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Impact and role of asymptomatic, pre-symptomatic and mild-symptomatic patients on SARS-CoV-2 transmission in COVID-19 pandemic

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Since December 2019, an ongoing pandemic COVID-19 is rapidly transmitted to almost all over the globe due to the silent epidemic nature of the causative agent, SARS-Corona Virus-2 through asymptomatic, pre-symptomatic, mild-symptomatic COVID patient. Transmission of SARS-CoV-2 takes place via the person who has exposed to the virus but does not exhibit any symptom or suffers from mild symptoms related to illness, but not surrendered. Critical understanding of asymptomatic cases or incidences of symptomless and mild symptomatic people need to be investigated deeply through early diagnosis and precautionary management to prevent the super-spreading nature and rapid infection. In order to contain the infection further in the community, the pathological immune response of the respective affected person and their viral load needs to be investigated, which is briefly reviewed in the following article.

Keywords: COVID-19, pandemic, asymptomatic, pre-symptomatic, mild-symptomatic.

Introduction

The Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) has explored the real story behind the increasing number of infections throughout the globe, which makes our socio-economic condition as stand-still. Hence, we are leaving in the paralyzed community. The relevant research for better understanding of COVID-19 is being carried out to investigate the mode of transmission of infection and spread of Coronavirus-2. The symptoms of people with COVID-19 depends on the severity of the diseases. Versatile type of symptoms ranging from mild to severe like fever, cough and shortness of breath, are the most common symptoms in a patient who are hospitalized compared to those non-hospitalized mild diseases with loss of smell or taste or both, redness of the eye, diarrhoea. A study on 1099 hospitalized patient reveals that the fever is related with 44% cases during admission on day one, but eventually, 89% was reported with a fever after hospitalization in later stage[1]. Fatigue, muscle pain and headache are some of the other symptoms associated with cases, who are not hospitalized. Many people with COVID-19 experienced gastrointestinal symptoms like nausea, vomiting and diarrhea[2]. In addition to it, loss of smell and taste with the onset of respiratory symptoms is most common, especially among women and young patient, who does not need hospitalisa-tion[3]. Infected persons without signs or symptoms of an illness are called as pre-symptomatic (detection of CoV-2 RNA by RT-PCR, before the onset of symptom). The asymptomatic persons are CoV-2 RNA positive without showing symptoms during the entire incubation period. These vital pieces of information have been illustrated by several reports[4–11]. However, investigation on this subject suggested that the wide range of asymptomatic or mild symptomatic (suffering from the loss of smell, taste or both, fatigue, dizziness headache, mild cough without fever) carrier silently transmit the virus of COVID-19 infection to healthy people of the community around the market, shopping mall, transport vehicles and other public places. The

approach of our article is to focus on the vital information based on the transmission of infection from the symptomatic, asymptomatic and pre-symptomatic persons to others for controlling the pandemic outbreak of COVID-19.

The methodology of evidence collection

We have collected the evidence on the asymptomatic, pre-symptomatic, mild-symptomatic infection and its characterization followed by further transmission by literature survey in PubMed and Google scholar from January 2020 to July 24, 2020. Keywords such as COVID-19, pre-symptomatic, asymptomatic and transmission has been used in individual and in combination for the studies. Our search includes a review article, original research article, brief report, correspondence and case study.

Evidence showing the infection and transmission of COVID-19

Asymptomatic infection and transmission:

Asymptomatic COVID-19 cases are those who are positive for SARS-CoV-2 RNA by RT-PCR test and thereby confirmed about their infection status. Antibody detection, antigen-based ELISA, and reverse transcriptase-polymerase chain reaction (RT-PCR) are generally used to confirm the presence of viral RNA and proteins, respectively, in people suspected of CoV-2 infection. Pre-symptomatic or asymptomatic patients unknowingly transmitted SARS-CoV-2 infection to other people during their journey from Wuhan towards another city in Hubei Province[12–19]. One couple infected with CoV-2 during a mass gathering of the Chinese Spring Festival in Shanghai[20]. Some investigation reported that the infected cases demonstrated the transmission of SARS-CoV-2 to other members, while pre-symptomatic or asymptomatic cases are found within families[12–14,16], during sharing of meals[13,15], or during visits with hospitalized family members[12,16].

