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Comparative Microscopic Pathology of SARS-COVID 19 Infection in Human and Corona Virus Infection in Animals: A Review

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ABSTRACT

COVID 19is also known as Coronavirus disease 2019 and is an extremely contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which leads to producing great public health importance worldwide as well as in animals. At present COVID 19 is spreading throughout the world. The microscopical lesions are caused by covid19 is mainly affects upper respiratory tract and coronavirus infection also affects bronchiolar epithelial cells and type II pneumocyte of respiratory tract. Here we review the microscopical lesions caused by SARS COVID 19 in human and corona virus infection in animals is described for the benefit of the public.

Key words: Comparative microscopic pathology, Coronavirus infection, Review, SARS-COV-2.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a highly contagious disease of human beings (Wu et al., 2020; Zhou et al., 2020; Zhu et al., 2020). The most common symptoms are fever, cough, headache, gastrointestinal symptoms, liver injury, olfactory and gustatory dysfunctions (Lechien et al., 2020; Lin et al., 2020; Zhang et al., 2020). Computerized tomography (CT) imaging features of the chest are the ground glass opacities in bilateral multiple lobular, consolidation, adjacent pleura thickening and combined linear opacities (Xu et al., 2020). COVID-19 has been considered the sixth public health emergency of international concern (PHEIC) by the World Health Organization (WHO) (Eurosurveillance Editorial Team, 2020).

Coronaviruses (CoVs) are belonging to a large group of positive-sense RNA, enveloped viruses is producing a variety of diseases in various mammalian and avian hosts, including humans, cattle, pigs, chickens, cats, mice and many other species (Fehr et al., 2015).

The probable natural reservoir host of SARS-CoV-2 was a bat and in this whole-genome was highly similar to a bat coronavirus RaTG13 along with a genome sequence identity of 96.2% (Zhou et al., 2020). SARS-CoV is transmitted to humans through masked palm civets and the previous Middle East respiratory syndrome coronavirus (MERS-CoV) is transmitted dromedary camels (Alagaili et al., 2014). Pangolin might be the potential intermediate host for SARS-CoV-2 due to its multiple lineages of pangolin coronavirus were like SARS-CoV-2 (Lam et al., 2020; Zhang et al., 2020). The present cases in the human population are mostly occurring along with co-morbid conditions of diabetes. hypertension and heart disease are susceptible to this virus (Wang et al., 2020). SARS-CoV-2 pathogenesis is highly complex with multiple factors leading to severe lung injury

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followed by virus dissemination to several organs (Jiang and Christine 2007).

COVID-19 infection caused aggressive inflammatory reaction due to release of more pro-inflammatory cytokines leads to hyperactive host immune response to the SARS-CoV-2 virus (Dina et al., 2020). SARS-CoV-2 virus is having a spike glycoprotein on the envelope which can bind to specific receptors of ACE2 on the host cell membrane (Li et al., 2003) and it is mainly expressed on type II alveolar epithelial cells, surface of epithelial cells in the oral, nasal mucosa and nasopharynx, with a weak expression indicating that the lungs are the primary target of SARS-CoV-2 (Hamming et al., 2004; Zou et al., 2020) and kidneys, heart and blood vessels, liver, pancreas and also regulates alterations in circulating lymphocytes and the immune system (Huang et al., 2020; Mehta et al., 2020; Xu et al., 2021). Increase in the release of inflammatory cytokines and chemokines in the fluid followed by SARS CoV2 infection leading to acute

respiratory distress and multiple organ failure (Deshmukh et al., 2021).

In wild animals, mainly canids had seroprevalence against CCoVs (1.7%), felids to FCoVs (2%) and various bovids to BCoVs (range, 6.6-13.3%) (Evermann, et al., 1980; Foreyt and Evermann, 1985; Evermann, et al., 1988; Tsunemitsu et al., 1995).

In this review paper, describe the various microscopical lesions of COVID 19 infection and compare the microscopic pathology of coronavirus infection in animals.

