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Epidemiology, Duration of Virus-Carrying, Infectivity, and Management of Asymptomatic SARS-CoV-2 Carriers in Wuhan, China

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Abstract

Asymptomatic SARS-CoV-2 carriers have the underlying ability to spread the virus and seed new outbreaks, which has been given public concerns. 178 asymptomatic SARS-CoV-2 carriers between March 1 and May 1, 2020, in Wuchang District of Wuhan, China, was enrolled. Demographic, epidemiology, infectivity, and management data were collected and analyzed, and the final date of follow-up was July 15, 2020. The mean age of this population was 47.5 years, 98.3 % were adults, and 49.4 % were males. Healthcare workers (16.3 %), bank staff (11.2 %), employees in service industries (14.6 %), and retirees (24.2 %) were the main populations of asymptomatic carriers. 32.6 % suffered from one or more comorbidities. 29.8 % of carriers had a history of symptoms onset, in which 96.9% tested IgG positive. The mean duration of virus-carrying was 64.1 (± 24.6) days, and there were household transmissions. Asymptomatic carriers were immediately isolated and received integrated medicine therapy for 14 days, and they tested SARS-CoV-2 negative within the first two months of follow-up since they were released from quarantine. Most asymptomatic carriers were adults and employees in service industries. The mean duration of virus-carrying exceeds 60 days and household transmissions supported infectivity of asymptomatic carriers. Early detection, isolation, and treatment were effective public health interventions.

Keywords: Asymptomatic SARS-CoV-2 carrier; epidemiology; duration of virus-carrying; infectivity; management; follow-up

Key messages:

Most asymptomatic carriers were adults, and the employees in service industries.

The mean duration of virus-carrying can exceed 60 days before confirmed by nucleic acid test.

The household transmissions supported the infectivity of asymptomatic carriers.

Committing proactive case-identification, isolation and treatment are effective public health interventions.

1. Introduction

SARS-CoV-2 has resulted in an outbreak of viral pneumonia in Wuhan, China, in December 2019, and the World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic on March 11, 2020. More than 14 million COVID-19 cases have been confirmed worldwide on July 19, 2020 **[1]**, while the number of infected cases is still rapidly increasing in many countries, which requires a coordinated international response. The clinical manifestations of SARS-CoV-2 infected cases are protean, including asymptomatic carriers, pneumonia of varying degrees of severity, and even death.

Following a containment phase from January to April in 2020, Wuhan has transitioned to the mitigation phase. The Wuhan city reopened, and citizens were allowed to resume working since April 8, 2020. Meanwhile, people must accept temperature tests before entering public places (e.g., such as supermarkets, restaurants, and hotels) and patients with clinical symptoms and signs (e.g., fever, dry cough, fatigue, and sore throat) onset must be reported to the healthcare organizations for further testing. The effectiveness of symptom-based interventions may largely depend on the infectiousness and fraction

of asymptomatic infection **[2]**. However, many infected cases are likely asymptomatic but potentially carry the virus.

Asymptomatic SARS-CoV-2 carriers refer to the infected subjects who have positive tests for viral nucleic acid but with mild or non-symptoms. These patients represent a population that could be easily neglected in epidemic prevention, since some patients did not realize being infected, and they may not seek health care or diagnosis, which may further lead to the underlying transmission of SARS-CoV-2. However, the characteristics of epidemiology, infectivity, management, and outcomes of asymptomatic carriers remain limited. The empirical studies have indicated that the potential contribution of the asymptomatic carrier to total infection is 17.9 to 30.8 % **[3,4]**, and some studies have reported the contagious capacity of asymptomatic carriers **[5-7]**. This evidence revealed the transmission of asymptomatic carriers and highlighted that fulminating cases were not only viral sources. But the limited number of cases necessitated the interpretation of the generalizability of their findings, and they did not differentiate whether these asymptomatic carriers were only asymptomatic initially or throughout the infection. Therefore, it is essential to fully understand the asymptomatic SARS-CoV-2 carriers to control the pandemic of COVID-19.

