



## Review

### A comprehensive review of histopathological findings of infections induced by COVID-19

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**Abstract:** The severe acute respiratory syndrome (SARS)-Coronavirus (CoV2) virus, first identified in Wuhan, China, caused the coronavirus disease 2019 (COVID-19) which soon became a global pandemic, as labelled by the World Health Organization (WHO). The transmission method of the infection is primarily through droplets of various sizes. The SARS-CoV2 virus leads to a severe respiratory illness which in the first place causes the simulation of the acute respiratory syndrome. In order to diagnose of COVID-19 efficiently, samples with infection probability need to be examined through histopathological methods. Survival chances of the infected can remarkably increase if the virus is diagnosed timely by reverse transcription-polymerase chain reaction (RT-PCR) or computed tomography (CT) scan of the chest. One of the destructive effects of COVID-19 is the formation of ground-glass opacity (GGO) in the lungs which might be regarded to be equivalent to high-altitude pulmonary edema (HAPE). COVID-19 acts very similarly to SARS and Middle East Respiratory Syndrome (MERS) which can be inactivated by the chemical compounds of ethanol and sodium hypochlorite. Epidemiologic characteristics of COVID-19 have been indicated by numerous studies; however, there is still a lack of details of pathologic changes in the lung. The present comprehensive review is an attempt to assess and cover the current state of knowledge on COVID-19 disease based on the histopathologic studies conducted before May 2020.

**Key words:** COVID-19; Pneumonia; Clinical features; Biopsy; Histopathological changes.

## Introduction

In December 2019, COVID-19 emerged in China and quickly became a pandemic which spread all over the world and caused acute pneumonia (1). Right following its advent, various examinations and studies were conducted to figure out COVID-19 transmission chains and the probable effective medical treatments (2,3). As characterized by Zhu et al, COVID-19 is an infectious disease induced by parasites, viruses, and bacteria that spread between vertebrates and humans (1). The sequencing of the viral genome has been done in some studies whose results revealed its similarity to SARS in 80% of cases and bat-borne zoonotic coronaviruses in more cases (1,4).

In February 2020, the name COVID-19 was given to the virus by WHO (5). According to the Coronavirus Study Group of the International Committee on Taxonomy of Viruses, COVID-19 is a coronavirus variant that caused the spread of SARS in 2002-3; therefore, this new virus is called SARS-Corona Virus 2 (SARS-CoV-2) (6). This virus causes a severe resolved disease which can be fatal due to progressive respiratory failure and massive alveolar damage. Its case fatality rate has

been reported to be 2%. According to the statistics, COVID-19 afflicted approximately 6.08 million people by May 2020, 370 thousand of whom died and 2.57 million recovered (7).

Similar to clinical presentations associated with the SARS virus, lower respiratory samples obtained from COVID-19 victims have the highest viral load (8). In addition, detecting the RNA of COVID-19 from blood and stool samples has raised the worry that similar to the SARS virus, it can involve multiple organs (9). Angiotensin-converting enzyme 2 (ACE2) in both COVID-19 and SARS acts like a typical cellular entry receptor (3). The outbreak of SARS limited and its mortality was high; however, COVID-19 has a remarkably higher speed of spread and a lower rate of mortality (10).

The transmission pace of COVID-19 among humans is outstandingly high, and the mortality rate varies, such that it causes more deaths among the elderly and those with weak immune systems or underlying conditions (8,11). The present body of knowledge on pathology and pathogenesis of COVID-19 is based on a limited number of described cases and investigations into the available knowledge about similar coronaviruses like MERS-CoV and SARS-CoV. It is highly significant to

evaluate COVID-19 pathologically and specify its cellular localization and distribution within tissues in order to clarify its pathogenesis and assist with the development of methods to prevent or treat the disease (12-16).

It should be noted that there are very few reports on tissue tropism and histopathologic manifestations of fatal COVID-19 cases (17). Lack of sufficient information reveals the fact that a large number of infected cases have imposed a lot of pressure on medical systems all over the world. Patient management and antiviral development can be significantly affected by accurate documentation of the COVID-19 pathobiology (13). Gastrointestinal and pulmonary involvement has been shown by most histopathological studies of COVID-19; however, they used a limited number of cases or samples (12). The current comprehensive review of recent histopathologic studies up to May 2020 was carried out in order to cover the available shortcomings in this regard.

## Methods

By conducting a comprehensive review of the most recent related studies, the present study was aimed at determining the major histopathological features of COVID-19. For this purpose, the keywords related to coronavirus, COVID-19, SRAS, histopathological investigations, and infectious respiratory disease were searched on Science Direct, UpToDate, EMBASE, Google Scholar, and Pub-Med databases in order to identify the study articles that had been published by May 2020. COVID-19 was primarily chosen as the main subject, followed by adding histopathological findings of infections caused by COVID-19 in order to obtain more related articles. Finding the most relevant recent articles was the second step. Finally, to perform the review, Cochran's seven-step model was employed:

Step 1: Determining the year

Step 2: Specifying the inclusion criteria: All quantitative and qualitative studies published in English, whose full text was available, were searched, leading to the selection of 218 articles.

