Postmortem Findings Associated With SARS-CoV-2
Systematic Review and Meta-analysis

Swati Satturwar, MD,* Mary Fowkes, MD, PhD,† Carol Farver, MD,‡ Allecia M. Wilson, MD,‡
Albino Eccher, MD,§ Ilaria Girolami, MD,§ Elisabet Pujadas, MD, PhD,† Clare Bryce, MD,†
Fadi Salem, MD,† Siraj M. El Jamal, MD,† Alberto Paniz-Mondolfi, MD, PhD,†
Bruce Petersen, MD,† Ronald E. Gordon, PhD,† Jason Reidy, MSc,† Filippo Fraggetta, MD,‖
Desiree A. Marshall, MD,¶ and Liron Pantanowitz, MD, MHA‡

Abstract: Coronavirus Disease 2019 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome–associated Coronavirus 2 (SARS-CoV-2), has become a global threat to public health. COVID-19 is more pathogenic and infectious than the prior 2002 pandemic caused by SARS-CoV-1. The pathogenesis of certain disease manifestations in COVID-19 such as diffuse alveolar damage (DAD) are thought to be similar to SARS-CoV-1. However, the exact pathogenesis of COVID-19 related deaths remains poorly understood. The aim of this article was to systematically summarize the rapidly emerging literature regarding COVID-19 autopsies. A meta-analysis was also conducted based on data accrued from preprint and published articles on COVID-19 (n = 241 patients) and the results compared with postmortem findings associated with SARS-CoV-1 deaths (n = 91 patients). Both autopsy groups included mostly adults of median age 70 years with COVID-19 and 50 years with SARS-CoV-1. Overall, prevalence of DAD was more common in SARS-CoV-1 (100.0%) than COVID-19 (80.9%) autopsies (P = 0.001). Extrapulmonary findings among both groups were not statistically significant except for hepatic necrosis (P <0.001), splenic necrosis (P < 0.006) and white pulp depletion (P <0.001) that were more common with SARS-CoV-1. Remarkable postmortem findings in association with COVID-19 apart from DAD include pulmonary hemorrhage, viral cytopathic effect within pneumocytes, thromboembolism, brain infarction, endotheliitis, acute renal tubular damage, white pulp depletion of

the spleen, cardiac myocyte necrosis, megakaryocyte recruitment, and hemophagocytosis.

KEY POINTS

(1) A meta-analysis of autopsy findings was conducted based on data from articles on Coronavirus Disease 2019 (COVID-19), (n = 241 patients) and Severe Acute Respiratory Syndrome–associated Coronavirus 1 (SARS-CoV-1) deaths (n = 91 patients).
(2) Diffuse alveolar damage (DAD) was the most common cause of mortality in both viral groups.
(3) Notable extrapulmonary postmortem findings associated with COVID-19 include thromboembolism, brain infarction, endotheliitis, acute renal tubular damage, white pulp depletion of the spleen, cardiac myocyte necrosis, megakaryocyte recruitment, and hemophagocytosis.

INTRODUCTION

Autopsies remain the gold standard to understand the pathogenesis of new and emerging diseases. Autopsies performed during previous coronavirus pandemics, due to Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV-1 in 2002, and Middle East Respiratory Syndrome (MERS) caused by MERS-related coronavirus (MERS-CoV) in 2012, provided insights into their pathogenesis that contributed to improved patient management.[1,2] Since the initial 2019 outbreak in Wuhan, China almost every country has subsequently been affected by COVID-19 caused by the novel Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-CoV-2). While most infected individuals have recovered from COVID-19, many have become seriously ill, especially the elderly and those with underlying comorbidities (eg, hypertension, diabetes).[3] Unfortunately, the mortality rate among severely ill patients, despite medical intervention such as ventilation, has been high with an overall global mortality rate of 7% to 15%.[4,5]

Studies have shown that SARS-CoV-2 is an RNA virus that belongs to the same family of beta coronaviruses as SARS-CoV-1 and MERS-CoV. Minor differences in the spike protein of SARS-CoV-2 are associated with its increased transmission rate.[6] Both SARS-CoV-1 and SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE-2) receptor for binding to host cells. It is speculated that the pathogenesis of COVID-19 is similar to that of SARS. Although acute respiratory distress syndrome (ARDS), and its histologic hallmark DAD, is considered to be the most common cause of death in COVID-19, the pathologic basis of why ARDS occurs only in a subset of patients and why only a subset of these afflicted individuals die is unclear.[7,8] Furthermore, the clinical course of severe and fatally ill patients with COVID-19 has been complicated by cardiac injury, shock, and thrombosis including pulmonary embolism and stroke.[9]

The literature regarding COVID-19 is rapidly emerging with articles progressively unraveling the pathogenesis and underlying pathology of this infectious disease based largely on either gross examination only, limited autopsy case reports, small postmortem series, and partial autopsy findings.[10–14] Despite the active appeal to perform autopsies on COVID-19 patients, the current overall autopsy rate appears to be low.[15–18] The paucity of autopsy data is not surprising because initially there were recommendations to suspend postmortems on patients with suspected/confirmed COVID-19 infection.[19] Also, performing postmortem examinations on COVID-19 patients is risky and requires an autopsy facility with appropriate biosafety accessories.[20] Fortunately, there has been a recent drive to boost postmortem services during this pandemic.[21] This is important because many critical questions about COVID-19 remain to be answered. For example, apart from ARDS what role do other processes such as direct nonpulmonary tissue viral infection, immune dysregulation, primary thrombosis, disseminated intravascular coagulation (DIC), and secondary infections play in fatal COVID-19 disease?[22–25] Clearly, there is an urgent need to characterize the underlying pathology of COVID-19 to better understand the pathogenesis of this disease and more effectively treat infected patients.

The aim of this review article was to systematically summarize the available emerging literature regarding COVID-19 autopsies. The intent was to additionally conduct a meta-analysis to compare postmortem findings in decedents of COVID-19 to previously published findings in SARS-CoV-1 associated deaths.

MATERIALS AND METHODS

A review of the English and non-English literature in online archival databases up to June 2020 was performed. There were 15 articles about autopsies on patients with confirmed SARS-CoV-1[1,26–39] and 24 articles detailing autopsies on patients with confirmed COVID-19[11–14,40–59] that were included (Supplemental Digital Content Table 1, http://links.lww.com/PAS/B82). Two of the SARS-CoV-1 articles referred to the same group of 8 patients,[26,27] but because they provided different clinical and pathologic details in each paper both were included without duplicating the patient count. A total of 332 patients were identified including 91 with SARS-CoV-1 infection and 241 with COVID-19. All of the papers concerning SARS-CoV-1 were previously published, whereas only 15 (62.5%) of the papers about COVID-19 autopsies were accepted in the peer-reviewed literature at the time of submitting this review with the remaining preprint articles analyzed available on medRxiv or bioRxiv. One COVID-19 paper of a pregnant woman with COVID-19 has since been withdrawn by the authors.[47]

Specific patient age was provided for 131 patients (60 with SARS-CoV-1, 71 with COVID-19), allowing for an age comparison for both patient groups. The normality of the distributions of patient age was examined using the Shapiro-Wilk normality test. As the data were not normally distributed, the Mann-Whitney test was used to compare SARS-CoV-1 and COVID-19 patient ages. One article provided age ranges for each of the 11 patients in their study,[52] and these were added to a categorical summary of age with the other 131 patients. The Pearson χ^2 test was used to determine if the proportion of cases with SARS-CoV-1 or COVID-19 was different among categorical data variables (sex, age category, race/ethnicity, documented comorbidities, and microscopic pathologic details including inflammation, thromboembolic findings, and necrosis). Pooled prevalence and their 95% confidence intervals of histopathologic findings was calculated using the DerSimonian-Laird random-effects model after double-arcsine transformation. Double-arcsine transformation is the appropriate choice when the sample size is small and/or extreme proportions need to be handled.[60,61] A formal Egger test detected no publication bias.[62] Statistical significance was assumed at P-value <0.05. Analyses were performed using IBM SPSS Statistics 22 and software R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) with R Studio 1.2.5033 environment (R Studio Inc., Boston, MA).

The selected images included in this manuscript were acquired from a total of 157 autopsies performed at the aforementioned institutions, as well as from 26 personal consultation cases of autopsies performed at other institutions on patients with confirmed SARS-CoV-2.

Autopsy Procedure

Since the outbreak of COVID-19, several articles have emphasized the need to conduct autopsies using standardized protocols and recommended using at least a Biosafety Level-2 autopsy facility.[20,63–65] Guidelines were also proposed for forensic pathology.[66] Although performing a complete body autopsy is ideal, alternative options utilized to minimize the risk of SARS-CoV-2 transmission to autopsy staff have included performing limited postmortems with in situ sampling or minimally invasive puncture/core biopsy autopsies[11,12,67] of only major target organs with or without opening the entire body. Autopsy procedure recommendations have included utilizing adequately trained staff, minimizing the number of people in the autopsy suite, and allowing only one person to handle knives. The autopsy facility should

include an airborne infection isolation room with negative pressure and a minimum number of air changes per hour. If an airborne infection isolation room is not available, a portable high-efficiency particulate air recirculation unit has been recommended to reduce aerosols.

In addition to universal precautions, additional airborne safeguards as well as eye protection are recommended during these autopsies. Personal protective equipment recommendations include double surgical gloves with cutproof synthetic mesh gloves in between, impermeable/fluid-resistant gown, waterproof apron, face shield or goggles, N-95 or higher disposable respirators, as well as donning surgical scrubs, shoe covers, and a surgical cap. Postmortem swabs for COVID-19 testing have been recommended from the upper respiratory tract (eg, nasopharyngeal swab) or lower respiratory tract (eg, swab from each lung).[68,69] Aerosol-generating procedures (eg, use of an oscillating bone saw) are to be avoided. If brain removal is performed using an oscillating saw, the use of a vacuum shroud or containment box has been recommended.[70] Standard precautions along with the use of personal protective equipment are also recommended when transferring bodies, including disinfecting the outside of body bags after use. Specimens collected for biobanking have included unfixed tissue, swabs, or blood stored at −80°C, as well as formalin-fixed tissue.[64,71]

Epidemiology and Clinical Setting

Articles about SARS-CoV-1 were mostly from China (n = 11, 73%) with 2 published from Singapore and 1 each from Taiwan and Canada. Articles about COVID-19 arose mostly from the United States (n = 11, 46%), then China (n = 5, 21%), with 2 published from Switzerland and 1 each from Austria, France, Germany, Iran, Italy, and Japan. Table 1 summarizes the autopsy procedures employed (Supplemental Digital Content Table 2,

TABLE 2. Age Distribution by Virus Group in Autopsy Publications

Age (y)	n (%)		Higher Proportion	χ^2	P
	COVID-19* (N = 82)	SARS-CoV-1† (N = 60)			
≤ 39	4 (4.9)	19 (31.7)	SARS	18.318	< 0.001
40-59	12 (14.6)	23 (38.3)	SARS	10.478	0.001
60-79	41 (50.0)	14 (23.3)	COVID	10.383	0.001
80+	25 (30.5)	4 (6.7)	COVID	12.098	0.001

*82 of the 241 (34.0%) COVID-19 patients from included articles had patient-level age information; the remaining 86 patients provided only summary information (average, range) or no age information.
†60 of the 91 (65.9%) SARS-CoV-1 patients from included articles had patient-level age information; the remaining 31 patients provided summary information (average, range) or no age information.

http://links.lww.com/PAS/B83). The clinical course (Supplemental Digital Content Table 3, http://links.lww.com/PAS/B84) for COVID-19 in these papers ranged from 0 to 61 days after the onset of illness to the time of death, compared with 1 to 108 days for SARS-CoV-1 patients. The initial clinical presentation for COVID-19 was similar to SARS-CoV-1. The majority of infected patients presented with fever, cough, shortness of breath, myalgia and other variable symptoms depending upon organ involvement (eg, diarrhea, headache).

