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MICROSCOPICAL FINDINGS IN COVID-19: WHICH DIVERSITY?

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ABSTRACT

Purpose: The main goal of this paper is to present a review study of the different publications reporting histopathological findings regarding SARS-COV-2 from the beginning of the epidemic till today in order to use the overall finding to clarify the pathogenesis.
Methods: A literature review was carried out. Relevant papers were identified and Data related to general settings and pathological features of patients COVID-19 were extracted, classed and compared.
Results: Seven publications were examined. Overall 80 patients COVID-19 underwent histopathological examination. There was a general predominance of males. Range of age mean (50 - 78.5). The features of the exudative and proliferative phases of Diffuse Alveolar Disease (DAD) were noted in the diverse series: capillary congestion, necrosis of pneumocytes, hyaline membrane, interstitial edema, pneumocyte hyperplasia and reactive atypia. Although, thromboembolic events were as well reported in patients with COVID-19.
Conclusion and perspectives: We try to understand the pathogenesis of SARS-CoV-2 and the molecular events triggered by its binding to target organs receptors, mainly the lung. It will be probably the subject of new therapeutic methods.

Keywords: CoVID-19 pathogenicity; Diffuse alveolar damage; Microthrombi; SARS-CoV-2.

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INTRODUCTION

The First case was reported from Wuhan, in China, on 31 December 2019, the ongoing outbreak of a novel coronavirus SARS–CoV-2 causes great global concerns. Based on the advice of the International Health Regulations Emergency Committee (***IHREC***) and the fact that the other countries also reported cases, the WHO declared that the outbreak of COVID-19 constitutes an international Public Health Emergency on 30 January 2020. As the coronavirus pandemic has unfolded, all eyes have been on the medical workers and public health disease detectives fighting on the front lines to bring the coronavirus under control. However, little is known about the causes of death and the virus's pathologic features. Many studies on COVID-19 epidemiology and clinical characteristics have been published, but data on pathologic changes for this disease are still scarce. New studies were be done to facilitate understanding of the pathogenesis of COVID-19 and improve clinical strategies against the disease. So far, however, histopathologic data based on routine biopsy samples or autopsies are still lacking. Nevertheless, postmortem testing is helpful and important when it is balanced by the logistical feasibility of doing it. Despite modern diagnostic tests, pathology is still of great importance and may be a key to understanding the biological characteristics of SARS–CoV-2 and the pathogenesis of the disease. Some findings will represent true virus related pathology, while others will reflect superimposed processes or unrelated illnesses.

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METHODS:

Our study is a systematic review of microscopic findings of COVID-19 published between February and June 2020. A documentary research was carried out on Medline database using PubMed and also on Google Scholar. The following keywords were used:

- (COVID-19 OR SARS-CoV-2 OR 2019-nCoV)
- AND (autopsy OR biopsy sample OR pathological findings OR pathogenicity)

Inclusion criteria: We have taken into consideration manuscripts describing general sitting and pathological findings. Relating to these later, we considered the damages of the organs mentioned in at least two articles. The following criteria are included pathological features of 'Lungs', 'Vessels', 'Heart', 'kidneys' and 'Liver'.

Exclusion criteria: We have excluded the pathological features related to the organs noted only in one publication.

Hence, the histological features of bowel, pharynx, adrenal glands, bone marrow, lymph node and brain were excluded.

Data extraction: In each study, there is some missing data and therefore each one when is taking in consideration alone will not be efficient. We proposed to represent all of data in a complementary way between seven studies taking into account our proposed inclusion and exclusion criteria's. Table I and Table II summarize the data collected.

Data criteria's presentation: We have separated the data into two categories that are:

- General settings: relating to patient history, specimen collection, age, sex
- **Pathological features: summarize** histologic changes in the following organs: 'Lungs' , 'Vessels' 'Heart', 'kidneys' and 'Liver'

Data synthesis: For each pathological finding, we computed the weighted means based on the sample size of each study included in the synthesis.

RESULTS:

Between February and June 2020, seven publications were examined. The Three first papers were from China [1- 3] in reported cases. Subsequently, four more series were published by Italian [4] Switzerland [5], American [6] and German [7] researchers. The largest series are those from Italy and Switzerland with 38 and 21 respectively. Overall 80 patients COVID-19 underwent histopathological examination (n=80), 35 cases on complete autopsies, 43 on post-mortem biopsies and on living samples in 2 cases as shown in **Table I**.

