Asymptomatic Coronavirus infections

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ABSTRACT

According to the World Health Organization (WHO), the emergence of viral diseases represents a serious public health risk, and as the pandemic of the novel coronavirus has been developed, an increasing number of asymptomatic patients have been found, causing worldwide anxiety.

This study aimed to detect the role of asymptomatic people in transmission and spread of disease.

The reviewed studies around the world showed considerable variations in proportion of asymptomatic COVID-19 cases among different groups (children, pregnant women, elderly, others). Most of the studies confirmed the important role of these cases in COVID-19 transmission and as a result, the importance of quantification of asymptomatic infections as it is fundamental for effective public health responses to prevent and control the outbreaks.

Keywords: Asymptomatic , Coronavirus infections, COVID-19

Coronavirus

A human coronavirus was isolated for the first time from the nasal secretions of a male child with a common cold in 1965 by Tyrell and Bynoe (Singhal 2020). Because of the morphological similarity of virus with a solar corona under an electron microscope (crown-like), it was termed coronavirus; such appearance is because of the protein spikes radiating from the surface of virus (Figure 1).

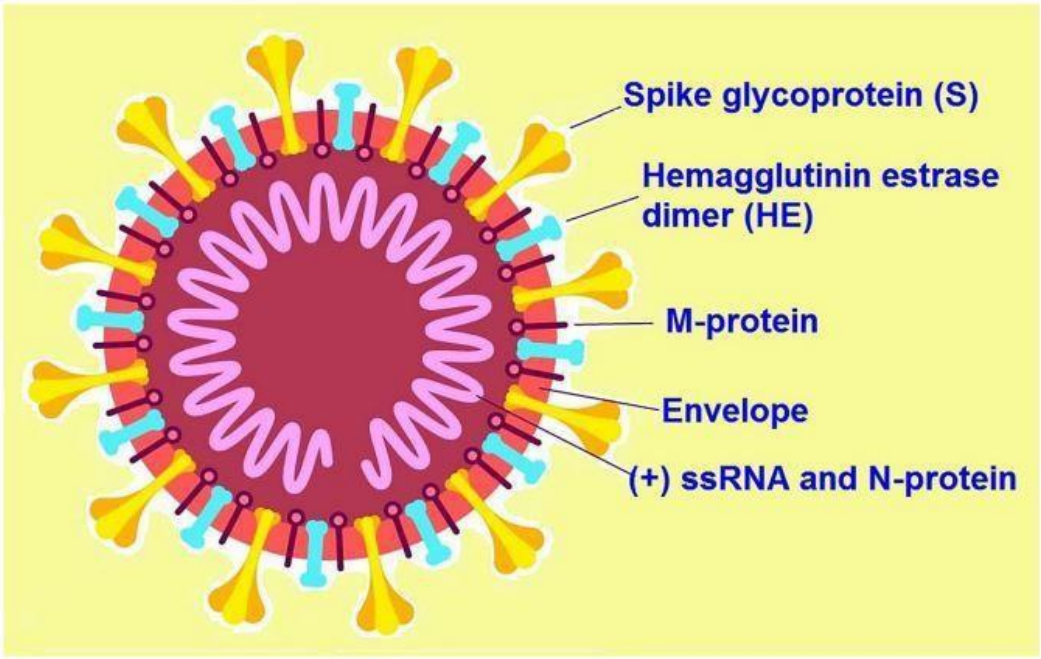

Fig. 1: Typical structure of 2019-nCoV (Esakandari et al, 2020).

Coronavirus is an enveloped virus, with two major proteins: spike [S] glycoprotein and the trans-membrane [M] glycoprotein. The S glycoprotein is an antigen that binds to the receptor and is responsible for cellular fusion. M glycoprotein has a role in envelope formation and virion assembly (Ujike and Taguchi 2015; Jacofsky et al, 2020). Their genome is positive single-stranded RNA with about 26–32 Kbp, is among the largest genomic RNA known viruses (Comas 2019; Mousavizadeh and Ghasemi 2021).

The Coronavirus belong to the family Coronaviridae, which have four subfamilies including alpha, beta, gamma, and delta. The alpha and beta coronaviruses originate from mammals, while gamma and delta coronaviruses have been identified in pigs and birds. Beta-coronaviruses are also called bat-coronavirus.

