

# Importance and Guidelines of Postmortem Examination on COVID-19 Cases: An Overview

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## Abstract

Since the outbreak of COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in December 2019, in Wuhan, China, the COVID-19 has spread to 216 countries, areas, and territories and killed more than 400,000 people worldwide. On March 11, the World Health Organization (WHO) declared COVID-19 a pandemic. The pathological findings of COVID-19 by postmortem biopsy were first reported in April 2020. Since then, there have been many publications regarding the postmortem pathological findings of different organs of COVID-19 patients. Well-performed systemic autopsy examination on patients with related diseases, acute respiratory distress syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus has provided critical information for better understanding the pathogenesis of the emerging infectious diseases in the past. An overview on the importance and guidelines of postmortem examination on suspected or confirmed COVID-19 patients is presented.

**Keywords:** Autopsy, COVID-19, guideline, pathological findings, SARS-CoV-2

## INTRODUCTION

In the past half century, a striking trend in medical education and practice has been the decline in the rate of autopsies conducted throughout the world, although full autopsy remains the standard, innovative, and selective approaches to postmortem diagnosis which can provide useful clinical and epidemiological information.<sup>[1]</sup> We have witnessed a significant decrease in hospital autopsies in China in the recent 30 years. The majority of pathology residents and hospital pathologists have no autopsy training. On the other hand, the number of medicolegal autopsy cases has sharply increased due to legal litigations. The medical examiners/forensic pathologists have played an important role not only in medicolegal death investigation but also in public safety and epidemic/pandemic disease surveillance as well. During the COVID-19 pandemic, a group of forensic pathologists at Tongji Medical College conducted the first systemic autopsy examination on a COVID-19 patient on February 16, 2020 in Wuhan. Their pathological discoveries have been included in the latest version of the guideline for the diagnosis and treatment

of the infectious disease released by the National Health Commission.<sup>[2]</sup> We present an overview of the guidelines and importance of postmortem examination on patients whose deaths were caused by or related to COVID-19 infection based on literature review.

## GUIDELINES

Since the outbreak of COVID-19, there have been 85,018 confirmed cases and 4646 deaths caused by COVID-19

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reported in China. The Chinese CDC has issued guidelines of investigation and management of close contact of COVID-19 cases, guidelines of epidemiological investigation of COVID-19, and 6 editions of protocol for prevention and control of COVID-19.<sup>[3]</sup> Five editions of Annex 4 of the Prevention and Control Plan Coronavirus Disease (COVID-19: Laboratory Testing Guideline) have been issued by the National Health Commission of China.<sup>[3]</sup> This technical guideline is formulated to guide disease control agencies and relevant institutions at all levels to carry out laboratory testing for COVID-19. Forensic pathologists and hospital pathologists conducted postmortem examination on COVID-19 patients based on regulations from central and local health departments. In February, a total of 11 systemic autopsies were performed on COVID-19 patients. Nine of the 11 autopsies were conducted by forensic pathologists and the other two cases were conducted by hospital pathologists.<sup>[4]</sup> According to the forensic pathologists who conducted all the nine autopsies, a formal consent was obtained from the next of kin before the autopsy. The autopsies were performed in a modified operation room in the hospital with high-efficiency particulate air filters in the air supply and exhaust systems. Personal protective equipment (PPE), including gas mask, impermeable protective clothing, and three layers of gloves worn by the autopsy team. The entire autopsy room and all the equipment were decontaminated once the autopsy was finished. The patient's body was cremated after autopsy. All the autopsy personnel were closely monitored and isolated for at least 2 weeks with no reported illness.

Since the COVID-19 rapidly spreads to the world, guidelines regarding autopsy protocol in cases of suspected or confirmed COVID-19 have been issued by the WHO,<sup>[5]</sup> the United States,<sup>[6-8]</sup> Italy,<sup>[9]</sup> and England.<sup>[10]</sup> The United States CDC guidelines provide recommendations for biosafety and infection control practices during specimen collection and handling, including during autopsy procedures. The guidance can be used by medical examiners, coroners, pathologists, other workers involved in providing postmortem care, and local and state health departments. Postmortem activities should be conducted with a focus on avoiding aerosol-generating procedures and ensuring that if aerosol generation is likely (e.g., when using an oscillating saw) that appropriate engineering controls and PPE are used. These precautions and the use of standard precautions are appropriate work practices to help prevent direct contact with infectious material, percutaneous injury, and other hazards related to moving human remains and handling embalming chemicals.<sup>[6-8]</sup> The Royal College of Pathologists (RCPATH) of England issued a briefing on autopsy practice relating to possible cases of COVID-19 in February. The brief guidance was produced by the RCPATH to aid mortuary staff and pathologists in deciding if a postmortem examination is appropriate on a possible COVID-19 death and to advise them on the possible risks associated with such a case and how to reduce these risks. It also covers the diagnosis of COVID-19 at postmortem examination. In general, if a death

is believed to be due to confirmed COVID-19 infection, there is unlikely to be any need for a postmortem examination to be conducted and the Medical Certificate of Cause of Death should be issued.<sup>[10]</sup> However, there is some variability in the guidelines. It is the authors' recommendation that universal precaution should be the key to reduce the risk of potential exposure to COVID-19 while conducting postmortem examination during the pandemic.

