

Gross, Histopathological, and Ultrastructural Features in Patients with COVID-19: A Literature Review

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Abstract

The coronavirus disease (COVID-19) outbreak has led to swift efforts to learn about its clinical course, prognostic markers, and complications. Consequently, there is a lot of scattered information available regarding severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) but its pathophysiology is still poorly understood. Gross and microscopic findings are very important for understanding any disease, including COVID-19. This literature review examines and summarises the biopsy, gross autopsy, and other histopathological findings that have been reported in various organs in COVID-19 patients to increase the understanding of the disease. Many histopathological findings in various organs were nonspecific, especially in the liver and brain, while others were particular to SARS-CoV-2. Therefore, further histopathological studies and autopsies are necessary to obtain consistent and reliable findings in those with COVID-19 to fully understand the pathogenesis of the disease and the impact it has on individual organs.

INTRODUCTION

The analysis of biological samples has always played a vital part in understanding pathological processes of diseases. As the outbreak of the coronavirus disease (COVID-19) turned into a global pandemic, new information has emerged regarding various aspects of the

disease. However, the current understanding about the precise nature and reaction patterns in various organs and tissues in response to this infection is lacking and poorly understood. In the large number of original studies available on the subject matter, it can be difficult to get a full picture of the effect that COVID-19 has on the body as a whole, as many studies show

conflicting results. In this literature review, the authors examined and summarised the macro- and micropathological findings present in each organ system in a COVID-19 patient in already published literature.

METHODS

Until 11th July 2020, PubMed and Embase were searched for related published articles. In both electronic databases, the following search strategy was applied and these keywords (in the title or abstract) were used: “COVID 19” OR “coronavirus” AND “biopsy” OR “autopsy” OR “histopathology”.

RESULTS

Lungs (n=215 cases)

A reported gross examination was available for 89 cases that tested positive for COVID-19. The macroscopic examination in all cases showed findings that ranged which patchy to diffuse areas of consolidation to severe and extensive suppurative infiltrates. A common finding was an increased lung weight in 70 cases;¹⁻⁹ they were more than one standard deviation heavier than average weight. Lungs consisting of firm parenchyma with regions of dark-coloured to reddish haemorrhagic areas, with focal demarcation and severe congestion were found in 38 cases.^{3-5,7-12} Visible pulmonary thromboembolism were noted in 27 cases,^{3,13-16} some of them with associated infarcts after prophylactic dose anticoagulant therapy, suggesting that pulmonary thrombi were formed despite anticoagulant therapy.¹³ In some cases, visibly enlarged peritracheal and peribroncheal lymph nodes were found.^{7,10,11}

Histopathological examination was available for 190 COVID-19 positive cases. The most commonly reported histopathological finding was diffuse alveolar damage, reported in all but one case¹⁷ ranging from hyaline membrane formation, alveolar wall oedema, fibrin deposits within the alveoli, severe capillary congestion and severe syncytial cell and Type II pneumocyte hyperplasia, and desquamation to diffuse necrosis of alveolar lining cells.^{2,4-6,8-13,15,18-27} One recently performed prospective cohort study reported that diffuse alveolar damage was the primary abnormality

in hospitalised patients and almost every patient positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) died without medical intervention.¹ Predominantly, inflammatory CD3+ and CD4+ T cells were found near precapillary and postcapillary vessel walls along with macrophages and abundant polymorphonuclear leukocytes whereas the number of CD8+ T cells was lower in comparison in most cases.^{2,5,6,10,16,17,19,28,29} CD61+ megakaryocytes were abundantly found actively producing platelets and located within pulmonary capillaries, further indicating the stimulation of the coagulation cascade.^{6,5,20}

