

# Coronavirus disease 2019: current understanding of its pathophysiology and histopathological findings

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Although there have been many studies describing the clinical and histological features about the novel coronavirus disease 2019 (COVID-19) infection, there is lack of pathological data conducted on biopsies or autopsies. This review aimed to identify histopathological manifestation together with the pathophysiology of COVID-19.

The COVID-19 epidemic is now a global health crisis. Close contact transmission has greatly accelerated the spread of the disease, resulting in severe morbidity and mortality. The patient may be completely asymptomatic or show clinical signs and symptoms as a result of numerous systems or organs being affected. The condition might manifest itself clinically as a mild, moderate, or severe illness. According to the system affection, the lesions differ in intensity and histological features. This review summarizes the current knowledge on COVID-19-associated histopathological manifestation in multiple organ systems.

## Keywords:

Covid, Coronavirus, pathophysiology-histopathologyx

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## Introduction

Coronavirus disease 2019 (COVID-19) which was first reported in Wuhan, China and most commonly spread through respiratory droplets has led to the worldwide diffusion causing great threat to people [1].

Initially, the described manifestations were flu-like symptoms but an outbreak of a series of severe acute atypical viral pneumonia and pandemic COVID-19 was developed [2]. The pathogen responsible for these infections was belonging to the family of coronavirus and named by WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The latter had been reported to be highly homologous to SARS-CoV, which caused the respiratory pandemic in 2002–2003 [3,4]. The outbreak of COVID-19 was started since August, 2019 as zoonotic spread from a seafood market in Wuhan, Central China and described as a pandemic by WHO and subsequently was recognized to be transmitted from human-to-human and spread to ~200 countries worldwide [5,6].

Transmission from one person to other clusters of affected families has appeared, and health-care workers have proven person-to-person transmission [7]. This kind of transmission is thought to occur among close contacts through the airborne route (spread through the air), or aerosol route coming from respiratory droplets emitted through breathing, sneezing, and coughing of the patients [7–9]. Pathogen-bearing droplets can travel from 7 to 8 m

and can remain stable and persist on surfaces for up to 96 h. The mean incubation period was reported to be 5.2 days (4.1–7.0) [8].

The highest incidence of severe cases occurs in adults more than or equal to 60 years of age, most commonly in adult males; however, the median age of the patients was between 34 and 60 years. Fewer COVID-19 cases have been reported in children of less than 15 years. COVID-19 is also more likely to infect persons with chronic diseases such as cerebrovascular and cardiovascular diseases and diabetes, and severe manifestations are most likely associated with bacterial and fungal infections [10,11]. However, this review will focus on the following:

## Coronavirus disease 2019 pathophysiology

The virus spreads from person to person through respiratory droplets and aerosols. Once the virus enters the body, it connects to host receptors and enters host cells through membrane fusion or endocytosis once inside the body. The spike (S), membrane (M), envelop (E), and nucleocapsid (N) proteins are the four structural proteins found in coronaviruses [12–15].

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In humans, the spike protein is the major protein involved in the pathogenesis. The virus that causes the COVID-19 pandemic interacts to the angiotensin-converting enzyme-2 (ACE-2) receptor in body cells through the S-protein (spike-shaped viral protein), which may be changed by the enzyme transmembrane proteinase to allow viral particles to enter the cell more easily [16]. The virus's spike protein, through its receptor-binding domain (RBD), attaches to a human cell surface receptor protein called ACE-2, which is encoded by the ACE-2 gene, and is then primed by the auxiliary protein TMPRSS2 (transmembrane protease, serine 2), which is expressed by epithelial cells in specific tissues, including those in the aerodigestive tract [17–19]. The S-protein, which protrudes from the viral surface and is responsible for host attachment and penetration, is seen extending from the viral surface. This protein is made up of two functional subunits (S1 and S2), with S1 being responsible for binding to the host cell receptor and S2 being responsible for fusing the viral and host cellular membranes [12].

The virus enters the epithelial cells of the pulmonary alveoli after membrane fusion, and the viral contents are discharged inside. The virus replicates inside the host cell and either forms a negative strand RNA or undergoes transcription by a preexisting positive single-stranded RNA. With the production of new proteins in the cytoplasm, these freshly created negative strands continue to make new positive strands, a process known as translation [20,21]. Through RNA polymerase activity, the virus replicates and forms a negative strand RNA from the preexisting single-strand positive RNA inside the host cell (transcription). This freshly produced negative strand RNA is used to generate new positive strands, which are then translated into new proteins in the cell cytoplasm [2,20,21].

