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## The pathologic autopsy of coronavirus disease 2019 (COVID-2019) in China : a review

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### Abstract

The coronavirus disease 2019 (COVID-2019) emerged in Wuhan, China, has rapidly spread to many countries across all six WHO regions. However, its pathobiology remains incompletely understood and many efforts are underway to study it worldwide. To clarify its pathogenesis to some extent, it will inevitably require lots of COVID-2019-associated deaths at pathologic autopsy. Pathologists from all over the world have raised concern with pathologic autopsy relating to COVID-2019. The issue of whether a person dies from COVID-2019 infection or not always is an ambiguous problem in some cases, and ongoing epidemiology from China may shed light on it. This review retrospectively summarizes the research status of pathologic autopsy in COVID-2019 in China, which will be important for the cause of death, prevention, control and clinical strategies of COVID-2019. Moreover, it points out several challenges at autopsy. We believe pathological studies from China enable to correlate clinical symptoms and pathological features of COVID-2019 for doctors and provide an insight into COVID-2019 disease.

### Keywords

Infectious disease; Pathologic autopsy; COVID-2019; Pneumonia

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## Introduction

Coronavirus disease 2019 (COVID-2019) is a seriously infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This coronavirus was firstly identified as the causative organism by Chinese facilities by deep sequencing analysis of patients' respiratory tract samples.<sup>1</sup> Its clinical symptoms include fever, cough, and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhea, sore throat, loss of smell, and abdominal pain.<sup>2</sup> Terribly, some patients associated with SARS-CoV-2 infection progress to pneumonia and multi-organ failure, which are extremely harmful to humans. Until now, the disease is rapidly spreading across all six WHO regions. As of 26 April 2020, in total, more than 2,804,796 cases of COVID-2019 have been reported in 197 countries (A total of 84,338 confirmed cases were reported in China, 195,351 cases were confirmed in Italy, and 1,094,846 cases were confirmed in the United States).<sup>3</sup> The virus is thought to spread mainly from human-to-human transmission. It took 67 days from the outbreak of COVID-19 to a total of 100,000 cases, the second 100,000 cases took 11 days, and the third 100,000 cases took only four days.<sup>4</sup> It has reported that the overall mortality is 4.6 percent; ranging from 0.2 percent to 15 percent according to age group and underlying diseases.<sup>5</sup> In clinical practice, the possibility of infection is commonly confirmed by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab. On the other hand, the infection can also be diagnosed from a combination of symptoms and radiological evaluation such as computerized tomography (CT)<sup>6-9</sup> and chest X-ray.<sup>10-11</sup> Even worse, there is currently no vaccine to prevent COVID-2019. Until recently, Chinese scholars have made a lot of progress in etiology, epidemiology, diagnosis and therapeutic strategies, etc. Although many studies on COVID-2019 epidemiology and clinical characteristics have been published, studies on the histopathological characteristics of each tissue are relatively insufficient due to barely accessible autopsy. To advance research progress of COVID-2019, pathologic autopsy is inevitable method to discover the changes of tissues and clarify its etiology and pathogenesis to some extent and finally determine whether a therapy is proper and reasonable. Thus, a comprehensive theory of pathogenesis for this newly emerged infectious disease is essential. By April 5, professor Bian's team of the Army Military Medical University in Chongqing, China, has declared to accomplish the pathologic autopsies of 39 cases positive for COVID-2019 and established the first pathological bank of this disease in the world. However, some available pathologic data have not attracted wide attention. This review summarizes the research status of pathologic autopsy in COVID-2019

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restricted from China, which will facilitate understanding for the cause of death and improve clinical strategies against COVID-2019 worldwide.

## **Pathologic autopsy and COVID-2019**

As the availability and quality of imaging techniques, CT and chest X-ray together with RT-PCR have been important modalities in assisting in the diagnosis and management of patients with COVID-2019 pneumonia. For example, Shi and colleagues<sup>6</sup> analysed chest CT images from 81 patients positive for COVID-2019 pneumonia and discussed temporal changes of COVID-2019 pneumonia since onset of symptoms, which provides insight in the evolution of the disease and its corresponding imaging changes. Guan et al.<sup>7</sup> have investigated chest CT images from 53 patients confirmed COVID-2019 infection, by which they demonstrated pulmonary lesions in majority of patients were predominantly distributed peripherally in the subpleural area. On the other hand, Pan et al.<sup>8</sup> have studied the chest CT images from 21 patients with RT-PCR confirmed COVID-19 infection and they found that lung abnormalities on chest CT showed greatest severity approximately 10 days after initial onset of symptoms. Ai et al.<sup>9</sup> have investigated the consistency of chest CT as compared with comparison to RT-PCR assay among 1014 patients in Wuhan, China and suggested that the sensitivity of chest CT was 97% based on positive RT-PCR results. Although chest CT has been shown to be an effective imaging technique for lung-associated disease diagnosis, chest X-ray is more widely available due to its faster imaging time and considerably lower cost than CT. Zhang et al.<sup>10</sup> have collected 100 chest X-ray images of 70 patients confirmed with COVID-2019 and demonstrated that chest X-ray is critical for efficient and reliable COVID-2019 screening. Meanwhile, Abbas et al.<sup>11</sup> have adopted their previously developed (convolutional neural networks) classification of COVID-2019 chest X-ray images and its accuracy approaches to 95.12%. CT and chest X-ray are the most common and widely used diagnostic imaging techniques for COVID-2019, which greatly accelerate the speed of disease screening, especially in epidemic areas and alleviate the lack of nucleic acid kits. Whereas, CT and chest X-ray are not able to confirm COVID-2019, directly prove the distribution of the virus in tissues, or analyze the cause of death in cases. Pathologic autopsy will primarily provide critical insights into the pathogenesis of COVID-2019 in humans.

