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Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review

Stefania Caramaschi¹ · Meghan E. Kapp² · Sara E. Miller³ · Rosana Eisenberg² · Joyce Johnson² · Garretson Epperly⁴ · Antonino Maiorana¹ · Guido Silvestri^{5,6} · Giovanna A. Giannico²

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Abstract

The severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) pandemic has had devastating effects on global health and worldwide economy. Despite an initial reluctance to perform autopsies due to concerns for aerosolization of viral particles, a large number of autopsy studies published since May 2020 have shed light on the pathophysiology of Coronavirus disease 2019 (COVID-19). This review summarizes the histopathologic findings and clinicopathologic correlations from autopsies and biopsies performed in patients with COVID-19. PubMed and Medline (EBSCO and Ovid) were queried from June 4, 2020 to September 30, 2020 and histopathologic data from autopsy and biopsy studies were collected based on 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 58 studies reporting 662 patients were included. Demographic data, comorbidities at presentation, histopathologic findings, and virus detection strategies by organ system were collected. Diffuse alveolar damage, thromboembolism, and nonspecific shock injury in multiple organs were the main findings in this review. The pathologic findings emerging from autopsy and biopsy studies reviewed herein suggest that in addition to a direct viral effect in some organs, a unifying pathogenic mechanism for COVID-19 is ARDS with its known and characteristic inflammatory response, cytokine release, fever, inflammation, and generalized endothelial disturbance. This study supports the notion that autopsy studies are of utmost importance to our understanding of disease features and treatment effect to increase our knowledge of COVID-19 pathophysiology and contribute to more effective treatment strategies.

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✉ Giovanna A. Giannico
giovanna.giannico@vumc.org

¹ Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia—AOU Policlinico of Modena, Modena, Italy

² Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

³ Department of Pathology, Duke University Medical Center, Durham, NC, USA

⁴ Hunt Optics & Imaging, Inc, Pittsburgh, PA, USA

⁵ Emory Vaccine Center and Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA

⁶ Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

Introduction

The severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection has affected most countries worldwide, with 34,026,003 confirmed cases and 1,015,107 deaths estimated by the World Health Organization as of October 1st, 2020 [1]. SARS-CoV-2 is a new member in the betacoronavirus genus of the family of Coronaviridae [2–6]. Coronavirus disease-2019 (COVID-19) caused by human-to-human transmission occurs by virus contact with oral, nasal, or ocular mucosa [2], commonly by inhalation of small droplets exhaled by an infected person [4, 7]. SARS-CoV-2 infects the host by binding to the angiotensin-converting enzyme 2 (ACE2) receptor with its structural spike glycoprotein (S protein) [2, 6, 8, 9]. The ACE2 receptor is localized on several human tissues, including pulmonary, renal, cardiovascular, and gastrointestinal epithelia, and is expressed by arterial and venous endothelial cells and arterial smooth muscle cells [10], making them potential targets for SARS-CoV-2 infection [2].

SARS-CoV-2 has an overall lower case fatality rate (0.0–29%), although variable by country, than that of Severe Acute Respiratory Syndrome coronavirus (SARS, 9.5%) and Middle East Respiratory Syndrome coronavirus (MERS, 34.4%), but more efficient and aggressive viral transmission [2, 4, 11–16]. Although the clinical course of COVID-19 ranges from an asymptomatic condition to severe multi-organ failure leading to death, respiratory tract flu-like manifestations, such as fever and dry cough, are the most commonly reported symptoms [3–6, 11, 12, 17–19]. Elderly patients, males, and subjects with comorbidities, such as obesity, diabetes, hypertension, and cardiovascular disease, appear most affected and have a worse prognosis [3, 4, 11, 12, 17–19].

Few autopsies were initially performed due to concern surrounding aerosolization and infectivity of the virus. Moreover, most initial autopsies in COVID-19 patients were limited, often restricted to sampling of lungs [20, 21]. More recently, in compliance with biosafety recommendations of several international regulatory agencies, including the World Health Organization [22], the Centers for Disease Control and Prevention (CDC) [23], and the European Centre for Disease Prevention and Control [24], rapidly expanding autopsy literature has become available. This review will summarize the current histopathologic findings in COVID-19 derived from autopsy and biopsy studies.

Methods

Eligibility criteria, search strategy, study selection criteria, manuscript quality evaluation, and data collection are reported in the Supplemental Material.

Results

A total of 58 articles describing 662 patients, met inclusion criteria. At the time of this manuscript preparation, we analyze 508 decedents from 43 studies, including 121 full autopsies with or without brain (14 studies), 76 limited autopsies (6 studies), 17 full and 4 limited autopsies (1 study), 7 standard autopsies and 7 in situ dissections (1 study), 63 full, 3 limited and 2 biopsies (1 study), 13 minimally invasive autopsies (MIA) (2 studies), 1 in situ dissection (1 study), 18 postmortem biopsies (5 studies), and 176 autopsies with modality unspecified (NOS) (12 studies); and 151 living patients (14 studies), including 148 biopsies (12 studies) and 3 surgical specimens (2 studies). Autopsies from 2 decedents and a surgical specimen from 1 survivor were included together in 1 study.

The quality analysis revealed that 18 (31%) articles included in this review were of high quality, 25 (43%) were

Table 1 Demographic and clinical characteristics of the COVID-19 patient cohort.

Characteristic	N. patients	Mean (Range or %) or N (%)
Age	660 ^a	70 (17–96)
Gender	662	
		Male 451 (68)
		Female 211 (32)
Ethnicity	206	
		Caucasian 61 (30)
		African American 68 (33)
		Asian 5 (2)
		Hispanic 57 (28)
		African 1 (0)
		Other 6 (3)
		Unknown 8 (4)
Comorbidities	525	
		Hypertension 299 (57)
		Diabetes 174 (33)
		COPD/Asthma 93 (18)
		Obesity 103 (20)
		Congestive Heart Failure 50 (9)
		PAD/CVD/MI 130 (25)
		Cardiomyopathy 23 (4)
		Chronic Kidney Disease 82 (16)
		Liver disease/Cirrhosis 16 (3)
		Cerebrovascular disease 15 (3)
		Dementia/Alzheimer/Parkinson 51 (10)
		Cancer 64 (12)
		Transplant/Immunosuppression 17 (3)

^aAge was not reported in 2 patients [42].

of moderate quality, and 15 (26%) were of low quality (Supplementary Table 1).

The demographic findings and the pathologic characteristics are summarized in Tables 1 and 2, respectively.

Lung

COVID-19 lung injury has been described in 263 cases from 28 studies, including 138 full autopsies, 73 limited autopsies, 14 combined in situ and standard autopsies, 3 surgical resections, 5 postmortem biopsies, 10 ultrasound-guided MIAs, 1 in situ dissection, 1 transthoracic needle biopsy, and 19 autopsies NOS [25–52].

An early study in 2 patients undergoing lobectomy for lung adenocarcinoma and retrospectively found to have SARS-CoV-2 infection at surgery showed exudative and proliferative acute lung injury with edema, inflammatory

Table 2 Summary of main histopathologic findings in COVID-19.

