A Family Cluster of Severe Acute Respiratory Syndrome Coronavirus 2 Infections

Xuesong Gao

Beijing Ditan Hospital, Capital Medical University <https://orcid.org/0000-0002-7193-4981>

Zheng Yuan

Beijing Ditan Hospital, Capital Medical University

Di Yang

Beijing Ditan Hospital, Capital Medical University

Hongjie Li

Beijing Ditan Hospital, Capital Medical University

Yijin Zhang

Beijing Ditan Hospital, Capital Medical University

Ping Gao

Beijing Ditan Hospital, Capital Medical University

Xiaomin Liu

Beijing Ditan Hospital, Capital Medical University

Wenshan Zhao

Beijing Ditan Hospital, Capital Medical University

Te Xiao

Beijing Ditan Hospital, Capital Medical University

Xuefei Duan (✉ duanxuefei@vip.sina.com)

Beijing Ditan Hospital, Capital Medical University

Research Article

Keywords: COVID-19, SARS-CoV-2, clinical characteristics, human–human transmission, treatment

Posted Date: March 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16921/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at European Journal of Clinical Microbiology & Infectious Diseases on April 8th, 2020. See the published version at <https://doi.org/10.1007/s10096-020-03880-1>.

Abstract

Background In December 2019, the outbreak of 2019 novel coronavirus disease (COVID-19) began in Wuhan, Hubei Province, China. The disease has rapidly spread from Wuhan to other provinces and other countries. Clinical and epidemiological knowledge is limited. We aimed to describe the clinical and epidemiological characteristics of a family cluster of COVID-19 in Beijing.

Methods We reported a family cluster of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases in Beijing, China. We obtained and analyzed clinical and epidemiologic data from these patients. Throat swab samples were tested for SARS-CoV-2 using real-time reverse transcriptase-polymerase chain reaction assays.

Results This family comprised three laboratory confirmed cases with clinical symptoms. All three patients had close contact with a relative from Wuhan, Hubei Province. Chest computerized tomography revealed ground-glass opacities and consolidation. Patient 1 was finally intubated and mechanical ventilated. Patient 2 received high-flow oxygen therapy. The clinical condition of Patient 3 has resolved.

Conclusion SARS-CoV-2 infections tend to clusters. Advanced age and comorbidities are associated with adverse outcomes. Physicians should be aware of contact history so that infected patients can be identified promptly and further spreading prevented.

Introduction

In December 19, a pneumonia called 2019 novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, China [1,2].

As of February 20, 2020, there have been a total of 74,675 confirmed cases in China and 1073 confirmed cases outside of China [3]. Although SARS-CoV-2 was thought to have a zoonotic origin and early cases were reported to be associated with exposure to the seafood market in Wuhan, person-to-person transmission has been observed [4,5]. At present, the emergence, development, and underlying mechanism of immunity and clinical outcomes of patients with COVID-19 outside Wuhan are limited. Here, we report the epidemiologic and clinical features of a family cluster of SARS-CoV-2 infections that occurred in Beijing who did not have a history of travel to Wuhan.

Methods

Patients

On February 2, 2020, three patients came to Beijing Ditan Hospital with fever and ground-glass opacities on chest CT scans. Diagnosis of COVID-19 and clinical classification was made according to Diagnosis and Treatment of Pneumonia Caused by 2019nCoV (version 6) [6]. There were no exclusion criteria.

This study was approved by the Institutional Review Board of Beijing Ditan Hospital. We obtained written consent from the patients.

Data collection

The clinical data, including the medical history, physical findings, exposure history, underlying comorbidities, laboratory tests, and chest computerized tomography (CT) findings, were collected from medical records and the patients. Clinical outcomes were followed up until February 20, 2020.

A surveillance reporting form was used to collect epidemiologic data, including demographic characteristics, travel history within the last 14 days, a history of contact with a person to have SARS-CoV-2 infection, a history of contact with a person with fever or respiratory tract symptoms, or a history of contact with the Huanan seafood wholesale market in Wuhan.

Laboratory tests

Blood counts, blood biochemistry, coagulation function, procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and myocardial enzyme spectrum, influenza A virus RNA, influenza B virus RNA, H1N1 influenza virus RNA were performed at the laboratory in Beijing Ditan Hospital. All tests for SARS-CoV-2 were performed at the laboratory in Beijing Ditan Hospital and confirmed at the Beijing Centers for Disease Control and Prevention (CDC).

