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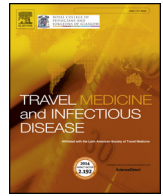
A cross-sectional comparison of epidemiological and clinical features of patients with coronavirus disease (COVID-19) in Wuhan and outside Wuhan, China

Ziying Lei[a,b,2], Huijuan Cao[a,b,2], Yusheng Jie[a,b,2], Zhanlian Huang[a,b], Xiaoyan Guo[a,b], Junfeng Chen[a,b], Liang Peng[a,b], Hong Cao[a,b], Xiaoling Dai[a,b], Jing Liu[a,b], Xuejun Li[a,b], Jianyun Zhu[a,b], Wenxiong Xu[a,b], Dabiao Chen[a,b], Zhiliang Gao[a,b,1], Jian-Rong He[c,1,**], Bing-Liang Lin[a,b,1,*]

[a] Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China
[b] GuangDong Provincial Key Laboratory of Liver Diseases, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[c] Nuffield Department of Women's and Reproductive Health, University of Oxford, UK

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has spread outside the initial epicenter of Wuhan. We compared cases in Guangzhou and Wuhan to illustrate potential changes in pathogenicity and epidemiological characteristics as the epidemic has progressed.
Methods: We studied 20 patients admitted to the Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou, China from January 22 to February 12, 2020. Data were extracted from medical records. These cases were compared with the 99 cases, previously published in Lancet, from Wuhan Jinyintan Hospital from January 1 to January 20, 2020.
Results: Guangzhou patients were younger and had better prognosis than Wuhan patients. The Wuhan patients were more likely to be admitted to the ICU (23% vs 5%) and had a higher mortality rate (11% vs 0%). Cases in Guangzhou tended to be more community clustered. Diarrhea and vomiting were more common among Guangzhou patients and SARS-CoV-2 RNA was found in feces. Fecal SARA-CoV-2 RNA remained positive when nasopharyngeal swabs turned negative in some patients.
Conclusions: This study indicates possible diminishing virulence of the virus in the process of transmission. Yet persistent positive RNA in feces after negative nasopharyngeal swabs suggests a possible prolonged transmission period that challenges current quarantine practices.

1. Introduction

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae, with a genome ranging from 26 to 32 kilobases in length [1]. Among the several coronaviruses that are pathogenic to humans, most are associated with mild clinical symptoms, with two notable exceptions: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [2,3], which have caused more than 10000 cumulative cases in the past two decades with mortality rates of 9.5% and 34.4% respectively [4–6]. In December 2019, a novel pneumonia, termed coronavirus disease 2019 (COVID-19), emerged in Wuhan, China and has been proven to be caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]. All the twenty-

seven first cases reported by December 31, 2019 were closely related to exposure with the Huanan Seafood Market in Wuhan [8]. By analyzing the genome sequence of SARS-CoV-2, it was speculated that the pathogen originated in bat, the natural reservoir host, and then transmitted to humans via an uncertain wild animal intermediate host [9]. There is convincing evidence that the human-to-human transmission has occurred since the end of December 2019 or the early January 2020 [10]. To control the spread of COVID-19, the Wuhan authority has sealed off the entire city from outside contact since Jan 23, 2020. However, it's estimated that five million people have left Wuhan before the "lockdown" and travelled throughout China [11]. By April 1, 2020, the disease has affected over 200 countries, with over 880,000 confirmed cases and 44220 deaths [12–18]. In China, substantial attention has focused mainly on Wuhan, whereas the detailed information regarding the disease outside Wuhan is rarely reported [19,20]. Furthermore, little is known about the changes in pathogenicity, clinical manifestations and mode of transmission of SARS-CoV-2 when the epidemic expanded beyond Wuhan.