Another broad finding was pulmonary thromboembolism with fibrinous thrombi in small and large pulmonary arterioles, in some cases with haemorrhagic foci.^{5,6,20-23,30} In a comparative study, the lungs presented structurally deformed capillaries, showing abrupt calibre changes such as intussusceptive pillars within the capillaries and hallmarks of endothelial cell swelling, loss of contact with basal membrane, and disruption of intercellular junctions on electron microscopy.² In multiple cases, ultrastructural examination showed distended cytoplasmic vacuoles within the pneumocytes with viral cytopathic changes and intracellular SARS-CoV-2. Virions were seen extracellularly among the cilia and within the cytoplasm of respiratory epithelial cells in the upper airway.^{2,6,7,10,14,18,22,27} Immunohistochemistry of viral antigens was positive in the upper airway, bronchiolar and submucosal gland epithelium, Type I and II pneumocytes, alveolar macrophages, and lung hyaline membranes.²² Superimposed bronchopneumonia was described in 19 cases with mostly neutrophilic infiltrate.^{4,19,20}

Cardiovascular system (n=67 cases)

Cardiovascular gross findings were reported in 19 autopsy cases that tested positive for COVID-19. The most commonly reported gross findings in seven cases were large vessel occlusions characterised by intimal and medial thickening with luminal narrowing.³¹⁻³³ Other reported gross findings in two cases included thin myocardial trabecula, streaking of right atrial wall myocardial tissue,⁷ and mottling parenchyma with a soft and rubbery texture.⁶ The most significant gross findings generally seen were cardiomegaly and right ventricular dilatation, which were attributed to pre-existing underlying diseases

such as hypertension, diabetes, and obesity. No significant gross findings were observed in the remaining 10 cases.

Histopathological autopsy findings were available for 59 cases of COVID-19 positive patients. Unlike in other similar viral infections that caused viral myocarditis, there were no reported cases of COVID-19 myocarditis. The most commonly reported histopathological finding was myocyte necrosis, observed in almost all the cases except for one case.⁷ Changes to the myocardium included irregularity in shape with a darkened cytoplasm, though these changes were not sufficient for interpretation as acute myocardial injury in four cases;²⁴ mild myxoid oedema; mild myocyte hypertrophy; focal nuclear pyknosis, in one case;⁷ and moderately enlarged cardiomyocyte with hyperchromatic nuclei and vacuolar degenerative change in three cases.³¹ The presence of diffuse lymphocytic endothelitis and apoptotic bodies were shown in 34 cases.³²⁻³⁵

A study proposed that SARS-CoV-2 might not directly impair the heart, because they observed scarce interstitial mononuclear inflammatory infiltrates in the myocardial tissue without substantial cardiac muscle tissue damage in their patient with COVID-19.³⁶ There was also evidence of direct viral infection of endothelial cells, endothelitis with diffuse endothelial inflammation, and micro- and macrovascular thrombosis, both in the venous and arterial circulations, in 26 cases.³⁴

In conclusion, cardiomegaly was most likely a result of pre-existing heart disease. Although histopathological cardiac findings were notable for absence of lymphocytic myocarditis, myocyte necrosis was the most commonly reported finding.

Gastrointestinal (n=24)

The most common gross finding was multiple and diffuse punctate haemorrhages in the stomach (n=3) and duodenal mucosa (n=1).^{37,38} Other gross findings (n=2) included increased liver volume and an enlarged gallbladder.^{37,38}

In all of the 24 cases, there was mild-to-moderate hepatic lobular or portal lymphocytic infiltration.^{18,19,24,38,39} Four cases showed centrilobular sinusoidal dilatation.²⁴ Minimal-to-mild micro- and macrovesicular steatosis was

seen in ten cases.^{18,19,38} Patchy and multifocal hepatic necrosis were seen in 13 cases.^{19,24,38} These findings were mostly nonspecific and can be attributed to direct viral-induced cellular injuries and potential hepatotoxicity from therapeutic drugs, or be representative of pre-existing chronic liver disease that was exacerbated during COVID-19, and COVID-19-related hyperinflammatory reactions.⁴⁰ SARS-CoV-2 particles without membrane-bound vesicles in hepatocyte cytoplasm were also identified.³⁸

Central nervous system (n=79 cases)

Clearly reported gross examination was available for 41 cases that tested positive for COVID-19. The macroscopic examination showed findings that ranged from mild swelling and cerebral oedema in three cases,^{4,41,42} to disseminated haemorrhagic lesions throughout the cerebral white matter (size ranging from 1 mm to 1 cm) and scattered punctate subarachnoid haemorrhages in two cases.^{41,43} Hydrocephalus internus was present in two cases.⁴ No abnormalities were seen in 23 cases apart from those which were already associated with the patients' prior comorbidities such as atherosclerosis and Parkinson's disease (n=16).⁴