Step 3: Study selection: The main subject was COVID-19, followed by adding histopathological investigations, problems, and requirements. Evaluating the titles and summaries revealed that 51 articles were more related to the main title, which were chosen and the rest were excluded. Figure 1 below summarizes the process of selecting the articles. At last, following the PRISMA table, the retrieved articles were categorized based on their major concern, including histopathological findings, infectious respiratory disease, COVID-19, and SARS.

Step 4: Assessing the quality of the articles: For this purpose, the articles were studied fully. The articles containing significant information on COVID-19 histopathological findings were chosen and analyzed.

Step 5: Extracting the data: Studying the article text thoroughly led to the selection of 11 articles with significant points on the main aim of the study.

Step 6: Analyzing the collected data: The data obtained from reviewing the studies were described, compared, and analyzed qualitatively.

Step 7: Presenting the results: The results of the review are presented as research findings.

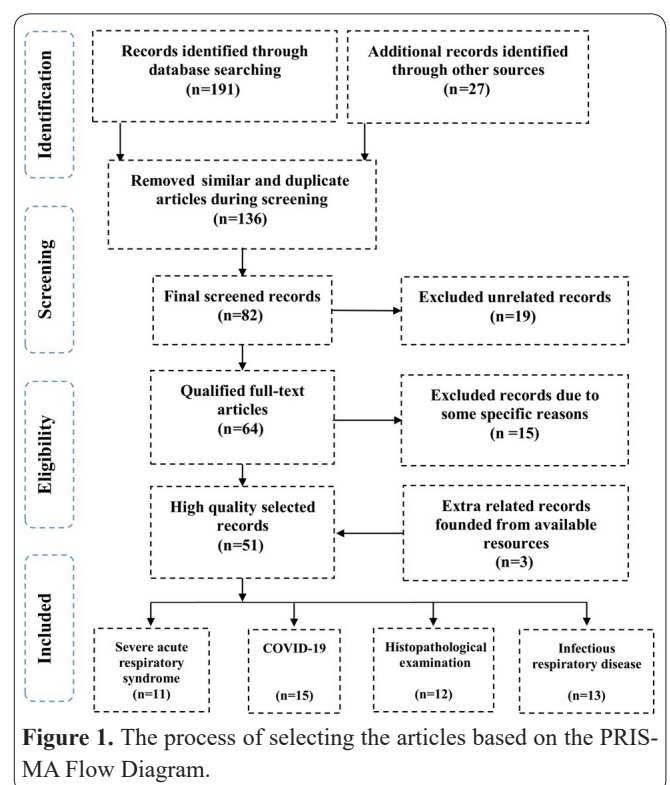
## COVID-19 controlling strategies

COVID-19 pandemic can be responded to at individual, laboratory, hospital, and society levels. Measures taken at the society level include restricting travels and large gatherings like sports, cultural, religious, and educational events (18). These measures are mainly aimed at preventing the rapid spread of the virus and avoiding excessive pressure and burden on healthcare systems, all mentioned measures are used mainly as a mitigation strategy. In addition to these measures, there should be other measures aimed at protecting patients with routine annual and preventive health visits from being infected. Moreover, the capacity of the hospitals should be raised to be prepared to respond to large infected cases (19).

Crucial healthcare measures need to be prioritized, leading to a decrease in inpatient admissions and unnecessary outpatient visits (19). Healthcare staff of laboratories and medical centers need to work in shifts in order to minimize risky contact between people. Tan *et al* recommended that laboratory staff need to check their temperature twice a day for early identification of COVID-19 and accurately perform viral testing, isolation, and quarantine measures in critical situations (20). Quarantine and consultation with doctors or healthcare professionals are the primary preventive measure for individuals suspected of COVID-19. In addition, sufficient equipment should be provided for laboratory workers so that they can cope with emergency and contingency plans for patients who are quarantined due to COVID-19 (21).

## Gross Findings

During autopsy surgical procedures, the results of the gross examination of the COVID-19 patients' lungs indicated that their tracheae were mildly erythematous and had normal caliber. The lungs get heavier almost in

