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Features of family clusters of COVID-19 patients: A retrospective study

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Abstract

Background: To investigate and compare the clinical and imaging features among family members infected with COVID-19.

Methods: We retrospectively collected a total of 34 COVID-19 cases (15 male, 19 female, aged 48 ± 16 years, ranging from 10 to 81 years) from 13 families from January 17, 2020 through February 15, 2020. Patients were divided into two groups: Group 1 - part of the family members (first-generation) who had exposure history and others (second-generation) infected through them, and Group 2 - patients from the same family having identical exposure history. We collected clinical symptoms, laboratory findings, and high-resolution computed tomography (HRCT) features for each patient. Comparison tests were performed between the first- and second-generation patients.

Results: In total there were 21 patients in Group 1 and 20 patients in Group 2. For Group 1, first-generation patients had significantly higher white blood cell count (6.5 × 10^9/L (IQR: 4.9–9.2 × 10^9/L) vs 4.5 × 10^9/L (IQR: 3.7–5.3 × 10^9/L); P = 0.0265), higher neutrophil count (4.9 × 10^9/L (IQR: 3.6–7.3 × 10^9/L) vs 2.9 × 10^9/L (IQR: 2.1–3.3 × 10^9/L); P = 0.0111), and higher severity scores on HRCT (3.9 ± 2.4 vs 2.0 ± 1.3, P = 0.0362) than the second-generation patients. Associated underlying diseases (odds ratio, 8.0, 95% confidence interval: 3.4–18.7, P = 0.0013) were significantly correlated with radiologic severity scores in second-generation patients.

Conclusion: Analysis of the family cluster cases suggests that COVID-19 had no age or sex predominance. Secondarily infected patients in a family tended to develop milder illness, but this was not true for those with existing comorbidities.

1. Introduction

The novel 2019 coronavirus pneumonia (COVID-19) is caused by a newly discovered coronavirus (SARS-CoV-2) and recognized in December, 2019 in Wuhan, Hubei province, China in [1–3]. COVID-19 spread very quickly and widely across China [4] and imported cases began to present in other countries [5]. Evidence of human-to-human transmission was firstly reported by Jasper Fuk-Woo Chan et al., who detailed the exposure history of a family with six members [6]. Later, the first case reported in Vietnam also came from a family cluster [7]. Close contact with suspected or confirmed diagnosis of COVID-19 was then listed as one of the criteria of exposure history in the guidelines from National Health Commission of the People’s Republic of China (NHC, PRC). Policy was developed to forbid large scale family meetings, and unnecessary visits were outlawed. Despite this, many people traveled during the epidemic due to the Spring Festival in China, a culturally significant time for family meetings. This resulted in a cascade of patients exposed to the COVID-19 infection through parties or family meetings [8]. By 8 a.m. on February 25th, a total of 77269 patients were diagnosed with COVID-19 pneumonia in China. Among these, 2596...
deaths and 9915 severe cases were reported. It is clear that family clusters were common in the development of this epidemic. SARS-COV-2 belongs to the Coronaviridae family, all of which possess a single-strand, positive-sense RNA genome, and have the ability to infect a range of mammalian and avian hosts [9]. Several transmission model studies have estimated the basic reproduction number \( R_0 \) of SARS-COV-2 to range from 2 to 4 [4], which means that one case of COVID-19 will generate 2 to 4 additional cases during the course of its infectious period [10]. Therefore, a common route of infection of patients in this epidemic was through close contact with a family member, similar to previous infections such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [11]. The rapid spread of the SARS-CoV-2 virus was enabled by ease of transmission via respiratory and fecal-oral route, moderate environmental persistence, and lack of durable immunity following infection.

Other than exposure history, fever, and other respiratory symptoms, pneumonia findings on chest imaging and abnormal laboratory findings are the main clues in the screening workflow of COVID-19 patients [12]. Several case reports of family clusters have previously been published, indicating the importance of early detection and isolation of the infected patients, as well as special caution needed for asymptomatic family members [6,13,14]. However, the features of these family clusters have not been systematically investigated, especially the similarities and dissimilarities between the first- and second-generations of COVID-19 within a family. Therefore, we retrospectively collected consecutive cases of infected family clusters to establish common clinical and imaging features of infected family clusters.