Histopathological examination was available for 65 COVID-19 positive cases. Here, 33 cases showed no microscopic abnormalities; one case mimicked glioma on imaging but on histopathological examination was negative for malignancy and positive for encephalitis.⁴⁴ Reactive gliosis, neuronal satellitosis, perivascular haemorrhage,⁴⁵ and disseminated haemorrhagic cerebral white matter lesions⁴¹ were found in eight, five, one, and one case, respectively. Other neuropathological findings included characteristics resembling vascular and demyelinating lesions. For example, the scattered necrotic neurons of acute hypoxic injury with red degeneration and oedema in the cerebrum (cortex), cerebellum (Purkinje cell layer), and hippocampus (CA1) were observed in 19 cases.^{41,46} Infarcts in brainstem, deep grey nuclei, or spinal cord were absent. In one case, the subcortical white matter had macrophage clusters with axonal injury and a perivascular acute disseminated encephalomyelitis-like appearance.⁴¹ No thrombi, vasculitis, or abnormalities of the olfactory bulb were observed in any cases.^{39,41} Focal leptomeningeal inflammation was detected in

one brain specimen⁴⁶ while no inflammation was present in the leptomeninges of another case.⁴¹ Perivascular lymphocytic clusters were detected in three brain specimens.^{41,46}

Kidney (n= 43)

The histopathological effects of COVID-19 in kidney tissues were reviewed for 43 cases. Here, 32 cases reported severe acute tubular necrosis, showing diffuse proximal tubular injury with the loss of brush border, vacuolar degeneration, mild fibrosis in the interstitium, and lymphocyte infiltration on microscopy while severe glomerular injury was absent.⁴⁷⁻⁴⁹ The vacuoles seen on light microscopy correlated with double-membrane vesicles containing virion particles by electron microscopy.⁴⁹ Infrequent haemosiderin granules, pigmented casts, and lumen-obstructing red blood cell aggregates were also observed. Vasculitis, interstitial inflammation, or haemorrhage were absent.⁴⁸ Electron microscopy demonstrated virus-like particles are in the tubular epithelium and podocytes.⁴⁸ The virus was not only directly cytotoxic, but also had the ability to initiate CD68+ macrophage and complement C5b-9 deposition to mediate tubular pathogenesis.^{47,50}

In a separate study that evaluated 10 patients with proteinuria and COVID-19, all renal biopsies showed renal tubular acidosis without evidence of the virus in the biopsied tissue.⁵¹

Skin (n=111)

The clinical presentation of skin in COVID-19 patients showed findings including urticarial, vesicular, and petechial or purpuric eruptions; erythema multiforme; vascular complications such as acro-ischaemia, livedo, necrosis, or gangrene and chilblain; and maculopapular eruptions including morbilliform rash, plaques, and pityriasis rosea.⁵²

Histopathological examination was available for 30 COVID-19 positive cases. The most common finding, present in 18 cases, was significant degree of perivascular infiltration of the superficial dermis by lymphocytes, eosinophils, and neutrophils in vasculitic pattern with accompanying papillary oedema and extravasation of red blood cells.^{44,53-58} Thrombogenic vasculopathy, found in seven cases, was associated with widespread epidermal or papillary dermal or dermohypodermal and adnexal necrosis.

Adnexal necrosis spared ducts, but was present in the secretory portion of sweat coil.^{54,56,58} Other epidermal findings included spongiosis, basal cell vacuolation, suprabasal acantholytic ballooning keratinocytes, parakeratosis, and dyskeratotic.^{56,57} Superficial and deep dermal lichenoid infiltrate was also found in one case of chilblains.⁵³ Immunohistochemistry showed extensive C5b-9 deposition within the vessels of the dermis.⁵⁴

Testes (n=13)