We conducted a comparative examination for all the studies included and we have gathered the different features that are summarized as follow:

Features	Observation and Remarks
Sex: male-female ratio	predominance of male sex
Age	min(mean)=50 ; max(mean)=78.5
Length of hospital Stay	have a range between 0 hour and 28 days
Number of intubated patients	15/35 = 42.85%
Time between death and autopsy	have a range between 1 hour and 5 days
Preexisting of chronic medical conditions:	100% confirmed by all studies

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Table I: General settings in different studies

	Sufang T et al. February 20, 2020 (China)	Zhe Xu et al. February 25, 2020 (China)	Sufang T et al. March 20, 2020 (China)	Luca C et al. April 22, 2020 (Italy)	Menter et al. May 4,2020 (Switzerland)	Lisa M.B et al. May 5, 2020 Okalahoma, (USA)	Wichmann D et al. May 6, 2020 (Germany)
General settings							
Cases	n=2	n=1	n=4	n= 38	n=21	n=2	n=12
Complete autopsies	-	-	-	-	Yes	Yes	Yes
Post-mortem biopsies	-	Yes	Yes	Yes	-	-	-
Living samples	Yes	-	-	-	-	-	-
Sex: male-female ratio	1/1	1/0	3/1	33/5	17/4	2/0	9/3
Mean age (years)	78.5 [73-84]	50	73 [59 – 81]	69 [32-86]	76 [53 – 96]	59.5 [42-77]	73 [52- 87]
Length of hospital Stay (hours, days, range)	24.5 days (20-29)	6 days	28 days (15-25)	6.87 days (1-23)	5.7 days (0-16)	0- few hours	-
Number of intubated patients		-	-	-	6/21 (30%)	2/2 (100 %)	7/12 (58%)
Time between death and autopsy (hours, days, range)	-	-	1 h	-	33.2 h [11- 84.5]	-	1-5 days
Preexistence of chronic medical conditions	2/2	1/1	4/4	38/38	21/21	2/2	12/12

All of The authors cited that autopsies were performed in Airborne Infection Isolation Autopsy Rooms and the personnel used the correct Personal Protection Equipment (PPE), according to "Engineering control and PPE recommendations for autopsies".

Tissues were predominantly fixed in 4% buffered formalin and processed under standard biosafety measures to slides stained with Hematoxylin–eosin. Histological evaluation was performed by pathologists with expertise in the field. Additional samples from selected cases were fixed in Glutaraldehyde for electron microscopy in Italy [4] and USA [6].

The histopathological findings are summarized in **Table II**.

Table II: Pathological features in different studies

		Sufang T et al. February 20, 2020 China	**Zhe Xu et al. February 25,2020 China**	**Sufang T et al. March 20, 2020 China**	**Luca C et al. April 22, 2020 Italy**	**Menter et al. May 4, 2020 Switzerland**	**Lisa M.B et al. May 5, 2020 Oklahoma, USA**	**Wichmann D et al May 6, 2020 Germany**
	Pathological features							
Lung	Pulmonary capillary congestion	1/2	1/1	4/4 100%	38/38 100%	21/21 100%	38/38 100%	11/12 92%
	Diffuse alveolar damage (DAD), exudative, hyaline membrane	1/2	1/1	3/4 75%	Mean 31 [0-38]	16/21 76%	Mean 31 [0-38]	8/12 66%
	DAD, proliferative	2 /2	-	1/4 25%	16,41 [0-38]	8/21 38%	16,41 [0-38]	2/12 16%
	Reactive pneumocytes and syncytial cells	2/2	1/1	2/4 50%	19/38 50%	11/21 52%	19/38 50%	4/12 33%
	Micro-thrombi of alveolar capillaries	-	-	1/4 25%	33/38 86%	5/11 45%	33/38 86%	4/12 33%