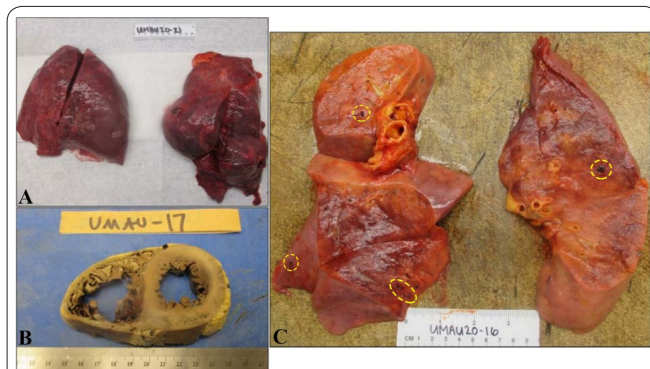


**Figure 1.** The process of selecting the articles based on the PRISMA Flow Diagram.

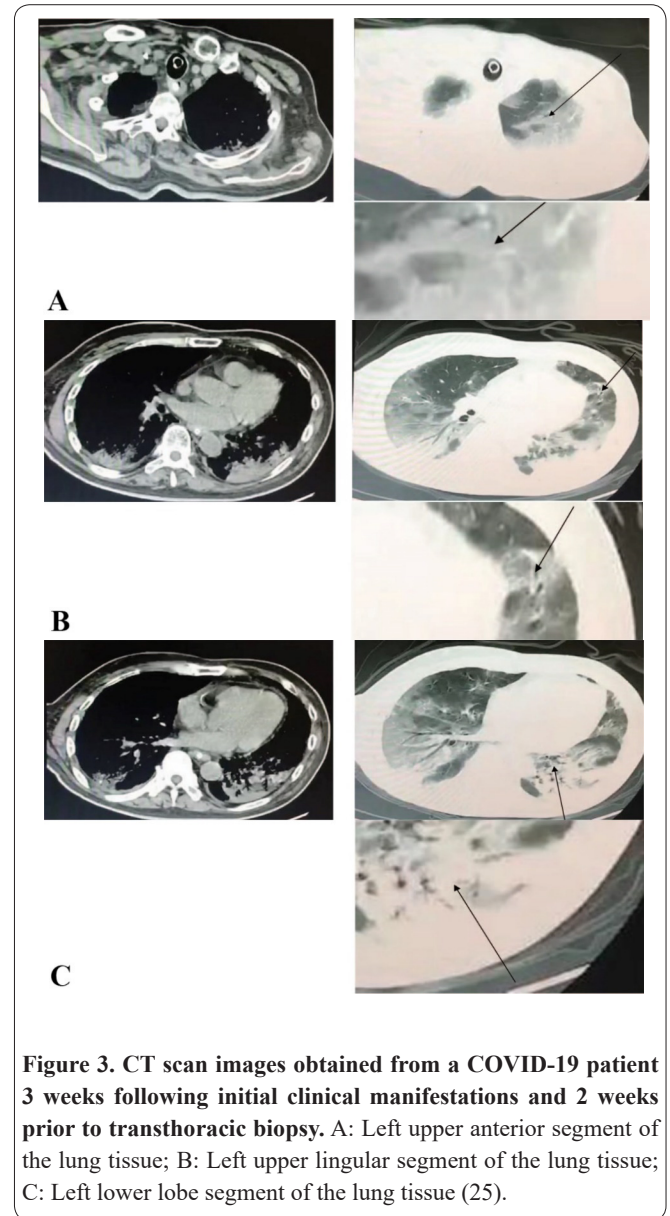
all cases, such that the left lung rises from ranging from 583±216g to 680-1030g, and the right from 663±239g to 800-1050g. Moreover, it has been reported that lungs infected with COVID-19 have been reported to have usual fissures and lobes; however, prior partial lobectomy on the right lung was observed in some died cases (15). COVID-19 patients are commonly characterized by having pink froth in their airways and thick, white mucous in their bronchi. They have also reported having mild to moderate serosanguinous pleural and pericardial effusions. In addition, diffusely edematous and firm parenchyma is reported in each lung, which is a shared characteristic with acute respiratory distress syndrome (ARDS). As seen in Figure 2A, except for one of the deceased patients, all others were diagnosed with regions of dark-colored hemorrhage with focal demarcation throughout the peripheral parenchyma in their lungs. On cut sections, the areas with hemorrhage on the external surface indicated frank hemorrhage (22).

Due to obstruction of the respiratory tract, about half of COVID-19 patients might experience heart failure. However, myocardial and endocardia membranes are not much likely to undergo inflammatory cellular infiltration (23). There is an apparent focal irregularity in the shape of the myocardium with darkened cytoplasm; however, such changes are not enough to be interpreted as an acute myocardial injury. According to the results of the study conducted by Sufang *et al*, myocardial hypertrophy, interstitial fibrosis, and focal edema associated with COVID-19 disease are of various degrees, indicating prior changes in underlying diseases like hypertension-associated myocardial hypertrophy and past ischemic injury (24).

Cardiac and pulmonary pathology in COVID-19 were studied by Sharon *et al* who reported right ventricular dilatation and cardiomegaly as the most important gross findings. Massive dilatation was observed in one patient with right and left ventricular cavities being respectively 3.6 and 3.4 cm in diameter (Figure 2B). In all cases, the surface of the myocardium was free of significant lesions, red-brown, and firm, and no significant stenosis or acute thrombus formation was observed in their coronary arteries. They also observed the cut surfaces of the lung tissue had alternating areas of tan-grey consolidation with patchy areas of hemorrhage ranging from 3-6 cm in their greatest diameter. Moreover, small,



**Figure 2. Gross findings of the heart and lungs.** A: Lungs with patches of dark-colored hemorrhage and bilateral pulmonary edema; B: A heart with extreme right ventricular dilatation and straightening of the interventricular septum; C: Cut sections of the lung with thrombi within peripheral small vessels (yellow ellipses) (22).



