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| ANA 404: INTRODUCTION TO HISTOPATHOLOGY | April 17  2020 | |
| COVID-19; THE WORLDWIDE EPIDEMIC. | | OSAMOR MICHELLE 16/MHS01/213 |

As of December 2019, an outbreak of pneumonia of an unknown aetiology was discovered in Wuhan City, Hubei province of china; after which a novel coronavirus was identified and termed COVID-19

What is coronavirus?

According to World Health Organisation (W.H.O), Coronavirus are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging common cold to more severe diseases such as Middle East Respiratory Syndromes (MERS) and Severe Acute Respiratory Syndrome (SARS).

COVID-19

Background:

The first 27 cases of pneumonia of unknown aetiology were discovered on the 31st of December, 2019 in Wuhan city (H. Lu *et al*., 2020). Wuhan is the most populous city in central China with a population exceeding 11 million. These patients most notably presented with clinical symptoms of dry cough, dyspnea, fever, and bilateral lung Cases were all linked to Wuhan's Huanan Seafood Wholesale Market, which trades in fish and a variety of live animal species including poultry, bats, marmots and snakes (tang *et al*., 2020).The causative agent was identified from throat swab samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC) on 7th January 2020, and was subsequently named Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2). As of January, 2020; it had been discovered that the virus had spread to 19 countries with a total of 11791 confirmed cases, including 213 deaths. It was since then that the W.H.O has declared the virus a Public Health Emergency of International concern and gave it the name; COVID-19 (Yu-Ju Wu *et al*., 2020). In general, COVID-19 is an acute resolved disease but it can also be deadly, with a 2% case fatality rate. Severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure. As of Feb 15, about 66 580 cases have been confirmed and over 1524 deaths. However, no pathology has been reported due to barely accessible autopsy or biopsy (Zhe Xu *et al*., 2020). Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin of COVID-19 (Rothan *et al*., 2020).

To date, most SARS-CoV-2 infected patients have developed mild symptoms such as dry cough, sore throat, and fever. The majority of cases have spontaneously resolved. However, some have developed various fatal complications including organ failure, septic shock, pulmonary oedema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS) (Chen *et al*., 2020). 54.3% of those infected with SARS-CoV-2 are male with a median age of 56 years. Notably, patients who required intensive care support were older and had multiple comorbidities including cardiovascular, cerebrovascular, endocrine, digestive, and respiratory disease.

Aetiology

In preliminary report, complete viral genome analysis reveals that the virus shares 88% sequence identity to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, but more distant from severe acute respiratory syndrome coronavirus (SARSCoV) (Lu *et al*., 2020). Hence, it was temporarily called 2019-novel coronavirus (2019-nCoV). Coronavirus is an enveloped and single-stranded ribonucleic acid named for its solar corona like appearance due to 9-12 nm-long surface spikes (Wang *et al*., 2020). There are four major structural proteins encoded by the coronaviral genome on the envelope, one of which is the spike (S) protein that binds to angiotensin-converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell (Kirchidoefer *et al*., 2016, Xu *et al*., 2020). On February 11, 2020, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses finally designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on phylogeny, taxonomy and established practice (Gorbalenya *et al*., 2020). Soon later, WHO named the disease caused by this coronavirus as Coronavirus Disease 2019 (COVID-19) (W.H.O , 2020). On the basis of current data, it seems that COVID-19 might be initially hosted by bats, and might have been transmitted to humans via pangolin (Lam *et al*., 2020) or other wild animals (Zhao *et al*., 2020, Zhang *et al*., 2020) sold at the Huanan seafood market but subsequent spread via human-to-human transmission.

Pathogenesis

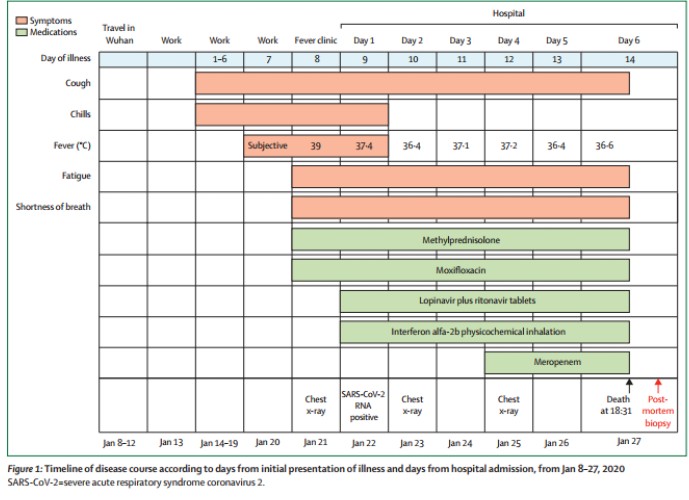
Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms (Zhu *et al*., 2019, W.H.O, 2020). Other than SARS-CoV-2, there are six known coronaviruses in humans: HCoV-229E, HCoV-OC43, SARS-CoV, HCoVNL63, HCoV-HKU1, and MERS-CoV (Li *et al*., 2019, Su *et al*., 2016, Chen *et al*., 2020). Coronavirus has caused two large-scale pandemics in the last two decades: SARS (Peiris *et al*., 2004) and MERS (Zaki *et al*., 2012, Zhou *et al*., 2020).