Results

Clinical characteristics

Patient 1 was a 72-year-old female with hypertension. She presented to the emergency department with 10 h of fever (maximum temperature of 38.1°C) and muscle soreness in the late evening of February 2, 2020. The patient's oxygen saturation was 98% while she was breathing ambient air. A chest CT scan showed ground-glass opacities in the upper lobe of the right lung (Fig. 1). After admission, she initially received antiviral therapy with lopinavir/ritonavir and aerosol inhalation of interferon-alpha in addition to supplemental oxygen delivered by nasal cannula at 2 liters per minute. She was diagnosed with COVID-19 because her throat swab sample was nucleic acid positive for SARS-CoV-2. Laboratory results are summarized in Table 1. On the second hospital day, she developed intermittent atrial fibrillation. She was treated with low dose of Betaloc. The patient was still feverish with the maximum temperature of 39°C, and she received antipyretic therapy. A second chest CT revealed bilateral lung disease with an increasing number of ground-glass opacities and a crazy-paving pattern on February 7. On February 10, she complained of worsening dyspnea. Oxygen saturation decreased to 90%–92% while the patient was breathing 10 liters of oxygen with the use of an oxygen mask. Blood-gas evaluations showed type I respiratory failure. She was transferred to the intensive care unit (ICU) immediately, where she received high-flow nasal oxygen therapy. She was finally intubated and given mechanical ventilation for severe acute respiratory distress syndrome (ARDS) on February 14. A third chest CT showed decreased ground-

glass opacities, and her fever finally resolved on February 19. However, her throat swab sample was still nucleic acid positive on February 19.

Patient 2 was a 47-year-old male and the son of Patient 1. They presented to the emergency department on February 2, 2020. He complained of a 5-day history of high fever (maximum temperature of 39.2°C), and cough. A chest CT scan showed bilateral ground-glass opacities with consolidation (Fig. 2). A throat swab nucleic acid test was positive for SARS-CoV-2. After admission, he was also treated with lopinavir/ritonavir and aerosol inhalation of interferon-alpha. However, his condition deteriorated with high fever (40.0°C) and shortness of breath. A second chest CT showed extensive bilateral ground-glass opacities and consolidation on February 8. Blood-gas evaluations showed type I respiratory failure. Then, he was transferred to the ICU with ARDS. The patient's oxygenation improved with high-flow nasal oxygen. His fever resolved on February 9. His nucleic acid test became negative after February 15. His clinical conditions improved, and he was transferred back to the general ward on February 18. He continued to receive supplemental oxygen delivered by nasal cannula at 2 liters per minute. His oxygen saturation remained at 98%.

Patient 3 was a 45-year-old female and the wife of Patient 2. They presented to the emergency department on February 2, 2020. She complained of having fever (maximum temperature of 37.7°C) and cough for 5 days. A chest CT scan showed bilateral ground-glass opacities and consolidation in the lower-right lobe (Fig. 3). A throat swab sample was positive for SARS-CoV-2. She received lopinavir/ritonavir and aerosol inhalation of interferon-alpha. Her fever resolved from the second hospital day. Results of routine blood counts and blood-gas evaluations were normal. A chest CT scan revealed partial absorption of the lesion on February 14. However, she was still hospitalized due to the persistent positive nucleic acid tests.

Epidemiologic investigation

The family cluster of 3 patients (Patients 1–3) drove from Beijing to Xinyang, Henan province on January 24, 2020. The family stayed in their own house throughout their trip. They shared meals with a relative from Wuhan on January 27, 2020. They had no history of contact with other people with fever or respiratory tract symptoms, contact with wild animals, visits to the Huanan seafood market in Wuhan, or consumption of game meat in restaurants. After they drove back to Beijing on January 27, 2020, the 3 patients lived in one apartment. Patient 1 stayed in one room while Patients 2 and 3 stayed in another. Patients 2–3 presented with fever and cough on January 29, 2020. Patient 1 presented with fever on February 2, 2020. The incubation period was estimated to be between 2 and 6 days. According to what they had been told, the relative from Wuhan has not been ill so far.

Discussion

Here we report a familial cluster of pneumonia due to SARS-CoV-2 infection. Three of four family members presented to hospital with symptoms. They were diagnosed with COVID-19 for nucleic acid-positive for SARS-CoV-2. The most likely course of transmission was that Patients 1–3 acquired the

infection from one asymptomatic person, their relative from Wuhan, while sharing meals. The patients' relative might have acquired the infection from the community, as he had no clear exposure history. The second possibility was that one of Patients 1–3 became infected by this relative and transmitted it to the other two patients in the car while driving back to Beijing. Overall, these findings suggested person-to-person transmission.

