



Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster

Feng Ye^{a,1}, Shicai Xu^{b,e,1}, Zhihua Rong^c, Ronghua Xu^a, Xiaowei Liu^a, Pingfu Deng^a, Hai Liu^d, Xuejun Xu^{a,*}

^a Department of Neurosurgery, The Second People's Hospital of Chengdu, Chengdu, China

^b Department of Spine Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China

^c Department of Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China

^d Luzhou Center for Disease Control and Prevention, Luzhou, China

^e Department of Surgery, People's Hospital of Luxian County, Luzhou, China



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ABSTRACT

Objectives: With the ongoing outbreak of COVID-19 around the world, it has become a worldwide health concern. One previous study reported a family cluster with an asymptomatic transmission of COVID-19. Here, we report another series of cases and further demonstrate the repeatability of the transmission of COVID-19 by pre-symptomatic carriers.

Methods: A familial cluster of five patients associated with COVID-19 was enrolled in the hospital. We collected epidemiological and clinical characteristics, laboratory outcomes from electronic medical records, and also verified them with the patients and their families.

Results: Among them, three family members (Case 3/4/5) had returned from Wuhan. Additionally, two family members, those who had not traveled to Wuhan, also contracted COVID-19 after contacting with the other three family members. Case 1 developed severe pneumonia and was admitted to the ICU. Case 3 and Case 5 presented fever and cough on days two through three of hospitalization and had ground-glass opacity changes in their lungs. Case 4 presented with diarrhea and pharyngalgia after admission without radiographic abnormalities. Case 2 presented no clinical nor radiographic abnormalities. All five cases had an increasing level of C-reactive protein.

Conclusions: Our findings indicate that COVID-19 can be transmitted by asymptomatic carriers during the incubation period.

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1. Introduction

On Dec 31, 2019, the government of Hubei Province, China, first reported a group of confused patients with pneumonia (The Central Government of the People's Republic of China, 2020). Metagenomics sequencing analysis revealed a novel coronavirus, which was officially named SARS-CoV-2 and is the cause of the disease called COVID-19 (World Health Organization, 2020a). The

National Health Commission (NHC) established COVID-19 as a category B infectious disease with A-class management on Jan 20 (The Central Government of the People's Republic of China, 2020). Furthermore, on Jan 30, the WHO issued a Public Health Emergency of International Concern (PHEIC) alarm and appealed to specialists all over the world to work together to control the rapid spread of COVID-19. As of Mar 8, there had been 80,859 confirmed COVID-19 patients in China, including 3,100 deaths. Internationally, over 100 countries have now reported laboratory-confirmed cases, including a total of 24,031 cases (World Health Organization, 2020b). As of March 27, 2020, the World Health Association reports that there are 465,915 confirmed cases of COVID-19 worldwide; 21,031 have died, a mortality rate of about 4.5%.

The first clinical data from 41 individuals with a confirmed diagnosis of COVID-19 from Wuhan, China, have been published (Huang et al., 2020). Most of them had been directly exposed to the

* Corresponding author at: Department of Neurosurgery, The Second People's Hospital of Chengdu, 10 Qingyun South Street, Chengdu, Sichuan 610021, China.

E-mail addresses: yefeng19930@126.com (F. Ye), xsc691092906@163.com (S. Xu), doctorzhang@126.com (Z. Rong), 1442416311@qq.com (R. Xu), 625289749@qq.com (X. Liu), 743371203@qq.com (P. Deng), liuhai6233@163.com (H. Liu), docxj@163.com (X. Xu).

¹ These authors contributed equally to this study.