Microscopic pathology on the respiratory system Human

Microscopically lung revealed interalveolar haemorrhages, diffuse alveolar damage, desquamation of alveolar epithelial cells, amphophilc granular cytoplasm, type II pneumocyte hyperplasia, and hyaline membrane formation (Xu et al., 2020; Cai et al., 2020; Carsana et al., 2020; Fox et al., 2020, Magro et al., 2020; Bradley et al., 2020) interalveolar neutrophilic infiltration, pulmonary congestion, edema (Magro et al., 2020; Bradley et al., 2020), plug formation, microthrombi formation, fibrinoid necrosis of the blood vessels, infiltration of mononuclear cells predominantly lymphocytes (Cai et al., 2020; Kuang et al., 2020; Luo et al., 2020; Xu et al., 2020; Menter et al., 2020; Pernazza et al., 2020; Yao et al., 2020; Zeng et al., 2020) and monocytes (Xu et al., 2020; Pernazza et al., 2020; Konopka et al., 2020; Tian et al., 2020a; Tian et al., 2020b; Yao et al., 2020), presence of syncytial giant cells and interstitial fibrosis (Copin et al., 2020).

The microscopical lesions in the infection increase with other comorbid conditions hypertension, chronic kidney disease, obstructive sleep apnea and metabolic diseases like diabetes and obesity (Zhu et al., 2020; Tian et al., 2020a) characterized by intra-alveolar hemorrhages, plug formation, hyaline membrane, type II pneumocyte hyperplasia, fibrinoid necrosis of the small vasculature and abundant intra-alveolar neutrophil infiltration and it was suggestive of bacterial infection leading to bronchopneumonia (Huang et al., 2020).

Animals

The microscopical lesion in lungs of felines revealed phlebitis is observed in small to medium sized veins is mediated by virus infected monocytes/macrophage with few T-cells and neutrophils causes progression into granuloma (Kipar et al., 2005). Metalloproteinase-9 enzyme expression was increased by activated monocytes leads to endothelial barrier dysfunction and subsequent extravasation of monocytes causing perivascular and vascular damage (Kipar et al., 2001; Drechsler et al., 2011; Tekes et al., 2016).

Histological lesions caused by canine corona virus in lungs of dogs showed fibrinopurulent infiltrate extending from alveoli into bronchioles and bronchi, macrophages with erythrophagocytosis in the alveoli, perivascular serous-fibrinous edema and mural fibrinoid vascular necrosis, with

infiltration of monocytes and neutrophils (Evermann et al., 2005; Zappulli et al., 2008).

BCoVs infection caused the respiratory lesions of petechiae with mucopurulent material in the trachea and bronchointerstitial pneumonia with intra-bronchiolar syncytial cells (Ellis, 2019), type II pneumocytes hyperplasia (Park et al., 2007).

In ferret, the microscopical lesions in lung such as severe lymphoplasmacytic perivasculitis and vasculitis, more type II pneumocytes, macrophages and neutrophils in the alveolar septa and alveolar lumen and a mild peribronchitis (Shi et al., 2020).

In wild cats (*Felis silvestris*), lungs revealed acute inflammation of alveoli, marked intra-alveolar hemorrhage, infiltration of macrophages were seen in alveolar and bronchiolar lumen and in addition to that marginated mononuclear cells were also seen in the pulmonary veins and arterioles (Watt *et al.*, 1993).

MHV strain (MHV-S) in mouse produces the following histological lesion such as mild olfactory mucosal necrosis, neuronal necrosis of olfactory bulbs and interstitial pneumonia (Barthold and Smith, 1983; Leibowitz *et al.*, 2010). In the lung revealed hyaline membrane and fibrin deposition, infiltration with lymphocytes, macrophages and neutrophils (Leibowitz *et al.*, 2010).

Parker's Rat Corona Virus (PRC) caused respiratory tract lesions of necrotizing rhinitis, laryngitis, tracheitis, bronchitis, hyperplasia and infiltration of lymphocytes, plasma cells and macrophages (Liang *et al.*, 1995; Bihun and Percy, 1995; Miura *et al.*, 2007; Percy and Barthold, 2016). Interstitial pneumonia characterized by leukocyte infiltration in the alveolar wall and type I pneumocytes hyperplasia was recorded (Funk *et al.*, 2009; Miura *et al.*, 2021). Type II pneumocytes can be a target cell of sialodacryoadenitis virus (SDAV) in respiratory infections and spontaneous animal model to study HCoVs in Rat coronavirus infection (Funk *et al.*, 2009).