COVID-19 patients were statistically significantly older (median = 70.0 y) than SARS-CoV-1 patients (median = 50.0 y, U = 949.00, P < 0.001) (Table 2). Of note, COVID-19 patients were more likely than SARS-CoV-1 patients to be 60 to 79 years old ($\chi^2 = 10.383$, P = 0.001) and 80+ years old ($\chi^2 = 12.098$, P = 0.001). Table 3 compares patient race among both viral groups showing that with SARS-CoV-1 infections were restricted to Asian populations, but that COVID-19 infections present in all examined ethnic groups. With COVID-19, of 234 autopsies that specified sex, there were 161 (68.8%) males and 73 (31.2%) females. With SARS-CoV-1, of 80 autopsies that specified sex, there were 57 (71.3%) males and 23 (28.8%) females. There was not a significant association between gender and virus group ($\chi^2 = 0.168$, P = 0.682). Table 4 and Supplemental Digital Content Table 3 (http://links.lww.com/PAS/B84) summarizes patient comorbidities indicating that hypertension was the most common comorbid disease overall. Nearly all of the listed comorbidities were documented in a higher proportion for COVID-19 patients, with the exception of

TABLE 1. Summary of Type of Autopsy, Organs Examined, and Timing of Diagnosis

Autopsy Parameters	n (%)	
	COVID-19 (N = 241)	SARS-CoV-1 (N = 91)
Autopsy type		
Whole body autopsy	130 (53.9)	57 (62.6)
Partial/punch autopsy	110 (45.6)	34 (37.4)
Not specified	1 (0.4)	0 (0.0)
Organ(s) examined		
Lung	157 (65.1)	72 (79.1)
Kidney	124 (51.5)	31 (34.1)
Liver	92 (38.2)	44 (48.4)
Heart	100 (41.5)	30 (33.0)
Spleen	92 (38.2)	39 (42.9)
Brain	71 (29.5)	27 (29.7)
Gastrointestinal	53 (22.0)	28 (30.8)
Other organ(s)	36 (14.9)	39 (42.9)
Endocrine	26 (10.8)	24 (26.4)
Genitourinary	15 (6.2)	19 (20.9)
Timing of diagnosis		
Antemortem	236 (97.9)	88 (96.7)
Postmortem	5 (2.1)	3 (3.3)
Days to death (range)	0-61	1-108

TABLE 3. Deceased Patient Race/Ethnicity by Virus Group

Race/Ethnicity	n (%)	
	COVID-19* (N = 157)	SARS-CoV-1† (N = 67)
Caucasian	44 (28.0)	0 (0.0)
African American	26 (16.6)	0 (0.0)
Asian	52 (33.1)	67 (100.0)
Hispanic	34 (21.7)	0 (0.0)

*157 of the 241 (65.1%) COVID patients from included articles provided race.
†67 of the 91 (73.6%) SARS patients from included articles provided race.

TABLE 4. Documented Patient Comorbidities by Virus Group

Comorbid Disease	n (%)		Higher Proportion	χ^2	P
	COVID-19* (N = 234)	SARS-CoV-1† (N = 35)			
Hypertension	131 (56.0)	5 (14.3)	COVID	21.177	<0.001
Diabetes	68 (29.1)	2 (5.7)	COVID	8.620	0.003
Obesity	32 (13.7)	0 (0.0)	COVID	5.433	0.020
Lung disease	31 (13.2)	1 (2.9)	COVID	3.136	0.077
Heart disease	83 (35.5)	8 (22.9)	COVID	2.164	0.141
Kidney disease	31 (13.2)	1 (2.9)	COVID	3.136	0.077
Cancer	25 (10.7)	4 (11.4)	SARS	0.018	0.895
Immunocompromised	12 (5.1)	0 (0.0)	COVID	1.879	0.170

*234 of the 241 (97.1%) COVID-19 patients from included articles had comorbidity details provided.
†35 of the 91 (38.5%) SARS-CoV-1 patients from included articles had comorbidity details provided.

cancer. COVID-19 patients were more likely to have hypertension, diabetes, and/or obesity than SARS-CoV-1 patients ($\chi^2 = 21.177$, $P < 0.001$; $\chi^2 = 8.620$, $P = 0.003$; $\chi^2 = 5.433$, $P = 0.020$, respectively).

Pulmonary radiology features were similar in both groups with a chest x-ray or computed tomography scan findings showing bilateral ground-glass opacities with or without consolidation. Laboratory test results were reported in some studies. The most notable findings for COVID-19 were leukocytosis with relative lymphocytopenia, variably increased lactate dehydrogenase, increased blood urea nitrogen, decreased glomerular filtration rate, increased international normalized ratio, and increased D-dimers.[11,12,40,47,48,52,53] SARS-CoV-1 patients were also reported to present with lymphocytopenia.[31,36,38]

Pulmonary Pathology Findings

The gross findings in COVID-19 autopsies were notable for heavy lungs with edema, congestion, with or without consolidation, and in some cases, hemorrhage was observed (Fig. 1). In COVID-19 cases, there was a mild serosanguinous pleural effusion (n = 7) and pleural adhesions (n = 8). According to Calabrese et al[72] pleural effusions were detected in more than half of the patients with COVID-19. Tracheitis was present in a subset of COVID-19 patients.[40]

The main histopathologic lung findings in available studies are summarized in Table 5 (Supplemental Digital Content Table 4, http://links.lww.com/PAS/B85 and Supplemental Digital Content Table 5, http://links.lww.com/PAS/B86). The spectrum of microscopic abnormalities seen in COVID-19 overlapped with those reported in SARS-CoV-1. All of the SARS-CoV-1 patients showed DAD, which was statistically significantly higher than COVID-19 ($\chi^2 = 12.029$, $P = 0.001$). The majority of COVID-19 patients exhibited features of DAD (Fig. 2), with most cases showing early acute DAD (Fig. 3). Histologic features suggestive of the different phases of DAD reported in COVID-19 autopsies included acute DAD (n = 74), proliferative DAD (n = 22), mixed acute/proliferative DAD (n = 42), and fibrotic/chronic DAD (n = 20). For SARS-CoV-1 autopsies, the histologic features of the different phases of DAD included: acute DAD (n = 39) (Fig. 4), proliferative DAD (n = 20), mixed acute/proliferative DAD (n = 23), and fibrotic/chronic DAD (n = 33). Additional findings included severe type II pneumocyte hyperplasia,

desquamation of pneumocytes, squamous metaplasia, focal fibroblast plugs, interstitial thickening, mild patchy chronic inflammation, intra-alveolar hemorrhage (Fig. 5), megakaryocytes,[14,43,46] and hemophagocytosis.[55] A significantly higher proportion of SARS-CoV-1 patients had hemorrhage and/or vascular injury identified in their lungs ($\chi^2 = 28.643$, $P < 0.001$; $\chi^2 = 14.681$, $P < 0.001$, respectively). Vascular injury was noted in both viral groups, with most of the involved COVID-19 cases showing lymphocytic endotheliitis[44,47,51,53] with[41] or without necrosis of the vessel wall, cytoplasmic vacuolization, or endothelial detachment.[56] Vascular injury described in the articles was mainly endotheliitis due to inflammation of small capillary sized blood vessels/capillaritis. Very few articles included the term vasculitis. The

FIGURE 1. Right lung shown in the sagittal section from a 68-year-old woman who died of COVID-19 after 3 weeks of ventilation for ARDS showing diffuse hemorrhagic congestion (lung weight = 1130 g; normal adult mean weight = 300 to 350 g).

TABLE 5. Key Microscopic Lung Pathology Findings

	COVID-19		SARS-CoV-1				
Histopathology	Total	n (%)	Total	n (%)	Higher Proportion	χ^2	P
DAD*	157	127 (80.9)	54	54 (100.0)	SARS	12.029	0.001
Hyaline membranes	157	126 (80.3)	54	49 (90.7)	SARS	3.122	0.077
Inflammatory cells†	157	115 (73.2)	54	45 (83.3)	SARS	2.487	0.135
Microthrombi	157	93 (59.2)	54	33 (61.1)	SARS	0.059	0.808
Hemorrhage	157	56 (35.7)	54	42 (77.8)	SARS	28.643	< 0.001
Vascular injury‡	157	33 (21.0)	54	26 (48.1)	SARS	14.681	< 0.001
Pulmonary embolism	157	13 (8.3)	54	6 (11.1)	SARS	0.393	0.531

*Approximate number of different phases of DAD as per the histopathologic data provided in the articles: For COVID-19: acute DAD (n = 74), proliferative DAD (n = 22), mixed acute/proliferative DAD (n = 42), and fibrotic/chronic DAD (n = 20). For SARS-CoV-1: acute DAD (n = 39), proliferative DAD (n = 20), mixed acute/proliferative DAD (n = 23), and fibrotic/chronic DAD (n = 33).

†Inflammatory cells were present in the interstitium predominantly. For COVID-19: lymphocytes (n = 76), plasma cells (n = 6), neutrophils (n = 3), macrophages (n = 3), and inflammatory cell type not specified (n = 1). For SARS-CoV-1: macrophages (n = 34) and lymphocytes (n = 25).

‡Vascular injury described in the articles was mainly endotheliitis due to inflammation of small capillary sized blood vessels/capillaritis. Very few articles included the term vasculitis. Literature was not consistent in providing details about vasculitis and included endothelial denudation also as vasculitis. For COVID-19: small vessel/capillary endotheliitis (n = 28), vascular injury with/due to denudation of small to medium-sized vessel (n = 5). For SARS-CoV-1: small vessel endotheliitis (n = 9) and vascular injury with/due to endothelial denudation (n = 17).

literature was inconsistent in providing details about vascular injury and ranged from endothelial denudation to vasculitis. In COVID-19 autopsies, for the reported cases with small vessel/capillary endotheliitis (n = 28) most were due to lym-