Organ	Histopathologic findings	N. studies	N. total cases (%)	N. cases with lesions (%)	References
Lung	DAD	28	263 (100)		[25–52]
		28	230 (87)		[25–52]
				53 (23)	[26–31, 35, 36, 38, 41, 43, 45, 46, 51]
				77 (33)	[29, 32, 37, 40, 41, 43, 44]
				18 (8)	[28, 29, 31, 34, 36, 41, 43, 47, 49, 51]
				1 (0)	[32]
				1 (0)	[28]
				86 (33)	[26, 28, 29, 31, 34, 35, 37, 39, 41, 45, 46, 48, 51, 52]
				152 (58)	[26–31, 35–37, 40, 41, 43–49, 52]
				143 (54)	[27, 29–31, 34, 36, 37, 39, 41, 45, 47–52]
				52 (20)	[29, 31, 34–37, 45, 51]
				50 (19)	[27, 28, 37, 44]
				123 (47)	[25–31, 37, 41, 44, 46, 47, 50, 51]
				52 (20)	[34, 36, 37, 41, 47–49, 51]
				52 (20)	[27, 29, 31, 36, 37, 44, 48]
				44 (17)	[29, 33, 45, 51]
				21 (8)	[26, 29–31, 40, 41, 46]
				64 (24)	[29, 46, 50]
				30 (11)	[26, 28, 29, 37, 40, 41, 43]
	Heart	Acute bronchopneumonia (aspiration or secondary infection)			
Acute pneumonia/bronchopneumonia NOS ^a					
Organizing pneumonia		22	191 (100)		[30, 31, 38, 44, 50, 52]
					[29, 48, 50, 51]
					[26–33, 35, 36, 39, 40, 42, 44, 45, 52, 55–60]
				27 (14)	[30–32, 39, 40, 44, 56, 59]
				16 (8)	[29, 31, 55, 56]
				8 (4)	[35, 45, 56]
				5 (3)	[59, 60]
				34 (18)	[59]
				18 (9)	[56]
				1 (0)	[40]
				3 (2)	[29, 40, 56]
				1 (0)	[45]
				10 (5)	[27, 32, 40, 56]
				11 (6)	[40, 56]

Table 2 (continued)

Organ	Histopathologic findings	N. studies	N. total cases (%)	N. cases with lesions (%)	References	
Kidney	Microvascular venous thrombosis	22	189 (100)	2 (1)	[40]	
	Acute tubular injury			131 (69)	[26, 27, 29–31, 33, 39, 40, 44, 45, 47, 62–72]	
	Endothelial injury/microthrombi/TMA			22 (12)	[29, 31, 39, 40, 44, 45, 62–72]	
	Cortical necrosis			2 (1)	[27, 29, 40, 44, 62, 63, 70]	
	Infarct			3 (2)	[47, 70]	
	Pigmented tubular casts/rhabdomyolysis			7 (4)	[62, 66]	
	Collapsing glomerulopathy			19 (10)	[44, 63, 66, 70]	
	Glomerulonephritis			7 (4)	[62, 64–68, 70–72]	
	Acute pyelonephritis			2 (1)	[62, 63, 66, 70]	
			5	22 (100)	[63]	
		Normal or Chronic Changes			20 (91)	[26, 31, 78–80]
Upper GI	Gastric Hemorrhage			2 (9)	[26, 79, 80]	
	Duodenal Hemorrhage			1 (5)	[31, 78]	
			8	101 (100)	[78]	
		Normal or Chronic Changes			59 (58)	[26, 30, 33, 38, 39, 78–80]
	Shock Changes			40 (40)	[26, 39, 78–80]	
	Mesenteric Ischemia			2 (2)	[38]	
	Ischemic Enterocolitis/Colitis			3 (3)	[33]	
			19	164 (100)	[30]	
		Centrilobular Congestion			73 (45)	[26, 27, 29–33, 35, 36, 38, 39, 44, 78–80, 85, 87–89]
		Shock Liver			44 (27)	[30, 31, 38, 39, 44, 79, 87]
	Pancreas	Steatosis			45 (27)	[44]
Hepatocyte Necrosis/Apoptosis				27 (16)	[26, 27, 29–31, 35, 39, 44, 85, 87, 89]	
Lymphocytic Infiltrate				42 (26)	[29, 31, 33, 36, 39, 44, 80, 89]	
Cholestasis				11 (7)	[27, 31, 32, 35, 36, 39, 44, 80, 85, 88]	
			6	44 (100)	[39, 80]	
		Normal or Chronic Changes			36 (82)	[26, 30, 31, 39, 79, 80]
Pancreatic Islet Cells Degeneration				3 (7)	[26, 30, 31, 79]	
Focal Pancreatitis				5 (11)	[80]	
			13	161 (100)	[39]	
		Congestion/Hemorrhage			47 (29)	[26, 27, 30–32, 38, 39, 44, 78–80, 98, 99]
Spleen		Hemophagocytosis			2 (1)	[27, 30, 38, 39, 44, 79, 98]
	Vasculitis/Arterial Thrombosis			2 (1)	[78, 98]	
	Red Pulp Hemorrhage			4 (2)	[44, 98]	
					[27, 44]	

Table 2 (continued)

Organ	Histopathologic findings	N. studies	N. total cases (%)	N. cases with lesions (%)	References
Lymph Nodes	Necrotizing Granulomas			1 (1)	[79]
	Lymphocytes Depletion			29 (18)	[27, 39, 44, 80, 98]
	White Pulp Atrophy			25 (15)	[27, 31, 39, 98]
	Parenchymal Necrosis			5 (3)	[5, 80]
	Acute Splenitis/Neutrophils Infiltration			57 (35)	[29, 30, 44, 98]
			8	45 (100)	[26, 29, 31, 39, 44, 78, 79, 89]
	Congestion			17 (38)	[29, 39]
	Hemophagocytosis			9 (20)	[31, 44, 78]
	Necrotizing granulomas			1 (2)	[79]
	Lymphocytes depletion			16 (36)	[39, 44]
Skin	Reduction/absence germinal centers			11 (24)	[39]
	Increased reactive plasmablasts			5 (11)	[29]
			4	16 (100)	[44, 79, 80, 88]
	Normal or Chronic Changes			2 (12)	[79]
	Perivascular Mononuclear/Lymphocytic infiltrate			11 (69)	[44, 80]
	Endothelial changes/fibrin microthrombi			3 (19)	[80]
	Purpura			1 (6)	[44]
	Petechiae			1 (6)	[88]
			12	109 (100)	[27, 29, 31, 32, 39, 43, 44, 115–119]
	Central Nervous System			47 (43)	[27, 31, 32, 39, 119]
			28 (26)	[29, 43, 116, 118]	
Normal or Chronic Changes			5 (5)	[117]	
Acute hypoxic injury			6 (5)	[117]	
Encephalitis			4 (4)	[117]	
Lymphocytic Meningitis			3 (3)	[44, 115, 118]	
Petechial Bleeding			5 (5)	[117, 118]	
Perivascular Hemorrhage			2 (2)	[115, 118]	
Axonal Injury/Degeneration			1 (0)	[118]	
White Matter Changes			7 (6)	[118, 119]	
ADEM-Like Changes			37 (34)	[119]	
Infarct			34 (31)	[119]	
Astrogliosis					
Lymphocytic infiltrates					

^aNot including alveolar space inflammation, acute (29/63) and chronic (63/68) in Borezuk et al. [50] due to the possible overlap of these cases.