**Figure 3. CT scan images obtained from a COVID-19 patient 3 weeks following initial clinical manifestations and 2 weeks prior to transthoracic biopsy.** A: Left upper anterior segment of the lung tissue; B: Left upper lingular segment of the lung tissue; C: Left lower lobe segment of the lung tissue (25).

firm thrombi existed in the sections of the peripheral parenchyma of some cases (Figure 2C) (22).

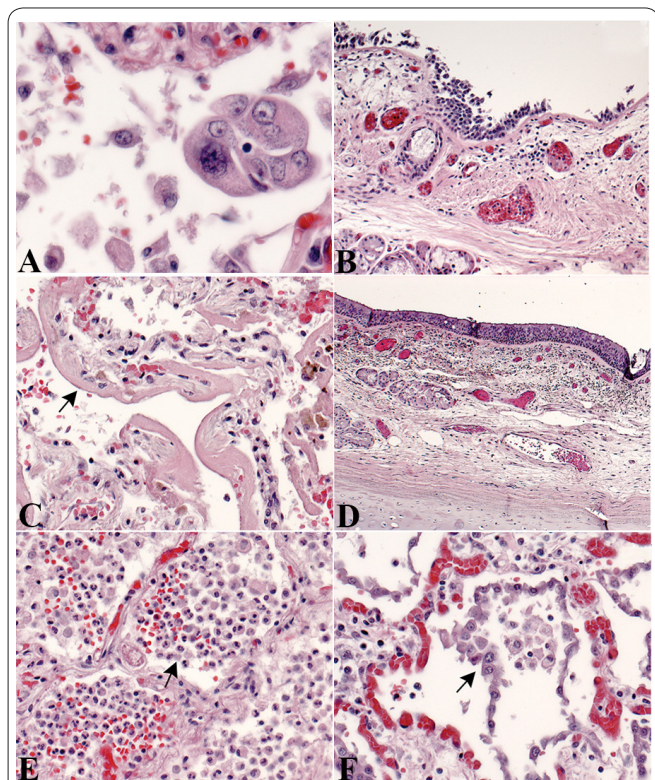
In their study, Huilan *et al* described the histopathologic changes in a COVID-19 patient's lungs. For this purpose, a transthoracic 14-gauge needle biopsy was employed to obtain a lung tissue from the left upper anterior segment (Figure 3A, arrow), left upper lingular segment (Figure 3B, arrow), and left lower lobe (Figure 3C, arrow), coinciding with ground-glass opacities on chest computed tomography (CT) (25). Biopsy lung sections were analyzed using hematoxylin-eosin staining, and immunostaining for COVID-19 was carried out as reported by Zhou *et al* (26) and Corman *et al* (27). As revealed by the CT scans, there was patchy bilateral ground glass like opacifications (Figure 3A-C, arrows). In spite of antiviral therapies, as they reported, hemodynamic instability and respiratory continued, leading the death of the patient 3 weeks following the diagnosis.

### COVID-19 laboratory examinations

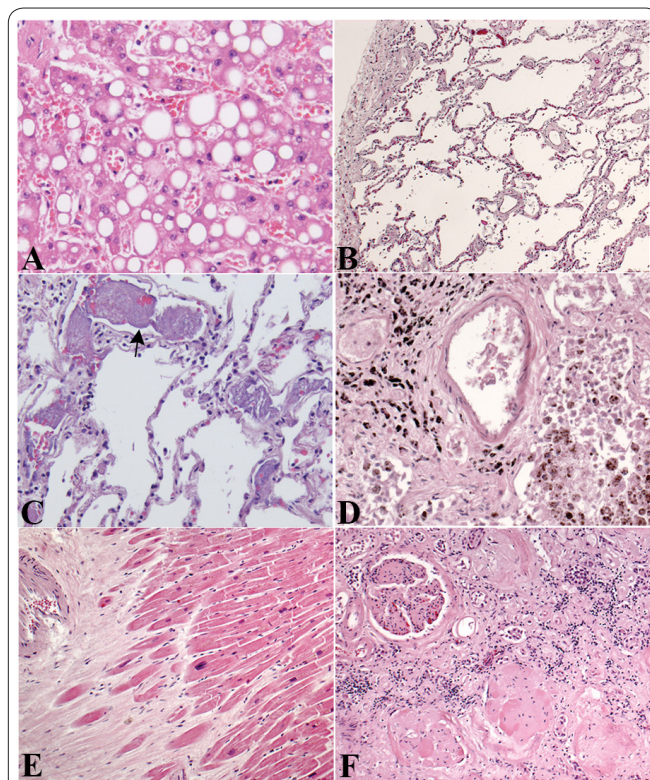
If hospitals adopt preventive measures and restrict and postpone the virus activities, fewer specimens will be sent to cytology and histology laboratories, helping the laboratories have the chance to change the workflow

and reassess their staffing needs. However, it is highly significant to inform clinical service departments and providers about delays or changes in service in order to avoid overwhelming the laboratories with requests for test results (28). Histology laboratories can play a restricted role for patients with known COVID-19. As for COVID-19, the only role of histology laboratories is excluding superimposed pulmonary infections in sputa and other respiratory specimens. Being nonspecific in sputa, the histologic features indicate the underlying acute pulmonary injury pattern (15).