To detect the infection source of COVID-19, China CDC researchers collected 585 environmental samples from the Huanan Seafood Market in Wuhan, Hubei Province, China on 1 January and 12 January 2020. They detected 33 samples containing SARS-CoV-2 and indicated that it originated from wild animals sold in the market (Chinese center for disease control and prevention, 2020). Then, researchers used the lung fluid, blood, and throat swab samples of 15 patients to conduct laboratory tests. These laboratory tests found that the virus-specific nucleic acid sequences in the sample are different from those of known human coronavirus species. Laboratory results also indicated that SARSCoV-2 is similar to some of the beta (β) coronaviruses genera identified in bats (Yang *et al*., 2020, Wang *et al*., 2020, Tang *et al*., 2020), which is situated in a group of SARS/SARS-like CoV (Zhang *et al*., 2020). To conduct next-generation sequencing from bronchoalveolar lavage fluid and cultured isolates, researchers enrolled nine inpatients in Wuhan with viral pneumonia and negative in common respiratory pathogens. The results of this next-generation sequencing indicated that SARS-CoV-2 was more distant from SARS-CoV (with about 79% sequence identity) and MERS-CoV (with about 50% sequence identity) than from two bat-derived SARS-like coronaviruses – bat-SL-CoVZC45 (with 87.9% sequence identity) and bat-SL-CoVZXC21 (with 87.2% sequence identity) (Roujian *et al*., 2020). Studies also reported that COVID-19S-protein supported strong interaction with human ACE2 molecules despite the dissimilarity of its sequence with that of SARS-CoV (Yang *et al*., 2020, Xu *et al*., 2020).

Histopathological findings

In general, COVID-19 is an acute resolved disease but it can also be deadly, with a 2% case fatality rate. Severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure. As of Feb 15, about 66 580 cases have been confirmed and over 1524 deaths. However, no pathology has been reported due to barely accessible autopsy or biopsy. Here, we investigated the pathological characteristics of a patient who died from severe infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by postmortem biopsies.

From a previous article, A 50-year-old man was admitted to a fever clinic on Jan 21, 2020, with symptoms of fever, chills, cough, fatigue and shortness of breath. He reported a travel history to Wuhan Jan 8–12, and that he had initial symptoms of mild chills and dry cough on Jan 14 (day 1 of illness) but did not see a doctor and kept working until Jan 21 (figure 1). Chest x-ray showed multiple patchy shadows in both lungs (appendix p 2), and a throat swab sample was taken. On Jan 22 (day 9 of illness), the Beijing Centers for Disease Control (CDC) confirmed by reverse real-time PCR assay that the patient had COVID-19. He was immediately admitted to the isolation ward and received supplemental oxygen through a face mask, according to the article. He was given interferon alfa-2b (5 million units twice daily, atomisation inhalation) and lopinavir plus ritonavir (500 mg twice daily, orally) as antiviral therapy, and moxifloxacin (0·4 g once daily, intravenously) to prevent secondary infection. Given the serious short ness of breath and hypoxaemia, methylprednisolone (80 mg twice daily, intravenously) was administered to attenuate lung inflammation.



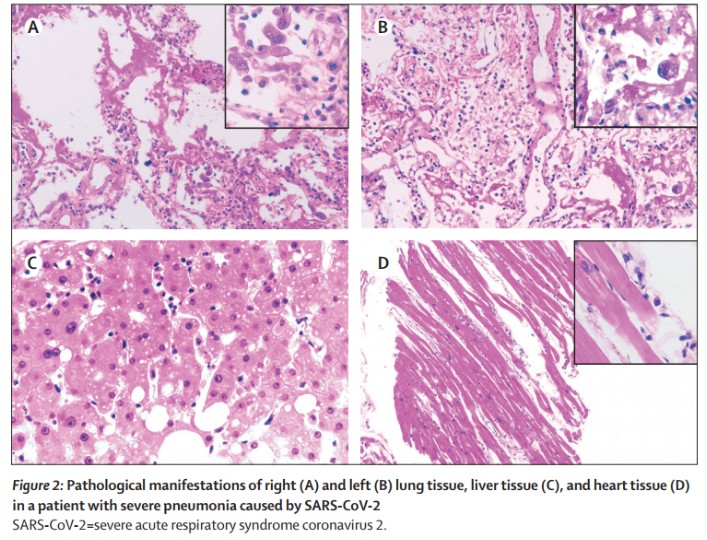
Laboratory tests results are listed in the appendix (p 4). After receiving medication, his body temperature reduced from 39·0 to 36·4 °C. However, his cough, dyspnoea, and fatigue did not improve. On day 12 of illness, after initial presentation, chest x-ray showed progressive infiltrate and diffuse gridding shadow in both lungs. He refused ventilator support in the intensive care unit repeatedly because he suffered from claustrophobia; therefore, he received high-flow nasal cannula (HFNC) oxygen therapy (60% concentration, flow rate 40 L/min). On day 13 of illness, the patient’s symptoms had still not improved, but oxygen saturation remained above 95%.

