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Risk factors associated with occurrence of COVID-19 among household persons exposed to patients with confirmed COVID-19 in Qingdao Municipal, China

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Abstract

Tracing and isolation of close contacts is used to control outbreaks of coronavirus disease 2019 (COVID-19) in China. However, risk factors associated with the occurrence of COVID-19 among close contacts have not been well described. A total of 106 household contacts were included in this study, of whom 19 developed into COVID-19 cases, and the secondary attack rate was 17.9%. Multivariable analysis showed that increasing risk of occurrence of COVID-19 among household contacts was associated with female index patients (adjusted hazard ratio [aHR] = 3.84, 95% CI = 1.07–13.78), critical disease index patients (aHR = 7.58, 95% CI = 1.66–34.66), effective contact duration with index patients > 2 days (aHR = 4.21, 95% CI = 1.29–13.73), and effective contact duration > 11 days (aHR = 17.88, 95% CI = 3.26–98.01). The sex and disease severity of index patients with COVID-19 and longer effective contact duration with patients with confirmed COVID-19 could help epidemiologists to identify potential COVID-19 cases among household contacts at an early stage.

KEYWORDS

close contacts, COVID-19, household contacts, risk factor, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world since it was first recognized in late 2019 (Ghinai et al., 2020). As of April 23, 2020, COVID-19 has resulted in more than two million patients in 213 countries/regions and has become a public health emergency of international concern on January 30, 2020 (World Health Organization, 2020b; Yuen, et al., 2020). Isolation of cases and close contacts are the two most critical strategies used in China for COVID-19 control and prevention (National Health Commission of the People's Republic of China, 2020b); all close contacts are required to be in concentrated isolation for 14 days, and at least two SARS-CoV-2 RT-PCR tests should be conducted during the isolation period. Previous studies revealed that in most scenarios, highly effective case isolation and contact tracing and isolation are enough to control a new outbreak of COVID-19 within 3 months (Zhou et al., 2020).

Most reports of person-to-person COVID-19 transmission have been among household contacts (Ghinai et al., 2020), where the symptomatic secondary attack rate has been estimated to be 10.5% (Burke et al., 2020). However, risk factors associated with occurrence of COVID-19 among household contacts have been rarely reported. We assumed that the demographic and exposure (including exposure duration, location, and frequency of contact with a COVID-19 patient) characteristics of household contacts and the features of index patients with COVID-19 that correspond to each household contact were associated with the occurrence of COVID-19 among household contacts. Therefore, in this study, the

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data of household contacts and the index patients with COVID-19 from January 20, 2020 to March 27, 2020 in Qingdao Municipal were systematically collated, and secondary attack rates and risk factors associated with occurrence of COVID-19 among household contacts were explored.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This prospect cohort study included all household contacts of patients with confirmed COVID-19 in Qingdao Municipal between January 20, 2020 and March 27, 2020.

This study was approved by Qingdao Municipal for Disease Control and Prevention. All data used in this study are anonymous, such that the individual information cannot be identified.

2.2 | Data collection

We defined each household contact as an independent subject, and the index patient with confirmed COVID-19 that each contact was corresponding to was considered as part of the household contacts. Data used in this study included two parts: the index patients with confirmed COVID-19 and household contacts. Demographic, clinical, and laboratory data of index patients with confirmed COVID-19 were extracted from the web-based National Notifiable Infectious Disease Reporting Information System (NNIDRIS) and epidemiological investigation reports. Demographic, exposure (including exposure duration, location, and frequency of contact with a patient with confirmed COVID-19), and illness onset (including onset of confirmed COVID-19 case and asymptomatic COVID-19 case) data for household contacts were collected from the electronic registration list which was recommended by the Chinese guidance for COVID-19 (version 5.0) (National Health Commission of the People's Republic of China, 2020a).