## LITERATURE ANALYSIS OF AUTOPSY REPORTS

With "COVID-19" and "autopsy" as the search term, publications were searched between January 1, 2020 and June 1, 2020. The search results were statistically analyzed by "statistics" function, including publication by dates, countries, and journals.

### Distribution of literature by dates

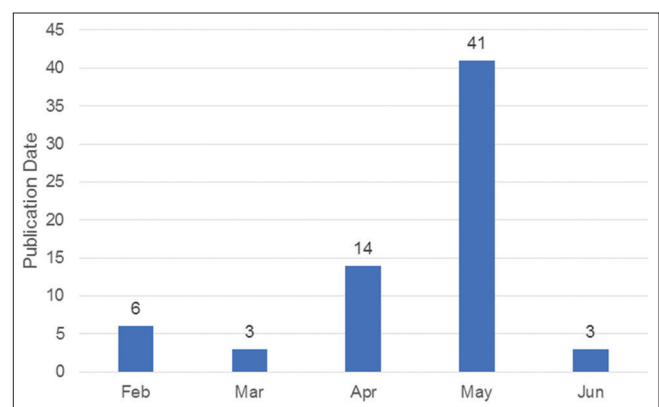
From January 1, 2020 to June 1, 2020, there were totally 67 published articles related to COVID-19 and autopsy in the PubMed database. Worldwide, the number of publications related to COVID-19 autopsy was picked in May 2020 [Figure 1].

### Distribution of literature by authors' countries

From January 1, 2020 to June 1, 2020, COVID-19-related autopsy reports came from 16 countries, including the United States, China, and Italy. The American scholars published the most literature, up to 20 articles, accounting for 29.9% of all the literature. The Chinese scholars published 19 papers, accounting for 28.4%, followed by Italy (9 articles, 13.4%), Germany ( $n = 4$ , 5.97%), Switzerland ( $n = 3$ , 4.4%), and Iran ( $n = 2$ , 3.0%). Scholars from Brazil, Australia, Japan, Lebanon, Paraguay, UK, Spain, Turkey, and Hungary each published one article [Figures 2 and 3].

### Distribution of literature by journals

From January 1, 2020 to June 1, 2020, the journals with the most publication on COVID-19 autopsy findings were Chinese journals (Fa Yi Xue Za Zhi, Zhonghua Bing Li Xue Za Zhi) and Ann Intern Med, with 7, 4, and 3 publications, respectively.



**Figure 1:** Distribution of literature on COVID-19-related autopsies from 2020.1–2020.2 in PubMed database

Figure 4 shows the distribution of literature by journal names. Among them, seven journals have impact factor >9 including New England J Med (NEJM), Lancet and JAMA

**Distribution of literature by the type of articles**

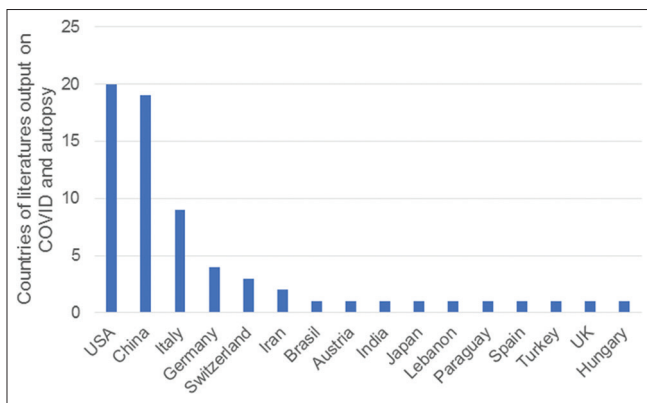
There were six types of COVID-19 autopsy-related publications, namely autopsy research findings (*n* = 45); autopsy review (*n* = 9), case reports (*n* = 6), editorials (*n* = 5), and autopsy guideline (*n* = 1); and one retracted article [Figure 5].