Experimental infection with SARS-CoV in guinea pigs showed the lesions of alveolar walls thickening due to hyperplasia of type II pneumocyte, fibrin exudate within the interstitium, hyaline membrane formation and scattered fibroblast proliferation in the lungs (Liang *et al.*, 2005).

In birds, Infectious bronchitis (IB) is caused by Avian Corona Virus (AvCoVs) (Catroxo et al., 2011) belongs to the Gammacoronaviruses, subgenus Igacovirus (Zhuang et al., 2020). The microscopic lesions of IBV are loss of cilia, sloughing of nasal mucosal epithelial cells, epithelial cell hyperplasia, mucosal gland hypertrophy with heterophilic and lymphocytic infiltration. Pneumonia with hemorrhages, oedema, desquamation, fibrinous exudate with infiltration of lymphocytes and heterophils. Wild birds carry gammacoronaviruses asymptomatically and it could act as a genetic reservoir for future emerging pathogenic CoVs (Chu et al., 2011). In this regard, surveillance of wild birds is a very important.

Microscopic pathology on the cardiovascular system

Human

Heart revealed mild pericardial oedema (Liu et al., 2020), serosanguinous pericardial effusion (Fox et al., 2020), mild myocardial edema (Yao et al., 2020; Tian et al., 2020b), interstitial fibrosis (Tian et al., 2020b), interstitial mononuclear cells (Xu et al., 2020; Fox et al., 2020; Yao et al., 2020; Bradley et al., 2020; Tavazzi et al., 2020) and lymphocytic infiltration (Bradley et al., 2020; Liu et al., 2020; Wichmann et al., 2020). Endothelial cell inflammation was also observed (Varga et al., 2020).

Animals

Vascular necrosis and necrotizing myocarditis were observed in the heart of mountain lion (Stephenson *et al.*, 2013).

Microscopic pathology of blood vessels

Human

The presence of viral inclusions along with inflammatory cells and apoptotic bodies in the endothelial cells (Xiao *et al.*, 2020). Oedema in the alveolar capillaries and small vessels with the presence of fibrin thrombi, neutrophils and CD61+ megakaryocytes (Fox *et al.*, 2020).

Animals

Ferret systemic coronavirus showed granulomas around the vessels and includes adventitia of vessels.

In wild animals, cheetahs showed histological lesions in blood vessels such as systemic vasculitis and perivasculitis and cheetah virus compared to other FCoV strains did not s show cell fusion in the form of syncytia in in vitro studies (Evermann *et al.*, 1988).

In wild cats (*Felis silvestris*), the following histological lesions of marked thickening of the tunica adventitia, with infiltration of macrophages, lymphocytes and neutrophils in the medium-sized arteries and veins (Watt *et al.*, 1993).

Microscopic pathology on the liver and biliary system

Human

The liver revealed mild steatosis, patchy hepatic necrosis, Kupffer cell hyperplasia, sinusoidal dilatation (Xu et al., 2020; Yao et al., 2020; Tian et al., 2020b; Yao et al., 2020; Bradley et al., 2020; Varga et al., 2020; Schweitzer et al., 2020), lymphocytic infiltration (Xu et al., 2020; Tian et al., 2020a; Bradley et al., 2020) and endotheilitis (Varga et al., 2020).

Animals

Histological lesions in dogs revealed hepatocellular necrosis (Zappulli *et al.*, 2008).

In wild cats (Felis silvestris), the corona virus infection produces the marked thickening of serosal surface by fibrin deposition with diffuse leucocytic infiltration in the liver. Sequential stages of hepatic necrosis associated with syncytial formation were also observed (Watt et al., 1993).

In mouse hepatitis virus (MHV- Murine CoV) produces multifocal to coalesce acute necrosis with syncytia in the parenchymal and endothelial cells of liver. In addition to that syncytia was not seen in immunocompetent mice (Percy and Barthold, 2016). Microthrombi in sinusoids (Belouzard et al., 2012).

In avian IBV infection caused congestion of the central vein and hepatic sinusoids, hepatocellular degeneration, necrosis, thickening and hyalinization of the portal vein wall and infiltration of lymphocytes and heterophils (Xia *et al.*, 2018; Ghany and Elseddawy, 2019; Jackwood and De Wit, 2020).

