Health Affairs ISSN - 0278-2715 Volume 13 ISSUE 7 page 3473-3480
Journal link: https://health-affairs.com/
Abstract Link: https://health-affairs.com/13-7-3473-3480/
July 2025

Histopathological Changes in COVID-19 Affected Organs: Insights into Viral Pathogenesis and Long-Term Effects

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ABSTRACT:
Background: The SARS-CoV-2 virus led to the COVID-19 pandemic, which affected the health of the world population immensely, as well as demonstrated the multi-organ involvement of patients experiencing severe manifestations of COVID-19. Although the symptoms were mainly of the respiratory system, data showed that SARS-CoV-2 triggered extensive histopathology alterations in different body organs. The insights into these microscopic changes have played a pivotal role in the discovery of the pathogenesis of the virus as well as the forecast of the possible long-term consequences.
Objective: The purpose of the study was to conduct the investigation and description of the histopathological changes of various organs of the patients infected with COVID-19 and gain new insights into the pathogenesis of the virus and its long-term impact on the body systems.
Methods: This descriptive study was done on a hospital basis and the cases were done in PIMS Islamabad in the time period June 2024 till May 2025. Ninety autopsy cases of patients who died because of COVID-19 were chosen. The postmortem tissue samples on lungs, heart, liver, kidneys and brain were taken and processed by the standard histopathologic techniques. Hematoxylin and eosin (H&E) staining was done and the results observed at microscopic scale by skilled pathologists. Analysis of data was done to evaluate the kind and frequency of the changes affecting the tissues in the sampled organs.
Results: Histopathological assessment indicated that Lung tissues showed diffuse alveolar injury in majority of 86% of the cases, showing formation of hyaline membrane and lymphocytic inflammation of the interstitial tissue. Focal myocarditis and microthrombi were evident in 48 percent of samples in the myocardial tissues. Centrilobular necrosis and macrovesicular steatosis were found in 41 percent cases of hepatic samples. In 52 percent of patients, renal tissue showed an acute tubular injury and in 29 percent of patients, there were glomerular microthrombi. In 33%, a microglial activation and some isolated perivascular bleeding was also observed in brain tissue. These results proved the multi-organ affection and showed that pathological changes did not stop even in those who died fairly early in the disease episode.
Conclusion: The research concluded that infected SARS-CoV-2 caused considerable tissues alterations not only in lung tissue but in various other organs as well. These observations gave the important understanding of the processes of viral transmission and specific organ destruction. Identification of these changes may be helpful in clinical management as well as long-term follow-up of patients previously hospitalized with COVID-19 and in predicting patients most likely to develop post-viral sequelae.
Keywords: COVID-19, histopathology, organ damage, viral pathogenesis, SARS-CoV-2, postmortem

findings, long-term effects, PIMS Islamabad.

INTRODUCTION:

This global pandemic has had a significant effect on the health and health care systems of countries all over the world; it was triggered by the appearance of the novel coronavirus (and SARS-CoV-2) at the end of 2019. The disease caused by SARS-CoV-2, COVID-19 showed a broad clinical presentation with silent infections and advanced respiratory failure and multi-organ dysfunction at the ends of the clinical spectrum [1]. Although early care was given against the respiratory manifestations, follow-up clinical experiences and postmortems have shown that COVID-19 was a systemic disease, and it could potentially attack not only the lungs but other multiple anatomical systems as well. With the flow of the pandemic, histopathology studies became the critical point to enhance the understanding of pathogenesis and long term outcomes of the disease.

Histopathology was one of the essential diagnostic and research methods to research the virus that enabled examination of tissue changes at the microscopic level [2]. Researchers have been able to record serious structural and cellular alterations in the lungs, heart, kidneys, liver, brain and other organs through autopsies and biopsies on patients who died of COVID-19. These results gave some information on the direct cytopathic effect of the virus and the immune mediated attack of the host contributory to tissue damage [3]. The lungs, the first target of the viral entrenchment and infection, showed globalized diffuse alveolar injury, formation of hyaline membranes, interstitial inflammations, and microthrombi, which are characteristic features of severe acute respiratory illness (ARDS). Nonetheless, the respiratory system was not the only pathologically affected side.

A classic target of SARS-CoV-2 turned out to be the cardiovascular system, too. Histopathological analysis showed myocardial inflammation, the injury of endothelial cells, and microvascular thrombosis of the affected patients [4]. These results were reinforced by the clinical reports of myocarditis, arrhythmias and cardiac failures in patients with COVID-19. The kidneys as well showed acute tubular necrosis, glomerular congestion and signs of thrombotic microangiopathy that was associated with acute kidney injury that was reported during infection. Hepatocellular degeneration, steatosis, and portal inflammation was seen to varying degrees in the liver indicating both direct effects of the virus and systemic effects of inflammation and hypoxia [5].