The immune response is triggered when the virus infects the host cells, causing a flood of inflammatory cytokines and chemokines to be secreted. Following infection, numerous cytokines are released in body fluids, resulting in severe respiratory distress and multiple organ failure. This also explains why most COVID-19 patients have mild symptoms at the start of the disease, whereas the conditions of a few affected patients suddenly worsen after being diagnosed in hospital, which could be due to the body producing excessive cytokines after the disease, resulting in a 'cytokine storm' in the body [22].

### Coronavirus disease 2019 etiology

While adapting to their new human hosts, SARS-CoV-2, like other RNA viruses, is susceptible to genetic evolution with the formation of mutations over time, resulting in mutant variations with different features than their ancestral strains. Several SARS-CoV-2 variants have been identified over the course of the pandemic. According to WHO's most recent epidemiological bulletin, five SARS-CoV-2 strains have been detected since the pandemic began on December 11, 2021 [23] as follows:

- (1) Alpha (B.1.1.7): people infected with this version had a more severe disease than people infected with other circulating virus types [24,25].
- (2) Beta (B.1.351): this variation has numerous spike mutations, three of which are located in the RBD and improve ACE receptor-binding affinity, increasing the chance of transmission [26–28].
- (3) Gamma (P.1): the spike protein in this version shows mutations. The RBD contains three alterations (L18F, K417N, and E484K), which are similar to the Beta variation [29].
- (4) Delta (B.1.617.2): this variation reveals 10 mutations in the spike protein and has spread rapidly over the world [30].
- (5) Omicron (B.1.1.529): it has more than 30 modifications to the virus's spike protein, as well as a dramatic increase in the frequency of cases [31]. Omicron has a 13-fold higher viral infectivity than the Delta version and is 2.8 times more infectious [32]. From the end of November 2021 to January 17, 2022, global daily SARS-CoV-2 infections grew by more than 30 times, although reported COVID-19 cases increased by just six times [33,34]. Because the number of asymptomatic or mild cases has increased in comparison to prior SARS-CoV-2 variations [35,36], the global infection-detection rate has decreased from 20 to 5% [33].

By March 2022, the Omicron version will have infected a major percentage of the world. With continuous increases in COVID-19 vaccination, the use of a third vaccine dosage in many countries, and high levels of infection-acquired immunity, global SARS-CoV-2 immunity should be at an all-time high for some time. The world should expect low levels of virus spread for a few weeks or months [37].

COVID-19 will become another recurring disease that health systems and societies must deal with. For example, in most nations, the death toll from Omicron appears to be comparable to that of a

terrible influenza season in Northern Hemisphere countries. COVID-19 will resurface after the Omicron wave, but the pandemic will not [37].

#### **Clinical features of coronavirus disease 2019**

The virus spreads from person to others through respiratory droplet transmission. This occurs when a person is exposed to someone who is actively sneezing or coughing. Also, transmission of the virus may occur through fomites used by an infected person such as blankets, bedsheets, thermometers, and kitchen utensils [38,39].

The incubation period is 5–6 days, but can be up to 14 days. During this period, the infected person can transmit the virus to healthy individuals, this period is known as the presymptomatic period. The patients of COVID-19 most commonly present with fever, malaise, dry cough, breathlessness, and body aches [40–42]. Although some patients may present with asymptomatic, mild, moderate, or severe disease, some others may present with gastrointestinal symptoms such as vomiting, abdominal pain, and diarrhea [43].

The commonly seen complications of COVID-19 were acute respiratory distress syndrome, acute respiratory failure, sepsis, disseminated intravascular coagulation, pulmonary embolism, and acute liver and kidney failure [44].

#### **Histopathological findings in coronavirus disease 2019**

The WHO recommends that all specimens should be regarded as potentially infectious [8]. Many of these samples are also submitted to pathology laboratories; hence it is important to take adequate precautions while collecting, handling, and transporting clinical specimens to protect ourselves and our staff [45]. In this review, we focus on discussing the pathological finding in the following systems.

##### *Histopathological findings of the respiratory system*

Patients with upper respiratory tract usually show mild or moderate symptoms, while those with lower respiratory tract infections usually present with features of pneumonia up to acute respiratory failure. The severity of disease usually increases with the presence of other morbidities such as diabetes, hypertension, chronic kidney disease, and obesity [22,46].

Macroscopically, lungs appear congested with patches of hemorrhagic necrosis [22]. Microscopically, the prominent features are vascular degeneration, alveolitis with infiltration of mononuclear

inflammatory cells along with desquamation and formation of hyaline membrane. Also, there is massive fibrinous exudate with interstitial thickening and hyperplasia of type II alveolar epithelium. Large vessel thrombi with presence of red blood cells in the alveolar lumen along with formation of fibrin plugs. Diffuse hyperplasia of type II alveolar epithelium alongside with presence of fibrinoid vascular necrosis. Squamous metaplasia with infiltration of inflammatory cells mainly neutrophils, macrophages, and monocytes in the alveolar lumen, indicating bronchopneumonia (Fig. 1a–f) [22,46,47].