Histopathological examination was available for 13 COVID-19 positive cases. Out of these, 11 cases showed swollen, vacuolated Sertoli cells. Intratubular cell detachment from basement membranes of the seminiferous tubules was noted. No inflammatory cells were found within the seminiferous tubules while the interstitium showed oedema and infiltration of T lymphocytes and histiocytes. Out of the same 11 cases, 18.2%, 45.5%, and 36.4% of cases showed <10%, 10–50%, and >50% injury to seminiferous tubules, respectively, while mild to no tubular injury was present in five cases of COVID-19 negative controls. The Leydig cell count was also significantly lower than in the control group. Normal spermatogenesis was observed in all cases as ACE-2 was not expressed in spermatogonia but widely present in Sertoli and Leydig cells.⁵⁹ The rest of the two cases showed orchitis.⁴⁵

Table 1, 2 and 3 show the patient demographics such as sex, age, comorbidities, and country the study was conducted in.

LIMITATIONS AND RECOMMENDATIONS

The data or cases available for review were very limited as many hospitals discontinued autopsies on COVID-19 cases to limit the spread of the virus. Further, larger studies are needed to assess the effect of COVID-19 in different organs, especially on the central nervous system, kidneys, and the gastrointestinal tract. The authors also recommend that more studies are conducted in areas with higher prevalence of comorbidities, such as viral hepatitis or tuberculosis, so that the effects of specific pre-existing conditions on the outcome of the virus can be determined. Studies comparing the effects of COVID-19 on various organs in healthy patients versus in those with pre-existing conditions will also be helpful.

Table 1: Pulmonary findings in patients with coronavirus disease (COVID-19).

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
Lung	Xu et al., ¹⁸ 2020	1	China	50	Male	Lung injury, ARDS
	Grimes et al., ¹⁴ 2020	2	USA	Middle-age	Male	HTN, asthma, HIV compliant with antiretroviral therapy
	Ackerman et al., ² 2020	7	USA	Mean(\pm SD): 68(\pm 9.2), and 80(\pm 11.5)	Female: 2; male: 5	NA
	Aguiar et al., ⁵ 2020	1	Switzerland	31	Female	Morbid obesity
	Duarte-Neto et al., ⁴⁵ 2020	10	Brazil	NA	NA	NA
	Beigmohammadi et al., ¹⁹ 2020	7	Iran	Mean (range): 67.85 (46–84)	Female: 2; male: 5	HTN (57.0%), RA (14.2%), none (28.5%)
	Brown et al., ¹⁷ 2020	1	USA	NA	NA	NA
	Deshpande, et al., ¹³ 2020	11	USA	NA	NA	HTN, DM, obesity, COPD, CAD, cancer, cerebrovascular disease (4 patients), pulmonary embolism (1 patient)
	Dolhnikoff et al., ²⁰ 2020	10	Brazil	Mean (range): 67.8 (33–83)	Female: 5; male: 5	HTN, DM, IHD, COPD (7 patients)
	Fox et al., ⁶ 2020	10	USA	Range: 44–78	NA	HTN, DM, obesity, immunosuppressed (1 patient)
	Jain et al., ²¹ 2020	NA	NA	NA	NA	NA
	Konopka et al., ¹ 2020	8	USA	Average (range): 53 (22–80); 49 (33–63)	Female: 6; male: 2	Idiopathic bronchiectasis and pneumonia, suffered acute intraparenchymal brain haemorrhage (1 patient)
	Lax et al., ³ 2020	11	Austria	Mean/median (range): 81.5/80.5 (75–91)	Female: 3; male: 8	HTN (81%), DM (45%), cerebrovascular disease (36%), dementia (36%)
	Li et al., ⁴⁰ 2020	NA	China	NA	NA	NA
	Martines et al., ²² 2020	8	USA	Median: 73.5 (two <65)	NA	HTN (75%), CKD (75%), cardiovascular disease (75%), obesity (62.5%), DM (50%)
	Menter et al., ⁴ 2020	21	Switzerland	Mean (range): 76 (53–96)	Female: 4; male: 17	HTN (100%), cardiovascular disease (71%), smoker (38%), pre-obesity/obesity, DM (33%), chronic neurological condition (23.8%), COPD (14.2%), malignancy (14.2%), CLD (9.5%), CKD (19%), acquired immunosuppression (4.7%)
Pernazza et al., ²³ 2020	1	Italy	61	Male	Lung adenocarcinoma	

Table 1 continued.

