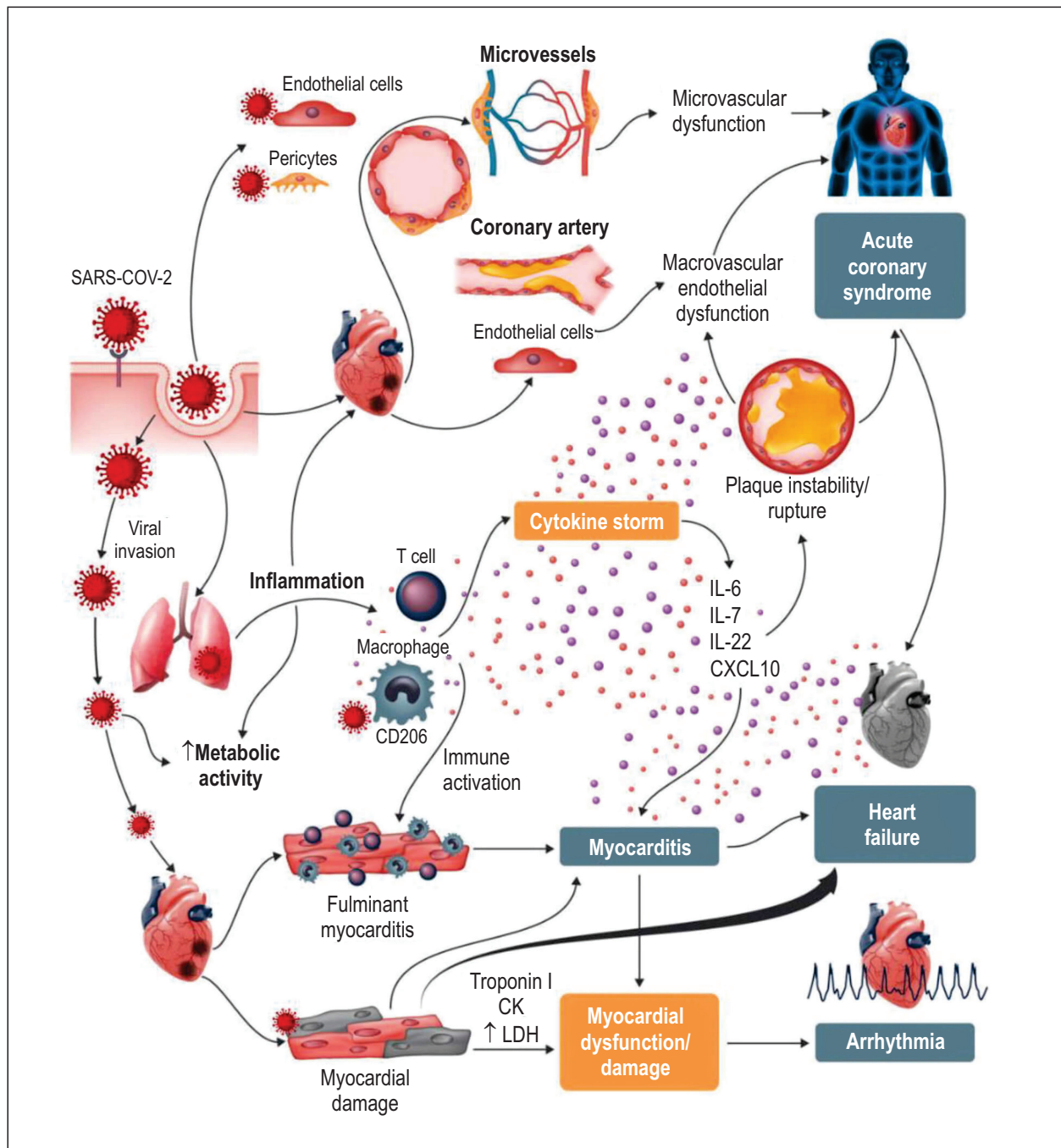


Source/Credit: Adapted from Geng and colleagues [89].

the cardiovascular manifestations and important issues related to COVID-19 and the cardiovascular system as follow:

- a. The SARS-CoV-2 attaches to the host receptor ACE2 for mediate entry into cells. ACE2, which is expressed in the lungs, heart, and vessels, is an important member of the renin-angiotensin system (RAS), and critical in the pathophysiology of cardiovascular disease (CVD);
- b. CVD and COVID-19 likely implicates in the dysregulation of the RAS/ACE2 system because of SARS-CoV 2 infection and the comorbidities, such as hypertension;
- c. CVD may be the earliest aspect in COVID-19, but may be secondary to acute lung injury, which drives to improved cardiac workload, a critical problem in patients with pre-existing hypertension;
- d. ACE2 (receptor of COVID-19) is expressed in the myocardium, which could head to myocardial damage;
- e. Cytokine storm, which starts from an imbalance of T-cell activation with a dysregulated discharge of interleukin (IL)-6, IL-17, and other cytokines, may contribute to CVD in COVID-19;
- f. Immune system overexpressed along with immunometabolism modifications may result in plaque vulnerability, contributing to acute coronary events;
- g. COVID-19 also causes acute cardiac injury in patients with elevated high-sensitivity cardiac troponin-I (hscTnI) levels [22, 90].
- h. CK-MB and hs-cTnI are high in severely ill patients in the intensive care unit (ICU), which suggests myocardial injury [85,91].
- i. Higher cTnI level was also associated with higher complications and mortality [92];
- j. Left ventricular dysfunction, persistent hypotension, acute myopericarditis, myocarditis, arrhythmia, and heart failure have also been reported in COVID-19 patients [29, 91, 93-95].
- k. Interstitial mononuclear inflammatory infiltration in heart tissue also provides evidence of myocarditis in COVID-19 patients [96].
- l. 7% of deaths in COVID-19 patients have been attributed to myocardial injury [97].
- m. Other cardiac manifestations include acute myocardial infarction, fulminant heart failure, and dysrhythmias [98].
- n. Arrhythmia with COVID-19 infection was >17% in some studies [29, 85].
- o. Range from mild chest pain with preserved ejection fraction(EF) to profound cardiovascular collapse requiring extracorporeal membrane oxygenation (ECMO).
- p. Echocardiography may show a regional wall motion abnormality or global hypokinesis with or without pericardial effusion [99, 100].
- q. Initial electrocardiogram may show low voltage QRS complexes in the limb leads, ST-segment elevations in leads I, II, VL, V2-V6, and PR elevation and ST depressions in aVR [99, 100].

Also, Gulati and colleagues [68] proposed the mechanisms of cardiac injury in patients with COVID-19 that include overexpression of ACE2 in patients with chronic cardiovascular disease,

Figure 11. Cardiovascular damage in COVID-19.

SARS-COV-2 anchors on transmembrane ACE2 to enter the host cells including type-2 pneumocytes, macrophages, endothelial cells, pericytes and cardiac myocytes lead to inflammation and multi-organ failure. Infection of endothelial cells or pericytes is of particular importance because this could lead to severe microvascular and macrovascular dysfunction. In addition, immune over-reactivity can potentially destabilize atherosclerotic plaques and explain the development of acute coronary syndromes. Infection of the respiratory tract, particularly type-2 pneumocytes, by SARS-COV-2 is manifested by the progression of systemic inflammation and immune cell overactivation leading to "cytokine storm", resulting in increased levels of cytokines such as IL-6, IL-7, IL-22 and CXCL10. Subsequently, it is possible that activated T cell and macrophages may infiltrate infected myocardium resulting in the development of fulminant myocarditis and severe cardiac damage. This process may be further intensified by a cytokine storm. Similarly, the viral invasion may cause cardiac myocyte damage directly leading to myocardial dysfunction and contribute to the development of arrhythmias. From Guzik et al., COVID-19 and the Cardiovascular system - implications for risk assessment, diagnosis and treatment options. *Cardiovasc Res.*, 2020, doi: 10.1093/cvr/cvaa106.