Pathologic autopsy developed rapidly in the 18<sup>th</sup> century, which reached its peak in the middle of

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20<sup>th</sup> century was regarded as a scientific pathology to study human diseases.<sup>12</sup> Since then, pathologic autopsy has become a very important method to understand the pathologic basis of disease and the cause of death. As early as 2003, the pathogenesis of the severe acute respiratory syndrome (SARS), which was caused by SARS-CoV and began to break out in Guangdong province, China, initially remained poorly understood. Ding et al.<sup>13</sup> from Nanfang Hospital Guangdong have investigated clinical pathology of three patients who died of SARS by pathologic autopsy. They found that the lungs, immune organs, and systemic small vessels are the main targets of virus attack, so that extensive consolidation of the lung, diffuse alveolar damage with hyaline membrane formation, respiratory distress, and decreased immune function are the main causes of death. Thus, SARS enables to result in injury to multiple organs, although the predominant pathology involves the lungs. Subsequently, Franks et al.<sup>14</sup> have studied postmortem lung sections from 8 patients who died from SARS, in which they emphasized the predominant pattern of lung injury in all 8 cases typical of diffuse alveolar damage (DAD) and the histology varied according to the duration of illness. In 2005, Gu et al.<sup>15</sup> have investigated 18 autopsies of patients who had suspected SARS and found that SARS virus seemed to be capable of infecting multiple cell types in several organs; immune cells and pulmonary epithelium were identified as the main sites of injury. A comprehensive theory of pathogenesis is proposed for SARS with immune and lung damage as key features. Middle East respiratory syndrome (MERS) is caused by MERS-CoV in 2012 with most cases occurring in Saudi Arabia and the United Arab Emirates, leading to human infections and person-to-person spread globally.<sup>16</sup> Some oriented autopsies were performed to supply critical knowledge for understanding the pathogenesis. Even a small number of autopsies have found important information about the pathological mechanism of Middle East respiratory syndrome. For example, Ng et al.<sup>17</sup> have conducted first autopsy on a fatal case of MERS-CoV in the world and emphasized that the main histopathologic finding in the lungs was DAD. Additionally, immunohistochemistry (IHC) and double staining techniques showed viral MERS-CoV were predominantly localized to alveolar and epithelial syncytial cells. At about the same time, Walker<sup>18</sup> has conducted a pathologic autopsy on a dead case of MERS and found MERS-CoV in alveolar cells, multinucleate syncytial cells and bronchial submucosal gland. Afterwards, Alsaad et al.<sup>19</sup> have investigated pathogenesis, viral localization and histopathological features of MERS-CoV in humans in a 33-year-old male who acquired MERS-CoV infection. In their study, histopathological examination showed necrotising pneumonia, pulmonary DAD, and pathologic changes of other organs. Meanwhile, viral particles were localized in the pneumocytes, pulmonary macrophages, renal proximal tubular epithelial cells and macrophages infiltrating the skeletal muscles. Because of the importance of autopsy to study the basic pathology, it is an indispensable research method for the study of infectious diseases.

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The SARS and MERS-associated coronaviruses are both considered HG3 pathogens; Resembly, SARS-CoV-2 has recently been categorised as a HG3 organism.<sup>20</sup> A comprehensive theory of pathogenesis for this newly emerged infectious COVID-2019 is still lacking. Although China has made great progress in preventing and controlling infectious diseases, more effective treatment and prevention strategies are strongly required. Unfortunately, we have not been able to produce vaccines to cure infectious COVID-2019. Thus, the pathological characteristics, cause of death, distribution of pathogens in tissues remain an urgent problem worldwide, which probably provides supports for the therapies of COVID-2019. As the People's Daily reports, there were three important pathological findings at autopsy in China: (i) the blockage of small airways by secretions affected gas exchange in lungs, suggesting the importance of clinical symptomatic therapies such as atomization and sputum suction; (ii) virus particles are primarily distributed in the lung tissues of most postmortem studies, providing important informations for clinical strategies; (iii) human immune system suffers from serious damages, which guides clinical therapies to improve the immunity of patients.<sup>21</sup> To further explore its pathogenicity and lethality of COVID-2019, we urgently need to obtain more pathological knowledge of COVID-2019 through autopsy, especially from China. What's more, further studies are warranted to investigate the mechanism underlying pathological changes of this disease.

### **Pathologic autopsy in COVID-2019 from China**

On February 16, 2020, Liu and his team from Tongji medical college, Wuhan, performed the first systematic anatomy of COVID-2019's corpse, an 85-year-old male.<sup>22</sup> They have estimated that the lung injury is obvious by microscopic zones, an inflammatory lesions (pale) are predominantly in the left lung as shown in Figure 1A. By naked eye, the left lung shows patchy peripheral hemorrhage of parenchyma (Figure 1B), and alveoli of the lungs lose their elasticity. In addition, the cut surfaces display fibrous cords appearance with lots of sticky secretion exudation from pulmonary alveoli (Figure 1C). Foam-like mucus secretions are present in trachea and bronchus, respectively (Figure 1D and 1E). All of these pathologic changes suggest that SARS-CoV-2 infection causes inflammation characterized by injuries of large airway and alveoli. Previously, it predicts that the pathological characteristics of COVID-2019 in lung injury resemble those caused by SARS, due to the similarities between SARS-COV-2 and SARS-CoV in its genome sequence, biological behavior and clinical manifestations.<sup>13, 23-24</sup> From the observation of systematic anatomy, pulmonary fibrosis and consolidation are not as serious as those caused by SARS, but the sticky secretion is more than that of SARS. On the one hand, this anatomy is of great significance to discover the lesions of other tissues. An amount of yellow fluid is found in the pericardial cavity and epicardium involves by a slight edema. The myocardial section is grayish red (Figure 1G). Among the digestive system, small intestinal tract is of normal color with segmentary dilatation (Figure 1H). Fi-

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nally, they also have estimated that SARS-CoV-2 infection involves damage to the brain, liver, kidneys and other tissues. However, there is no microscopic assess of histological examination in the first pathologic autopsy from China.