Bioinformatics analysis shows that RNA sequence of 2019-nCoV is more than 90% similar to a batcoronavirus. It has been reported that the betacorona- viruses cause severe disease while the alphacoronaviruses cause asymptomatic or mildly symptomatic disease (Velavan and Meyer 2020; Li et al, 2020).

Infections of Coronavirus

In December 2019, an outbreak of pneumonia with unknown origin began in China, raising global health concerns due to the ease of transmission. To quickly diagnose and control the highly infectious disease, suspected people were isolated and diagnostic, therapeutic procedures were developed via patients‘ epidemiological and clinical data. After numerous studies, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of this acute respiratory tract infection, and the disease was dubbed ―coronavirus-19″ (COVID-19) by Chinese Scientists (Yuen et al, 2020; Schett et al, 2020).

Since it was being declared a global pandemic by the WHO, the virus and its variants has spread to 223 countries with more than 281 million cases, and more than 5.4 million deaths reported globally (Cascella et al, 2022). The U.S. has experienced the highest number of SARS-CoV-2 infections and COVID-19 related deaths followed by Brazil and India (Ahmad et al, 2021). However, the severity and case fatality rate significantly varies between countries, and it is affected by factors include age, gender, underlying preexisting conditions and other factors.

The presence of COVID-19 is manifested by several symptoms, ranging from

asymptomatic/mild symptoms to severe illness and death. Common symptoms include cough, fever, and shortness of breath. Other reported symptoms are weakness, malaise, respiratory distress, muscle pain, sore throat, loss of taste and/or smell (Lovato et al, 2020). Clinical diagnosis of COVID-19 is based on clinical manifestations, molecular diagnostics of the viral genome by RT-PCR, chest x-ray or CT scan, and serology blood tests. The most common laboratory abnormalities in patients with positive RT-PCR are lymphopenia, leukopenia, thrombocytopenia, elevated CRP and inflammatory markers, elevated cardiac biomarkers, decreased albumin, and abnormal renal and liver function (Paranjpe et al, 2020; Zhu et al, 2020). Early detection of an active COVID-19 infection by molecular diagnostic technique depends on the presence of a sufficient amount of viral genome in the patient sample and the sensitivity of the RT-PCR assay (Lu et al, 2020; Corman et al, 2020).

Serological tests identify people who have developed an adaptive immune response to the virus, as part of an active or prior infection (Lee et al, 2020). It seems that serological tests, along with PCR increase the sensitivity and accuracy of the diagnosis, but due to window period, immune tests do not help diagnose and screen in early infection (Hou et al, 2020). Chinese researchers have reported a variety of results related to immune response, such as a broad range of antibodies between people with mild symptoms of the virus, while fewer antibodies among younger people, and no trace of antibodies in some individuals (Jacofsky et al, 2020).

The main mode of transmission of the virus is through ingestion or inhalation respiratory droplet and contact transmission and high-concentration aerosols (Wofel et al, 2020). A German team found that some infected people 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 and the protective measures, including wearing protective masks, can prevent infection with new coronavirus to a certain extent (Rothe et al, 2020).

Asymptomatic Coronavirus infections

Asymptomatic infections have the same infectivity as symptomatic infections (Gao et al, 2021). Asymptomatic infections have no special incubation period due to No any clinical signs. The window-period of viral replication leads to false-negative results and problems in preventing COVID-19 expansion, and therefore optimized or screening methods that able to detect the 2019-nCoV even in low viral titers are fairly necessary (Cascella et al, 2022). 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 (Zou et al, 2020).

The virus invades cells by using angiotensin-converting enzyme 2 (ACE2) as its receptor (Zhou et al, 2020). 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(Kai and Kai 2020).

As a result, it is supposed that a lower level of ACE2 and weaker binding capacity with virus, 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 viral invasion in asymptomatic patients (Hu 2020). However, more clinical samples should be collected, and a relative examination of ACE2 should be performed and compared for different types of cases, as this would be helpful to explain its pathogenesis.

There are many studies on the incidence of asymptomatic infections, 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, such as in China‘s 1.6% may be underestimated (Team 2020).