Histopathologic changes caused by COVID-19 infection have been focused on by few studies none of which have evaluated all major organs fully (13). Benjamin et al reported the autopsy findings of deceased COVID-19 patients and indicated the pivotal role of lung damage in such patients, which led them to determine the mechanism for extra-pulmonary spread (29). Obstructive sleep apnea, diabetes, hypertension, and cardiac disease are the most prevalent conditions observed in COVID-19 patients (29,30). For the treatment of patients with such conditions, angiotensin II type 1 (AT1) receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors are usually used. Treatment through



**Figure 4. Pulmonary histopathology of COVID-19 patients died from severe acute respiratory syndrome COVID-19 infection.** A: Atypical pneumocytes with multiple enlarged nuclei, and expanded cytoplasm in a patient with proliferative diffuse alveolar damage (original magnification  $\times 40$ ); B: Extensive denudation of tracheal epithelium; mononuclear inflammation, mild edema, and submucosal congestion (original magnification  $\times 10$ ); C: Exudative phase of DAD characterized by excessive hyaline membranes lining alveolar spaces (arrow) (original magnification  $\times 20$ ); D: Tracheitis characterized by moderate mononuclear inflammation within the submucosa (original magnification  $\times 10$ ); E: Bronchopneumonia with filling of alveolar spaces by neutrophils and patchy hemorrhage (arrow) (original magnification  $\times 10$ ); F: Proliferative phase of DAD characterized by type II pneumocytes proliferation (arrow) (original magnification  $\times 20$ ). (35).



**Figure 5. Histopathologic findings of conditions in fatal COVID-19.** A: Extensive glomerulosclerosis in a patient's kidney suffering from renal disease (original magnification  $\times 10$ ); B: Emphysema in a patient's lung suffering from the chronic obstructive pulmonary disease (original magnification  $\times 5$ ); C: Pulmonary micro thrombosis (arrow) in the lung (original magnification  $\times 20$ ); D: Myocardial fibrosis, and mild cardiomyocyte hypertrophy in a patient's heart suffering from cardiomegaly (original magnification  $\times 5$ ); E: Hemosiderin-laden macrophages (brown pigment, bottom left), and anthracosis (black pigment, top right) in a patient's lung suffering from congestive heart failure (original magnification  $\times 20$ ); F: Steatosis in a patient's liver suffering from morbid obesity (original magnification  $\times 20$ ). (35).

such therapeutic methods; however, results in increased cellular response of the angiotensin-converting enzyme 2 (ACE2) receptor which also serves as the cellular receptor for viral entry (31). That is why Fang et al stated that increased cellular response of ACE2 might play a role in the high rate of death in such patients (32). In agreement with these reports, Benjamin et al remarked that prescriptions for ACEi were documented for just a few patients (29). Being expressed across some cell types, ACE2 provides context to the observation of the virus in various organ systems (33). In addition, Lu et al (2) reported ACE2 as the main host cell receptor of human pathogenic coronaviruses, which has an essential role in causing the ultimate infection by leading the virus into the cell.

Fever, shortness of breath, and cough have been reported in the majority of the deceased COVID-19 patients all over the world. However, congestion, runny nose and sneezing as respiratory symptoms are not common, which reveals the fact that COVID-19 prefers the lower respiratory tract, and electronic polymerase chain reaction (PCR) and microscopic examinations have shown this finding (30). The involvement of the pulmonary system of COVID-19 patients is the most important pathological finding reported by Benjamin et

al (29). Consistent with diffuse alveolar damage (DAD), hyaline membranes, intra-alveolar fibrin, pronounced reactive type II pneumocytes, and pulmonary edema have been reported in most patients. Similar findings have been reported for the outbreak of SARS 2002-3 (34). However, as opposed to SARS, the cells of COVID-19 are multinucleated giant (29, 35). Moreover, one patient in the study of Benjamin et al was detected to have cytoplasmic inclusions in the pneumocytes (29). Nucleoprotein aggregates identified in the cytosol in vitro ultrastructural studies of SARS can be a possible explanation for the etiology of such inclusions in COVID-19 (36).