All three patients successively presented with fever. The symptoms of this COVID-19 are also nonspecific, and fever is the most common symptom [7,8]. Although Patients 1–2 had mild symptoms at the time of admission, their dyspnea worsened in 7–10 day from the time of onset. The dynamic changes in chest CT scans were also consistent with clinical course. Therefore, radiological assessment of patients' progress plays an important role in the management of COVID-19. Currently, no specific antiviral treatment exists. Clinical management focuses on symptomatic treatment, with organ support for critical ill patients. Lopinavir/ritonavir and aerosol inhalation of interferon-alpha were used as soon as they were admitted. However, their clinical courses diverged. The conditions of Patient 1 became aggravated with positive nucleic acid tests; however, Patient 3 resolved with a positive nucleic acid test. Further randomized controlled trials are needed to evaluate efficacy of these antiviral medications, including remdesivir [9]. The pathophysiology mechanism of severity levels caused by SARS-CoV-2 is not well understood. It has been found to be associated with a cytokine storm, which is characterized by increased plasma concentrations of IL-2, IL-7, IL-10, MCP-1, MIP-1 α , and TNF- α in critical patients according to previous studies [10–12]. Xu et al. postulated overactivation of T cells may partly account for the severe immune injury [13]. These excessive immune responses lead to further lung injury. Corticosteroids were used frequently to treat severe patients. Huang et al. treated few severely ill patients with ARDS with low-to-moderate doses of corticosteroids [11]. Systemic corticosteroid was given to 44.5% of severe cases and 13.7% of non-severe cases [7]. However, none of these treatments were found to be effective [8,14]. In this setting, administration of corticosteroids has been conditionally recommended in our guidance⁶, but it has not been recommended by the WHO [15]. Intravenous injection with γ -immunoglobulin may be an alternative [14]. However, more clinical data are required to evaluate it.

Therefore, it is more important to early identify critically ill patients in the absence of effective treatments. As reported before, old men with comorbidities have been found to be associated with severe pneumonia [7,16,17]. Early diagnosis and treatment of elderly patients with comorbidities is an important target for preventing fatal outcomes. The neutrophil-to-lymphocyte ratio (NLR) ≥ 3.13 was recently identified as an independent risk factor for severe patients [18]. Low levels of CD4+T, CD8+T, and NK cells and higher levels of IL-6 and IL-10 cells were found in severe patients. T cell subsets and cytokines can be used as to predict the transition from mild to severe [19]. We observed lower levels of lymphocyte, CD4+T, CD8+T, and NK cells in Patient 1 and Patient 2 than in Patient 3, in line with these previous works. Liu et al. also established that the combinations of the reduced levels of album, lymphocyte, and increase levels of CRP and LDH might predict more severe acute lung injury [20].

In conclusion, cases of SARS-CoV-2 tend to emerge in clusters. Elderly patients with comorbidities were associated with severe and fatal respiratory disease such as ARDS. Physicians should be aware of

contact history for patients to promptly identify patients and prevent further spreading. Early diagnosis, early isolation, and early management are crucial to curbing transmission and reducing mortality.

Declarations

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Funding

Construction of high-level health technical personnel in the Beijing health system (2014-3-093). China's National Science and Technology Major Project (2018ZX10715-005-003-002).

Author contributions statement This study was designed by Xuefei Duan, Xuesong Gao, and Di Yang. The data were collected by Zheng Yuan, Hongjie Li, Yijin Zhang, Ping Gao and Te Xiao. The manuscript was drafted and written by Xiaomin Liu, and Wenshan Zhao; revised by Xuefei Duan and Xuesong Gao; and finally reviewed by all the authors. All authors approved the final version for submission and are able to account for its content.

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

Ethical approval This study was approved by the Ethics Committee of Beijing Ditan Hospital.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China Novel Coronavirus I, Research T (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. doi:10.1056/NEJMoa2001017
2. World Health Organization (2019) <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Accessed February 20, 2020
3. World Health Organization (2019). https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200220-sitrep-31-covid-19.pdf?sfvrsn=dfd11d24_2. Accessed February 20, 2020
4. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, Xing F, Liu J, Yip CC-Y, Poon RW-S, Tsoi H-W, Lo SK-F, Chan K-H, Poon VK-M, Chan W-M, Ip JD, Cai J-P, Cheng VC-C, Chen H, Hui CK-M, Yuen K-Y (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. doi:10.1016/s0140-6736(20)30154-9

5. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. doi:10.1056/NEJMoa2001316
6. Diagnosis and Treatment of Pneumonia Caused by 2019nCoV (version 6).
<http://www.nhc.gov.cn/xcs/zhengcwj/202002/8334a8326dd94d329df351d7da8aefc2.shtml> (in Chinese). Accessed February 20, 2020
7. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, Liu L, Shan H, Lei C-l, Hui DSC, Du B, Li L-j, Zeng G, Yuen K-Y, Chen R-c, Tang C-l, Wang T, Chen P-y, Xiang J, Li S-y, Wang J-l, Liang Z-j, Peng Y-x, Wei L, Liu Y, Hu Y-h, Peng P, Wang J-m, Liu J-y, Chen Z, Li G, Zheng Z-j, Qiu S-q, Luo J, Ye C-j, Zhu S-y, Zhong N-s (2020). Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv preprint doi:10.1101/2020.02.06.20020974
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. doi:10.1001/jama.2020.1585
9. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK, Washington State -nCoV VCIT (2020) First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med*. doi:10.1056/NEJMoa2001191
10. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J (2020) Coronavirus infections and immune responses. *J Med Virol*. doi:10.1002/jmv.25685
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. doi:10.1016/s0140-6736(20)30183-5
12. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M (2020) Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet*. doi:10.1016/s0140-6736(20)30305-6
13. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang F-S (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. doi:10.1016/s2213-2600(20) 30076-x
14. Kui L, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC, Liu HG (2020) Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. doi:10.1097/CM9.0000000000000744
15. World Health Organization (2019) [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected). Accessed February 20, 2020

16. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia Ja, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. doi:10.1016/s0140-6736(20)30211-7
17. Yang Y, Lu Q, Liu M, Wang Y, Zhang A, Jalali N, Dean N, Longini I, Halloran ME, Xu B, Zhang X, Wang L, Liu W, Fang L (2020). Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. *medRxiv preprint* doi:10.1101/2020.02.10.20021675
18. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, Song M, Wang L, Zhang W, Han B, Yang L, Wang X, Zhou G, Zhang T, Li B, Wang Y, Chen Z, Wang X (2020). Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. *medRxiv preprint* doi:10.1101/2020.02.10.20021584
19. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z, Qiang M, Xiang J, Zhang B, Chen Y (2020). Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv preprint* doi:10.1101/2020. 02. 10.20021832
20. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* doi:10.1007/s11427-020-1643-8

Table

Table 1 Laboratory results of patients with COVID-19 on admission to hospital

Variables	Case 1	Case 2	Case 3	Reference Range
Age	72	47	45	
Gender	Female	Male	Female	
White blood cell	2.99	2.96	4.9	4-10
Count ($\times 10^9/L$)				
Neutrophil Count ($\times 10^9/L$)	1.98	1.63	2.94	2-8
Lymphocyte Count ($\times 10^9/L$)	0.76	1.07	1.63	1-5
Eosinophil Count ($\times 10^9/L$)	0.01	0.00	0.01	0.02-0.5
Hemoglobin (g/L)	131	157	109	110-150
Platelet count ($\times 10^9/L$)	156	133	263.4	100-300
Alanine aminotransferase (U/L)	18.9	83.7	25.1	7-40
Alanine aminotransferase (U/L)	19.5	46.3	28.1	13-35
Total bilirubin ($\mu\text{mol/L}$)	9.7	8.3	5.5	0-18.8
Creatine ($\mu\text{mol/L}$)	61.1	88.1	51.9	Male: 57-97 Female: 41-73
C-reactive protein (mg/L)	2.7	7.4	1.4	0-5
Lactate dehydrogenase (U/L)	161.4	200.9	366.9	120-250
Creatine kinase (U/L)	38.1	72.2	111.1	40-200
Creatine kinase-MB (U/L)	16.3	14.2	50.1	< 25
α -hydroxybutyric dehydrogenase (U/L)	130	155	324	74-182
Troponin $\square$ ($\mu\text{g/L}$)	< 0.01	< 0.01	< 0.01	< 0.01
Procalcitonin (ng/ml)	< 0.05	< 0.05	< 0.05	< 0.05
Serum amyloid A (mg/L)	6.3	106.4	6.5	0-10
Prothrombin time (s)	12.4	13.3	12	9.4-12.5
International Normalized Ratio	1.15	1.23	1.11	0.8-1.2
D-dimer (mg/L)	0.76	0.31	0.50	
CD4 (cell/ μl)	180	285	511	706-1125
CD8 (cell/ μl)	253	126	729	320-1250
NK (cell/ μl)	37	51	444	90-590
B (cell/ μl)	147	104	189	90-660
Lactate (mmol/L)	2.05	2.05	1.48	1.33-1.78

Figures

February 2

February 7

February 19

Figure 1

Chest CT of Patient 1

February 2

February 8

February 13

February 18

Figure 2

Chest CT of Patient 2

February 2

February 15

Figure 3