FIGURE 2. Forest plot for the prevalence of DAD in reported autopsy studies with COVID-19 versus SARS-CoV-1 (SARS) as the main subgrouping variable. CI indicates confidence interval.
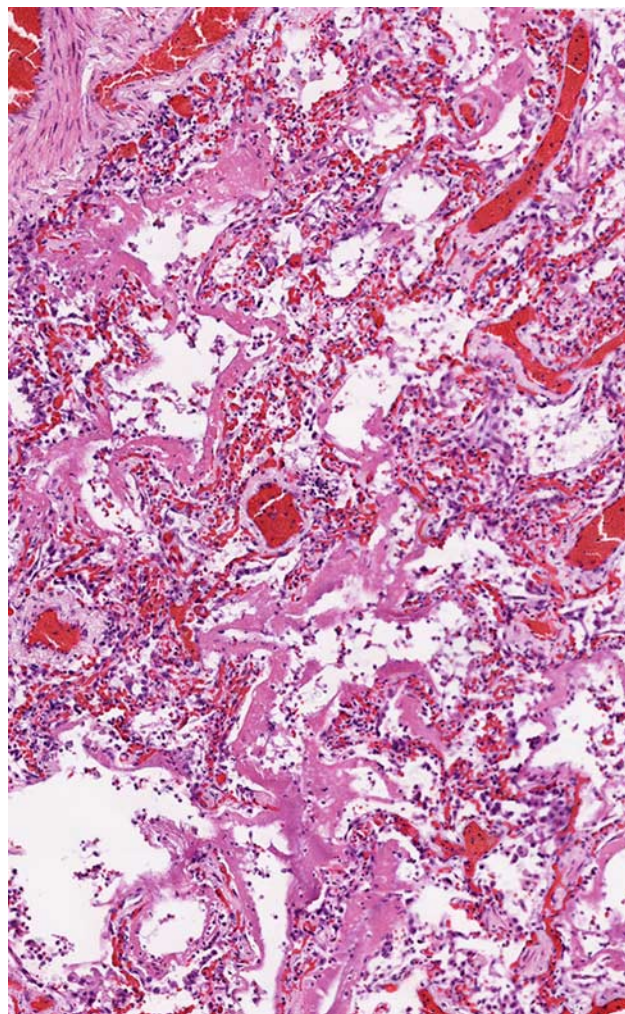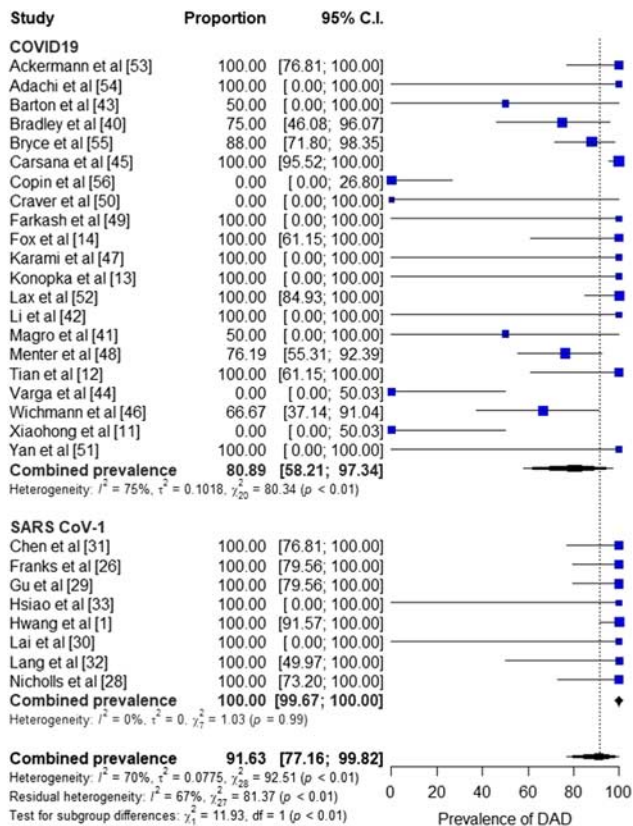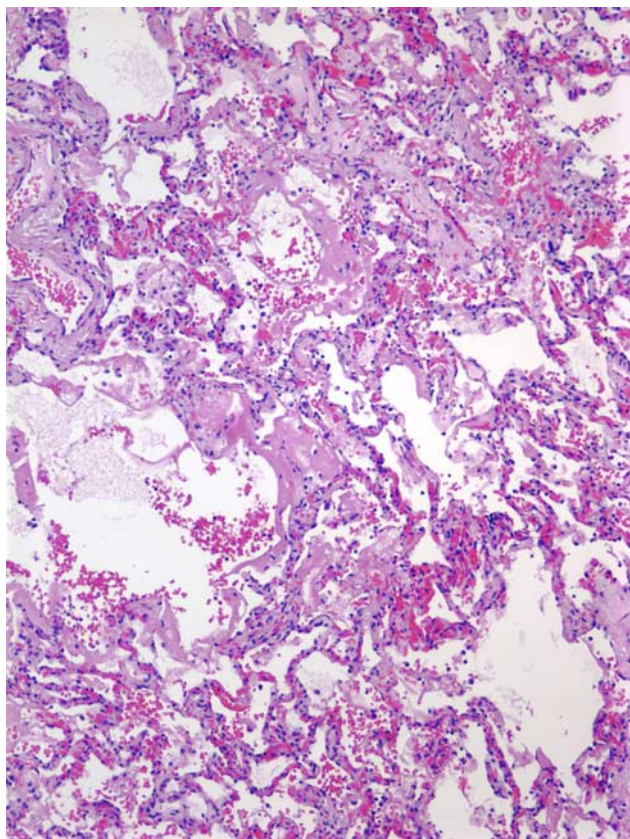

FIGURE 3. DAD associated with COVID-19. Hyaline membranes are present throughout the alveolar spaces in this acute phase of DAD (hematoxylin and eosin).

FIGURE 4. Lung tissue showing diffuse hyaline membrane formation and capillary congestion in early acute DAD from a patient infected with SARS-CoV-1 (hematoxylin and eosin). Note the similarity to Fig. 3. Image courtesy of Jeffrey L. Myers from the University of Michigan, Ann Arbor, MI.

phocytic endotheliitis or vascular injury with/due to endothelial denudation of small-sized to medium-sized vessels (n = 5). In SARS-CoV-1 cases, there was also small vessel endotheliitis (n = 9) and vascular injury with/due to endothelial denudation (n = 17). Vasculitis described in the papers appeared to be secondary and minimal without true vascular destruction or fibrinoid necrosis. Interstitial inflammation was present, but was not a prominent component in COVID-19. In COVID-19, the interstitial inflammatory cells were mostly T lymphocytes (CD4^{+}, CD8^{+})[11,43] with fewer B lymphocytes as opposed to increased macrophages seen in SARS-CoV-1.[26] Lymphocytic interstitial pneumonia is not an important finding in COVID-19 cases, as per our literature review. In general, lymphocytic interstitial pneumonia is a very rare entity and its pathology overlaps considerably with the chronic interstitial pneumonia that can be found in many different interstitial lung disease patterns (eg, hypersensitivity pneumonitis, and the early phase of acute DAD). Therefore, in the studies where this finding is referenced, this histopathology is most likely referring to a more general chronic interstitial pneumonia that is found in these lungs. In a small series of 6 COVID-19 patients evaluated by postmortem biopsy, Copin and colleagues found lymphocytic pneumonia in 1 patient who died within a week of presentation. The remaining cases in their
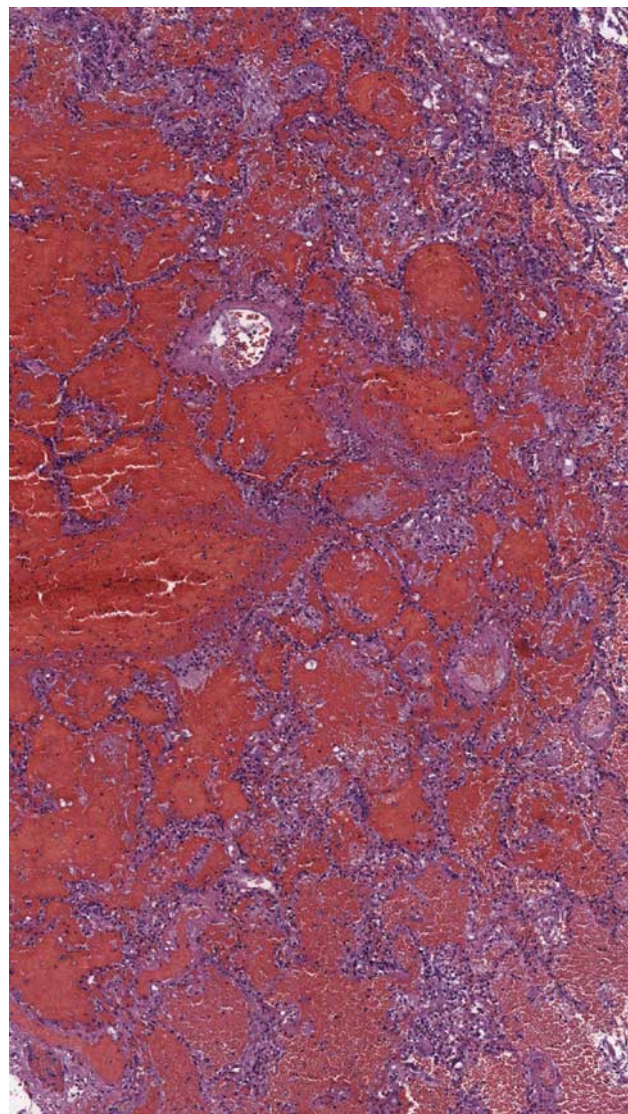

FIGURE 5. Marked alveolar hemorrhage associated with COVID-19. Blood and fibrin expanded alveolar spaces are shown consistent with alveolar hemorrhage (hematoxylin and eosin).

study, all with longer survival intervals (∼20 d), were diagnosed with an acute fibrinous organizing pneumonia (AFOP) pattern of lung injury.[56] Acute bronchopneumonia with superimposed bacterial or fungal infection was present in both COVID-19 (n = 29)[11,14,40,43,45,46,52,55] and SARS-CoV-1 (n = 14) cases.[1,26–28,33]

Pulmonary embolism, with or without associated deep venous thrombosis, was present in both groups. The thrombi in COVID-19 patients were comprised of fibrin[13,14,48] and/or platelets[45,48] and mostly involved small peripheral vessels like capillaries or arterioles, with some cases showing thrombi that also affected medium-sized vessels (Fig. 6) and the pulmonary artery. In the study by Carsana et al,[45] both lungs from COVID-19 patients showed thrombi occupying > 25% of the lung parenchyma associated with elevated D-dimer levels in > 50% of patients.
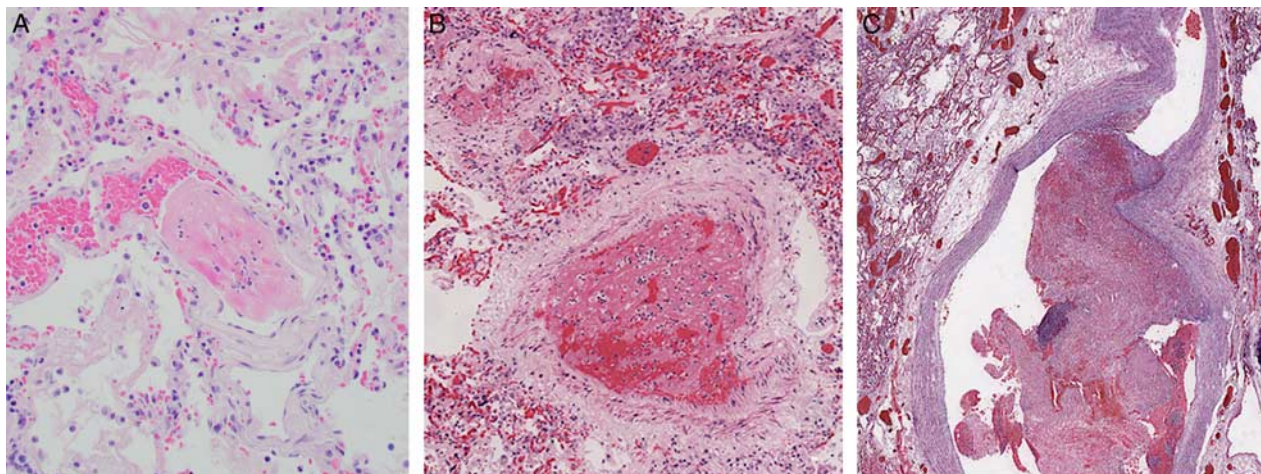
FIGURE 6. Early organizing thrombi are shown in small (A), medium (B), and large (C) vessels in the lung parenchyma of COVID-19 lungs (hematoxylin and eosin).

Multinucleated giant cells (Fig. 7) were common in both COVID-19 (n = 49) and SARS-CoV-1 (n = 44) cases. These giant cells were shown to be CD68$^+$ macrophages or thyroid transcription factor 1+ pneumocytes in COVID-19,[11] as opposed to mostly CD68$^+$ macrophages in SARS-CoV-1.[26] Viral-induced cytopathic effect (Fig. 8) was noted in several COVID-19 (n = 30) and some SARS-CoV-1 (n = 5) autopsies. The viral cytopathic effect described in these papers included reactive appearing type II pneumocytes with cytomegaly, nuclear enlargement, prominent nucleoli, and candidate intranuclear or intracytoplasmic viral inclusions. However, although SARS-CoV-2 viral particles have been isolated in both type I and II pneumocytes in several comprehensive studies to date,[73] the giant cells and those pneumocytes with possible viral cytopathic effect have yet to be further studied in detail.