2. Methods

This study was approved by the review board from the centers. Informed consents of the patients whose image data was used were waived for the retrospective study.

3. Study participants

Continuous patients coming to the centers for COVID-19 screening from January 17, 2020 to February 14, 2020 were initially reviewed. Patients with at least one family member suspected or confirmed diagnosis of COVID-19 were included. Clinical suspicion was based on exposure history, clinical symptoms, laboratory findings, and chest images. Final diagnosis was confirmed through the real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing of the specimen collected from bronchoalveolar lavage fluid (BALF) or sputum, according to the guidelines from WHO and NHIC, PRC [15]. Exclusion criteria were: (1) the patient or their family member did not complete laboratory examination, chest computed tomography (CT), or RT-PCR testing; (2) ambiguous history of contact tracing and illness onset, which would not enable us to sequence the infection; and (3) patients whose family members declined to participate.

The included families and patients were divided into two groups. Group 1 contained patients with evidence of human-to-human transmission from certain members (Only one or part of the members had exposure history and thus the left should be transmitted). For each family in Group 1, the members were sorted into the first- and second-generations of COVID-19 based on the time order of exposure history. For families in Group 2, the members with confirmed diagnosis of COVID-19 had completely identical exposure history and thus the order of the infection time could not be decided arbitrarily.

4. Clinical data collection

We collected the baseline characteristics, exposure history, clinical symptoms, duration from illness onset to CT, relations between the members, and the clinical outcome within the study date range from electronic medical history system and the nursing recordings. Comorbidities were recorded including hypertension, diabetes mellitus, tumor, recent surgery (within 2 weeks) and other disease which have potential impact on the immune status of the patients.

5. Computed tomography examination

The patients were imaged in three centers. Eleven patients from 4 families were imaged with a 1-mm section thickness, 256-detector CT scanner (Revolution CT, GE Healthcare, Milwaukee, Wis). Another 6 patients from one family were imaged with a 2-mm section thickness 128-detector CT scanner (Ingenuity Core, Philips Healthcare, Best, The Netherlands). The left 17 patients from another 7 families were imaged with a 1-mm section thickness, a 64-slice spiral CT scanner (SOMATOM Definition Flash, Siemens, Germany).

6. Image analysis

For each patient, the presence, distribution, and severity of ground-glass opacity (GGO), consolidation, as well as the presence of fibrosis were recorded. GGO was defined as an increase in lung parenchymal opacification without obscuration of the underlying vessels [16], while consolidation was defined as an increase in lung parenchymal with obscuration of the underlying vessels [17]. Fibrosis was defined as the presence of any of the following findings: irregular linear opacities, parenchymal bands, traction bronchiectasis and lung distortion [18]. Based on the visual grades used in previous CT studies of patients with SARS and MERS [18,19], we ranked each lobe according to the grade score as below: 0 = no lesion; 1 = lesion extent between 1 and 25%; 2 = lesion extent between 26 and 50% of the lobe; 3 = lesion extent between 51 and 75% of the lobe; 4 = lesion extent between 76 and 100% of the lobe.

7. Statistical analysis

Shapiro-Wilk tests, histograms, and Q-Q plot were used to assess the normality. Numerical data were expressed as mean ± standard deviation (SD) otherwise as median with interquartile range (IQR) according to the normality test. Categorical variables were presented as frequency and the corresponding percentage. For Group 1, comparison between the first- and second-generations group was done by performing Two-sided non-paired Student’s t-test or Wilcoxon’s test as appropriate for continuous variables, and Chi-square test for categorical variables. Then, each patient in the second-generation subgroup was paired with the first-generation patients (if multiple first-generation patients exist for first-generation patient, the variables were averaged). Logistic regression was used to select the predictors for severity on high-resolution CT (HRCT) of second-generation patients. For Group 2, Pearson’s correlation analyses were performed to examine the relationships of clinical and imaging variables between the family members. The results were expressed as Pearson’s correlation coefficients with P value. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed with R project (v. 3.3.1).