Wuhan wholesale seafood market, which sells freshly slaughtered game animals that were the original infection source (Huang et al., 2020). The present data strongly suggest that game animals or mammals were probably intermediate hosts of SARS-CoV-2 that originated from the Chinese horseshoe bat (Zhou et al., 2020; Lu et al., 2020). The virus has preferential tropism to human airway epithelial cells through the same cellular receptor as that for SARS, angiotensin-converting enzyme 2 (ACE2), which is a central body receptor for the surface glycoprotein S of the virus (Munster et al., 2020). The way to ascertain disease depends on positive real-time reverse transcription-polymerase chain reaction (rRT-PCR) results for SARS-CoV-2 nucleic acid. The associated mortality rates are 2–3% (World Health Organization, 2020b; Chen et al., 2020). Currently, there are no definite antiviral therapies or vaccines for COVID-19, although some drugs are under investigation.

With the extensive outbreak of COVID-19, a mass of studies in the larger population have been reported. Obviously, the total number of cases and transmission events have far exceeded those of SARS and H1N1. Wu et al. (2020) found that the mean R_0 of COVID-19 was approximately 2.68 (95% CI: 2.47–2.86). An increasing number of outbreaks of familial transmission stressed the possibility of person-to-person transmission (Chan et al., 2020; Rothe et al., 2020; Phan et al., 2020). The measures in which public health officials quarantine confirmed cases and isolate intimate patients are significant progress in controlling COVID-19. Another question for consideration is a group of asymptotically infected individuals, which may propagate the virus and impede infection control (Zhou et al., 2020; Zhang et al., 2020). Bai et al. (2020) presented clinical data showing a familial cluster of five patients with COVID-19 and one asymptomatic family member, which presumed the possibility of infection from asymptomatic carriers.

In this study, we report the clinical features of a family cluster involving five COVID-19 cases in Luzhou. Three cases came from Wuhan, and the other two cases had not left Luzhou recently. Our

data further verified the delivery of infection from asymptomatic carriers of COVID-19 during the incubation period.

2. Methods

On Feb. 4, a 50-year-old woman (Case 1) was admitted to the People's Hospital of Luxian County (Luzhou, Sichuan Province, China) with fever, dizziness, cough, and shortness of breath. On examination, her maximum temperature was 39.1 °C, and her blood pressure was 152/93 mmHg. A chest CT scan revealed massive shadows of high density in the lungs. The local CDC performed rRT-PCR tests for SARS-CoV-2 nucleic acid, and a throat swab was positive (Ct values, 19). Case 1 was diagnosed and immediately isolated.

Subsequently, forty-four other intimate contacts were admitted to our hospital for a general physical examination on Feb. 5. The local CDC ascertained that the nasopharyngeal or oropharyngeal swabs were positive for four cases (Case 2/3/4/5) according to the SARS-CoV-2 nucleic acid test (Table 2). All cases were admitted to the hospital and treated in isolation. A detailed data collection for the five patients was executed, and all patients underwent chest CT imaging. All the laboratory procedures for clinical samples have been previously reported (To et al., 2010). Nasopharyngeal and oropharyngeal swabs and stool and urine samples were obtained and maintained viral transport medium. Plasma was separated from EDTA bottles, and serum was separated from clotted blood bottles. Specimens were held between 2 °C and 8 °C and sent to the CDC. RRT-PCR tests for SARS-CoV-2 nucleic acid were performed by the local CDC; the detection reagents were from Maccura Biotechnology Co., Ltd, and Sansure Biotechnology Co., Ltd.

The Ethics Committee of the People's Hospital of Luxian County approved this study. We obtained written consent from all the patients about clinical data, radiographic pictures, information, etc.

Table 1
Summary of clinical features and laboratory results of a family cluster infected with COVID-19.

