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## Review Article

# Pathologic basis of coronavirus disease 2019 (COVID-19) – An overview of cellular affinities, pathogenesis, clinical manifestations, autopsy findings and sequelae

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## Abstract

The global terror instigated by coronavirus disease 2019 (COVID-19) cannot be underestimated and the need for drastic measures towards its control cannot be overemphasized. Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) following attachment of the virus to specific receptors in the body. The distribution of these specialized receptors in various organs and tissues of the body is responsible for the various clinical presentations associated with the disease after infection. Despite the higher risk of spread of the infection, autopsies have been carried out though with maximum precautionary measures and information provided to further elucidate the extent of damages caused by the disease. Pathologic mechanisms leading to death from COVID-19 include respiratory failure due to surfactant deficiency and consequent alveolar collapse, cardiac syncope from direct damage to cardiac muscles, peripheral paralysis, cytokine storm and excessive haemorrhage from impaired coagulation. In patients that recover, potential outcomes which could be short- and/or long-term have been recognized. As a means to develop effective control, eradication and prevention strategies, a proper understanding of the mechanisms of SARS-CoV-2 infection will fully ensure a positive breakthrough. Hence, in this article, the pathologic basis of COVID-19 are provided based on extensive literature searches, and proposed mechanisms of pathogenesis, clinical manifestations, autopsy findings and sequelae are being described.

## Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory syndrome of humans caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially referred to as 2019-nCoV, in the family *Coronaviridae* [1,2]. This causative virus SARS-CoV-2 belongs to the same group as the zoonotic Middle East respiratory syndrome coronavirus (MERS-CoV) [3,4]. Other coronaviruses reported to be responsible for mild respiratory diseases in humans include HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43 [5]. Transmission of SARS-CoV-2 involves contact of oral, respiratory and ocular mucous membranes with respiratory droplets and excreta containing the live virus from patients [6,7]. Though the virus has been reported to be of zoonotic origin, animal coronaviruses do not spread among humans [8]. Clinical manifestations of COVID-19, not limited to these, include fever, dry cough, weakness, dyspnoea, aches, diarrhoea, conjunctivitis and loss of taste and/or smell [9,10]. Severity of the disease is common among middle-aged and elderly patients with underlying disease conditions such as tumours, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease [11,12]. There is recovery after 1 week in patient with mild symptoms but death does occur in severe cases resulting from respiratory failure [9,13]. As there are no effective treatments and vaccines against COVID-19, prevention is targeted at avoidance of exposure to the causal virus [14]. However, in this review, the pathologic basis of COVID-19 with focus on the receptor and cellular targets, pathogenesis, clinical manifestations, gross and histopathology, and sequelae are being described.

### Receptors and cellular targets of SARS-CoV-2

The receptors reported to be attached by SARS-CoV-2 are angiotensin-converting enzyme-2 (ACE2) and transmembrane protease serine-2 (TMPRSS2) [15]. They are cell surface proteins which enhance virus entry into cells and spread to other cells, and are abundant in epithelial and endothelial cells of the respiratory tract, kidneys, intestines, arteries and heart [16,17]. However, these proteins have been documented to be abundant in certain cells of the respiratory conducting system (ciliated cells), lungs (alveolar type II cells) and intestines (enterocytes) evident by more RNA expression of these proteins than other cells [18]. Also, dendritic cell specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN or CD209) and lymphocytic cell-SIGN (L-SIGN or CD209L) could be other receptors that enhance SARS-CoV-2 entry into host cells. These receptors are reported to be differentially expressed in epithelial and endothelial cells of the lungs and kidneys in humans [19,20].

### Pathogenesis of SARS-CoV-2 infection

Following inhalation, ingestion or contact with ocular epithelium, there is attachment of SARS-CoV-2 to epithelial cells leading to an initial viral replication and inflammatory cellular reactions with limited innate immune response [16,21,22]. The incubation period has been estimated to range from 2.1-11.1 days with an average of 6.4 days [23].