8. Results

A total of 34 patients from 13 families were included in the final analysis, with 15 males and 19 females. The mean age of the included patients were 48 ± 16 years, ranging from 10 to 81 years. Group 1 contained 21 patients from 7 families and Group 2 contained 20 patients from 9 families. There were 3 patients from family d, 2 patients from family e, and 2 patients from family f fulfill the criteria for both groups (See in Fig. 1).
9. Clinical characteristics of the selected families

In Group 1, 1/21 (4.8%) patient had exposure to the Huanan Seafood Market, and 9/21 (42.9%) patients had a history of residency or travel to Wuhan. Also, 3/21 (14.3%) patients had no specific exposure history but reported being in a crowd of people at least once (based on history of travel or market shopping) within two weeks before onset of symptoms.

For Group 2, 1/20 (5.0%) patient had exposure to the Huanan Seafood Market, and the other 19 (95.0%) patients had a history of residency or travel to Wuhan.

Cough was the most common symptom (n = 27, 79.4%), followed by fever (n = 22, 64.7%), fatigue (n = 13, 38.2%), and sputum (n = 9, 26.5%) on admission (Table 1). Approximately half (n = 19, 55.9%) of patients presented with lymphopenia and 4/34 (11.8%) of patients presented with leukopenia.

10. Comparison between the first- and second-generation of patients with COVID

Group 1 contained 11 first-generation patients (Male/Female: 6/5; age: 46 ± 8 years) and 10 second-generation patients (Male/Female: 4/6; age: 42 ± 24 years). There was no significant difference in basic clinical characteristics between the two subgroups (Table 2). First-generation patients had numerically more clinical symptoms. Fever and cough were the most frequent symptoms for both subgroups.

First-generation patients had higher WBC count (6.5 × 10^9/L (IQR: 4.9–9.2 × 10^9/L) vs 4.5 × 10^9/L (IQR: 3.7–5.3 × 10^9/L), P = 0.0265) and neutrophil count (4.9 × 10^9/L (IQR: 3.6–7.3 × 10^9/L) vs 2.9 × 10^9/L (IQR: 2.1–3.3 × 10^9/L), P = 0.0111) than the second-generation group. Further analysis showed no difference of cases with regard to lymphopenia and leukopenia.

First-generation patients had higher severity scores on HRCT (3.9 ± 2.4 vs 2.0 ± 1.3, P = 0.0362). Fig. 2 shows a paired comparison of severity scores between first- and second-generation patients. Among the 12 paired relationships, 10/12 of the second-generation patients from 6 families had lower scores compared to paired first-generation patients. For the only one patient (E2) (male, Age: 81) with higher score than the first-generation (E1), chronic obstructive pulmonary disease and interstitial fibrosis was found on the CT images. Another patient (D2) with a similar severity score with the paired first-generation patient (D1) was a 66-year old male with hypertension. Thus, both of these cases had pre-existing conditions.

11. Correlation of clinical variables between the family members

The correlation of clinical variables between family members is listed in Table 3. For Group 2, age (r = 0.52, 95% confidence interval (CI): 0.10–0.78, P = 0.0191), body temperature (r = 0.85, 95% CI: 0.62–0.95, P < 0.0001), WBC count (r = 0.47, 95% CI: 0.04–0.76, P = 0.0363), number of lobes with consolidation (r = 0.50, 95% CI: 0.07–0.77, P = 0.0245), and number of lobes with fibrosis (r = 0.74, 95% CI: 0.44–0.89,
Table 1
Baseline characteristics of the included patients.