infiltrate, type 2 pneumocyte hyperplasia, and interstitial and/or focal intra-alveolar organization, but no obvious hyaline membrane formation. These findings significantly contribute to our understanding of the early findings in COVID-19 [34]. Frank diffuse alveolar damage (DAD) was reported in 230 cases [25–52] (Fig. 1A, B), including acute [26–31, 35, 36, 38, 41, 43, 45, 46, 51], acute and proliferative/organizing [29, 32, 37, 40, 41, 43, 44], proliferative [28, 29, 31, 34, 36, 41, 43, 47, 49, 51], proliferative/organizing and fibrotic [32] and fibrotic DAD [28]. Detailed findings included squamous metaplasia [27, 29, 30, 37, 44, 50, 51], pneumocyte reactive hyperplasia [27, 29–31, 34, 36, 37, 39, 41, 45, 47–52], multinucleated giant cells [29, 31, 34–37, 45, 51], interstitial lymphocytic infiltrate [26–31, 35–37, 40, 41, 43–49, 52] (Fig. 1C), interstitial/alveolar edema [26, 28, 29, 31, 34, 35, 37, 39, 41, 45, 46, 48, 51, 52], alveolar/interstitial thickening [34, 36, 37, 41, 47–49, 51], arteriolar microthrombi [25–31, 37, 41, 44, 46, 47, 50, 51], capillary megakaryocytes [27, 28, 37, 44], alveolar hemorrhage [27, 29, 31, 36, 37, 44, 48], necrotizing and non-necrotizing vasculitis [29, 33, 45, 51], and organizing pneumonia with intra-alveolar organizing exudates [29, 48, 50, 51] (Fig. 1D). Other findings included acute pneumonia with intra-alveolar neutrophilic inflammation, described as suggestive or indicative of aspiration or secondary infection [26, 28, 29, 37, 40, 41, 43]. Granulocytic infiltration of the alveoli and bronchi, resembling bacterial focal bronchopneumonia [30], areas of neutrophilic inflammation ranging from focal bronchial or bronchiolar inflammation to acute bronchopneumonia [31], granulocyte-dominated focal confluent bronchopneumonia [38], suppurative pneumonia [44], acute and chronic alveolar space inflammation [50], bilateral lobar pneumonia [52], bronchial/bronchiolar inflammation [26, 29–31, 40, 41, 46], and tracheobronchitis [29, 46, 50] were also described. These changes were isolated or in association with DAD.

Viral cytopathic effect (CPE) has been described in type 2 pneumocytes [28], in pneumocytes of unspecified type [35, 45, 50, 52], and alveolar epithelial cells [44]. Atypical enlarged multinucleated and syncytial pneumocytes are commonly seen in COVID-19 lungs and have also been previously described in SARS, MERS, and other viral infections affecting lungs. These have been attributed to viral CPE in type 2 pneumocytes/alveolar epithelial cells by some authors [53–55]. Viral inclusions were also reported [36, 48].

SARS-CoV-2 has been detected in 48 of 53 lungs by RT-PCR [26, 29–31, 36, 51, 52], 29 of 43 by immunohistochemistry (IHC) [31, 40, 41, 43, 49, 50], 13 of 23 by in situ hybridization (ISH) [50], 3 of 8 by next-generation sequencing (NGS) [41] and 6 of 6 by culture [50]. Viral protein was found by IHC in alveolar pneumocytes

(variably, type 1, 2 or both) [31, 41, 43, 49, 50], alveolar macrophages [40, 41, 43], hyaline membranes in acute DAD [41, 43], tracheobronchial respiratory epithelium [31, 41, 43, 50], and minimally in endothelial cells [41, 49]. Similarly, by ISH, viral RNA was identified in tracheal epithelium, hyaline membranes, and type 2 pneumocytes [50]. Timing from onset of symptoms affects detection. IHC identified SARS-CoV-2 nucleocapsid protein in acute phase (≤ 7 days) but not organizing DAD (>14 days from the onset of respiratory failure). Remdesivir's role in one of these two patients is unclear from this small study [43]. Similarly, viral detection by IHC, ISH, and NGS was more likely within the initial 10 days to 2 weeks from onset [50] and in acute as opposed to proliferative DAD. Viral protein and SARS-CoV-2 viral RNA were detected by IHC and NGS, respectively, in pneumocytes and early but not late hyaline membranes, possibly reflecting viral clearance [41]. Variable detection may also be associated with the type of SARS-CoV-2 antibody (nucleoprotein or spike protein) [41] and with viremia, as patients without viremia showed no or a low virus load [30]. Using RT-PCR, higher RNA copy numbers were detected in lung tissue than in brain, heart, testicle, and kidney tissue [29].

A few studies have demonstrated SARS-CoV-2 virions by transmission electron microscopy (TEM) within endothelial cells [56], type 2 pneumocytes [37, 56, 57], extracellularly associated with upper airway ciliated cells, and within alveolar macrophage phagosomes [57]. However, putative SARS-CoV-2 virions have been purportedly reported by TEM in other studies (Supplementary Table 2).

Heart

The heart has been evaluated in 19 postmortem studies, including 52 full and 13 limited autopsies, 1 limited in situ autopsy, 3 postmortem biopsies, 14 in situ and standard autopsies, 10 ultrasound-guided minimally invasive biopsies, and 90 autopsies NOS for a total of 184 patients [26–33, 35, 36, 39, 40, 42, 44, 45, 52, 58–60], and 3 endomyocardial biopsy studies in 7 surviving patients [61–63]. Pre-existing injury associated with hypertension and coronary artery disease, such as myocardial hypertrophy or interstitial fibrosis, are the most common findings in many studies [27, 29–32, 36, 45]. Amyloidosis was identified in 10–28% of patients [29, 31, 62]. Acute findings attributed to SARS-CoV-19 infection included acute myocarditis [30–32, 39, 40, 44, 59, 62], individual myocyte necrosis [29, 31, 58, 59], borderline myocarditis [62, 63], inflammatory cardiomyopathy [62], epicardial lymphocytic infiltrate [27, 32, 40, 59], lymphocytic endothelialitis [33], focal interstitial lymphocytic infiltrate [35, 45, 59], interstitial macrophages [59], and recent myocardial

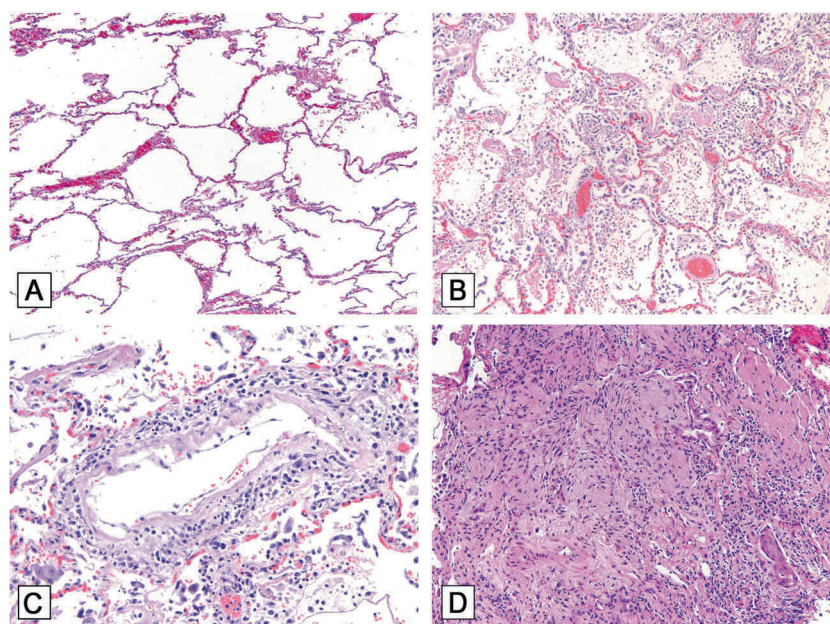


Fig. 1 Histopathologic findings of COVID-19 in the lung. **A** Normal lung with open alveoli and delicate alveolar septa containing thin capillaries lined by an attenuated alveolar epithelium (hematoxylin-eosin; original magnification $\times 200$). **B** Acute diffuse alveolar damage (DAD) with hyaline membranes lining alveolar spaces, pneumocyte hyperplasia, desquamation of alveolar epithelial cells into the alveolar spaces,

inflammatory infiltrates, and capillary congestion (hematoxylin-eosin; original magnification $\times 200$). **C** Perivascular inflammation (hematoxylin-eosin; original magnification $\times 400$). **D** Organizing pneumonia with granulation tissue plugs within the lumen of respiratory bronchioles (hematoxylin-eosin; original magnification $\times 200$).

infarction [29, 40, 59]. Fibrin microthrombi with or without megakaryocytes within the cardiac microvasculature [40, 59] and intramyocardial and epicardial venous thrombosis were identified [40]. Viral genome was detected by RT-PCR in 39 [30, 31, 36, 60, 63] of 66 patients [30, 31, 36, 51, 60, 62–64]. IHC using a monoclonal antibody to the spike protein was negative in one tested patient [31]. ISH detected viral RNA within interstitial cells, but the number of cases tested was not specified [60].