In some respect, microscopic assessments enable to show general layout and distribution of cells and provides a general overview of a tissue sample's structure, which are of significance for pathological analysis. Almost at the same time, Xu et al.<sup>25</sup> from PLA General Hospital, Beijing, have investigated the pathological characteristics of a 50-year-old patient by minimally invasive autopsy, who died from severe infection with SARS-CoV-2. In their study, hematoxylin-eosin (H&E) staining was carried out to analyze pathologic features of the lung tissues from this victim. Postmortem examination shows bilateral DAD with cellular fibromyxoid exudates (Figure 2A and B). And it reveals evident desquamation of pneumocytes and hyaline membrane formation on the right lung, indicating acute respiratory distress syndrome (ARDS; Figure 2A). On the other hand, the left lung tissue appears as pulmonary oedema with hyaline membrane formation, a suggestive of early-phase ARDS (Figure 2B). Moreover, interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes are observed in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei and amphophilic granular cytoplasm are identified in the intraalveolar spaces, emphasizing viral cytopathic-like changes. However, no obvious intranuclear or intracytoplasmic viral inclusions are observed. Besides, the liver specimens of the patient positive for COVID-2019 display moderate microvesicular steatosis, mild lobular and portal activity (Figure 2C), indicating possible injury caused by SARS-CoV-2 infection. Their results also demonstrate that there are a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue (Figure 2D). These pathological findings in this severe case of COVID-2019 provide new insights into the pathogenesis of SARS-CoV-2-associated pneumonia. More importantly, they have formulated a timely therapeutic strategy for similar severe patients. Unfortunately, the location and distribution of SARS-CoV-2 in the tissue are indistinct in this study.

To seek viral distribution of SARS-CoV-2 in the human tissues will provide direct evidence. Yao et al. have reported a postmortem study of 3 COVID-2019 deaths by minimally invasive autopsy in Chongqing, China, who died 17~19 d after the onset of symptoms.<sup>26</sup> Three persons had a mean±SD age of 70.3±8.1 years (range, 63~79 years). Of the 3 patients, there were no contact history of COVID-2019 for 2 patients. Afterwards, hematoxylin-eosin (H&E) and histochemical stainings were performed to assess pathologic features of the lung tissues, whereas IHC staining of SARS-CoV-2 antigen was conducted to analyze the infiltration of inflammatory cells as well as protein of SARS-CoV-2. They have observed that the alveolar structure suffers from damage to some extent. Besides, alveolar lesions occur in a variety of forms such as exudative inflammation, carnification, interstitial inflammation, fibrosis as well as focal

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hemorrhage. Even more, infected pneumocytes are encased between hyaline membranes, composed of fibrin and basement membranes. They have estimated that the exudate cells in alveolar cavity are mainly monocytes and macrophages. Also, they could see dilatation of capillary in pneumocytes, hyperemia, inflammatory cell infiltration, and occurrence of thrombosis. Furthermore, there are different degrees of interstitial fibrosis in some areas. The lungs of patients with COVID-2019 pneumonia suffer from significant pathological lesions and the histopathological changes are heterogeneous in severity. Besides, electron microscopy (EM) images show type II epithelial cells have enlarged nuclei and abundant cytoplasm, in which mitochondria swell. Moreover, there are more lamellar bodies, endoplasmic reticulum, and golgi apparatus. SARS-CoV-2 predominantly exists in the some type II epithelial cells and thin bronchial mucosa ciliated columnar epithelium cells. In contrast, no evidence of SARS-CoV-2 infection is observed in other tissues. In their study, they provide critical insights into the histologic changes, pathogenesis, and viral distribution of SARS-CoV-2 in humans. Meanwhile, more postmortem examinations are necessary to strengthen knowledge on pathogenesis and effectively therapeutic strategies for clinical management.

Besides, we have intense concern with whether the virus can infect other organs except for lung. Tian et al.<sup>27</sup> have performed postmortem of lung, liver, and heart in 4 patients by minimally invasive autopsy in Zhongnan Hospital, Wuhan, who died of COVID-2019 pneumonia. The patients' ages ranges from 59 to 81, including 3 males and 1 female. With approval from the patients' families and ethical committee of the hospital, postmortem punctures were performed on organs to gain knowledge about the pathology. By H&E and IHC stainings, microscopic features in the lung tissues varies among 4 cases and the predominant pulmonary histologic pattern is exudative-phase DAD with hyaline membrane formation and vascular congestion, suggesting an acute-phase manifestation (Figure 3A, B and C). Besides, Case 1 exhibits pneumocyte injury with focal epithelial sloughing and formation of syncytial giant cells (Figure 3A). It is worth mentioning that no presence of prominent inflammatory cellular infiltration is confirmed in Case 2 (Figure 3B), and Case 3 demonstrates focal interstitial thickening (Figure 3C). H&E staining in Figure 3D, E and F are carried out from Case 4. Together with hyaline membranes in some airspaces, large areas of intra-alveolar hemorrhages and fibrin cluster formation are observed nearby (Figure 3D). In addition, the alveolar wall contains increased stromal cells, fibrin, and infiltration by mononuclear inflammatory cells. From Figure 3E, type II pneumocyte hyperplasia results in interstitial thickening, along with fibrinoid necrosis of the small vessels (Figure 3E, inset). In Case 4, there is also evidence of consolidation by abundant intra-alveolar neutrophilic infiltration, consistent with bronchopneumonia of a superimposed bacterial infection (Figure 3F). These results demonstrates that main pathologic findings from the lungs include hyaline membrane formation, fibrin exudates, epithelial damage, and diffuse type II

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pneumocyte hyperplasia, which are all characteristics of DAD. On the other hand, mild thickening of alveolar walls is also evident in some cases, suggesting a more advanced stage of this illness. In their conclusion, the pathologic changes in the lungs are similar to those seen in the confirmed cases of SARS. However, it is a big pity that there are not enough regions of liver and heart to observe histopathological changes because of the limited scope of puncture samples.