Incidence of asymptomatic infections from other studies had some shortcomings, such as those in Korea and Washington, which showed

inaccurate results due to the small sample size (Ki 2020 and Kimball et al, 2020).

On the contrary, another study investigated 565 Japanese citizens evacuated from Wuhan, China at the end of January and found that the incidence of asymptomatic infections was 30.8% (Nishiura et al, 2020). 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% (Mizumoto et al, 2020). It was estimated that 17.9% to 33.3% of infected patients remain asymptomatic (Cascella et al, 2022).

Some researchers suggested that these previous studies overestimated the incidence, but in fact, a person truly has a higher risk if he has a close contact with diagnosed or suspected infected persons in a relatively confined space.

Regarding the proportion of asymptomatic patients in the general population, a systematic review study found that the proportion of diagnosed patients who were asymptomatic at initial testing ranged from approximately 20%–75% (Yanes-Lane et al, 2020). 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.

In a study done in different provinces in China, the asymptomatic cases were reported as more common in middle-aged people in Shenzhen (median age:49 years, 30.9% between 30 and 49 years) and a few younger people in Nanjing (median age:32.5 years) (Gao et al, 2021).

Sah and his colleagues estimated that more than one third of infections are truly asymptomatic, by analyzing over 350 studies, and they found the percentage of infections that never developed clinical symptoms and thus truly asymptomatic as 35.1%. At the time of testing 42.8% of cases exhibited no symptoms. Also found evidence of significantly greater asymptomaticity in children 46.7% compared with the elderly 19.7%. Greater asymptomaticity at younger ages suggests that heightened vigilance is needed among these individuals, to prevent spillover into the broader community (Sah et al, 2021). Body condition along with age may play an important role in the severity of infection, and this is related to different immune responses and other potential pathogenesis

Asymptomatic children

A study in Wuhan tracked the prevalence of 1391 children under 15 years old who had been in close contact with infected or suspected cases and the asymptomatic infections were common (Lu et al, 2020). The incidence of asymptomatic infections in the children is lower than that of the whole population; this is proposed to be related to the special immune response and ACE2 level in the children‘s bodies (Chen 2020).

A meta-analysis showed that about 26% of pediatric patients were asymptomatic. Compared with adults, children may be more inclined to have mild or asymptomatic infections, but they may have higher viral loads and longer latency and duration of viral shedding than adults. However, viral load is often influenced by the duration of infection and cannot be used as evidence of the strength of transmission. Some children do not show any symptoms but may develop radiological changes. Recently, a small number of children without respiratory symptoms have been found to develop a rare complication of the multisystem inflammatory syndrome, with overlapping features with Kawasaki disease. Also, some children are often accompanied by symptoms such as rhabdomyolysis and acute renal failure. These atypical symptoms should be addressed to optimize early identification and hospital management of the child. It is estimated that about 75% of paediatric patients have a history of family exposure (You et al, 2021).

Asymptomatic pregnant women

The proportion of obstetric patients presenting to the hospital with initial testing

asymptomatic was 95.1%, and the proportion remaining asymptomatic throughout the course of the infection was approximately 58.8% (Yanes-Lane et al, 2020). SARS-CoV-2 infection in pregnant women usually seems to be asymptomatic. Vertical transmission of SARS-CoV-2 to the fetus has been demonstrated in cases, but the risk of vertical transmission is low, at approximately 2%. Normal IgM and elevated IgG antibodies in newborns born to asymptomatic mothers have been reported. However, the shedding of the virus in asymptomatic women may also affect the treatment of newborns (You et al, 2021).

Asymptomatic transmission

Asymptomatic transmission of COVID-19 can be inferred from epidemiological and virological data (Furukawa et al, 2020).

A model study estimated that up to 50% of virus transmissions come from individuals who are asymptomatic, after considering scenarios with multiple COVID -19 infectious periods and varying rates of transmission from those who never displayed symptoms (Johansson et al, 2021). Now, evidence suggests that about one in five infected people will experience no symptoms, and they will transmit the virus to significantly fewer people than someone with symptoms. But researchers are divided about whether asymptomatic infections are acting as a

‗silent driver' of the pandemic.

