



Review

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Structural and physiological changes of the human body upon SARS-CoV-2 infection

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Abstract: Since December 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) has spread to many countries around the world, developing into a global pandemic with increasing numbers of deaths reported worldwide. To date, although some vaccines have been developed, there are no ideal drugs to treat novel coronavirus pneumonia (coronavirus disease 2019 (COVID-19)). By examining the structure of the coronavirus and briefly describing its possible pathogenesis based on recent autopsy reports conducted by various teams worldwide, this review analyzes the possible structural and functional changes of the human body upon infection with SARS-CoV-2. We observed that the most prominent pathological changes in COVID-19 patients are diffuse alveolar damage (DAD) of the lungs and microthrombus formation, resulting in an imbalance of the ventilation/perfusion ratio and respiratory failure. Although direct evidence of viral infection can also be found in other organs and tissues, the viral load is relatively small. The conclusion that the injuries of the extra-pulmonary organs are directly caused by the virus needs further investigation.

Key words: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Coronavirus disease 2019 (COVID-19); Pathological change; Pathogenesis

1 Introduction

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)), which belongs to the β -coronavirus family, is the pathogen of novel coronavirus pneumonia (coronavirus disease 2019 (COVID-19)). Since December 2019, when the initial outbreak of COVID-19 occurred in China, a series of effective preventive control and medical treatment measures have been implemented, and have brought the pandemic under control to a certain

extent. However, its incidence is still increasing globally. As of Mar. 14, 2021, there were more than 11.92 million COVID-19 patients worldwide, and the cumulative number of deaths had exceeded 2.6 million (<https://www.dynamed.com/condition/covid-19-and-cardiovascular-disease-patients>). At present, the effects of novel coronavirus infection on the structure and physiology of the human body are still not completely understood, and although the vaccine has been developed, there are currently no ideal specific therapeutic drugs for novel coronavirus pneumonia patients. This paper reviews recent research progress on structural and physiological changes of the human body caused by novel coronavirus infection, so as to provide relevant cues and direction for specific drug research on COVID-19 treatment.

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2 Biological traits of coronavirus

The coronavirus is circular in shape, with a diameter of about 125 nm (Malik, 2020). Because its spike glycoprotein protrudes from the surface, the virus displays a “corona” appearance, hence the name coronavirus. There are four genera of coronavirus: α -coronavirus, β -coronavirus, γ -coronavirus, and δ -coronavirus. Mammals are susceptible to α -coronavirus and β -coronavirus, birds to γ -coronavirus, and both mammals and birds to δ -coronavirus (Naqvi et al., 2020). The novel coronavirus (SARS-CoV-2), which leads to COVID-19, belongs to the β -coronavirus genus. For SARS-CoV-2, next-generation sequencing data have shown 79% and 50% homologies to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (Malik, 2020).

The coronavirus genome is constituted of a single-strand RNA (Wu F et al., 2020). Their genome is the largest of all RNA viruses, which usually range between 27 and 32 kb (Li, 2016). The RNA genome of coronavirus is encapsulated by a nucleocapsid protein (N) and is further enclosed within a lipoprotein envelope. There are at least three structural proteins associated with the viral envelope, in which membrane protein (M) and envelope protein (E) are involved in the assembly of the virus, and spike glycoprotein (S) mediates virus entry into host cells (Li, 2016; Shi et al., 2020). The S protein is committed to adhering the virus to host cells to initiate infection. It consists of three subunits, S1, S2, and S2' (Li, 2016), which play different roles in the adhesion of the virus to host cells. The S1 subunit can attach the virus to the host cell membrane via interaction with the angiotensin converting enzyme 2 (ACE2) receptor that initiates the infection process (Hoffmann et al., 2020). As a fusion protein, the S2 subunit contributes to the fusion of viruses with mammalian cell membranes. The S2 subunit functions as a fusion peptide (Naqvi et al., 2020). In addition to mediating viral entry, spike proteins are the major factors determining the host range and tissue orientation of the virus and are also the main inducers of the host immune response. E proteins contribute to viral assembly and release. E proteins can aggregate on host membranes and form protein-lipid pores which are involved in ion transport and considered to be potential drug targets (Fehr and Perlman, 2015). M proteins act

simultaneously with E, N, and S proteins and are involved in RNA packaging (Tang et al., 2020).

3 Pathogenesis of novel coronavirus infection

3.1 Invasion and replication of viruses

SARS-CoV-2 uses S proteins on its envelope to bind to ACE2 receptors on the cell membrane and relies on the synergistic activation of transmembrane serine protease 2 (TMPRSS2) (Hoffmann et al., 2020). Subsequently, the virus enters the host cell through membrane fusion (Offringa et al., 2020). After entry into the cell, it destroys the endoplasmic reticulum structure, forms a bilayer membrane vesicle structure (double-membrane vesicle (DMV)), and replicates and transcribes within it (Oudshoorn et al., 2017).