Zhang et al.<sup>28</sup> from Tongji Hospital, Wuhan, have carried out postmortem of a 72-year-old man with a history of diabetes by minimally invasive autopsy. His throat and pharyngeal swabs were positive for SARS-CoV-2 infection. Lung tissue was obtained by transthoracic 14-gauge needle from the left upper anterior segment. From H&E and immunostaining analysis for SARS-CoV-2 infection, histopathologic examinations of lung tissues reveal DAD. Immunostaining of lung sections with an antibody against Rp3 nucleocapsid protein (NP) protein, which is highly expressed on SARS-CoV-2, reveals there is an amount of the protein on alveolar epithelial cells (Figure 4B, top panel), along with exfoliative cells within the alveolar space (Figure 4B, bottom panel). In contrast, this type of viral proteins lie on blood vessels (Figure 4B, dashed blue line) or in the interstitial areas between alveoli (Figure 4B, bottom panel). Similar to as described previously, SARS-CoV-2 can be found on the lung tissues and the histopathologic changes are consistent with DAD.<sup>26</sup> On the other hand, Gao et al.<sup>29</sup> have conducted autopsies on 4 patients with COVID-2019 who died in the Huoshenshan Hospital, Wuhan and summarized that nucleocapsid protein is highly pathogenic for lung damage through MASP-2-induced overactivation of complement, indicating that the pathogenicity and death of SARS-CoV-2 correlates with over immune response. In this study, they have given advice that complement-activation through lectin pathway is prospective for the therapy of COVID-2019 disease.

As everyone knows, immune system is the body's defense against viral infections, which attacks pathogens and helps keep us healthy. However, it has already reported that lymphocytopenia is well established infected by the SARS-CoV-2.<sup>30</sup> Feng et al.<sup>31</sup> from Jinyintan Hospital, Wuhan, have observed that SARS-CoV-2 enables to directly infect secondary lymphoid organs from six cases with postmortem examinations. Firstly, spleens and lymph nodes (LNs) from 6 COVID-2019 patients were collected by standard examination at autopsy. In the same way, the virions in LNs were visually observed by TEM and pathological features were analyzed by H&E staining. Moreover, viral nucleocapsid protein (NP) antigen, cell apoptosis and proinflammatory cytokine expression were measured by IHC. In their study, the lymph follicles and paracortical areas in virus-infected tissues are not identifiable with wide distribution of necrotic and apoptotic lymphocytes, which results in a significant reduction of total lymphocytes as shown in Figure 5. Moreover, interstitial blood vessels have proliferation and expansion. Moreover, the spleens are congested, hemorrhagic, and lacking lymphoid follicles. Additionally, the spleen corpuscles



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are atrophic, along with hyperplasia of interstitial vessels and fibrous tissue in the splenic sinus. These results demonstrate that SARS-CoV-2 infection causes severe damage in human LNs and spleen.

In the same study, they have also investigated location and distribution of SARS-CoV-2 in secondary lymphoid tissues by expression of viral NP antigen. By IHC assay, it is evident that SARS-CoV-2 NP antigens can be observed in spleens and LNs from all of 6 autopsies, but in absence of normal healthy controls (see Figure 6A and B). In the spleen, SARS-CoV-2 is primarily distributed in red pulp and blood vessels, although occasionally in presence of white pulp in Figure 6A. In lymph nodes, SARS-CoV-2 are observed within marginal sinus of lymph nodules, capillaries, germinal centers as well as cytoplasm, whereas nucleus is negative for expression of viral NP antigen (Figure 6B). Then they also have performed addition staining to identify the LN cell types prone to SARS-CoV-2 infection. Immunofluorescent double staining confirmed that the majority of SARS-CoV-2 are observed in ACE2-overexpressed cells and CD68-overexpressed macrophages. While, CD3-overexpressed T cells and B220-overexpressed B cells are tolerant of SARS-CoV-2 infection. Moreover, these results have also illustrated that SARS-CoV-2 is observed in CD169-overexpressed macrophages in the subcapsular sinus of LNs. Thus, SARS-CoV-2 infection enables to directly infect human LNs and spleens, leading to tissue damage and lymphocyte reduction.

Apart from the respiratory and immune system, it is vague whether SARS-CoV-2 can also directly infect other tissues such as the kidney or induce acute renal failure. Diao et al.<sup>32</sup> have investigated kidney tissues by postmortem examinations from 6 patients positive for SARS-CoV-2 infection in Wuhan. In their research, H&E staining demonstrates that acute renal tubular damage can be observed in all 6 cases, while the glomeruli are intact (see Figure 7). Then, they have employed *in situ* IHC assay to analyze distribution of SARS-CoV-2 in kidney tissues by the expression of viral NP antigen and found that SARS-CoV-2 is restricted to the renal tubular cells of the infected tissues. This study has demonstrated that kidney tissues from 6 cases of postmortems have severe acute tubular necrosis but no evidence of glomerular pathology. And that SARS-CoV-2 was primarily accumulated in kidney tubules, which directly infects human kidney tubules and induces acute tubular damage as well as urine transmission.