Here, we summarized the epidemiologic and clinical characteristics of 20 laboratory-confirmed cases of COVID-19 in Guangdong who hospitalized in the 3rd affiliated hospital of Sun Yat-sen University from January 22 to February 18, 2020, and compared these cases with previous reported cases in Wuhan, aiming to provide information for understanding the changes in clinical manifestations and transmission model.

2. Methods

2.1. Study design and participants

The study was approved by the Third Affiliated Hospital of Sun Yat-Sen University Ethics Committee, and oral consent was obtained from patients. All confirmed patients with COVID-19 admitted to the Third Affiliated Hospital of Sun Yat-Sen University from Jan 22 to Feb 12, 2020 were enrolled and followed-up until February 18, 2020. All patients with COVID-19 enrolled in this study were diagnosed according to the WHO interim guidance [21]. To compare the epidemiological and clinical characteristics between patients in Guangdong and Wuhan (epidemic area), we included previously published data on 99 cases diagnosed in Wuhan Jinyintan Hospital from January 1 to January 20, 2020. Wuhan patients were followed-up until January 25, 2020 [22].

2.2. Data collection

The epidemiological characteristics (including recent exposure history), clinical symptoms and signs, radiologic and laboratory findings were extracted from electronic medical records. Radiologic assessments included chest X-ray or computed tomography (CT). Laboratory assessments consisted of complete blood count, blood chemistry, coagulation test, liver and renal function, electrolytes, C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase and creatine kinase. ARDS was defined according to the Berlin definition [23].

2.3. Laboratory confirmation of SARS-Cov-2 infection

The viral nucleic acid testing-based laboratory confirmation of SARS-CoV-2, performed by the hospital's laboratory and the key laboratory of Guangdong Centre for Disease Control and Prevention (CDC), China, was determined by real-time RT-PCR according to the Chinese national CDC recommended protocol. Firstly, the nasopharyngeal swab was collected every 2 days during hospitalization. Then the RNA samples from the nasal swab specimens were extracted and subjected to the real-time RT-PCR test using SARS-Cov-2 specific primers and probes. Specifically, the primers for the open reading frame 1 ab (ORF1ab) are 5′-CCCTGTGGGTTTTACACTTAA-3' (Forward) and 5′-ACGATTGTGCATCAGCTGA-3' (Reverse); the corresponding probe is

Table 1
Baseline characteristics and epidemiology of patients with COVID-19 within and outside Wuhan.

|	Guangzhou[#1] (N = 20)	Wuhan[#2] (N = 99)	P values
Characteristics			
Age, years, Mean (SD)	43.2 (14.0)	55.5 (13.1)	< 0.001
Range	25–64	21–82	
≤39	9 (45.0%)	10 (10.1%)	0.002
40-49	4 (20.0%)	22 (22.2%)	
50-59	2 (10.0%)	30 (30.3%)	
60-69	5 (25.0%)	22 (22.2%)	
≥70	0 (0.0%)	15 (15.2%)	
Sex			0.198
Female	10 (50.0%)	32 (32.3%)	
Male	10 (50.0%)	67 (67.7%)	
Chronic medical illness	7 (35.0%)	50 (50.5%)	0.229
Cardiovascular and cerebrovascular diseases	5 (25.0%)	40 (40.4%)	0.209
Digestive system disease	3 (15.0%)	11 (11.1%)	0.703
Endocrine system disease	1 (5.0%)	13 (13.1%)	0.460
Malignant tumor	0 (0.0%)	1 (1.0%)	1.000
Respiratory system disease	1 (5.0%)	1 (1.0%)	0.309
Admission to intensive care unit	1 (5.0%)	23 (23.2%)	0.072
Signs and symptoms			
Fever	16 (80.0%)	82 (82.8%)	0.752
Cough	11 (55.0%)	81 (81.8%)	0.017
Shortness of breath	2 (10.0%)	31 (31.3%)	0.052
Myalgia	7 (35.0%)	11 (11.1%)	0.013
Sore throat	4 (20.0%)	5 (5.1%)	0.043
Diarrhea	5 (25.0%)	2 (2.0%)	0.001
Nausea and vomiting	3 (15.0%)	1 (1.0%)	0.015
More than one sign or symptom	18 (90.0%)	89 (89.9%)	1.000
Fever, cough, and shortness of breath	2 (10.0%)	15 (15.2%)	0.734
Comorbid conditions			
Any	3 (15.0%)	33 (33.3%)	0.118
ARDS	1 (5.0%)	17 (17.2%)	0.302
Acute renal injury	0 (0.0%)	3 (3.0%)	1.000
Acute respiratory injury	1 (5.0%)	8 (8.1%)	1.000
Septic shock	1 (5.0%)	4 (4.0%)	1.000
Ventilator-associated pneumonia	0 (0.0%)	1 (1.0%)	1.000
Epidemiological survey			
Exposure to Huanan seafood market	0 (0.0%)	49 (49.5%)	< 0.001
Live history in epidemic area[a]	14 (70.0%)	99 (100.0%)	< 0.001
Community cluster outbreak	10 (50.0%)	2 (2.0%)[#3]	< 0.001
Close contacts with COVID-19 patient	6 (30.0%)	NA	NA