The genome of coronavirus contains a 5' cap structure and a 3' poly(A) tail, similar to eukaryotic messenger RNA (mRNA), so it can be translated just like eukaryotic mRNA (Fehr and Perlman, 2015). In the overall process of RNA replication, the replicase is translated firstly and then a replicase complex is assembled. Afterwards, RNA replication and subgenomic RNA synthesis are carried out, and finally mature virus particles are formed. After assembly, the virus is transported to the surface of the cell within vesicles and released by exocytosis (Malik, 2020).

3.2 Immunopathological effects of virus infection

When a virus enters a cell, its antigen presented by the antigen presentation cells (APCs) is then recognized by the cytotoxic T lymphocytes (CTLs), and stimulates humoral and cellular immunity in the human body (Li XW et al., 2020). Acute respiratory distress syndrome (ARDS) is considered to be the leading cause of death in patients with COVID-19 (Li JZ et al., 2020). One of the main mechanisms of ARDS is the cytokine storm, which involves upregulation and activation of many inflammatory cytokines in tissue cells (mainly immune cells) after microbial infection of the body, causing ARDS (Song et al., 2020). Some studies have shown that inflammatory cytokines in serum are significantly increased in most patients with severe COVID-19, including interferon (IFN), interleukin (IL), tumour necrosis factor (TNF), colony-stimulating factor (CSF), IFN- γ -induced protein (IP10), C-reactive protein (CRP), monocyte chemotactic protein-1 (MCP1), and

macrophage inflammatory protein 1- α (MIP1 α) (Mef-tahi et al., 2020; Zheng et al., 2020).

3.3 Evasion of the immune system by coronavirus

In addition to the direct effects of viral infection and resulting immunopathological damage, immune evasion by the coronavirus is also one of the mechanisms, which promotes disease. Coronavirus has multiple ways to escape immune responses. Viruses are strictly parasitic within cells, thus avoiding the effects of antibodies, the complement system, and drugs. Pattern recognition receptors (PRRs) are mainly expressed on the surface of innate cells and can identify conserved components of exotic microorganisms, namely pathogen-associated molecular patterns (PAMPs). Nevertheless, SARS-CoV and MERS-CoV can induce cells to produce PRR-deficient DMVs and replicate and transcribe within these vesicles, thus avoiding attack by the host immune system (Snijder et al., 2006; Oudshoorn et al., 2017). Interestingly, SAR-CoV-2 can activate the immune response by PRR. Nuclear factor- κ B (NF- κ B), Janus kinase/signal transducers and activators of transcription (JAK/STAT), and other pathways can be activated after the cells are infected by SAR-CoV-2 through recognizing PRRs, thus activating the immune response (Catanzaro et al., 2020). It is believed that SARS-CoV-2 can achieve immune evasion through the coding of 22 *N*-linked glycosylation sites, the structure of open reading frame 3b (ORF3b), and the methylation of 5' cap of viral RNA (Tan and Tang, 2021). Antigen presentation is also affected by the coronavirus, for example, by down-regulation of gene expression associated with antigen presentation (Menachery et al., 2018). ORF8 in SARS-CoV-2 genomes could bind to major histocompatibility complex-1 (MHC-1) to disrupt antigen presentation and initiate immune evasion (Park, 2020).

4 Damage inflicted by novel coronavirus on the human body

After Professor Liang LIU's team of Huazhong University of Science and Technology (Wuhan, China) conducted the first autopsy of a patient who died of COVID-19 in January 2020, other teams and organizations worldwide have also carried out autopsies on deceased COVID-19 patients. We are therefore able to summarize the structural and histological changes

caused by SARS-CoV-2 infection observed in these autopsies.

4.1 Respiratory system

Gross observations: Dark-red bleeding areas and gray-white lesions were observed in cases with severe inflammatory lesions, which exhibited a patchy shape. The lung tissue felt tough and firm as in diffuse edema, and tissue weight was increased (Barton et al., 2020; Sekulic et al., 2020; Suess and Hausmann, 2020). White mucus or pink foam could be seen within the bronchial lumen; and in the case of inflammatory lesions, a large amount of viscous secretions overflowed from the alveoli and fibrous cords were observed. There could be mild to moderate pleural effusions on both sides (Ducloyer et al., 2020; Fox et al., 2020; Suess and Hausmann, 2020).