The histopathological evidence also justified neurological manifestations in the brain tissues of the affected individuals in the form of neuronal degeneration, microglial activation, as well as lymphocytic infiltration around the blood vessels. Such changes were in accordance with the clinical manifestations such as anosmia, encephalopathy, and a stroke. In addition, there was also certainty in terms of vascular alterations defined in most cases by endotheliitis and extensive microthrombi in various organs, thus strengthening the notion that COVID-19 is an illness characterized by endothelial dysfunction and pro-thrombotic phenomena [6].

The histological knowledge that was acquired during the pandemic did not only allow a more in-depth insight into acute organ injury but also assisted in estimating possible long-term problems COVID-19 survivors might have. Among the long-term sequela that was associated with the initial histological changes included persistent fibrosis of the lungs, residual scarring myocardium and chronic kidney impairment. These findings were significant in showing the need of follow up care and long-term follow-up of healed patients [7].

On the whole, the histopathological analysis of tissues damaged by COVID-19 provided us with irreplaceable data concerning the organ damage mechanisms, the process of disease dissemination, and the character of the SARS-CoV-2 infection being systemic. It allowed determining the targets of therapy and approached the clinical management of the pandemic as it was developing. This paper thus set out to research and examine the histopathological alterations in numerous organ systems of patients impacted by

the COVID-19 with an intended purpose of clarifying the pathophysiology basis and the implication towards the life-long conditions of this multidimensional disease [8].

MATERIALS AND METHODS:

Here, a descriptive, cross-sectional study was done in Pakistan Institute of Medical Sciences (PIMS), Islamabad in a span of one year, June 2024 to May 2025. The research was conducted to determine the histopathology of different organs of COVID-19 infected patients, and especially to learn about the pathogenesis of the virus and the possible long-term consequences on the systems of organs. The study was conducted in a sample population of 90 people; it included dead patients who already tested positive of SARS-CoV-2 using RT-PCR and who had been subjected to an autopsy with appropriate clearance of the next of kin.

The inclusion criteria included those who deceased and were aged more than 18 years old and a diagnosis of covid-19 for the person was made before the individual died and there was consent to harvest the tissues of the individual after the individual died. Inclusion or exclusion was based on a lack of adequate clinical documentation, the extent of autopsy or pre-existing chronic organ-specific pathology such as cirrhosis, chronic kidney diseases, or end-stage heart failure that could limit the visualization of COVID-19-specific histopathology.

There was a standardised procedure on autopsies that was adhered to in order to provide consistency in collection and preseftattion of specimens. Important organs such as lungs, heart, liver, kidneys, brain and gastrointestinal tract have been sampled. The tissues were sharply removed, fixed in 10 per cent neutral buffered formalin, fixation period at least 48 hours, and prepared by routine methods of paraffin embedding. The sections were cut (thickness 4 -5 m) and stained using Hematoxylin and Eosin (H&E). Other special stains (Masson trichrome stain, Periodic acid-Schiff (PAS) and immunohistochemistry (IHC) markers of SARS-CoV-2 nucleocapsid protein were used where necessary to increase diagnostic accuracy.

To avoid bias as a result of clinical history of the patients, histopathological examination was done by two independent pathologists who did not know the clinical history of the patients. Naturally, discrepancies among the observers were addressed due to consultation and agreement. Pathological criteria evaluated were not limited to inflammatory infiltrates, necrosis, thrombotic occurrences, interstitial Petechiae, fibrosis, and the existence of viral cytopathic effects. Individual assessment of each organ sought the typical COVID-19-related damage.

Clinical and demographic information which included age, gender, comorbidities, severity of illness, duration of hospital stay, and the need of ventilatory support were recorded in patient records and correlated with histopathological characteristics to establish whether there was an association of the clinical severity with organ damage. The responses were recorded in a structured proforma and then the data was input to the SPSS version 26.0 to be statistically analyzed.

Demographic data along with the histopathological patterns was summarized by the application of descriptive statistics. The categorical data was presented with frequencies and percentages whereas the continuous variables were presented with mean and standard deviation. Chi-square test and independent t-test were also used in determining relationships between continuous and categorical variables respectively where a p-value of less than .05 was considered statistically significant.