**Analysis of literature published by New England J Med, lancet and JAMA**

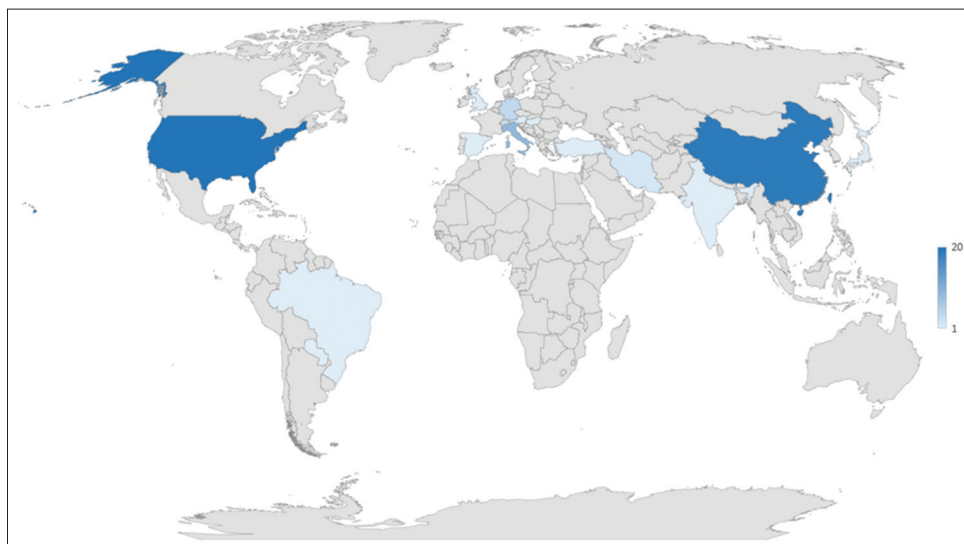
In May 2020, NEJM published a paper titled “Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19.” The authors examined seven lungs obtained during autopsy from patients who died from COVID-19 and compared them with seven lungs obtained during autopsy from patients who died from acute respiratory distress syndrome secondary to influenza A (H1N1) infection and ten age-matched, uninfected control lungs. The lungs were studied with the use of seven-color immunohistochemical analysis, micro-computed

tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression. The results showed patients who died from COVID-19-associated or influenza-associated respiratory failure; the histologic pattern in the peripheral lung was diffuse alveolar damage with perivascular T-cell infiltration. The lungs from patients with COVID-19 also showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of the intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with COVID-19 as in patients with influenza (*P* < 0.001).<sup>[11]</sup>

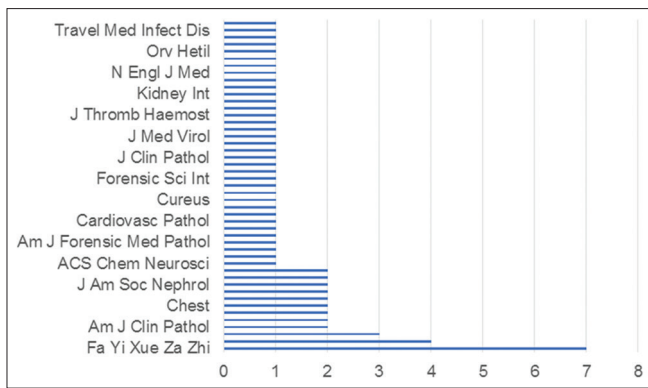
In May 2020, JAMA published an article titled “Postmortem Examination of Patients with COVID-19.” Between April 4 and April 19, 2020, the authors conducted serial 10 postmortem examinations on patients with proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who died at the University Medical Center Augsburg (Germany). In all cases, disseminated diffuse alveolar damage at different stages was the major histologic finding. Diffuse alveolar damage was detectable in all lobes but appeared unevenly distributed with pronounced manifestation in middle and lower lung fields. Signs of exudative early-phase acute diffuse alveolar damage with hyaline membrane formation, intra-alveolar edema, and thickened alveolar septa with perivascular lymphocyte-plasmocytic infiltration were consistently found. Organizing-stage diffuse alveolar damage with pronounced fibroblastic proliferation, partial fibrosis, pneumocyte hyperplasia leading to interstitial thickening and collapsed alveolus, and patchy lymphocyte infiltration was the predominant finding. In areas of organizing diffuse alveolar damage, reactive osseous and squamous metaplasia were observed. Fully established fibrosis was most prominent in patient 1, ultimately leading to almost



**Figure 2:** Distribution of published literature by authors’ countries of literature on COVID-19-related autopsy findings (2020.1–2020.6)