Pre-symptomatic infection and transmission:

The cases of pre-symptomatic transmission have come in light also from other countries before the occurrence of widespread community transmission. A significant report from a German businessman who had infected with SARS-CoV-2 after exposure to a mild symptomatic colleague visiting from China[20]. Before becoming symptomatic, this man comes in contact with two other colleagues who subsequently diagnosed as COVID-19 patient. A further investigation of seven COVID-19 clusters from Singapore was carried out to explain the pre-symptomatic transmission and illustrated that pre-symptomatic primary patients travel from high-incidence countries transmit the virus to persons in the local community[21]. In this context, all primary patients had distinct periods of initial exposure and pre-symptomatic persons come in close contact with secondary patients who had no known exposure previously. Pre-symptomatic primary patients have 3 to 11 days incubation period that depends on the extent of exposure. For pre-symptomatic primary patients with travel history to an area of active transmission, the time from last exposure to the onset of symptom may range from ≥ 2 to ≥ 9 days.

Thus, several reports on the transmission of COVID-19 by the pre-symptomatic patient were confirmed[21–23] along with the exposure of secondary cases reported 1–3 days before the source patient established as symptomatic. Based on the various modelling data, the percentage transmission of COVID-19 by pre-symptomatic persons is about 48 and 62% in Singapore and China, respectively[24,25]. There is a significant uncertainty that needs to be explained, for which in-depth research to be undertaken in the context of influences of transmission of SARS-CoV-2 by pre-symptomatic infection on an overall understanding of the dynamic of pandemics. Pre-symptomatic patients express their symptomatic manifestation in later stage due to their delayed immune-pathological response. So, it is terrifying to inform that those kinds of patients spread the infection to other healthy people around public places before being symptomatic.

Mild symptomatic infection and transmission:

The mild symptoms linked with SARS-CoV-2 is fever, cough, sore throat, malaise, headache and muscle pain without shortness of breath, dyspnea on exertion. Most of the mild-symptomatic patients with COVID-19 can be managed through home-isolation or telemedicine or remote visits. Some of the patients may also be affected by rapid clinical and pathological progress[1,26]. The patient appears to be healthy with mild COVID-19. Little information in the context to the management of mild COVID-19 is available for antiviral or immune-mediated therapy. However, if mild symptomatic COVID-19 patients are not adequately managed, isolated or tracked; then they could infect to a more significant number of healthy people with high viral load. So, initial stage, proper tracing, tracking and testing should be undertaken carefully

for the suspected persons followed by isolation. This could prevent the further spread of COVID-19 in community-level to contain this pandemic.

Risk of Covid-19 infection at a different setting

Recent evidence from different parts of the world suggested that COVID-19 may be transmitted from person to person contact as the primary mode of infection. The respiratory droplets generated by breathing, sneezing, coughing, even talking, and direct contact with infected objects or pre-symptomatic or asymptomatic person might be the source of infection.

The risk of infection with asymptomatic or pre-symptomatic remains high. However, it is imperative to note that on the basis of some reports the detection of viral RNA in the body does not mean the presence of viable and transmissible virus[27]. Still, the transmissible events are reported at various part of China[28], wherein the individual with the asymptomatic or pre-symptomatic condition successfully transfer the infectable virus. A relevant study conducted on a cluster of youngsters of age group 16–23 years, regarding the transmission of asymptomatic COVID-19, confirmed that SARS-CoV-2 hold strong infectivity during the incubation-period[29]. Further Feng *et al*., 2020 documented the results of the previous study representing the asymptomatic carrier of COVID-19 transmit infection among people[30] and equally responsible for increased transmissibility and infectivity of SARS-CoV-2 in Wuhan and outside Wuhan. The consequence is local outbreaks, epidemic and further contribution in a global pandemic. However, the degree of its contribution to the epidemic is not significant in China due to the presence of limited data.