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	Bronchopneumonia, diffuse	-	-	1/4 25%	-	6/21 29%	-	-
	Bronchopneumonia, focal	-	-	-	-	4/21 19%	-	3/12 25%
	Emphysema	-	-	-	-	6/21 29%	-	4/12 33%
	Pulmonary embolism	-	-	-	-	4/21 19%	-	4/12 33%
	Prominent lymphoid infiltrates	1/2 50%	1/1	2/4 50%	31/38 81%	3/21 14%	31/38 81%	-
	Pulmonary hemorrhage	1/2 50%		1/4 25%	33/38 87%	3/21 14%	33/38 87%	-
	Pulmonary edematous	1/2	1/1	-	37/38 97%	-	37/38 97%	-
	Lung cancer	2/2	-	-		-	-	1/12 8%
	Amyloidosis of pulmonary vessels	-	-	-	-	3/21 14%	-	-
	Severe mucous tracheitis	-	-	-	-	6/21 29%	-	-
	Intracytoplasmic viral inclusions	Yes	-	-	Yes	-	Yes	-
	Electron microscopy	-	-	-	Yes	Yes	Yes	-
Vessels	Vasculitis	-	-	-	-	1/21 5%	-	-
	Deep venous thrombosis	-	-	-	-	-	-	7/12 58%
Heart	Myocardial hypertrophy	-	-	2/4 50%	-	15/21 71%	-	6/12 50%
	coronary heart disease	-	-	-	-	-	-	9/12 75%
	Senile amyloidosis	-	-	-	-	6/21 29%	-	-
	Peracute myocardial cell necrosis	-	-	-	-	3/21 14%	-	-
	Acute myocardial infarction	-	-	-	-	1/21 5%	-	-
	Atherosclerosis	-	-	-	-	-	-	7/12 58%
Kidney	Acute tubular damage	-	-	-	-	14/15 93%	-	-
	Shock kidneys	-	-	-	-	-	-	1/12 8%
	Disseminated intravascular coagulation	-	-	-	-	3/17 18%	-	-
	Hypertensive nephropathy	-	-	-	-	2/17 12%	-	-
	Diabetic nephropathy	-	-	-	-	2/17 12%	-	-
	renal nephrosclerosis	-	-	-	-	-	-	1/12 8%
Liver	Steatosis	-	1/1	1/4 25%	-	7/17 33%	-	2/12 16%
	Chronic congestion	-	-	1/4 25%	-	-	-	2/12 16%
	Shock necrosis	-	-	1/4 25%	-	5/17 29%	-	3/12 25%

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ASH/NASH	-	-	-	-	3/17 24%	-	-
cirrhosis	-	-	1/4 25%	-		-	-
Immunohistochemistry	-	CD4, CD8, CD38	CD3, CD4, CD8, CD20, CD5, CD23	CD45, CD68, CD61, TTF1, P40, Ki67	CD3, CD4, CD8, CD20, CD68, MUM1, TTF1, fibrin TTR	CD45, CD68, CD61, TTF1, P40, Ki67	CKAE1/AE3

We noted the following pathologic findings:
Microscopic changes in the lungs varied among the seven studies. Nevertheless, they were all consistent with pulmonary capillary congestion (96.25%) and Diffuse Alveolar Damage (DAD) (76.25%), reveling the importance of exudative phase of the disease. Microthrombi of alveolar capillaries (55%) and pulmonary edema (50%) were largely observed by Luca C et al [4] and in a comparable way between the other studies except those from China [1; 2]. Reactive pneumocytes and syncytial cells were moderately reported by different authors (48.75%). Prominent lymphoid infiltrates (48.75%) and pulmonary haemorrhage (48.75%) were frequent in Italian's study. They were moreover reported in few cases by the other authors except those from Germany [7]. DAD in proliferative phase were mild (36.5%), principally reported by Menter et al in 38%. Emphysema were only reported by Switzerland [5] and German [7] studies in 29% and 33% respectively. Similarly pulmonary embolism in 19% and 33%. Bronchopneumonia in focal or diffuse form were uncommon. Only Menter et al in 14% and 29% respectively described amyloidosis of pulmonary vessels and severe mucous tracheitis [5]. DAD were associated to lung cancer in three cases from Germany (n=1) [7] and China (n=2) [1].
The representation of lung lesions in all patients was distributed as showen in **Table III**.