	Case 1	Case 2	Case 3	Case 4	Case 5
Relationship	Mother of Case 2	Son of Case 1	Father of Case 5	Mother of Case 5	Son of Case 3 and 4
Age (years)	50	28	50	51	23
Sex	Female	Male	Male	Female	Male
Occupation	Farmer	Worker	Trader	Trader	Trader
Chronic medical illness	Hypertension, emphysema	None	None	None	None
<i>Presenting symptoms and signs</i>					
Fever	+	–	+	–	+
Cough	+	–	+	–	+
Dizziness	+	–	–	–	–
Shortness of breath	+	–	–	–	–
Stiffness	–	–	–	–	–
Diarrhoea	–	–	–	+	–
Pharyngalgia	–	–	–	+	–
Body temperature (°C)	39.1	36.2	38.2 (hospital exposure)	37.0	38.0 (hospital exposure)
Oximetry saturation (%)	low 90% (hospital exposure)	94%	92%	92%	98%
White blood cell count ($\times 10^9$ cells/L) (normal range 4.00–10.00)	12.4 (↑)	6.12	9.57	7.44	8.24
Neutrophil count ($\times 10^9$ cells/L) (normal range 1.80–6.30)	7.82 (↑)	3.57	4.11	5.25	3.13
Lymphocyte count ($\times 10^9$ cells/L) (normal range 1.10–3.20)	0.84 (↓)	1.03 (↓)	1.07 (↓)	1.70	2.46
Haemoglobin (g/dL); (normal range 120–160)	140	152	166 (↑)	147	164 (↑)
Platelet count ($\times 10^9$ cells/L) (normal range 100–300)	88 (↓)	156	187	72 (↓)	242
C-reactive protein (mg/L) (normal range 0.0–5.0)	189.2 (↑)	10.5 (↑)	9.0 (↑)	43.5 (↑)	24.7 (↑)

NA = not available. + = positive. – = negative. ↑ = above normal range. ↓ = below normal range.

3. Results

We documented and analyzed the clinical symptoms, laboratory results, and history of five cases with verified COVID-19, as presented in Table 1. The relationship between the five cases and their general information is shown in Fig. 3.

Case 1, a 50-year-old woman, had lived in Luzhou year-round and had hypertension and chronic emphysema disease. Between Jan 23 and Jan 25, she attended the family reunion dinner with her family members (Case 2/3/4/5). On Jan 30, they celebrated the Spring Festival together. Because of the limits on access, Case 1 could not leave her hometown in the countryside, where there had been no previous reports of COVID-19. Furthermore, she had not been in contact with any person returning from Wuhan (except Case 3/4/5). In particular, Case 1 did not present any symptoms until Feb. 1. She became ill with fever and a non-productive cough; she took drugs at that time. By the evening, Case 1 started feeling better and continued to enjoy the Spring Festival. However, two days later, a fever of 38.6 °C recurred, along with dizziness, non-productive cough, and shortness of breath. She was brought to the hospital by her son on Feb. 4 (Fig. 2). The laboratory examination

revealed an increased level of white blood cell count ($12.4 \times 10^9/L$), neutrophil count ($7.82 \times 10^9/L$), C-reactive protein level (189.2 mg/L) and a low lymphocyte count ($0.84 \times 10^9/L$) and platelet count ($88 \times 10^9/L$) (Table 1). CT images showed massive shadows of high density in the lungs (Fig. 1). Case 1 developed severe pneumonia and was placed in the ICU as dyspnoea increased, with hypoxemia on day two of hospitalization. As of Feb. 15, her clinical condition had improved, and her oxygen saturation values recovered to 94% on supplemental oxygen. A nasopharyngeal and an oropharyngeal swab obtained on admission day ten remained positive for SARS-CoV-2 (Table 2).

Case 2, a 28-year-old man, was living in Luzhou. He had not come to an area where COVID-19 was spreading or had contact with any fever or pneumonia patients. He had just attended the family reunion dinner with his family members, including his mother (Case 1)/uncle (Case 3)/aunt (Case 4)/cousin (Case 5), on Jan 23 through 25. After his diagnosis of COVID-19, he never had an elevated temperature, and there were no abnormal symptoms except an increased level of C-reactive protein (10.5 mg/L) and a reduced lymphocyte count ($1.03 \times 10^9/L$). Chest CT images showed no significant abnormalities (Fig. 1).

