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Review Article

A systematic review of asymptomatic infections with COVID-19

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Abstract Since the outbreak of coronavirus disease 2019 (COVID-19) in late December 2019, it has brought significant harm and challenges to over 200 countries and regions around the world. However, there is increasing evidence that many patients with COVID-19 are asymptomatic or have only mild symptoms, but they are able to transmit the virus to others. There are difficulties in screening for asymptomatic infections, which makes it more difficult for national prevention and control of this epidemic. This article reviews the characteristics, treatment, and outcomes of asymptomatic infections with COVID-19, hoping it would be helpful for early prevention and control of this severe public health threat worldwide.

Introduction

At the end of December 2019, the novel coronavirus pneumonia began to spread in Wuhan, China. The World Health Organization (WHO) officially named this disease coronavirus disease 2019 (COVID-19) on February 11, 2020. At the same time, the International Committee on Taxonomy of Viruses (ICTV) announced that the new coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the outbreak, COVID-19 has brought major harm and challenges to more than 200 countries and regions around the world. To date, more than 3,000,000 cases have been confirmed worldwide and the cumulative deaths have exceeded 200,000.[1,2]

COVID-19 initially has been divided into four types: mild, moderate, severe, and critical cases.[3] However, with the global outbreak of coronavirus, there is increasing evidence that many infections of COVID-19 are asymptomatic, but they can transmit the virus to others. Asymptomatic infections refer to the positive detection of nucleic acid of SARS-CoV-2 in patient samples by reverse transcriptase-polymerase chain reaction (RT-PCR), but have no typical clinical symptoms or signs, and no apparent abnormalities in images, including lung computed tomography (CT).[4] The

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clinical characteristics of asymptomatic infections and other types of COVID-19 are shown in Table 1. Early recognition of an infected person and cutting off the route of transmission are key points to control COVID-19. However, most asymptomatic infections do not seek medical assistance due to no obvious clinical signs and poor prevention awareness, which contribute to the rapid spread of COVID-19. Therefore, it is a great challenge to prevent and control this specific type of patient globally, which requires more attention worldwide.

Infectivity

Asymptomatic infections have the same infectivity as symptomatic infections.[5] It has been reported that a 53-year-old UK patient with an asymptomatic COVID-19 infection may cause 11 infections.[6] A report pointed out that one asymptomatic person who experienced 19 days from contact with the source of infection to RT-PCR confirmation may have infected 5 people.[7] These asymptomatic cases may play a role in the transmission and therefore pose a significant challenge to infection control.

Estimates of the incidence of asymptomatic infections will clarify the epidemiological potential of COVID-19 transmission and understanding of the true universality of the disease. There are many studies on the incidence of asymptomatic infections (Table 2), but each study has its limitations. First of all, due to insufficient awareness of asymptomatic infections and limited detection capabilities in the early stage of the outbreak, China's 1.6% may be underestimated.[8] On the contrary, another study investigated 565 Japanese citizens evacuated from Wuhan at the end of January and found that the incidence of asymptomatic infections was 30.8%.[9] Another example is the "Diamond Princess" cruise ship, which was isolated in Japanese waters in early February due to COVID-19 infection found that the incidence of asymptomatic infections was 51.7%.[10] Some researchers suggested that the above two studies overestimated the incidence, but in fact, a person truly has a higher risk if he has close contact with diagnosed or suspected infected persons in a relatively confined space. Incidence of asymptomatic infections from other studies had some shortcomings, such as those in Korea[11] and Washington,[12] which showed inaccurate results due to the small sample size. One case in Wuhan tracked the prevalence of 1391 children under 15 years old who had been in close contact with infected or suspected cases.[13] The incidence of asymptomatic infections in the children is lower than that of the whole population, we propose that it is related to the special immune response and ACE2 level in the children's bodies.[14] According to these studies, the ability of asymptomatic infections to spread the virus is not low, and these patients are likely to cause a new round of outbreaks. Therefore, finding asymptomatic infections is the key point for early prevention and control of COVID-19 worldwide.

The incubation period is the approximate time from the first exposure to the virus until the clinical symptoms or signs onset, and patients can also transmit the virus in this period.[15] Asymptomatic infections have no special incubation due to no clinical signs. However, a recent research found that the viral load detected in asymptomatic populations were similar to that in symptomatic patients, indicating that asymptomatic infections have the potential for transmission, which may occur early in the course of infection.[16] Since the viral nucleic acid positivity refers to that the virus load in samples reaches a certain limit, but the infectivity mainly depends on whether the virus is in a reproductive state.[17] That is, sometimes, despite ongoing high viral loads, no live virus can be isolated, which means that viral nucleic acid positivity does not indicate infectivity.[18] It is also proved by a clinical study in which the recovered COVID-19 patients who had no obvious clinical

Table 1 Clinical characteristics of asymptomatic infections and other types of COVID-19.[2,3]