Microscopic observations: In a minimally invasive autopsy performed on patients who died of COVID-19 (Xu et al., 2020), diffuse alveolar damage (DAD) was found in the lungs of many patients, but the pathological changes of DAD in different parts of the lung were discordant and often displayed heterogeneity in the same patient (Sekulic et al., 2020). The pathological features of COVID-19-related DAD were not unique, indicating that there may be similar pathogenesis and etiological factors to other DAD (Konopka et al., 2020). DAD morphological progress includes three stages: exudation (1–7 d), proliferation (8–20 d), and fibrosis (20 d) (Castro, 2006). According to available autopsy reports, COVID-19-related DAD was usually at the acute exudation stage or proliferation stage (Polak et al., 2020), with only a few cases being classified at the fibrosis stage (Fox et al., 2020).

Acute exudative DAD is mainly characterized by diffuse alveolar exudation, with varying degrees of serous and fibrin exudates in the alveolar cavity which may be accompanied by the formation of hyaline membranes. Reactive hyperplasia of type II alveolar epithelial cell (AECII) was observed in many cases (Bradley et al., 2020). The nuclei of AECII were observed to be large and be deeply stained, with strong pleomorphism, suggesting viral cytopathic changes with diffuse epithelial shedding (Duarte-Neto et al., 2020). Capillary dilation and congestion were seen in the alveolar septum, and hyaline thrombosis and mixed thrombosis within blood vessels were also observed (Polak et al., 2020). Other findings were inflammatory cell infiltration:

predominantly monocytes, macrophages and a few multinucleated giant cells, lymphocytes, eosinophils, and neutrophils (Bradley et al., 2020). Some areas of interstitial fibrosis occurred in varying degrees, and fibroblast proliferation was seen (Polak et al., 2020).

A major feature of DAD in the hyperplastic stage is the organization of intra-alveolar exudates and alveolar septal fibrosis, which is more common in patients with long-term illness and hospitalization (Duarte-Neto et al., 2020). Cellulose exudation is seen in the alveolar cavity, and the hyaline membrane is replaced by proliferating fibroblasts, with fibroblast thrombus being formed in some alveolar cavities. In COVID-19 autopsies, the alveolar septal was thickened, with fibrosis and massive fibroblast hyperplasia. Local pulmonary tissue consolidation occurred, with infiltration by a small number of monocytes, macrophages, and small lymphocytes. Notably, secondary infection could overlap with viral infection, resulting in suppurative inflammation. A large number of bacteria and fungi were detected in some cases, suggesting that severe bacterial or fungal infections were secondary to DAD caused by coronavirus (Zhou et al., 2020).

Coronavirus particles were found in the cytoplasm of tracheal and bronchial mucosal epithelial cells and AECII, as observed under electron microscopy. The quantitative polymerase chain reaction (qPCR) test for SARS-CoV-2 on the tissues in some cases was positive in lung tissues (Tian et al., 2020).

Extensive alveolar injury, exudation, interstitial inflammatory thickening, and thrombosis are the causes of ventilation disorders. Airway epithelial hyperplasia, shedding, and mucus congestion increase ventilation obstruction. These changes are regarded as the pathological basis of fatal respiratory failure (Bian and The COVID-19 Pathology Team, 2020).

4.2 Circulatory system

According to autopsy reports from 23 COVID-19 patients provided by five USA research institutions, the major organ damage in COVID-19 patients is not only in the lungs but also in the heart, which aggravates the circulatory system to enter the procoagulant state (Buja et al., 2020).

Gross observations: the weight of the heart increased slightly or negligibly. Cardiac enlargement and right ventricular dilatation were found. Under microscopy, scattered individual cardiomyocyte necrosis was

observed, but no large or confluent area of cardiomyocyte necrosis was observed. There was no significant inflammatory lymphocytic infiltration (Buja et al., 2020). There is little evidence of direct infection and replication of SARS-CoV-2 in cardiac cells (Imazio et al., 2020). Myocardial tissue damage may involve several potential mechanisms, including coronavirus-associated acute myocarditis, increased cytokine secretion, and hypoxia-induced cardiomyocyte apoptosis. Inflammation may be a potential mechanism of myocardial injury (Buja et al., 2020).