2.3 | Definitions

According to the Chinese management guidance for COVID-19 (version 6.0) (National Health Commission of the People's Republic of China, 2020b), a COVID-19-confirmed case was defined as a person presenting with fever or other respiratory symptoms who had a positive result of SARS-CoV-2 detection in respiratory specimens by real-time RT-PCR methods. A COVID-19 asymptomatic case was defined as a person presenting with positive SARS-CoV-2 detection in respiratory or other specimens by real-time RT-PCR methods without clinical symptoms. Close contacts were defined as persons who had a short-range contact history for 2 days before the onset of symptoms in COVID-19-suspected and -confirmed cases, or 2 days before the collection of samples from asymptomatic cases without taking effective protective measures, such as family members in the same house, direct caregivers, and medical staff who provided direct medical care, colleagues in the same office or workshop, etc. Household contacts who did not meet the above definition or where it could not be distinguished which COVID-19 patient they had contact with, were excluded from our study. Leukopenia was defined as white blood cell count under 4×10^9 per litre. Lymphocytopenia was diagnosed as blood lymphocyte count under 0.8×10^9 per litre. The illness severity of COVID-19 was classified as mild, general, severe, and critical according to the Chinese guidance of COVID-19 (version 6.0) (National Health Commission of the People's Republic of China, 2020b), and the illness severity used in our study referred to the most serious status during the total course of the disease. The effective contact duration for the close contacts was defined as the contact days with index patients with confirmed COVID-19, which was calculated as the last contact date minus the start contact date, and all dates were corresponding to the definition of close contacts (please refer to the definition of close contacts above). Contact frequency was categorized as occasionally or normal and often based on the Chinese guidance of COVID-19 (version 6.0) (National Health Commission of the People's Republic of China, 2020b). The outcomes of household contacts included confirmed COVID-19, asymptomatic COVID-19, and maintained negative SARS-CoV-2 PCR test results during the isolation period. Being diagnosed with confirmed or asymptomatic COVID-19 was defined as the occurrence of COVID-19 among household contacts.

2.4 | Data analysis

The overall secondary attack rate was calculated by dividing the number of COVID-19 cases developed from contacts by the total number of contacts, and the rate was calculated for each variable group. The original number of confirmed COVID-19 patients associated with these 106 contacts was summarized, and the average and median number of contacts corresponding to one confirmed COVID-19 patient were calculated. Continuous and categorical variables for both confirmed COVID-19 patients and household contacts were presented as medians (interquartile range, IQR) and numbers (%). To explore the risk factors associated with occurrence of COVID-19 among household contacts, we reclassified the continuous variables as categorical variables, and univariable and multivariable Cox regression models were used. Crude hazard ratio (cHR) and adjusted hazard ratio (aHR) with 95% confidence interval (95% CI) were presented as the outcomes of models to compare the secondary attack rate in each group. We excluded variables from univariable analysis if their between-group differences were not significant and if the numbers of events were too small to calculate the HR.

A two-sided p value < 0.05 was considered statistically significant. All analyses were done by using R statistical software (version 3.6.1, The R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Characteristics of patients with confirmed COVID-19 and household contacts

A total of 187 household contacts were identified in Qingdao City. After excluding 71 who did not meet the definition of close contacts and 10 where it was not possible to distinguish which COVID-19 patient they had contact with, we included 106 household contacts in the final analysis. Nineteen contacts had a positive result of SARS-CoV-2 by real-time RT-PCR, and the secondary attack rate was 17.9%. Of the 19 patients with COVID-19, 13 developed clinical symptoms and were defined as confirmed cases, and 6 presented with no clinical symptoms at the moment of positive result of SARS-CoV-2 and were classified as asymptomatic cases.

Thirty-one confirmed COVID-19 patients were associated with these household contacts. The average number of household contacts corresponding to one patient with confirmed COVID-19 was 3.4 (*SD* = 2.7) and the median number was 3 (IQR: 2–4), ranging from 1 to 13.