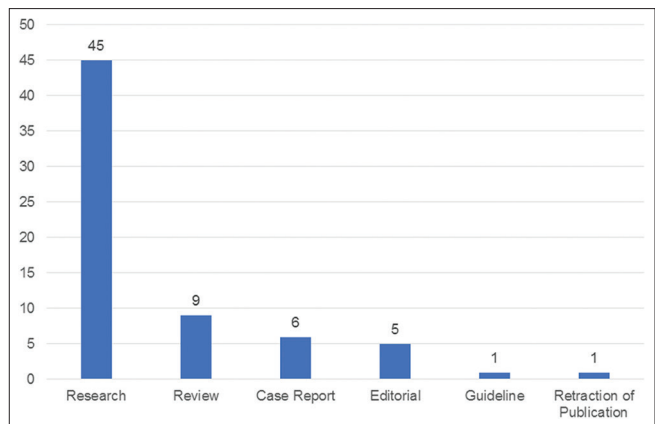
**Figure 3:** Distribution of published literature by authors’ countries of literature on COVID-19-related autopsy findings (2020.1–2020.6)



**Figure 4:** Distribution of COVID-19 autopsy findings by journals (2020.1–2020.6)

complete destruction of pulmonary parenchyma. In five patients, minor neutrophil infiltration was indicative of secondary infection and/or aspiration. Mild lymphocytic myocarditis and signs of epicarditis were detectable in four and two cases, respectively. Liver histology showed minimal periportal lymphoplasmacellular infiltration and signs of fibrosis. There was no morphologically detectable pathology in other organs. Specifically, no signs of encephalitis or central nervous system vasculitis were found. At the time of autopsy, SARS-CoV-2 was still detectable in the respiratory tracts of all patients. Polymerase chain reaction testing was positive in pleural effusion but negative in all cerebrospinal fluid samples. Whether myoepicardial alterations represented systemic inflammation or early myocarditis is unclear; criteria for true myocarditis were not met. The central nervous system involvement by COVID-19 could not be detected.<sup>[12]</sup>

In May 2020, *Lancet* published a paper titled “Endothelial cell infection and endotheliitis in COVID-19.” The authors reported three autopsy examinations. They found evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation. Although the virus uses angiotensin-converting enzyme 2 (ACE2) receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury, the ACE2 receptor is also widely expressed on endothelial cells, which traverse multiple organs. Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis. The findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with the presence of viral bodies) and of the host inflammatory response. In addition, the induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19 endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This



**Figure 5:** Distribution of literature by the type of articles

hypothesis provides a rationale for therapies to stabilize the endothelium while tackling viral replication, particularly with anti-inflammatory anticytokine drugs, ACE inhibitors, and statins.<sup>[13]</sup>

One review article published by the Arch Pathol Lab Med, in May 2020<sup>[14]</sup> was entitled “SARS-CoV-2 Pandemic: Review of the Literature and Proposal for Safe Autopsy Practice.” The authors present a review of the literature and a proposal for COVID autopsy protocols. The review provided an operating protocol that can be useful for all clinical and forensic autopsies with particular reference to the safety methods to be applied to the examination of positive or suspected COVID-19 cases regarding both autopsy procedure and collection/analysis of biological samples.

### COVID-19 AUTOPSY GUIDELINES AND CASE REPORTS IN CHINA

COVID-19 has been included in Category B infectious diseases and is prevented and controlled according to Category A infectious diseases. In order to establish a diagnosis or conduct further research, a postmortem examination may be desired on a possible COVID-19 death. To guide the personnel engaged in the autopsy to carry out the safe operation and to ensure the safety of the pathologists and personnel involved in postmortem examination during the epidemic, the Chinese Pathological Society, the Chinese Pathologist Association, and the Pathology and Pathophysiology National Key Discipline at Shantou University Medical College formulated the guidance to COVID-19 case autopsy.<sup>[15]</sup>

Based on related laws and regulations, such as the Law of the People’s Republic of China on Prevention and Control of Infectious Diseases, the clinical manifestations and epidemiological characteristics of COVID-19, and the related guidelines on the prevention and control of the outbreak, combined with the practical work of forensic pathology examination, Mao *et al.* provided Guide to the Forensic Pathology Practice on Death-Related COVID-19 (Trial Draft).<sup>[16]</sup> The guide includes information on the scene

investigation, autopsy room requirements, personal prevention and protections, external examinations, autopsy, and auxiliary examinations.

To investigate the pathological characteristics and the clinical significance of COVID-19, minimally invasive autopsies from the lung, heart, kidney, spleen, bone marrow, liver, pancreas, stomach, intestine, thyroid, and skin were performed on three patients died of COVID-19 pneumonia in Chongqing, China.<sup>[17]</sup> Various damages were observed in the alveolar structure, with minor serous exudation and fibrin exudation. The lungs showed alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation, and hyaline membrane formation.

In conclusion, although the pathogenesis of COVID-19 remains to be studied further, much has been learned from well-performed autopsy examinations on COVID-19 patients. Universal safety precaution should be carried out while conducting postmortem examination on any deaths during the COVID-19 pandemic and in the future.

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### Conflicts of interest

There are no conflicts of interest.

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