Type	Clinical characteristics	RT-PCR test for COVID-19
Asymptomatic	No clinical symptoms and chest imaging findings.	Positive
Mild	Mild clinical symptoms, such as fever, fatigue, cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache. No abnormal chest imaging findings.	Positive
Moderate	Mild or moderate clinical features. Chest imaging showed mild pneumonia manifestation.	Positive
Severe	Suspected respiratory infection symptoms, plus any of the following: Shortness of breath, RR $\geq$ 30 breaths/min; At rest, oxygen saturation $\leq$93%; $Pa0_2/Fi0_2 \leq$ 300 mmHg (1 mmHg = 0.133 kPa). Chest imaging showed the lesions significantly progressed $>$ 50% within 24—48 h was a severe disease.	Positive
Critical	Rapid progress of disease, plus any of the following: Respiratory failure, and need mechanical ventilation; Shock; Combined with other organ failure requires ICU monitoring treatment.	Positive

RT-PCR, reverse transcriptase-polymerase chain reaction; RR, respiratory rate; $Pa0_2$, arterial partial pressure of oxygen; $Fi0_2$, oxygen concentration; ICU, intensive care unit.

Table 2 The incidence of asymptomatic infections with COVID-19 in different studies.

	China[8] (n = 72,314)	Japan[9] (n = 565)	Diamond Princess[10] (n = 3711)	Korea[11] (n = 28)	Washington[12] (n = 76)	Wuhan Children[13] (n = 1391)
RT-PCR positive cases	56,128	13	634	28	23	171
Asymptomatic cases	889	4	328	3	13	27
Incidence rate (%)[a]	1.6	30.8	51.7	10.7	56.5	15.8

[a] As of the data published in the literature, the proportion of asymptomatic infections in the population with positive nucleic acid test.

symptoms were detected to be positive for SARS-CoV-2 by hyper-sensitive viral nucleic acid re-examination methods, but these patients had not caused new infections.[19] Due to the limited data from current studies, we think that it is necessary for us to be highly vigilant to asymptomatic infections. Moreover, viral nucleic acid positivity has been reported not to be always considered, and more clinical studies are still needed to verify that. A previous study found that the median period of asymptomatic patients from viral nucleic acid positive to negative was 9.5 days, the longest was up to 21 days among the 24 asymptomatic cases.[20] Then in another study found that the median period from contact to diagnosis and the last positive nucleic acid test was 19 days (8—24 days) and 21.5 days (10—36 days), respectively.[21] The median period from diagnosis to negative nucleic acid test was 7.5 days (2—20 days) with normal or atypical chest CT infections and 12.5 days (8—22 days) with typical CT findings.[21] However, an asymptomatic infection should be quarantined for 14 days until now,[22] more studies are still needed to assess the infectivity duration of asymptomatic cases. And if necessary, more attention should be paid to some special infectious individuals who need longer segregation due to the result of nucleic acid test.

Distribution

The most likely source of asymptomatic infections is close contacts of patients who have been diagnosed or suspected, and family clusters have been presented before. Also, colleagues, friends, and people who coincide with the trajectories of diagnosed or suspected patients are all regarded as high-risk populations.

Familial cluster has made the epidemic challenging to prevent and control. Some family members do not have any clinical manifestations, but the nucleic acid test result is positive, and this has become a major difficulty in the prevention and treatment of COVID-19. In one case report, all three of the family members were diagnosed with COVID-19, and only one family member had clinical symptoms.[23] Another family cluster report showed that the first patient was in good health without clinical manifestations, including fever and cough, and denied having primary diseases. He went to the local hospital for treatment only because of urticaria. The patient stated that he had lived in the local area for a long time and had not been to the epidemic area. However, the investigation of the disease control experts found that the patient had close contact with his relatives in Hubei Province one week before the onset of symptoms. Finally, by investigating the family members and close contacts of the patient, three pulmonary CT scans were normal, but the nucleic acid test results were positive.[24] Family members of COVID-19 patients, even without any symptoms, should be closely monitored and examined to rule out infection. These cases also highlight the need for a close epidemiological investigation to prevent the omission of possible sources of contamination.

Different individuals may have different clinical signs. Studies have shown that asymptomatic infections are more common in populations of young and middle-aged individuals with functional performance status without underlying diseases. It was reported that asymptomatic cases were more common in middle-aged people in Shenzhen (median age:49 years, 30.9% between 30 and 49 years)[25] and a few younger people in Nanjing (median age:32.5 years).[20] Above all, age and body condition may play an important role in the severity of COVID-19, and this is related to different immune responses and other potential pathogenesis.

Pathogenesis

Similar to SARS-CoV, SARS-CoV-2 invades cells by using angiotensin-converting enzyme 2 (ACE2) as its receptor.[26] Because ACE2-mediated angiotensin II (Ang ll) degradation plays an important role in the pathogenesis of severe lung failure after a viral infection, the severity of the virus infection is closely related to the maturity and binding capacity of ACE2.[27] Therefore, we supposed that a lower level of ACE2 and weaker binding capacity with SARS-CoV-2 should be a major factor that leads to the absence of any clinical manifestations for asymptomatic infections. It has been reported that only a specific mild immune response is caused by the SARS-CoV-2 invasion in asymptomatic patients.[28] However, more clinical samples should be collected, and a relative examination of ACE2 should be performed and compared for different types of COVID-19 cases, as this would be helpful to explain its pathogenesis.