Several studies have demonstrated direct invasion of respiratory epithelial cells by coronavirus using a variety of ancillary techniques including reverse transcriptase–polymerase chain reaction (PCR), transmission electron microscopy (TEM), immunofluorescence, in situ hybridization, and immunohistochemistry (IHC) directed against the nucleocapsid protein and spike protein. In patients with COVID-19, TEM detected the virus in type II pneumocytes more often than in type I pneumocytes, bronchial epithelial cells, and endothelial cells.[11,40,45] Involvement of type II pneumocytes by SARS-CoV-2 was more common than type I pneumocytes, as opposed to SARS-CoV-1 that affected more type I pneumocytes.[11,28–30,40,45] Schaefer et al[74] in their series of 7 autopsies reported that SARS-CoV-2 infection of epithelial cells in the lungs and airways was best detected during the acute phase of lung injury and was absent in the organizing phase of DAD. For SARS-CoV-2, RNAscope® probes complementary to the viral spike (S) and the spike sense strand messenger RNAs permit direct visualization of viral transcripts in routine formalin-fixed paraffin-embedded tissue. Detection of the spike protein (S) indicates the presence of SARS-CoV-2 within the cells while detection of the anti-sense strand shows the presence of active viral replication in the infected cells.[75] For both probes, cytoplasmic dot-like hybridization signals (Fig. 9) confirm the presence of nondegraded RNA that increase in numbers proportional to
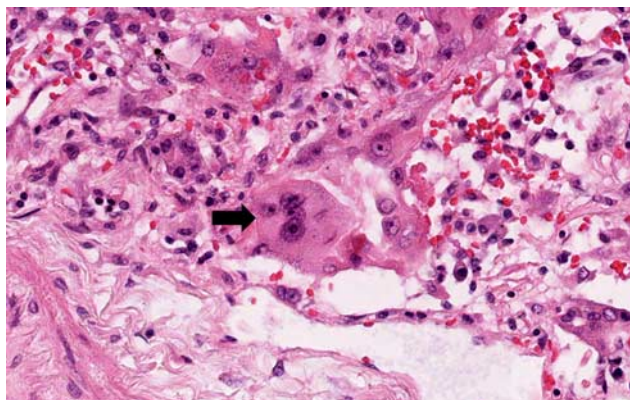

FIGURE 7. Multinucleated giant cells (arrow) as shown in this image can be detected scattered in alveolar spaces throughout COVID-19 lungs (hematoxylin and eosin).
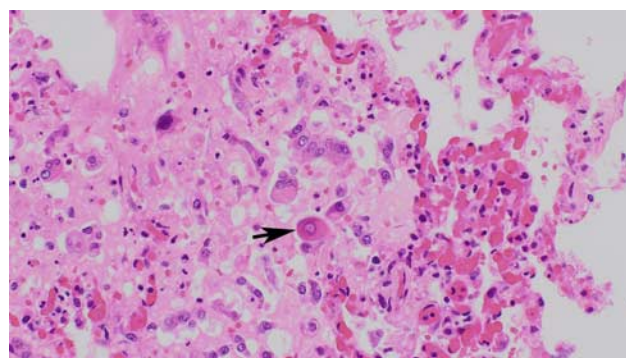

FIGURE 8. Possible COVID-19 viral cytopathic effect (arrow) within pneumocytes exhibiting enlarged, pink, and smudgy nuclei (hematoxylin and eosin). This finding may be seen in DAD of other causes.
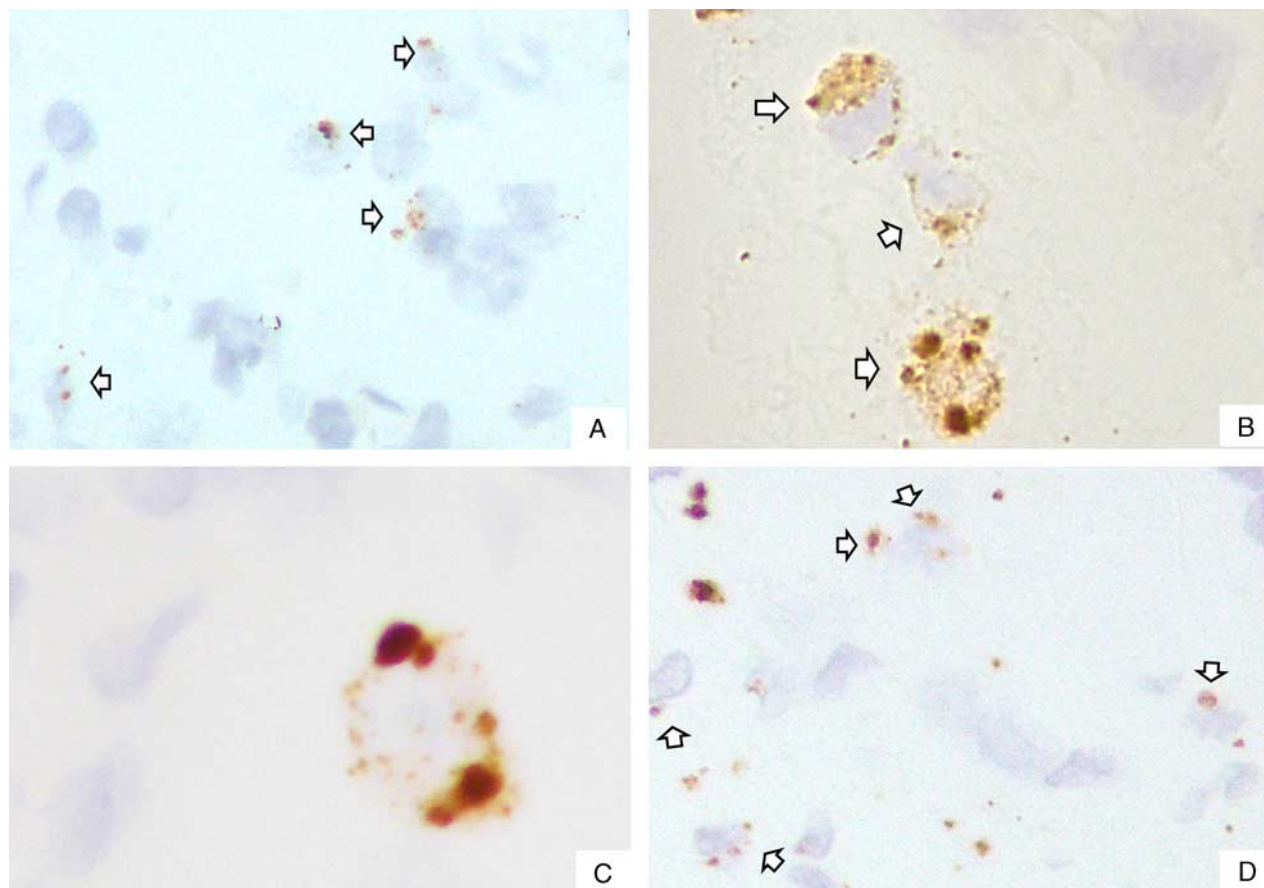
FIGURE 9. In situ hybridization for messenger RNA encoding the SARS-CoV-2 spike protein (S) is visualized as dark brown signals located in the cytoplasm of infected cells (arrows), low power at ×400 (A) and high power at ×1000 (B, C) with some signals showing coalescence into globules (C). The antisense messenger RNA strand of the spike protein is shown (arrows) indicative of active viral replication, low power at ×400 (D).

the viral load in the cells, ranging in size variability from fine dots to a coalescent of such signals forming larger globules. Ultrastructural studies with MERS similarly localized viral particles within pneumocytes.[76] Ackermann et al[53] also detected a greater number of ACE-2 receptors in alveolar pneumocytes, lymphocytes and endothelial cells of COVID-19 patients compared with other viruses.

Cardiac Pathology Findings

Gross pathology findings of the heart in patients who died of COVID-19 included cardiomegaly with ventricular hypertrophy, correlating with a clinical history of hypertension. The main postmortem histopathologic findings in the heart from available studies are summarized in Table 6 and Supplemental Digital Content Tables 6 and 7 (http://links.lww.com/PAS/B87, http://links.lww.com/PAS/B88). There was not a statistically significant relationship between COVID-19 and SARS-CoV-1 for microscopic heart findings. Nonspecific degenerative changes were noted in some COVID-19 studies.[11,14,51] Myocyte necrosis in COVID-19 was present only as individual cell necrosis,[11,14,50] focally involving both ventricles similar to SARS-CoV-1.[27] Inflammatory cells in COVID-19 were comprised of lymphocytes (CD4$^+$ > CD8$^+$),[55] focally involving the interstitium and epicardial surface. In COVID-19 there were also cases reported with lymphocytic[40] (Fig. 10) and eosinophilic myocarditis.[50] For

TABLE 6. Summary of Microscopic Heart Pathology Findings

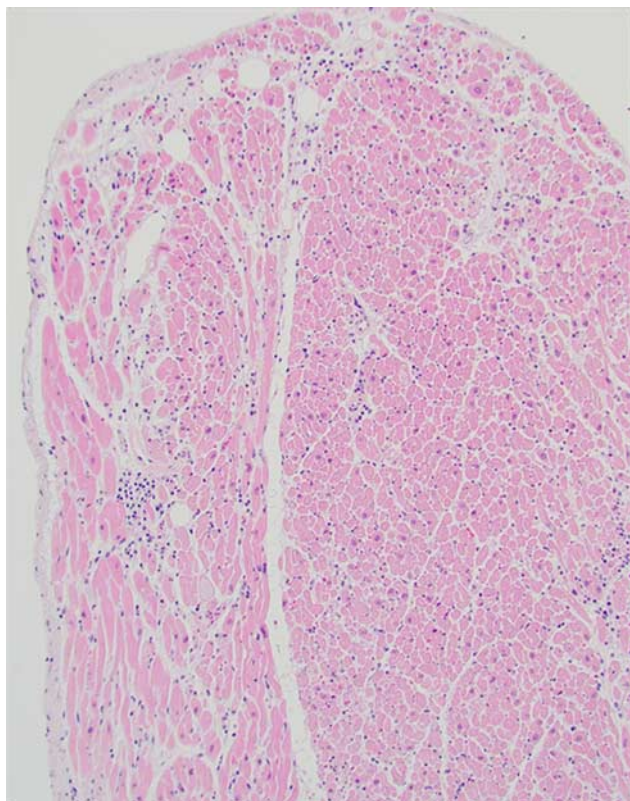| Histopathology	COVID-19		SARS-CoV-1		Higher Proportion	χ^2	P
	Total	n (%)	Total	n (%)			
Inflammatory cells	99	24 (24.2)	8	0 (0.0)	COVID	2.500	0.114
Myocyte necrosis	87	7 (8.0)	8	2 (25.0)	SARS	2.455	0.117
Acute myocardial infarction	99	3 (3.0)	8	1 (12.5)	SARS	1.845	0.174
Lymphocytic myocarditis	99	3 (3.0)	8	0 (0.0)	COVID	0.249	0.617
Eosinophilic myocarditis	99	1 (1.0)	8	0 (0.0)	COVID	0.082	0.775

FIGURE 10. Section of the heart from a patient that died with COVID-19 with lymphocytic myocarditis showing a diffuse lymphocytic infiltrate (hematoxylin and eosin). This patient also had methicillin-sensitive *Staphylococcus aureus* and influenza A infections. Low-level SARS-CoV-2 RNA was detected within the myocardium.

SARS-CoV-1 cases, no significant inflammation was noted. Thrombosis of small vessels was noted in some COVID-19 cases (n = 5)[51,55] and infrequently with SARS-CoV-1 cases (n = 2).[27] Hemophagocytosis was reported in the heart by Bryce et al.[55] Both coronaviruses were detected within myocytes and the interstitium by PCR.[12,27,40,46]

Genitourinary System Pathology Findings

Renal microscopic findings in both viral groups are summarized in Table 7 and Supplemental Digital Content Tables 6 and 7 (http://links.lww.com/PAS/B87, http://links.lww.com/PAS/B88). There was not a statistically significant relationship between COVID-19 and SARS-CoV-1 with respect to renal findings. The main histopathologic findings were acute tubular damage (Fig. 11)

and focal to diffuse microthrombi in both groups. Hypertensive and diabetic changes were noted in a few studies that correlated with clinical morbidity.[40,48,57] In the COVID-19 group, additional postmortem findings reported included the presence of interstitial inflammatory cells comprised of lymphocytes and macrophages[58] and vascular injury such as endotheliitis.[57] Other incidental findings included amyloidosis (n = 1) and an angiomyolipoma (n = 1). A plurality of ancillary tests (TEM, IHC, immunofluorescence, in situ hybridization) have detected SARS-CoV-2 viral particles within proximal renal tubules more so than distal tubular epithelial cells[40,48,49,57] or podocytes[48,49] (Fig. 12), whereas the SARS-CoV-1 virus mostly involved the distal tubular epithelium.[29] Associated findings with COVID-19 autopsies were complement deposition[58] and activation of thrombotic pathways with DIC.[48] Other genitourinary system findings reported in COVID-19 patients included an incidental renal oncocytoma, prostate vein thrombosis,[46] benign prostatic hyperplasia, damage to the testicular parenchyma,[77] and testicular atrophy.[43,46]

Brain Pathology Findings

Examination of the brain in COVID-19 patients showed focal punctate subarachnoid hemorrhages, punctate brain stem hemorrhage, and focal hypoxic changes without significant inflammation or necrosis (Supplemental Digital Content Table 8, http://links.lww.com/PAS/B89). A study by Bryce et al[55] showed thrombi in small vessels with associated microhemorrhages and acute infarction (Fig. 13). In 1 case, there was a large cerebral artery infarct.[55] The majority of cases exhibited minimal inflammation, only slight neuronal loss, no myelin loss using Luxol fast blue, no microglial nodules, and no viral inclusions. The study by Gu et al[29] on SARS-CoV-1 reported the presence of focal hypoxic changes. SARS-CoV-2 was detected in brain tissue by reverse transcriptase-PCR.[46] Menter et al[48] also detected slightly higher levels of this virus within the olfactory bulb compared with the brainstem.

