Clinical characteristics and infectivity of asymptomatic carriers of SARS-CoV-2 (Review)

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Abstract. Since December 2019, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic. At present, confirmed patients are the main source of infection, while a number of studies have indicated that asymptomatic carriers also have the ability to spread the virus. As of September 29, 2020, as the first country to report coronavirus disease 2019 (COVID-19), China has 375 asymptomatic infections according to the National Health Commission of China. Asymptomatic carriers have become the current focus of global epidemic prevention and control efforts. The present review article provides a brief introduction on the clinical characteristics and infectivity of asymptomatic carriers, and makes suggestions for the identification of asymptomatic carriers.

Contents

1. Introduction

In December 2019, the first case of pneumonia of unknown etiology was identified in Wuhan, China (1). Subsequently, the pathogen was isolated and officially named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, due to its marked similarity with the agent of Severe Acute Respiratory Syndrome (SARS) (2). SARS-CoV-2 primarily spreads through respiratory droplets and close contact, and all populations are susceptible (3). Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared by the World Health Organization (WHO) as a public health emergency of international concern on January 30, 2020 and a pandemic on March 12, 2020. As of September 28, 2020, the number of globally confirmed cases was over 32.7 million and the number of mortalities was >991,000, according to WHO statistics (4).

As the epidemic progresses, the prevention and control of asymptomatic carriers has gradually become the focus of the global epidemic control effort. For example, at present, China and certain other countries have entered the stage of remission, although sporadic new cases, imported cases and asymptomatic carriers remain risk factors for spreading the virus (5). According to statistics from the National Health Commission of China, there were 375 asymptomatic carriers currently under medical observation by September 29 (6). One study initially estimated that asymptomatic carriers, pre-symptomatic and mild infection of COVID-19 may account for 60% of all infections (7). In addition, the majority of these patients may not self-isolate, and spread the virus to others unconsciously, as they are unaware that they have been infected with SARS-CoV-2 (8). Therefore, asymptomatic carriers of COVID-19 should be taken seriously because they serve a crucial role in disease transmission. The present review aims to discuss the clinical characteristics and infectivity of asymptomatic carriers and provide suggestions to control these potential hidden sources of infection.

2. Demographic characteristics

The studies in the present review identified that the demographic characteristics of asymptomatic carriers are significantly correlated with age. In a study of 147 asymptomatic carriers in Anhui, China, male carriers accounted for 51.7% and carriers <20 years old accounted for 15.6% (9). Hu *et al* (10) reported the epidemiological and clinical data of 24 asymptomatic infections with COVID-19, and identified

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that people <15 years old were more likely to be asymptomatic carriers compared with patients >15 years. The study by Wang *et al* (11), which reviewed the clinical information of 55 asymptomatic carriers in Shenzhen, China, confirmed that 27% of asymptomatic carriers were <18 years old. Rawat *et al* (12) confirmed that children were more likely to have asymptomatic infections compared with adults; their data indicated that 27% of pediatric COVID-19 cases were asymptomatic carriers and that only 7% of adult patients had no symptoms (12). This result was also verified in Zhejiang, China, where, among 36 children with confirmed COVID-19, 28% were asymptomatic carriers (13). Tan *et al* (14) identified that asymptomatic carriers were relatively young (mean age, 34.5 years old). Current evidence suggests that the asymptomatic carriers with SARS-CoV-2 vary by age, however, to the best of our knowledge, no studies have identified differences in sex between asymptomatic carriers.

Previous data may also explain why asymptomatic carriers are more likely to be young people. For example, it may be that the gene expression of angiotensin converting enzyme II (ACE2) in nasal epithelial cells is age-dependent. ACE2 is the host receptor for SARS-CoV-1 and SARS-CoV-2 (15). Bunyavanich *et al* (16) demonstrated that ACE2 gene expression increased with age, with the lowest expression in younger children (<10 years old; n=45). In addition, Do *et al* (17) argued that cytokine storms in adults promote stronger inflammatory responses compared with that in younger people. Wu *et al* (18) also demonstrated that older patients (60-85 years old) and middle-aged patients (40-59 years old) were more likely to induce higher neutralizing antibodies titers compared with younger patients (15-39 years old), which has been shown to be associated with disease severity (19).