Wuhan is still faced with the risk of COVID-19 outbreak due to asymptomatic carriers since massive resuming work and school are in progress. It is crucial to fully identify and isolate asymptomatic infected citizens. The 10-days (from May 15 to May 24, 2020) of universal nucleic acid testing covered more than 9 million citizens had been conducted by committing proactive case-identification and a total of 320 asymptomatic carriers were confirmed, according to the reports from the Wuhan Municipal Health Commission **[8]**. We aimed to characterize the epidemiology, assessment the duration of virus-carrying, infectivity, management, and outcomes of asymptomatic SARS-CoV-2 carriers.

2. Materials and Methods

2.1 Participants

This is a retrospective study conducted in the Wuchang District of Wuhan. Asymptomatic carriers tested positive for SARS-CoV-2 in throat-swab using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) were extracted from the municipal Notifiable Disease Report System. We selected participants who met the following criteria: a) had tested and retested positive nucleic acid testing; b) had lived in Wuhan for more than half a year; c) had no self-reported influenza disease three months before they were confirmed SARS-CoV-2 infection; d) had full information on demographic, epidemiological, clinical features, and management; e) had been followed-up more than 2 months after they were released from quarantine. All asymptomatic SARS-CoV-2 carriers were divided into two subgroups: one was the cases who had a history of signs or symptomatic onset before infection confirmed, the other refers to the cases without symptoms all the time.

2.2 Data collection

For all asymptomatic carriers, their information on demographic (e.g., age, gender, and occupations), epidemiology (e.g., exposure history, close-contact information, and timelines of events), clinical symptoms data (e.g., fever, and respiratory symptoms onset), management (e.g., isolation, treatment, and follow-up), and outcomes (signs and symptoms onset, and results of rechecked nucleic acid tests) were collected by our investigators through direct communication and interview. In the epidemiological investigation, to acquire the above information, asymptomatic carriers were asked the following question in the interview: (1) What do you do for a living? Their answers were then divided into five categories, including healthcare workers (doctors, nurses, hospital cleaners, and medical technicians), bank staff (bank clerk, manager, and security), employees in service industries (employees in the supermarket, restaurant, and other public services), retirees, and others (students, and unemployed). (2) Have you ever been to the medical-institutes (but not as an infected case) or contacted confirmed cases before infected? (3) Did any members of your family and does the community infect? If “yes”, they were further asked the date of infection. (4) Have you had signs of fever, respiratory (dry cough, fatigue, nasal congestion, rhinorrhea, sore throat, and myalgia), and gastrointestinal symptoms? If “yes”, they were further asked the date of symptoms onset. (5) Do you have any chronic disease (e.g., hypertension, diabetes, cardiovascular or cerebrovascular diseases, cancers, and lung disease)? (6) Did you ever have SARS-CoV-2 nucleic acid or IgM/IgG antibody test? If “yes”, they were further asked the date and results of these tests.

2.3 Follow-up and management

Once infection confirmed, these asymptomatic carriers were immediately isolated and therapied in the designated hospitals for at least 14 days of centralized quarantine and medical observation according to China's measures for managing asymptomatic carriers, until they had no clinical symptoms onset and had the virus cleared (2 consecutive samples of nucleic acid tests showed negative on different days). Furthermore, all asymptomatic carriers were followed up to report whether they have signs or symptoms onset and required the SARS-CoV-2 nucleic acid test for at least 1 time per month.

Ethics approval was exempted since all data were collected and analyzed from asymptomatic carriers according to the policy for public health outbreak investigation of emerging infectious diseases issued by the National Health Commission of the People’s Republic of China.

2.4 Statistical analysis

The underlying duration of SARS-CoV-2 carrying was defined as the days between the date of previous symptoms onset or the date of contacting COVID-19 cases and the date of confirmed infection by RT-PCR.