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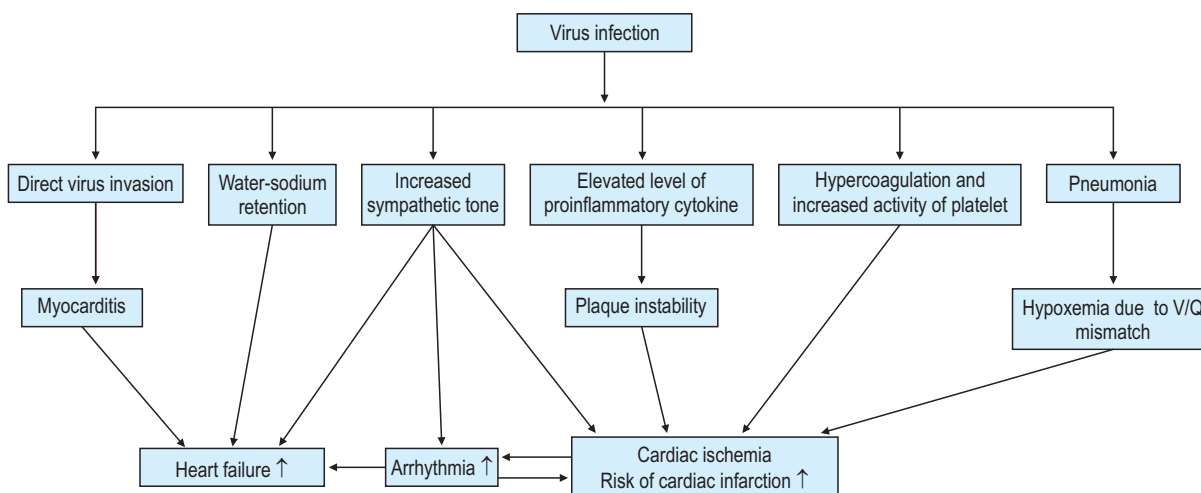
cytokine storm triggered by an imbalanced response by type 1 and type 2 helper cells, hypoxemia resulting in myocardial damage, plaque rupture, coronary vasospasm, or direct vascular injury [22, 85]. They also explained the possible complex interplay between the immunologic deregulation of the cytokines and T cells and the underlying cardiovascular or related metabolic conditions. Virally-induced systemic inflammation may also promote coronary plaque rupture and have a pro-coagulant effect necessitating the intensification of medical therapy [101].

As previously explained, cardiovascular cells also express ACE2 at high levels, which has a role in regulating blood pressure and cardiac contractility [102]. COVID-19 infection, therefore, might trigger a drastic immune response which leads to the “cytokine storm” and subsequently the injure of cardiac tissue [103, 104]. Cytokine storm is a clear contributor to COVID-19-related myocardial injury, demonstrated by Wu and colleagues in a study that showed the association of the increasing levels of IL-6 and high hs-TnI levels [88], a cardiac-selective biomarker of myocardial infarction and injury [105], which is significantly increased in severe or deceased COVID-19 patients when compared to patients with milder symptoms [22, 29, 92, 106, 107].

Also, elevated NT-proBNP levels had to be noticed since patients with elevated cTnI were more likely to have elevated levels of NT-proBNP2 [92]. All these findings suggest the relationship between cardiac injury, cardiac dysfunction, and poor outcome, and monitoring cardiac troponin I during hospitalization may help predict the progression of the disease [107].

The mechanism of cardiac complications is not completely defined, however, the systemic and overexpressed inflammatory responses due to pneumonia, which is a highly pro-inflammatory disease [95], and elevated levels of cytokines (C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), procalcitonin, interleukin-1beta (IL-1 β), Tumor necrosis factor-alpha (TNF- α), Interleukin-10 (IL-10) [22, 30, 108], the direct damage by the virus [96, 102], the instability of coronary plaque and hypoxia (The instability of coronary atherosclerotic plaques [109], the increased coagulation activation and platelet-aggregating activity [110], and hypoxemia due to abnormal ventilation/perfusion(V/Q) lead to decreased myocardial oxygen supply and myocardial ischemia [92] (Figure 12). According to Ma and colleagues [111] cytokines have an important role in infection control, but they can also lead to tissue

Figure 12. Possible mechanisms of cardiac complications in patients with COVID-19.



Source/Credit: Ma and colleagues [111].

damage and dysfunction. The level of cTnI was positively associated with plasma high-sensitivity CRP2, which suggested the possible role of an inflammatory storm in the development of cardiac injury. TNF- α had been detected in patients with heart failure [112] and the positive correlation between TNF- α expression and the severity of heart failure, left ventricular dilation/hypertrophy and dysfunction was confirmed [113-115]. Increased level of IL-1 β was found in patients with acute myocarditis [96] and elevated concentration of IL-6 was detected in patients with acute myocardial infarction and heart failure [96]. The level of IL-6 predicted the adverse cardiovascular events following acute coronary syndrome and chronic heart failure [116, 117]. Serum IL-8 level elevated in patients with acute myocardial infarction is associated with mortality in patients with acute coronary syndrome [119]. IL-10 was increased in patients with acute myocarditis [120] and it predicted the poor outcome of Takotsubo cardiomyopathy [121]. So the virus triggers a series of immune responses and the production of cytokines storm may contribute to the systemic presentation and multiple organ dysfunctions.

Thromboembolic Manifestations

The lungs are unequivocally the most affected organ in COVID-19, followed by heart, liver, kidney, and brain. But even though COVID-19 is characterized by hyperfibrinolysis, as evidenced by elevated levels of D-dimer, systemic microthrombi in the circulatory system and hemorrhages that affect the organs have been recorded to happen as a result of noncoordinated responses between the coagulation and fibrinolysis systems [40].

Coagulopathy

Coagulopathy usually increases the D-dimer concentration in patients with COVID-19, a moderate decrease in platelets, and a prolongation of the prothrombin time [122]. Coagulopathy in COVID-19 cases seems to be a combination

of disseminated intravascular dissemination (DIC) and localized pulmonary thrombotic microangiopathy, which in severe patients can have a considerable impact on organ dysfunctions. Proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukins (IL), including IL-1 and IL-6, [122], IL-6, are also commonly found in severe Covid cases, and can induce tissue factor expression on mononuclear cells, which in turn activates coagulation and thrombin generation. TNF- α and IL-1 are the principal mediators stimulating the suppression of endogenous anticoagulant pathways. According to Levi and colleagues, as well as other previously mentioned authors, the patients most severely affected by COVID-19 can present a cytokine storm profile characterized by high concentrations of proinflammatory cytokines and chemokines [123, 124]. COVID-19 infections are also known to cause the activation of the fibrinolytic system. Researches in urokinase-type plasminogen activator knock-out mice showed a urokinase-driven pathway stimulating fibrinolysis as a critical factor in lethality. Additionally, patients infected with human severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) had plasma concentrations of tissue-type plasminogen activator (t-PA) 6-times higher than patients with no infection (appendix).

Inflammation-induced endothelial cell injury could result in a large release of plasminogen activators, which could justify the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19 [122]. Thrombotic microangiopathy is typically caused by pathologically enhanced platelet-vessel wall interaction due to ultra-large von Willebrand factor multimers. The coagulation abnormalities seen in COVID-19 propose a hypercoagulable state and are compatible with an enhanced risk of venous thromboembolism/thromboinflammation or COVID-19-associated coagulopathy (CAC) [78, 125-129]. Elevated levels of D-dimer (D-dimer is a degradation product of cross-linked fibrin indicating increased

thrombin generation and fibrin dissolution by plasmin) are one of the major contributors to clot formation in severe COVID-19 infection [128], and can lead to pulmonary embolism and acute stroke (even in patients younger than 50 years of age without risk factors), as well as the formation of microthrombi and limb ischemia [124, 125, 130-132].