|                      | Total patients (n = 34) | Group 1 (n = 21) | Group 2 (n = 20) |
|----------------------|------------------------|------------------|------------------|
| Age, years a          | 48 ± 16                | 44 ± 17          | 52 ± 14          |
| Sex, no. (%)          |                        |                  |                  |
| Male                  | 15 (44.1)              | 9 (42.9)         | 9 (45.0)         |
| Female                | 19 (55.9)              | 12 (57.1)        | 11 (55.0)        |
| Number of Families    | 13                     | 7                | 9                |
| Comorbidities, no. (%)| 9 (26.5)               | 6 (28.6)         | 4 (20.0)         |
| Body temperature, °C  | 37.8 ± 1.2             | 37.4 ± 1.1       | 37.9 ± 1.5       |
| Clinical symptoms, no. (%) |                |                  |                  |
| Fever                 | 22 (64.7)              | 12 (57.1)        | 13 (65.0)        |
| Cough                 | 27 (79.4)              | 16 (76.2)        | 15 (75.0)        |
| Sputum                | 9 (26.5)               | 4 (19.0)         | 6 (30.0)         |
| Fatigue               | 13 (38.2)              | 8 (38.1)         | 9 (45.0)         |
| Pharyngalgia          | 4 (11.8)               | 3 (14.3)         | 1 (5.0)          |
| Dyspnea               | 6 (17.6)               | 3 (14.3)         | 4 (20.0)         |
| Digestive             | 3 (8.8)                | 1 (4.8)          | 3 (15.0)         |
| Laboratory findings   |                        |                  |                  |
| WBC count, x10^9/L    | 5.5 (4.3–7.5)          | 5.1 (3.7–6.5)    | 6.3 (5.0–8.8)    |
| Leukopenia, no. (%)   | 4 (11.8)               | 4 (19.0)         | 2 (10.0)         |
| Lymphocytes count, x10^9/L | 1.0 (0.6–1.5)   | 1.2 (0.9–1.5)    | 1.0 (0.4–1.5)    |
| Lymphopenia, no. (%)  | 19 (55.9)              | 10 (47.6)        | 11 (55.0)        |
| Neutrophil count, x10^9/L | 3.6 (2.9–5.4)  | 3.5 (2.5–4.9)    | 4.9 (3.5–7.6)    |
| Eosinophil count, x10^9/L | 0.01              | 0.02             | 0.01             |
| CRP, mg/L             | (0.00–0.04)            | (0.00–0.04)      | (0.00–0.03)      |
| Duration from illness onset to CT, days | 5.0 (3.5–7.0) | 3.5 (2.3–6.5) | 3.5 (2.3–6.5) |
| HRCT features         |                        |                  |                  |
| Severity Scores on HRCT a | 3.5 ± 2.1          | 3.0 ± 2.1        | 3.8 ± 2.1        |
| Unifocal/Multifocal, no. (%) | 25 (73.5)       | 14 (66.7)        | 16 (80.0)        |
| GGO, no. (%)          | 32 (94.1)             | 19 (90.5)        | 19 (95.0)        |
| Consolidation, no. (%)| 18 (52.9)             | 13 (61.9)        | 10 (50.0)        |
| Fibrosis, no. (%)     | 17 (50.0)             | 8 (38.1)         | 12 (60.0)        |

HRCT: high-resolution computed tomography; COVID-19: coronavirus Disease 2019; WBC: white blood cell; CRP: C-reactive protein.
GGO: ground-glass opacity.

a Values given as mean ± standard deviation, otherwise median with (25th, 75th percentiles).

P = 0.0002) were significantly correlated with each other. The severity scores on HRCT and laboratory findings showed no significant correlation between the two groups.

For Group 1, Logistic regression tests showed that the only significant predictors of severity of second-generation patients were the presence of comorbidities (OR, 8.0, 95% CI: 3.4–18.7, P = 0.0013) and high body temperature (3.0, 95% CI: 1.5–6.0, P = 0.0136).

12. Case study with contrary pattern between first- and second-generations

Two contrary patterns of features between family members could be found among the included families (Figs. 3 and 4).

For family c, one patient (male, 47 years) had a history of residency in Wuhan within two weeks before onset of illness, and was thus recognized as the first-generation in this family. His chest imaging showed moderate pneumonia which manifested as diffuse GGO with consolidation. Another patient (female, age: 76 years), whose only exposure history was close contact with the first patient, was thus recognized as the second-generation of COVID-19, and presented only with mild changes on HRCT. Another member of this family reported no COVID-19 infection and was thus not enrolled in this study (Fig. 3).