Descriptive data were displayed as frequencies (percentages) for categorical variables and as means (standard deviations or ranges) for continuous variables. The differences in the distribution of demographic, epidemiological characteristics, and history of chronic disease between asymptomatic carriers with and without previous symptoms onset were tested by the student's t-test or Chi-square test, respectively. A two-sided with the p-value < 0.05 was considered as the level to reject the null hypothesis. All statistical analyses were performed with the SAS program (version 9.4; SAS Institute, Carry, NC).

3. Results

3.1 Demographical and epidemiological characteristics of asymptomatic carriers

A total of 178 asymptomatic carriers between March 1 and May 1, 2020, were enrolled **(see Table)**. The mean age of the population was 47.5 years, and 98.3 % were adults. There were approximately equal numbers of male and female carriers (88 vs. 90). Healthcare workers (16.3 %), bank staff (11.2 %), employees in service industries (14.6 %), and retirees (24.2%) were the principal populations of asymptomatic carriers. 49 (27.5 %) of the 178 carriers had met the medical institutes. 58 (32.6 %) patients suffered from one or more comorbidities, and the most four common comorbidities included hypertension (18.0), cardiovascular or cerebrovascular diseases (7.9 %), liver or kidney diseases (7.9), and diabetes (5.6 %). Over half (55.6 %) of the participants had SARS-CoV-2 IgM/IgG antibody test, and 88.9 % of them had positive IgG test results, 53 (29.8 %) of the 178 asymptomatic carriers had a history of signs and symptoms onset before they were confirmed infection by RT-PCR. At the onset of illness, fever, dry cough, chest tightness or pain, and fatigue were the four most common symptoms. These carriers with previous symptoms were more likely to be older (50.7 vs. 46.2), males (52.8 % vs. 48.0 %), had comorbidities (39.6 % vs. 29.6 %) and tested IgG positive (96.9 % vs. 85.1 %), but fewer had been to the medical institutes (17.0 % vs. 32.0 %) when compared with the 125 carriers without any signs and symptoms all the time, although some of these results were not statistically significant.

Table 1. Demographic, epidemiological and clinical characteristics of asymptomatic SARS-CoV-2 carriers

Characteristics	**Total (N=178)**	**Had signs and symptoms**		***P*-value***
		Ever (N=53)	Never (n=125)	
Age, years (range)	47.5 (5~89)	50.7 (20~89)	46.2 (5~89)	0.096
Subgroup, No. (%)				
< 18	3 (1.7)	0 (0.0)	3 (2.4)	
18~<40	55 (30.9)	17 (32.1)	38 (30.4)	
40~<60	75 (42.1)	16 (30.2)	59 (47.2)	
60~<80	40 (22.5)	17 (32.1)	23 (18.4)	
>=80	5 (2.8)	3 (5.7)	2 (1.6)	
Gender, No. (%)				0.556
Male	88 (49.4)	28 (52.8)	60 (48.0)	
Female	90 (50.6)	25 (47.2)	65 (52.0)	
Occupations, No. (%)				0.181
Hospitals	29 (16.3)	6 (11.3)	23 (18.4)	
Banks	20 (11.2)	6 (11.3)	14 (11.2)	
Service industries	26 (14.6)	6 (11.3)	20 (16.0)	
Retiree	43 (24.2)	19 (35.8)	24 (19.2)	
Others	60 (33.7)	16 (30.2)	44 (35.2)	
Medical institutes contact, No. (%)				0.040
No	129 (72.5)	44 (83.0)	85 (68.0)	
Yes	49 (27.5)	9 (17.0)	40 (32.0)	
Signs and symptoms, No. (%)				