Immunostaining of lung sections with a rabbit polyclonal antibody to the Rp3NP of SARS-CoV-2 showed prominent expression on alveolar epithelial cells including damaged, desquamated cells within the alveolar spaces [48].

Ultrastructural examination revealed type II pneumocytes harbor many autophagosomes, which is characterized by double membranes and the presence of cytoplasmic organelles. These autophagosomes that contain viral aggregates showed also to be present in the epithelial cells of trachea and within the mucous in tracheal lumen [17].

##### *Histopathological findings in the gastrointestinal tract*

The pathogenesis of gastrointestinal tract injury is unknown and may be considered due to direct ACE-mediated viral toxicity of the mucosa of the intestine, cytokine-induced inflammation, and vascular abnormalities [49].

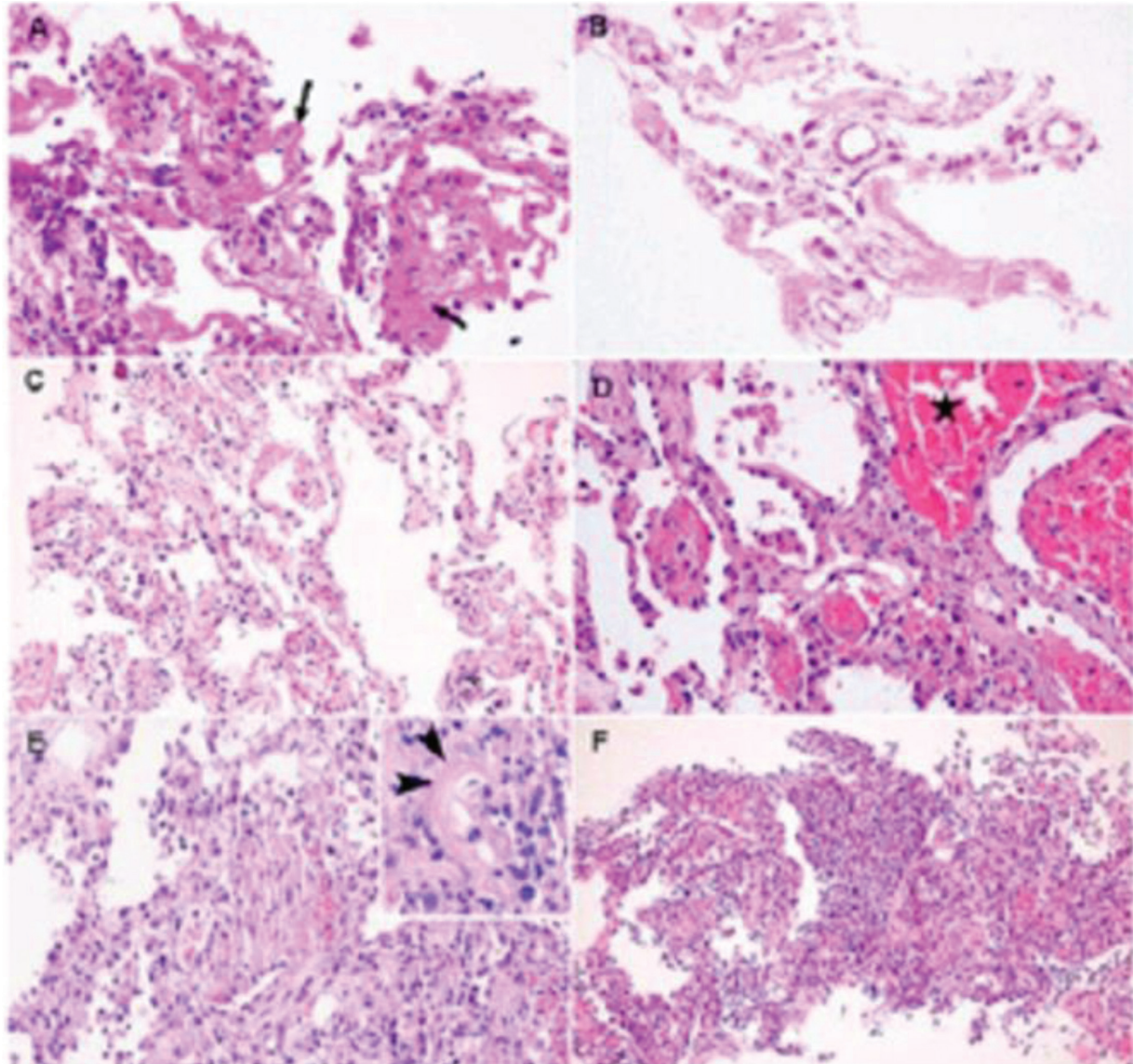
Common symptoms with COVID-19 were decreased appetite, abdominal pain, nausea, vomiting, diarrhea, and gastrointestinal bleeding [46].