Among the 106 patients with confirmed COVID-19, the median age was 45 (IQR: 39–57) years with 72 (67.9%) patients under 55 years old, and 55 (51.9%) patients were male. Comorbidities were present in 24 (22.6%) patients, with hypertension (14, 13.2%) being the most common comorbidity. The most common symptoms on admission were fever (95, 89.6%) and fatigue (46, 43.4%), followed by cough (36, 34.0%) and myalgia (24, 22.6%). Leukopenia and lymphocytopenia occurred in 34 (32.1%) and 21 (19.8%) patients, respectively. The number of patients with a neutrophil percentage > 70% was 42 (39.6%), and 41 (38.7%) patients had a lymphocyte percentage between 0% and 19%. The median duration from illness onset to hospital admission was 3 days (IQR: 2–5), whereas the median time to diagnosis was 4 days (IQR: 3–5). The proportion of patients with mild, general, severe, and critical disease severity was 7.6%, 57.6%, 24.5%, and 10.4%, respectively (Table 1).

Among the 106 household contacts, 55 (51.9%) were male and the median age was 37 (IQR: 21–52) years. The median effective contact duration with patients with COVID-19 was 4 (IQR: 1–6) days, with 57 (53.8%) experiencing effective contact between 3 and 11 days, and 9 (8.5%) with effective contact duration > 11 days (Table 1).

3.2 | Risk factors associated with occurrence of COVID-19 among household contacts

In univariable analysis, the HR of occurrence of COVID-19 among household contacts was higher in contacts whose index patients with confirmed COVID-19 were female (cHR = 3.34, 95% CI: 1.20–9.27), over 55 years old (cHR = 2.58, 95% CI: 1.05–6.36), and being classified as having critical disease on admission (cHR = 4.21, 95% CI: 1.41–12.58). Lymphocyte count ≤ 0.8×10^9 per litre, neutrophil percentage > 70%, and lymphocyte percentage ≤ 19% among index patients with confirmed COVID-19 were also associated with developing into COVID-19 cases for household contacts. In addition, effective contact duration > 11 days (cHR = 4.96, 95% CI: 1.33–18.50) for household contacts was also related to the occurrence of COVID-19.

We included four variables (sex, age, and disease severity of index patients with confirmed COVID-19, and effective contact duration) in our multivariable regression model. We found that female sex (aHR = 3.84, 95% CI: 1.07–13.78) and critical disease severity (aHR = 7.58, 95% CI: 1.66–34.66) of index patients with confirmed COVID-19, effective contact duration between 3 and 11 days (aHR = 4.21, 95% CI: 1.29–13.73), and effective contact duration > 11 days (aHR = 17.88, 95% CI: 3.26–98.01) were associated with occurrence of COVID-19 among household contacts (Table 2).

4 | DISCUSSION

In this study, by analysing the prospect cohort dataset of household contacts and index patients with COVID-19 in Qingdao Municipal, we found the secondary attack rate of COVID-19 was 17.9%. Being female and being classified as having critical disease during admission for index patients were risk factors associated with the occurrence of COVID-19 among household contacts. Moreover, prolonged contact duration with patients with confirmed COVID-19 would also promote the occurrence of COVID-19 among household contacts.

Transmission inside households has become an important part of SARS-CoV-2 transmission, with several confirmed case clusters from households being found (Chan et al., 2020; Guan et al., 2020; Wang, Ma, Zheng, Wu, & Zhang, 2020). Our study revealed a secondary attack rate of 17.9% among household contacts, which was similar with another study conducted in Hubei Province (16.3%) (Li et al., 2020) and higher than the rate in the United States (10.5%) (Burke et al., 2020), but lower than the rate found in a certain hospital in Wuhan City (30%) (Wang et al., 2020). Anyhow, the rate is much higher than the one of the two other coronaviruses that cause pneumonia epidemics, with 5% for the Middle East respiratory syndrome coronavirus (MERS-CoV) (Drosten et al., 2014) and 10.2% for the severe acute respiratory syndrome coronavirus (SARS-CoV) (Wilson-Clark et al., 2006). This is in accordance with the fact that SARS-CoV-2 has caused infected cases in ever greater quantities and is spreading in a much higher speed than MERS-CoV and SARS-CoV (Chowell et al., 2015; Huang et al., 2020; Liu, Gayle, Wilder-Smith, & Rocklov, 2020; Park, Jung, Kim, & Park, 2018).