In respiratory infection, there is propagation and migration of the virus down the conducting airways to the gas exchange system with subsequent greater innate immune response trigger accompanied by increased expression of interferon  $\gamma$ -induced protein 10 (IP-10 or CXCL10) [18]. The IP-10 has been reported to show abundant expression in alveolar type II cells following infection by SARS-CoV-2 [18,24]. This is followed by apoptosis of infected cells leading to loss of majority of type II cells, release of greater amount of viral particles and infection of adjacent type II cells [25]. Alveolar type I cells function in the process of gas exchange between the alveoli and blood while type II cells play roles in surfactant protein secretion and are the precursor cells for type I cells, hence, this major loss of type II cells will then trigger epithelial regeneration via secondary pathways [18,26,27].

In oral infection, the virus attaches to epithelial cells of the esophagus and enterocytes of the ileum and colon via ACE-2 and TMPRSS2 receptors [28,29]. This leads to viral replication within infected cells, cellular apoptosis activation and release of viral particles which in turn infect adjacent epithelial cells and enterocytes [22]. Also, there is exaggerated inflammatory response via chemokine and cytokine release with consequent aggregation of inflammatory cells and damage to the epithelium [21,30].

In ocular infection, there could be initial virus replication in the epithelial cells of the eyes and possible migration of viral particles via the nasolacrimal duct into the nasal cavity [31-33]. However, expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 genes in human primary conjunctival and pterygium cell lines and in mouse cornea have been documented [34]. The evidence of SARS-CoV-2 attachment to receptors and/or presence of ACE-2, TMPRSS2 and/or CD209L receptors in the ocular epithelia requires further investigation.

### Clinical manifestations of SARS-CoV-2 infection

The clinical manifestations documented for COVID 19 include pyrexia, respiratory, gastrointestinal, hepatic, renal, cardiac, neurological, ocular, olfactory, haematological and cutaneous [35].

The pyrexia may be associated with direct interaction of SARS-CoV-2 with the organum vasculosum of the lamina terminalis (OVLT) and/or indirectly via the stimulation of cytokine release (such as interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)- $\alpha$ ) which then act on the OVLT to cause fever [36].

Respiratory manifestations include respiratory distress, nasal congestion and sore throat. The respiratory distress resulted from lung compensatory mechanism on the hypoxia induced by inflammatory damages caused by SARS-CoV-2 infection of alveolar type II cells [18,37]. Nasal congestion and sore throat could be suggested to result from damages by SARS-CoV-2 infection of epithelia of the nasal cavity and nasopharynx respectively [38].

Gastrointestinal manifestations include diarrhoea, nausea, vomiting, abdominal pain and anorexia [39,40]. The possible

mechanisms for diarrhoea include malabsorption, intestinal secretion imbalance and enteric nervous system activation resulting from direct virus entry via ACE-2 receptors [30]. The direct/indirect destruction of intestinal epithelia due to inflammatory responses to the virus as ACE-2 is an important regulator of intestinal inflammation and intestinal flora disruption by the virus could possibly induce the diarrhoea [28,41]. In patients undergoing antibiotic and/or antiviral therapy, diarrhoea could result from dysbiosis in the intestine induced by these drugs [41]. Also, alterations in respiratory flora due to SARS-CoV-2 have been suggested to affect the digestive system via immune regulation thus leading to diarrhoea [30,42]. Nausea and vomiting may be suggested to result from damages to the gastrointestinal tract (GIT) mediated by serotonin/dopamine. Possible mechanisms preceding nausea and vomiting episodes involve high amplitude, retrograde peristaltic contractions of small intestine from distal to proximal part on antroduodenal manometry [43,44]. The abdominal pain could be associated with noxious stimuli generated from damages caused by and/or inflammatory responses to the virus [45]. Anorexia in COVID-19 is as a result of complex mechanisms ranging from the illness to stimulation of the satiety centre of the central nervous system.