For family e, two patients (a couple, with a mean age of 46 years) had a travel history to Wuhan within two weeks before onset of illness. Both patients had mild clinical symptoms and only minimal or no change on HRCT at admission. The third patient (male, 81 years) had no other exposure history and were assumed to be infected by the couple. The clinical symptoms and HRCT findings were obviously more severe in the second-generation infection in this family (Fig. 4).

13. Discussion

Family cluster is an important route of transmission of COVID-19. In this multi-center study, we retrospectively investigated the clinical and imaging features of 34 patients from 13 families. Patients with secondary infection presented a generally milder course of illness than family members who were infected initially, while patients who presented with underlying diseases could develop even more severe pneumonia. Family members who shared a similar exposure history might have cross infection with each other, as presented by significant correlations of clinical and imaging features between them. These results add to the growing body of literature supporting rigorous and rapid isolation of infected patients, as well as close surveillance and repeat testing of family members who have close contact with patients.

The age of the infected patients reported in our study ranged from 10 to 81 years. There was no gender preponderance of the viral illness. This was consistent with the previous reports of family clusters [6]. Various transmission routes could be found in these family clusters. For secondarily infected family members, most were living together with infected patients and thus shared meals and air conditioners with each other. A prior study by Lirong Zou et al. indicated a similar virus load in the upper respiratory tract in symptomatic and asymptomatic patients [20], and later there was bioinformatics evidence for the potential digestive system infection of COVID-19 [21]. The above evidences...
load reported previously [6], patients with more severe changes on computed tomography; GGO: ground-glass opacity.

 tween the first- and second-generation of patients would require further HRCT should have a greater viral load. Our study provides additional ones. Given the correspondence between the imaging findings and viral samples should be taken from different sources (swab, BALF, and feces) reported cases when only one source of sample is tested [22, 23], multiple various source of virus transmission. Our study demonstrated no dif-

demonstrated multiple places the virus could stay and thus implied a various source of virus transmission. Our study demonstrated no difference in age and sex with regard to probability of infection. Therefore, we recommend rigorous isolation for family members confirmed with COVID-19 to avoid transmission to other family members. Besides, considering the rising incidence of false negatives in some of the reported cases when only one source of sample is tested [22,23], multiple samples should be taken from different sources (swab, BALF, and feces) and sent for testing for the members suspicious of being infected in family cluster cases.

Our study showed that secondarily infected family members presented generally milder radiological change than the initially infected ones. Given the correspondence between the imaging findings and viral load reported previously [6], patients with more severe changes on HRCT should have a greater viral load. Our study provides additional clues to this, in that symptom severity appears to be worse in the first-generation, but whether this difference of viral load existed between the first- and second-generation of patients would require further validation. A systematic review performed by Riccardo Castagnoli et al. reported that pediatric patients had generally mild respiratory symptoms and a relatively lower chance of severe status compared with adults [24]. This finding is consistent with another case report of pediatric case in family clusters [25]. Although our study included only one pediatric patient in the second-generation subgroup, numerical difference in age was found between the first- and second-generation patients. Thus, we cannot exclude the possibility that the age difference might contributed to lower severity of symptoms for second-generation patients. Besides, although the difference in the duration between onset of symptom and CT examination didn’t differ between the first- and second-generations, bias might be caused by this time delay of examination for the first-generation patients, since slightly longer of duration could be noticed for them, which is reported associated with severer change on HRCT [26]. Therefore, Caution should be exercised when applying these lessons clinically.

Nevertheless, older patients and those with underlying basic disease could develop even more severe illness. The current standard for SARS-CoV-2 diagnosis is genetic testing or RT-PCR [27], but multiple and repeat testing of samples derived from various parts of the respiratory tract might be needed to achieve a final diagnosis of SARS-CoV-2 infection [28,29]. There may be bias from specimens taken during a period of relatively low viral replication at the beginning stages of the disease [23]. Since clinical symptoms are not specific for patients with COVID-19, the key question is how to better recognize suspicious patients to ensure early isolation for prevention and clinical management of this disease. A previously reported family cluster showed a spectrum of CT findings and suggested potential role of the immune status [30]. Our study adds to this literature by reporting a correlation of severity with the accompanying comorbidities of these patients. Our results correspond to an earlier study which determined that compromised immunity could be a risk factor for SARS-CoV-2 infection [31]. Therefore, for families of infected patients, attention and special care should be given, especially to older members, and those with underlying diseases.