Data are n (%) unless specified otherwise. N is the total number of patients with available data. ARDS = acute respiratory distress syndrome. COVID-19 = coronavirus disease −19. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and *t*-test for continuous variables. #1 Admitted to the Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou from January 22 to February 12, 2020, the last follow-up was on February 18, 2020.
#2 Diagnosed in Wuhan Jinyintan Hospital from January 1 to January 20, 2020, the last follow-up was on January 25, 2020. #3 Only include the cases without long-term exposure to Huanan seafood market.
NA, not available.
  [a] Epidemic area refers to Wuhan and other epidemic areas in Hubei Province.

5′-CY3-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3′. Primers for nucleocapsid protein (N) are 5′-GGGGAACTTCTCCTGCTAGAAT-3' (Forward) and 5′-CAGACATTTTGCTCTCAAGCTG-3' (Reverse); the corresponding probe is 5′-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-
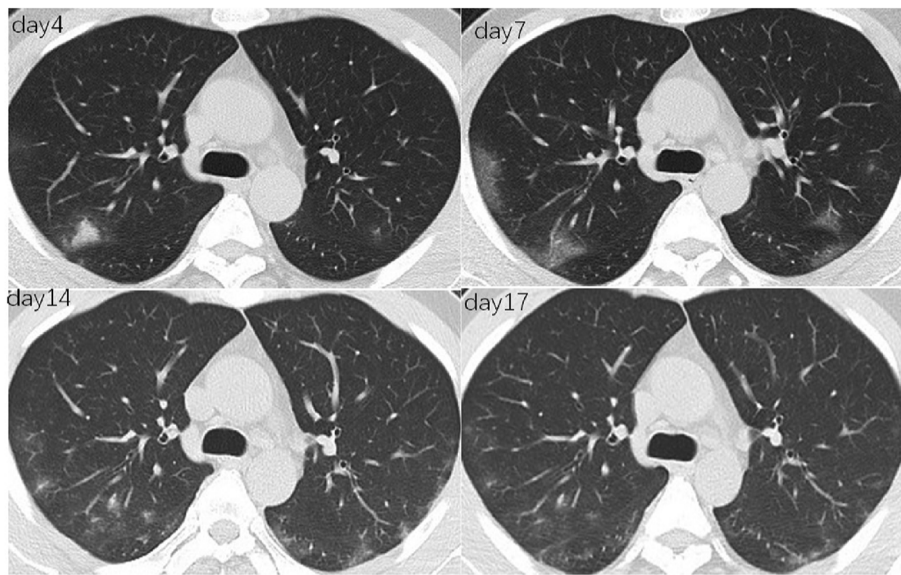
3′. The clearance of SARS-CoV-2 was defined as two consecutive negative results with qPCR detection at an interval of 24 h.