Kidney

A detailed pathologic examination of kidney injury in COVID-19 is highlighted in 22 studies including 194 patients. Kidney histopathology was available in 189 patients (1 patient was reported in 2 studies), including 9 (full and limited) autopsy studies [26, 27, 29, 30, 33, 39, 40, 65, 66], 1 study with combined standard autopsy and in situ dissection [31], 3 studies with minimally invasive/in situ limited dissection [44, 45, 47] and 9 renal biopsy studies [67–75].

Excluding glomerular lesions attributable to pre-existing injury, such as diabetic nephropathy and arteriosclerosis/arterionephrosclerosis, the most common finding in COVID-19 is acute tubular injury with tubular dilation, epithelial cell sloughing with luminal debris, and cytoplasmic vacuolization with occasional necrosis [29, 31, 39, 40, 44, 45, 65–75].

Frank cortical necrosis [47, 73], pigmented tubular casts/rhabdomyolysis [44, 66, 69, 73], acute pyelonephritis [66], thrombotic microangiopathy with endothelial injury, and glomerular or arteriolar fibrin thrombi were additional findings [27, 29, 40, 44, 65, 66, 73] (Fig. 2A), but parenchymal infarct was a rare event [65, 69].

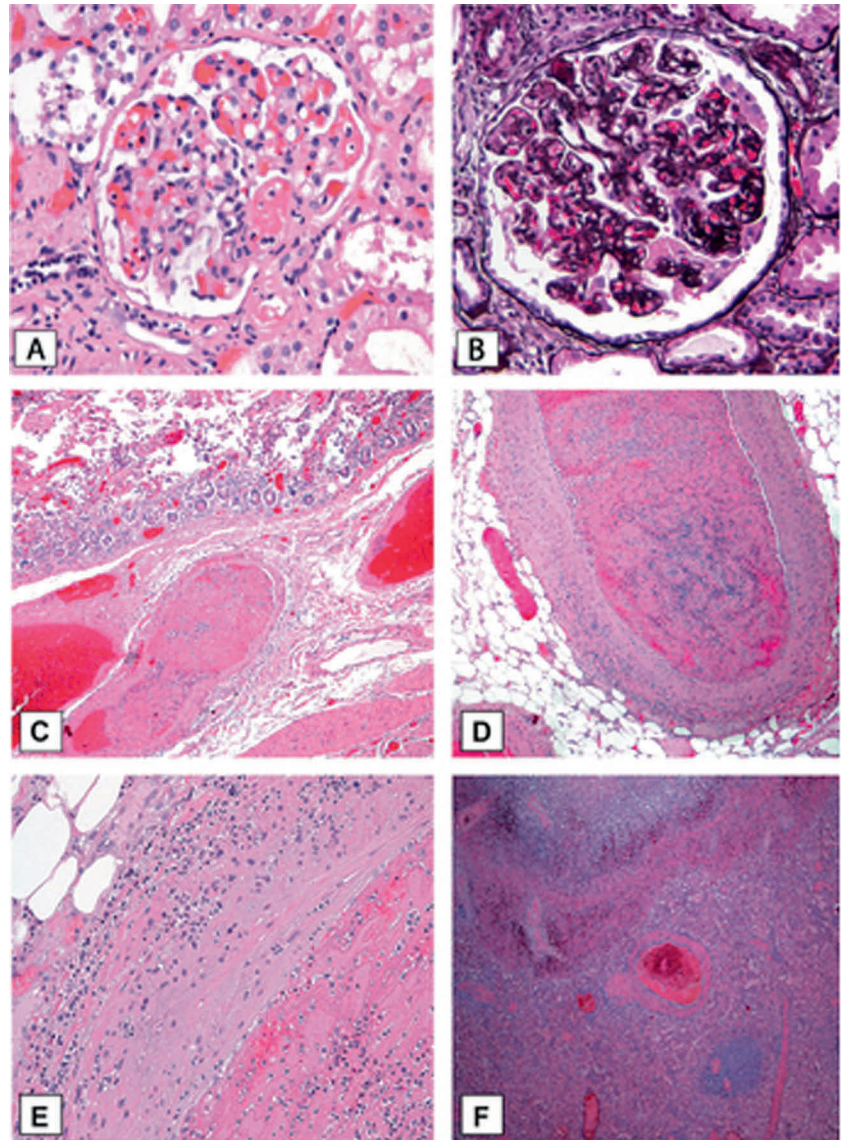
Immunofluorescence (IF) showed negative or non-specific IgM and C3 in 36 of 45 cases. TEM was performed in 54 cases. Fibrinogen positivity within fibrin thrombi (1 case) [65], IgA nephropathy (1 case) [65], membranous glomerulopathy (2 cases), lupus nephritis (1 case), anti-glomerular basement membrane glomerulonephritis (1 case) [69], crescentic glomerulonephritis [73], segmental granular capillary IgG without C3 (but with scattered humps observed by EM, described in the EM section below), and mesangial and capillary IgA (with corresponding mesangial and subendothelial deposits seen by EM) [66] have been described.

Deposits were described in 3 cases, 1 with IgA nephropathy [65], and 2 with paramesangial, subendothelial, and subepithelial “hump-like”, and scant isolated mesangial deposits [66]. Minimal change disease [69] and collapsing glomerulopathy have been described in 19 patients (1 patient reported in 2 different series) [69, 70], of whom 18 were African American and 1 was African [65, 67–71, 73–75] (Fig. 2B). In 1 case, tubular microcysts accompanied the

Fig. 2 Histopathologic findings of COVID-19 in the kidney, small bowel and spleen.

A Thrombotic microangiopathy with glomerular capillary loop and arteriole fibrin thrombi (hematoxylin-eosin; original magnification $\times 400$).

B Glomerulus with segmental capillary collapse and overlying podocyte hyperplasia (Jones methenamine silver; original magnification $\times 400$). **C** Small bowel thrombus and mucosal ischemic changes (hematoxylin-eosin; original magnification $\times 100$). **D** Spleen hilar thrombus (hematoxylin-eosin; original magnification $\times 200$). **E** Detail of Fig. D with transmural vascular inflammation (hematoxylin-eosin; original magnification $\times 400$). **F** Splenic thrombosis and infarct (hematoxylin-eosin; original magnification $\times 100$).



glomerular lesion, reminiscent of HIV-associated nephropathy. In these reports, 15 of 19 patients tested for APOL1 gene abnormalities had G1/G1, and 6 had G1/G2 high-risk alleles.