The symptoms of liver involvement due to COVID 19 include increased activities of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase and alkaline phosphatase [9,35,46]. These could be associated with direct damage to hepatocytes by SARS-CoV-2 or as a complication of immune responses to the infection [47].

Renal symptoms reported in patients with COVID-19 include decreased urinary output, edema due to fluid retention and other symptoms indicative of acute kidney injury [48]. The proposed mechanisms of these symptoms are multifactorial and could result from cytokine-induced damage, hypoxemic injury, intra-abdominal hypertension, fluid imbalance, hypoperfusion, rhabdomyolysis-related tubular toxicity, endotoxin and immune-associated glomerulonephritis [49].

Cardiac symptoms include myocarditis and arrhythmias, and could be associated with direct damages to myocardium from SARS-CoV-2, hypoxaemic injury, hypoperfusion, systematic inflammation enhancement and down-regulation of ACE2 receptors [30,50].

Nervous, ocular, olfactory and gustatory symptoms reported to be associated with SARS-CoV-2 infection include dizziness, headache, acute cerebrovascular disease, ataxia, seizures, impaired consciousness, nerve pain, meningoencephalitis, vision impairment, conjunctivitis, and loss of taste and smell [41,51,52]. Angiotensin converting enzyme 2, direct viral damages, hypoxic injury and immune complex destruction of neurons are proposed mechanisms responsible for these symptoms observed in SARS-CoV-2 infection [53].

On haematology, the symptoms of SARS-CoV-2 infection documented include lymphopaenia, thrombocytopaenia, coagulation disorders and thrombotic complications such as venous thromboembolism, arterial thrombotic event, activated

partial thromboplastin and prothrombin times [54,55]. The lymphopaenia could be due to active lymphocyte destruction by SARS-CoV-2, excessive apoptotic signal induction by the virus in infected lymphocytes and/or suppression of myeloid cells in the bone marrow directly by the virus or indirectly by secondary mediators. The thrombocytic disorders observed could be associated with direct viral destruction of the cells or indirectly through interference with thrombocyte formation, coagulation and/or destruction of endothelial cells [22].

Cutaneous manifestations of COVID 19 include erythematous rashes, chickenpox-like vesicles, and finger/toe cyanosis, skin bullae and dry gangrene linked to acro-ischaemia [56,57]. These presentations could result from allergic reactions and thromboemboli formation induced by SARS-CoV-2.

### Gross pathological Observations due to SARS-CoV-2 infection

Autopsy reports of patients that died of COVID-19 have been focused on the respiratory system but findings on other organs are also documented. The nasal cavity down to the trachea revealed the presence of frothy exudates and hyperaemic epithelial surfaces [52]. These could result from possible excessive exudate production during the inflammatory processes and/or aspiration of fluid from the stomach. The lungs showed very large, extremely heavy and brittle appearance with evidence of hepatizations indicating pneumonia [58,59]. This pneumonia could be due to secondary bacterial infection resulting from immunosuppression caused by SARS-CoV-2. Also, deep vein thromboses and fatal pulmonary embolisms linked to coagulopathy resulting from the viral infection have been reported [55]. Patterned alternations of pale and hyperaemic areas resembling 'zebra stripes' on pleura and cut surfaces of the lungs have been documented and could be proposed to result from the destructive effects of SARS-CoV-2 on endothelial cells [60].

Autopsy findings that could be observed in the GIT include erosions and ulcerations of oesophageal mucosal surface due to refluxed gastric acid caused by vomiting; erosions and ulcerations of intestinal epithelial surfaces caused by the direct virus injury and/or action of secondary mediators. Also, haemorrhagic areas on the serosal surfaces of the intestines and mesenteric congestion are expected. The liver presents congestion with rough surfaces and could be cirrhotic. Enlarged kidneys (hydronephrosis) and haemorrhagic areas on the surfaces could be seen.