Hematopoietic System Pathology Findings

The bone marrow showed varying degrees of decreased trilineage hematopoiesis and in some cases of COVID-19, there was left-shifted myelopoiesis[11,48] (Supplemental Digital Content Table 8, http://links.lww.com/PAS/B89). In addition, increased megakaryocytes were reported in association with SARS-CoV-1.[30] In COVID-19 patients there was lymphoid depletion of lymph nodes, increased plasmablasts in lymph nodes, and white pulp depletion of the spleen.[11,40,55,59] One study reported

TABLE 7. Summary of Microscopic Kidney Pathology Findings

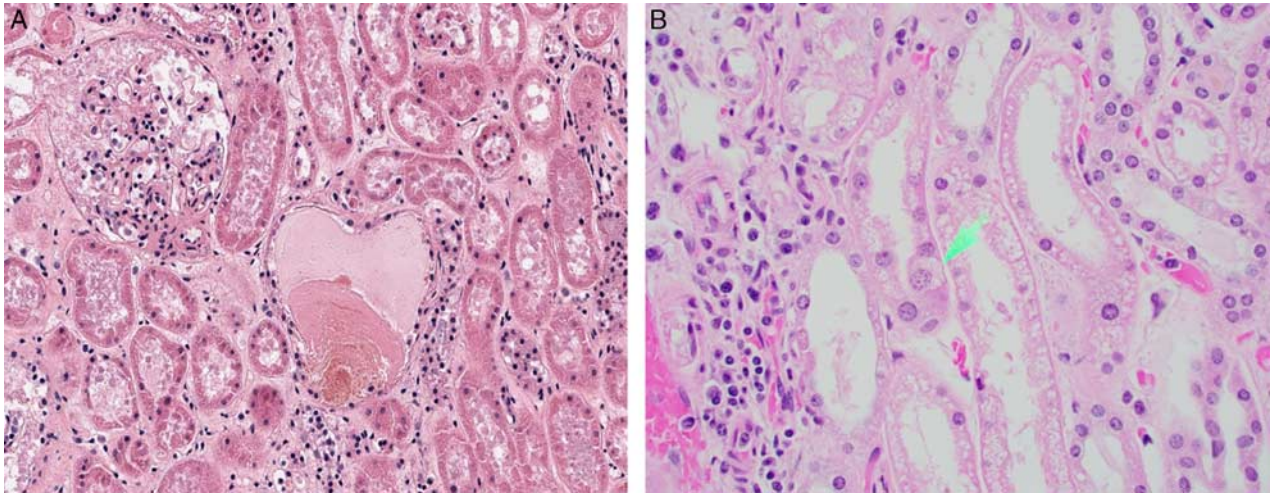| Histopathology	COVID-19		SARS-CoV-1		Higher Proportion	χ^2	*P*
	Total	n (%)	Total	n (%)			
Acute tubular damage	121	62 (51.2)	8	6 (75.0)	SARS	1.700	0.192
Fibrin thrombi	109	7 (6.4)	8	2 (25.0)	SARS	3.623	0.057
Inflammatory cells	83	6 (7.2)	8	0 (0.0)	COVID	0.619	0.431
Endotheliitis	109	3 (2.8)	8	0 (0.0)	COVID	0.226	0.635

FIGURE 11. Renal tubular injury. A, Section of a kidney from a deceased patient with COVID-19 showing acute tubular damage with coagulative necrosis of tubules and focal shedding of epithelial cells into the lumen. The interstitium shows edema and a few infiltrating mononuclear inflammatory cells (hematoxylin and eosin). B, Renal tubular injury with vacuolization, mitotic figure (green arrow), and focal interstitial inflammation (hematoxylin and eosin).

increased immunoblast-like cells in lymph nodes.[78] IHC identified specific depletion of CD3^{+}, CD4^{+}, and CD8^{+} lymphocytes in COVID-19.[59] All SARS-CoV-1 patients in which the spleen was examined also showed white pulp depletion,[27–29] a finding that was statistically significantly higher than in COVID-19 patients ($\chi^2 = 45.377$, $P < 0.001$). Necrosis of the spleen was more frequent with SARS-CoV-1 ($\chi^2 = 7.511$, $P = 0.006$), whereas inflammation was more commonly encountered in COVID-19 ($\chi^2 = 5.195$, $P = 0.023$) (Table 8). Bryce et al[55] reported hemophagocytosis in the bone marrow, lymph node and spleen (Fig. 14). Increased CD68^{+} activated large macrophages were reported in SARS-CoV-1 patients.[29] Thrombi were not documented in any of the spleens examined.

Hepatic Pathology Findings

In both groups of patients studied (Supplemental Digital Content Tables 6, 7, http://links.lww.com/PAS/B87, http://links.lww.com/PAS/B88), the liver showed focal hepatocyte degeneration and necrosis, a mild portal and periportal lymphocytic infiltrate, rare lobular lymphocytic infiltrate, steatosis, and lymphocytic endotheliitis. A significantly higher proportion of SARS-CoV-1 patients had hepatocyte necrosis[27,37] and/or portal inflammation in their liver ($\chi^2 = 19.221$, $P < 0.001$; $\chi^2 = 10.501$, $P = 0.001$, respectively) (Table 9). A higher proportion of COVID-19 patients had thrombi and/or lobular inflammation, but there was not a statistically significant difference. Also, hemophagocytosis was noted by Bryce et al[55] in their series of patients with COVID-19.
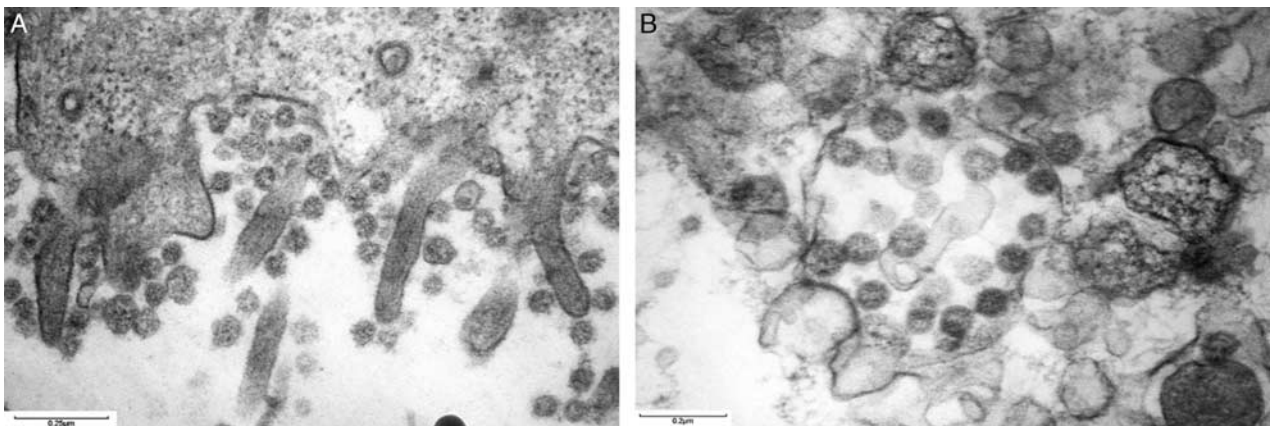

FIGURE 12. TEM of SARS-CoV-2 in Vero cells (African green monkey kidney epithelial cells). A, Multiple viral particles along the cell surface are shown displaying a distinct electron-dense surface with radiating peplomeric projections (bar: 0.25 µm). B, Ultrastructural details on a replicating vesicle. Note that the virions are spherical with some pleomorphism and measuring ~80 to 110 nm in diameter. The surface is covered by an array of projections (peplomers) with the presence of multiple internal electron-dense dots that correspond to cross-sections of the nucleocapsid (bar: 0.2 µm).
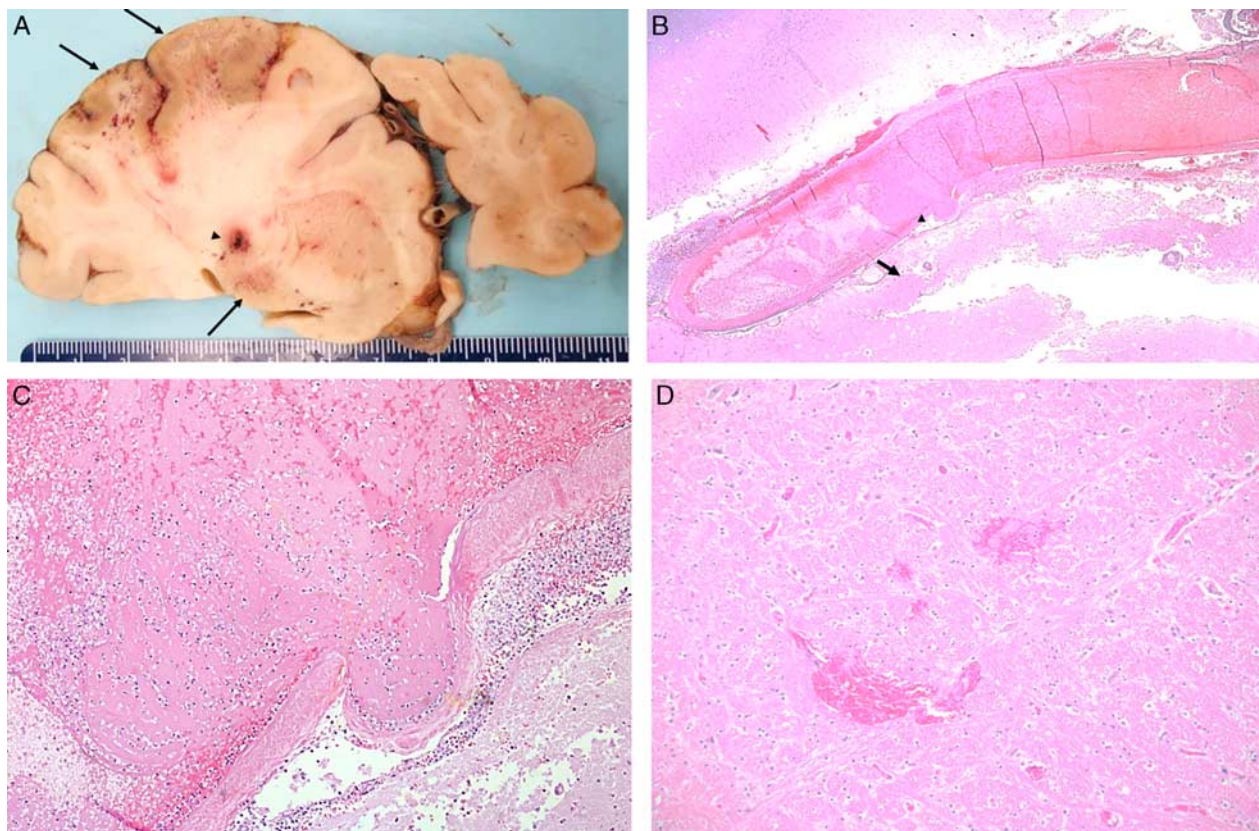
FIGURE 13. Neuropathology findings. A, Coronal section of the right cerebral hemisphere in a patient that died of COVID-19 showing acute infarcts (arrows) and thrombosed vessels (arrowhead). B, A brain-blood vessel with a thrombus (arrowhead) is shown occluding the entire lumen. Note the perivascular mononuclear inflammatory cells and towards the bottom of the image (arrow) necrotic cortical brain parenchyma (hematoxylin and eosin). C, Higher magnification showing the organized thrombus within the blood vessel (hematoxylin and eosin). D, Brainstem with acute microhemorrhage (hematoxylin and eosin).

