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TRANSMISSION OF CORONAVIRUS DISEASE-19 THROUGH ASYMPTOMATIC AND PRE-SYMPTOMATICS IS A CHALLENGE TO CONTAINMENT: A RETROSPECTIVE OBSERVATIONAL STUDY.

Microbiology

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ABSTRACT

Transmission by persons not having symptoms can arise from two different scenarios. One is Pre- symptomatic (i.e. infectious before development of symptoms) and other is Asymptomatic (who never experience typical clinical symptoms or signs during their entire course of illness). It is very difficult to differentiate the pre-symptomatic from asymptomatic in initial stages and it still remains a stumbling block. Rigorous laboratory testing, isolating all positive cases irrespective of symptoms and active surveillance can help in identification of the asymptomatic/ pre-symptomatic cases which can further help in prevention and control of COVID-19.

KEYWORDS

Asymptomatic, COVID-19, Pre-symptomatic

INTRODUCTION

The continuous spread with devastating consequences of Coronavirus disease 2019 (COVID-19) have prompted widespread concern around the world and was declared a pandemic on March 11, 2020 by World health organization (WHO). [1]

Since the outbreak, COVID-19 has harmed and challenged more than 200 countries and regions worldwide leading to more than 30 lakh cases and approximately 20 lakh deaths. [2,3]

Studies have documented that Coronavirus spreadsfrom human to humanvia aerosols or contact with inanimate materials or objects contaminated by the infection competent viruses.[4] With the global outbreak of Coronavirus, there is increasing evidence that many infections of COVID-19 are asymptomatic apart from being mild, moderate, severe and critical. [5] The point of concern for people not having symptoms is that even they can transfer the virus to others.

Transmission by persons not having symptoms can arise from two different scenarios. One is Pre- symptomatic (i.e. infectious before development of symptoms) and other is Asymptomatic that refers to the positive detection of nucleic acid of Severe Acute Respiratory Syndrome- Coronavirus-2 (SARS-CoV-2) in patient samples by Real Time Reverse Transcriptase Polymerase Chain Reaction (RT PCR) but never experience typical clinical symptoms or signs and no apparent abnormalities in images including lung Computed Tomography (CT). [6]

Most of the asymptomatic/pre- symptomatic individuals do not seek any medical assistance due toabsence of any obvious signs and symptoms and such poor prevention awareness leads to rapid spread of the disease. [7]

Literature says that virus replicates actively in upper respiratory tract and SARS-CoV-2 is more effective in spreading through shedding from pharynx. [8] During initial days with very mild grade symptoms, pathogen gets released quickly and transmit to others by coughing or sneezing. [9]The same has also been reported by Johansson MA *et. al.* that asymptomatic/ pre-symptomatic transmission of SARS-CoV-2 from people who are not coughing or sneezing, accounts for up to 59% of all the transmissions occurring globally[10] andeven speaking produces thousands of aerosol and droplet particles which are more than sufficient to spread the infection.[11]

When clinical symptoms are not apparent, detection by RT-PCR is only way left to diagnose such asymptomatic/ pre-symptomatic infectious sourcesmaking prevention and control of COVID-19 a very difficult task.We presume that there is a large proportion of asymptomatic/ pre-symptomatic individuals who have never beentested, as they never felt that they are infected due to lack of presentation of any obvious symptoms. Even if these individuals are in a hospital for some other reason, a doctor would not suspect them to get tested for COVID-19.That's why it is not possible to screen and differentiate such individuals from truly healthy populations and they keep on spreading infection into the community and posing a huge challenge for COVID-19 prevention and control.[12] . Thus, it is apparently very difficult to contain the spread following only symptom based screening. However, it would also have negative effects on boththe economy as well as on social activities if active screeningof individuals who do not have COVID-19 symptoms is started.

Apart from this, due to improperly collected samples or high rate of false negative results by RT-PCR tests, there is a chance of miss diagnosis of such asymptomatic/pre-symptomatic individuals, making the situation even more troublesome. [13]

There can be several ways to find asymptomatic/pre-symptomatic carriers-

1. Testing of close contacts of all confirmed positives.
2. Investigation of cluster outbreaks of COVID-19 by active detection.
3. Tracing the potential sources of infection in covid-19 patients.
4. Screening of population with a travel history.
5. Active surveillance or opportunistic screening.