A cluster of 42 people with symptomatic COVID -19 diagnosed from 23 December 2020 and onward in Beijing's Shunyi district was caused by an asymptomatic carrier from Indonesia, according to an epidemiological investigation and viral genome sequencing (Zhang 2021). And at least 12 of 33 local clusters of infections identified during April 2020 to June 2021 originated from people with no symptoms, according to data from the Chinese Centre for Disease Control and Prevention (Gao et al, 2021).

Also it has been reported that a 53- year-old patient with an asymptomatic COVID-19 infection may cause 11 infections in UK (Gulland 2021). Another report in China 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 (Bai et al, 2020). 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.

Interfamily transmission

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 families, susceptible individuals have more time and opportunity for exposure to the virus; therefore, the probability of transmission in the family is higher than that in the community, the duration of virus shedding in the asymptomatic was obviously longer than the symptomatic (You et al, 2021).

In China, a study reported that all family members were diagnosed with COVID-19, and only one family member had clinical symptoms (Chan et al, 2020). Also in China, 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. 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 other 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 (Lu et al, 2021). Du and his colleagues, reported in their article 14 children with mild or conventional types of COVID-19; all of which were transmitted within the family (Du et al,

2020).

A study in the UK reported that nearly 70% of cases were transmitted within the family after extensive community control measures were taken.

Other studies have demonstrated that interfamily transmission may be the main route of SARS-CoV-2 infection in children. It was detected that the presence of SARS-CoV-2 in contaminated household environments, and the virus remains viable and infectious on surfaces for up to 7 days (You et al, 2021).

The risk of transmission increases in contaminated household environments. Maintaining a clean environment, ventilation for more than 2 hours and avoiding non biological surface transmission, the key to avoiding home transmission.

Hospital transmission

Hospitals are high-risk areas. Effective measures must be taken to protect medical staff and prevent nosocomial infections. Examinations in dermatology, ophthalmology, head and neck surgery are considered to be high-risk procedures for transmission of SARS-CoV-2 from asymptomatic patients (You et al, 2021).

Prevention and control

Most people with an asymptomatic infection do not seek medical assistance due to no obvious clinical signs and poor prevention awareness. Several prediction models have indicated that the identification and isolation of all infected individuals, including those who are asymptomatic, is important for controlling the spread of COVID-19. 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 (Johansson et al, 2021).

Estimation the influence of asymptomatic infections on outbreaks is challenging, like in the UK, for example, a failure to integrate testing programs into clinical care has made it difficult to evaluate the role of asymptomatic carriers in transmission (Pollock and Lancaster 2020).

As the clinical symptoms are hidden, and only immunology or nucleic acid detection technology are dependent 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 confirmed diagnosed or suspected patients.

A person with an asymptomatic infection should be quarantined for 14 days (Gao et al, 2020). 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 (Lan et al, 2020). For this purpose, the combination of repeated nucleic acid detection and chest CT imaging examination should be effectively carried out for those highly suspected infections (Ai et al, 2020).

In a worst scenario of unmitigated growth, researchers estimated that testing asymptomatic people may identify the virus five to eight days earlier than it would be detected in symptomatic people, a significant difference. During the five day delay, disease prevalence would have the potential to increase 10-fold (Gao et al, 2021). Thus, in order to control the pandemic, the identification of asymptomatic infections is critical. One model estimated that if 45% of asymptomatic people could be identified and isolated, complete lockdown would not be needed (Mayorga et al, 2020).

Conclusions

- All of the reviewed studies showed that, the ability of asymptomatic infections to spread the virus should be considerable, since asymptomatic patients are likely to cause a new round of outbreaks.
- Although asymptomatic people may be less infectious than those with symptoms,

asymptomatic infections account for a large proportion of all SARS-CoV-2 infections. Furthermore, asymptomatic people may have more contacts than people with symptoms, as those who are unwell will isolate.

- 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 infection.
- Estimations of the incidence of asymptomatic infections may clarify the epidemiological potential of transmission and understanding of the true universality of the disease.

Recommendations

- A serious global attention is required to the role of this specific type of infections as they play an important role in the community transmission and pandemics, which pose a significant challenge to infection control.
- Epidemiological investigations for finding asymptomatic infections among family members of patients, even without any symptoms are needed to prevent the omission of possible sources of contamination.
- Clinical Characterization of pediatric asymptomatic (COVID-19) cases is necessary to control the pandemic, because children act as carriers

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