Clinical Features

VTE — Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is very common in ICU patients.

Arterial events — There are also reports of arterial thrombosis, including in the central nervous system (CNS) (Figure 13).

CNS — acute ischemic stroke associated with COVID-19 over a two-week period, with symptoms suggesting large-vessel occlusion [133].

Limbs —limb ischemia [134].

Microvascular thrombosis —microvascular thrombosis in the lungs [129, 135].

Bleeding — Bleeding is less common than clotting in patients with COVID-19, but it may occur, especially in the setting of anticoagulation.

The laboratory findings for coagulation abnormalities in COVID-19 are [136]:

- Prothrombin time (PT) and aPTT normal or slightly prolonged;
- Platelet counts normal or increased (mean, 348,000/microL);
- Fibrinogen increased (mean, 680 mg/dL; range 234 to 1344);
- D-dimer increased (mean, 4877 ng/mL; range, 1197 to 16,954);
- Factor VIII activity increased (mean, 297 units/dL);
- VWF antigen greatly increased (mean, 529; range 210 to 863), consistent with endothelial injury or perturbation;
- Minor changes in natural anticoagulants: small decreases in antithrombin and free protein S; a small increase in protein C;
- Reaction time (R) shortened, consistent with increased early thrombin burst, in 50 percent of patients;
- Clot formation time (K) shortened, consistent with increased fibrin generation, in 83 percent;

Figure 13. Catheter-directed cerebral angiography.



A Pre-thrombectomy angiogram demonstrates an occluded distal basilar artery (arrow). B, Postthrombectomy angiogram demonstrates successful restoration of the posterior circulation.

Source/Credit: Lushina and colleagues [78].

- Maximum amplitude (MA) increased, consistent with greater clot strength, in 83 percent;
- Clot lysis at 30 minutes (LY30) reduced, consistent with reduced fibrinolysis, in 100 percent;
- Circulating prothrombotic microparticles;
- Neutrophil extracellular traps (NETs).

Hematology Manifestations

Gulati and colleagues [68], reported in their study the common hematology manifestations as follow:

- Lymphopenia is a frequent finding [48, 137].
- Neutrophilia may help to predict intensive care unit (ICU) admissions.
- Hemoglobin seems to be mostly unaffected by COVID-19 infection.
- DIC is a rare complication [48].
- Mild thrombocytopenia is present in one-third of patients [48].
- Higher levels of D-dimer for patients admitted in ICU [138].
- Thromboembolic events in severe patients with higher PT and d-dimer levels, which indicate the disseminated intravascular coagulation (DIC) or a highly inflammatory state [139].
- Increased levels of circulatory cytokines, ferritin, C-reactive protein, and procalcitonin also seem to correlate with the severity of the disease [15, 140].

Gastrointestinal Manifestations

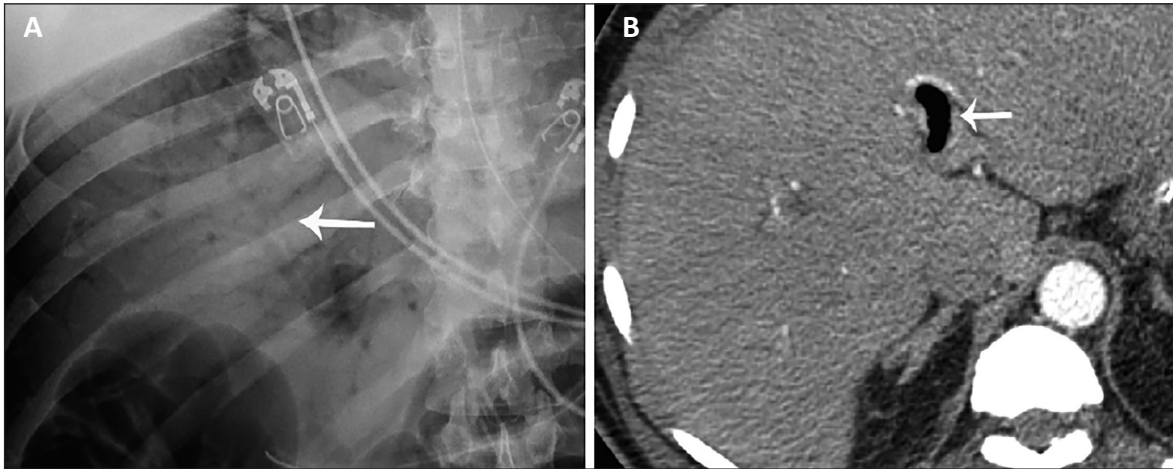
The symptoms of SARS-CoV-2 infection could vary, and in addition to affecting respiratory epithelial cells and alveolar cells, there is evidence that the virus could affect the digestive system [31]. In the intestines, ACE2 plays an important role in maintaining amino acid balance and regulating the expression of antimicrobial peptides and the equilibrium of the intestinal flora. The evidence shows the viral nucleic acid detected in stool specimens of patients with COVID-19, which explains the occurrence

of diarrhea in coronavirus infection. Wong and colleagues [141] showed that SARS-CoV-2 encodes and expresses the spike (S) glycoproteins which bind to ACE2. So, the expression of viral nucleocapsid protein in the gastric, duodenal, and rectal epithelium is visualized in COVID-19 [142]. It might explain diarrhea in infected-COVID-19 patients. The SARS-CoV-2 binds the cell-surface receptor ACE2, which regulates the intestinal inflammatory response, and enters into the cell. They also showed that ACE2 expression is high in epithelial cells in proximal and distal intestines, and because the intestinal epithelium is in direct contact with exogenous pathogens, the cells there could be the first affected by the virus after the consumption of SARS-CoV-2-infected wild animals. That is why diarrhea can be an important sign of infection and clinical manifestation [31, 143].

Studies pointed to the increased recognition of gastrointestinal symptoms in COVID-19 patients (> 50%) [144], and sometimes this is the only symptom of the patients [29, 144]. Loss of appetite and diarrhea are the usually reported symptom, with vomiting and abdominal pain being less frequent [22, 29, 48, 144]. The gastrointestinal symptoms may delay seeking medical care [8x] because patients do not correlate GI with COVID-19. The virus is detectable in stool in more than 50% of COVID-19 patients [22], and the feces remains positive for as long as four weeks [145]. It is not clear if the fecal-oral route is a significant manner of transmission.

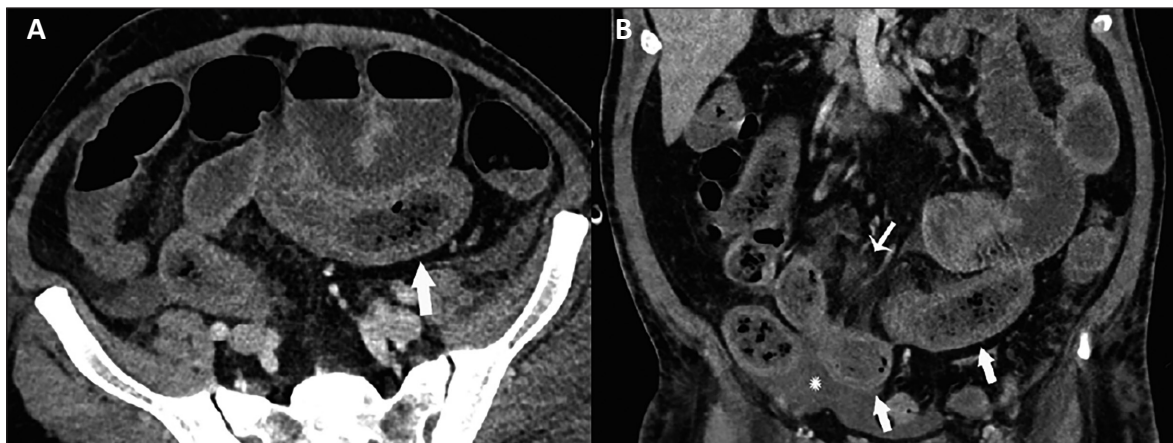
Bhayana and colleagues [146] reported in a study with 412 patients, of which 34% had gastrointestinal symptoms, similar to recent reports [49, 147]. CT was the most commonly performed exam for abdominal pain or sepsis, and for elevated liver enzymes, the ultrasound. Such were the findings: bowel wall thickening, pneumatosis, and portal venous gas (Figures 14 and 15). Pneumatosis and portal venous gas were frequently present in patients with mesenteric ischemia [148]. All the findings suggest that SARS-CoV-2 has a direct inflammatory effect on vascular endothelium [149, 150], and systemic coagulopathy is common in critically ill patients

Figure 14. Abdominal radiograph (A) in a 52-year-old man demonstrates portal venous gas (thin arrow in A), suggestive of bowel infarction. Post-operative CT (B) also demonstrates portal venous gas (thin arrow in B).