3. Ratio of asymptomatic carriers among all infected persons

It is not easy to accurately estimate the proportion of asymptomatic carriers among patients with confirmed COVID-19, as the total number of asymptomatic carriers will not be identified unless all people are systematically screened. Moreover, without follow-up observation, it is also difficult to distinguish between pre-symptomatic persons (symptomatic later in the course of the disease) and the asymptomatic carriers (asymptomatic during the whole duration of the disease) (20). Wang *et al* (21) identified 1,012 patients with non-severe COVID-19 disease with positive reverse transcriptase polymerase chain reaction (RT-PCR) results in Wuhan, China, of which 30 (3.0%) were asymptomatic (21). In Shanghai, China, another study showed that 3.9% of the 328 adults diagnosed with COVID-19 were asymptomatic carriers (13 cases) (22). However, a study in Jinan, China, observed that 11 of 47 confirmed patients (23.4%) were asymptomatic carriers (23). According to statistics from the Chinese Center for Disease Control and Prevention, on February 11, China recorded a total of 72,314 patients, including 889 asymptomatic cases (1.2%) (24). However, this statistic was measured prior to the large-scale screening of patients with COVID-19 in China, so the proportion may be less compared with the real data. One study estimated that the rate of asymptomatic carriers was 30.8% (95% CI, 7.7-53.8%) among 565 Japanese individuals evacuated from Wuhan, China (25). There are also studies using published data for statistical model analysis, estimating that the asymptomatic proportion of COVID-19 cases on the Japanese cruise ship Princess Diamond was 17.9% (95% CI, 15.5-20.2%) (26). In a cohort of children, Qiu *et al* (13) identified that 10 (28%) of 36 pediatric patients infected with COVID-19 were completely asymptomatic. Similarly, in another study of children with COVID-19, 20 (27%) of 74 cases were asymptomatic infections (27). In addition, the study by Rawat *et al* (12), examining patients in the United States of America, demonstrated that 27% of pediatric patients with COVID-19 had no symptoms, while only 7% of adult patients had no symptoms (12). Notably, a study conducted in a large hospital in Wuhan, China also found that the asymptomatic infection rate among healthcare workers was 9.7% (88/908) (28). From these studies, it can be observed that the proportion of asymptomatic carriers varies widely in different studies. In addition, the true prevalence of asymptomatic carriers may be lower compared with current estimates due to the inclusion of pre-symptomatic infections in some cross-sectional studies.

4. Radiological and laboratory data

Asymptomatic carriers differ from confirmed patients not only in their symptoms, but also in their laboratory and chest CT results. At present, no uniform pattern in laboratory and radiological manifestations of asymptomatic carriers has been established. Meng *et al* (29) collected clinical information on 58 asymptomatic patients with COVID-19 pneumonia and identified that all carriers had a normal laboratory and abnormal chest CT results. The main CT features of asymptomatic patients were ground-glass opacity [(GGO) 55, 94.8%] at admission. However, among the 24 asymptomatic carriers in Nanjing, China, lymphopenia and leukopenia were not obvious, and chest CT images were normal in the majority of young carriers (<15 years old) (10). Yu and Yang (30) also reported 2 asymptomatic carriers with normal lymphocyte count and chest CT images. Similarly, Wang *et al* (11) reported increased C-reactive protein and lactate dehydrogenase levels in 10 and 13 carriers, respectively, and only 11 patients (including two with severe infections) exhibited leukopenia, from the follow-up results of 55 asymptomatic carriers (11). A study from Zhou *et al* (22) followed up 13 cases of asymptomatic carriers, of which 2 patients had leukocytes below the normal range. A recent study identified that 3 of 11 (27.3%) persistent asymptomatic patients with SARS-CoV-2 infection did not have typical chest CT results and the GGO of other carriers had been absorbed in nearly 5 days (31). Ali and Ghonimy (32) examined 44 asymptomatic cases of COVID-19 and identified that the main features of their CT results were GGO (93%; n=41) and surrounding distribution (77.3%; n=34). In summary, these studies suggest that radiological and laboratory abnormalities vary and laboratory findings and chest CT images can be normal in asymptomatic carriers. Therefore, SARS-CoV-2 infection cannot be ruled out on the basis of normal radiological and laboratory results.

5. Infectivity and transmission risk of asymptomatic carriers

A number of studies have confirmed that asymptomatic carriers can transmit the virus. In Anyang, Henan, China, a family cluster of 5 patients with COVID-19 was infected with SARS-CoV-2

by contact with asymptomatic family members (33). In Nanjing, COVID-19 was also transmitted by asymptomatic carriers to cohabiting family members (10). Yu and Yang (30) described an asymptomatic carrier who had transmitted SARS-CoV-2 to his brother following close contact. Recently, an asymptomatic carrier resulted in 13 secondary cases of infection, reportedly as an asymptomatic super spreader (34). In summary, it is almost unquestionable that asymptomatic carriers have infectivity.