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
	Popa et al., ¹⁰ 2020	1	Romania	88	Male	HTN, DM, with permanent electrical cardio-stimulation, history of TIA, immobilised in bed
	Scendoni et al., ¹⁵ 2020	2	Italy	Female: 62; male: 44	Female: 1; male: 1	Male: polymyositis Female: HTN, autoimmune hypothyroidism, DM
	Schaefer et al., ¹⁶ 2020	7	USA	Average: 62.4	Female: 2; male: 5	SLE, RA, pulmonary fibrosis, CKD, interstitial lung disease, MGUS, CAD, HTN, DM, cardiomegaly, atherosclerosis, dementia, status post-leg amputation, COPD, NASH
	Shao et al., ²⁹ 2020	1	China	65	Male	None
	Suess et al., ¹¹ 2020	1	Switzerland	59	Male	HTN, DM
	Tian et al., ¹² 2020	2	China	Female: 84; male: 73	Female: 1; male: 1	Male: HTN, DM, adenocarcinoma
	Tian et al., ²⁴ 2020	2	China	NA	NA	NA
	von der Thüsen, van der Eerden ²⁵ 2020	41	The Netherlands	NA	NA	NA
	Wang et al., ²⁶ 2020	2	China	Female: 53; male: 62	Female: 1; male: 1	Female: DM and HTN
	Yan et al., ⁷ 2020	1	USA	44	Male	Obesity
	Zeng et al., ²⁷ 2020	1	China	55	Female	None
	Zhang et al., ²⁸ 2020	1	China	72	Male	DM and HTN
	Conde et al., ⁸ 2020	1	Spain	69	Male	None
	The COVID-19 Autopsy, ⁹ 2020	1	Spain	54	Male	HTN, gout, migraine, OSA
	Schaller et al., ³⁹ 2020	12	Germany	Median: 79	Female: 3; male: 7	HTN (41%), DM (16%), COPD (16%), malignancy (16%), obesity (16%)
	Tian S et al., ²⁴ 2020	4	China	Median: 73	Female: 1; male: 3	DM and HTN

ARDS: acute respiratory distress syndrome; CAD: coronary artery disease; CKD: chronic kidney disease; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HTN: hypertension; IHD: ischaemic heart disease; MGUS: monoclonal gammopathy of undetermined significance; NA: not available; NASH: non-alcoholic steatohepatitis; OSA: obstructive sleep apnoea; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TIA: transient ischaemic attack.

Table 2: Cardiovascular findings in patients with coronavirus disease (COVID-19).

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
CVS	Becker et al., ³² 2020	4	USA	Mean: 50	Male	NA
	Buja et al., ³¹ 2020	4	USA	Range: 44–76	Female: 1; male: 3	Obesity, DM, CKD
	Centurión et al., ³⁶ 2020	15	Paraguay	NA	NA	NA
	Craver et al., ³⁵ 2020	1	USA	17	Male	NA
	Fox et al., ⁶ 2020	10	USA	Range: 44–78	NA	HTN, obesity, DM
	Pons et al., ³⁴ 2020	26	France	Mean: 65	NA	NA
	Tian et al., ²⁴ 2020	4	China	Range: 59–81	Female: 1; male: 3	Pneumonia
	Varga et al., ³³ 2020	3	Switzerland	Range: 58–71	Female: 1; male: 2	HTN, renal transplant patient

CKD: chronic kidney disease; CVS: cardiovascular system; DM: diabetes mellitus; HTN: hypertension; NA: not available.

Table 3: Findings in other organ systems in patients with coronavirus disease (COVID-19) (gastrointestinal tract, central nervous system, renal, skin, testes).

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
GIT	Wang et al., ³⁸ 2020	156	China	Mean: 51	Male: 82	DM, HTN, digestive system disease, endocrine system disease, nervous system disease, chronic respiratory disease
	Schaller et al., ³⁹ 2020	10	Germany	Mean (range): 79 (64–90)	Male: 7	CAD, COPD, CKD, DM, morbid obesity, endocrine system disease, CML, adenocarcinoma of the lung
	Beigmohammadi et al., ¹⁹ 2020	7	Iran	Mean (range): 67.9 (46–84)	Male: 5	DM, HTN, CAD, digestive system disease, RA
	Xu et al., ²⁷ 2020	1	China	50	Male: 1	NA
	Adachi et al., ³⁷ 2020	1	Japan	84	Female: 1	NA
	Tian et al., ²⁴ 2020	4	China	Mean (range): 73 (59–81)	Male: 3	CLL, CLD, HTN, DM, renal transplantation
CNS	Duarte-Neto et al., ²⁰ 2020	9	Brazil	Median (range): 69 (33–83)	NA	NA

Table 3 continued.