2.4. Statistical analysis

Continuous variables were expressed as mean (SD) or median (IQR) and compared with the *t*-test or Mann-Whitney *U* test; categorical variables were expressed as frequency (%) and compared by χ^2 test or Fisher's exact test between the cases in Guangzhou and Wuhan. For laboratory indicators, we categorized the results into normal or abnormal (increased or decreased). We used SPSS (IBM, version 26.0) for all analyses.

2.5. Role of the funding source

Funding sources had no role in this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Demographics, baseline characteristics and clinical characteristics

All the COVID-2019 patients (N = 20) admitted in the Third Affiliated Hospital of Sun Yat-sen University were enrolled, including 10 males and 10 females. Patients in Guangzhou were younger than those in Wuhan (43.2 vs 55.5 years, $P < 0.001$). Among Guangzhou patients, 14 had a history of living or travelling in Wuhan, and 6 were local incident patients with a history of close contact with confirmed cases. 10 Guangzhou patients were from seven clusters, including five family clusters, one cruise ship cluster and one driving tour cluster to Wuhan, while only two shoppers were community clustered among Wuhan patients.

Patients in both cities mainly manifested fever, cough and myalgia. Cough (82% vs 55%, $P = 0.017$) and shortness of breath (31% vs 10%, $P = 0.052$) were more prevalent among patients in Wuhan, while patients in Guangzhou had a higher prevalence of diarrhea (2% vs 25%, $P = 0.001$) and vomiting (1% vs 15%, $P = 0.015$). Higher percentages of patients were admitted to the ICU (23% vs 5%, $P = 0.072$) and complications (33% vs 15%, $P = 0.118$), such as ARDS (17% vs 1%, $P = 0.302$) in Wuhan (Table 1).

3.2. Laboratory, imaging, and pathogenic characteristics of patients with COVID-19

Blood routine and biochemical data of the patients in Guangzhou were basically normal, and only 25% of the patients had a lymphocyte count of less than 1.0×10^9/L. The lymphocyte count, hemoglobin and albumin of patients in Wuhan were significantly lower, while inflammatory biomarkers, blood erythrocyte sedimentation rate (ESR), CRP and PCT were significantly higher than those in Guangzhou (all P values < 0.05). Chest CT scan indicated bilateral involvement in both cities. Based on Guangzhou data, the main manifestations were multiple patches (90%), ground-glass opacity (80%) and interstitial lesions (80%). Invasive lesions were presented in 55% of patients (Fig. 1). Multiple mottling and ground-glass opacity were more common in Guangzhou patients (14% vs 60%, $P < 0.001$) (Table 2).

3.3. Treatment and prognosis of patients with COVID-19

In both cities, most patients were mainly treated with antibiotics or antivirus therapy, including Lopinavir and Ritonavir (Kaletra), arbidol, ribavirin and aerosol inhalation of interferon alpha, 13 (65%) patients were given combination antivirus therapy (data only available in Guangzhou patients) (Table 3). 27%–30% of patients were treated with immunoglobulin and 20% with thymosin alpha-1 (data only available in Guangzhou patients) to regulate immunity. 25% of patients in Guangzhou, compared to 19.2% in Wuhan, with severe pulmonary inflammation and decreased oxygenation index received short-term corticosteroids treatment, with methylprednisolone 1 mg/kg/day for 3 days. More patients in Wuhan needed oxygen treatment than those in Guangzhou (75% vs 40%, $P = 0.001$). By the last follow-up date, the patients in Guangzhou have a higher discharged rate and lower mortality rate than those in Wuhan ($P = 0.005$).

3.4. SARS-CoV-2 RNA in nasopharyngeal swabs and feces

Among Guangzhou patients, SARS-CoV-2 RNA in nasopharyngeal swabs disappeared at an average of 12 days (maximum, 22 days). SARS-CoV-2 RNA in feces turned negative in 4–16 days. In two cases, the fecal RNA did not turn negative until 5 and 6 days after negative nasopharyngeal swab.