Our study found that disease severity of the index patients was related to the occurrence of secondary infections, which was consistent with the result presented in a previous study (Zou et al., 2020). The disease severity was positively linked to the viral load of COVID-19 (Liu et al., 2020), and patients with serious or critical condition usually experienced higher viral loads in the respiratory tract than patients with mild or asymptomatic condition, while the transmission of SARS-CoV-2 was associated with modest viral loads in the respiratory tract (Zou et al., 2020). Although severe or critical

TABLE 1 Characteristics of index patients with confirmed COVID-19 and relationship with the occurrence of COVID-19 among household contacts

Feature	Total (col, %)	No. of infections (row, %)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Overall	106 (100)	19 (17.9)		
Demographics and clinical characteristics of index patients with confirmed COVID-19				
Gender				
Male	55 (51.9)	5 (9.1)	Ref	Ref
Female	51 (48.1)	14 (27.5)	3.34 (1.20–9.27)	3.84 (1.07–13.78)
Age group				
0-54	72 (67.9)	9 (12.5)	Ref	Ref
55-	34 (32.1)	10 (29.4)	2.58 (1.05–6.36)	0.59 (0.16–2.24)
Underlying diseases				
Yes	24 (22.6)	1 (4.4)	Ref	
No	82 (77.4)	18 (23.3)	6.12 (0.82–45.83)	
Fever (temperature > 37.2°C)				
Yes	95 (89.6)	18 (18.9)	Ref	
No	11 (10.4)	1 (9.1)	0.46 (0.06–3.41)	
Cough				
Yes	36 (34.0)	5 (13.9)	Ref	
No	70 (66.0)	14 (20.0)	1.49 (0.54–4.13)	
Myalgia				
Yes	24 (22.6)	3 (12.5)	Ref	
No	82 (77.4)	16 (19.5)	1.62 (0.47–5.56)	
Fatigue				
Yes	46 (43.4)	9 (19.6)	Ref	
No	60 (56.6)	10 (16.7)	0.84 (0.34–2.06)	
Time from illness onset to hospital admission, days				
0–7	92 (86.8)	15 (16.3)	Ref	
>7	14 (13.2)	4 (28.6)	1.88 (0.62–5.65)	
Time from illness onset to laboratory confirmation, days				
0–7	87 (82.1)	13 (14.9)	Ref	
>7	19 (17.9)	6 (31.6)	2.32 (0.89–6.10)	
Disease severity status				
Mild and general	69 (65.1)	9 (13.0)	Ref	Ref
Severe	26 (24.5)	5 (19.2)	1.52 (0.51–4.55)	2.34 (0.70–7.84)
Critical	11 (10.4)	5 (45.5)	4.21 (1.41–12.58)	7.58 (1.66–34.66)
Laboratory findings				
White blood cell count × 10^9 per L				
Unavailable	9 (8.5)	1 (11.1)	-	
0–4	34 (32.1)	7 (20.6)	Ref	
>4	63 (59.4)	11 (17.5)	0.83 (0.32–2.15)	
Lymphocyte count, ×10^9 per L				
Unavailable	58 (54.7)	10 (17.2)	-	
>0.8	27 (25.5)	1 (3.7)	Ref	
0–0.8	21 (19.8)	8 (38.1)	12.36 (1.54–98.95)	
Neutrophil percentage, %				

(Continues)

TABLE 1 (Continued)

Feature	Total (col, %)	No. of infections (row, %)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Unavailable	19 (17.9)	1 (5.3)	-	
0–70	45 (42.5)	5 (11.1)	Ref	
>70	42 (39.6)	13 (31.0)	3.11 (1.11–8.73)	
Lymphocyte percentage, %				
Unavailable	23 (21.7)	2 (8.7)	-	
>19	42 (39.6)	4 (9.5)	Ref	
0–19	41 (38.7)	13 (31.7)	3.76 (1.23–11.55)	

TABLE 2 Characteristics of household contacts and relationship with the occurrence of COVID-19 among household contacts