Source/Credit: Bhayana and colleagues [146].

Figure 15. Axial (A) and coronal (B) CT of the abdomen and pelvis with IV contrast in a 57-year-old man with a high clinical suspicion for bowel ischemia. There was generalized small bowel distension and segmental thickening (arrows), with adjacent mesenteric congestion (thin arrow in B), and a small volume of ascites (* in B).



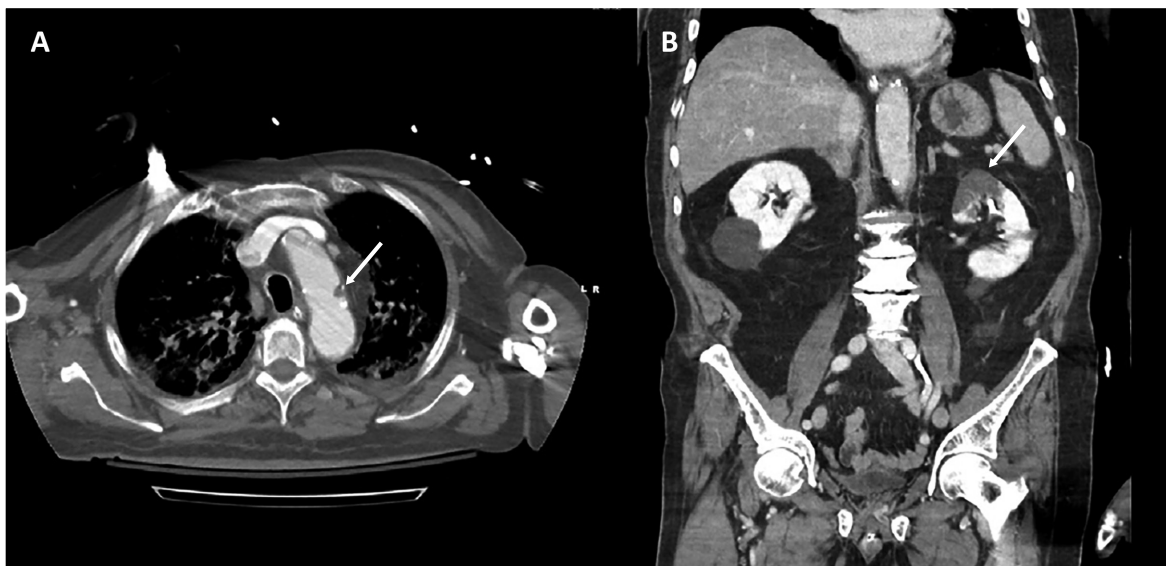
Source/Credit: Bhayana and colleagues [146].

with COVID-19 [41]. This can be supported by descriptions of microvascular injury and vascular imaging abnormalities [146].

Renal Manifestations

According to Gulati and colleagues [68], acute renal dysfunction in COVID-19 in early stages is not uncommon [151, 152]. The incidence of acute kidney injury is around 15% with a

high mortality rate of 60%-90% [30, 44]. Other clinical manifestations have been reported such as albuminuria or proteinuria on admission (44%-63%), hematuria (27%), elevated urea (13%-27%), and creatinine (14%-19%), and low eGFR (13%) [152]. Images evidence present active renal edema and inflammation, and renal infarct (Figure 16) [152]. Renal involvement is associated with a worse prognosis [30, 44, 153]. The SARS-COV-2 has been detected in renal tissue and the urine

Figure 16. Renal infarct.

A, Axial contrast-enhanced CT of the chest demonstrates a filling defect in the aortic arch (arrow) consistent with thrombus. B, Coronal contrast-enhanced CT of the abdomen and pelvis demonstrates a wedge-shaped low-attenuation region in the superior pole of the left kidney (arrow) consistent with renal infarct.
Source/Credit: Lushina and colleagues [78].

[154], and the presence of ACE2 receptors in the Leydig cells and seminiferous tubules, it could lead to a testicular injury [155].

Li and colleagues [156] reported in a retrospective analysis that the proportion of patients with acute renal insufficiency (ARI) was low, although the mortality rate was high (>90 %). Also, Fan and colleagues in another study reported that besides severe respiratory dysfunction, 3% - 10% of the patients showed renal insufficiency, and 7 % had acute kidney injury, and had ACE2 highly expressed in renal tubular cells, mesenchymal cells, and testicular and vas deferens cells [155]. The viral nucleic acid was isolated from the urine samples of SARS-CoV-2 patients, which indicate that the kidney's injury is high or occurs after the SARS-CoV-2 infection. Both viral infection and antiviral therapy have potential nephrotoxicity and may cause kidney injury, according to Zhang and colleagues [31].

Hepatic Manifestations

Zhang and colleagues also analyzed the effects of the virus Cov (SARS-COV-1, MERS, and SARS-

COV-2) on the liver and concluded that this VIRUS can alter liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 14%-53% of the cases, and in patients with SARS-CoV-2 and it is present hepatic pathologies disorders (chronic viral hepatitis, nonalcoholic fatty liver disease, alcoholic hepatitis, immune-mediated liver disease) in 2%-11% of the cases [31].

Gulati and colleagues [68] analyzed studies available for hepatic manifestation in COVID-19, and calculated 51% of patients with COVID-19 as having an abnormal liver function on admission (elevated liver enzymes, bilirubin, and LDH levels) [157], and the liver dysfunction may be related to damage to the cholangiocytes lining the biliary epithelium, due to the higher expression of ACE2 receptors [15]. They also reported that patients with fatty liver disease have been seen to have about a 6-fold higher chance of severe disease in the presence of coexisting obesity [48].

Pathogenetic Hypothesis

The hepatic involvement seems to have a multifactorial origin [158]:

- a. Direct damage: caused by the binding of the virus to ACE2 receptors expressed in lung, kidney, and gastrointestinal tract, and endothelial cells of the liver [12, 159, 160];
- b. Intestinal translocation: In the patients that have diarrhea (2%-10%), SARS-CoV-2 RNA has been detected in blood and stool samples, which demonstrates how its RNA could “translocate” from the intestinal lumen [154, 161-163].
- c. Drug hepatotoxicity: Zhang and colleagues [161] observed that liver function tended to alter during and after the infection with COVID-19. They have a hypothesis that it could be a “residual effect” due to the drugs taken during the infection, as a side effect of the therapies used against the infection. This theory is also reinforced by Rismanbaf and colleagues [164]. Liu and colleagues [165] analyzed 32 patients and observed that liver damage was prominent in severe patients under medical therapy; and
- d. Immune-mediated inflammation: the “cytokine storm”, especially, in severe forms of COVID-19 may cause liver damage [123] due to increased levels of interleukin (IL)-2, IL-7, IL-6, interferon- γ , and tumor necrosis factor- α [166].