**Histopathology and immunohistochemistry**

It is difficult to clinically differentiate COVID-19 from other respiratory viral infections due to its similar clinical characteristics shared by febrile illnesses with a cough lasting for several days before its progression to severe pneumonia. Moreover, COVID-19 and other respiratory viral infections might be asymptomatic or have minimal symptoms (37-39). In addition to respiratory failure, severely ill patients have been reported to have elevated inflammatory biomarkers, thrombocytopenia, leukopenia, lymphocytopenia, renal and hepatic dysfunction, chills, arthralgia or myalgia, and fatigue. In these cases, histopathologic lesions that are directly attributed to the virus are restricted to respiratory tissues (40-42).

Routine hematoxylin-eosin stains were performed for histopathologic evaluation by Huilan et al (25). Afterwards, they used a Mach 4 Universal AP Polymer Kit with Permanent Red Chromogen and a rabbit polyclo-

nal antibody raised against SARS-CoV nucleocapsid at 1:100 dilutions to conduct an IHC assay for COVID-19. Finally, they used heat-induced epitope retrieval with a citrate-based solution (Biocare Medical) to pretreat the slides. Furthermore, they performed suitable negative controls in parallel by utilizing normal rabbit serum in place of the primary antibody. Afterwards, by testing controls created from COVID-19 infected Vero cells embedded with normal human tissues, they validated cross-reactivity of the anti-SARS antibody with COVID-19 (25). This option was utilized as the positive control for following IHC assays (43).

According to the histopathologic findings of the study conducted by Martinez et al and their results of testing FFPE tissues, mild to moderate tracheobronchitis consistently existed and was characterized by mononuclear inflammation, with submucosal congestion and epithelial denudation (Figure 4). They reported diffuse alveolar damage (DAD) as the predominant lung pathology, and 87.5% of the patients had acute phases and/or organizing phases (35). However, no clear correlation between DAD pathologic phase and known symptom duration has been reported, which might be due to the underestimation of illness duration and under-recognition of early symptoms in elderly residents of long-term care facilities (LTCF) (44).

As revealed by studying histopathologic findings associated with underlying conditions in fatal COVID-19 disease, 50%, 50%, 37.5%, 25%, and 12.5% had hemosiderin-laden macrophages, hemorrhage, mucus aspiration, emphysema, and microthrombi, respectively (Figure 5) (35). Most elderly people suffering from COVID-19 had anthracosis caused by chronic carbon accumulation, and all of them had pulmonary hilar lymph

**Table 1.** Histological findings of COVID-19 in different organs of a human body (24,51).

Patients (Gender)	Age	Past medical history	Heart	Liver	Lung
1 (M)	59	Post-renal transplantation for 3 months	Myocardial hypertrophy, interstitial fibrosis, and focal mild edema; no inflammatory cellular infiltration	Scanty lymphocytes in the portal tracts, mild increase in sinusoidal lymphocytes, Kupffer cells hyperplasia in focal sinusoids, patchy hepatic necrosis in the periportal area and centrilobular area, mild zone 3 sinusoidal dilatation	Organizing-phase DAD: hyaline membrane; abundant intra-alveolar neutrophilic infiltration, focal fibrinoid necrosis of small vessel wall, early organization, interstitial thickening, intra-alveolar hemorrhages
2 (M)	74	Variceal rupture bleeding, renal cirrhosis	Not sampled	Pre-existing Cirrhosis; specimen too limited for further assessment	Acute-phase DAD: formation of mainly hyaline membranes
3 (F)	78	Chronic lymphocytic leukemia	Myocardial hypertrophy, interstitial fibrosis, and focal mild edema; no inflammatory cellular infiltration	Ductopenia in some portal tracts, neoplastic lymphocytic accumulation in portal tracts, focal mild macrovesicular steatosis, nuclear glycogenation in hepatocyte	Acute-phase DAD: hyaline membrane; focal sloughing of pneumocytes alternating with type II pneumocyte hyperplasia and syncytial giant cells formation; focal lymphocytic infiltration (changes of CLL)
4 (M)	81	Hypertension, diabetes,	Not sampled	Mild increase in sinusoidal lymphocytes, patchy hepatic necrosis, mild zone 3 sinusoidal dilatation	Acute-phase DAD predominant: hyaline membrane; mild inflammatory cellular infiltration, vascular congestion, focal interstitial thickening

nodes. In addition, as seen in Figure (5), approximately 75% of the patients had hemophagocytosis in their subcapsular sinuses and sinus histiocytosis in their lymph nodes. Furthermore, pathologic findings of extrapulmonary tissues revealed an association of focal myocardial fibrosis, cirrhosis, hepatic steatosis, acute renal tubular injury, and chronic renal disease (Figure 5). However, none of the cases had myocarditis or myocardial necrosis or remarkable histopathologic changes in their intestine (35).