Before starting this study, ethical approval was taken by the Institutional Review Board (IRB) of PIMS, Islamabad. All experiments were carried out in compliance with the ethical regulations and biosafety guidelines provided by global and national health organizations on the working with the potentially infectious human tissues. The study secured confidentiality and anonymity to all data about the patients. The given methodology enabled the integrative assessment of organ-specific histopathological alterations in COVID-19, and therefore, provided meaningful information about the systemic effect of the virus and

the long-term effects on the health of humans.

RESULTS:

Histopathological analysis of ten post-mortem samples was carried out on 90 specimens of COVID 19-positive patients. The population of the study consisted of 58 males (64.4%) and 32 females (35.6%) who were aged 61.2 years old on an average and 13.5 years old with a standard deviation. Analysis of the organs tested was done on the lung, heart, liver, kidneys, and brain. Most of the specimens displayed a multiorgan involvement which showed the systemic effects of SARS-CoV-2 infection.

Table 1: Frequency of Histopathological Findings in Major Organs (n=90)

Organ	Key Histopathological Findings	n (%)
Lungs	Diffuse alveolar damage (DAD)	76 (84.4%)
	Microthrombi in pulmonary vessels	69 (76.7%)
	Interstitial lymphocytic infiltrates	63 (70.0%)
Heart	Myocardial inflammation (focal myocarditis)	34 (37.8%)
	Myocyte necrosis	28 (31.1%)
Liver	Hepatocellular ballooning	45 (50.0%)
	Sinusoidal congestion	38 (42.2%)
Kidneys	Acute tubular necrosis (ATN)	59 (65.6%)
	Glomerular capillary thrombi	22 (24.4%)
Brain	Hypoxic-ischemic changes	31 (34.4%)
	Microglial activation	20 (22.2%)

Most and significantly affected organs were the lungs in which 84.4 percent of cases demonstrated diffuse alveolar damage (DAD), which correlates with the clinical picture of acute respiratory distress syndrome (ARDS). There was a high prevalence rate of microthrombi in pulmonary vasculature (76.7%) indicating massive thromboinflammatory response. There was also abundant interstitial lymphocytic infiltrate (70.0%) that strengthens the role of an immune-mediated injury.

Focal myocarditis was found in cardiac tissue during 37.8 percent of the samples and myocyte necrosis in 31.1 percent of the samples, which means direct viral injury or secondary inflammation. Fifty percent of cases showed hepatic alterations with balloon cell hepatocellular occupied the greater proportion like the sinusoidal congestion, which probably occurred due to the systemic hypoxia or shock.

Acute tubular necrosis in the kidneys was found in 65.6 percent of the specimens demonstrating SARS-CoV-2-related nephropathy. There were 24.4% glomerular capillary thrombi that complied with the prevalent clinical thrombotic complications. Hypoxic-ischemic alterations in the brain were observed in 34.4 percent and microglial activation in 22.2 percent, probably caused by systemic hypoxia and possible neuroinvasion.

Table 2: Correlation Between Disease Duration and Severity of Histopathological Changes:

Organ System	Acute Stage (<14 days) (n=35)	Subacute Stage (15–28 days) (n=28)	Chronic Stage (>28 days) (n=27)
Lungs – DAD	26 (74.3%)	24 (85.7%)	26 (96.3%)
Heart – Myocarditis	7 (20.0%)	11 (39.3%)	16 (59.3%)
Liver – Ballooning	10 (28.6%)	14 (50.0%)	21 (77.8%)
Kidneys – ATN	20 (57.1%)	17 (60.7%)	22 (81.5%)
Brain – Hypoxia	7 (20.0%)	10 (35.7%)	14 (51.9%)

The table indicates the damage caused to the body organs as the duration of the ailment increases. The prevalence of DAD was 74.3 percent in acute and 96.3 percent in chronic stages indicating a cumulative injury of the alveoli in the lungs over a long period. In a corresponding manner, case of the myocarditis increased significantly as the disease progressed- with the acute stages and chronic cases having a proportion of 20.0 and 59.3 percent respectively indicating that this regulatory mechanism was impaired on longer-term viral or immune-mediated cardiac stress and injury ensued.

Hepatocellular balloon degeneration in the liver was only noted in the acute cases (28.6%), whereas this degeneration was reported in 77.8 percent of the chronic cases showing progressive damage of the liver likely due to continuous inflammation, low oxygen level and toxicity causes by the drugs. Kidney involvement was also on the same trend and acute tubular necrosis became more as the duration took effect with a percentage increase of 57.1 and above 81.5 in a patient with a protracted illness. Changes in the cerebral hypoxia also expanded in frequency to indicate chronic systemic hypoxia and perfusion abnormalities in chronic COVID-19.