The COVID-19 epidemic is progressing much faster than it was anticipated. A better control would have been possible if the transmission of virus was limited to just the period of illness in which patient remains symptomatic. Instead, by the time second generation of individuals start showing symptoms, third generation is already infected creating a chain of rapid spread of infection. [10]

These asymptomatic/ pre-symptomatic cases play a major role in transmission of infection and pose a significant challenge to infection control strategies. [14] Therefore early recognition of these cases plays a pivotal role in prevention and control of COVID-19 disease, but has remained a huge challenge till date.[12]

Previous studies have also shown that just like in symptomatic cases, even in asymptomatic patients median period of viral nucleic acid positive to negative was 9.5 days (maximum 21 days) [15] and 7.5 days(2-20 days)[16] and thus they remain infectious for a similar period of time as symptomatic cases. The most likely source of infection for asymptomatic/ pre-symptomatic infections are contacts or family members of the patients who have been diagnosed or suspected to have SARS-CoV-2 infection.

In our setup, out of 500 randomly selected SARS- CoV-2 positive patients by RT PCR in December 2020, 65% of cases (325/500) were found to be asymptomatic/ pre-symptomatic,when the data was analyzed retrospectively. These numbers were found to be higher than those reported by Mizumoto K *et al*[17] who found 51.7 % (328/634) as asymptomatic cases on board of the diamond princess cruise ship and by Kumball A *et al* who hasreported 56.5% (13/23) as asymptomatic in his study done in Washington. [18] (Table1)

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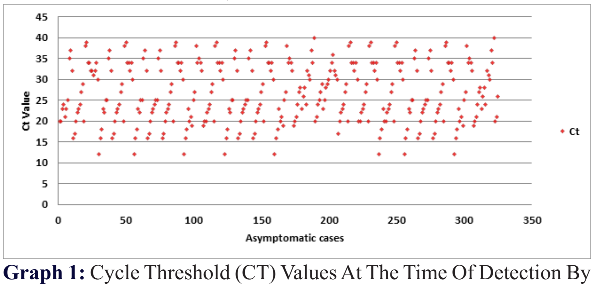
Table 1: Incidence Of Asymptomatic Infections With COVID-19 In Different Studies.

	Diamond princess (n=3711)	Washington (n=76)	Tertiary care center, Jaipur (India) (n= 6500)
RT PCR positive cases	634	23	500
Asymptomatic cases	328	13	325
Incidence rate (%)	51.7	56.5	65

Most of the asymptomatic patients were in the age group of 20- 40 years in our study. Same observations were made in another study where asymptomatic cases were more common in younger or middle aged population without any underlying disease (median age: 49 years in Shenzen and median age of 32.5 years in Nanjing) [15], Looking at this, we can presume that age, immune status of the body and other factors may play an important role in deciding the outcome of disease severity i.e. whether someone will remain asymptomatic or will present with mild or moderate symptoms.[7]

Cycle threshold (Ct) values at the time of detection by RT PCR forthese asymptomatic cases ranged from 16-40, indicating presence of same viral loads and hence equal capability of spreading the infection as symptomatic cases.[GRAPH 1] A recent research has reported that viral load detected in asymptomatic/ pre-symptomaticindividualsare similar to that in symptomatic indicating asymptomatic/ pre-symptomatic individuals have the same potential of spreading infection as that of symptomatic ones. [19] That's why even all the asymptomatic individuals who are RT PCR positive for SARS-CoV-2 shouldbe isolated for 14 days. [20]



Graph 1: Cycle Threshold (CT) Values At The Time Of Detection By RT PCR For Asymptomatic Cases.

SARS-CoV-2 invades host cells via Angiotensin Converting enzyme-2 (ACE-2) receptors on the cells [3] and degradation of ACE2-mediated angiotensin II (Ang II) plays an important role in the pathogenesis of severe lung failure after a viral infection. The severity of infection depends on the maturity and binding capacity of ACE-2. [21] A lower level of ACE- 2 receptors and a weaker binding capacity with SARS-CoV-2 virus can be some of the major factors leading to lesser or absence of symptoms in asymptomatic individuals.[7] More elaborate studies on role of ACE- 2 receptors in different types of COVID-19 cases should be conducted as this would be helpful in understanding the pathogenesis of the disease among the asymptomatic individuals.

In the absence of appropriate and widespread use of therapeutics and vaccines that can decrease infectivity , morbidity and mortality, successful control can't rely solely on identifying and isolating only symptomatic cases even if effectively implemented, this strategy would be insufficient. [10]

Rigorous laboratory testing, isolating all the positive cases irrespective of symptomsand active surveillancecan help in identification of the asymptomatic/ pre-symptomatic cases which can further help in prevention and control of COVID-19.

It is very difficult to differentiate the pre-symptomatic from asymptomatic in initial stages and it still remains a stumbling block. So, it is recommended to screen all the high risk groups such as close contacts of all the suspected and diagnosed cases for early identification of asymptomatic /pre symptomatic individuals to control of this disastrous pandemic. COVID appropriate behavior like wearing masks and maintaining social distancing at all times will keep individuals safe from infectious, though asymptomatic /pre symptomatic individuals ,and reduce the transmission in the community.

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