Microscopically, gastric tissue may show epithelial degeneration, necrosis, and mucosal shedding along with inflammatory infiltration in the lamina propria and submucosa. Submucosa also revealed dilated and congested blood vessels. Gastrointestinal mucosa revealed varying degrees of degeneration, shedding, and necrosis [50].

##### *Histopathological findings in the liver*

Hepatic injury mostly occurs in those with moderate to severe illness. Microscopically, liver cell degeneration parallel to focal necrosis has been detected together with densely lymphocytes infiltration in portal triad and showed CD20 immunopositivity. Liver may show signs of fibrosis indicative of cirrhosis. Hepatic sinusoids are dilated and show mild sinusoidal

Figure 1



Histopathological changes in the lungs of COVID-19 patients. (a) Infiltration of lung tissue by mononuclear inflammatory cells, along with desquamation of alveolar epithelium and formation of hyaline membrane (arrow). (b) Hyaline membrane formation with no signs of inflammatory cell infiltrate. (c) Interstitial thickening with hyperplasia of type II alveolar epithelium. (d) Red blood cells present in the alveolar lumen (asterisk) along with the formation of fibrin plugs. (e) Diffuse hyperplasia of type II alveolar epithelium and presence of fibrinoid vascular necrosis (inset). (f) Infiltration of inflammatory cells, predominantly neutrophils into the alveolar lumen, indicative of bronchopneumonia (hematoxylin and eosin stain), cited from Tian *et al.* [46]. COVID-19, coronavirus disease 2019.

lymphocytic infiltration. Periportal and centrilobular areas show necrosis indicative of injury (Fig. 2a–f) [51].

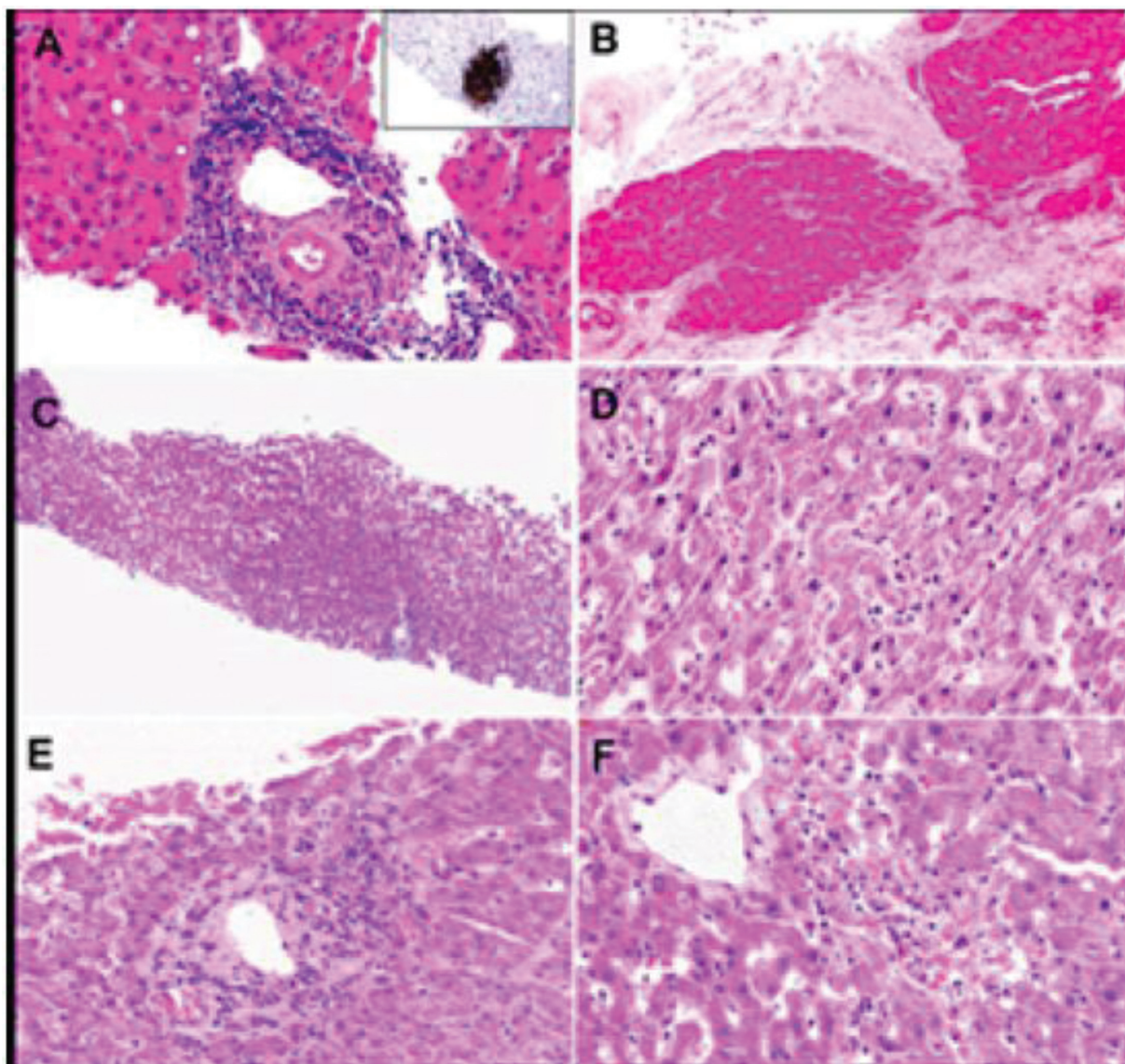
#### *Histopathological findings in the urinary tract (kidney)*