Fever	27 (15.2)	27 (50.9)	-	
Headache	3 (1.7)	3 (5.7)	-	
Nasal congestion	0 (0.0)	0 (0.0)	-	
Pharygodynia	4 (2.2)	4 (7.5)	-	
Dry cough	15 (8.4)	15 (28.3)	-	
Chest tightness or pain	10 (5.6)	10 (18.9)	-	
Fatigue	9 (5.1)	9 (17)	-	
Anorexia	4 (2.2)	4 (7.5)	-	
Nausea or vomiting	2 (1.1)	2 (3.8)	-	
Original comorbidities, No. (%)	58 (32.6)	21 (39.6)	37 (29.6)	0.192
Hypertension	32 (18.0)	11 (20.8)	21 (16.8)	
Diabetes	10 (5.6)	6 (11.3)	4 (3.2)	
Cardiovascular or cerebrovascular disease	14 (7.9)	5 (9.4)	9 (7.2)	
Liver or kidney diseases	14 (7.9)	5 (9.4)	9 (7.2)	
Cancer	6 (3.4)	1 (1.9)	5 (4.0)	
Immune deficiency	3 (1.7)	0 (0)	3 (2.4)	
COPD	1 (0.6)	1 (1.9)	0 (0)	
Other lung related disease	10 (5.6)	4 (7.5)	6 (4.8)	
Had the antibody test, No. (%)	99 (55.6)	32 (60.4)	67 (53.6)	0.267
Subgroup, No. (%)				
IgM positive	34 (34.3)	15 (46.9)	19 (28.4)	0.070
IgG positive	88 (88.9)	31 (96.9)	57 (85.1)	0.081
IgM and IgG positive	28 (28.3)	14 (43.8)	14 (20.9)	0.018

Note: Values were shown as frequencies (percentages) for categorical variables and as means (standard deviations or ranges) for continuous variables.

*Chi-square test for categorical variables, Student's t-test for continuous variables.

3.2 Duration for carrying SARS-CoV-2

The underlying duration of virus-carrying was shown in Figure 1, with a mean value of 64.1 (± 24.6) days among all asymptomatic SARS-CoV-2 carriers. The mean duration between the date of previous symptoms onset and the date of confirmed infection was 65.1 (± 25.0) days for 53 asymptomatic carriers **(Figure 1A)**, and the two highest frequency distribution was in the group of 60- < 70 days and 70- < 80 days **(Figure 1B)**. There were 12 of 125 asymptomatic carriers without symptoms all the time that had a definite date of contacting COVID-19 cases. The means duration between the date of close contact and the date of confirmed infection was 59.8 (± 23.3) days **(Figure 1C)**, and the highest frequency distribution was in the group of 60- < 70 days **(Figure 1D)**. There was no difference in the duration of virus-carrying between asymptomatic carriers with and without previous signs and symptoms (*p*-value = 0.506).