Table III: Distribution of lung lesions

Pathological features of lung	Percentage
Pulmonary capillary congestion	96.25%
Diffuse alveolar damage (DAD), exudative hyaline membrane	76.25%
Microthrombi of alveolar capillaries	55%
Pulmonary edematous	50%
Reactive pneumocytes and syncytial cells	48.75%
Prominent lymphoid infiltrates	48.75%
Pulmonary haemorrhage	48.75%
DAD, proliferative	36.5%
Emphysema	12.5%
Bronchopneumonia, focal	11.25%
Pulmonary embolism	10%
Bronchopneumonia, diffuse	8.75%
Amyloidosis of pulmonary vessels	7.5%
Lung cancer	3.75%
Severe mucous tracheitis	3.75%

Intracytoplasmic viral inclusions were observed in two cases, morphologically in one case by Sufang T et al [1] and through an ultrastructural examination in another case by Luca C [4].
Transmission electron microscopy revealed fibrin precipitates within alveolar capillaries in two other cases [5].
Immunohistochemistry reactions were performed on selected cases in 6 studies, Chinese [2, 3] , Italian [4], German [7], American [6] and Switzerland [5] using different antibodies (CD45, CD68, CD61, TTF1, p40, CK AE1/AE3, CD3, CD4, CD8, MUM1, CCR6) to better characterize inflammatory infiltrate, epithelial cells and fibrosis as summarized in **Table II**.
Concerning vessels findings, deep venous thrombosis reported by Wichmann D et al in Germany in 58% [7]. Moreover, vasculitis were cited in one of 21 cases in Switzerland by Menter et al (5%) [5].
Heart findings described in four studies (Switzerland [5], USA [6], China [3] and Germany [7]). They reflect superimposed processes correlating with the high prevalence of hypertension in different studies.

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First and foremost myocardial hypertrophy and atherosclerosis. Peracute myocardial cell necrosis reported only in three cases (14%) by Menter et al. (Table II).

Samples of Kidney were examined in three studies (Switzerland, USA and Germany): acute tubular damage was detectable in 93% (14/15) and disseminated intravascular coagulation in 18% (3/17) according to Menter et al. [5]. Shock kidneys was seen in 8% (1/12) as reported by Wichmann D, et al. [7]. Apart from findings related to SARS–CoV-2 infection, patients showed other histopathologic findings related to their chronic preexisting conditions. As like as hypertensive nephropathy, diabetic nephropathy and renal nephrosclerosis. (Table II)

The liver biopsy specimens were considered in five studies (Switzerland [5], USA [6], 2 from China [2; 3] and Germany [7]). The lesions mainly included shock necrosis (57%) and steatosis (32%). Chronic congestion, ASH/NASH and cirrhosis were identified in patients with chronic liver disease.

DISCUSSION

At first of their publications, defiance of authors has largely diverged. Sufang T et al and Zhe Xu et al, believe it was imperative to report the findings of routine histopathology for better understanding the mechanism by which the SARS-CoV-2 causes lung injury. They showed through their report cases that the pathologic basis of the COVID-19 pneumonia are diffuse alveolar damage, hyaline membrane formation and pneumocyte atypical hyperplasia [1-3]. Further, to appreciate the pathogenesis of SARS-COV-2, studies including more patients with different ages and physiological backgrounds were required. After, Luca C et al [4], Menter et al [5] and Wichmann D et al [7] have included a large series and they got new sightings. The main relevant finding was the presence of platelet-fibrin thrombi in small arterial vessels [4]. Major findings that implied an impaired microcirculation include pulmonary capillarostasis and the presence of microthrombi in the lungs and kidneys despite anticoagulation [5]. The high incidence of thromboembolic events suggests an important role of SARS-COV-2 induced coagulopathy [7]. These findings provide an insight into the complexity of COVID-19 pathophysiology. They fit into the clinical context of coagulopathy which dominates in these patients and which is one of the main targets of therapy. The above studies have shown that changes in the kidney, liver and heart are limited or related to the underlying diseases. They suggested that additional studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19–related death, as well as possible therapeutic interventions to reduce it.

