**Aetiology of COVID-19**

**INTRODUCTION**

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China (Bogoch *et al.*, 2020; Lu *et al., 2020)*. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, named by WHO on Feb 11, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58) (Zhao *et al., 2020)*.

The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019 (Du Toit *et al., 2020)*. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died (Ren *et al.,*2020).

By January 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension and cardiovascular disease (Huang *et al.,* 2020). These patients were presumed to be infected in that hospital, likely due to nosocomial infection. It was concluded that the COVID-19 is not a super-hot spreading virus (spread by one patient to many others), but rather likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. In addition, only patients that got clinically sick were tested, thus there were likely many more patients that were presumably infected. As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (COVID-19) were reported in 25 provinces (districts and cities) in China (Lu *et al., 2020) 7*.

The China National Health Com- mission reported the details of the first 17 deaths up to January 22, 2020. On January 25, 2020, a total of 1975 cases were confirmed to be infected with the COVID-19 in mainland China with a total of 56 deaths (Wang *et al., 2020)*. Another report on January 24, 2020 estimated the cumulative incidence in China to be 5502 cases (Nishiura *et al., 2020)*. As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case fatality rate was calculated to be 2.2% (170/7824) (Bassetti *et al.,* 2020). The first case of COVID-19 infection confirmed in the United States led to the description, identification, diagnosis, clinical course, and management of this case.

**Virological characteristics of SARS-CoV-2**

SARS-CoV-2 is the causative pathogen of COVID-19, identified as the seventh type of coronavirus to infect humans (Zhu *et al.,* 2020). Six other kinds of coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) with high mortality rate (Su *et al., 2016)*. According to the genome characteristics, coronavirus is separated into four genera: α-CoV, β-CoV, γ-CoV, and δ-CoV (Su *et al.,* 2016). Deep sequencing revealed that this novel coronavirus isolated from lower respiratory tract samples of patient with COVID-19 belongs to β-CoV (Zhu *et al., 2020)*.

Coronavirus has the appearance of crown under electron microscopy. They are enveloped viruses with a single- strand, positive-sense RNA genome, which is the largest known genome for an RNA virus (Forni *et al., 2017*). All coronaviruses share the same genome organization and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 nonstructural proteins, followed by ORFS for four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Forni *et al., 2017)*. The SARS-CoV-2 protein also contains eight accessory proteins (Wu *et al., 2020*). Spike protein plays an essential role in binding to receptors and is critical for determining host tropism and transmission capacity. It is functionally divided into S1 domain and S2 domain, responsible for receptor binding and cell membrane fusion respectively. The receptor binding domain (RBD) of β-CoV is commonly located in the C-terminal domain of S1 (Lu *et al.,*2020)15. A team analyzed the cryogenic electron microscopy (Cryo- EM) structure of the SARS-CoV-2 spike protein and found that it has 10 to 20-fold higher binding affinity to human angiotensin-converting enzyme 2 (ACE2) than SARS- CoV does (Wrapp *et al., 2020)*.

Phylogenetic analysis of the evolution history showed that SARS-CoV-2 shared a closer sequence homology toward the genomes of SARS-CoV than to that of MERS-CoV ( Xu *et al., 2020)*. SARS-CoV-2 is highly similar to a bat coronavirus RaTG13, with an overall genome sequence identity of 96.2% (Zhou *et al.,*2020), indicating that bat, which was discovered to be the natural reservoir host of various SARS-related coronaviruses ( de Wit *et al., 2016)*, may also be the original host of SARS-CoV-2. The intermediate host in the process of transmission remains uncertain.