Wang and Chai [167] performed RNA sequencing and found specific ACE2 expression in bile duct cells, suggesting that it is important to monitor the liver function of SARS-CoV-2 patients, especially liver indicators involving bile duct function. In the case of liver dysfunction, targeted treatment and care should be given promptly [31,168]. According to Zhang and colleagues [31], ACE2 expression in the lungs reduces SARS-CoV-2 spike protein-induced lung injury via the renin-angiotensin system. Wang and colleagues presented RNA sequencing analysis in patients with inflammatory bowel disease (IBD) or colitis and showed that ACE2 expression in colon cells was positively correlated with the regulation of viral infection and congenital cellular immunity and was negatively correlated

with viral transcription, protein translation, phagocytosis, and complement activation [15x]. So, ACE2-mediated SARS-CoV-2 infection may be a double-edged sword concerning susceptibility and immunity [31].

Neurologic Manifestations

The neurological symptoms of COVID-19 include dizziness, headache, nausea, vomiting, and hypoesthesia (hyposmia, hypogeusia, and hypopsia), which may indicate that the virus enters the CNS and causes injury in nuclei or neural circuits. This is confirmed by postmortem studies of COVID-19 patients with neurological symptoms [169, 170]. The development of hyposmia, hypogeusia, and hypopsia could be a sign of the presence of the virus in CNS via intranasal and oral routes [171].

Gulati and colleagues [68], summarized the neurologic manifestations of COVID-19:

- a. Anosmia
- b. Dysgeusia [172].
- c. Acute cerebrovascular accidents, altered mental status, and myopathy occurred in approximately one-third of patients.
- d. Confusion and agitation (most common neurologic symptoms)
- e. Corticospinal tract signs: increased deep tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes [173].
- f. Acute hemorrhagic necrotizing encephalopathy [174].
- g. Guillain-Barré syndrome: lower-limb weakness and paresthesia as well as facial diplegia and ataxia [171].
- h. Neurological involvement affected more patients with severe COVID-19, and patients with central neurologic symptoms also had severe lymphopenia, thrombocytopenia, and uremia [171].
- i. The magnetic resonance imaging (MRI) currently presents leptomeningeal enhancement with bilateral frontotemporal hypoperfusion [173].

- j. Electroencephalography showed mostly nonspecific changes with findings consistent with encephalopathy.
- k. Cerebral spinal fluid (CSF) analysis may show oligoclonal bands or elevated IgG levels, however, the significance of these findings is uncertain.
- l. Ocular manifestations of COVID-19 need attention. Studies with animals demonstrated that ACE2 and TMPRSS2 (Transmembrane Serine Protease 2) are also expressed in the conjunctiva [91]. The conjunctivitis is present in 31.6% of COVID-19 patients but is common in patients with severe disease or as an initial presentation of the disease [97].
- m. SARS CoV-2 has been isolated from conjunctival swabs [91].

The pathology of severe viral infections is closely associated with the development of a systemic inflammatory response syndrome (SIRS) [175].

Viral Encephalitis

Encephalitis is inflammatory lesions in the brain parenchyma caused by pathogens, including neuronal damage and nerve tissue lesions [175], characterized by symptoms such as headache, fever, vomiting, convulsions, and consciousness disorders [176]. SARS-CoV-2 can cause encephalitis as described in the Xiang and colleagues study [177]. Also, patients with severe COVID-19 infection often suffer from hypoxia and viremia [178], which has the potential to cause toxic encephalopathy, characterized by headache, dysphoria, mental disorder, and delirium, loss of consciousness, coma, and paralysis [179-181]. Moreover, patients with COVID-19 (40%) have headaches, disturbed consciousness, and other brain dysfunction manifestations [132].

Acute Cerebrovascular Disease

The infection by SARS-CoV-2 has been widely reported to lead to an acute cerebrovascular disease due to the cytokine

storm syndromes, [123, 182]. Also, critically ill patients with severe SARS-CoV-2 infections often show elevated levels of D-dimer and severe platelet reduction, which may render these patients prone to acute cerebrovascular events [183].

Mechanisms of CoV Infections on the Nervous System Damage (Figures 17 and 18)

Direct Infection Injury

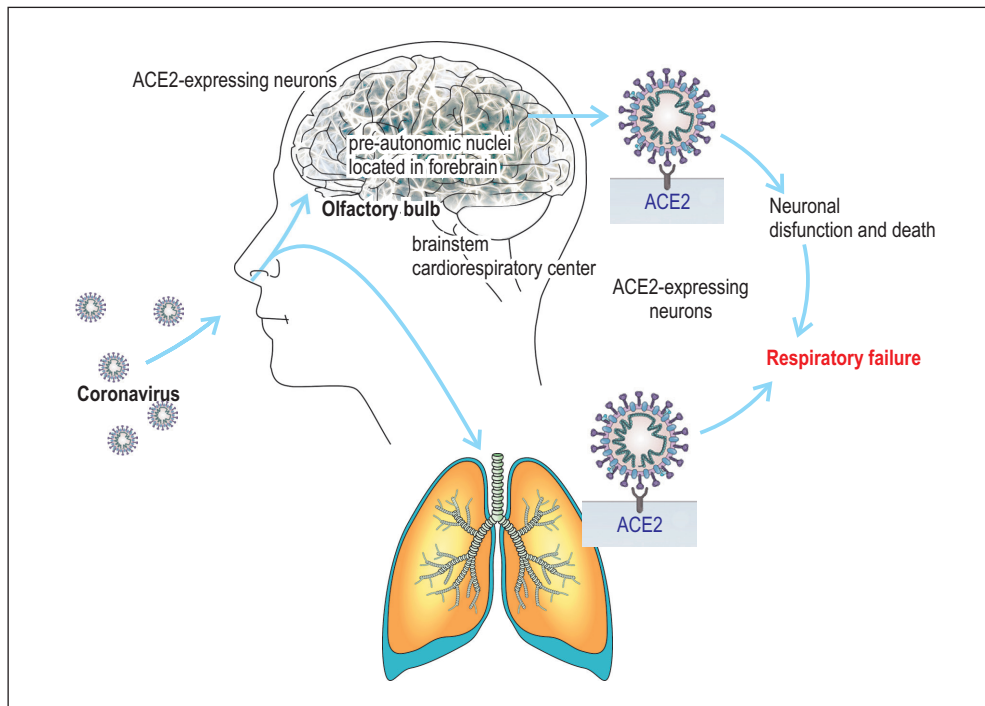
The genetic material of SARS-COV-2 has been detected in nervous system tissue samples (such as cerebrospinal fluid or brain), suggesting the virus invasion in the nervous system, which can cause nerve damage [184, 185].

Blood Circulation Pathway

Although there is rare evidence that SARS-CoV-2 invades the nervous system via the blood circulation pathway [185, 186], however, further studies are needed.