Feature	Total (col, %)	No. of infections (row, %)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Demographics and contact characteristics of household contacts				
Gender				
Male	55(51.9)	8(14.5)	Ref	
Female	51(48.1)	11(21.6)	1.54(0.62–3.83)	
Age group				
0-54	83(78.3)	17(20.5)	Ref	
55-	23(21.7)	2(8.7)	0.40(0.09–1.73)	
Effective contact days				
1-2	40(37.7)	5(12.5)	Ref	Ref
3-	57(53.8)	10(17.5)	1.89(0.65–5.53)	4.21(1.29–13.73)
>11	9(8.5)	4(44.4)	4.96(1.33–18.50)	17.88(3.26–98.01)
Relationships with index patients				
Spouse	16(15.1)	4(25.0)	Ref	
Non-spouse	90(84.9)	15(16.7)	0.64(0.21–1.92)	
Contact frequency				
Normal or occasional	39(36.8)	4(10.3)	Ref	
Often	67(63.2)	15(22.4)	2.33(0.77–7.02)	

Abbreviation: COVID-19, coronavirus disease 2019.

Note: col, %: percentage of column totals; row, %: percentage of row totals; crude hazard ratio: outcomes from univariable Cox regression models; adjusted hazard ratio: outcomes from multivariable Cox regression models; Ref: reference.

COVID-19 patients may not be in a severe or critical state at the moment of contacting their household members, they might still experience higher viral loads than mild or general cases. That could explain the high secondary attack rate among household contacts with critical index patients. Interestingly, our study found female index patients indicated a higher risk of occurrence of COVID-19 among households. This might be attributed to the higher frequency of contact with others in the family.

In this study, we identified that effective contact durations of 3–10 days and > 11 days presented a 4 and 17 times higher risk, respectively, compared to an effective contact duration of 1–2 days. That highlighted the fact that quick and accurate identification of cases for isolation or quarantine remains a key pillar of public health efforts to contain COVID-19 (Kam et al., 2020). First, healthcare facilities are critical for control and prevention of COVID-19. Targeted control strategies include rapid identification and isolation of all potentially infectious patients, including a high index of suspicion for transmissible disease, and implementation of universal infection control procedures in all facilities in the healthcare settings (Frieden & Lee, 2020; Lloyd-Smith, Galvani, & Getz, 2003; World Health Organization, 2020a). Second, the community control measures which were implemented in Hong Kong during the SARS outbreak (Frieden & Lee, 2020) should be performed in COVID-19 outbreaks. Community-wide non-pharmaceutical interventions, including risk communication to the public on social distancing, hand and respiratory hygiene, and

criteria for either self-isolation or safer presentation to the hospitals, could be carried out in the community. During the SARS outbreak, effective communication appears to have reduced duration from illness onset to hospital admission and decreased the number of persons with whom patients had contact before isolation (Yu et al., 2007).

Our study has some limitations. First, dozens of index patients did not include laboratory test results in their epidemiological investigation reports, including white blood cell count, lymphocyte count, and neutrophil and lymphocyte percentage, while these variables seemed meaningful based on the univariable analysis results in our study. Second, the cycle threshold (Ct) values in real-time PCR tests of index patients with COVID-19 were not available in our study, which might be an important factor to drive the occurrence of COVID-19 among household contacts. Third, only 106 households were enrolled, and large-scale surveys are needed to further illustrate this issue. However, data used in this study were comprehensive and reliable data on household contacts right now available in Qingdao Municipal, and all results from this city-level data were carefully analysed and interpreted to reduce possible confounding factors.

In summary, being female, critical disease severity in index patients with COVID-19, and prolonged contact duration with index patients with COVID-19 were the predictors of onset of COVID-19 among household contacts. More variables including Ct values and other laboratory findings of index patients with confirmed COVID-19 should be further collected and analysed to comprehensively define the influence factors of occurrence of COVID-19 among household contacts.

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CONFLICT OF INTEREST

All authors declare no competing interests.

AUTHOR CONTRIBUTION

Hualei Xin: conceptualization, investigation, data analysis, methodology, supervision, and writing of the original manuscript. **Fachun Jiang:** investigation, data analysis, methodology, and supervision. **Aili Xue:** investigation, data analysis, and supervision. **Jiwei Liang:** data analysis and supervision. **Jingfei Zhang:** data collection. **Feng Yang:** data collection. **Yalin Han:** conceptualization, investigation, data analysis, methodology, and supervision.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this paper and its Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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