ACE-2 is observed to be upregulated in corona patients, and immunostaining with SARS-CoV-2 antibody was shown to be positive in the renal tubules. Other factors attributed to acute renal injury include abnormal coagulation and systemic hypoxia [52].

Some patients with COVID-19 suffered new-onset proteinuria. Microscopically, proximal tubules injury

with loss of brush border, vacuolar degeneration in tubular epithelial cells and swollen glomerular endothelial cells with protein exudate in the cavity were detected. Other changes include presence of thrombi in capillaries and tubular epithelial cell edema together with edema of interstitial spaces of the distal and collecting tubules. Glomeruli showed ischemic contraction and Bowman's capsule showed presence of accumulated plasma. Tubular deposition of hemosiderin granules, calcium deposits, and pigmented casts were observed (Fig. 3a–f) [9].

Figure 2



Histopathological changes in the liver of COVID-19 patients. (a) Dense portal infiltration by atypical small lymphocytes (inset: CD20 immunostaining) and focal glycogenated nuclei in hepatocytes have also been observed. (b) Hepatic nodules showing fibrosis, indicative of cirrhosis. Cirrhotic nodules with thick fibrosis. (c) Hepatic sinusoids are dilated and filled with lymphocytes. Mild sinusoidal dilatation with increased lymphocytic infiltration. (d) High-power view showing sinusoidal lymphocytes. (e, f) Periportal and centrilobular areas show necrosis, indicative of injury (hematoxylin and eosin stain), cited from Tian *et al.* [46]. COVID-9, coronavirus disease 2019.

By electron microscope, clusters of viral particles with distinctive spikes were observed in the epithelium of the tubules and podocytes [53].

#### *Histopathological findings of the cardiovascular system*

Reports have shown that viral infection usually cause infectious myocarditis; however, CoV-19 patients showed hypertrophied cardiomyocytes, with focal edema, inflammatory infiltrates, fibrosis, degeneration, and interstitial hyperplasia along with signs of lymphocytic myocarditis [9].

Ultrastructural findings show presence of CD4-T cells with inflammatory infiltrates along with swelling of myocardial cells [54].