In the afternoon of day 14 of illness, his hypoxaemia and shortness of breath worsened. Despite receiving HFNC oxygen therapy (100% concentration, flow rate 40 L/min), oxygen saturation values decreased to 60%, and the patient had sudden cardiac arrest. He was immediately given invasive ventilation, chest compression, and adrenaline injection. Unfortunately, the rescue was not successful, and he died at 18:31 (Beijing time). Biopsy samples were taken from lung, liver, and heart tissue of the patient. Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates (figure 2A, B). The right lung showed evident desquamation of pneumocytes and hyaline mem brane formation, indicating acute respiratory distress syndrome (ARDS; figure 2A).

The left lung tissue displayed pulmonary oedema with hyaline membrane formation, suggestive of early-phase ARDS (figure 2B). Inter stitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multi nucleated syncytial cells with atypical enlarged pneumocytes character ised by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intraalveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified.

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection.4,5 In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity (figure 2C), indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury.

From previous reports, there were a few interstitial mononuclear inflammatory infil trates, but no other substantial damage in the heart tissue (figure 2D). Peripheral blood was prepared for flow cytometric analysis. It was found that the counts of peripheral CD4 and CD8 T cells were substantially reduced, while their status was hyperactivated, as evidenced by the high proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions (appendix p 3). Moreover, there was an increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells (appendix p 3).



Additionally, CD8 T cells were found to harbour high concentrations of cytotoxic granules, in which 31·6% cells were perforin positive, 64·2% cells were granulysin positive, and 30·5% cells were granulysin and perforin double-positive (appendix p 3). Our results imply that overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, accounts for, in part, the severe immune injury in this patient. X-ray images showed rapid progression of pneumonia and some differences between the left and right lung. In addition, the liver tissue showed moderate microvesicular steatosis and mild lobular activity, but there was no conclusive evidence to support SARS-CoV-2 infection or drug-induced liver injury as the cause.

There were no obvious histological changes seen in heart tissue, according to previous reviews, suggesting that SARS-CoV-2 infection might not directly impair the heart. Although corticosteroid treatment is not routinely recommended to be used for SARS-CoV-2 pneumonia, according to our pathological findings of pulmonary oedema and hyaline membrane formation, timely and appropriate use of corticosteroids together with ventilator support should be considered for the severe patients to prevent ARDS development. Lymphopenia is a common feature in the patients with COVID-19 and might be a critical factor associated with disease severity and mortality.3 Our clinical and pathological findings in this severe case of COVID-19 can not only help to identify a cause of death, but also provide new insights into the pathogenesis of SARS-CoV-2-related pneumonia, which might help physicians to formulate a timely therapeutic strategy for similar severe patients and reduce mortality.

Therapeutics/treatment options

The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. Currently, there are no speciﬁc antiviral drugs or vaccine against COVID19 infection for potential therapy of humans. The only options available were the use of broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the speciﬁc antiviral becomes available (Lu *et al*., 2020). The treatments that have so far been attempted showed that 75 patients were administrated existing antiviral drugs. The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days (Chen *et al*., 2020). Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly eﬀective in the control of 2019nCoV infection in vitro. These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be considered to treat COVID-19 infection (Wang *et al*., 2020). Furthermore, there are a number of other compounds that are in development. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic inﬂuenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection (Toots *et al*., 2019). Along those lines, until more speciﬁc therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1),RNA synthesis inhibitors. It is clear however, that more research is urgently needed to identify novel chemotherapeutic drugs for treating COVID-19 infections. In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans. Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interactions.

Future of COVID-19 on public health

Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and eﬀorts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. A guideline was published for the medical staﬀ, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV (Jin *et al*., 2020). The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection (Tang *et al*., 2020, Guan *et al*., 2020). The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as faecal and urine samples that can potentially serve as an alternative route of transmission (Assiri *et al*., 2013, Lee *et al*., 2003). China and other countries have implemented major prevention and control measures including travel screenings to control further spread of the virus (Carlos *et al*., 2020). Epidemiological changes in COVID-19 infection should be monitored taking into account potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs. There remains a considerable number of questions that need to be addressed. These include, but are not limited to, details about who and how many have been tested, what proportion of these turned positive and whether this rate remains constant or variable. Very few paediatric cases have so far been reported; this due to lack of testing or a true lack of infection/susceptibility? Of the ones that have so far been tested, how many have developed severe disease and how many were tested positive but showed no clinical sign of disease? There are some basic questions that would provide a framework for which more speciﬁc and detailed public health measures can be implemented.

