Clinical features of familial clustering in patients infected with 2019 novel coronavirus in Wuhan, China

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ABSTRACT

An epidemic caused by SARS-Coronavirus-2 (SARS-CoV-2) infection has appeared in Wuhan City in December 2019. The disease has shown a "clustering epidemic" pattern, and family-clustered onset has been the main characteristic. We collected data about 130 cases from 35 cluster-onset families (COFs) and 41 cases from 16 solitary-onset families (SOFs). The incidence of 2019 coronavirus disease (COVID-19) in COFs was significantly higher than that of SOFs. Our study also showed that patients with exposure to high-risk factors (respiratory droplets and close contact), advanced age, and comorbidities were more likely to develop COVID-19 in the COFs. In addition, advanced age and elevated neutrophil/lymphocyte ratio (NLR) were risk factors for death in patients with SARS-CoV-2 infection in the COFs.

1. Introduction

Since December 2019, cases of SARS-Coronavirus-2 (SARS-CoV-2) infected pneumonia have been found in Wuhan, Hubei Province, China. Since the start of the epidemic, a total of 80,958 patients have been diagnosed with 2019 coronavirus disease (COVID-19) in China as of March 11, 2020. SARS-CoV-2 is highly infectious, and mainly transmitting via respiratory aerosols or droplets. Most people are generally susceptible to it. The clinical manifestations are mainly fever, fatigue and dry cough (Huang et al., 2020; Chen et al., 2020a).

In contrast to SARS, SARS-CoV-2 infection had a "clustering epidemic" pattern, and family clustering of disease is the main characteristic (Chan et al., 2020a). According to China-WHO statistics, the 344 clusters reported in Guangdong and Sichuan provinces involved a total of 1308 cases, most (78 %–85 %) of which occurred in family members (The General Office of the National Health and Health Commission and the Office of the State Administration of Traditional Chinese Medicine, 2020). However, the transmission path, persistent transmission rate, clinical characteristics, and prognostic outcomes of cluster-onset families (COFs) are currently unknown. Therefore, this article retrospectively analyzed the epidemiological, clinical characteristics and prognosis of 35 COF patients diagnosed with COVID-19. A preliminary study was conducted to evaluate the relationship between epidemiological factors, such as exposure route and incidence sequence, and the incidence, clinical manifestation and prognosis of patients in COF to provide a strong basis for epidemic control.

2. Methods

2.1. Clinical data collection

A retrospective epidemiological investigation and analysis of COVID-19 cases was conducted in accordance with the National Epidemiological Survey Program for New Coronavirus Infected Pneumonia Cases (General Office of the National Health and Health Commission, 2020a) by mainly collecting data from cases with clustered onset in the family. Data from some solitary-onset families (SOFs), where only one person was infected, were also collected as a control. Full-time investigators conducted in-depth epidemiological investigations on the patients one-by-one, and the incidence of some family members was obtained through history collection or telephone follow-up. The main contents of the data collected included general information of the patients and their close contact family members, epidemiological history (incidence, exposure history), clinical manifestation, previous history, medical treatment, degree of illness, laboratory results, CT diagnosis, length of hospital stay, and prognosis. The data

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were relatively complete, accurate, true and reliable. COVID-19 data were collected from January 1, 2020, to March 11, 2020.

COVID-19 was diagnosed according to the Chinese New Coronavirus Pneumonia Diagnosis and Treatment Program (trial version 7) (The General Office of the National Health and Health Commission and the Office of the State Administration of Traditional Chinese Medicine, 2020). COVID-19 cases included confirmed cases and clinically diagnosed cases. Clinically diagnosed cases were defined as those with a clear epidemiological history and clinical manifestations that met any two of the following three criteria: (1) fever and/or respiratory symptoms; (2) imaging features of COVID-19 (Li et al., 2020a); (3) normal or decreased white blood cell count and normal or decreased lymphocyte count in early onset. A confirmed case was defined as one with the following etiology or serology evidence based on clinical diagnosis: (1) positive for SARS-CoV-2 by the real-time PCR nucleic acid test in respiratory or blood samples (World Health Organization, 2019); (2) viral gene sequencing was highly homologous to known new coronaviruses; or (3) positive detection of SARS-CoV-2-specific IgM antibodies and IgG antibodies. Familial clustered onset referred to two or more confirmed cases or asymptomatic infections found in a single family, with the possibility of interpersonal transmission due to close contact or the possibility of infection due to co-exposure, within 14 days. Close contacts were mainly those who have not take effective protection from close contact with the suspected and confirmed cases 2 days before symptoms appeared, or the asymptomatic infected persons 2 days before the specimen collection (General Office of the National Health and Health Commission, 2020b).