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
	Menter et al., ⁴ 2020	18	Switzerland	Median (range): 76 (53–96)	Female: 4; male: 17	HTN, CAD, DM, ESRD, obesity, chronic neurological condition, CLD
	Reichard et al., ⁴¹ 2020	1	USA	71	Male: 1	CAD
	Liu et al., ⁴² 2020	1	NA	NA	NA	NA
	Bradley et al., ⁴³ 2020	14	USA	Median (range): 74 (42–84)	Female: 8; male: 6	HTN, CKD, OSA, DM, obesity
	Efe et al., ⁴⁴ 2020	1	NA	35	Female: 1	None
	Solomon et al., ⁴⁶ 2020	18	NA	Median (interquartile range): 62 (53–75)	Female: 4; male: 14	DM (12 patients), HTN (11), CAD (5), hyperlipidaemia (5), CKD (4), prior stroke (4), dementia (4), treated anaplastic astrocytoma (1)
	Schaller et al., ³⁹ 2020	10	Germany	Median (range): 79 (64–90)	Male: 7	Leukaemia, HTN, hypothyroidism, COPD, CKD, cardiomyopathy, obesity, DM, atrial fibrillation, CAD
Kidney	Su et al., ⁴⁸ 2020	26	China	69	Female: 7; male: 19	Renal failure, multiple organ dysfunction, clinical signs of kidney injury (nine patients)
	Diao B et al., ⁴⁷ 2020	6	China	Range: 21–92	NA	HTN (three patients)
	Farkash EA et al., ⁴⁹ 2020	1	China	53	Male: 1	Aortic dissection repair complicated by renal failure, obesity, hyperlipidaemia
	Sharma P et al., ⁵¹ 2020	10	China	Mean: 66	Female: 5; male: 5	DM, HTN
Skin	Duarte-Neto et al., ²⁰ 2020	12	Brazil	Median (range): 69 (33–83)	NA	NA
	Kolivras et al., ⁵³ 2020	1	NA	23	Male: 1	Psoriasis
	Magro et al., ⁵⁴ 2020	5	NA	Range: 32–73	Female: 2; male: 3	Females: no comorbidities Males: CAD, DM, heart failure, ESRD, obesity
	Diaz-Guimaraens et al., ⁵⁵ 2020	1	Spain	48	Male: 1	HTN
	Gianotti et al., ⁵⁶ 2020	3	Italy	Range: 57–89	Female: 2; male: 1	NA
	Ahouach et al., ⁵⁷ 2020	1	NA	57	Female: 1	NA
	Llamas-Velasco et al., ⁵⁸ 2020	1	NA	61	Male: 1	DM

Table 3 continued.

Organ	Study	Number of cases	Country of origin	Age (years)	Sex	Comorbidities
Testes	Duarte-Neto et al., ²⁰ 2020	2	Brazil	Median (range): 69 (33–83)	Male: 1	NA
	Yang et al., ⁵⁹ 2020	11	China	Mean (range): 65 (42–87)	Male: 1	HTN, CKD, CAD, neoplasia (two patients had no comorbidities)

CAD: coronary artery disease; CKD: chronic kidney disease; CLD: chronic liver disease; CLL: chronic lymphocytic leukaemia; CML: chronic myelogenous leukaemia; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GIT: gastrointestinal tract; HTN: hypertension; NA: not available; OSA: obstructive sleep apnea; RA: rheumatoid arthritis.

CONCLUSION

In conclusion, the many findings in multiple organs could not be definitively attributed to

SARS-CoV-2 as many patients had underlying pre-existing conditions; therefore, further case-control type studies are required to credit the histopathological findings to SARS-CoV-2.

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