### **The challenge of the autopsy and development**

COVID-2019 has spread to many countries in a very short period of time, and the number of deaths has exceeded 193,000 by now. In the past month and a half, China has carried out more than 30 autopsies, by which it demonstrates the lung is the main target organ attacked by SARS-CoV-2; however, some other organs such as liver, kidney, and spleen are also damaged to some extent. The results of those pathologic autopsies will give a preliminary insight into understanding of COVID-2019, which is helpful

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for pathogenesis and clinical strategies of patients, but still limited. To fundamentally find the pathogenicity and lethality of COVID-2019, a larger number of urgent autopsies are required. To date, we find that there are still many challenges: (i) there are currently more than 110,000 deaths from COVID-2019 in elderly population. One expert from China points out that COVID-2019 requires more autopsies in various patient populations, the rate of which is best to reach 10% of victims. For example, Ruan et al. have pointed out that death cause of COVID-2019 patients may be due to virus-activated “cytokine storm syndrome” or fulminant myocarditis, which requires adequate autopsy studies to confirm this point of view.<sup>33</sup> (ii) there are individual discrepancy among patients with evident COVID-2019 disease. Due to patients positive for COVID-2019 with different ages, evolutionary stages as well as underlying disease, the pathogenesis, damage of organs, outcome, and lethality of COVID-2019 are totally different. In this situation, it is urgent to summarize some common rules in the pathological evolution of COVID-2019 by autopsy. (iii) most of the current autopsies are by a minimally invasive autopsy. Although it has also obtained a certain diagnostic value by minimally invasive autopsy, the scope of the tissues is vague and it doesn't enable to comprehensively reflect the morphological and pathological changes of whole organs, resulting in omission of some clinical features. (iv) the recent autopsies have failed to effectively instruct clinical therapies of COVID-2019.

## Summary

COVID-2019 is a seriously infectious disease caused by virus of SARS-CoV-2. Some patients associated with SARS-CoV-2 infection progress to pneumonia and multi-organ failure, which are extremely harmful to humans. Until recently, this disease is rapidly spreading all of the world. Even worse, there is currently no vaccine to control COVID-2019. Chinese scholars have already made a lot of progress in clinical researches, especially in pathology, to control large-scale prevalence and incidence of the epidemic disease. Although CT and chest X-ray are effective methods to roughly diagnose the COVID-2019, they do not enable to profoundly provide insight into this epidemic disease from pathological perspectives. Pathologic autopsy is an inevitable method to discover the changes of tissues and clarify its etiology and pathogenesis to some extent and finally determine whether a therapy is proper and reasonable. Thus, a comprehensive theory of pathogenesis for this newly emerged infectious disease is essential. To explore its pathogenicity and lethality of COVID-2019, we urgently need to obtain the relevant pathological knowledge of COVID-2019 through autopsy, especially from China. To fundamentally find more pathogenicity and lethality of COVID-2019, a larger number of urgent autopsies are strongly required. To date, we find that there are still many challenges. This review will force a rethink how to deal with COVID-2019 in the future.

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## Specific contributions of all named authors

**Writing:** Baoyong Zhou, Wei Zhao, Ruixi Feng, Qiling Peng, Ning Jiang;

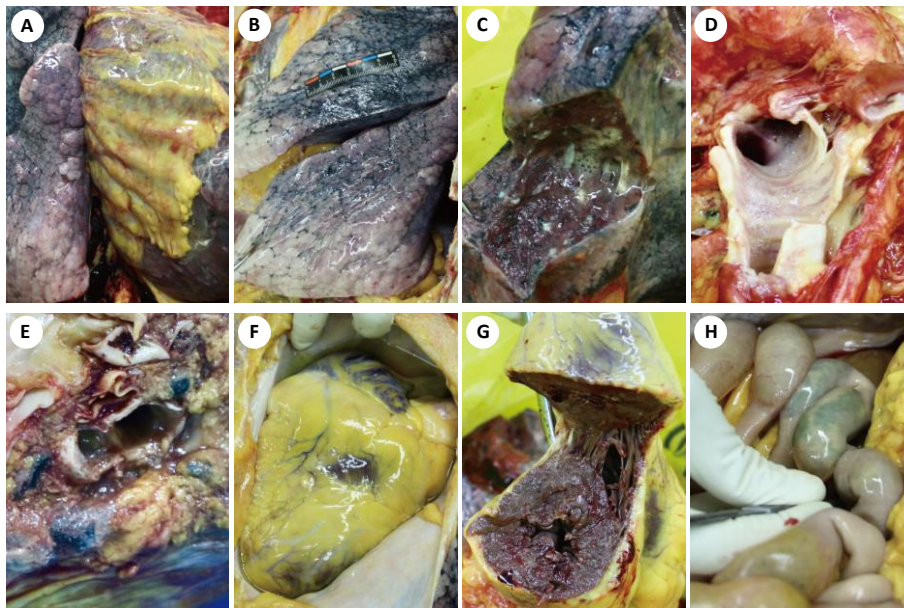
**Literature Review:** Xiaohui Zhang, Xuemei Li, Yang Zhou, Li Peng, Yixin Li, Jinyan Zhang, Jing Luo, Lingyu Li, Jingxian Wu;