The study on the transmission events of Chinese patients outside the Hubei Province, it was reported that 12.6% of the transmission occurred before the symptoms appeared in source patients[31]. The chances of pre-symptomatic transmission might have increased due to the spread of respiratory droplets in surroundings or through other indirect activities, including talking and vocal activities like singing around crowded public places with low humidity[32]. The evidence of transmission with the pre-symptomatic carrier now increases the challenge of COVID-19 containment measures to be done and required for large-scale early detection and isolation of symptomatic patients. Therefore, the magnitude of such impact of pre-symptomatic cases depends upon the extent and duration of transmissibility, which needs to be measured, but unable to establish till date. The large serological study is being carried out in China, which would help understand such type of transmission by carrier in China, Germany and the United State; the results of which are being awaited.

Health implication of the mode of transmission of COVID-19:

Both asymptomatic and pre-symptomatic persons are capable of transmitting the virus to others, has various implications. The first implication is associated with pre-symptomatic and asymptomatic, where case fatality rate with CoV-2 may become lower than that of what we are expecting today[33,34]. Knowing the transmission of COVID-19 from asymptomatic could help make the strategy for the intervention of community infection to slow down to the spread of the virus. In this context, the CDC has recommended observing physical distancing[35], covering face with three-ply masks or cloths[36] and universal masking in health care facilities[17] to check the spread of COVID-19 from asymptomatic, pre-symptomatic and mild-symptomatic carriers.

Conclusion

The recognition of pre-symptomatic and asymptomatic transmission of COVID-19 raised some critical issues that need to be explained. The transmission of SARS-CoV-2 by the asymptomatic or pre-symptomatic carrier has occurred at a different proportion. Such type of infection with SARS-CoV-2 is the silent source of transmission. The evidence derived from the study of pre-symptomatic transmission in Singapore and other areas[4,17] corroborated viral transmission which may occur in the absence of symptoms and before a symptom appears, can guide us to design and development of new intervention strategy of COVID-19 pandemic. The immunopathological parameters, complete blood count, and viral load quantification in the oral or throat swab of asymptomatic, pre-symptomatic and mild-symptomatic cases could give us the exact blueprint for designing of easy diagnostic tools and novel therapeutic strategy. The understanding of the mode of silent transmission of COVID-19 with special emphasis on contract time between COVID victims and normal healthy people may help to prepare guidelines and protocol for the successful management of transmission of infection, too. Containment measures that reinforce effective intervention toward the possibility of pre-symptomatic transmission may include the period before a symptom ap-

pears in the contact. These findings from different studies strongly support the way how to control the pandemic COVID-19. Social distancing, use of appropriate masks, frequent washing of hand with soap water for 20–40 s, avoid to touch in the face, nose and mouth with fingers, gargling and steaming with hot salty-water just after arrival in residence from outside (public places) are the major public health preventive measures requires to be followed as a useful intervention to circumvent the COVID-19 pandemic. Finally, preventive strategy for the normal healthy person can be adopted by taking immunomodulatory food and self-cautiousness and concerning regarding the pre-existing pathological complications related to COPD, diabetes, cardiac disorders, blood coagulopathy, and other inflammatory disorders might be helpful to defend the viral infection originating from asymptomatic, pre-symptomatic or mild symptomatic COVID-19 patient.

Evidence on the transmission of COVID-19 may suggest that the large-scale infection of SARS-CoV-2 may be due to asymptomatic, pre-symptomatic or mild symptomatic cases. New innovative intervention measures as discussed in the above-cited text in connection to early COVID-19 detection and subsequent transmission and infectivity, to be applied, if COVID-19 is to be mediated by silent asymptomatic or pre-symptomatic carriers. The characterization of the SARS-CoV-2 strain isolated from the asymptomatic, pre-symptomatic or mild symptomatic COVID-19 patient should be done to investigate the virulence factor, viral load, genetic material and infectivity of the virus. This outcome of such a study may also give us guidance and novel information to contain and manage the COVID-19 pandemic caused by the lethal zoonotic viral strain of SARS-CoV-2.

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