**SYMPTOMS**

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days ( Li *et al., 2020)*. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days ( Wang *et al., 2020).* This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients > 70-years old compared with those under the age of 70 ( Wang *et al., 2020).* The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, head- ache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia ( Ren *et al*., 2020; Huang *et al.,* 2020; Wang *et al*., 2020; Carlos *et al., 2020)*. Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death ( Huang *et al., 2020).* In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs ( Lei *et al., 2020)* that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treat- ment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities (Lei *et al.,* 2020]

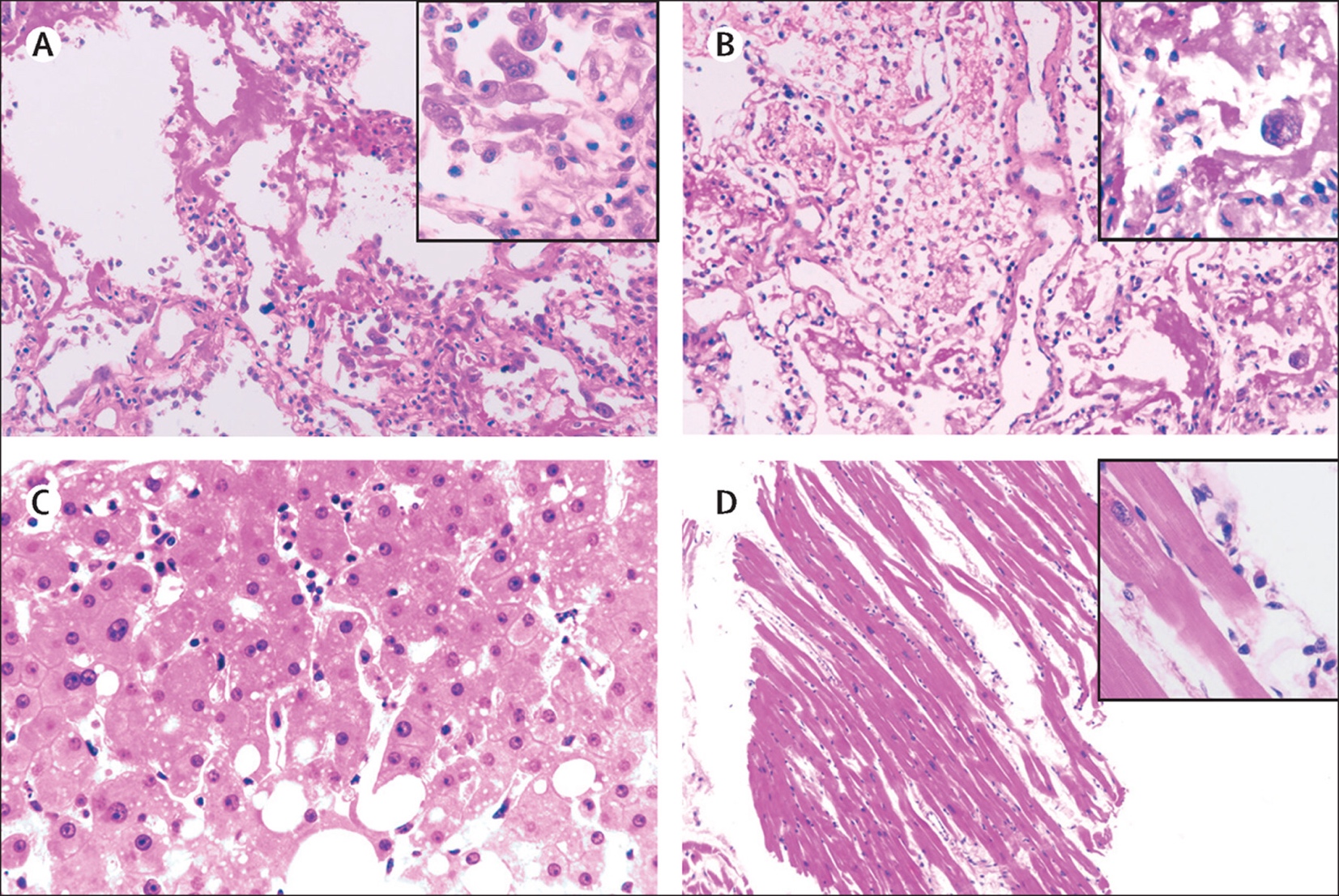
**PATHOGENESIS**

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths ( Wang *et al., 2020).*  The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years (Wang *et al.,* 2020).

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-in- flammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection (Lei *et al.,* 2020). The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed (Lei *et al.,* 2020).

The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Huang *et al.,* 2020). Significantly high blood levels of cytokines and che mokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity (Huang *et al.,* 2020).