**Discussion:** Changhong Yang, Meijiao Wang, Yong Zhao, Kejian Wang, Huarong Yu

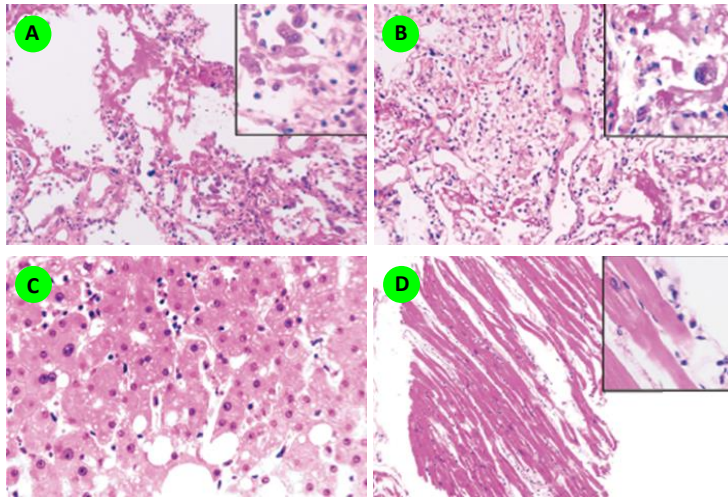
## Reference

1. Zhu N, Zhang D, Wang W, Li X, Yang, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* 2020.
2. Center for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19) Symptoms. 2020.
3. Globally, as of 2:00 pm CEST, 26 Apr 2020, there have been 2,804,796 confirmed cases of COVID-19, including 193,722 deaths, reported to WHO. 2020, <https://who.sprinklr.com/>.
4. WHO Director-General's opening remarks at the media briefing on COVID-19-23 March 2020.
5. Coronavirus (COVID-19) Mortality Rate. 2020, [www.worldometers.info](http://www.worldometers.info).
6. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect. Dis.* 2020.
7. Guan CS, Lv ZB, Yan S, et al. Imaging Features of Coronavirus disease 2019 (COVID-19): Evaluation on Thin-Section CT. *Acad. Radiol.* 2020.
8. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020, 200370.
9. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology* 2020, 200642.
10. Zhang J, Xie Y, Li Y, Shen C, Xia Y., COVID-19 Screening on Chest X-ray Images Using Deep Learning based Anomaly Detection. <https://arxiv.org/abs/2003.12338>. 2020.
11. Abbas A, Abdelsamea MM, Gaber MM. Classification of COVID-19 in chest X-ray images using DeTraC deep convolutional neural network. <https://arxiv.org/abs/2003.13815>. 2020.
12. Finkbeiner WE, Ursell PC. *Autopsy pathology: a manual and atlas*. Elsevier Health Sciences: 2009.
13. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J. Pathol.* 2003, 200 (3), 282-289.
14. Franks TJ, Chong PY, Chui P, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. *Hum. Pathol.* 2003, 34 (8), 743-748.
15. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* 2005, 202 (3), 415-424.
16. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet* 2015, 386 (9997), 995-1007.
17. Ng DL, Al Hosani F, Keating MK, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. *Am. J. Pathol.* 2016, 186 (3), 652-658.
18. Walker, D. H., Value of autopsy emphasized in the case report of a single patient with Middle East respiratory syndrome. *Am. J. Pathol.* 2016, 186 (3), 507.

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19. Alsaad KO, Hajeer AH, Al Balwi M, et al. Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection—clinicopathological and ultrastructural study. *Histopathology* 2018, 72 (3), 516-524.
20. Public Health England. COVID-19: safe handling and processing for laboratories, 2020, <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories/wuhan-novel-coronavirus-handling-and-processing-of-laboratory-specimens>.
21. 29 COVID-2019 deaths have been dissected in China. <http://www.rmzxb.com.cn/c/2020-03-24/2543192.shtml> (in Chinese).
22. Liu Q, Wang R, Qu G, et al. A report on the general observation of the necropsy of a newly developed coronavirus pneumonia. *J. Forensic Med.* 2020, 36, 1004-5619. DOI:10.12116/j.issn.1004-5619.2020.01.00.
23. Li, F., Structure, function, and evolution of coronavirus spike proteins. *Annu. Rev. Virol.* 2016, 3, 237-261.
24. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020, 395 (10223), 507-513.
25. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med.* 2020, 8 (4), 420-422.
26. Yao X, Li T, He Z, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Chin. J. Pathol.* 2020, 49, E009. doi: 10.3760/cma.j.cn112151-20200312-00193.
27. Tian, S.; Xiong, Y.; Liu, H.; Niu, L.; Guo, J.; Liao, M.; Xiao, S.-Y., Pathological Study of the 2019 Novel Coronavirus Disease (COVID-19) through Post-Mortem Core Biopsies. 2020, <https://www.preprints.org/manuscript/202003.0311/v1>.
28. Zhang H, Zhou P, Wei Y, et al. Histopathologic Changes and SARS-CoV-2 Immunostaining in the Lung of a Patient With COVID-19. *Ann. Intern. Med.* 2020.
29. Gao T, Hu M, Zhang X, et al. Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. 2020, <https://www.medrxiv.org/content/10.1101/2020.03.29.20041962v2>.
30. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct. Target Ther.* 2020, 5 (1), 1-3.
31. Chen Y, Feng Z, Diao B, et al. The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes. 2020, <https://www.medrxiv.org/content/10.1101/2020.03.27.20045427v1>.
32. Diao B, Feng Z, Wang C, et al. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. 2020, <https://www.medrxiv.org/content/medrxiv/early/2020/03/06/2020.03.04.20031120.full.pdf>.
33. Ruan Q, Yang K, Wang W, Jiang L, Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020, 1-3.