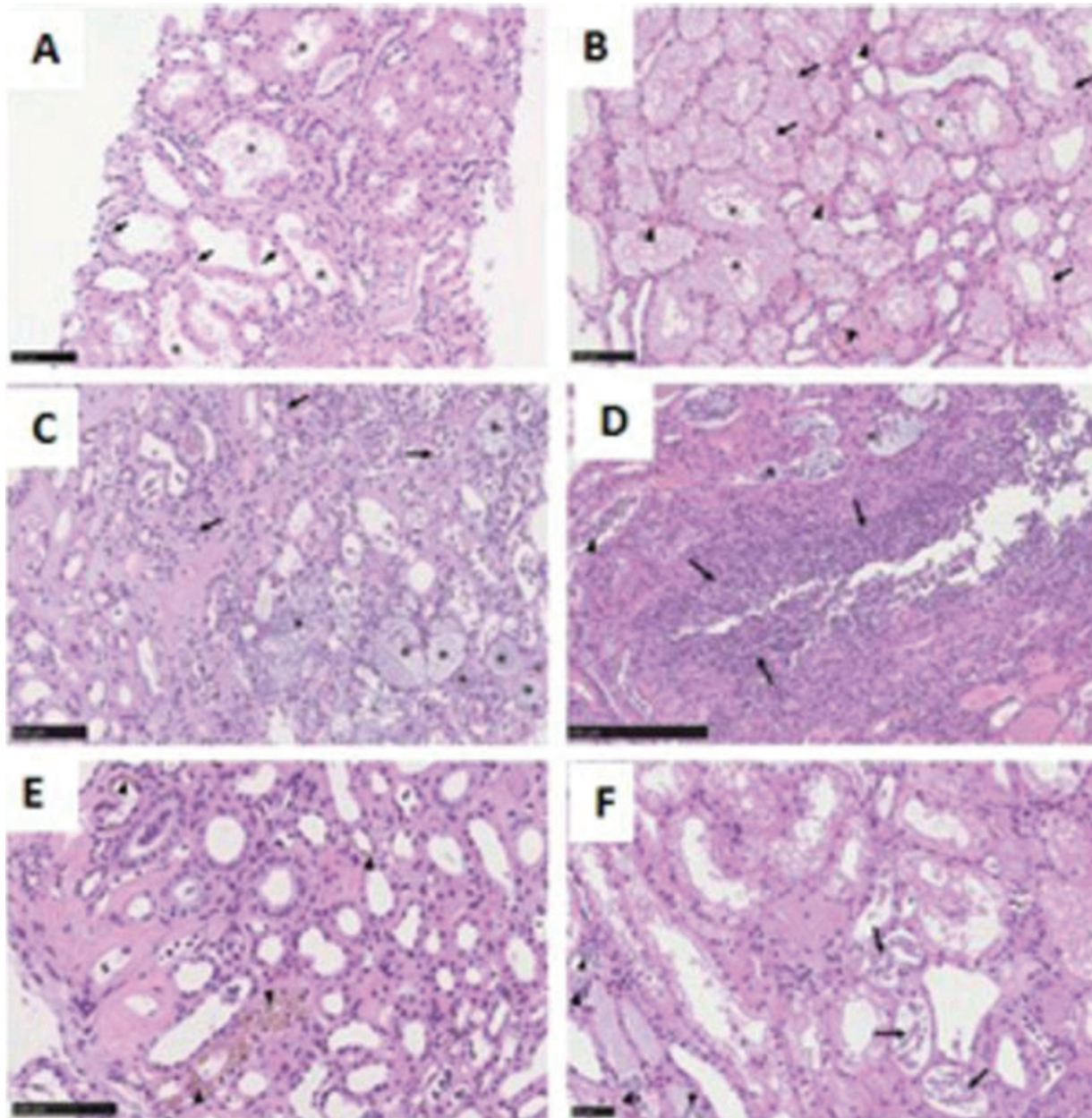
Endomyocardial biopsy shows endocarditis; viral particles were observed in interstitial cells with damaged cell membranes along with inflammatory infiltrates [55].

The endothelial cells of blood vessels show presence of viral inclusions along with inflammatory cells and apoptotic bodies [50].

#### *Histopathological findings of the cerebrovascular system*

Headache and dizziness are the commonest CNS manifestation, while loss of smell and taste are the most common symptoms of the peripheral nervous system. Other rare symptoms include stroke, convulsions, ataxia, and acute encephalopathy [56,57].

Figure 3



Histopathological changes in kidneys of COVID-19 patients. (a) Epithelium of proximal convoluted tubules shows decreased/loss of the brush border. (b) Tubular epithelial cells show vacuolar degeneration (arrows), leading to collection of necrotic debris in the lumen (asterisks). Blocked peritubular capillaries due to erythrocytic aggregates (arrowheads). (c, d) Inflammatory cells (arrowhead) infiltrate the tubules and arcuate artery (arrows), bacterial foci (asterisks) is also observed. (e, f) Tubular deposition of hemosiderin granules, calcium deposits (arrowhead), and pigmented cast (arrow). Bars=(f) 50  $\mu$ m, (a–c, e, g, h) 100  $\mu$ m, and (d) 250  $\mu$ m (hematoxylin and eosin stain), cited from Su *et al.* [52]. COVID-9, coronavirus disease 2019.

Postmortem examination of patients with COVID-19 showed widespread brain lesions including manifestation of hypoxic ischemic brain injury with edema and neurological degeneration [58]. COVID-19 RNA was present in the cerebrospinal fluid and brain tissue of autopsied patients with neurological manifestations [59,60].

#### *Histopathological findings of the genital system (testis)*

As ACE-2 receptors are present in Sertoli cells, Leydig cells, and seminiferous tubules, there is an association

between corona virus family and orchitis in males [8]. Many reports observed that Sertoli cells are the most susceptible than germ cells.