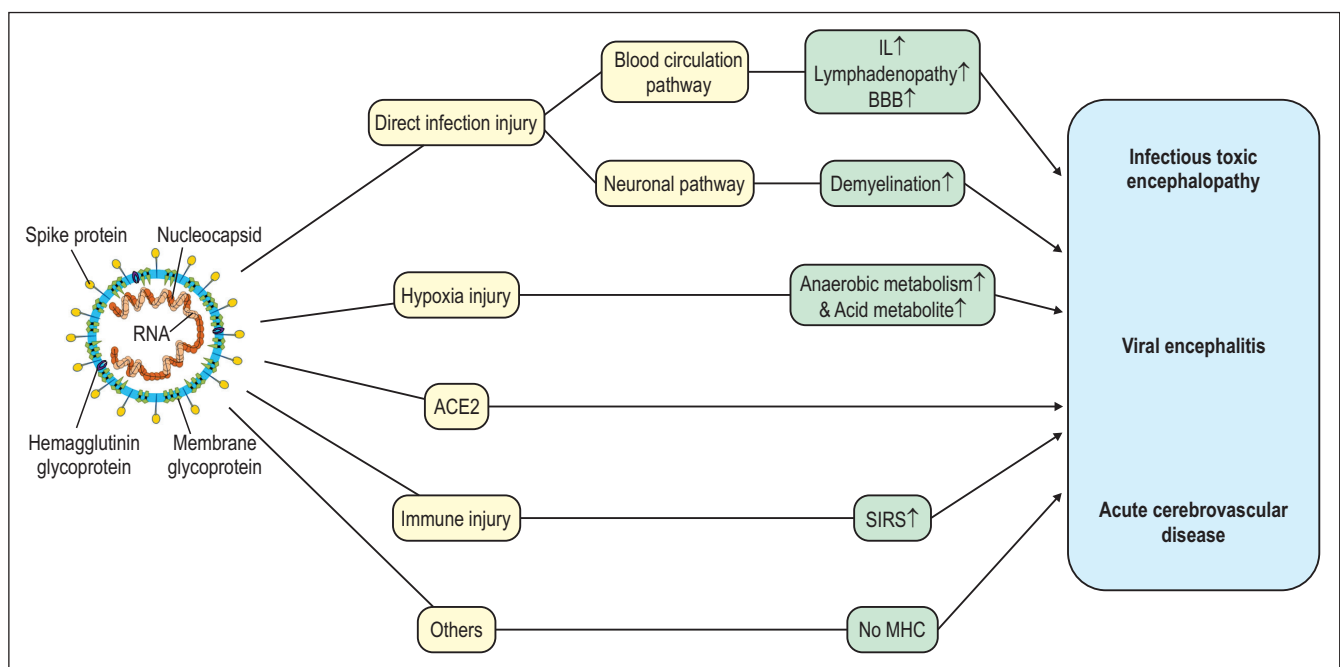
According to Netland and colleagues [187], for penetrating the nervous systems by the hematogenous pathway, the virus must infect the endothelial cells of the blood-brain-barrier (BBB), and then invades the CNS. The entrance of SARS-CoV-2 into human cells is propitiated by ACE2 [9]. Notwithstanding the neural pathway is by the olfactory nerve, there are many infected sites indirectly related to the olfactory bulb that indicate non-neuronal routes for viral infection, such as the hematogenous route. This pathway is following: SARS-CoV-2 encodes the surface glycoprotein spike that binds to ACE2 and mediates viral entry [188]; the spike protein is cleaved by proteases and releases a signal peptide to promote virus entry into host cells [189]. The virus infects the epithelial cells and also the resident, infiltrating, and circulating immune cells, which carry the virus to other systems, causing the extrapulmonary symptoms, including fever, myalgia, fatigue and kidney dysfunctions [151], acute myocardial injury [120], CNS and pulmonary symptoms [77, 132, 142].

Figure 17. The mechanisms of coronaviruses infections and neurological damage caused by coronaviruses.



Source/Credit: Adapted from Wu and colleagues [175].

Figure 18. Pathogenesis of nervous system injury caused by coronaviruses.



ACE2: angiotensin-converting enzyme 2; BBB: blood brain barrier; IL: interleukin; MHC: major histocompatibility complexes; SIRS: systemic inflammatory response syndrome.

Source/Credit: Adapted from Wu and colleagues [175].

Digestive Tract Route

Single-cell RNA sequencing data show a positive correlation between the expression of ACE2 in colon cells with genes controlling virus infection, and innate and cellular immunity [171], but a negative correlation with virus transcription, protein translation, humoral immunity, phagocytosis, and complement activation [190]. Based on these conclusions, Li and colleagues [171] consider SARS-CoV-2 may bind with ACE2 in the gastrointestinal tract and destroy the barrier of gastrointestinal epithelial cells, rise the production of inflammatory cytokines, reduce gastrointestinal absorptive ability, and enhance secretion through the gastrointestinal mucosa. The disorder caused by SARS-CoV-2 infection generates the production of many inflammatory agents, which lead to a cytokine storm. The spike protein of SARS-CoV-2 is different from SARS-CoV-1. In SARS-CoV-2, the spike has a site that is activated by furin, a host cell enzyme that is located in many human tissues, including intestine and lung. The virus gets into the intestines and attaches to specific host-cell receptors in order to enter and infect host cells to produce more virions. When there are sufficient virions expanded, they are released into the enclosing environment where they can infect more resident host cells.

Enteroviruses (poliovirus, coxsackievirus, and echovirus) reproduce in the intestine and can penetrate intestinal epithelial cells [191]. The inflammatory reply to host cell death can reduce the expression of the intestinal barrier proteins ZO-1, occludin, or claudin 3, and disrupts the intestinal barrier [192, 193]. Besides, the inflammatory response can also begin intestinal microbiota disturbance, which aggregates the injury of the intestinal mucosa barrier structure. So, the virus can simply access the blood circulation through the broken intestinal barrier, while viruses in lymphoid tissue can affect distant organs through the lymphatic pathway. The virus can also penetrate local peripheral nerves and after replication can proceed along their axons to the CNS.

However, there is no immediate evidence to prove that SARS-CoV-2 can enter the CNS retrogradely via the intestinal branch of the vagus nerve. The broken gastrointestinal environment may affect the integrity of the BBB through immune, neural, and humoral pathways, thus aiding the passage of the peripheral virus into the CNS [171].

Neuronal Pathway

The neuronal pathway is an important channel for neurotropic viruses to access the CNS. Viruses can move by infecting sensory or motor nerve endings, reaching retrograde or anterograde neuronal transport through the motor proteins, dynein, and kinesins [184, 187]. An example of a neuronal pathway is the olfactory neuron transport. The anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain is a channel between the nasal epithelium and the CNS. It has been proposed that the neural pathway happens after the droplets carrying SARS-CoV-2 land in the nasal cavity and adheres to the nasal mucosa, pharynx, cavum larynges, or trachea. If the virus adheres to the nasal mucosa, it may directly infect olfactory sensory neurons in the olfactory epithelium and then could be moved into the CNS through the olfactory nerve [187, 195]. As a result, the SARS-COV-2 can enter the brain through the olfactory region in the early stages of infection [195, 196] and then cause injuries such as inflammation and demyelinating reaction in the brain in the brain.

About hypogeusia, three cranial nerves are responsible for the sense of the taste: the facial nerve (VII), the glossopharyngeal nerve (IX), and the vagus nerve (X). So, the hypogeusia caused by SARS-COV-2 could result from damage to any of these three nerves (VIII, IX, and X). For hypopsia, there is limited data that supporting direct infection of the optic nerve by SARS-CoV-2, according to research carried out by Shunbun University in Japan [195, 196]. SARS-CoV-2 may cause a neurogenic refractory dyspnea [197, 198]. Also, viruses in neurons “escape from immune

surveillance” and can, therefore, replicate when the immunity of the host is impaired or weakened, which is similar to the varicella-zoster virus [199, 200].

Smell and Taste Dysfunction in Patients with COVID-19

The American Academy of Otolaryngology-Head and Neck Surgery and the British Association of Otorhinolaryngology recommend that these symptoms be added to the list of primary screening symptoms for COVID-19. The conclusion of the lost or reduced ability to smell or taste, resulting from a neurotropic or neurovirulent viral infection targeting the olfactory system, remains incomplete but could be an explanation of neuronal pathway [201].

Hypoxia Injury

The proliferation of SARS-CoV-2 in lung cells causes diffuse alveolar and interstitial inflammatory exudation, edema, and the formation of transparent membranes and these events compromise the gas exchange disorders causing hypoxia in the CNS, increasing anaerobic metabolism in the mitochondria of brain cells [202]. The accumulation of acid can cause cerebral vasodilation, swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion [202]. If the hypoxia continues, it could lead to intracranial hypertension, and brain function deterioration, drowsiness, bulbar conjunctival edema, and even coma [202]. Hypoxia may also induce the occurrence of acute cerebrovascular disease such as acute ischemic stroke.