Prevention and control

The main mode of transmission of COVID-19 is through droplet and contact transmission and high-concentration aerosols. Droplet transmission occurs when nearby people ingest or inhale respiratory droplets (produced when an infected person coughs or sneezes). The successful isolation of live virus from throat swabs is a significant difference from SARS, suggesting that viral replication in upper respiratory tissues is active and that SARS-CoV-2 is more effective than SARS-CoV in spreading through active

shedding of pharyngeal viruses.[18] A German team found that some people with COVID-19 had high levels of virus in their throat swabs when their initial symptoms were mild, meaning that the pathogen was quickly released and transmitted to others by coughing or sneezing (droplet transmission).[29] This means that protective measures, including wearing protective masks, can prevent infection with new coronavirus to a certain extent.

Most people with an asymptomatic infection do not seek medical assistance due to no obvious clinical signs and poor prevention awareness. More epidemiological methods, including close contact screening, cluster epidemic surveys, and follow-up surveys of the source of infection, were used to identify people with asymptomatic infections. The significance of asymptomatic infections as a source of infection depends on the distribution in the population and the amount and duration of virus elimination. However, clinical symptoms are hidden, and we can only rely on immunology or nucleic acid detection technology to obtain information about the infection; therefore, this kind of infectious source cannot be effectively identified, making it very difficult to prevent and control. Nucleic acid testing should be performed in persons who have contacted diagnosed or suspected COVID-19 patients. A person with an asymptomatic infection should be quarantined for 14 days.[22] After the quarantine period expires, in principle, those who have negative test results for two consecutive samples of nucleic acid (sampling interval of at least 24 h) can be released from quarantine. If symptoms occurred during quarantine, the person should be admitted immediately. However, due to the limitations of specimen collection and detection methods, the influence of the high false-negative rate of the RT-PCR should be paid attention to, which may lead to missed diagnosis or delay in effective diagnosis.[30] For this purpose, the combination of repeated nucleic acid detection and chest CT imaging examination should be effectively carried out for those highly suspected SARS-CoV-2 infections.[31]

Treatment and outcome

The latest guidelines from the Chinese health authorities indicate,[3] for the treatment of COVID-19, suspected and confirmed cases should be treated in isolated hospitals with effective isolation and protection conditions. Divided into (1) general treatment: close monitoring of vital signs and symptomatic support treatment. (2) antiviral therapy: patients with a positive nucleic acid test result can be given α-interferon, lopinavir/ritonavir, ribavirin, chloroquine phosphate, etc. (3) mechanical ventilation treatment and rehabilitation plasma treatment for severe patients. (4) traditional Chinese medicine treatment.

There is currently controversy regarding the treatment of asymptomatic infections. Some researchers supported that antiviral therapy could fasten viral clearance on asymptomatic infections.[20,24] While, it has been reported that isolation and close observation are enough for asymptomatic infections. In one report, lopinavir/ritonavir and abidol were not reported to be effective in improving symptoms or accelerating viral clearance.[32] It was also reported that despite the treatment of aerosolized interferon (IFN) $\alpha 2\beta$, and two tablets of lopinavir/ritonavir (200mg/50 mg) were used twice a day for 10 days, viral nucleic acid results were still positive, which showed that these antiviral drugs did not seem to be effective. In addition, side effects were observed after antiviral therapy, such as liver impairment.[33] Therefore, antiviral treatments not suggested for asymptomatic infections now, maybe more clinical studies are needed to further confirm its effectiveness. Until now, isolation and close observation are regarded as a better option for these asymptomatic infections.

A few people with an asymptomatic infection may develop into symptomatic cases during isolation, but the vast majority will heal on their own. A study of 24 asymptomatic patients showed that all asymptomatic patients did not develop severe disease or death, of which 18 (75.0%) were virus cleared after antiviral treatment, 9 were discharged from the hospital, and 9 were kept in the hospital for observation. In particular, one case was positive again even after the nucleic acid test negative for twice.[20] They can only be discharged after having at least two consecutive negative nucleic acid test results (tested 24 h apart).[2] Some patients turn positive again after being discharged, so further isolation treatment and continuous nucleic acid testing can also be recommended for discharged patients. It is recommended to continue the isolation management, and health examinations should be continued for 14 days after being discharged, and regular follow-up visits should be conducted in the 2nd and 4th weeks after being discharged.[3]

Conclusions

This manuscript reviewed the epidemiological characteristics and prevention measures of people with an asymptomatic infection of COVID-19. However, the research evidence is very limited, and the specific characteristics of asymptomatic infections need to be further clarified. In summary, rigorous epidemiological investigations and laboratory testing are helpful in identifying people with asymptomatic infection. To better prevent and control the risk of COVID-19 disease, it is recommended to screen for high-risk populations such as close contacts, especially in one confined space with diagnosed or suspected infected patients, which will be helpful for early control this global epidemic effectively.

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