Histologically, testis demonstrates extensive germ cell destruction along with edematous Sertoli cells and reduced spermatogenesis. The basement membrane becomes thickened with peritubular fibrosis along with vascular congestion and leukocytic infiltration in the interstitial tissue. Tubular cells show sloughing into the lumen. Sertoli cells show

vacuolation, swelling, and cytoplasmic rarefaction [61]. Inflammatory infiltration could affect the function of Leydig cells with decreased production of testosterone. On the other hand, lymphocytic infiltrates along with histiocytes could damage the blood–testis barrier with direct destruction of the seminiferous tubules. Immunohistochemical staining showed CD3-positive lymphocytes and CD68-positive histiocytes (Fig. 4a–f) [63].

Like other viruses, coronavirus could activate the inflammatory cytokines and potentiate autoimmune response. This may cause orchitis with testicular damage leading to infertility and increase the chances of testicular tumors [64].

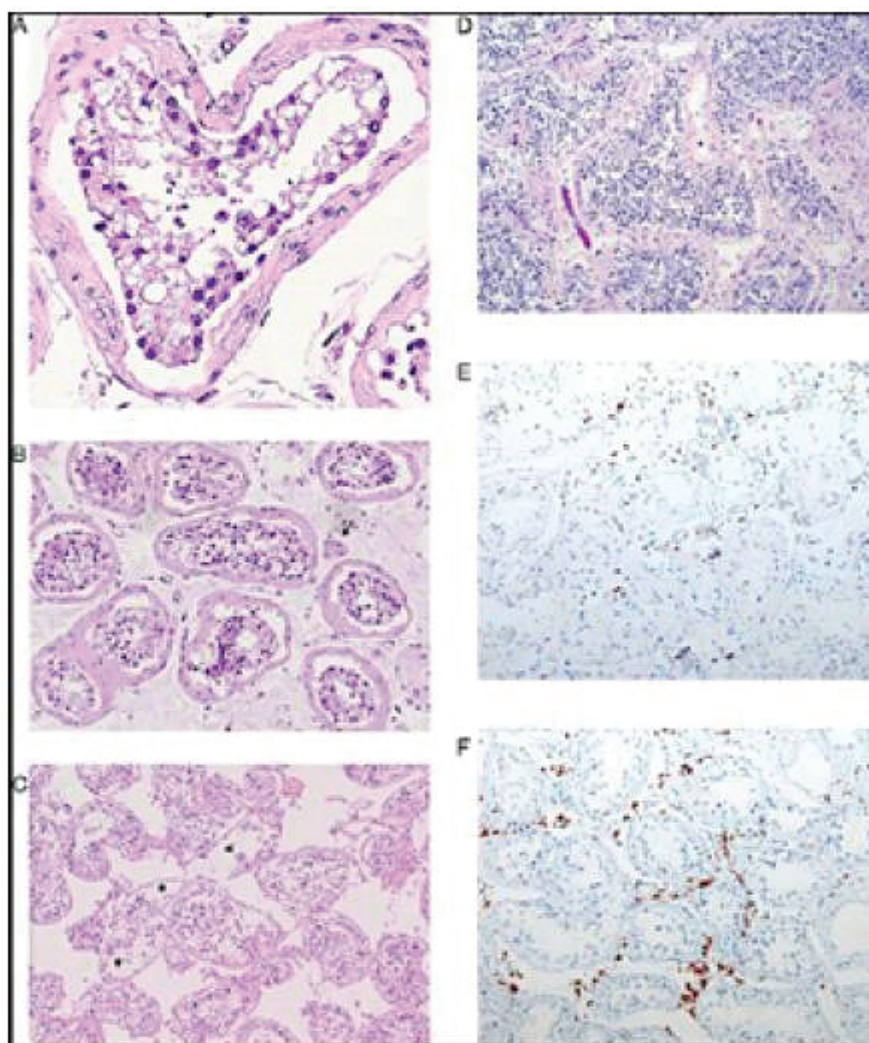
#### *Histopathological cutaneous manifestations with coronavirus*

The virus can reach the skin through endothelial cells of blood vessels, which abundantly express ACE-2 giving features of vasculitis. Immune response with activated Langerhans cells leads to a cascade of reactions [65].

Although some cases of COVID-19 pass unnoticed other patients may show signs of dermatitis, urticarial, chicken pox-like vesicles, erythematous rash, purpuric papules, which may be painful (Fig. 5a–d) [67].