The heart is enlarged with ventricular hypertrophy and atrial dilatation; myocardium appeared pale and flabby, with evidence of ischemic or inflammatory changes and valvular calcifications; and endocardial petechial haemorrhages. The enlargement and hypertrophy resulted from compensatory mechanisms on the induced hypoxia due to reduced lung capacity. The haemorrhages resulted from SARS-CoV-2 damages to endothelial cells and thrombocytes [61].

### Histopathological findings due to SARS-CoV-2 infection

In the lung sections of patients that died of COVID 19,



lesions observed under light microscopy include exudative and proliferative phases of diffuse alveolar damage (DAD) and these comprise capillary congestion, desquamation and necrosis of pneumocytes, hyaline membranes, interstitial and intra-alveolar oedema, hyperplasia of alveolar type 2 cells, atypical squamous metaplasia, and thrombi containing platelet-fibrin [52,59,62]. The interstitial inflammatory infiltrate consisted mainly of lymphocytes and multinucleated syncytial cells [58,59]. SARS-CoV-2 particles in the pneumocytes have been demonstrated using electron microscopy [52]. These findings are associated with inflammatory reactions triggered by the virus following infection and destruction of epithelial and endothelial cells [63]. Also, the release of secondary mediators and actions of macrophages could further exacerbate the lesions observed.

In the heart, there is hypertrophy of myocytes with focal necrosis, interstitial and vascular fibrosis, haemorrhages and mononuclear cells infiltration of adventitia. Tubular-interstitial inflammation, interstitial fibrosis and glomerular sclerosis are observed in the kidneys and in the liver, microvascular congestion, steatosis and necrosis of hepatocytes have been reported [61].

### Sequelae of SARS-CoV-2 infection

The sequelae of SARS-CoV-2 infection include recovery or death. Recovery will only be achieved in the presence of robust immune responses (innate and acquired) and effective epithelial regeneration [18]. Due to the decreased immune competency, reduced mucociliary clearance and retarded epithelial regenerative capacity associated with increase in age, elderly patients present higher risk of contracting COVID-19 with imminent death. These could have resulted from uninterrupted virus replication and readily spread to the gas exchange units of the lung [18,64].

Following recovery from COVID-19, sequelae reported in the pulmonary system include pulmonary fibrosis resulting from abnormal wound healing and severe scarring [65]. Myocardial lesions such as infection-related myocarditis, reduced systolic function and cardiac arrhythmias have been documented as sequelae in the heart following COVID-19 [50,66]. Nervous sequelae include decline in short- and long-term cognition, cerebrospinal complications, encephalopathies, muscle injuries, depression, anxiety, psychotic disorders, anosmia and aguesia [67-69]. Other possible sequelae of COVID-19 include liver and kidney injuries depicted by abnormal liver and kidney function tests [52,70].

### Conclusions

The pathologic mechanisms of COVID-19 have demonstrated multisystemic involvements mediated by the presence of ACE2, TMPRSS2, CD209 and CD209L receptors in various organs. Deaths due to COVID-19 could be associated with respiratory failure resulting from surfactant deficiency and consequent alveolar collapse, cardiac syncope from direct damage to cardiac muscles, peripheral paralysis, cytokine storm and excessive haemorrhage from impaired coagulation.

Despite efforts put in place to get autopsy findings from patients that died of COVID-19, further investigations are required to get exclusive data on lesions involving other organs such as the brain and spinal cord. In doing so, the mechanisms of SARS-CoV-2 infection can fully be elucidated and proper preventive/treatment protocol can be developed. However, it could be speculated that damages to various organs and tissues in COVID-19 resulted from direct viral injury and/or indirectly via secondary reactions induced by the viral infection. Also, haemorrhagic lesions could be said to have resulted from SARS-CoV destruction of endothelial cells and/or viral induced coagulopathies.

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