Table 2
Comparison of Laboratory data and Outcome of Patients with COVID-19 Within and Outside Wuhan.

	Guangzhou[#1] (N = 20)	Wuhan[#2] (N = 99)	P values
Blood routine			
Leucocytes (× 10^9/L, normal range 3.5–9.5)	5.2 (1.6)	7.5 (3.6)	0.006
Lymphocytes (× 10^9/L, normal range 1.1–3.2)	1.4 (0.7)	0.9 (0.5)	0.003
Platelets (× 10^9/L, normal range 125.0–350.0)	205.0 (62.6)	213.5 (79.1)	0.652
Hemoglobin (g/L, normal range 130.0–175.0)	139.3 (15.3)	129.8 (14.8)	0.010
Blood biochemistry			
Increased alanine aminotransferase	4 (20.0%)	28 (28.3%)	0.584
Increased aspartate aminotransferase	3 (15.0%)	35 (35.4%)	0.113
Increased total bilirubin	1 (5.0%)	18 (18.2%)	0.192
Albumin (g/L)	44.8 (5.6)	31.6 (4.0)	< 0.001
Decreased	1 (5.0%)	97 (98.0%)	< 0.001
Increased serum creatinine	1 (5.0%)	3 (3.0%)	0.526
Increased creatine kinase	5 (25.0%)	13 (13.1%)	0.183
Increased myoglobin	2/17 (11.8%)	15 (15.2%)	1.000
Infection-related biomarkers			
Erythrocyte sedimentation rate (mm/h, normal range 0–15)	19.3 (13.2)	49.9 (23.4)	< 0.001
C-reaction protein (mg/L, normal range 0–6)	25.0 (29.3)	51.4 (41.8)	0.002
Procalcitonin (ng/mL, normal range 0–0.05)	0.08 (0.09)	0.5 (1.1)	< 0.001
Chest X-ray and CT finding			
Unilateral pneumonia	2 (10.0%)	25 (25.3%)	0.239
Bilateral pneumonia	18 (90.0%)	74 (74.7%)	0.239
Multiple mottling and ground-glass opacity	12 (60.0%)	14 (14.1%)	< 0.001
Peripheral pneumonia	17 (85.0%)	NA	NA
interstitial lesions	16 (80.0%)	NA	NA
Ground-glass opacity	16 (80.0%)	NA	NA
Multiple patches	18 (90.0%)	NA	NA
Multiple Infiltration	11 (55.0%)	NA	NA
Nodule	4 (20.0%)	NA	NA
Lung consolidation	4 (20.0%)	NA	NA
Pleural effusion	2 (10.0%)	NA	NA

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease −2019 *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and *t*-test for continuous variables.

#1 Admitted to the Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou from January 22 to February 12, 2020, the last follow-up was on February 18, 2020.

#2 Diagnosed in Wuhan Jinyintan Hospital from January 1 to January 20, 2020, the last follow-up was on January 25, 2020.

NA, not available.

4. Discussion

By comparing cases from the Third Affiliated Hospital of Sun Yat-sen University between January 22 to February 18, 2020 and Wuhan Jinyintan Hospital between January 1 to January 25, 2020, this study revealed the changes in pathogenicity and epidemic characteristics of COVID-19 in the epidemic process. Both hospitals are designated hospital for COVID-19. Although small in number, the Guangzhou patients were a random sample at an early stage when cases started being imported into a major city. The different admission time in the two

Table 3
Treatment and prognosis of patients with COVID in Guangzhou and Wuhan.