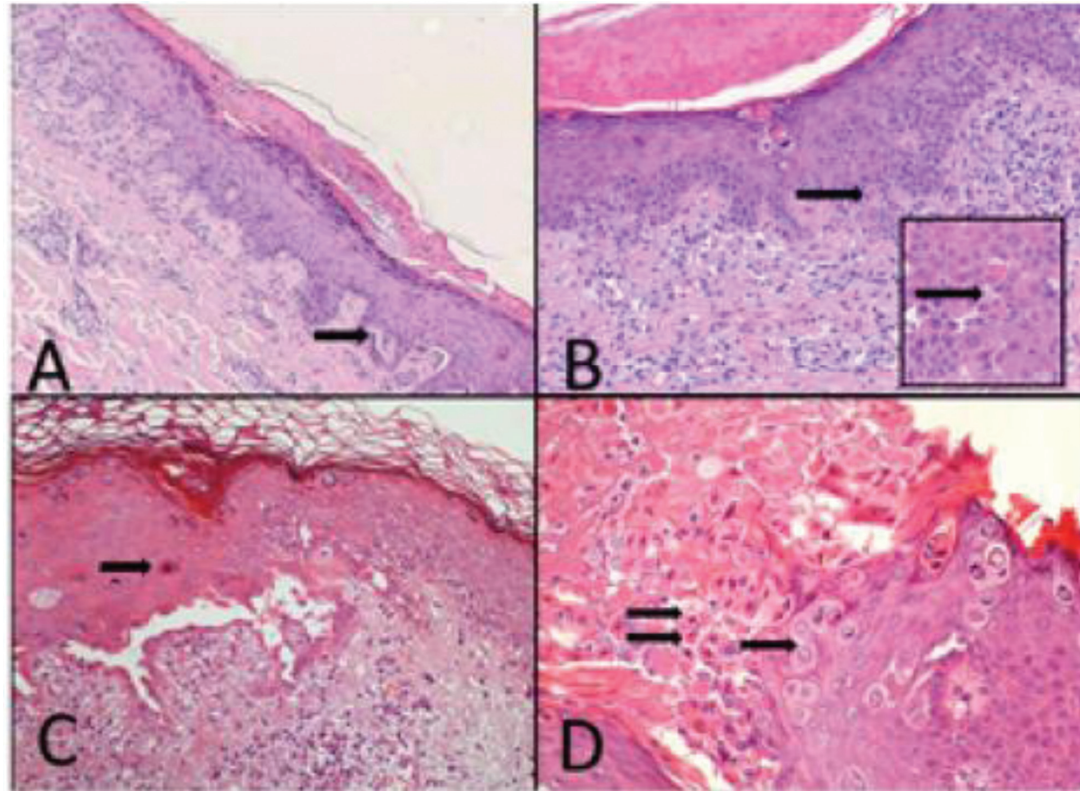
While there is no correlation with the duration or severity of the disease, sometimes persons with

**Figure 4**



Pathological changes observed in testes from patients with COVID-19. (a and b) Defoliated and edematous sertoli cells with vacuoles along with reduced spermatogenesis and scattered Leydig cells (arrow). (c) Tubular cells show sloughing into the lumen (asterisks), indicative of injury. There is marked interstitial edema. (d) Non-COVID testis with protracted disease showing interstitial edema with infiltration of inflammatory cells (hematoxylin and eosin stain). (e) Immunohistochemical findings showing CD3-positive+T lymphocytes and (f) CD68-positive+histiocytes, cited from Yang *et al.* [62]. COVID-9, coronavirus disease 2019.

Figure 5



Histopathological changes in the skin of COVID-19 patients. (a) Acanthosis with presence of cleft (arrow) observed in the skin of COVID-19 patients. Parakeratosis is also observed along with abnormal keratinization. (b) Localized necrotic keratinocytes (arrow) with abnormal keratinization (inset), with lymphocytic infiltration (arrow). (c) Acantholytic cleft with an adjacent apoptotic keratinocyte (arrow). (d) Pseudo-herpetic features (arrow) along with apoptotic keratinocytes (double arrow), cited from Gianotti *et al.* [66]. COVID-9, coronavirus disease 2019.

COVID come with only cutaneous manifestation mostly in the hand, feet, trunk, and other exposed parts of the skin [68].

As ACE-2 is expressed in the stratum basale, smooth muscle cells of the skin, cells around hair follicles, cells of sebaceous and eccrine glands, and signs of inflammation had been observed. They include vascular plasmacytic and lymphocytic infiltration around blood vessels along with acanthotic, parakeratosis, dyskeratotic, and necrotic keratinocytes. Pseudo-herpetic features with apoptotic keratinocytes are observed [66].

In-situ hybridization and immunostaining using polyclonal SARS nucleocapsid protein showed no virus-induced cytopathic alteration or intranuclear inclusions [69].

## Conclusion

Information regarding the histopathological features in COVID-19 is limited. Although the virus is mainly respiratory and immune systems, other systems like urinary (kidney), gastrointestinal tract, cardiovascular,

reproductive (testis), nervous system, and skin are not spared especially in elderly patients, more often if comorbidities are also present. This review would help the clinician and researchers to understand the tissue pathology which can further better planning for the management of the disease and avoiding other health risks.

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## Conflicts of interest

There are no conflicts of interest.

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