Microscopic pathology on the kidney

Human

The SARS COV-2 infected kidney revealed segmental glomerulosclerosis (Menter *et al.*, 2020; Diao *et al.*, 2020), podocyte vacuolation, plasma accumulation in bowman's space, congestion, arteriosclerosis (Menter *et al.*, 2020; Su *et al.*, 2020; Kissling *et al.*, 2020), proximal tubular epithelial cell degeneration (Bradley *et al.*, 2020), necrosis, fibrin and hyaline thrombi (Yao *et al.*, 2020; Liu *et al.*, 2020) and interstitial lymphocytic infiltration (Yao *et al.*, 2020; Su *et al.*, 2020). ACE2 is to be upregulated in the COVID 19 patients and tubules showing positive to the immunostaining with SARS-CoV-2 nucleoprotein antibody (Yao *et al.*, 2020).

Animals

Histological lesions in dogs revealed tubular epithelial cell necrosis (Zappulli *et al.*, 2008).

Kidney of IBV infected birds revealed interstitial nephritis with hemorrhages, tubular degeneration and necrosis, edema of Bowman's capsule and dilated renal tubules with urate crystals, cast and lymphocytic and heterophilic infiltration (Xia *et al.*, 2018; Ghany and Elseddawy, 2019; Jackwood and De Wit, 2020).

Microscopic pathology of oesophagus, stomach and intestine

Human

The oesophagus showed lymphocytic infiltration. Degeneration and necrosis of gastric mucosa, congestion and edema, mononuclear dell infiltration (lymphocytes, monocytes and plasma cells) in the stomach and segmental dilatation, lymphoplasmacytic infiltration in the lamina propria of the intestine (Yao et al., 2020; Tian et al., 2020b; Liu et al., 2020; Xiao et al., 2020). Specific epithelial damage and endotheilitis were also recorded in the gastrointestinal tract.

Animals

CCoVs infection in dogs revealed chronic lymphoplasmacytic inflammation with mild fibrosis, crypts necrosis and villi necrosis (Zappulli *et al.*, 2008; Evermann *et al.*, 2005).

BCoVs infections in cattle produced the lesions of sloughed villi, villous atrophy, villous fusion, increased crypt depth, crypt micro-abscesses, crypt hyperplasia and hemorrhages in the lamina propria with mononuclear cell infiltration (Park *et al.*, 2007; Singh *et al.*, 2020).

In equine corona virus infection in equines revealed diffuse necrotizing enteritis (Shi *et al.*, 2020). Hemorrhages, attenuation of villi, loss of mucosal epithelium, crypt microabscesses, fibrin and pseudomembrane deposition, often associated with secondary bacterial colonization, infiltration of histiocytes, lymphocytes, neutrophils and eosinophils in the lamina propria and the submucosa along with fibrin thrombi mainly on post capillary submucosal venules (microthrombosis). In addition to that Crypt enterocytes showed single 1.5 to 3 µm diameter, irregularly round intracytoplasmic eosinophilic inclusion bodies within clear vacuoles up to 4 µm diameter and lymphocytolysis of Peyer's patches of ileum (Giannitti *et al.*, 2015).

In Ferret enteric CoV caused the lesions of hyperemic mucosa, atrophy, fusion and blunting and vacuolar degeneration and necrosis of the apical epithelium diffuse lymphocytic enteritis, with villus. The antigen was not localized in the large intestine, lymph nodes, spleen, esophagus, stomach and parotid salivary glands (Wise *et al.*, 2006). Systemic corona virus in ferret showed granuloma in various organs (Murray *et al.*, 2010; Autieri *et al.*, 2015; Lescano *et al.*, 2015; Doria-Torra *et al.*, 2016).

In swine corona virus infection in pigs revealed the lesions of villous atrophy and necrosis (Madson *et al.*, 2014), attenuation, swelling, flattening, karyomegaly and cytoplasmic vacuolation of superficial enterocytes (Park and Shin, 2014; Madson *et al.*, 2014; Wang *et al.*, 2016) crypt hyperplasia and syncytia formation (Stevenson *et al.*, 2013) in the intestine.

Vasculitis and fibrinoid nesrosis was seen in the small, large intestine and mesenteric lymph node of Mountain lion affected with corona virus infection (Stephenson *et al.*, 2013).