2.2. Statistical Analysis

Categorical variables were expressed as counts and percentages, and they were analyzed using the $\chi2$ or Fisher's exact test. Continuous variables are presented as the mean and standard deviation ($\pm$ SD). Student's t test or one-way ANOVA were used for statistical comparisons, where appropriate. Multinomial (binary) logistic regression was applied to evaluate factors associated with deaths in COFs. Two-sided P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS 19.0 software (SPSS, Chicago, IL, USA).

3. Results

3.1. Characteristics of cluster-onset families

By March 11, 2020, a total of 130 people from 35 COF were admitted at Hankou Hospital of Wuhan City, including 35 new-onset patients, 59 secondary patients and 36 non-infected family members (Table 1). There were also 16 SOFs with 41 people, including 16 new-onset patients and 25 non-infected family members. The average age of the onset in the COF patients was 58.7 $\pm$ 16.0 years old, and 46.9 % were females, while the average age of onset in the SOF patients was 61.6 $\pm$ 10.2 years old, and females accounted for 37.5 %. There were no significant difference between the two groups. For the onset members of the COFs, 76.6 % had fever symptoms, while 68.8 % of SOFs had fever symptoms. The next most common symptom in COFs was cough (52.1 %), while chest tightness (9.6 %) and diarrhea (13.8 %) were less common. The most common "other" symptoms in COFs were anorexia (20.2 %) and expectoration (13.8 %). Among COF patients, 41.5 % had at least one comorbidity (such as hypertension and diabetes), compared with 56.3 % in SOF patients. At the time of admission, the proportion of severe cases and critical cases in COF patients was 41.5 % and 14.9 %, respectively. The respective proportions in SOF patients was 62.5 % and 6.3 %, indicating that the proportion of severe and critical cases in the enrolled patients was high. A total of 68.9 % of inpatients in the COFs had lymphopenia, and 17.8 % had leukopenia. In addition, 81.3 % of inpatients in the SOFs had lymphopenia, and 12.5 % had leukopenia. In

terms of diagnosis, the positive rate on the nucleic acid test in COF patients (67 %) was higher than that in SOF patients (53.3 %), but the difference was not statistically significant (P > 0.05). There were 3 (4.8 %) patients with positive nucleic acid and normal chest CT and 23 (28 %) patients with multiple negative nucleic acid tests and chest CT with typical features of COVID-19, suggesting that the false negative rate for nucleic acid detection was relatively high.

3.2. Epidemiological history

Among the self-reported causes of infection in new-onset patients in the COFs (Fig. 1), the most common was cross-infection in the community (45.7 %), followed by hospital exposure history (14.3 %), vegetable market or supermarket exposure (11.4 %), and a history of seafood or fruit market exposure in south China for a few (8.6 %). In COFs, the transmission rates of respiratory droplets in secondary and non-infected patients were 11.9 % and 66.7 %, respectively, while the transmission rates of respiratory droplets with close contacts were 88.1 % and 33.3 %, respectively. In SOFs, the proportion of respiratory droplet and respiratory droplet transmission with close contacts was 40 % and 60 %, respectively (Fig. 2).

3.3. Analysis of high-risk factors for COVID-19 incidence in COFs

In COFs, the incidence of COVID-19 was as high as 72.3 %, which was significantly higher than the 39.0 % COVID-19 incidence in the SOFs. Statistical analysis found that the proportion of exposure to high-risk factors (respiratory droplets + close contact) in the secondary group (88.1 %) was significantly higher than that in the non-infected group (33.3 %), and the difference was statistically significant (P < 0.001). The average age of the secondary infection group was 54.9 $\pm$ 16.7 years, which was much older than that in the non-infected group (36.3 $\pm$ 20.8 years), and the difference was statistically significant (P < 0.001). In addition, 33.9 % of patients in the secondary infection group had comorbidities, which was higher than 5.6 % of patients in the non-infected group that had comorbidities, and the difference was statistically significant (P = 0.001) (Table 2).