	Guangzhou[#1] (N = 20)	Wuhan[#2] (N = 99)	P value
Treatment			
Oxygen therapy	8 (40.0%)	75 (75.8%)	0.001
Mechanical ventilation	2 (10.0%)	17 (17.2%)	0.738
Non-invasive (ie, face mask)	1 (5.0%)	13 (13.1%)	0.460
Invasive	1 (5.0%)	4 (4.0%)	1.000
CRRT	0 (0.0%)	9 (9.1%)	0.354
ECMO	0 (0.0%)	3 (3.0%)	1.000
Antiviral therapy	16 (80.0%)	75 (76.0%)	0.781
Kaletra*	16 (80.0%)	NA	NA
Arbidol	13 (65.0%)	NA	NA
Interferon alpha atomized inhalation	5 (25.0%)	NA	NA
Ribavirin	1 (5.0%)	NA	NA
Combination of two antiviral drugs	9 (45.0%)	NA	NA
Combination of three antiviral drugs	4 (20.0%)	NA	NA
Antibiotic therapy	17 (85.0%)	70 (70.7%)	0.271
Glucocorticoids	5 (25.0%)	19 (19.2%)	0.550
Intravenous immunoglobulin therapy	6 (30.0%)	27 (27.3%)	0.789
Thymosin alpha1	4 (20.0%)	NA	NA
Chinese traditional medicine	20 (100.0%)	NA	NA
SARS-CoV-2 RNA positive at admission			
Nasopharyngeal swabs	20 (100.0%)	99 (100.0%)	1.000
Feces (n/N, %)	4/7 (57.1%)	NA	NA
Duration of SARS-CoV-2 RNA positive			
Nasopharyngeal swabs (N = 20) (days)	12.0 (7.5, 15.5)	NA	NA
Feces (N = 4 of 7) (range, days)	4.0–16.0	NA	NA
Clinical outcome			
Outcome			0.005
Remained in hospital	6 (30.0%)	57 (57.6%)	
Discharged	14 (70.0%)	31 (31.3%)	
Died	0 (0.0%)	11 (11.1%)	

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. CRRT = continuous renal replacement therapy. ECMO = extracorporeal membrane oxygenation. P values for comparing two groups were derived using Fisher's exact test for categorized variables and *t*-test for continuous variables. *Kaletra: Lopinavir and ritonavir.

#1 Admitted to the Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou from January 22 to February 12, 2020, the last follow-up was on February 18, 2020.

#2 Diagnosed in Wuhan Jinyintan Hospital from January 1 to January 20, 2020, the last follow-up was on January 25, 2020.

NA, not available.

hospitals could represent two stages of the epidemic, while treatment and follow-up time are the same, which may well reflect the changing clinical and epidemiological characteristics of the disease.

The median ages of cases in Wuhan reported by Cao and Zhang were 49.0 and 55.5 years respectively[8,22], while patients in Guangzhou were relatively younger, with the median age of 43.2 years. There have been reports of cases in children, indicating all ages are susceptible [24]. Compared with patients in Guangzhou, patients in Wuhan were more severe, reflected by that Wuhan patients had a higher incidence of dyspnea and ARDS, higher levels of inflammatory biomarkers and worse prognosis. These differences could be due to age and pre-existing conditions [8,25,26]. However, in the present study, we did not observe an evident difference in underlying disease between Guangzhou

patients and Wuhan patients. We speculate that the differences may be related to that the diminishing pathogenicity of the virus after transmission of multiple generations [5,27], however, further studies are required to confirm this hypothesis. Besides, patients in Guangzhou were more aware of the disease; thus, they visited the hospital at the earlier stage with less severe symptoms. Furthermore, given the experience in Wuhan, the health authorities in Guangzhou were well-prepared for the epidemic and were able to carry out comprehensive screening, early case identification and contact tracing and timely treatment.