In earlier cross-sectional studies, no significant differences in viral titers and transmission efficiency were identified between asymptomatic and symptomatic patients. A study showed that the viral load in asymptomatic patients was similar to that of symptomatic patients (35). Chen *et al* (36) followed up and investigated 2,147 close contacts in Ningbo, Zhejiang, China, with a total infection rate of 6.15%, while there was no significant difference in the infection rate between the confirmed cases and asymptomatic cases (6.30 and 4.11%, respectively) (36). Concomitantly, Yin and Jin (37) analyzed the transmission rate of 157 symptomatic cases and 30 asymptomatic cases of COVID-19 and identified that there was no significant difference in the transmission rate between symptomatic and asymptomatic patients. However, none of these studies excluded pre-symptomatic patients in the incubation period. Another study in Korea including 3 pre-symptomatic patients and 10 asymptomatic carriers suggested that pre-symptomatic patients in the incubation period may have an increased viral load compared with asymptomatic carriers (38). Therefore, the transmission efficiency of asymptomatic carriers estimated by these studies may be increased compared with the real data. Subsequently, increasing evidence suggests that true asymptomatic carriers may have a decreased risk of transmission than symptomatic patients. The study by Liu *et al* (9) showed that the secondary attack rate of 131 asymptomatic carriers was 2.6% (24/914), while the secondary attack rate of 16 confirmed cases was 9.7% (23/236), further demonstrating that the transmission risk of asymptomatic carriers was decreased compared with that of the confirmed cases. In China, a study including 12 asymptomatic carriers in Wuhan also identified that only one carrier has transmitted the virus to a close contact (14). Chen *et al* (39) tracked 9 asymptomatic carriers and identified that none of them had transmitted SARS-CoV-2 to others, so they speculated that the absence of symptoms such as sneezing and coughing may interfere with virus shedding and decrease the risk of infection. In addition, a systematic review showed that the relative risk of asymptomatic carriers transmission was decreased by 42% compared with symptomatic transmission, while there were no differences in viral load (40). In light of the data from these studies, asymptomatic carriers may have a weaker transmission efficiency compared with symptomatic patients. However, the transmission ability of asymptomatic carriers cannot be ignored, as some of them may develop into super spreaders. There is no doubt that the early identification of asymptomatic carriers and the prevention of the further spread of the virus are critical to disease control.

6. Transmission period of asymptomatic carriers

The study in Korea calculated that the median duration of virus shedding (from the first confirmed positive RNA test result to the first negative RNA test result) in asymptomatic carriers was 4.5 days (2.5-9 days), and all asymptomatic carriers were almost non-infectious after isolation of 14 days (38). However, the study from Hu *et al* (10) showed that the median spread interval was 9.5 days (up to 21 days), and the actual infection period may be longer as the exact date of the first infection is uncertain for some carriers. Tan *et al* (14) demonstrated that the median duration of virus shedding was 11.5 (9-14) days among 12 carriers in Wuhan, 2 of which were found to have positive RNA results lasting up to 2 months (14). Long *et al* (41) also reported a median duration of viral shedding of 19 (15-26) days in 37 asymptomatic carriers. Meanwhile, Pan *et al* (42) retrospectively analyzed 26 persistently asymptomatic SARS-CoV-2 carriers and identified that the median time from diagnosis to negative nucleic acid testing was 7.5 days (2-20 days) for carriers with normal or atypical chest CT findings, compared with 12.5 days (8-22 days) for those with typical GGO (42). These studies have shown that SARS-CoV-2 can remain present in asymptomatic carriers for a long period of time as long as 2 months and carriers with abnormal chest CT findings may have a longer transmission period.

7. Advice to identify asymptomatic carriers

Asymptomatic carriers can transmit the virus as an unseen source of infection, which is a great challenge for epidemic prevention and control, so the importance of implementing social distancing measures and using masks cannot be overemphasized. It is also of vital importance to identify and isolate asymptomatic carriers at an early stage. The question of how asymptomatic carriers can be identified earlier remains. At present, the detection of SARS-CoV-2 virus infection mainly depends on nucleic acid, serum antibody and chest CT. As the chest CT images of some asymptomatic carriers are entirely normal, particularly in young people, the present study only discussed the detection of nucleic acids and antibodies. Studies have shown that nucleic acid detection has the disadvantages of high false-negative rate and low sensitivity, although it is widely used (28,43,44). The positive rates of RT-PCR detection of sputum specimens, nasal swabs and throat swabs were 74.4-88.9, 53.6-73.3 and 29.6-61.3%, respectively (44). In contrast, the sensitivity and specificity of the rapid IgM-IgG combined antibody test were 88.7 and 90.6%, respectively (43). There is also evidence that the sensitivity of total antibodies is increased compared with that of IgM or IgG alone (45). A study identified that the asymptomatic infection rate confirmed by RT-PCR alone was 4.2% (38/908), while combined with RT-PCR test and serological detection was 9.7% (88/908) (28).

Considering the available data, the combination of serum antibody testing and nucleic acid testing is recommended to identify asymptomatic carriers in high-risk areas or high-risk populations. Confirmed asymptomatic carriers should be subject to centralized quarantine and observation for at least 14 days until they receive 2 consecutive negative nucleic acid test results (at least 24 h apart).

8. Conclusions

Based on the literature, the present review identified that the proportion of asymptomatic carriers of SARS-CoV-2 in all

infections varies significantly between different studies, but asymptomatic infection may be correlated with age. Among the young population, the proportion of asymptomatic carriers may be increased. There is no uniform pattern of laboratory and radiological findings in asymptomatic carriers, and some asymptomatic carriers may have completely normal chest CT and laboratory results. It is almost certain that asymptomatic carriers can transmit SARS-CoV-2, but they may have a decreased risk of transmission compared with symptomatic patients. At present, the management of asymptomatic carriers should become a focus of epidemic prevention, particularly in countries with stable epidemics. Dual detection of serum antibodies and nucleic acids in high-risk areas and high-risk groups and quarantining for at least 14 days is recommended following diagnosis as an asymptomatic carrier.

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WZ and FX made significant contributions to select the topic of the review. WZ was responsible for the collection and collation of documents and writing draft manuscripts. HZ, FX and XW revised the writing of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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