3.4. Analysis of high risk factors for deaths in COFs

The mortality rate in the COFs was 10.0 %, while the mortality rate for all affected people is as high as 13.8 %. Statistical analysis found that the average age of the patients who died was 72.0 $\pm$ 9.8 years, which was much older than that of the patients who did not die (56.6 $\pm$ 15.8 years), and the difference was statistically significant (P = 0.001). The proportion of shortness of breath or dyspnea in the patients who died (92.3 %) was higher than that in the patients who did not die (29.6 %), and the difference was statistically significant (P < 0.001). A total of 69.2 % of patients who died had comorbidities, which was higher than that among those who did not die, and the difference was statistically significant (P = 0.03). In addition, the neutrophil/lymphocyte ratio (NLR) in the patients who died was higher than that in the patients who did not die, and the difference was statistically significant (P < 0.001). Whereas multiple logistic regression analysis identified that age (OR = 1.18, 95 %CI: 1.01 − 1.37, Wald = 4.18, P = 0.04) and NLR (OR = 1.31, 95 %CI: 1.06 − 1.62, Wald = 6.26, P = 0.01) were associated with deaths in COFs (Table 3).

4. Discussion

With the development of the COVID-19 epidemic, the proportion of the incident cases occurring in clusters continues to increase. The virus has spread to the community through people who come into contact with the seafood market, forming community transmission, and person-to-person and clustered transmission has been occurring in many communities and families in Wuhan (World Health Organization, 2020;

Table 1
The features of COVID-19 in COFs and SOFs.

		Clustered-onset families: 35 groups (n = 130)			Solitary-onset families: 16 groups (n = 41)	P value
		All patients (n = 94)	New-onset patients (n = 35)	Secondary patients (n = 59)	All(new-onset) patients(n = 16)	
Age, years		58.7 ± 16.0	65.2 ± 12.3	54.9 ± 16.7	61.6 ± 10.2	0.47
Sex	man	51(54.3 %)	17(48.6 %)	34(57.6 %)	10(62.5 %)	0.54
	woman	43(45.7 %)	18(51.4 %)	25(42.4 %)	6(37.5 %)	
Signs and symptoms	Fever	72	31	41	11	0.72
	Cough	49	19	30	9	0.76
	Fatigue	36	16	20	7	0.68
	Dyspnea	36	17	19	9	0.18
	Chest tightness	9	2	7	2	0.72
	Diarrhea	13	7	6	0	–
	others	35	20	15	9	0.15
Visiting time	≤ 1 week	22	5	17	7	0.64
	>1 week	37	19	18	9	
Comorbidity[a]	Hypertension	24	11	13	4	1.00
	Diabetes	19	11	8	4	0.66
	CHD	7	3	4	3	–
	CVD	3	2	1	1	–
	Cancer	2	2	0	0	–
	Other	12	6	6	4	–
Disease severity	Light or Normal	41	8	33	5	0.26
	Heavy	39	17	22	10	
	Critical	14	10	4	1	
Approach to treatment	Hospital	72	33	39	16	–
	Fixed-point isolation	22	2	20	0	
Nucleic acid test	Positive	61	24	37	8	0.35
	Negative	24	8	16	7	
	Unknown	9	3	6	1	
Chest CT Viral Pneumonia	Yes	90	35	55	16	–
	No	4	0	4	0	
Routine blood	WBC	5.5(3.6 − 7.8)	5.8(4.0 − 9.1)	4.5(3.5 − 7.1)	6.3(4.1 − 11.5)	0.19
	L	0.9(0.7 − 1.4)	0.8(0.6 − 1.4)	1.0(0.8 − 1.3)	0.7(0.5 − 1.0)	0.25
Length of stay		15.0 (10.5 − 22.0)	14.5 (7.8 − 20.0)	13.5 (11.8 − 16.8)	18.0 (12.5 − 23.5)	0.44
Prognosis	Recovered	18	2	16	1	0.12
	Improved	61	21	40	13	
	Unhealed	2	1	1	1	
	Death	13	11	2	1	