Immune Injury

According to Wu [175], nervous system damage caused by viral infection may be mediated by the immune system [203]. An over immunity response by the body could be abnormally initiated in severe pneumonia caused by CoV infection [123, 204]. The CoV infections and its ability to infect macrophages, microglia, and astrocytes in the CNS

is important. A neurotropic virus can activate glial cells and induce a pro-inflammatory state [197], such as interleukin (IL)-6, which has an important member of the cytokine storm that is positively correlated with the severity of COVID-2019 symptoms [17]. Additionally, researches have proved that primary glial cells cultured in vitro secrete many inflammatory factors such as IL-6, IL-12, IL-15, and TNF- α after being infected with CoV [205]. Moreover, activation of immune cells in the brain causes chronic inflammation and brain injury.

Still according to Wu, Angiotensin-converting enzyme 2 (ACE2) is a cardio-cerebral vascular protection factor existing in a variety of organs, including the nervous system and skeletal muscles, playing a major role in regulating blood pressure and anti-atherosclerosis mechanisms [206]. SARS-CoV-2 may cause abnormally raised blood pressure and enhance the risk of a cerebral hemorrhage. Besides, as the spike protein of SARS-CoV-2 binds with ACE2 expressed in the capillary endothelium, the virus may also break the blood-brain barrier and enter the CNS by affecting the vascular system [198].

SARS-CoV-2 was detected in patient's cerebrospinal fluid and brain tissue from autopsy. However, the route of the virus to central nervous system needs further studies. In this Zhang and colleagues' study, they suggested that the virus can migrate after infecting sensory or motor nerve endings. Under the action of motor proteins, dynein and kinesins, the viruses can achieve neuronal transport in a way of retrograde or anterograde. Based on the unique anatomical structure of olfactory nerves and olfactory bulb, it becomes a channel between the nasal epithelium and the CNS [31]. So, in the early stages of SARS-CoV-2 infection of the respiratory system, olfactory tract becomes an important channel for virus transmission to brain. Several studies also presented that coronavirus can invade the CNS from the periphery through neural pathways [175]. In addition, studies have shown that

some coronaviruses can invade brainstem via a synapse-connected route from the lungs and airways. Zhang and colleagues suggest that the infection of CNS by SARS-COV-2 might be one reason for the acute respiratory failure due to the specific neurological symptoms such as headache, epilepsy, and confusion, is similar to symptoms of intracranial infection, and in some cases, intracranial infection-related symptoms have been the initial symptoms, coming before the symptoms of pulmonary infection, such as cough, fever, and dyspnea [175].

As SARS-CoV-2 binds to ACE2, some patients with underlying hypertension may have unusually high blood pressure and increased risk of intracranial hemorrhage after SARS-CoV-2 infection [175] due to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may increase the expression of ACE2. It is therefore important to adjust antihypertensive drug dosages in SARS-CoV-2 patients with underlying hypertension.

Musculous Manifestions

Patients with myopathy have a higher inflammatory response and a higher association

with hepatic and renal disease. Gulati and colleagues [68] listed some muscular manifestations such as:

- a. Myalgia is a common presenting symptom of COVID-19 infection.
- b. 36% of patients develop muscle pain during the illness [130].
- c. High creatinine kinase (CK) levels present in 14%-33% of patients [22, 41, 106, 131].
- d. Rhabdomyolysis has been reported in patients with COVID-19 with MYO levels >12,000 ug/L and CK levels >11,000 U/L [132].

Skin Manifestations

Cutaneous manifestations of COVID-19 increased since they might be useful in the early diagnosis triage of COVID-19-positive patients and their risk stratification (Table 2). Wollina and colleagues [207] reported chilblain-like acral eruptions, purpuric and erythema multiforme-like lesions associated to children and young adult patients who are either asymptomatic or develop a mild disease. In contrast, acro-ischemic lesion and maculopapular rash are often seen among adult patients who run a more severe course. Urticaria with pyrexia has diagnostic significance since this

Table 2. Cutaneous sign of COVID-19 disease.

Vascular complications	Acro-ischemia Livedo-like Necrosis Chilblain-like eruptions
Maculopapular eruption	Morbiliform Plaques Pityriasis rosea-like eruptions
Urticarial rash	
Vesicular eruption	Vesicle Bullous eruption Chickenpox-like rash
Petechiae/ Purpuric eruptions	
Erythema multiforme-like rash	
Palmar erythema	
Perifollicular eruption	
Pruritus	
Mucosal lesions	Enanthema
Androgenetic alopecia	

combination is an early symptom of an otherwise not confirmed SARS-CoV-2 infection. Careful registration of possible cutaneous manifestations of the COVID-19 pandemic is warranted.

Gulati and colleagues [68] noted in their study that common cutaneous manifestations present as follow:

- a. Erythematous rash, widespread urticaria, and chickenpox like vesicles [59].
- b. Pruritis is uncommon.
- c. Several recent case series have reported a viral exanthum similar to chilblains disease in patients with COVID-19 [62].

Other Manifestations

Guillain-Barré syndrome has also been reported, with onset 5 to 10 days after initial symptoms [208].

A multisystem inflammatory syndrome possibly associated with COVID-19, with clinical features similar to those of toxic shock syndrome and Kawasaki disease, has also been described in children [47].

Figure 19 summarizes the main injuries caused by SARS-COV-2 in the human body.

Comorbidities, Symptoms, and Risk

The spectrum of symptomatic infection ranges from mild to critical, however, most infections are not severe [22, 29, 30, 47, 72, 74, 77, 210, 211]. The critical cases can occur in healthy individuals of any age, but it predominantly occurred in patients with advanced age or underlying medical comorbidities such as [44, 212-214]:

- Immunocompromising conditions [215]
- Male over 65 [216];
- Smoking patients [216];
- Hypertension [217];
- Diabetes mellitus [217];
- Chronic obstruction pulmonary disease (COPD) [217];
- Cardiovascular disease [217];
- Cerebrovascular disease [217];

- Chronic lung disease [217];
- Cancer (in particular hematologic malignancies, lung cancer, and metastatic disease) (in particular hematologic malignancies, lung cancer, and metastatic disease) [218];
- Chronic kidney disease [217];
- Obesity [217];
- Liver disease [219], although specific data regarding risks associated with these conditions are limited [40, 220].

Laboratory Findings

Diagnostic Tests - RT-PCR

The diagnosis of COVID-19 is performed by detection of SARS-CoV-2 RNA by nucleic acid amplification tests (NAATs), primarily reverse transcription-polymerase chain reaction (RT-PCR) [47]. Numerous RT-PCR assays are used around the world to detect SARS-CoV-2; and different assays amplify and detect different regions of the SARS-CoV-2 genome. Common gene targets include nucleocapsid (N), envelope (E), spike (S), and RNA-dependent RNA polymerase (RdRp), as well as regions in the first open reading frame [221].

Reverse transcription PCR (RT-PCR) is positive in 59%-78.2% of cases, and is the gold standard method to detect COVID-19 [222, 223]. This method, however, is time-consuming and expensive. Often times it can present a false-negative result due to the low specificity of the RT-PCR when compared to the sensibility of the test, especially if the sample is collected from the upper respiratory tract. In this case, if the clinic is consistent with COVID-19, it is important to admit the patient as a positive case [224, 225].

Serological Methods (IgM and IgG)

Serologic tests detect antibodies to SARS-CoV-2 in the blood, and those that have been adequately validated can help identify patients who have had COVID-19 [47]. Serologic tests are

less likely to be reactive in the first several days to weeks of infection, and thus may have less utility for diagnosis in the acute setting [226-230]. This assay requires 15 min to generate results and can be used for rapid screening in clinics however has a very low specificity [230].