**HISTOPATHOLOGICAL FINDINGS**



***Figure 2: Pathological manifestations of right (A) and left (B) lung tissue, liver tissue (C), and heart tissue (D) in a patient with severe pneumonia caused by SARS-CoV-2***

***SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.***

Biopsy samples were taken from lung, liver, and heart tissue of a 50-year-old COVID-19 patient. Histological examination showed bilateral diffuse alveolar damage with cellular bromyxoid exudates ( figure 2A, B). The right lung showed evident desquamation of pneumocytes and hyaline membrane 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). Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterised by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intra- alveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified. (Wu *et al*., 2020; Huang *et al.,* 2020; Chan *et al.,* 2020; Ding *et al., 2003)*

**REFERENCE**

Bogoch, A. Watts, A. Thomas-Bachli, C. Huber, M.U.G. Kraemer, K. Khan, Pneumonia of unknown etiology in wuhan, China: potential for international spread via commercial air travel, J. Trav. Med. (2020), https://doi.org/10.1093/jtm/ taaa008.

[2] H. Lu, C.W. Stratton, Y.W. Tang, Outbreak of pneumonia of unknown etiology in wuhan China: the mystery and the miracle, J. Med. Virol. 92 (4) (2020) 401–402, https://doi.org/10.1002/jmv.25678.

[3] S. Zhao, Q. Lin, J. Ran, S.S. Musa, G. Yang, W. Wang, et al., Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak, Int. J. Infect. Dis. : IJID : Off. Publ. Int. Soc. Infect. Dis. 92 (2020) 214–217, https://doi. org/10.1016/j.ijid.2020.01.050.

A. Du Toit, Outbreak of a novel coronavirus, Nat. Rev. Microbiol. 18 (123) (2020), https://doi.org/10.1038/s41579-020-0332-0.

[5] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, et al., Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chinese

Med J (2020), https://doi.org/10.1097/CM9.0000000000000722.

C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020)

497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[7] H. Lu, Drug treatment options for the 2019-new coronavirus (2019-nCoV), Biosci.

Trends (2020), https://doi.org/10.5582/bst.2020.01020.

[8] 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,

https://doi.org/10.1002/jmv.25689.

[9] 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).

M. Bassetti, A. Vena, D. Roberto Giacobbe, The Novel Chinese Coronavirus (2019-

nCoV) Infections: challenges for fighting the storm, Eur. J. Clin. Invest. (2020)

e13209, , https://doi.org/10.1111/eci.13209.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, ShiW,LuR,NiuP,ZhanF,MaX,WangD,XuW,WuG,GaoGF, Tan W; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382(8): 727–733

12. SuS,WongG,ShiW,LiuJ,LaiACK,ZhouJ,LiuW,BiY,Gao GF. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 2016; 24(6): 490–502

Forni D, Cagliani R, Clerici M, Sironi M. Molecular evolution of human coronavirus genomes. Trends Microbiol 2017; 25(1): 35–48

14. Wu A, Peng Y,Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z, Zhang Z, Wang J, Sheng J, Quan L, Xia Z, Tan W, Cheng G, Jiang T. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020 Feb 7. [Epub ahead of print] doi: 10.1016/j.chom.2020.02.001

15. LuR,ZhaoX,LiJ,NiuP,YangB,WuH,WangW,SongH,Huang B,ZhuN,BiY,MaX,ZhanF,WangL,HuT,ZhouH,HuZ,Zhou W,ZhaoL,ChenJ,MengY,WangJ,LinY,YuanJ,XieZ,MaJ, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395(10224): 565–574

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020 Feb 19. [Epub ahead of print] doi: 10.1126/science.abb2507

XuX,ChenP,WangJ,FengJ,ZhouH,LiX,ZhongW,HaoP. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020; 63(3): 457–460

18. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798): 270–273

Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dy-

namics in wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med.

(2020), https://doi.org/10.1056/NEJMoa2001316.

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, https://doi.org/10.

1164/rccm.2014P7.

[14] 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.

de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14(8): 523–534

Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dy-

namics in wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med.

(2020), https://doi.org/10.1056/NEJMoa2001316.

[13] 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, https://doi.org/10.

1164/rccm.2014P7.

[14] 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.