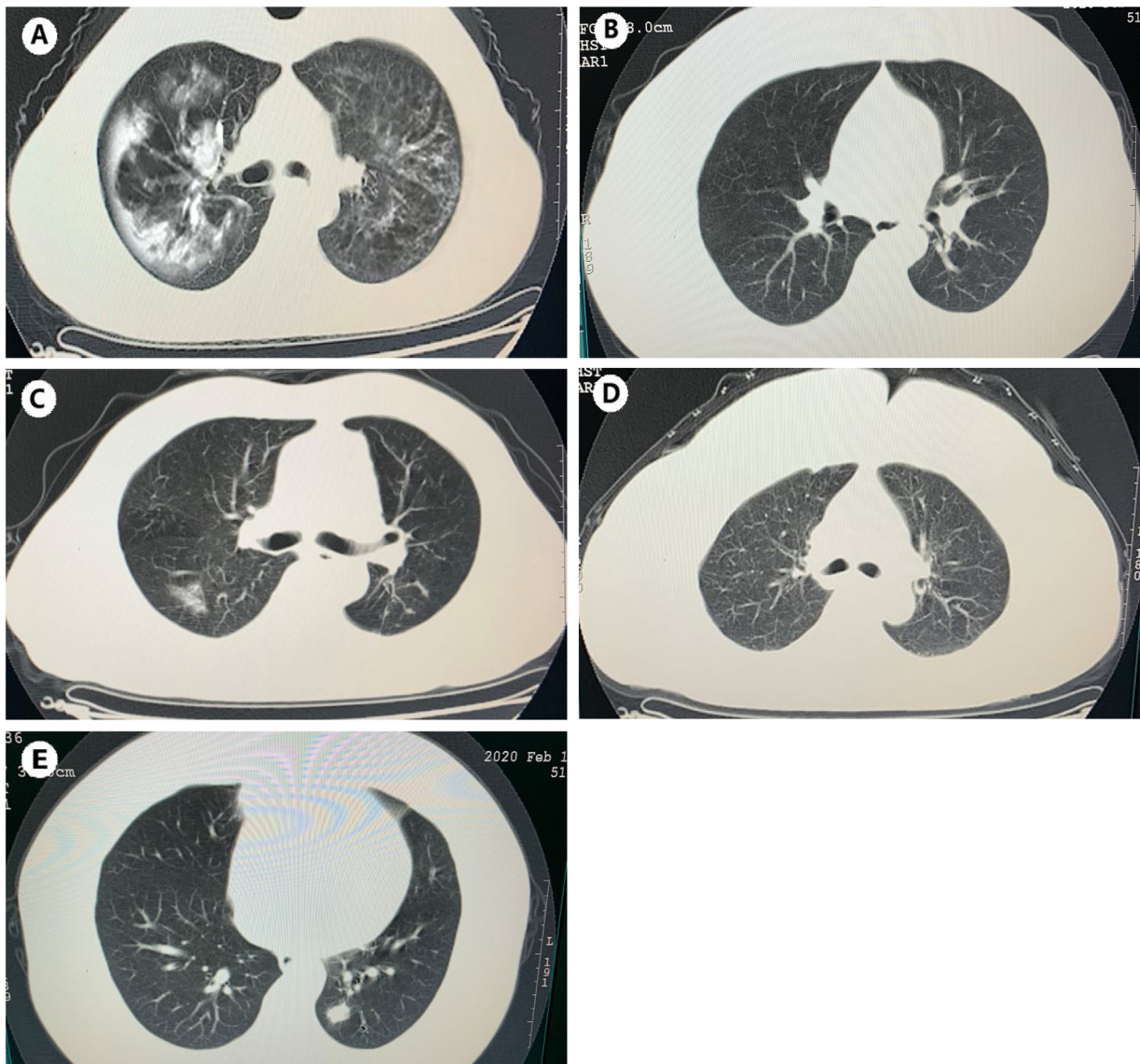


Fig. 1. Respectively, the chest CT images of five Cases. (A) Massive shadows of high density of Case 1. (B/D) No abnormalities of Case 2 and Case 4. (C/E) Ground-glass changes of Case 3 and Case 5.