SARS-CoV-2 IHC/IF showed viral protein in tubules in 3 of 32 cases [66, 69, 73]. ISH detected viral RNA with a manual but not an automated test in 2 of 33 cases [65, 69, 70, 75]. RNA was positive in 8 of 15 patients by RT-PCR [30, 31], negative in 3 by Nanostring analysis [75] and in 1 by RT-PCR [72], and yielded a low copy number by RT-PCR in 16 cases [29].

Gastrointestinal tract

The gastrointestinal tract (GI) is a potential target of SARS-CoV-2 due to ACE2 receptor expression by the GI mucosa

[10, 76]. GI symptoms, including diarrhea, nausea, vomiting, anorexia, and abdominal pain [11, 77] have been described in 3–61.1% of COVID-19 patients [11, 77, 78] either at illness onset or during hospitalization [77]. Subjects with GI symptoms have a longer interval from illness onset to hospital admission, and symptoms become more pronounced with disease progression [78]. About 3% of patients present only with GI symptoms and without respiratory complaints [78–80].

The lower GI (LGI) tract is more likely to be involved than upper GI (UGI); thus, we report the autopsy finding separately. Of note, detailed postmortem histological examination of the GI tract often lacks in the literature, owing to more focused descriptions of lung histopathology [20] and challenges of autolytic changes. Viral RNA detected in GI tissue by RT-PCR generally correlates with

disease severity and is more reliable than RNA detected in the stool [77].

Upper gastrointestinal tract (UGI)

UGI postmortem examination has been reported in 22 cases from 5 studies comprising 12 full autopsies [26, 31, 81, 82], 3 MIAs [83] and 7 in situ dissections [31]. Although most cases had neither significant gross nor histological pathological changes in esophagus, stomach or duodenum [82, 83], gaseous stomach, punctate gastric and duodenal hemorrhages, and multifocal gastric hemorrhage have been described [26, 31, 81], although with unclear etiologic relationship to SARS-CoV-2, and corresponding to the endoscopic findings of 4–6 mm bleeding and round ulcers, sometimes fused and covered with what has been termed “white moss” in COVID-19 patients [77].

Lower gastrointestinal tract (LGI)

LGI postmortem findings have been reported in 8 studies including 98 full [26, 30, 33, 38, 39, 81, 82] and 3 MIAs [83]. The most common finding is a lack of intestinal abnormality [26, 39, 81, 82]. Chronic inflammation [26, 83], shock [38], and ischemic changes in the small bowel have been described [84] (Fig. 2C). Endothelialitis and apoptotic bodies have been reported in 2 autopsies and in the resected small intestine of a survivor. In 2 of 3 cases, mesenteric ischemia led to small bowel resection [33]. Similar findings of enterocolitis associated with ischemic colitis have been reported in 3 of 12 postmortem examinations [30].

Intestinal ischemic damage has been described during endoscopic and surgical procedures and confirmed with histologic examination [84–86]. Other histological features included apoptotic bodies and endothelial hobnail and bizarre nuclear shapes resulting from direct viral CPE, identified by IHC for the nucleocapsid protein of SARS-CoV-2 [84].

Liver

Hepatic injury with elevated liver enzymes and total bilirubin and decreased albumin has been described in up to 44% of COVID-19 patients [11, 87–89]. Abnormal liver function is associated with disease severity [88, 89], worse pulmonary involvement [88], and prolonged hospital stay [87].

The liver has been analyzed in 164 patients from 19 studies, including 123 full autopsies, 13 MIAs, 7 in situ dissections, 8 post-mortem biopsies and 13 autopsies NOS [26, 27, 29–33, 35, 36, 38, 39, 44, 81–83, 88, 90–92]. The most frequent postmortem histological features are

centrilobular congestion [30, 31, 38, 39, 44, 82, 90], most likely attributable to shock [44], and mild to moderate steatosis, predominantly macrovesicular and centrilobular [26, 27, 29–31, 35, 39, 44, 88, 90, 92], and probably associated with preexistent obesity and diabetes mellitus [44]. Hepatocyte necrosis has been described in 23 cases with individual cell, multifocal, or massive distribution [29, 31, 33, 36, 39, 44, 83, 92]. Clustered or scattered apoptotic hepatocytes and binuclear or occasionally multinuclear syncytial hepatocytes with apparent nucleolus and condensed chromatin have been observed in 2 post-mortem biopsies [88]. Mild to moderate lymphocytic infiltrate is present in the periportal zone [27, 31, 32, 35, 36, 39, 44, 83, 88, 91]. Cholestasis with canalicular bile plugs and nuclear pleomorphism of cholangiocytes have been described in 10 and 9 cases, respectively [39, 83].

Although RT-PCR for detection of SARS-CoV-2 has not frequently been performed in postmortem samples, 10 of 31 cases resulted positive with high titers in 6 [30, 36], and low in 4 [31, 81, 82]. No SARS-CoV-2 RNA was found in the bile of 4 patients [39].

Pancreas

High plasma levels of amylase or lipase have been reported in 9 of 52 (17%) patients [93, 94], 6 of whom (67%) also exhibited moderate hyperglycemia [93]. Many COVID-19 patients have diabetes [95], but whether this is associated with death remains controversial [96]. Patients with alterations of pancreatic enzymes have a higher incidence of GI symptoms, more severe illness on admission, lower levels of CD3+ and CD4+ T cells, higher liver enzymes, and higher erythrocyte sedimentation rate compared to subjects without altered values [93].

The pancreas has not been commonly investigated in COVID-19 postmortem examinations. Current available data refer to 6 studies with 44 patients, including 34 full autopsies, 3 MIAs, and 7 in situ dissections [26, 30, 31, 39, 82, 83] with most reports showing no significant abnormalities [26, 30, 31, 82]. Degeneration of a few pancreatic islet cells without abnormalities in the exocrine pancreas [83] and asymptomatic focal pancreatitis in 5 of 11 patients (45%) [39] have been reported. However, severe pancreatitis has been rarely reported in clinical studies [97]. An additional autopsy study published during the review process of this manuscript reports pancreatitis in 2 of 8 (25%) patients, 1 frankly necrotic-hemorrhagic and another with microscopic acute inflammation but without macroscopic abnormality [98]. These findings may represent a direct viral effect [93], consistent with ACE2 receptor expression in the exocrine and endocrine pancreas [94], an indirect effect of respiratory failure, or a harmful immune response induced by SARS-CoV-2 infection [93].

Spleen and lymph nodes

Lymphocytopenia has been reported in up to 83.2% of COVID-19 patients, especially elderly, subjects with comorbidities, and severe disease [4, 11, 93, 99, 100]. Total T cell counts, CD8 + T cells, or CD4 + T cells lower than 800, 300, or 400/ μ L, respectively, have been associated with poor survival [99].

Spleen and lymph nodes have been investigated in several postmortem examinations [26, 27, 29–32, 38, 39, 44, 81–83, 92, 101], providing evidence of a variety of tissue injury patterns. However, SARS-CoV-2 RNA and viral antigens' detection are controversial and rarely demonstrated in lymphoid organs [27, 31, 81, 82].

The spleen has been examined in 13 studies from 161 patients, including 123 full and limited autopsies, 8 MIAs, 7 in situ dissections, 10 post-mortem biopsies, and 13 autopsies NOS [26, 27, 30–32, 38, 39, 44, 81–83, 101, 102]. Post-mortem findings include lymphocytes depletion [27, 39, 44, 83, 101], white pulp atrophy [27, 31, 39, 101], parenchymal necrosis [5, 83], and vascular involvement including congestion, hemorrhage, infarction [27, 30, 38, 39, 44, 82, 101], vasculitis and arterial thrombosis [44, 101] (Fig. 2D–F). Acute splenitis [29, 30, 44], neutrophil infiltration [101], splenomegaly lacking lymphoid follicles and showing necrotizing granulomas [82], and hemophagocytosis have also been described [81, 101].