Additionally, autopsy reports indicated that blood clots and microangiopathy were present in the small blood vessels and capillaries of the lungs, accompanied by bleeding that caused death (Ackermann et al., 2020). Elevated D-dimer was detected in some patients. This finding may suggest pulmonary vascular endothelial injury. SARS-CoV-2 infects the host through the ACE2 receptor, which is expressed in multiple organs of the human body, including the lung, heart, kidney, and intestine. Endothelial cells also displayed expression of ACE2 receptors. Varga et al. (2020) found the presence of viral inclusion bodies within endothelial cells in patients with COVID-19, and the accumulation of inflammatory cells associated with endothelial cells was also found in various organs. Both direct infection of endothelial cells by the coronavirus and the recruitment of immune cells mediated by the immune system can lead to extensive endothelial dysfunction with apoptosis. Endothelial dysfunction is the main determinant of microvascular dysfunction. It causes vasoconstriction by changing vascular balance, leading to organ ischemia, tissue edema, and inflammation in a coagulation-promoting state (Buja et al., 2020).

4.3 Digestive system

Histological changes in the liver of COVID-19 patients were limited (Tian et al., 2020); these could manifest as hepatocyte degeneration, punctate necrosis, fragment necrosis, bridging, or massive necrosis with neutrophil infiltration (Duarte-Neto et al., 2020). Lymphocyte infiltration and slight hepatic sinus dilatation were observed within the hepatic lobules of deceased COVID-19 patients (Tian et al., 2020). The gallbladder was highly filled and the mucosal epithelium was exfoliated (Duarte-Neto et al., 2020). Bile thrombus was seen in the small bile duct (Bradley et al., 2020). There was moderate microvascular steatosis

and some necrotic hepatocytes were seen around the central vein, but no portal vein inflammation was observed (Suess and Hausmann, 2020; Xu et al., 2020). There is no clear positive evidence that SARS-CoV-2 can cause liver injury directly. Drug-induced liver injury, previous history of chronic liver disease, and COVID-19-associated elevated inflammatory response may also cause liver injury.

4.4 Urinary system

Under light microscopy, glomerular segmental hyperplasia or necrosis, swelling of endothelial cells, and a small amount of protein exudate were observed in the balloon cavity (Bian and The COVID-19 Pathology Team, 2020). The renal tubular lumen was widened, while the renal tubular epithelium was flat, exhibiting interstitial edema, mild inflammatory cell infiltration, and fibrous hyperplasia (Menter et al., 2020). Occasionally, hemosiderin granules, protein tube types, and pigmented tube types were found. The proximal tubules were diffusely damaged. The brush border disappeared, and vacuoles were denatured or even necrotic (Su et al., 2020). Transparent tube type was common in distal tubules. There was noticeable red blood cell aggregation blocking the capillary lumen, and a few cases exhibited diffuse intravascular coagulation and small fibrin thrombus in glomerular capillaries, with hyaline thrombus also in evidence (Menter et al., 2020).

Microscopic examination showed that spherical virus particles with coronavirus characteristics found within proximal tubule epithelial cells and podocytes may be the cause of acute tubular necrosis and proteinuria in some patients. Viral particles in podocytes may be associated with occasional vacuolation, disappearance of pod processes, and detachment of podocytes (Su et al., 2020). Besides the direct toxicity of SARS-CoV-2, factors leading to acute kidney injury include coagulation abnormalities, systemic hypoxia, and possible drug- or hyperventilation-related rhabdomyolysis.

Immunohistochemical (IHC) staining revealed no specific aggregation of different inflammatory cells, with T and B cells being mixed in non-specific scar tissues infiltrated by lymphocytes and scattered macrophages. CD235a staining confirmed that microvascular obstructions were mainly composed of red blood cells (Su et al., 2020).

4.5 Nervous system

Central nervous system complications have been observed to occur in a deceased COVID-19 patient. The autopsy revealed mild brain swelling and hemorrhagic lesions within the white matter of the cerebral hemisphere. There was axonal damage and accumulation of macrophages around the lesion (Reichard et al., 2020). Cerebral hyperemia and edema, and degeneration and ischemic changes of some neurons were also seen in other cases. Some cases showed neurasthenia, perivascular inflammatory cell infiltration, and focal cerebral infarction. A few cases showed brain hernias (Bian and The COVID-19 Pathology Team, 2020). A number of studies have also shown that after SARS-CoV-2 infection, patients suffered from disorders of smell, taste, or the respiratory center (Wu YS et al., 2020). The detection of viral copies by SARS-CoV-2-specific qPCR showed that the viral load in nerve tissue was relatively low, but the viral load in the olfactory bulb was slightly higher than that in the brain stem, which supported the hypothesis that the virus entered the brain through plates (Menter et al., 2020).