Correlating to recent studies, genetic and molecular exploration of SARS-COV-2 enable to enlighten pathogenicity of this virus. Herein, we summarize the probable SARS-COV-2 pathways. The genetic sequence revealed that the 2019-nCoV belongs to the β-coronavirus genus, with a 79.0% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV [8]. It has four major structural proteins: the spike surface glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein [9, 10]. The spike protein binds to host receptors via the receptor-binding domains of angiotensin-converting enzyme 2 (ACE2) [3, 11]. This protein mediates receptor binding and membrane fusion. It contains two subunits, S1 and S2. S1 encloses a receptor-binding domain (RBD), which is responsible for recognizing and binding with the cell surface receptor. S2 subunit is the "stem" of the structure, which contains other basic elements needed for the membrane fusion. The spike protein is the common target for neutralizing antibodies and vaccines [12]. The expression and distribution of the ACE2 in human body may indicate the potential infection routes of 2019-nCoV. Through the developed single-cell RNA sequencing (scRNA-Seq) technique and single-cell transcriptomes based on the public database, researchers analyzed the ACE2 RNA expression profile at single-cell resolution. High ACE2 expression was identified in type II alveolar cells (AT2) of lung [13, 14], esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes [15], myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [12, 13]. Moreover, ACE2 expressed in endothelial cells from small and large arteries, in arterial smooth muscle cells, and in Leydig cells and Sertoli cells (at protein level) [3]. These findings indicated that those organs with high ACE2-expressing cells should be considered as potential high risk for 2019-nCoV infection [12]. Cells of the Immune system such as B and T lymphocytes, and macrophages were consistently negative for ACE2 [16]. Inoculation of the 2019-nCoV onto surface layers of human airway epithelial cells in vitro causes cytopathic effects and cessation of the cilium beating of the cells. Initial plasma IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and vascular endothelial growth factor concentrations were higher in 2019-nCoV-infected patients as compared to healthy controls. Furthermore, ICU patients showed higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α than non-ICU patients. These results suggest that immunopathology may

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also play a relevant role in the development of disease severity [8]. Hence, the emergence of the idea of using immunomodulators by some researchers. The mentioned mechanism may include all of tissue with ACE expression.

Nevertheless, the foremost pathological findings interest the lung, which makes it possible to raise the question, does the alveolar microenvironment promote the manifestation of SARS-COV-2? To answer this question, the authors propose to put on highlight of various airways components and their changes during the infection. Alveolar septa contain Type I alveolar cells, representing about 40% of the epithelial cell population but lining 90% of the alveolar surface. Type II alveolar cells, approximately 60% of the cells, covering only 10% of the alveolar surface area. The free surface of type II alveolar cells is covered by short microvilli with high ACE2 expression. The cytoplasm displays dense membrane-bound lamellar bodies, representing secretory granules containing pulmonary surfactant, which spreads over a thin layer of fluid that normally coats the alveolar surface [17]. The alveolar macrophages, also called dust cells derive from bone-marrow monocytes and are frequently seen in the alveolar lumen and interstitium. They are sentinel cells migrating over the luminal surface of the alveolus, activated by inflammatory cytokines, and contribute to the endothelial cell damage. Alveolar dendritic cells (DC) actively monitor for antigens the alveolar air space and take them up for presentation to T cells. The lack of antiviral cytokine response (IFN-α, IFN-β, and IL-12p40), moderate up-regulation of proinflammatory cytokines (TNF-α and IL-6), signifcant up-regulation of inflammatory chemokines (MIP-1α, RANTES, IP-10, and MCP-1), induction of chemokine receptors (CCR) expression and strong expression of TRAIL observed in SARS-CoV infected DCs suggested possible mechanisms of immune escape and amplification of immunopathology in SARS [18]. Dendritic processes extend into the surfactant layer. Alveolar capillaries are lined by continuous endothelial cells juxtaposed to type I alveolar cells through a dual basal lamina produced by these two cells. They contain angiotensin converting enzyme ACE1 [17] and express ACE2 [3]. Therefore, proinflammatory substances cause the attachment of neutrophils to endothelial cells releasing proteolytic enzymes and damage them. The alveolar-capillary barrier becomes permeable and cells and fluid enter the interstitium and alveolar space. Following the endothelial cell injury, Type I alveolar cells die, denuding the alveolar side of the barrier. Fibrin and cell debris accumulated in the alveolar lumen form a hyaline membrane. Fibrin inhibits the synthesis of surfactant by type II alveolar cells, which proliferate to reestablish the production of surfactant, and differentiate into type I alveolar cells. If the initial damage is severe, interstitial fibroblasts proliferate, progressive interstitial and intra-alveolar fibrosis develops, and gas exchange is seriously affected [17]. These data remain to be approved and to lead to new therapeutics approach.