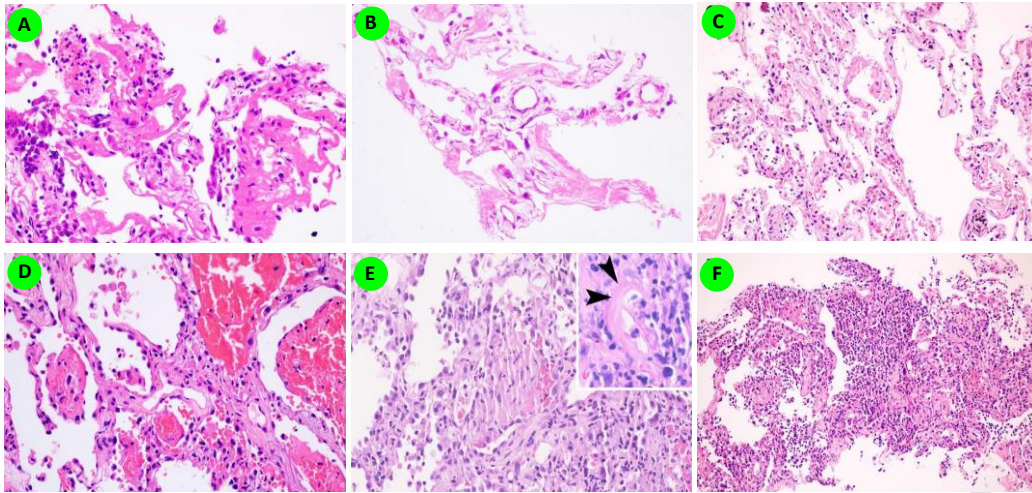
**Figure 1. COVID-2019 pathology in the lung, bronchus, heart and intestine, which is firstly performed in China.<sup>22</sup> (A-C)** Lung of a COVID-2019 victim who died 18 d after the onset of initial symptoms. From image A, we can see the right pleura thickened and has extensive adhesion to the right lung. On the other hand, There is a patchy grey lesion in the left lung. A pale viscous fluid is overflowed and fibrous cords can be observed on the cut surface. (D-E) Foam-like mucus secretions are present in trachea and bronchus, respectively. (F) Characteristics of pericardial cavity and epicardium. (G) The myocardial section is grayish red. (H) small intestinal tract. Images adapted from reference 22, with permission.



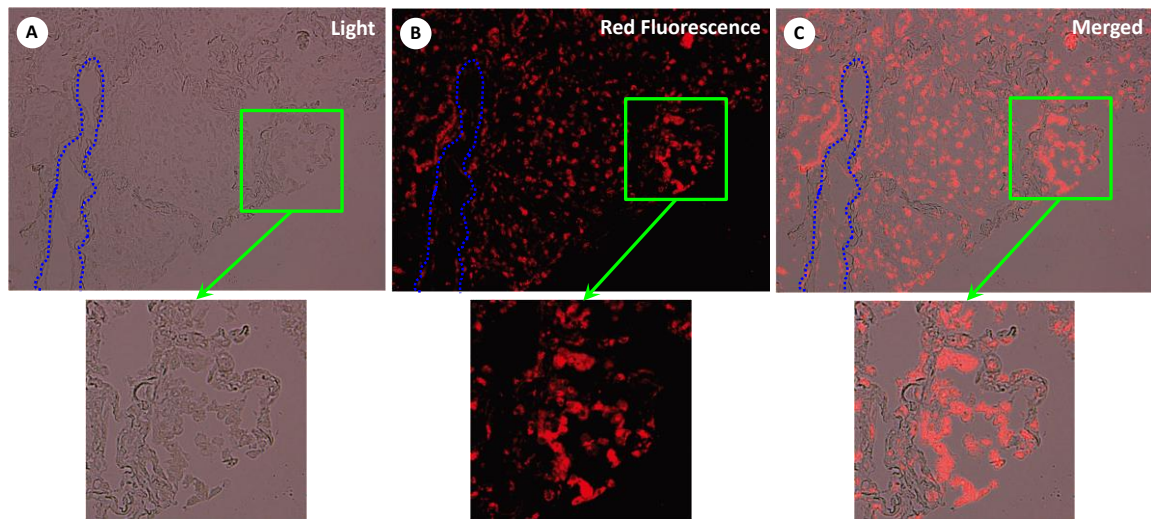
**Figure 2. Histopathologic patterns from 50-year-old patient positive for COVID-2019 by hematoxylin-eosin (H&E) staining in PLA General Hospital, Beijing.<sup>25</sup> Pathological manifestations of (A) right and (B) left lung tissue, (C) liver tissue, and (D) heart tissue. In this study, the location and distribution of SARS-CoV-2 are not observed. Images adapted from reference 25, with license No. 4804150814683.**

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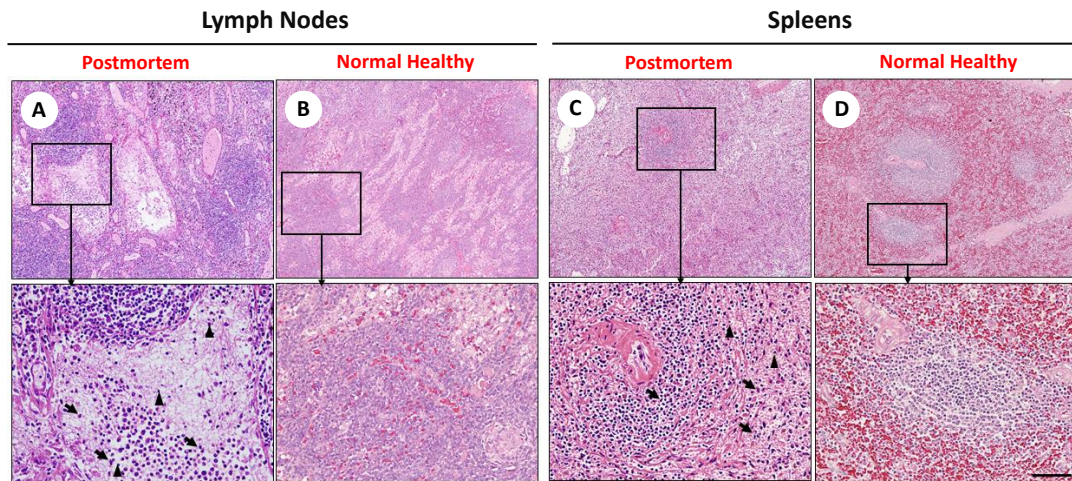