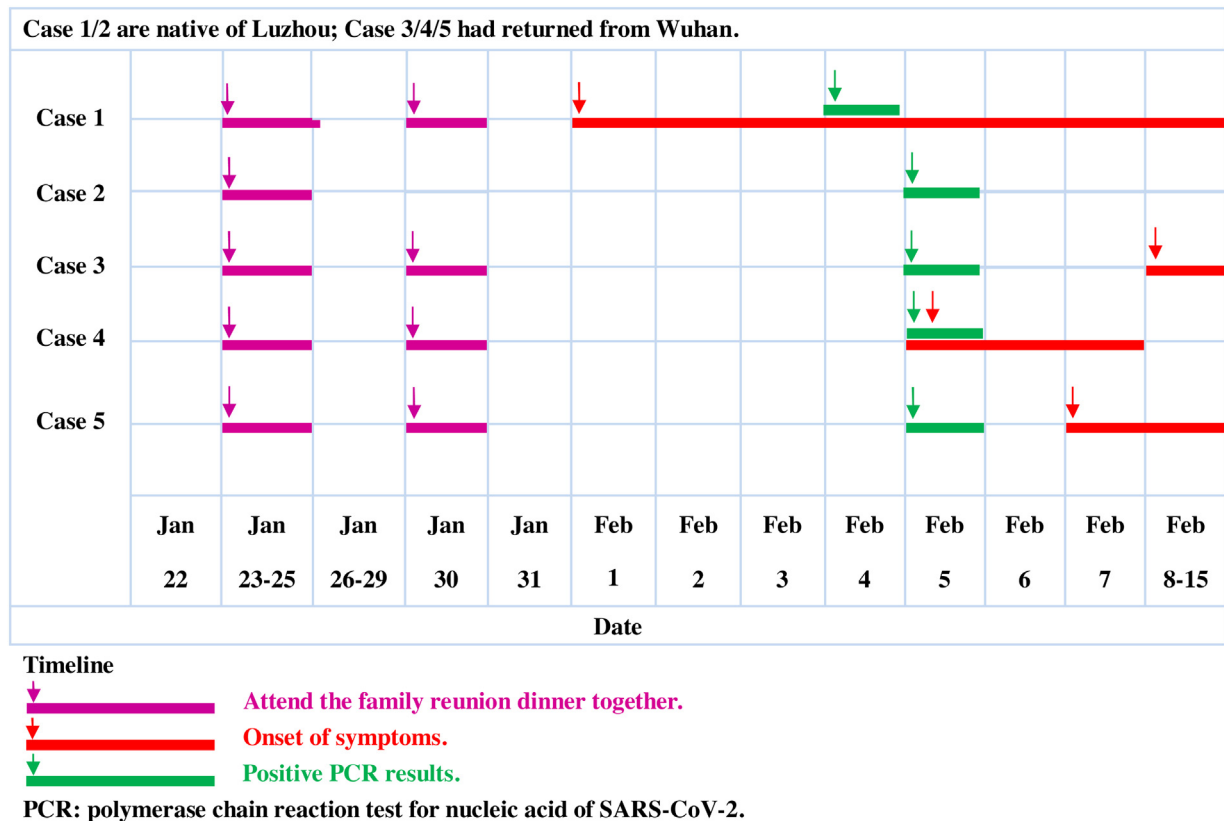


Fig. 2. Timeline of exposure to the asymptomatic carrier of COVID-19 which leads to a familial cluster infection.

On Jan. 22, Case 4, a migrant who did business in Wuhan, drove back to Luzhou with Case 3 and Case 5 for the Spring Festival. On Feb 5, she also was admitted to the hospital, and a nasopharyngeal swab was positive for SARS-CoV-2 (Ct values, 26). Her chest CT images were standard (Fig. 1). From Jan 22 to Feb. 4, Case 4 did not present any symptoms until 7 PM on Feb 5. She started having slight pharyngalgia and diarrhea (3–5 times per day) without an increased body temperature or cough.