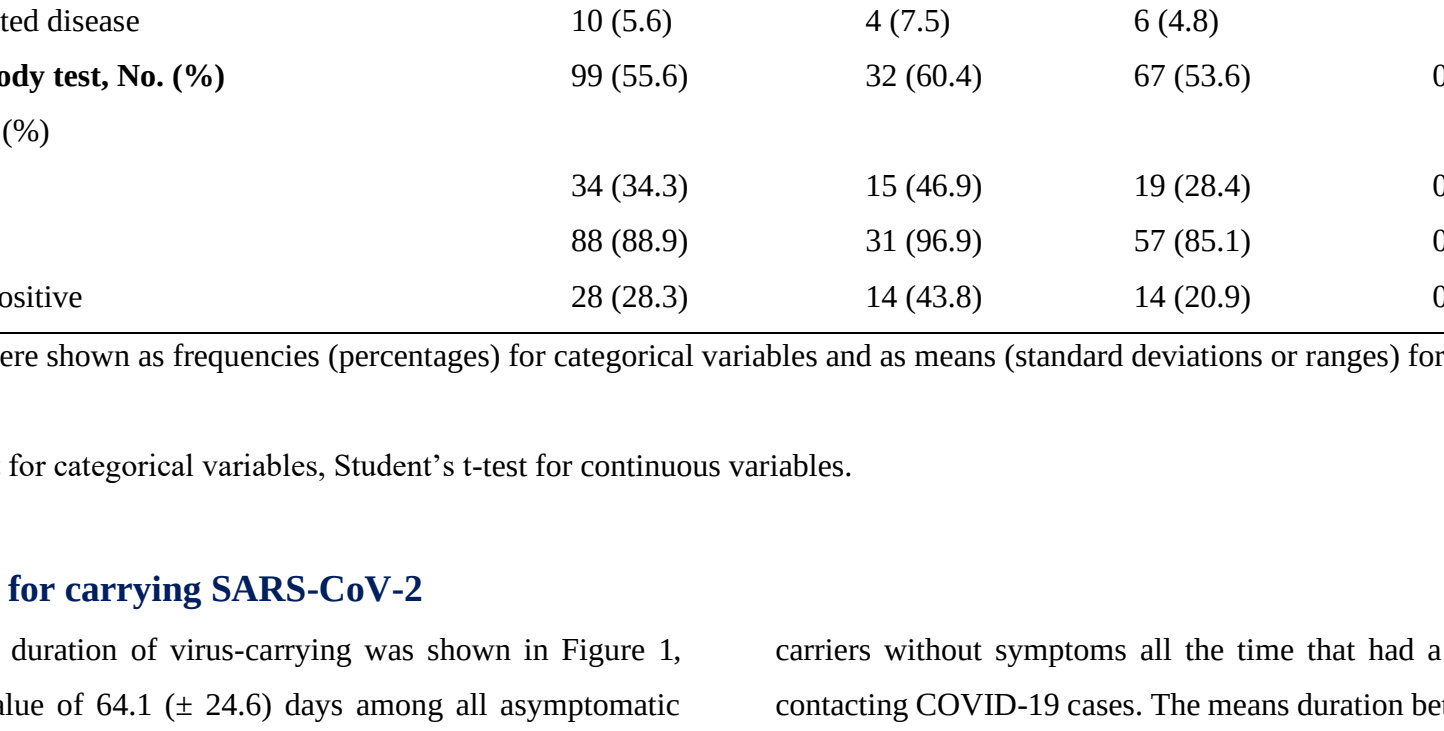

Figure 1: The underlying duration and frequency distribution of virus-carrying in asymptomatic SARS-CoV-2 carriers.

(1) Time-intervals between the date of symptom onset and date of confirmed infection by SARS-CoV-2 nucleic acid test in asymptomatic carriers with previous symptoms (A), and their frequency distribution within different subgroups of the duration of virus-carrying (B).

(2) Time-intervals between the date of close contact with confirmed cases and date of confirmed infection by SARS-CoV-2 nucleic acid test in asymptomatic carriers without previous symptoms all the time (C), and their frequency distribution within different subgroups of the duration of virus-carrying (D).

3.3 Transmission of asymptomatic carriers

There were 4 asymptomatic carriers within 4 families revealed a typical asymptomatic transmission to their family members, respectively **(Figure 2)**. The epidemiological investigation showed that carrier 1, carrier 3, carrier 5, and carrier 7 had a history of contacting suspected or confirmed cases, while carrier 2, carrier 4, carrier 6, and carrier 8 reported they had never contacted other COVID-19 cases, except for their family members, since they were self-isolated at home during the lockdown of Wuhan.

In **family 1**: carrier 1 (wife) had a fever and cough that lasted for 2 weeks since January 23, 2020, while as the close contact, carrier 2 (husband) also had 2 days of fever since January 26, 2020. Then, they had no signs and symptoms onset that lasted for over two months. On April 12 and April 15, 2020, they tested positive for SARS-CoV-2, respectively. In **family 2**: carrier 3 (husband) had 11 days of pharygodynia since February 3, 2020, while he and his wife (carrier 4) tested positive for SARS-CoV-2 on April 30, 2020. In this period, carrier 4 did not have any symptoms onset. In **family 3** and **family 4**: as the first infected member in these two families, the carrier 5 (father) and carrier 7 (husband) kept closely contact carrier 6 (son) and carrier 8 (wife) for more than two months, respectively. Then, all of them tested positive for SARS-CoV-2 nucleic acid.