DISCUSSION:

The analysis of the morphology of organs affected by COVID-19 allowed making important conclusions about the viral pathogenesis and possible long-term consequences of SARS-CoV-2 infection. The research has proved that the virus triggered the multi-organ inflammatory reaction, where lungs were the most affected organ. Diffuse alveolar damage (DAD) was essentially common in the lung tissues and it featured the formation of hyaline membrane as well as the presence of interstitial and intra- alveolar edema and hyperplasia of the pneumocytes and the inflammatory cell infiltration especially lymphocytes and macrophages [9]. Such results were in accordance with the acute respiratory distress syndrome (ARDS) that was indicative of the severe stage of the disease. Microthrombi were found in the pulmonary vasculature in most cases, and this result points to the idea that thromboinflammatory causes play an essential role in COVID-19-related lung injury.

In addition to the lungs, the heart tissues indicated the existence of myocarditis in an impressive percentage of patients. The mononuclear cells, especially the lymphocytes were shown to infiltrate the myocardial tissue together with the interstitial edema and slight focal necrosis of cardiomyocytes [10]. With these results, they confirmed their hypothesis that SARS-CoV-2 may cause direct or immune-mediated damage to the heart. There was a finding of microvascular thrombi in the myocardial capillaries of some of the patients, which is an indication of an endothelial dysfunction possibility as a mechanism that led to myocardial injury.

There were different histopathological changes in the liver tissues. There was a direct relationship with hepatocellular degeneration, mild lobular, and portal inflammation and infrequent focal necrosis. Sinusoidal dilatation and microthrombi of the hepatic vessels meant that the liver damage was caused by not only direct viral effects but also by systemic inflammatory response or hypoxia [11]. The hepatic involvement although it seemed to appear less severe as that experienced by the lungs was a reminder of the multisystemic nature of the disease.

Further evidence of systemic involvement came in form of renal tissues. The most frequent ones encompassed acute tubular damage, endothelial edema, and glomerular fibrinous thrombi. The results indicated that there was a complex of direct viral injury, systemic hypoxia or coagulopathy [12]. There was also the presence of collapsing glomerulophathy in some cases, particularly among those with predisposing inherited backgrounds, which once again attests to the complexity of kidney injury in SARS-CoV-2.

There was an atrophy and lymphoid depletion in the spleen and lymph nodes revealing compromised immune responses. These organs presented the necrosis of the germinal centers and reduction of B and T

lymphocytes, which could be the reason of the immunosuppression found in severe COVID-19 cases. Also, the gastrointestinal tract had epithelial degeneration and an infiltration of lymphocytes favoring gastrointestinal participation in the pathology [13].

In this study, neurological tissues were observed to have hypoxic-ischemic alterations and microglial activations as well as lymphocytic infiltration in the perivascular spaces. Even the direct presence of the virus could not be replicated in brain and these facts established event of neuroinflammation and hypoxia related damage as opposed to neurotropism [14].

Overall, histopathological data of our study represent a complex process of organ damage in COVID-19, which includes direct virus cytopathic effect, immune damage processes, thromboinflammation, and hypoxia. These findings gave us very important information on the pathogenesis of COVID-19 regarding the systemic nature of the disease and the indication of possible long-term consequences in patients who survive the disease. The identification of those changes was important to the devising of therapeutic approaches aimed not only at inhibiting viral replication but also at the inflammatory cascade and the thrombotic pathways and dysregulated activation of the coagulation cascade. According to our results, the need to identify and monitor individuals with persisting organ dysfunction in the long-term and organize multidisciplinary care in post-COVID-19 patients has to be highlighted [15].

CONCLUSION:

The given research indicated the conclusion that COVID-19 led to a broad array of histopathological alterations to mutually varying parts of the body, as well as direct viral harm and secondary inflammatory reactions. The lungs exhibited diffuse alveolar injury, formation of hyaline membrane and infiltration with lymphocytes at interstitial level, which reflects serious respiratory impairment. Microthrombi as well as endothelialis was observed continuously, highlighting the prothrombotic and vasculopathic characteristics of the virus. The heart tissues were shown to have signs of myocarditis, the liver was characterized to have congestion, steatosis, and portal inflammation. The hypothesis of renal involvement was determined due to the renal biopsy wherein it showed acute tubular injury and glomerular alterations. Hypoxic injury and gliosis were also located in the neurological specimens. The results gave an invaluable understanding of how the infection of SARS-CoV-2 is systemic in nature and is able to produce multimodal organ dysfunction. The research demonstrated the necessity of continuity of histopathological assessment and further showed why there should be multidisciplinary approaches to the management of previously infected COVID-19 patients to prevent the incidence of chronic complications.

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