Besides respiratory failure, the cause of death was multiorgan failure in 16% and cardiac arrest in 9%. In addition to that, high incidence of thromboembolic events in patients with COVID-19 were found with an increased D-dimer levels, a sign of coagulopathy [7]. This can be explain by releasing of tissue factor (TF) following the endothelial cell injury, which may be associated with bacterial superinfection. TF binds to factor VIIa to convert factor X into factor Xa and initiate the common pathway of blood clotting and to a subsequent thrombin generation [17]. Moreover, the binding of TF to its natural ligand, factor VII, leads to intracellular signalisation which induces the synthesis of proinflamatory cytokines, with subsequent leukocyte activation and majoration of the pathophysiological process. Besides, the TF pathway inhibition can be an alternative therapeutic in severe COVID-19. Influential evidence, however, prospective studies are needed to confirm and validate this hypothesis.

CONCLUSION & PERSPECTIVES:

Understanding the pathogenesis of SARS-COV-2 and the molecular events triggered by its binding to these receptors at target organs may be the subject of new therapeutic interventions.

FUNDING AND COMPETING INTERESTS:

None declared.

REFERENCES

1. 1 Sufang T et al. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. Journal of Thoracic Oncology.
2. 2 Zhe X et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. www.thelancet.com/respiratory Vol 8 April 2020
3. 3 Sufang T et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through post-

ISSN: 2351-8200
JMSR 2020; Vol. VII, N 2: 870- 877

mortem core biopsies. Modern Pathology 2020; doi:10.1038/s41379-020-0536-x
4. 4 Luca C et al. Pulmonary post-mortem findings in a large series of COVID-19 cases from Northern Italy. https://doi.org/10.1101/2020.04.19.20054262.
5. 5 Menter T et al. Post- mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. doi:10.1111/HIS.14134
6. 6 Lisa MB, Eric JD, Edana S, Subha G, Sanjay M. COVID-19 Autopsies, Oklahoma, USA. Am J Clin Pathol 2020;XX:1-9 2020 May 5;153(6):725-733.
7. 7 Wichmann D et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med. 2020; Epub ahead of print. German COVID-19 Autopsy Data Show Thromboembolism, 'Heavy' Lungs
8. 8 Jia L et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. Journal of Medical virology DOI: 10.1002/jmv.25709.
9. Aiping W et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe 2020
10. Xing-Y G et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013; 503(7477):535-538.
11. Jun L et al. Crystal structure of the 2019-nCoV spike receptor-binding domain bound with the ACE2 receptor. BioRxiv 2020
12. Hao X, Liang Z, Jiaxin D, Jiakuan P, Hongxia D, Xin Z, Taiwen L, Qianming C. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science (2020) 12: 8; https://doi.org/10.1038/s41368 020-0074-x
13. Xin Z, Ke C, Jiawei Z, Peiyi H, Jie H, Zeguang H. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. Front. Med. http://journal.hep.com.cn/fmd/EN/ 10.1007/s11684-020-0754-0 (2020).
14. Hao Z et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. Preprint at https:// www.biorxiv.org/content/10.1101/2020.01.30. 927806v1 (2020).
15. Xiaoqiang C et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Preprint at https://www.biorxiv.org/content/10.1101/ 2020.02.03.931766v1 (2020).
16. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, Van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631–637. DOI: 10.1002/path.1570
17. Abraham LK, Laura LT. Histology and cell biology. An Introduction to Pathology. Canada: Elsevier, 2016, 4th ed p. 429.
18. Lau YL, Peiris JSM, Law HKW. Role of dendritic cells in SARS coronavirus infection. Hong Kong Med J 2012; 18 (Suppl 3):S28-30