4.6 Reproductive system

Under light microscopy, it was observed that testicular samples of deceased COVID-19 patients exhibited different degrees of spermatogenic cell reduction and injury, obvious damage to the seminiferous tubules, swelling, vacuolation and shedding to the lumen of supporting cells, and decrease of interstitial cells along with interstitial edema and mild inflammation of lymphocytes (Yang et al., 2020). In some cases, no virus particles were observed by transmission electron microscope (TEM). No virus was detected within testicular samples by qPCR in a majority of patients (Yang et al., 2020). These findings suggest that although testicular parenchyma is significantly impaired, no virus is present in the testes in most cases. Thus, testicular damage may not be directly caused by the viral infection.

4.7 Hematopoietic system

Red blood cells, medullary cells, and megakaryocytes decreased in most cases, with a few cases showing obvious hyperplasia (Bian and The COVID-19 Pathology Team, 2020).

4.8 Immune system

Lymphocyte composition of spleen and lymph nodes was observed to decrease in varying degrees (Pessoa et al., 2020), with CD4⁺ and CD8⁺ T cells decreasing significantly (Bian and The COVID-19 Pathology Team, 2020). Within the spleen, splenic nodules underwent atrophy were decreased or became deficient (Pessoa et al., 2020). Additionally, lymphocyte degeneration and necrosis and macrophage proliferation were observed (Bradley et al., 2020). Hemorrhage and anemia infarction were commonly observed in the spleen. Nevertheless, coronavirus particles were observed in the cytoplasm of macrophages in only a few cases under electron microscopy. qPCR detection of 2019 novel coronavirus viral nucleic acids showed mostly negative results (Pessoa et al., 2020).

5 Conclusions

COVID-19 infection mainly occurs in the lungs, and the most prominent and important pathological changes are DAD and formation of pulmonary microthrombus, which can easily lead to hypoxia and thus respiratory failure. The disease may also involve various other organs and tissues (Table 1). Through qPCR detection of viral nucleic acids, electron microscopy, and IHC staining, SARS-CoV-2 RNA and viral particles have been detected in extrapulmonary tissues such as

spleen, heart, liver, gallbladder, kidney, stomach, breast, testis, skin, nasopharynx, and oral mucosa, but the viral load is relatively small and not all COVID-19 patients exhibit direct evidence of viral infection in extrapulmonary tissues. Therefore, the injury of extra-pulmonary tissues may be caused by direct infection of the virus, a serious inflammatory reaction triggered by viral infection, or necrosis of tissue cells caused by hypoxia; or it may arise from the basic medical history of the patient. Elucidation of precise mechanisms requires analysis of more pathological biopsies.

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Author contributions

Zhonglin WU, Qi ZHANG, Guo YE, Hui ZHANG, and Boon Chin HENG took the lead in writing the manuscript. Zhonglin WU and Qi ZHANG completed manuscript framework firstly. Yang FEI and Bing ZHAO revised, edited, and checked the final version. Jing ZHOU conceptualized and designed this study. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Zhonglin WU, Qi ZHANG, Guo YE, Hui ZHANG, Boon Chin HENG, Yang FEI, Bing ZHAO, and Jing ZHOU declared that they have no conflict of interest.

Table 1 Main pathological changes after SARS-CoV-2 infection in different organs

Organ	Main pathological changes after SARS-CoV-2 infection	Reference
Lung	Inflammatory lesions; different degrees of diffuse alveolar damage	Xu et al., 2020
Heart	Procoagulant state and thrombosis	Buja et al., 2020
Liver	Hepatocyte degeneration and necrosis, neutrophil and lymphocyte infiltration	Duarte-Neto et al., 2020; Tian et al., 2020
Gallbladder	Gallbladder filling and mucosal epithelial exfoliation	Duarte-Neto et al., 2020
Kidney	Glomerular segmental hyperplasia or necrosis; diffuse damage to the proximal tubules; transparent tube type common in distal tubules; inflammatory cell aggregation	Bian and The COVID-19 Pathology Team, 2020; Menter et al., 2020; Su et al., 2020
Brain	Different degrees of cerebral congestion and edema; some neurons ischemic, degenerative, and infarcted; inflammatory cell aggregation; disorders of smell, taste, or respiratory center	Bian and The COVID-19 Pathology Team, 2020; Reichard et al., 2020; Wu YS et al., 2020
Testes	Reduction and injury of parenchymal and stromal cells; mild inflammation	Yang et al., 2020
Hematopoietic system	Reduction or proliferation of red blood cells, bone marrow cells and megakaryocytes	Bian and The COVID-19 Pathology Team, 2020
Spleen	Hemorrhage and anemia infarction; atrophied, shrunk or absent splenic nodules; lymphocyte degeneration and necrosis	Pessoa et al., 2020

This article does not contain any studies with human or animal subjects performed by any of the authors.

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