Gastrointestinal Tract Pathology Findings

In a few COVID-19 cases the gastrointestinal tract showed mesenteric ischemia.[44] The stomach and intestines in patients with COVID-19 showed epithelial degeneration, necrosis, shedding, congestion, as well as mild lymphocyte and plasma cell infiltration.[11] There was focal gastric hemorrhage[40] and in 2 COVID-19 cases small vessel endotheliitis of the small intestine was identified[44] (Supplemental Digital Content Table 8, http://links.lww.com/PAS/B89). The pancreas was uninvolved in most cases. With SARS-CoV-1, patients showed atrophy of their mucosal lymphoid tissue (ie, decreased lymphocytes, depletion of follicles, and a burnt-out appearance of germinal centers) mostly in the pharynx, small intestine, and appendix.[30] Hyaline thrombi in small blood vessels of the small and large intestines and an associated pseudomembrane with necrotic mucosa was noted in 1 COVID-19 patient.[46]

Endocrine Organ Pathology Findings

In COVID-19 patients, the thyroid gland showed an incidental goiter in 1 patient[43] and the adrenal glands were reported to exhibit nodules in another.[46] In SARS-CoV-1 patients, Wei and colleagues studied the thyroid gland in detail and reported the destruction of follicular epithelial cells with their exfoliation into the follicle (Supplemental Digital Content Table 8, http://links.lww.com/PAS/B89). The presence of apoptosis was confirmed by a Terminal deoxynucleotidyl transferase dUTP Nick End Labeling

TABLE 8. Summary of Microscopic Pathology Findings in the Spleen

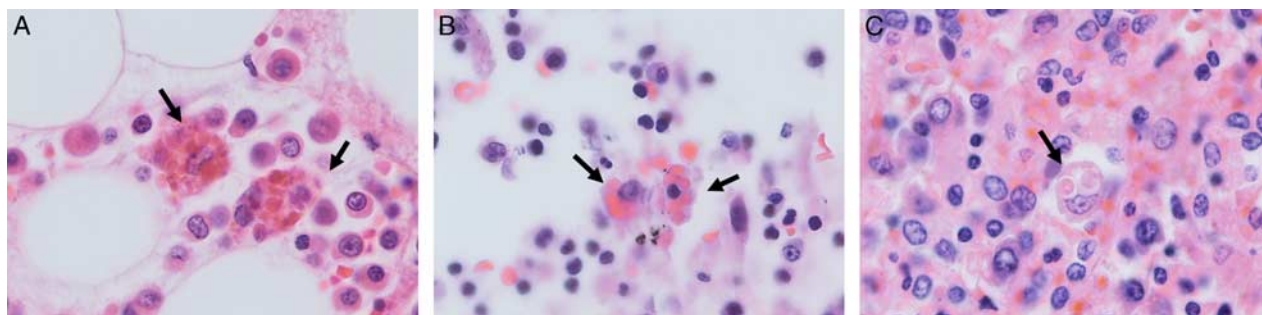| Histopathology	COVID-19		SARS-CoV-1		Higher Proportion	χ^2	P
	Total	n (%)	Total	n (%)			
White pulp depletion	81	18 (22.2)	23	23 (100.0)	SARS	45.377	<0.001
Inflammation	78	15 (19.2)	23	0 (0.0)	COVID	5.195	0.023
Necrosis	81	5 (6.2)	23	6 (26.1)	SARS	7.511	0.006
Thrombi	78	0 (0.0)	23	0 (0.0)	—	—	—

FIGURE 14. Hemophagocytic histiocytes (arrows) in COVID-19 autopsies from the bone marrow (A), subcapsular sinus of a lymph node (B), and spleen (C) (hematoxylin and eosin).

(TUNEL) DNA fragmentation assay.[38] No lymphocytic or neutrophilic infiltrate was reported. Also, no increased parafollicular cells were seen.

Musculoskeletal System Pathology Findings

Skeletal muscle involvement in SARS-CoV-1 was reported by Leung et al[39] with notable findings including myofiber necrosis, macrophage infiltration, and scant regenerative fibers. COVID-19 studies did report on musculoskeletal findings (Supplemental Digital Content Table 8, http://links.lww.com/PAS/B89).

DISCUSSION

COVID-19 caused by infection with SARS-CoV-2 can have variable clinical presentations ranging from a mild asymptomatic respiratory illness to fulminant ARDS, multiorgan failure, and death in a subset of patients. Given the pressing need to characterize the underlying pathology associated with COVID-19 many pathologists spanning the globe bravely began performing autopsies and reporting their postmortem findings in these deceased patients. This article, to the best of our knowledge, represents one of the largest systematic reviews and meta-analysis of postmortem findings that have been reported associated with SARS-CoV-2. This review also uniquely compares the pathology of COVID-19 to previously published findings in SARS-CoV-1 associated deaths. There are several limitations of this study. Given the rapid pace at which the literature is expanding on this topic we may not have captured every article published on the topic, which includes newer articles. Some of the articles included were preprint papers without peer review. Also, as we relied on the data documented in these papers it was not always possible to extract all of the clinical, laboratory and pathology details desired, nor the cause of death or clinical correlation in all cases. In addition, the overall number of published COVID-19 cases was higher than that for SARS-CoV-1, which may have affected comparisons.

Unlike SARS-CoV-1 where prior autopsy publications arose largely from China, with COVID-19 such articles spanned the globe, which probably reflects the widespread pandemic and high case fatality rate in many countries. Our analysis corroborates what has been reported in antemortem studies and large autopsy series,[79] which is that mortality due to COVID-19 occurs mostly in infected patients who are elderly (median = 70.0 y), males, and those with an underlying comorbid disease such as hypertension, diabetes, and/or obesity. This is significantly different from patients who succumbed to SARS-CoV-1, as those patients were slightly younger and without such reported comorbidities. Of note, entirely reporting comorbid disease was more prevalent in COVID-19 articles.

The most prominent pathologic manifestation of COVID-19 was the pulmonary findings, which was likely the most common cause of symptoms and death in afflicted patients.[14,80–88] This review shows that the majority of patients who died from COVID-19 had bilateral DAD, similar to SARS-CoV-1 and MERS. The histopathologic findings of DAD from COVID-19 appear to be indistinguishable from other causes of DAD.[89] The acute/exudative phase of DAD is characterized by inflammatory cell-mediated alveolar damage with alveolar edema and/or hemorrhage, capillary congestion, and hyaline membranes with or without microvascular thrombi. The proliferative/organizing phase of DAD shows type II pneumocyte hyperplasia, reactive pneumocytes, alveolar wall thickening, and myofibroblast proliferation, whereas the chronic/fibrotic phase shows honeycomb lung

TABLE 9. Summary of Microscopic Liver Pathology Findings

	COVID-19		SARS-CoV-1				
Histopathology	**Total**	**n (%)**	**Total**	**n (%)**	**Higher Proportion**	**χ^2**	**P**
Hepatocyte necrosis	85	16 (18.6)	15	11 (73.3)	SARS	19.221	< 0.001
Portal inflammation	82	13 (15.9)	15	8 (53.3)	SARS	10.501	0.001
Thrombi	82	15 (18.3)	15	0 (0.0)	COVID	3.246	0.072
Lobular inflammation	82	3 (3.7)	15	0 (0.0)	COVID	0.566	0.452

with collagenous fibrosis of alveolar spaces and an interstitium with thickening of the alveolar wall along with squamous metaplasia of alveoli. Of the typical phases of DAD (acute/exudative and proliferative/organizing), these autopsy studies revealed that COVID-19 patients mostly showed lungs with an exudative phase compared with SARS-CoV-1 patients, indicating more early severe involvement of the lungs in COVID-19 patients and earlier death. Indeed, this finding corresponds to the average number of days from disease onset to death, which was up to 61 days for COVID-19 compared with 108 days for SARS-CoV-1 patients. More recently, fibrosing DAD has been reported in patients with a longer duration of COVID-19 illness and hospitalization.[90] However, Polak et al[91] showed that patients can also present with >1 pattern, either simultaneously or consecutively. The diagnosis of AFOP was mentioned in some articles as a prominent pattern of lung injury in COVID-19 patients. AFOP can be seen in all forms of acute lung injury (DAD and acute pneumonia). Therefore, in autopsy articles biased by core biopsies only, the predominance of AFOP may be explained by the limited sampling. In COVID-19, pulmonary interstitial inflammation was surprisingly subtle which differs from other viral infections where interstitial pneumonitis is typically a prominent feature.[92]

Two notable postmortem findings reported in the lungs of COVID-19 patients, typically not encountered in association with DAD, include marked pulmonary hemorrhage and scattered multinucleated giant cells. Fatal hemorrhagic pneumonia has previously rarely been reported in association with other viral infections.[93,94] While the etiology of pulmonary hemorrhage is unclear, studies have suggested that in severe cases of COVID-associated pneumonia there may be microvascular injury mediated by activation of complement pathways.[41] Also, the possibility of therapy-induced hemorrhage, especially due to high ventilation pressures in cases early in the pandemic, may have caused some of the hemorrhages if there is increased endothelial fragility in the setting of complement activation. The reason for multinucleated giant cell formation with COVID-19 is also unclear. However, similar syncytial giant cells have been reported in the lungs with other viral infections and may represent a cellular reaction to a marked proinflammation, cytokine-rich milieu.[95]

The pathologic findings detected in other organs may help explain some of the extrapulmonary manifestations of COVID-19.[96–99] Ancillary tests have detected coronavirus within most nonpulmonary organs including the heart, kidney, brain, gastrointestinal tract, liver, spleen, bone marrow, lymph nodes, and blood vessels and when present above typical levels of viremia, raise the possibility of direct viral infection of tissues.[12,40,44,48,49,53,55,57,59,65] SARS-CoV-2 was also isolated from the middle ear and mastoid in 2 autopsy cases,[100] and was detected in the retina in 3 of 14 eyes from deceased COVID-19 patients.[101] The heart appears to be an important target organ of SARS-CoV-2 because in some fatal infections postmortem examination revealed individual myocyte necrosis, myocarditis and increased interstitial macrophages.[102] Clinically, patients with COVID-19 have been reported to have electrocardiogram abnormalities, in-

creased troponins, and even more sinister cardiac-related events such as cardiogenic shock.[103,104] These findings raise suspicion for targeting of the heart by SARS-CoV-2. Most pathology studies have revealed nonspecific individual myocyte necrosis, a finding common in critically ill patients, particularly those with shock. Whereas cases of COVID-19 were identified with myocarditis and patchy mononuclear infiltrates,[55] significant inflammation in the heart was not a finding reported with SARS-CoV-1 infection.[105] Interestingly, Farina et al[106] suggested that the heart may be a source of latent or persistent infection.