[a] Comorbidity includes hypertension, diabetes, coronary heart disease (CHD), chronic obstructive pulmonary disease, tuberculosis, chronic bronchitis, chronic kidney disease, cancer, cerebrovascular disease (CVD), hepatitis B and immunodeficiency.
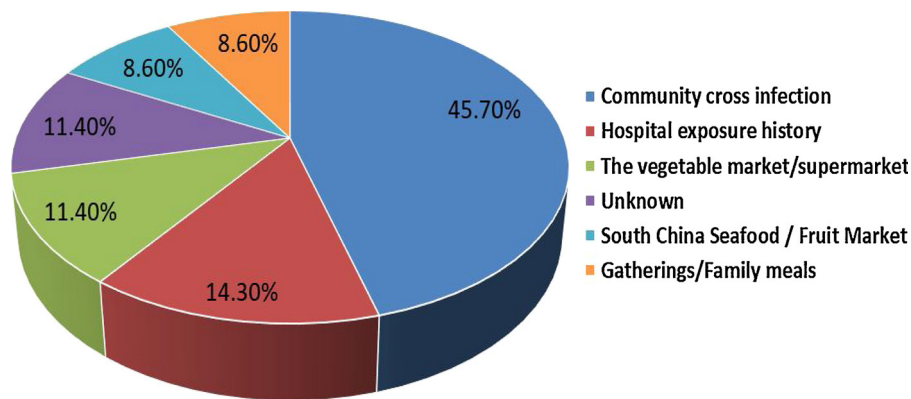

Fig. 1. Self-determined cause of infection in new-onset patients with family clustering.

Chan et al., 2020b; Wu et al., 2020; Paules et al., 2020; Chen et al., 2020b).

In this study, a total of 130 people from 35 COFs admitted to Hankou Hospital of Wuhan City were collected. According to the analysis of the self-reported cause of infection in the new-onset patients, most of the reasons reported were cross-infection in the community, history of hospital exposure, and visits to densely populated places (supermarkets and various bazaars), which were related to the significant increase in the flow of people around the Spring Festival in China (hua et al., 2020). The incidence of COVID-19 was higher in the

COFs than in the SOFs. The reasons include the following: 1. The included families were from local designated hospitals for infectious diseases, and the proportion of cases with critical illness was high; 2. The exposure to risk factors, such as respiratory droplets and close contact, were higher in COFs, and the possibility of aerosol or contact transmission caused by the presence of feces and urine in families was not excluded (Holshue et al., 2020). Consistent with the results of other recent studies (Li et al., 2020a; Chen et al., 2020b; Li et al., 2020b), the most common symptoms in COFs were fever (76.6 %), cough (52.1 %), and fatigue (38.3 %). However, the proportion of patients with cough
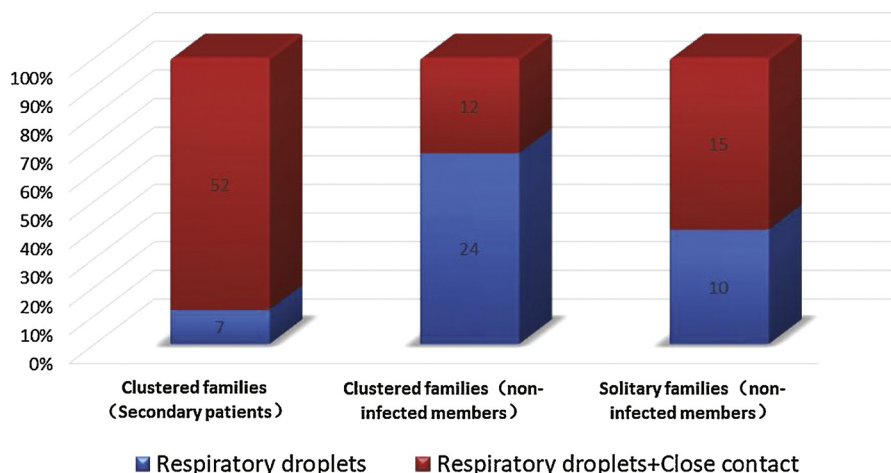
Fig. 2. Routes of transmission in COFs and SOFs.

and other symptoms as the first symptoms (without fever) was not low, especially for elderly and critically ill patients, which reminds us that screening of high-risk groups should be more comprehensive. At the same time, some atypical or uncommon symptoms also appeared in the COFs, such as anorexia (20.2 %) and diarrhea (13.8 %).

At present, nucleic acid detection in nasal or pharyngeal swabs is still the main method to diagnose COVID-19, but the positive rate was only 40 %–60 %. Our study also found that there were 23 COF patients (28 %) whose chest CT showed typical COVID-19 characteristics despite multiple negative nucleic acid tests, suggesting a higher false negative rate for the nucleic acid tests. Nucleic acid screening alone will cause a large number of imaging-suspected SARS-CoV-2 infectious pneumonia patients to be unable to obtain timely diagnosis and treatment, thus further delaying the control of the virus transmission pathway. Therefore, it is more practical to conduct detailed screening of suspected patients by adopting multiple methods, including detection of novel coronavirus serum-specific antibodies.