Lymph nodes have been investigated in 45 patients from 8 studies, including 33 full autopsies, 5 MIAs, and 7 in situ dissections [26, 29, 31, 39, 44, 81, 82, 92]. Postmortem examination revealed diffuse congestion with sinus dilatation, mainly in mediastinal, perihilar, and paratracheal lymph nodes [29, 39]. Histologic changes include decreased total lymphocytes with absence of germinal centers [39, 44], increased reactive plasmablasts in the interfollicular zone [29], and hemophagocytosis [31, 44, 81]. Rarely necrotizing granulomas have been reported in peribronchial lymph nodes [82].

Skin

Cutaneous manifestations have been described in up to 20.4% of COVID-19 patients, mainly in trunk and limbs [4, 103–116]. Clinical presentation most commonly includes erythematous rash [4, 104–106, 108, 111, 116] widespread urticaria [104, 112–114], varicella-like papulovesicular exanthem [104, 108, 113, 116], acrocyanosis, chilblains and other acral lesions [103, 109, 110, 114, 115, 117], livedoid eruptions [106, 107, 109] (Fig. 3), and purpura [105–107, 109].

Histopathologic examinations of survivors' skin biopsies reveal a superficial and deep perivascular infiltrate of lymphocytes or neutrophils with some eosinophils or occasional plasma cells [105, 108–111, 117]. Epidermal alterations include apoptotic, necrotic, and dyskeratotic keratinocytes,



Fig. 3 Cutaneous lesions in COVID-19. Livedo reticularis of skin in a patient with COVID-19.

occasionally resembling ballooning herpes-like cells [106, 108, 110, 113, 117], in some cases associated with vacuolar alteration, [110, 111, 113, 117] and focal acantholytic suprabasal clefts [108]. The most frequent dermal vascular lesions are thrombotic vasculopathy with fibrinoid or inflammatory thrombi and endothelial cell injury [106–109, 117]. Sweat gland necrosis, more evident in the secretory portion of the eccrine sweat coil and with preserved eccrine ducts, is described [109, 117]. Deposition of terminal complement components (C5b-9 and C4d) by IHC has been demonstrated in samples taken from cutaneous lesions and normal-appearing skin. Moreover, 1 case showed co-localization of C4d with SARS-CoV-2 spike glycoprotein within the cutaneous microvasculature [107]. RT-PCR and SARS-CoV-2 cultures were negative in skin lesion samples of other cases [109, 111].

Skin examination has been reported in 16 autopsies, of which 3 full and 13 MIAs from 4 studies [44, 82, 83, 91]. Many of these reports describe normal cutaneous layers and appendages, and mild perivascular lymphocytic infiltrate and petechiae [83, 91] with negative RT-PCR [82]. Dermatitis and a hypercoagulative status, possibly directly related to viral infection, were reported in 1 study. Superficial dermis perivascular mononuclear infiltrate in 11 of 13 cases [44, 83], dermis and hypodermis small vessels endothelial changes and fibrin microthrombi in 3 cases [83], and purpura in 1 case [44] were also described. These autopsy findings are consistent with the cutaneous manifestations described clinically and histopathologically in survivors.

Central nervous system

Autopsies documenting central or peripheral nervous system involvement in COVID-19 are scarce. Of 148 total autopsies from 12 studies including brain dissection,

description of neuropathologic findings are available in 109 patients [27, 29, 31, 32, 39, 43, 44, 118–122]. Of these autopsies, 15 were full, 10 were ultrasound-guided MIAs, and 84 were NOS. In most instances, brain autopsy findings were unremarkable or showed chronic features without acute morphologic alteration [27, 31, 32, 39, 122]. Major histopathologic features were acute hypoxic injury with neuronal loss [29, 43, 119, 121], encephalitis [120], lymphocytic meningitis [120], petechial bleeding [120], perivascular hemorrhage [44, 118, 121], axonal injury/degeneration [120, 121], white matter clusters of macrophages [118, 121], perivascular acute disseminated encephalomyelitis-like appearance [121], focal microscopic areas of necrosis with central loss of white matter and marked axonal injury [121], astrogliosis [122], lymphocytic infiltrates [122], and microscopic infarcts [121, 122]. SARS-CoV-2 nucleocapsid protein was identified in 9 of 26 brains by quantitative RT-PCR [29, 118, 119] but not by IHC [118, 119]. In 4 of 4 patients, copy numbers were generally low compared to other organs, but the olfactory bulb values were higher than those in the brainstem [29]. Interestingly, the cause of death in 3 of 6 patients younger than 65 was massive intracranial hemorrhage or pulmonary embolism. These patients exhibited diffuse petechial hemorrhage in the entire brain, and both groups of patients who died of vascular and cardiorespiratory causes showed lymphocytic pan-encephalitis and meningitis. Changes were seen in hippocampus, neocortex, cerebellum, and brainstem nuclei [120].

Coagulation alterations

Pulmonary embolism (PE) is a cause of death in a subset of COVID-19 patients. PE was described in 27 of 115 patients, of whom 39, including those with PE, had deep venous thrombosis [29, 30, 38, 39, 42].

Pulmonary thrombosis in small and medium-size pulmonary artery branches [39], as well as multi-organ thrombosis [42], was identified in 18 of 18 autopsies, of which 8 had associated pulmonary infarction [39]. Of note, 14 patients had received anticoagulation, suggesting that pulmonary thrombi formed despite treatment [39, 40]. Similarly, no significant association was found between anticoagulation therapy and presence of thrombi, with 46% (22 of 48) of anticoagulated patients having large thrombi and 88% (42 of 48) having arteriolar and capillary microthrombi in another study [50].

Multisystem inflammatory syndrome in children (MIS-C)

Postmortem examination of an 11-year-old child with MIS-C demonstrated heart failure as the primary determinant of

fatal outcome with myocarditis, pericarditis, and endocarditis [123]. In this case, SARS-CoV-2 was detected in heart tissue by RT-PCR and, purportedly by TEM. In the fatal case of a 17-year-old, the inflammatory infiltrate present within the heart was eosinophil-rich [90].

Discussion

The pathophysiologic mechanism of COVID-19 is still poorly understood. Autopsies have significantly contributed to our knowledge of the pathologic derangement occurring with COVID-19 and provided evidence for current treatment strategies. It is apparent from the growing number of autopsy studies that SARS-CoV-2 direct effects are primarily limited to the lung, while the ensuing systemic disease occurs through indirect rather than direct effects. This discussion will focus on the main systemic aspects of the disease and hypothesize a unifying pathogenic mechanism.