The main histopathologic finding in the kidneys from patients with COVID-19 was acute tubular damage. Such acute tubular injury can lead to acute renal failure and contribute to rapid clinical deterioration and mortality.[107] Neurological manifestations of COVID-19 (eg, headache, anosmia, or stroke among others) also appear to be common. While most postmortem central nervous system examinations have revealed limited pathology, a subset of studies showed pathology that included thrombi, acute infarction, punctate hemorrhage, and hypoxia/ischemia related changes.[108,109] Such observations suggest the role of endothelial dysfunction and thrombosis in neurological manifestations of COVID-19. Thus far, no postmortem reports of direct infectious complications such as meningitis/encephalitis have been identified at autopsy. In addition to direct infection, parainfectious complications in the setting of immune dysregulation remain a possibility as highlighted by the case report by Reichard et al[110] that showed vascular and acute disseminated encephalomyelitis–like pathology. The presence of high levels of coronavirus within the olfactory bulb supports viral entry into the brain via the lamina cribrosa, which may also explain the clinical findings of smell dysfunction in COVID-19 patients.[48] The hematological system was also affected in COVID-19. Peripheral blood lymphopenia was a common clinical feature of COVID-19, which corresponds to lymphoid depletion observed in the lymph nodes and white pulp depletion of the spleen. COVID-19 also causes gastrointestinal symptoms such as diarrhea and abdominal pain. Identification of SARS-CoV-2 RNA within the gastrointestinal tract as well as evidence of viral shedding in stool, suggest direct gut infection with epithelial injury as a source of symptoms. Ischemic changes were also identified, which could further explain gastrointestinal symptoms associated with COVID-19, although this is likely to occur later and in those with compromised perfusion.

Thrombosis was a common finding in almost all organs examined in COVID-19 patients. In the lungs, thrombi were described within all sized blood vessels ranging from capillaries to the pulmonary artery, and in one series they were identified bilaterally in over 25% of the pulmonary parenchyma.[45] Using 3-dimensional imaging technology Li et al[42] demonstrated that the extent of thrombi within small vessels associated with COVID-19 is massive and greater than anticipated. Microthrombi were also reported in the lungs from patients who died of SARS-CoV-1. On the basis of ultrastructural studies, alveolar-capillary microthrombi were reported to be 9 times more prevalent in patients with COVID-19 than in patients with influenza.[53] Pulmonary micro-

thrombi are known constituents of DAD encountered even in non-COVID conditions.[111,112] Thus, it is difficult to know if pulmonary thrombi are indicative of DAD with or without additional physiological derangements of critical illness including complement and/or DIC. In the brains of some COVID-19 patients thrombi were associated with hemorrhage and acute infarction. Small thrombi associated with COVID-19 have also been reported, albeit infrequently, in the dermis.[113] Some authors also report the presence of neutrophilic plugs trapped in various organs.[114] Widespread thrombotic disease clearly plays an important role in morbidity and more than likely accentuates mortality in these infected patients. The etiology of thrombus formation in infected individuals is likely multifactorial with proposed mechanisms including microvascular dysfunction, hyperimmune response or dysregulation, complement system dysregulation, and altered coagulability including DIC, all which may be further exacerbated by preexisting conditions.[23–25,115–118] Another pathologic finding identified in several organs was vascular injury. Vascular injury, specifically endotheliitis, was recorded in both the COVID-19 and SARS-CoV-1 groups. In COVID-19 cases this included lymphocytic inflammation, cytoplasmic vacuolization, endothelial detachment, and microscopic destruction of the blood vessel wall.[53] Vasculopathy is likely ascribed to a combination of direct viral injury, inflammation and/or complement-mediated vascular injury.[41,58] Adrenal insufficiency secondary to vasculopathy has been proposed as an important contributing factor to the cytokine storm observed in patients with severe COVID-19.[119]

Additional systemic findings noted in the COVID-19 group include features suggestive of direct viral cellular injury (eg, candidate viral cytopathic effect and multinucleated giant cell formation), as well as indirect viral-induced pathology (eg, hemophagocytosis and megakaryocyte recruitment). The viral-type cytopathic effect identified within scattered pneumocytes was much more common in COVID-19 than SARS-CoV-1 autopsies. Interestingly, this cytologic finding was not as well recognized in other organs. This may be related to the fact that a greater number of ACE-2 receptors, the cellular receptor of SARS-CoV-2, have been reported on pneumocytes and endothelial cells.[53,120] Some authors also report findings similar to smudge cells reminiscent of adenovirus-related pneumonitis.[121] A review article by Walsh and colleagues highlights the timeline of viral load in the COVID-19 disease course. Viral load of SARS-CoV-2 from upper respiratory tract samples peaks around symptom onset or a few days thereafter, and then becomes undetectable about 2 weeks later, corresponding to the organizing phase of COVID-19 related pneumonia.[74,122] Viral loads from sputum samples may contain higher levels of virus, peak later and persist for longer. This timeline may be valuable for the management/monitoring of COVID-19 pneumonia. Prilutskiv et al[123] report that in their small series of 4 autopsies lymphophagocytosis appears to be the predominant form of SARS-CoV-2 infection-associated hemophagocytosis observed. The reason for having an increased number of activated megakaryocytes in alveolar capillaries is unclear, but this phenomenon is believed to lead to increased platelet release with subsequent thrombotic pathway activation.[43,124,125]

In summary, this systematic review and meta-analysis reveal that overall autopsy findings are similar in both COVID-19 and SARS-CoV-1 groups. Although the lungs had the most pronounced pathologic findings, extrapulmonary disease was also identified but more variable. Similarities between COVID-19 and SARS-CoV-1 were that the deceased were mostly adults who developed DAD. However, death due to COVID-19 tends to affect more elderly men with preexisting comorbidities.[126] Notable pathologic findings associated with DAD, especially in COVID-19, include pulmonary hemorrhage, multinucleated giant cells, and viral cytopathic effect of pneumocytes. While most of the extrapulmonary histopathologic findings among both groups were not statistically significant, with COVID-19 there was more extensive thrombotic disease and multifocal endotheliitis. Tissue inflammation was surprisingly underwhelming in most of the organs examined. Further autopsies are needed including correlation with clinical finings to better elucidate the pathogenesis of SARS-CoV-2 infection and help contribute to the clinical management of infected patients.

REFERENCES

1. Hwang DM, Chamberlain DW, Poutanen S, et al. Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Mod Pathol.* 2005;18:1–10.
2. Ng DL, AlHosani 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;186:652–658.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506.
4. Worldometers. COVID-19 coronavirus pandemic; 2020. Available at: www.worldometers.info/coronavirus/. Accessed May 17, 2020.
5. Worldometers. COVID-19 coronavirus pandemic; 2020. Available at: www.worldometers.info/coronavirus/. Accessed July 17, 2020.
6. Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV: a comparative overview. *Infez Med.* 2020;2:174–184.
7. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care.* 2020;24:154.
8. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med.* 2020;46:1099–1102.

9. Danzi GB, Loffi M, Galeazzi G, et al. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020;41:1858.

10. Liu Q, Wang RS, Qu GQ, et al. Gross examination report of a COVID-19 death autopsy. *Fa Yi Xue Za Zhi*. 2020;36:21–23.

11. Xiaohong Y, Tingyuan L, Zhicheng H, et al. New coronavirus pneumonia (COVID-19) 3 cases of multiple-site puncture histopathological pathology of human remains. *Chin J Pathol*. 2020;49:291–293.

12. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novelcoronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol*. 2020;33:1007–1014.

13. Konopka KE, Wilson A, Myers J. Postmortem lung findings in an asthmatic with coronavirus disease 2019 (COVID-19). *Chest*. 2020;158:E99–E101.

14. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in COVID-19: the first autopsy series from New Orleans. *Lancet Respir Med*. 2020;8:681–686.

15. Salerno M, Sessa F, Piscopo A, et al. No autopsies on COVID-19 deaths: a missed opportunity and the lockdown of science. *J Clin Med*. 2020;9:1472.

16. Pomara C, Volti GL, Cappello F. COVID-19 deaths: are we sure it is pneumonia? Please, autopsy, autopsy, autopsy! *J Clin Med*. 2020;9:1259.

17. Barth RF, Colombus RH, Xinyang X, et al. A call to action the need for autopsies to determine the full extent of organ involvement associated with COVID-19. *Chest*. 2020;158:43–44.

18. Zhou B, Zhang W, Feng R, et al. The pathological autopsy of coronavirus disease 2019 (COVID-2019) in China: a review. *Pathog Dis*. 2020;78:ftaa026.

19. Occupational Safety and Health Administration (OSHA). Available at: www.osha.gov. Accessed May 17, 2020.

20. Lacy JM, Brooks EG, Akers J, et al. COVID-19: postmortem diagnostic and biosafety considerations. *Am J Forensic Med Pathol*. 2020;41:143–151.

21. Williamson AK. Creation and benefits of the "COVID Autopsy Listserve". *Arch Pathol Lab Med*. 2020;144:1160–1161.

22. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *J Thromb Haemost*. 2020;18:786–787.

23. Henry BM, Vikse J, Benoit S, et al. Hyperinflammation, derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular thrombosis. *Clin Chim Acta*. 2020;507:167–173.

24. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;5:475–481.

25. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.

26. 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;34:743–748.

27. Chong PY, Chui P, Lui AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore. *Arch Pathol Lab Med*. 2004;128:195–204.

28. Nicholls JM, Poon LLM, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet*. 2003;361:1773–1778.

29. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005;202:415–424.

30. Lai RQ, Feng XD, Wang ZC, et al. Pathological and ultra-microstructural changes of tissues in a patient with severe acute respiratory syndrome. *Chin J Pathol*. 2003;32:205–208.

31. Chen J, Xie YQ, Zhang HT, et al. Lung pathology of severe acute respiratory syndrome. *Chin J Pathol*. 2003;25:360–362.

32. Lang ZW, Zhang LJ, Zhang SJ, et al. A clinicopathological study on 3 cases of severe acute respiratory syndrome. *Chin J Pathol*. 2003;32:201–204.

33. Hsiao CH, Wu MZ, Hsies SW, et al. Clinicopathology of severe acute respiratory syndrome: an autopsy case report. *J Formos Med Assoc*. 2004;103:787–792.

34. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol*. 2004:622–630.

35. Tang JW, To KF, Lo AWI, et al. Quantitative temporal-spatial distribution of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) in post-mortem tissues. *J Med Virol*. 2007;79:1245–1253.

36. Zhan J, Deng R, Tang J, et al. The spleen as a target in severe acute respiratory syndrome. *FASEB J*. 2006;20:2321–2328.

37. Shi X, Gong E, Gao D, et al. Severe acute respiratory syndrome associated coronavirus is detected in intestinal tissues of fatal cases. *Am J Gastroenterol*. 2005;100:169–176.

38. Wei L, Sun S, Zhu CH, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol*. 2007;38:95–102.

39. Leung TW, Wong KS, Hui AC, et al. Myopathic changes associated with severe acute respiratory syndrome. *Arch Neurol*. 2005;62:1113–1117.

40. Bradley BT, Maioli H, Johnson R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet*. 2020;396:320–332.

41. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19infection: a report of five cases. *Transl Res*. 2020;220:1–13.

42. Li G, Fox SE, Summa B, et al. Multiscale 3-dimensional pathology findings of COVID-19 diseased lung using high-resolution cleared tissue microscopy. bioRxiv preprint. 2020.

43. Barton LM, Duval EJ, Stroberg E, et al. COVID-19 autopsies, Oklahoma, USA. *Am J Clin Pathol*. 2020;153:725–733.

44. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417–1418.

45. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from Northern Italy: a two-centre descriptive study. *Lancet Infect Dis*. 2020;20:1135–1140.

46. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med*. 2020;173:268–277.

47. Karami P, Naghavi M, Feyzi A, et al. Mortality of a pregnant patient diagnosed with COVID-19: a case report with clinical, radiological, and histopathological findings. *Travel Med Infect Dis*. 2020. [Epub ahead of print].

48. Menter T, Haslbauer JD, Neinhold R, et al. Post-mortem examinations of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77:198–209.

49. Farkash EA, Wilson AM, Jentzen JM. Ultrastructral evidence for direct renal infection with SARS-CoV-2. *J Am Soc Nephrol*. 2020;31:1683–1687.

50. Craver R, Huber S, Sandomirsky M, et al. Fatal eosinophilic myocarditis in a healthy 17-year-old male with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2c). *Fetal Pediatr Pathol*. 2020;39:263–268.

51. Lei Y, Sun S, Xu CH, et al. COVID-19 in a Hispanic woman: autopsy report with clinical pathological correlation. *Arch Pathol Lab Med*. 2020;144:1041–1047.

52. Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med*. 2020;173:350–361.

53. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120–128.

54. Adachi T, Chong JM, Nakajima M, et al. Clinicopathologic and immunohistochemical findings from autopsy of patient with COVID-19, Japan. *Emerg Infect Dis*. 2020;26:2157–2161.

55. Bryce C, Grimes Z, Pujadas E et al. Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. Available at: https://doi.org/10.1101/2020.05.18.20099960. Accessed May 17, 2020.

56. Copin MC, Parmetier E, Dubuurcq T, et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. *Intensive Care Med*. 2020;46:1124–1126.

57. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;219:219–227.

58. 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. Available at: https://doi.org/10.1101/2020.03.04.20031120. Accessed May 17, 2020.

59. Xia X, Xiaona C, Huaxiang P, et al. Pathological changes of the spleen in ten patients with coronavirus disease 2019(COVID-19) by postmortem needle autopsy. *Zhonghua Bing Li Xue Za Zhi*. 2020;49:576–582.

60. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45:139–145.

61. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist*. 1950;21:607–611.

62. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.

63. Hanley B, Lucas SB, Youd E, et al. Autopsy in suspected COVID-19 cases. *J Clin Pathol*. 2020;73:239–242.

64. Centers for Disease Control and Prevention. Collection and submission of postmortem specimens from deceased persons with known or suspected COVID-19: interim guidance; March 2020. Available at: www.cdc.gov/coronavirus/. Accessed May 17, 2020.

65. Public Health England. COVID-19: guidance for sampling and for diagnostic laboratories secondary COVID-19: guidance for sampling and for diagnostic laboratories; 2020. Available at: www. gov. uk/government/publications/wuhan novel-coronavirus-guidance-for-clinical-diagnostic-laboratories. Accessed May 17, 2020.

66. Fineschi V, Aprile A, Aquila I, et al. Management of the corpse with suspect,probable or confirmed COVID-19 respiratory infection – Italianinterim recommendations for personnel potentially exposed to materialfrom corpses, including body fluids, in morgue structures andduring autopsy practice. *Pathologica*. 2020;112:64–67.

67. The Royal College of Pathologists. Autopsy practice relating topossible cases of COVID-19 (2019-nCov, novel coronavirus from China 2019/2020); 2020. Available at: www.rcpath.org/. Accessed May 17, 2020.

68. Dell-Aquilla M, Cattani P, Fantoni M, et al. Postmortem swabs in the Sars-CoV-2 pandemic: report on 12 complete clinical autopsy cases. *Arch Pathol Lab Med*. 2020;144:1298–1302.

69. Youd E, Moore L. COVID-19 autopsy in people who died in community settings: the first series. *J Clin Pathol*. 2020;73:840–844.

70. Hasmi AH, Khoo LS, Koo ZP, et al. The craniotomy box: an innovative method of containing hazardous aerosols generated during skull saw use in autopsy on a COVID-19 body. *Forensic Sci Med Pathol*. 2020;16:477–480.

71. Hofman P, Puchois P, Brest P, et al. Possible consequences of the COVID-19 pandemic on the use of biospecimens from cancer biobanks for research in academia and bioindustry. *Nat Med*. 2020;26:890–898.

72. Calabrese F, Pezzuto F, Fortarezza F, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. *Virchows Arch*. 2020;477:359–372.

73. Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary parthology: a multi-institutional autopsy cohort from Italy and New York City. *Mod Pathol*. 2020;33:2156–2168.

74. Schaefer IM, Padera RF, Solomon IH. In situ detection of SARS-CoV-2 in lungs and airways of patients with COVID-19. *Mod Pathol*. 2020;33:2104–2114.

75. Bishop JA, Ma XJ, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. *Am J Surg Pathol*. 2012;3:1874–1882.

76. 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;72:516–524.

77. Yang M, Chen S, Huang B, et al. Pathological findings in the testes of COVID-19 patients: clinical implications. *Eur Urol Focus*. 2020;6:1124–1129.

78. Elsoukkary SS, Mostyka M, Dillard A, et al. Autopsy findings in 32 patients with COVID-19: a single-institution experience. *Pathobiology*. 2020. [Epub ahead of print].

79. Edler C, Schroder AS, Aepfelbacher M, et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med*. 2020;134:1275–1284.

80. Barth RF, Buja LM, Parwani AV. The spectrum of pathological findings in coronavirus disease (COVID-19) and the pathogenesis of SARS-CoV-2. *Diagn Pathol*. 2020;15:85.

81. Bosmuller H, Traxler S, Bitzer M, et al. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. *Virchows Arch*. 2020;477:349–357.

82. Hariri LP, North CM, Shih AR, et al. Lung histopathology in COVID-19 as compared to SARS and H1N1 influenza: a systematic review. *Chest*. 2020;159:73–84.

83. Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19 related deaths: a literature review. *Forensic Sci Med Pathol*. 2020. [Epub ahead of print].

84. De Michele S, Sun Y, Yilmaz MM, et al. Forty postmortem examinations in COVID-19 patients. *Am J Clin Pathol*. 2020;154:748–760.

85. Kommoss FKF, Schwab C, Taverner L, et al. The pathology of severe COVID-19 related lung damage. *Dtsch Arztebl Int*. 2020;117:500–506.

86. Eketunde AO, Mellacheruvu SP, Oreoluwa P, et al. A review of postmortem findings in patients with COVID-19. *Cureus*. 2020;12:e9438.

87. Grosse C, Gross A, Salzer HJF, et al. Analysis of cardiopulmonary fidnings in COVID-19 fatalities: high incidence of pulmonary artery thrombi and acure suppurative bronchopneumonia. *Cardiovasc Pathol*. 2020;49:107263.

88. AL Nemer A. Histopathologic and autopsy findings in patients diagnosed with coronavirus disease 2019 (COVID-19): what we know so far based on correlation with clinical, morphologic and pathobiological aspects. *Adv Anat Pathol*. 2020;27:363–370.

89. Konopka KE, Nguyen T, Jentzen JM, et al. Diffuse alveolar damage (DAD) from coronavirus disease 2019 infection is morphologically indistinguishable from other causes of DAD. *Histopathology*. 2020;77:570–578.

90. Li Y, Wu J, Wang S, et al. Progression to fibrosing diffuse alveolar damage in a series of 30 minimally invasive autopsies with COVID-19 pneumonia in Wuhan, China. *Histopathology*. 2020. Doi: 10.1111/his.14249.

91. Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol*. 2020;33:2128–2138.

92. Radoycich GE, Zuppan CW, Weeks DA, et al. Patterns of measles pneumonitis. *Pediatr Pathol*. 1992;12:773–786.

93. Donoso AF, León JA, Camacho JF, et al. Fatal hemorrhagic pneumonia caused by human metapneumovirus in an immunocompetent child. *Pediatr Int*. 2008;50:589–591.

94. Gilbert CR, Vipul K, Baram M. Novel H1N1 influenza A viral infection complicated by alveolar hemorrhage. *Respir Care*. 2010;55:623–625.

95. Villenave R, Thavagnanam S, Sarlang S, et al. In vitro modeling of respiratory syncytial virus infection of pediatric bronchial epithelium, the primary target of infection in vivo. *Proc Natl Acad Sci USA*. 2012;109:5040–5045.

96. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26:1017–1032.

97. Deshmukh V, Motwani R, Kumar A, et al. Histopathological observations in COVID-19: a systematic review. *J Clin Pathol*. 2020. Doi: 10.1136/jclinpath-2020-206995.

98. Mohanty SK, Satapathy A, Naidu MM, et al. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19)—anatomic pathology perspective on current knowledge. *Diagn Pathol*. 2020;15:103.

99. Remmelink M, De Mendonca R, D'Haene N, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. *Crit Care*. 2020;24:495.

100. Frazier KM, Hooper JE, Mostafa HH, et al. SARS-CoV-2 virus isolated from the mastoid and middle ear: implications for COVID-19 precautions during ear surgery. *JAMA Otolaryngol Head Neck Surg*. 2020;146:964–966.
101. Casgrande M, Fitzek A, Puschel K, et al. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocul Immunol Inflamm*. 2020;28:721–725.
102. Basso C, Leone O, Rizzo S, et al. Pathological features of COVID-19-associated myocardial injury: a mutlicentre cardiovascular pathology study. *Eur Heart J*. 2020;41:3827–3835.
103. Buja LM, Wolf DA, Zhao B, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas and review of autopsy findings from other United States cities. *Cardiovasc Pathol*. 2020;48:107233.
104. Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail*. 2020;22:911–915.
105. Fox SE, Li G, Akmatbekoy A, et al. Unexpected features of cardiac pathology in COVID-19 infection. *Circulation*. 2020;142:1123–1125.
106. Farina A, Uccello G, Spreafico M, et al. SARS CoV-2 detection in the pericardial fluid of a patient with cardiac tamponade. *Eur J Intern Med*. 2020;26:100–101.
107. Santoriello D, Khairallah P, Bomback AS, et al. Postmortem kidney findings in patients with COVID-19. *J Am Soc Nephrol*. 2020;31:2158–2167.
108. Al-Siraj S, Troakes C, Hanley B, et al. The spectrum of neuropathology in COVID-19. *Neuropathol Appl Neurobiol*. 2020. Doi: 10.1111/nan.12667.
109. Kantonen J, Mahzabin S, Mayranpaa MI, et al. Nueropathologic features of four autopsied COVID-19 patients. *Brain Pathol*. 2020;30:1012–1016.
110. Reichard RR, Kashani KB, Boire NA, et al. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol*. 2020;140:1–6.
111. Tomashefski JF, Davies P, Boggis C, et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol*. 1983;112:112–126.
112. Harms PW, Schimdt LA, Smith LB, et al. Autopsy findings in eight patients with fatal H1N1 influenza. *Am J Clin Pathol*. 2010;134:27–35.
113. Daurte-Neto AN, Almeida-Monteiro RA, Ferraz-da-Silva LF, et al. Pulmonary and systemic involvement of COVID-19 assessed by ultrasound-guided minimally invasive autopsy. *Histopathology*. 2020;77:186–197.
114. Schurink B, Roos E, Radonic T, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe*. 2020;1:E290–E299.
115. Rosenthal FR. Causes of venous thrombosis. *Thromb J*. 2016;14(suppl 1):24.
116. Foley JH. Examining coagulation-complement crosstalk: complement activation and thrombosis. *Thromb Res*. 2016;141(suppl 2):S50–S54.
117. Rizzo P, Sega FVD, Fortini F, et al. COVID-19 in the heart and the lungs:could we "Notch" the inflammatory storm? *Basic Res Cardiol*. 2020;115:31.
118. Lo MW, Kemper C, Woodruff TM. COVID-19: complement, coagulation and collateral damage. *J Immunol*. 2020;205:1488–1495.
119. Iuga AC, Marboe CC, Yilmaz MM, et al. Adrenal vascular changes in COVID-19 autopsies. *Arch Pathol Lab Med*. 2020;144:1159–1160.
120. Yuki K, Jufiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol*. 2020;215:108427.
121. Conde PN, Monraval PA, Medina CM, et al. Autopsy findings from the first known death from severe acute respiratory syndrome SARS-CoV-2 in Spain. *Rev Esp Pathol*. 2020;53:188–192.
122. Walsh KA, Jordan K, Clyne B, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. *J Infect*. 2020;81:357–371.
123. Prilutskiv A, Kritselis M, Shevotsov A, et al. SARS-CoV-2 infection-associated hemophagocytic lymphohistiocytosis. *Am J Clin Pathol*. 2020;154:466–474.
124. Falasca L, Nardacci R, Colombo D, et al. Postmortem findings in Italian patients with COVID-19 a descriptive full autopsy study of cases with and without co-morbidies. *J Infect Dis*. 2020;222:1807–1815.
125. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at sutopsy in COVID-19: a case series. *EClinicalMedicine*. 2020;24:100434.
126. Khalil M, Allen TC, Krdowska A. Acute respiratory distress syndrome: a review article. *AJSP Rev Rep*. 2017;22:3–7.