The proportion of severe and critical patients in the COFs was as high as 56.4 %, and the mortality rate in this group was as high as 13.8 %. Our statistical analysis found that advanced age and an elevated NLR were high risk factors for death in patients with COVID-19. The NLR has proven to be a useful indicator of systemic inflammation (Zahorec, 2001). In addition, the NLR is associated with mortality in critically ill patients (Salciccioli et al., 2015). Neutrophils and lymphocytes are an important part of the innate immune system. Neutrophils, whose count mainly reflects the function of innate immune cells, release a large number of cytokines and chemokines, promoting the formation of a cytokine storm (Xiang et al., 2018). Studies have shown that neutrophils can be used as antigen-presenting cells of anti-virus CD8 + T cells (Zhang et al., 2019). Our study found that, on the one hand, lymphopenia was not statistically significant different between the patients who died and those who survived. On the other hand, many

critically ill patients experienced an increase in leukocytes and neutrophils with a decrease in lymphocytes. We further suggested the possibility of bacterial infection as a result of procalcitonin. Mixed infection may be another risk for patients with COVID-19, and the NLR can be used as a predictor of infection and prognosis in patients with COVID-19 (Naess et al., 2017).

This study has some limitations. First, because some family members could only be accessed through medical history collection or telephone interviews, their laboratory or imaging examination records were incomplete. At the same time, a few cases were diagnosed in an outpatient department, so the corresponding medical information was relatively brief and the laboratory examination was not comprehensive. Second, case data were collected mainly in respiratory wards, where the majority of patients were in severe or critical condition, so our study may represent a subset of patients with more severe COVID-19. Furthermore, the number of cases included in this study was not very large, and the results need to be further verified by expanding the sample size.

In summary, compared with SOFs, COFs have higher infectivity and pathogenicity. In addition to the increased exposure to high-risk factors such as respiratory droplets and close contact, older patients, especially those with comorbidities, were more likely to be infected. The clinical symptoms of COFs were mainly fever, cough, fatigue, shortness of breath or dyspnea, and some patients also manifested as anorexia and diarrhea. COVID-19 patients with advanced age and elevated NLR are at high risk for poor prognosis in COFs.

Contributions

Minran Li and Jinzhong Li searched the literature, conceived the study, Xiaobing Gong designed the study, Minran Li and Jinzhong Li interpreted the results, and drafted the report. Zhigang Wang[2], Renzhou

Table 2
Analysis of high-risk factors for COVID-19 incidence in COFs.

		Secondary patients (n = 59)	Non-infected members(n = 36)	P value
Place of new-onset patient's onset	Hospital	6	8	0.11
	Community	53	28	
Disease severity in the new-onset patient	Light or Normal	11	7	0.94
	Heavy	31	18	
	Critical	17	11	
Exposure pathway	Respiratory droplets	7	24	0.00
	Respiratory droplets + Close contact	52	12	
Age of exposed person		54.9 ± 16.7	36.3 ± 20.8	0.00
Comorbidity	Yes	20	2	0.00
	No	39	34	

Table 3
Analysis of high-risk factors for death in COFs.

Parameter	Survivors(n = 81)	Deaths(n = 13)	P value	Multivariate			
				OR	95 %CI	Wald	P value
Age, years	56.6 ± 15.8	72.0 ± 9.8	0.00	1.18	1.01 − 1.37	4.18	0.04
Gender, M/F	42/39	9/4	0.24	0.59	0.02 − 16.34	0.10	0.76
Onset, New-onset/Secondary	57/24	9/4	1.00	0.14	0.00 − 8.00	0.92	0.34
Dyspnea, Yes/No	24/57	12/1	0.00	0.06	0.00 − 7.73	1.28	0.26
Visiting time, ≤ 1 week/ > 1 week	19/30	3/9	0.58	0.26	0.01 − 7.80	0.60	0.44
Comorbidity, Yes/No	30/51	9/4	0.03	1.25	0.02 − 77.45	0.01	0.92
NLR	3.6(2.1 − 5)	18.7(15.0 − 25.3)	0.00	1.31	1.06 − 1.62	6.26	0.01

Chen[3], and Dongyu Zeng collected the data. Taoyuan Li analyzed the data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2020.198043.

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