References

1. WMHC. Wuhan Municipal Health and Health Commission’s Briefing on the Current Pneumonia Epidemic Situation in Our City.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020.
3. Zhou P, Yang XL, Wang, XG, Hu B, Zhang L, Zhang W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin.
4. Li T, Wei C, Li W, Hongwei F, Shi J. Beijing Union Medical College Hospital on "pneumonia of novel coronavirus infection" diagnosis and treatment proposal (V2.0).
5. National Health Commission of People’s Republic of China. Prevent guideline of 2019-nCoV. 2020
6. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses.
7. Chen Y, Liu Q, Guo D. Coronaviruses: genome structure, replication, and pathogenesis.
8. Peiris JS, Guan Y, Yuen K. Severe acute respiratory syndrome. Nature Med. 2004;10:S88–97.
9. Zaki AM, Boheemen SV, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814–20.
10. Chinese Center for Disease Control and Prevention. 585 environmental samples from the South China Seafood Market in Wuhan, Hubei Province, China.
11. Lu H, Tang CW, Tang Y. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle.
12. Roujian L, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding.
13. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission.
14. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Jan 30:S0140-6736(20)30251-8
15. Wang Q, Wang YH, Ma JC, et al. Description of the first strain of 2019-nCoV, C-Tan-nCoV Wuhan Strain — National Pathogen Resource Center, China, 2020. 2020.
16. Kirchdoerfer RN, Cottrell CA, Wang N, et al. Pre-fusion structure of a human coronavirus spike protein.
17. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission.
18. Gorbalenya AE, Baker SC, Baric RS, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the coronavirus study group.
19. Lam TTY, Shum MHH, Zhu HC, et al. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. bioRxiv preprint first posted online February 18, 2020.
20. Zhang L, Shen FM, Chen F, Lin Z. Origin and evolution of the 2019 novel coronavirus. Clin Infect Dis. 2020 Feb 3:ciaa112.
21. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020.
22. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; published online Feb 3.
23. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
24. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-toperson transmission: a study of a family cluster. Lancet 2020; 395: 514–23.
25. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003; 200: 282–89.
26. Ng DL, Al Hosani F, Keating MK, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am J Pathol 2016; 186: 652–58.
27. W. Wang, J. Tang, F. Wei, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol. 92 (4) (2020) 441–447.
28. H. Nishiura, S.M. Jung, N.M. Linton, R. Kinoshita, Y. Yang, K. Hayashi, et al., The extent of transmission of novel coronavirus in wuhan, China, 2020, J. Clin. Med. 9 (2020).
29. M. Bassetti, A. Vena, D. Roberto Giacobbe, The Novel Chinese Coronavirus (2019nCoV) Infections: challenges for ﬁghting the storm, Eur. J. Clin. Invest. (2020) e13209.
30. M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, et al., First case of 2019 novel coronavirus in the United States, N. Engl. J. Med. (2020).
31. Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. (2020).
32. W.G. Carlos, C.S. Dela Cruz, B. Cao, S. Pasnick, S. Jamil, Novel wuhan (2019-nCoV) coronavirus, Am. J. Respir. Crit. Care Med. 201 (4) (2020) 7–8.
33. J. Lei, J. Li, X. Li, X. Qi, CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia, Radiology (2020) 200236, https://doi.org/10.1148/radiol. 2020200236.
34. Assiri, J.A. Al-Tawﬁq, A.A. Al-Rabeeah, F.A. Al-Rabiah, S. Al-Hajjar, A. AlBarrak, etal., Epidemiological,demographic, andclinicalcharacteristics of47cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study, Lancet Infect. Dis. 13 (2013) 752–761.
35. N. Lee, D. Hui, A. Wu, P. Chan, P. Cameron, G.M. Joynt, et al., A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (2003) 1986–1994.
36. L.T. Phan, T.V. Nguyen, Q.C. Luong, T.V. Nguyen, H.T. Nguyen, H.Q. Le, et al., Importation and human-to-human transmission of a novel coronavirus in Vietnam, N. Engl. J. Med. (2020),
37. W. Ji, W. Wang, X. Zhao, J. Zai, X. Li, Homologous recombination within the spike glycoprotein of the newly identiﬁed coronavirus may boost cross-species transmission from snake to human, J. Med. Virol. 92 (4) (2020) 433–440
38. N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, N. Engl. J. Med. 382 (2019) 727–733
39. N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513