A noteworthy finding of our study was the significant correlations found between patients with similar exposure history, and thus assumed to be infected through similar transmission route. We were not sure

Fig. 2. Paired comparison of the severity scores on HRCT between the first- and second-generations in each family of Group 1. A notably higher severity scores could be found in all the families except for family e. (Fam: family; HRCT: high-resolution CT).

Table 3 Pearson’s correlation coefficients between the family members.

|                        | r     | 95% CI      | P value |
|------------------------|-------|-------------|---------|
| Age, years             | 0.52  | [0.10, 0.78] | 0.0191  |
| Body temperature       | 0.85  | [0.62, 0.95] | 0.0001  |
| WBC count, x10⁹/L      | 0.47  | [0.04, 0.76] | 0.0263  |
| Lymphocyte count, x10⁶/L | 0.19  | [-0.28, 0.58] | 0.4245  |
| Neutrophil count, x10⁹/L | 0.31  | [-0.15, 0.66] | 0.1778  |
| Eosinophils count, x10⁶/L | -0.24 | [-0.62, 0.23] | 0.3100  |
| CRP, mg/L              | 0.24  | [-0.24, 0.63] | 0.3157  |
| Severity scores on HRCT | 0.44  | [0.00, 0.74] | 0.0530  |
| No. of lobes with GGO  | 0.43  | [0.02, 0.73] | 0.0611  |
| No. of lobes with consolidation | 0.50 | [0.07, 0.77] | 0.0245  |
| No. of lobes with fibrosis | 0.74 | [0.44, 0.89] | 0.0002  |

WBC: white blood cell; CRP: C-reactive protein; HRCT: high-resolution computed tomography; GGO: ground-glass opacity.

a Significance.
whether this correlation is due to the similar duration between the onset of illness and CT scan, or the similarities in the severity of pneumonia for these patients. Nevertheless, there does not seem to be a shared pattern of imaging findings or clinical presence across these patients. As the immune reaction to the viral infection varies with the immune status of the patients, it is reasonable to assume that viral load and degree of immune action would not necessarily be the same.

There are several limitations to this study which warrant discussion. First, this was a preliminary study of family clusters of COVID-19, thus only a limited number of patients were included, although data were collected from multiple centers. Second, within the study date range, all patients did not completely recover from pneumonia and thus we cannot compare the clinical outcomes between the family members. Considering the similarities and dissimilarities demonstrated in this study, future studies on the prognosis of family clusters is warranted. Third, in our comparison study between first- and second-generation patients, we rigorously excluded patients with a similar exposure history. However, it is possible that one family member was infected first, and subsequently infected the other. Finally, viral load data were not accessible for this study, therefore we are not able to provide direct and pathophysiological evidence for differences in severity between patients.

Future studies should track viral loads to determine how this relates to severity within patients, and upon transmission.

In conclusion, our data shows that COVID-19 is transmitted widely across ages in family clusters. Subsequently infected family members generally showed a milder severity course of disease than the seminal infection, while patients with underlying comorbid disease could develop more severe changes and thus warrant special attention.

CRediT authorship contribution statement

Kai-yue Diao: Conceptualization, Writing - original draft, Methodology. Xiao-chun Zhang: Resources, Data curation, Validation. Shan Huang: Writing - review & editing, Visualization. Han-lun Wang: Formal analysis, Software. Ya-dong Gang: Formal analysis, Software. Yu-ping Deng: Resources. Pei-lun Han: Investigation. Tong Pang: Investigation. Jun-ling Yu: Resources. Ying-kun Guo: Writing - review & editing. Zhi-gang Yang: Supervision, Funding acquisition, Project administration.
Declaration of competing interest

The authors declare that there are no conflicts of interest.

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