**Figure 3. Microscopic features in the lung tissues from victims who died of COVID-2019 pneumonia in Zhongnan Hospital, Wuhan.** (A) Case 1: Thick hyaline membrane together with desquamative pneumocytes and mononuclear inflammatory cells. (B) Case 2: More delicate hyaline membranes in absence of evident inflammatory infiltration. (C) Case 3: Focal hyaline membrane, type II pneumocyte hyperplasia and mild interstitial thickening. (D) Case 4: Alveolar spaces are filled with red blood cell exudation, and small fibrin plugs are present in adjacent alveoli. (E) Case 4: Organization with intra-alveolar fibroblasts along with fibrin and inflammatory cellular infiltration. Diffuse type II pneumocyte hyperplasia in the background (inset: fibrinoid vascular necrosis indicated by black arrow). (F) Case 4: Changes of bronchopneumonia with prominent neutrophilic infiltration filling up alveolar spaces. Images adapted from reference 27, with Creative Commons Attribution License

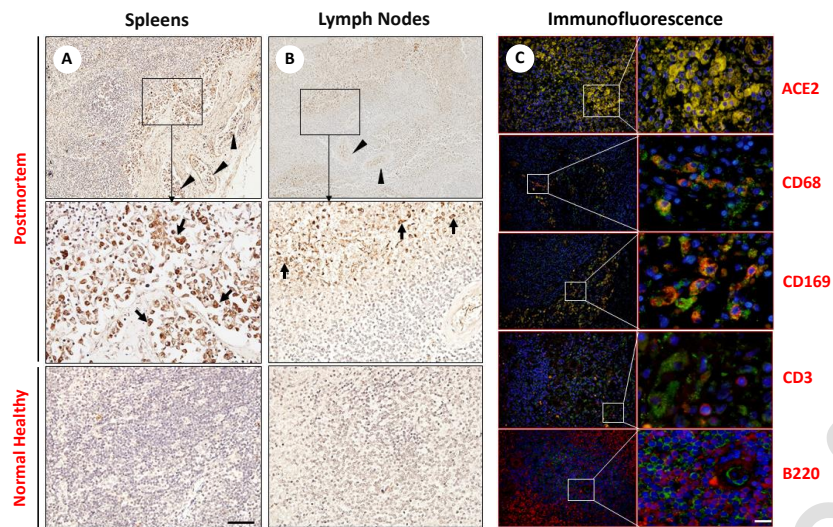


**Figure 4. Immunostaining of SARS-CoV-2 in lung sections from a 72-year-old victim in Jinyintan Hospital, Wuhan.** (A) Images were taken under light field; (B) and fluorescent conditions, respectively ( $100\times$  objective). Merged images were also generated. The dashed blue lines indicate the blood vessel. Immunostaining assay of SARS-CoV-2 was carried out by using a rabbit polyclonal antibody against the Rp3 NP protein, which is highly expressed on the surface of SARS-CoV-2, followed by probing with a Cy3-conjugated goat antirabbit IgG. Images adapted from reference 28, with permission.

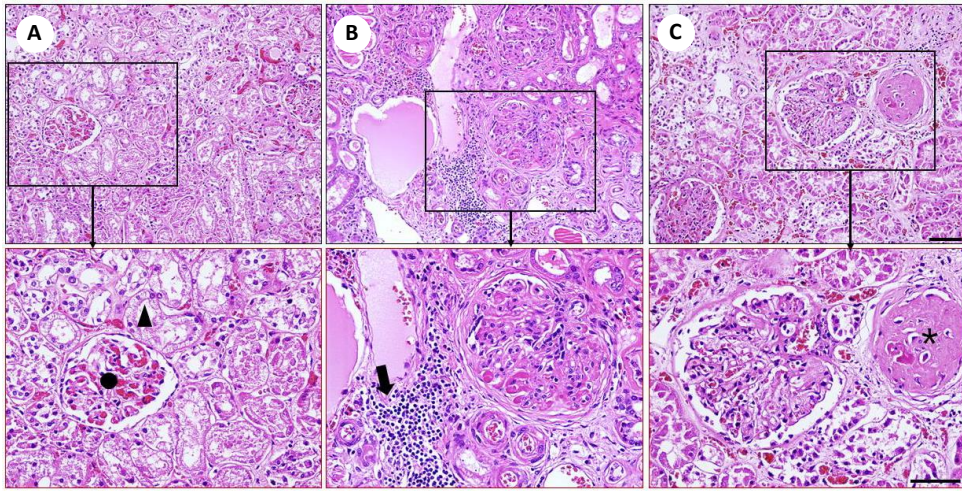




**Figure 5. Representative H&E staining comparison of lymph nodes (A and B) and spleen (C and D) tissues between one patient, who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan, and normal healthy control.<sup>31</sup> In these images, arrow indicated apoptotic lymphocytes, which emphasizes a significant reduction of total lymphocytes when one suffers from SARS-CoV-2 infection. Scale bar: 100  $\mu$ M. Images are obtained under a CC BY-NC-ND 4.0 International License**



**Figure 6. Distribution of SARS-CoV-2 in spleen and LN tissues by immunohistochemistry (IHC) assay from one patient who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan.<sup>31</sup> IHC comparison of SARS-CoV-2 distribution in spleen (A) and LN (B) tissues between one patient, who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan, and normal healthy control. (C) Immunofluorescent double staining analyzed viral NP antigen expression. Arrow indicated viral NP positive cells. Scale bar: 100  $\mu$ m. Images are obtained under a CC BY-NC-ND 4.0 International License.**



**Figure 7. Representative H&E staining of kidney tissues from 3 cases of COVID-2019 patients by postmortem examination in a hospital, Wuhan. ▲ : damage tubules; \*: scrap glomerulus; and arrow indicates infiltrated lymphocytes. Scale bar: 50  $\mu$ m. Images are obtained under a CC BY-NC-ND 4.0 International License.**

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