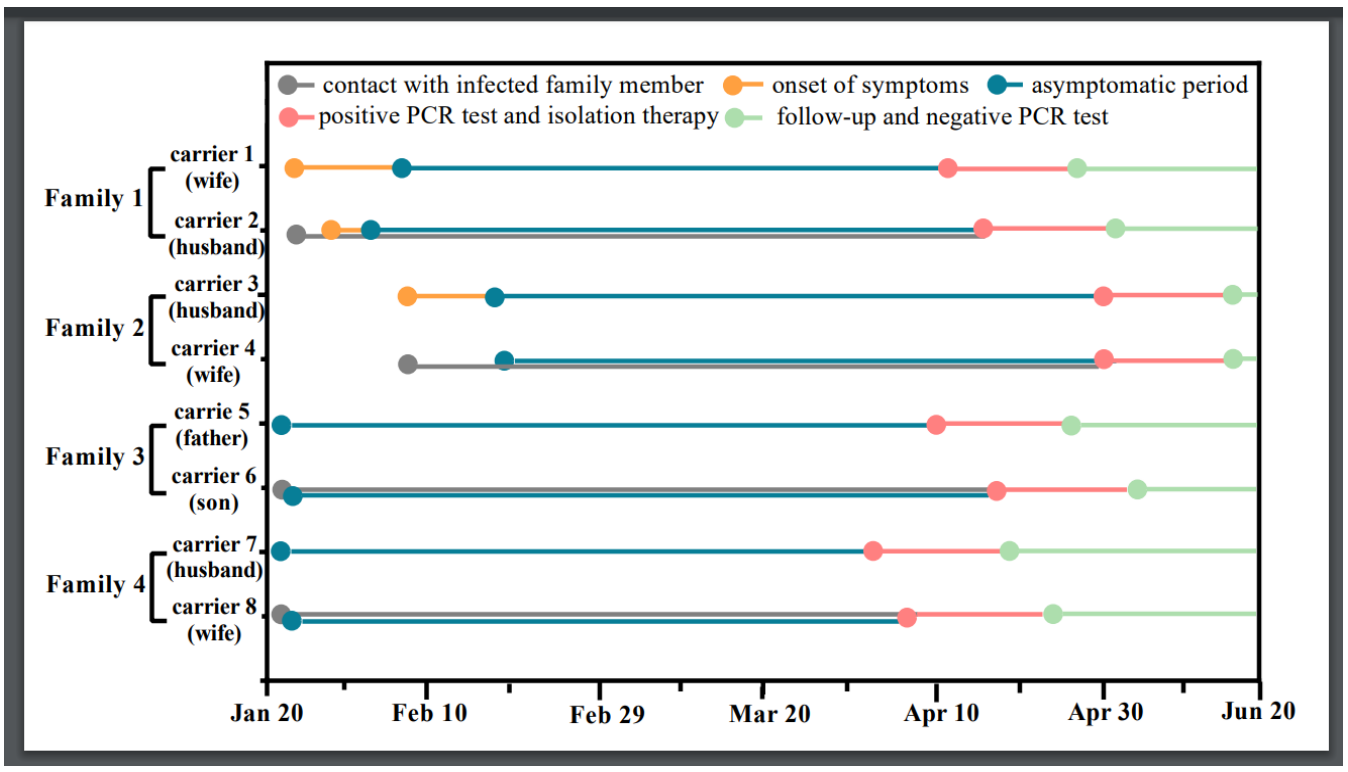

Figure 2: Timeline of a typical asymptomatic transmission from asymptomatic carriers to their family members

Note: There were 4 asymptomatic carriers within 4 families revealed a typical asymptomatic transmission to their family members, respectively. Carrier 1, carrier 3, carrier 5, and carrier 7 had a history of contacting suspected or confirmed cases, while carrier 2, carrier 4, carrier 6, and carrier 8 reported they had never contacted other COVID-19 cases.