In the mouse, the lesions caused by enterotropic MHV strains *viz.* severe necrotizing enterocolitis, haemorrhages, attenuation of villi, enterocytes and endothelial cells of mesenteric vessels had syncytia, leukocytic infiltration, occasionally hemorrhages and presence of eosinophilic intracytoplasmic inclusions (Percy and Barthold, 2016; Compton *et al.*, 2004).

Guinea pigs affected with CoVs revealed the following lesions of blunting, fusion of villi, necrosis and syncytia in the enterocytes of distal ileum (Jaax *et al.*, 1990).

In rabbits infected with Rabbit Enteric Corona Virus (RECoV) revealed blunting of villi, vacuolation and necrosis of enterocytes, mucosal edema, neutrophilic and mononuclear cell infiltration. Lymphoid cell necrosis in the lymphoid follicles and increased mitotic figures and more cells in intestinal crypts (Descoteaux and Lussier, 1990; Cavanagh, 2005).

In Turkey CoVs produced the lesions in the intestine viz. villi atrophy, multifocal marked pseudostratification of the epithelium, lymphocytic infiltration, lymphoid aggregates in the lamina propria and submucosa, heterophilic and plasmacytic infiltration (Gomaa *et al.*, 2009; Wickramasinghe *et al.*, 2014).

Microscopic pathology of brain

Human

The brain revealed hypoxic ischemia, hyperemia, oedema (Menter *et al.*, 2020) and neuronal degeneration (Solomon *et al.*, 2020; Moriguchi *et al.*, 2020; Mahammedi *et al.*, 2020). Subarachnoid hemorrhages were observed in one case (Bradley *et al.*, 2020). The possible route of entry of the virus into the brain by hematogenous route by breaching blood–brain barrier or retrograde neuronal spread involving olfactory nerves (Zubair *et al.*, 2020). The possible route of entry of SARS-CoV-1 and MERS-CoV in mice models is olfactory nerve (Agrawal *et al.*, 2015; Solomon *et al.*, 2020).

Animals

In ECoVs infection in the brain showed Alzheimer Type II astrocytes in the cerebral cortex with hyperammonemia (Giannitti *et al.*, 2015; Fielding *et al.*, 2015). In wild cats, the brain showed dilated perivascular spaces in the white matter (Mwase *et al.*, 2015). IBV affected birds brain revealed neuronal cell degeneration, satellitosis and neuronophagia and perivascular lymphocytic cuffing (Xia *et al.*, 2018; Ghany and Elseddawy, 2019; Jackwood and De Wit, 2020).

Microscopic pathology of the spleen

Human

Spleen revealed atrophy, congestion, hemorrhages, infarction, lymphoid cell depletion and necrosis (Xu et al., 2020; Yao et al., 2020; Wichmann et al., 2020; Chen et al., 2020).

Animals

Feline corona virus causes blood vascular wall necrosis and sporadic smooth muscle hyperplasia are mainly due to perivascular macrophages (Drechsler *et al.*, 2011) and monocytes rarely infiltrate the wall and usually adhere to endothelial cells (Kipar *et al.*, 2005). Macrophages repaved by B-cells and plasma cells further progresses into the granuloma (Kipar and Meli, 2014). Lymphoid cells mainly T-and B-cells depletion in the Lymphoid tissues and in the splenic red pulp, increase in a number of macrophages were seen (Kipar *et al.*, 2001).

CCoVs produced multifocal hyperemia and diffuse severe lymphoid depletion in the spleen, it was also observed in thymus and lymph nodes (Zappulli *et al.*, 2008). IBV affected spleen showed thickening and hyalinization of central arterioles with endotheliosis and lymphoid cell depletion (Xia *et al.*, 2018; Ghany and Elseddawy, 2019; Jackwood and De Wit, 2020).