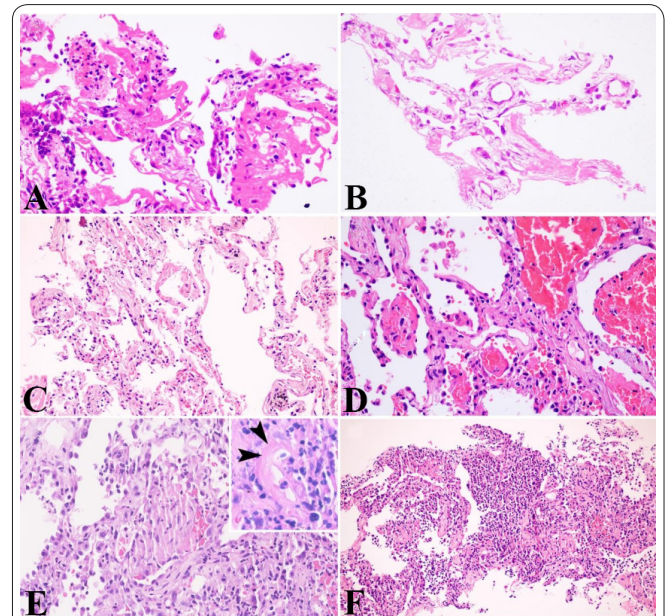
### COVID-19 cytology examinations

The existence of an elevated number of macrophages, which result in the formation of loose macrophage aggregates, is among sputa cytologic features. Nuclear changes like ground glass appearance of nuclei and multinucleation and cytoplasmic changes like the existence of foamy cytoplasm or larger cytoplasmic vacuoles might be shown by the macrophages (45). It might be necessary to send an aliquot to the cytology laboratory because bronchoalveolar lavage (BAL) fluid is sometimes obtained for viral identification (46,47) and is usually positive in case of when negative oropharyngeal and nasopharyngeal swab samples (48). However, there is no report on the cytologic findings of BAL samples of COVID-19 patients. Cytological examination of BAL fluid in patients suffering from MERS indicated large numbers of macrophages and neutrophils (41). According to the histopathology of COVID-19, MERS, and SARS, BAL specimens might also present squamous metaplasia, and features of repair, in conjunction with the existence of highly atypical alveolar type 2 pneumocytes and multinucleated cells indicating cellular and chromatin clearing, prominent nucleoli, and nuclear enlargement (49). These cytomorphologic features might be a potential pitfall for diagnosis.

### Histological findings of COVID-19

There are very limited data on pathologic changes of COVID-19 disease. Histologically findings are mainly in the lungs, including injury to hyperplasia of type II pneumocytes, hyaline membrane formation, and the alveolar epithelial cells, which are all elements of DAD. Consolidation by fibrin forming clusters in airspaces and fibroblastic proliferation with the extracellular matrix is obvious (50). It has also been reported that abundant intra-alveolar neutrophilic infiltration is included in the consolidation, which is in agreement with superimposed bacterial bronchopneumonia. The liver shows mild lobular infiltration by centrilobular sinusoidal dilatation and small lymphocytes. Also, patchy necrosis has been observed. The heart indicated only mild myocardial hypertrophy and focal mild fibrosis, which are changes that are probably caused by underlying conditions. Post-mortem examinations in some patients might demonstrate superimposed bacterial pneumonia and advanced DAD. Changes in the heart and liver are probably caused by underlying conditions (51).

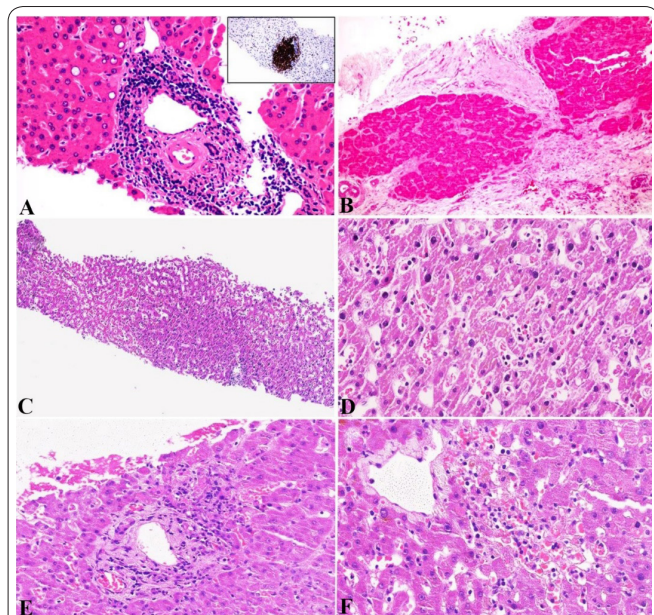
Sufang *et al* (24) used post-mortem core biopsy to examine the pathological influences of COVID -19 among four patients of different ages. The final results of their study are presented in Table 1 below. Although