The spectrum of respiratory involvement in COVID-19 is broad, ranging from asymptomatic infection to flu-like symptoms to variably severe pneumonia, multi-organ failure, and death. In cases with a progressive course, acute respiratory distress syndrome (ARDS) develops in 31–41.8% of COVID-19 patients. Mortality among those who develop ARDS is 52.5–93% [18, 124]. The clinical definition of ARDS is based on Berlin criteria [125, 126], and mild, moderate, and severe ARDS is associated with increased mortality (27%; 32%; and 45%). Most patients meeting clinical criteria for ARDS have histologic features of DAD [127–129]. ARDS may be caused by infection/sepsis, shock, trauma, aspiration, transfusion, drug reaction, oxygen toxicity, vaping-associated pulmonary injury, and connective tissue disease, but the pathognomonic histologic lesion is the same—hyaline membranes occurring as a response to alveolar and endothelial injury, causing capillary endothelial damage and leakage of plasma into the alveolar space [130]. This exudate admixed with cellular debris lines the alveolar surface impeding regular gas exchange. DAD progresses from an acute (exudative) phase characterized by hyaline membranes into an organizing/proliferative phase, lasting 1–3 weeks and characterized by interstitial proliferation of fibroblasts and myofibroblasts, type 2 pneumocyte hyperplasia, and squamous metaplasia. If the patient survives the acute and proliferative stage, there may be resolution, stabilization of the process, or progression to the fibrotic (chronic) phase with collagen deposition, architecture remodeling, and honeycomb lung. Residual functional impairment is the consequence of continued interstitial fibrosis and airspace remodeling. In typical DAD caused by various etiologies, microvascular thrombi are part of the spectrum of pathologic lesions, and extensive vascular remodeling may be seen [130, 131]. A contribution of

antibody-dependent enhancement (ADE) is being actively investigated in COVID-19. A role for ADE has been invoked in SARS-CoV and MERS infection, among other viral infections. Immune complexes resulting from ADE mechanisms could contribute to DAD [132].

In our study, 152 of 263 (58%) patients had pathologic evidence of interstitial pneumonia (morphologically defined by interstitial lymphocytic infiltrate), and 50 (19%) had acute pneumonia or bronchopneumonia. Aspiration or superimposed bacterial infection were likely the underlying etiology of acute pneumonia, based on the neutrophilic pattern of infiltration. Characteristic morphologic patterns of viral injury in the lung include interstitial inflammation, DAD, and necrotizing bronchitis/bronchiolitis [53]. In our study, 230 of the total 263 patients had DAD, and 152 had interstitial lymphocytic infiltrate/pneumonia, described as sparse in some cases. Previous studies have shown that bilateral pneumonia is both a cause and a mimicker of ARDS. In a pre-COVID-19 ARDS autopsy study, 58% of patients had pneumonia, while 42% had DAD only without pneumonia, and 36% of clinically suspected ARDS were histologically diagnosed as pneumonia, while 20% of cases clinically diagnosed as pneumonia had only DAD on autopsy [133]. Early ARDS studies show that sepsis with multi-organ failure is the cause of death in 84% of patients, while respiratory failure accounts for only 16% of fatalities [134–137]. A systemic inflammatory response with fever, elevated inflammatory markers (eg, D-dimer, ferritin), and release of the proinflammatory cytokines tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8 exceeding the body homeostatic mechanisms may determine a DAD injury and a systemic response independently of the presence of pneumonia, similar to that seen in some severe cases of COVID-19.

Thromboembolism is another emerging feature of COVID-19. Ackermann et al. compared lung autopsy findings in COVID-19, influenza A (H1N1), and uninfected controls. Although both cohorts shared similar DAD findings, COVID-19 patients had severe endothelial injury with disrupted endothelial cell membranes and more arterial but less venous vascular thrombosis than influenza patients. COVID-19 and influenza patients had greater expression of lung ACE2 compared to uninfected controls and more ACE2-positive endothelial cells and endothelial injury [25]. Heterogenous disease stages and treatment applied to both cohorts make interpretation of these results complex [138]. The issue of thromboembolism versus thrombosis in COVID-19 has been debated in recent literature [139–141]. Lax et al. distinguish thrombosis from thromboembolism based on subsegmental artery involvement, distribution of thrombotic material in multiple vessels, associated endothelialitis, subtotal or total filling of the occluded vessels, and distribution of thrombotic events in areas of hypostasis,

as opposed to the randomly distributed pattern of thromboembolism [39, 141]. Micro- and macrothrombosis of pulmonary arteries have been described with endothelialitis [51]. It is apparent that vascular thrombosis is a frequent phenomenon in COVID-19 autopsies. However, a thrombosis secondary to local inflammation frequently accompanies DAD secondary to diverse etiologies [130, 138, 142, 143]. Pulmonary infarcts are also seen with intubation in ARDS [140, 144]. These findings suggest the pulmonary microthrombi may not be specific to COVID-19 but are associated with ARDS. Thus, definitive pathogenetic distinction between coagulopathy, endotheliopathy, and vasculitis, and whether these are a result of direct viral effect or systemic inflammation does not emerge from these autopsy studies. In autopsies from COVID-19 inpatients, COVID-19 untreated decedents in the community, and SARS-CoV-2 negative DAD controls, all but 1 untreated community COVID-19 patient with focal fibrinous pneumonia had DAD. COVID-19 inpatient and community patients had similar lung histopathologic findings at autopsy, suggesting that DAD is a viral and not iatrogenic injury [145]. DAD in COVID-19 patients was histologically indistinguishable from DAD from other causes. Thrombosis was similar in SARS-CoV-2 positive patients and negative controls [145]. COVID-19, 2003 SARS, and H1N1 showed DAD in 88%, 98%, and 90% of patients, respectively, while 57% of COVID-19, 58% of SARS, and 24% of H1N1 influenza patients had pulmonary microthrombi [146], suggesting that these findings are not specific for COVID-19. Persistence of multisystemic thrombosis at autopsy in a subset of COVID-19 patients undergoing prophylactic inpatient anticoagulation suggests that microthrombosis may be secondary not only to a generalized endothelial disturbance but also to an inflammatory response with cytokine release, fever, and inflammation, which is known to be characteristic of ARDS [64, 147, 148]. Additional larger comparative studies are required to further clarify this issue, shed light on the use of prophylactic versus therapeutic anticoagulation and associated risk of complications, and prevent the systemic inflammatory response before the ineluctable chain of events caused by the cytokine storm is initiated.

Nonspecific shock injury in multiple organs was the main finding in this review. This injury is described in the GI system and kidney, occasionally accompanied by vasculitis or thromboembolic events. A prospective study of 701 patients admitted to a COVID-19 tertiary hospital in Wuhan showed that acute kidney injury occurred in 5.1% of patients [149]. This is reflected by the nearly global finding of acute tubular injury in our study. However, in the same study, 43.9% also had proteinuria, and 26.7% had hematuria [149]. African ancestry is a known risk factor for kidney disease, resulting from G1 and G2 risk alleles in the APOL1 gene [150]. Collapsing glomerulopathy is strongly

associated with APOL1 risk alleles [151]. Although the pathogenic role of APOL1 in kidney diseases is still unclear, collapsing glomerulopathy in the setting of APOL1 risk alleles homozygosity has been associated with HIV nephropathy, lupus nephritis, membranous glomerulopathy, interferon and pamidronate treatment [152–156]. Glomerular and inflammatory conditions, such as the COVID-19 cytokine storm, could result in a “second hit” injury superimposed on genetic susceptibility due to APOL1 risk variants [157, 158].

Hepatic injury in COVID-19 may be multifactorial, related to direct viral CPE, hypoxic damage, cytokine storm, sepsis, or drug hepatotoxicity [89, 159–161]. Moreover, patients may have underlying chronic liver disease, such as cirrhosis, hepatitis, or cancer, which may increase the risk of SARS-CoV-2 infection with immunosuppression [89, 159] and contribute to more severe liver damage, particularly with concurrent hypoxia [161]. Therefore, it is important to distinguish acute pathologic changes attributed to direct SARS-CoV-2 infection from chronic underlying diseases potentially predisposing to a fatal COVID-19 course and nonspecific secondary effects related to hypoxia, hypotension, or sepsis [39].