3.4 Management and follow-up of asymptomatic carriers

After asymptomatic SARS-CoV-2 carriers were confirmed, they were immediately put into the designated hospitals. Vitamins and some Traditional Chinese Medicine (such as ShuFeng JieDu or Lianhua Qingwen capsules) **[9]** were used for treatment, and none of the asymptomatic carriers developed any illness-onset during the 14 days of quarantine. After two consecutive samples of negative nucleic acid tests (time-interval between sampling should be at least 24 hours), they were released from quarantine. Furthermore, neither asymptomatic carriers nor their families tested positive for SARS-CoV-2 or have symptoms onset in the first two months of follow-up since quarantine ends.

4. Discussion

This study of asymptomatic SARS-CoV-2 carriers in Wuhan, China, provides insight into characterizing the epidemiology, duration of virus-carrying, infectivity, management, and outcomes of this population.

Our study of 178 asymptomatic carriers was younger than the largest epidemiological study of 32583 confirmed COVID-19 cases (47.5 vs. 56.7 years) in Wuhan, China **[10]**, which partially suggested asymptomatic infection was more likely to be found in young close contacts with higher immune function. The proportion of females was comparable between these two studies (50.6 % vs. 51.6 %) **[10]**, although there were studies showing the incidence of SARS-CoV-2 varied among the male and female populations **[11,12]**. 32.6 % of asymptomatic carriers had underlying comorbidities, which were lower then the first report about the 138 hospitalized COVID-19 cases in Wuhan (46.4 %) **[13]** but were higher than a nationwide analysis in China (25.1%) **[14]**. These differences could be attributed to the inconsistency of studied populations, as well as the differences among studies in terms of disease severity.

Less than 30 % of our studied asymptomatic carriers had a history of previous symptoms onset, leading to the inadequacy of symptom-based isolation to control asymptomatic carriers. Although only 99 (55.6 %) of 178 asymptomatic carriers had IgM/IgG antibody tests, 88.9 % of them tested IgG positive. Thus, the IgG antibody test may exhibit an adjunct to nucleic the acid test to identify not only COVID-19 cases with symptoms onset **[15**], but also the underlying asymptomatic carriers among the population with a high risk of infection, such as close contacts, and subjects from endemic areas. 75 (42.1%) of 178 asymptomatic carriers were healthcare workers, bank staff, and employees in service industries. Notably, almost one-third of our studied asymptomatic carriers had met the medical-institutes as patients with other diseases, family caregivers, or healthcare workers. This means that public places are at high risk of being the virus-contaminated areas, because the service staff and customers with asymptomatic infection in these places could likely freely shed the virus into the environment and might act as potential sources to propagate the epidemic **[16]**. Since the public health interventions were associated with improved control of the epidemic of COVID-19 in China **[10]**, South Korea **[17]**, and some regions of Europe **[18]**, wearing face masks, restriction of public activities, cancellation of social gatherings, identification, and isolation of asymptomatic SARS-CoV-2 carriers and their close contacts were associated with a reduction in the degree of transmission.

Previous studies revealed that older and a greater number of comorbid conditions were not only the risk factors of infection but also associated with poor outcomes for hospitalized COVID-19 cases **[13,19]**. Similarly, compared with asymptomatic carriers without any symptoms all the time, underlying comorbidities (e.g., hypertension and diabetes) were more common in those carriers who had a history of symptoms onset. This suggests that comorbid conditions were also associated with the risk of symptoms onset in asymptomatic carriers. Knowledge of the virulence, transmissibility, and immune system response of SARS-CoV-2 remains largely unknown. There was a study that reported asymptomatic carriers and symptomatic patients had a similar transmission potential since they had a comparable viral load [20]. In this study, family cluster infections due to human-to-human transmission were validated, and similar results were found in other studies **[21,22]**. This suggests that transmission of COVID-19 may occur with mild or no symptoms, and asymptomatic carriers may important drivers for the growth of the COVID-19 pandemic **[23]**.