Laboratory examination indicated an elevated C-reactive protein (43.5 mg/L), and decreased platelet count ($72 \times 10^9/L$). Case 4 was started on oxygen support at 2 L/min and was treated with oseltamivir (75 mg every 12 h), dioctahedral smectite powder (3 g every 8 h) and cefixime (100 mg every 12 h). Two days later, she felt better. Her rRT-PCR results were negative on Feb 15 (Table 2).

Case 3 and Case 5 are previously healthy men without a history of hypertension or type 2 diabetes. On days three through five of hospitalization, they developed fever and cough symptoms. Chest CT scans showed ground-glass opacities in the lungs (Fig. 1), and other laboratory examinations showed mildly decreased

lymphocyte counts (Table 1) and increased C-reactive protein (9.0/24.7 mg/L). Their infections were moderate. Although their symptoms had resolved except for the cough, they remained hospitalized because their rRT-PCR test results were positive as of Feb. 15 (Table 2).

4. Discussion

COVID-19 has been proven to be transmitted through the respiratory tract, digestive system, and mucosal surfaces (such as the conjunctiva) (Chan et al., 2020; To et al., 2020). Nosocomial infections in healthcare facilities also occur and highlight the significance of effective infection control (Zhang et al., 2020). At the onset, the symptoms are usually fever, cough, shortness of breath, and pharyngalgia or diarrhea (National Health Commission of the People's Republic of China, 2020). The emblematic radiologic characteristic is ground-glass opacities in the lungs. Laboratory data present as lymphocytopenia, hypoxemia, thrombocytopenia, and even liver and kidney dysfunction in severe pneumonia patients (Huang et al., 2020). At present, verified patients are the

Table 2 Results of rRT-PCR test for SARS-CoV-2 nucleic acid.

Specimen	Case 1		Case 2		Case 3		Case 4		Case 5	
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Nasopharyngeal swab	Feb. 4	Feb. 14	Feb. 5	Feb. 12	Feb. 5	Feb. 15	Feb. 5	Feb. 15	Feb. 5	Feb. 15
Oropharyngeal swab	NA	+(Ct 37)	+(Ct 30)	–	+(Ct 22)	+(Ct 33)	+(Ct 26)	–	NA	+(Ct 37)
Serum	+(Ct 19)	+(Ct 35)	+(Ct 23)	+(Ct 38)	+(Ct 21)	+(Ct 31)	NA	–	+(Ct 21)	+(Ct 34)
Urine	ND	–	ND	NA	ND	–	ND	–	ND	NA
Stool	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Ct values for rRT-PCR presented in parentheses. Lower Ct values indicate higher viral loads. Ct = cycle threshold. + = positive. – = negative. ND = not detected. NA = not available.