Acute myocardial injury, defined by elevated cardiac troponin levels, has been clinically described in 5–38% of COVID-19 patients [162, 163]. Patients with comorbidities or cardiovascular disease are more likely to present with cardiac symptoms. Myocardial injury is associated with a greater need for mechanical ventilation and higher in-hospital mortality [164]. Although a clinically significant component of COVID-19, myocardial injury appears to be limited in autopsy studies. A myocarditis meeting histopathological Dallas criteria was only identified in 27 of 191 patients (14%) in our study. Similarly, limited myocardial injury not meeting Dallas criteria, e.g., individual myocyte necrosis, focal myocardial lymphocytic infiltrate, or “borderline myocarditis” (the latter two forms representing the same entity but often separately described in a few studies) were identified in 16 (8%), 8 (4%), and 5 (3%) patients, respectively. SARS-CoV-2 genome in heart tissue was detected in 60% of our reviewed cases, but IHC for the spike protein was negative in 1 tested patient. Therefore, systemic inflammation secondary to cytokine release, endothelial inflammation, and associated microvascular thrombosis leading to multi-organ failure may be the main pathogenetic mechanisms associated with COVID-19 myocardial injury [164]. The long-term effects of COVID-19 myocardial injury are yet to be established. However, in pre-COVID studies, death for biopsy-proven viral myocarditis ranged from 19% at 5 years to 39% at 10 years, respectively [165, 166].

Ischemic stroke, encephalopathy, meningoencephalitis, acute necrotizing encephalitis, and Guillain-Barré syndrome

have been clinically documented in COVID-19 [167–172]. Although still limited, autopsy data seem to support a contribution of metabolic derangement in critically ill patients associated with hypoxemia and a systemic proinflammatory status, typical of COVID-19. SARS-CoV-2 genome has been demonstrated in 34% of brains, supporting a direct viral effect.

Two patterns of cutaneous COVID-19 manifestations have been identified. Exanthems, such as rash, urticarial eruptions, and chickenpox-like vesicles tend to occur early in the disease course and sometimes precede other systemic manifestations [114, 173]. Vascular lesions, such as chilblains, livedoid eruptions, and purpura, usually appear several days after the onset of general symptoms or even in their absence [114, 173]. The first group of lesions could represent an early response to the initial viral replication or the cytokine storm. In contrast, the second could result from a delayed cell-mediated immunologic response to the virus or an unbalanced coagulation state towards a prothrombotic microenvironment with microthrombi formation in the dermal vessels. The early cutaneous manifestations could aid in the prompt identification of asymptomatic patients, improve epidemiological tracking, and promote timely therapeutic management. The skin vascular lesions might represent a marker of systemic vessel injury. Therefore, these patients’ prognosis could improve after administration of anticoagulant and anti-inflammatory therapy.

In children, COVID-19 symptomatology is typically milder [174]. However, in April 2020, several children with no prior medical history presenting with fever, cardiovascular shock, and hyperinflammation syndrome were reported [175–180]. In May 2020, the CDC issued an advisory to report cases meeting criteria for multisystem inflammatory syndrome in children (MIS-C) [181], defined by fever and severe illness requiring hospitalization with multisystem (≥ 2) organ involvement, laboratory evidence of inflammation, and recent infection or exposure to SARS-CoV-2 within four weeks prior to symptoms onset in individuals aged <21 years. MIS-C is rare, with an estimated incidence of 2 per 100,000 [182]. As of September 17, 2020, a total of 935 confirmed cases with 19 deaths were reported in the US.

There are clinical and pathophysiologic similarities in MIS-C and Kawasaki disease (KD), a febrile illness affecting young children characterized by vasculitis that can result in coronary artery aneurysms. In two series of MIS-C, 73–78% of children were previously healthy, with the most common comorbidities being obesity and asthma [183, 184]. Similar to KD, MIS-C is a post-infectious phenomenon related to IgG-ADE rather than the result of acute viral infection [178, 185–187]. A predominantly gastrointestinal presentation (92%) [187] is frequent, while

respiratory symptoms (70%) are often due to severe shock, and ARDS is not a prominent feature [184]. Acute cardiac decompensation [188] and cardiovascular system involvement were present in 80% of patients with coronary artery aneurysms in 8% [183]. In contrast, MIS-C and KD differ in several aspects, including ethnicity, age of onset, clinical and immunologic manifestations. While ~80% of children with KD are predominantly of Asian descent and younger than five years (peak incidence around 10 months of age), children with MIS-C are predominantly of Hispanic and Afro-Caribbean descent and have a median age of 8.3–11 years [183, 184]. In KD, coronary artery abnormalities are more frequent than in MIS-C, occurring in 15–25% of patients and decreasing to 5% with prompt therapy, while these occur only in 1% of MIS-C cases. Left ventricle dysfunction and shock are also more likely in the latter. Immunologically, KD has an interleukin17A-mediated hyperinflammation, which is absent in MIS-C, and higher levels of biomarkers associated with arteritis and coronary artery disease. Furthermore, MIS-C has lower naïve CD4 + T cell and T follicular helper and increased central and effector memory subpopulations compared to KD [189]. MIS has also been reported in adults recently, although as a rare occurrence [190–192].

Putative SARS-Cov-2 virions or viral-like particles suggestive of SARS-Cov-2 have been purportedly identified by TEM in several recent reports. These highly contested reports [56, 102, 193–200] often describe physiological structures and organelles, such as clathrin-coated vesicles, multivesicular bodies, rough endoplasmic reticulum, and unidentified subcellular structures. This issue highlights the challenging task of identifying SARS-Cov-2 virions by TEM due to unfamiliarity with coronavirus morphology and morphogenesis, artifacts of delayed postmortem fixation, lack of detection due to possible viral clearing, and sensitivity of the methodology, as reviewed by Hopfer et al., and Bullock et al. [102, 201].

Limitations

Limitations of this study include its focus on COVID-19 histopathologic injury rather than laboratory, imaging, and macroscopic findings. In addition, disparate reporting methodologies emerged from the analyzed studies, accounting for vastly heterogeneous data in the literature. We chose to include only peer-reviewed articles and exclude pre-prints. Thus, some articles may have been missed if the initial pre-print was subsequently published. Similarly, given the fast pace of recent publications emerging on this topic, articles published during the editing and review stages of this manuscript were not included.

Conclusions

In summary, SARS-CoV-2 viral protein has been identified in situ only in a small proportion of extrapulmonary organs in a subset of patients, supporting a limited extrapulmonary direct effect of the virus. The predominant pathologic findings emerging from this review suggest that a unifying mechanism underlying the systemic clinical manifestation of COVID-19 is the characteristic inflammatory response of ARDS with cytokine release, fever, inflammation, generalized endothelial disturbance, and secondary multisystemic shock-injury. Although very preliminary, an additional contributing factor could be a detrimental immunologic response, such as ADE, which is being actively investigated in COVID-19.

Autopsies have reaffirmed their value to public health, aiding our understanding of novel diseases. Though limitations due to postmortem autolytic changes may hinder some studies, the increasing autopsy literature supports a wealth of information contributing to our understanding of COVID-19.

Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author contributions GAG and SC performed study concept, design, and development of methodology; GAG, SC and MEK provided acquisition, analysis, and interpretation of data, writing, review, and revision; SEM, RE, JJ, and GS provided review and revision; AM and GE provided technical and material support. All authors read and approved the final paper.

Compliance with ethical standards

Conflict of interest GE is a microscopy and imaging specialist at Hunt Optics & Imaging, Inc, Pittsburgh, PA. All other authors have no relevant disclosures.

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