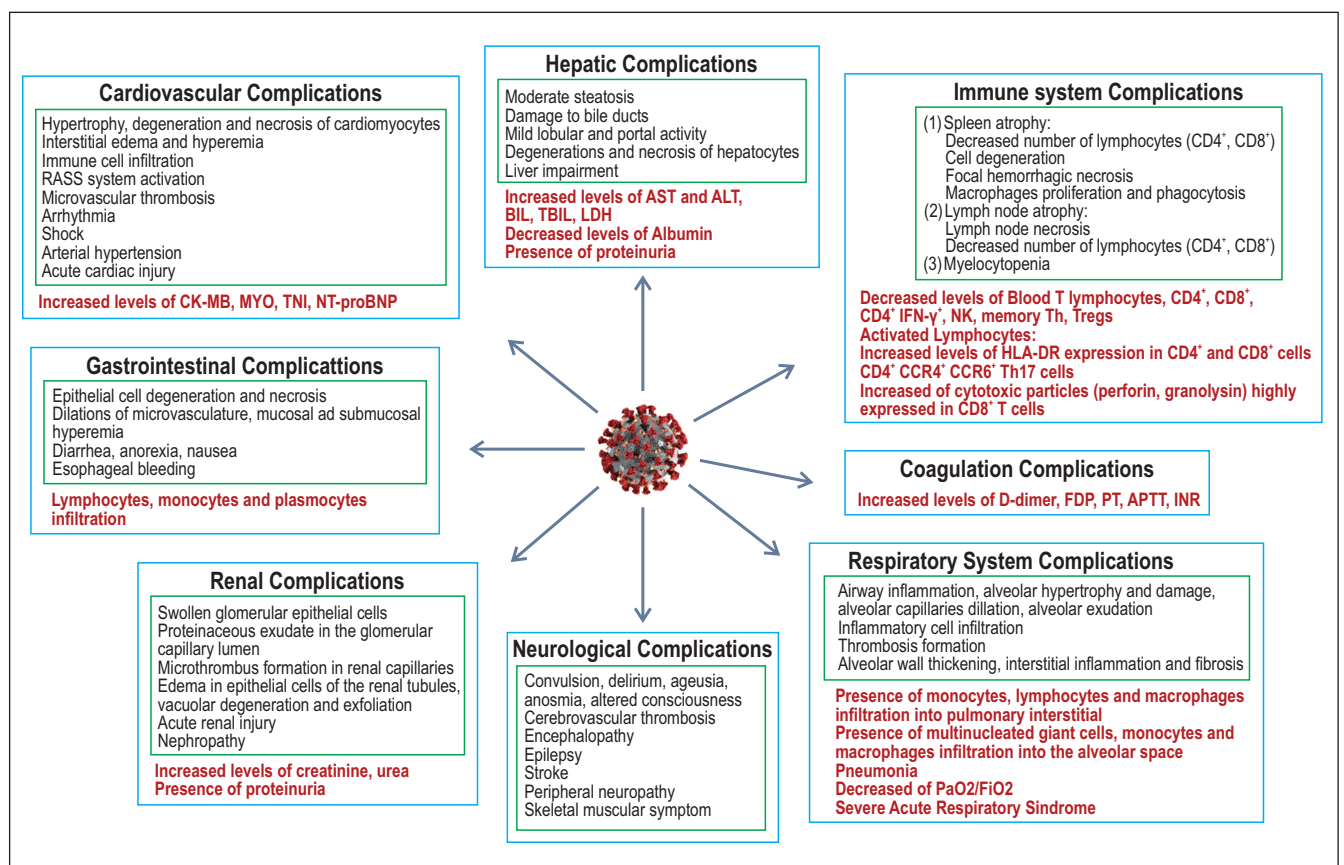
Routine Tests

The laboratory exams such as WBC, AST, Cr, hs-cTnI, PCT, LDH, and D-dimer could show the progress of the disease, but it is not a specific biomarker for COVID-19 [216].

Commonly, the exams of COVID-19 infection presents: [22, 29, 30, 47, 48, 50, 72, 210, 211, 231]:

- Lymphopenia (83.2%);
- Increased inflammatory markers (eg, ferritin, C-reactive protein, and erythrocyte sedimentation rate);
- Elevated aminotransaminase levels (usually hospitalized patients);
- Changes in albumin;
- Elevated lactate dehydrogenase;
- Elevated neutrophils (severity cases);
- Elevated D-dimer (>1 mcg/mL) (severity disease);

Figure 19. SARS-CoV-2 infection-induced impairment of multiple organ function.



Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; CNS, central nervous system; FDP, fibrinogen degradation products; HLA-DR, human leukocyte antigen DR; INR, international normalized ratio; LDH, lactate dehydrogenase; MYO, myoglobin; NK, natural killer cell; NT-proBNP, N terminal pro-B-type natriuretic peptide; PaO₂/FiO₂, oxygenation index; PNS, peripheral nervous system; PT, prothrombin time; RAAS, renin-angiotensin-aldosterone system; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; Th, helper T cell; TNI, troponin I.

Source/Credit: Adapted from Zhang and colleagues [209].

- Higher levels of D-dimer, CRP, and procalcitonin are associated with severity disease;
- Prothrombin time and D-dimer levels on admission were higher in the intensive care unit (ICU) patients than in non- ICU patients;
- Plasma concentrations of IL-2, IL-7, IL-10, and TNF- α were higher in ICU patients;
- Higher white blood cell and neutrophil counts (severe patients);
- Eosinopenia (severe patients);
- Elevated in procalcitonin levels (ICU patients);
- Elevated prothrombin time (PT);
- Elevated troponin;
- Elevated creatine phosphokinase (CPK);
- Progressive decline in the lymphocyte count and rise in the D-dimer over time were observed in nonsurvivors compared with more stable levels in survivors [29];
- Elevated proinflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses [22].
- Notably, decreases in CD8+ T cells and B cells in adults have been associated with severe COVID-19 and poor response to therapy [232];
- CD8+ T cell and B cell recovery has been associated with moderate disease [233];
- Decreasing in regulatory T cells also have been associated with a hyperinflammatory response in adults [234];
- The high hs-cTnI act is one of the specific biomarkers of myocardial injury [105].
- Elevation of creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), and lactate dehydrogenase (LDH) could indicate a cardiovascular injury.

Imaging Findings

In early or mild cases, Chest radiographs might be regular. Current abnormal radiograph findings were consolidations and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions [235].

Chest CTs in COVID-19 patients have a tendency of showing ground-glass opacification with or without consolidative abnormalities, peripheral distribution, and involve the lower lobes. Other findings, although less frequent, are pleural thickening, pleural effusion, and lymphadenopathy. Abnormalities have been identified in Chest CTs even before patients develop symptoms and viral RNA has been detected in upper respiratory specimens [47].

Conclusion

Since the outbreak, the development of supportive drugs, vaccines, and targeted antiviral drugs is underway. At the beginning of the outbreak, studies revealed that the SARS-COV-2 affected the lungs with of manifestation of respiratory symptoms. Because the virus' mechanisms take over the cells, binding with the ACE2 receptor, other symptoms were noticed by physicians and health care workers. As a result, news studies have emerged and confirmed new symptoms and probable route of the virus. These studies have demonstrated that the virus could affect and damage the respiratory system, circulatory system, digestive system, urogenital system, and central nervous system. This complicates potential clinical manifestations and makes it harder to treat such cases. We might be just beginning to understand this new virus and the effect in patients it has on patients during and after infections. A deeper understanding of this virus from biomedical research and epidemiological observation will provide important clues to etiologic research, diagnosis, differential diagnosis, treatment, and prognostic assessment regarding COVID-19.

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