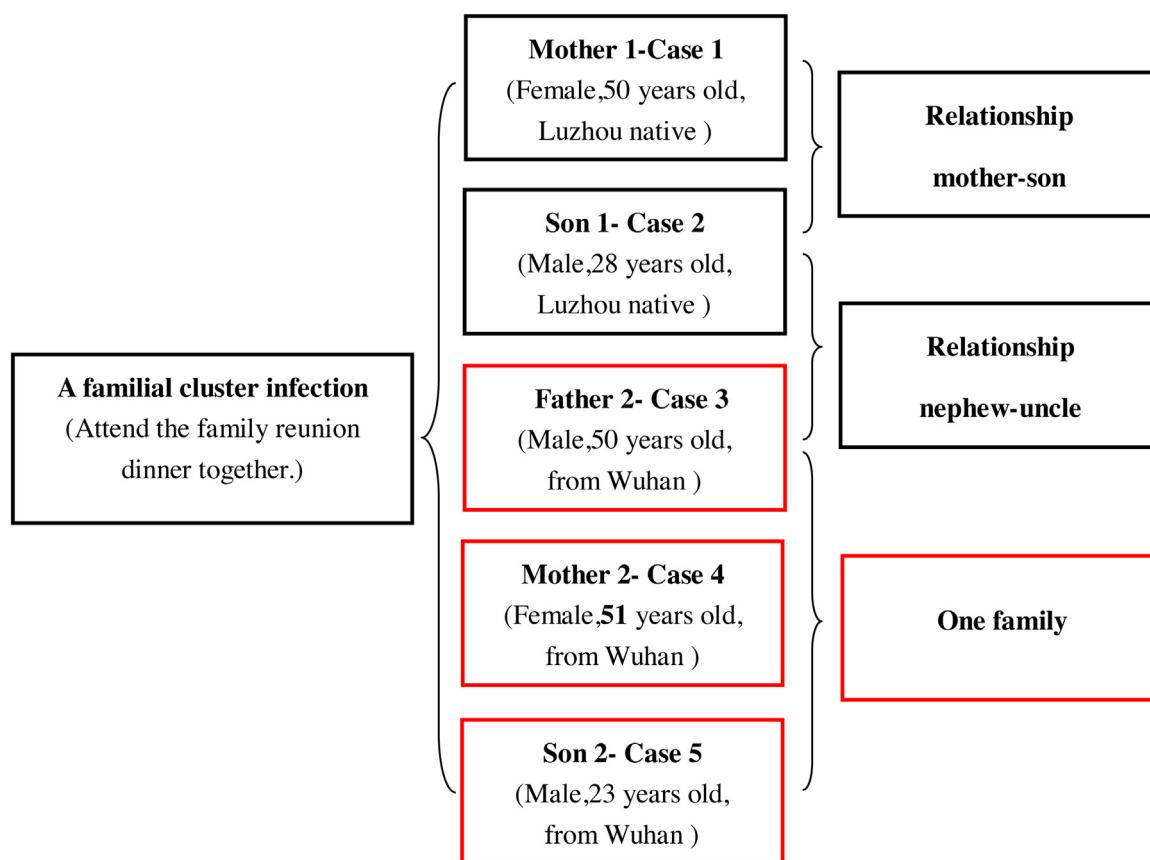


Fig. 3. The relationship between the 5 cases and their general information.

primary sources of infection, however asymptomatic carriers can also be a source to propagate the outbreak. These patients are not easy to detect when initially infected but may have abnormal symptoms later (Huang et al., 2020).

In this familial cluster of five patients associated with COVID-19 in Luzhou, China, Case 1 had contact with only her family members (Case 2/3/4/5), some of them must be asymptomatic carriers of COVID 19. It is certain that Case 2 through 5 had no abnormal symptoms before the outbreak of Case 1. Notably, COVID-19 is highly infectious and may be transmitted by asymptomatic carriers during the incubation period. The timeline events suggest that Case 4 was the most likely initial infection source, as the time of the onset of symptoms and negative rRT-PCR results was relatively earlier than Case 3 and Case 5 (Fig. 2). Case 2 was afebrile without any clinical signs, and his chest CT images showed no abnormalities on Feb. 5 and Feb. 15 (Fig. 1), which also proved the existence of asymptomatic carriers. Our findings provide evidence that asymptomatic carriers can be a latent source of COVID-19 infection. As the spread of COVID-19 is worsening worldwide, it is pressing to provide more information for an improved understanding of both the transmission and precautions to take to deal with COVID-19. Further studies on the mechanism in which asymptomatic carriers can acquire and transmit COVID-19 are warranted.

Ethical approval

The Ethics Committee of People's Hospital of Luxian County approved this study. We obtained written consent from all the patients about clinical data, radiographic pictures, information, etc.

Availability of data and materials

All data and materials used in this work are publicly available.

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Authors' contributions

All of the authors collected epidemiological and clinical data and discussed the results. F.Y. drafted the article. S.X. contributed to summarizing all clinical data. Z.R. and P.D. analyzed all epidemiological data. X.X and R.X. revised the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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