The reported median duration of viral shedding in asymptomatic carriers was 7 to 8 days **[24]**, which was much shorter than the value of 18.5 days in symptomatic cases [25]. However, there was a study that reported that asymptomatic patients might continue to test positive for up to 21 days **[22]**, while the longest duration of virus-carrying has not been determined. The mean duration for carrying SARS-CoV-2 could be as long as over 60 days before the asymptomatic carriers were confirmed by RT-PCR in our study, which was much longer than the current practice of 14 days quarantine in many regions **[26]**, suggest it is still necessary to maintain social distance and wear a mask for a certain period after the quarantine.

Until now, cohesive guidelines on how to effectively manage the asymptomatic carriers are also lacking. The 10 days of universally tested that covered more than 9 million inhabitants in Wuhan, China, with a detection rate of asymptomatic carriers was less than 0.3 per 10,000 population **[8]**. These asymptomatic carriers were immediately sent to the designated hospitals for isolation and treatment. Furthermore, their family members and other traced close contacts were also sent to the centralized medical observation sites, and their homes were fully disinfected to prevent the underlying transmission of coronavirus. There were no additional COVID-19 cases or asymptomatic carriers were reported in their communities, suggesting the effectiveness of committing proactive case identification by universal testing and isolation. Local screening and surveillance of asymptomatic carriers, or at least PCR testing should prioritize healthcare workers, bank staff, and other employees in service industries when resources are limited.

Currently, no specific treatments have been recommended for SARS-CoV-2 infection. Some Traditional Chinese Medicine (such as ShuFeng JieDu or Lianhua Qingwen capsules) has been used historically for the treatment of influenza-like illness in China **[27]**. The effects of Lianhua Qingwen against influenza B virus in vitro and in vivo have been evaluated **[28]**, and they were also recommended by the Chinese government as the antiviral drugs to treat and control the H1N1 pandemic. Similarly, our studied asymptomatic SARS-CoV-2 carriers received the integrated medicine of vitamins and some Traditional Chinese Medicine for 14 days, and all of them tested negative in nucleic acid before they were released from quarantine, suggesting the efficacy of such treatment for SARS-CoV-2 infection. More high-quality randomized controlled trials are needed in the future.

Our study has some limitations. First, it is challenging to differentiate mild asymptomatic carriers from patients with a common cold, inferring that in some influenza patients without the SARS-CoV-2 the nucleic acid test might be misdiagnosed as COVID-19 cases when based on symptom onset diagnosis. However, 96.9 % of asymptomatic carriers with a history of previous symptoms tested SARS-CoV-2 IgG positive, which indicated their past infection. Second, since the indeterminate date of the exact first infection in asymptomatic carriers, the duration for carrying SARS-CoV-2 could be overestimated or underestimated, the corresponding time-points are warranted. Third, knowledge about the route of transmission remains limited, we could not evaluate the transmission dynamics and specify the duration of viral shedding in asymptomatic carriers. Fourth, the relatively strong infectivity of asymptomatic carriers was reported in the incubation-period **[6]**, which possibly became weak as time goes on, the long duration of virus-carrying may not indicate highly contagious throughout the period. However, our results arouse concern about the prolonged duration of carrying SARS-CoV-2 in asymptomatic carriers. The dynamics of virus-carrying and infectious period of asymptomatic SARS-CoV-2 carriers need to be further clarified.

5. Conclusions

In summary, our analysis of a regional study in Wuhan, China, reveals that most asymptomatic SARS-CoV-2 carriers were over 18 years of age and worked as healthcare workers, bank staff, or other employees' in-service industries. Almost one-third of them had a history of previous symptoms onset. The household transmissions provide validly evidence supporting the infectivity of asymptomatic carriers, and the mean duration of virus-carrying can exceed 60 days before confirmed. Early detection, isolation, treatment of asymptomatic SARS-CoV-2 carriers, as well as active tracing of their close contacts were effective public interventions in the control of the COVID-19 epidemic.

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Declaration of competing interest:

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