Microscopic pathology of skin

Human

Dense perivascular lymphoplasmacytic infiltration was seen surrounding the swollen blood vessels with extravasation of red blood cells and intraluminal thrombi (Gianotti *et al.*, 2020; Kolivras *et al.*, 2020). COVID-19 positive patients

showed parakeratosis, acanthosis, dyskeratotic keratinocytes, necrotic keratinocytes, acantholytic clefts along lymphocytes satellitisms (Gianotti *et al.*, 2020). The virus reaches the cutaneous tissue through blood vessels. Endothelial cells are expressing more ACE2 and they can easily bind to spike protein and leads to viral invasion into the skin tissue followed by producing pathogenesis. Vasculitis is observed in the viral invasion by the inflammatory cell infiltration. The immune response begins to activation of Langerhans cells causing cascade reaction (Sungnak *et al.*, 2020)

Microscopic pathology of testes and prostate Human

Extensive germ cell destruction, basement membrane thickening, peritubular fibrosis, congestion and infiltration of leucocytes (Xu et al., 2006) and prostate showed thrombi (Wichmann et al., 2020). Association of coronavirus family and orchitis in humans has been found (Xu et al., 2006). ACE2 receptor is present in seminiferous tubules, Leydig cells, Sertoli cells and spermatogonia (Li et al., 2020). Histiocytic and lymphocytic infiltration in the testicular tissue (Shen et al., 2020).

Microscopic pathology of the adrenal gland Human

The adrenal gland revealed systemic angiopathy (Menter et al., 2020)

Microscopic pathology of eye

Human

SARS-COV-2 affected patients revealed conjunctivitis, hyperemia in the conjunctiva and chemosis (Wu et al., 2020).

Animals

African lions (*Panthera leo*) revealed the histological lesion of bilateral panuveitis with retinal detachment. Lymphoplasmacytic infiltration with scattered macrophages were seen diffusely or in the small vein area. The pigmented layer of the iris is lost and melanophages were seen scattered in the thickened iris and retina. Anterior chamber revealed eosinophilic proteinaceous exudate (Mwase *et al.*, 2015).

Microscopic pathology of the placenta

Human

The placenta from covid 19 affected patient revealed inflammatory infiltrates in the placenta and funisitis (Baud et al., 2020). SARS Cov 2 affected placenta showed epithelial damage and infiltration of inflammatory cells (Polak et al., 2020).

Discussion

Various animal and human diseases caused by corona viruses indicate the widespread prevalence in the ecosystem due to its change in shape, formation of new variant strains leads to new emergence of coronavirus in the world and it is now the recent outbreak is also the evidence of the nature

of the coronavirus. Corona virus affects most of all animals, birds, human beings and this might be caused the control of this disease is very critical and difficult.

CoVs is having positive-strand RNA viruses is having the ability to acquire genetic diversity by having some typical features of infidelity of the RNA-dependent RNA polymerase, the high frequency of homologous and heterologous RNA recombination and the large genomes (Gouilh *et al.*, 2011). This kind of genetic variability of this CoVs confirms its high potential of evolution that sometimes allowing them to overcome species barriers and host specificity (Baric *et al.*, 1995; Baric *et al.*, 1997; Thackray and Holmes, 2004).

The genomic diversity of CoVs produces their variation in species adaptation related to receptor binding ability, tissue tropism, causing localized to systemic diseases affecting different organs. SARS-CoV uses ACE2 as a receptor and SARS-COV is mainly infects ciliated bronchial epithelial cells and type II pneumocytes, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4) and infects non-ciliated bronchial epithelial cells and type II pneumocytes (Cui *et al.*, 2019).

The microscopical lesions in the animals and human cases are more or less similar mainly produces vascular thrombosis, fibrinous exudation, syncytia formation, lymphoid organ depletion and intestinal epithelial cell damage. Based on the lesions in animals and human beings the animals could be used as a model, important ring in epidemiological chain to be studied and monitored (Zappulli *et al.*, 2020). The SARS Cov2 infection-causing fatality mainly by DAD, coagulopathy and hemodynamic derangements.

CONCLUSION

The SARS CoV-2 infection-causing fatality mainly by DAD, coagulopathy and hemodynamic derangements. Pathogenesis, epidemiological, clinicopathological findings are essential to find out the target organ and treat the patient accordingly. The SARS CoV-2 virus is mainly affecting the respiratory system followed by the immune, cardiovascular, kidneys, gastrointestinal tract, testes and nervous system and is more. The findings are more severe in comorbid patients and elderly patients. The microscopical lesions in animals more or less similar to the human cases. In this regard, the animals could be used as an experimental animal model to study SARS CoV-2.

Conflict of interest: None.

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