**Figure 6. Histologic changes in the lungs.** A: Organization with intra-alveolar fibroblasts combined with fibrin and inflammatory cellular infiltration. Diffuse type II pneumocyte hyperplasia in the background (inset: fibrinoid vascular necrosis, arrow heads); B: More delicate hyaline membranes without obvious inflammatory infiltration; C: Case 3: mild interstitial thickening, type II pneumocyte hyperplasia, and focal hyaline membrane; D: Thick hyaline membrane combined with mononuclear inflammatory cells and desquamative pneumocytes; E: Bronchopneumonia changes with prominent neutrophilic infiltration filling up alveolar spaces; F: alveolar spaces filled with exudation of red blood cells, small fibrin plugs observed in adjacent alveoli (24).

nearly all patients had DAD, they were found to undergo different microscopic changes in their lungs (51). The formation of hyaline membrane sometimes happens, and vascular congestion might occur which may be combined with scant inflammatory cells (Figure 6B, C, D). In addition, giant syncytial cells form and pneumocyte injury with focal sloughing might occur. Focal lymphocytic infiltration might be observed in patients who have a history of chronic lymphocytic leukemia (CLL) (Figure 6B, D). Moreover, large areas of inter-alveolar hemorrhages and intra-alveolar fibrin cluster formation could be observed nearby in cases of more advanced changes with hyaline membranes remain in some airspaces (Figure 6C, F). Furthermore, elevated stromal cells, fibrin, and infiltration by mononuclear inflammatory cells can be seen in the alveolar wall (50,51). Small vessels might undergo fibrinoid necrosis, and interstitial thickening may happen as a result of hyperplasia of type II pneumocytes (Figure 6A). Some evidence has shown consolidation by abundant intra-alveolar neutrophilic infiltration, in line with bronchopneumonia of a superimposed bacterial infection (Figure 6E).

According to the data obtained from terminally ill hospitalized patients and reported by Sufang *et al* (24) and Cai *et al* (50), a common non-specific change and a mild sinusoidal dilatation were revealed by the liver sections. In addition, it was seen that portal tracts contain dense atypical small lymphocytes, focal macrovesicular steatosis, and nuclear glycogen accumulated in hepatocytes (Figure 7D). Thick fibrous bands and regenerative nodules were observed in the liver tissue of one of



**Figure 7. Pathological findings in the liver from all four cases.** A: Periportal zone with focal hepatic necrosis; B: Cirrhotic nodules with thick fibrosis; C: Mild sinusoidal dilatation with increased lymphocytic infiltration; D: Dense portal infiltration by atypical small lymphocytes (insert: CD20 immunostaining), and focal glycogenated nuclei in hepatocyte; E: Focal centrilobular hepatic necrosis; F: Higher power view indicating sinusoidal lymphocytes (24, 51).

the cases, which was in line with his cirrhosis history (Figure 7B). In addition to sinusoidal dilatation of the mild zone 3 (Figure 7C), half of the studied cases were found to have mild lobular lymphocytic infiltration (Figure 7F). However, the portal tracts had no significant lymphocytic infiltration. As seen in (7A, E), 25% of the patients had patchy hepatic necrosis in their periportal and centrilobular areas, with a very low possibility of obvious fatty changes.

## Conclusion

COVID-19 can easily spread between humans. Its spread can efficiently reduce through interventions, such as intensive contact tracing followed by isolation, quarantine, and travel restrictions. Other measures include disinfecting surfaces, washing hands, and wearing masks. Early diagnosis of COVID-19 and screening of suspected cases can be assisted by typical CT scan findings. COVID-19 has clustering onset, and older males with comorbidities are more likely to be infected. Hemoptysis, diarrhea, fatigue or myalgia, headache, expectoration, cough, and fever are the most common symptoms of COVID-19. Pathological and clinical findings in severe cases of COVID-19 can be used to determine the mortality cause. They can also provide useful insights into the pathogenesis of SARS-CoV-2-related pneumonia, which may finally lead to the management of severe cases and a decrease in death rate by helping with formulating timely therapeutic strategies. In some patients, superimposed bacterial pneumonia and advanced diffuse alveolar damage are the pathologic basis for COVID-19 pneumonia.

Underlying diseases and conditions determine the changes in the heart and liver of COVID-19 patients.

The histopathologic changes observed on postmortem transthoracic needle biopsies from a COVID-19 patient suffering from radiographic bilateral ground-glass opacities and respiratory failure were reported to be in line with DAD. These nonspecific findings might be a result of the response to some conditions leading to respiratory failure, they can help with the identification of the clinical course of COVID-19 disease. The results and findings of comprehensive and accurate investigations into the histopathologic manifestations of COVID-19 can help researchers and clinicians develop and adopt timely therapeutic and clinical interventions aimed at decreasing the mortality rate. Conducting studies on more COVID-19 patients of different ages is needed in order to further figure out the pathogenesis of COVID-19. Moreover, appropriate animal models should be created in order to mimic both the pattern of disease progression and infection in humans. Researchers' inability to obtain larger tissue specimens was seen as the most significant limitation. Therefore, future and further studies need to be carried out on larger samples of tissue samples obtained from COVID-19 patients of different ages.

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