In terms of clinical characteristics, we observed that the gastrointestinal symptoms such as diarrhea and vomiting were more prevalent in patients with later-onset in Guangzhou. Meanwhile, fecal RNA was positive in 4 out of 7 patients, indicating the possibility of gastrointestinal transmission. Xiao Fei also confirmed gastrointestinal infection by detecting SARS-CoV-2 in feces and gastrointestinal tissues [28]. These findings have important implications for patient triage and hospital risk zoning. Gastroenterology outpatient medical staff could be at higher risk when encountering COVID patients, thus more aggressive PPE protection and proactive patient screening are necessary. In addition, sufficient education and protocols should be given to caregivers who could be exposed to the patients' vomits and feces directly, and feces disposal should be managed properly to reduce environmental harzards. More importantly, we found that two patients' fecal virus RNA turned negative 5 and 6 days later than the nasopharyngeal swab respectively, suggesting that transimission of virus is possibly prolonged, and fecal virus RNA may be an indispensable indicator for lifting quarantines. Given that some "recovered" cases being tested positive again a few days after discharged have been reported recently [29], our findings highlight the importance of fecal virus test for patient management and quarantines. The health authority may also have to re-consider quarantine strategy for possible extended case management time and burden when distributing health resources.

Our findings also suggest that the modes of transmission have changed considerably with the spread of the disease. A large fraction of early reported cases in Wuhan were linked to Huanan seafood markets, whereas none of cases in Guangzhou had a history of exposure to wildlife markets. Furthermore, 10 patients from Guangzhou were involved in seven cases of clustering. This finding suggests strong community transmission poses a great challenge to the entire prevention and control. It resonates with the concept that the transmissibility increases while virulence decreases as virus spread [30]. As indicated by Tang's research, the L type of SARS-CoV-2 prevalent in the early stages of the outbreak in Wuhan, decreased after early January 2020, while the S type, which is less aggressive, have increased in relative frequency due to relatively weaker selective pressure [31]. Thus early detection and timely isolation is vital before a case becomes a cluster. It also raises the concern that the risk and benefit should be balanced in home quarantine for confirmed cases which could result in family case clusters.

At present, symptomatic, support treatment and airway maintenance are the main treatments, as there is no proven effective antiviral therapy. It is claimed that kaletra, remdesivir and chloroquine phosphate have antiviral effects from preliminary studies [32,33], but the results of clinical trials are yet to be released. Patients in Guangzhou mainly use kaletra + arbidol, some with severe pulmonary inflammation added interferon atomized inhalation, which has also achieved good treatment effect. Nevertheless, further research with control groups would be helpful to differentiate whether the effect is caused by drugs or patients' self-recovery of the disease.

Our study has limitations. First, the number of patients was small. Second, Wuhan cases are from published data, and more detailed information, such as the final prognosis of patients, could not be obtained.

In summary, our results suggest that the virulence of SARA-CoV-2 is possibly waning in the process of transmission and the clustering occurrence is becoming the primary model of transmission. In addition, our observation that fecal virus RNA turned negative later than the nasopharyngeal swab justifies that the concern of faecal-oral transmission and suggest that fecal virus RNA should be assessed before lifting quarantine.

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CRediT authorship contribution statement

Ziying Lei: Conceptualization, Investigation, Data curation, Formal analysis, Writing - original draft. **Huijuan Cao:** Formal analysis, Writing - original draft. **Yusheng Jie:** Investigation, Formal analysis. **Zhanlian Huang:** Investigation, Formal analysis. **Xiaoyan Guo:** Writing - original draft. **Junfeng Chen:** Investigation. **Liang Peng:** Resources. **Hong Cao:** Resources. **Xiaoling Dai:** Resources. **Jing Liu:** Formal analysis. **Xuejun Li:** Investigation. **Jianyun Zhu:** Investigation. **Wenxiong Xu:** Investigation. **Dabiao Chen:** Investigation. **Zhiliang Gao:** Resources, Writing - review & editing, Funding acquisition, Supervision. **Jian-Rong He:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. **Bing-Liang Lin:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no competing interests.

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