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Prolonged SARS-CoV-2 Detection and Reversed RT-PCR Results in Mild or Asymptomatic Patients

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ABSTRACT

COVID-19 is a contagious disease caused by the coronavirus that causes severe acute respiratory syndrome. COVID-19 was first identified at the end of 2019, and the disease has since spread far and wide, resulting in an on-going pandemic. Patients with COVID-19 presented with a variety of complaints, the most common of which were fever, cough, exhaustion, breathing difficulties, and loss of smell and taste. Patients typically start noticing changes in their health one to fourteen days after infection. Among those who experience changes in their health, the majority (81%) develop mild to moderate symptoms (up to mild pneumonia), while (14% develop severe symptoms) (dyspnoea, hypoxia, or more than 50% lung involvement on imaging) and 5% suffer critical symptoms (respiratory failure, shock or multi-organ dysfunction). At least 33% of those infected with this disease are asymptomatic and therefore do not experience or exhibit symptoms during the infection, despite the reality that they too can spread the disease. Some people continue to face a variety of effects known as long COVID for quite some time after recovery, and serious harm to organs has been observed. Studies are being conducted to learn more about the disease's long-term effects. SARS-CoV-2, like its homologous virus, SARS-CoV, which caused SARS in thousands of people in 2003, may well be transmitted from bats and lead to similar symptoms via a similar mechanism. COVID-19, on the other hand, has a lower severity and mortality rate than SARS but are much more communicable, negatively impacting more elderly people than youth and more men than women. I hope that this review contributes to a better understanding of COVID and the eradication of this dangerous disease.

Key words: COVID-19, RT-PCR, Rapid antigen, SARS-CoV-2, Diagnostic tools

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INTRODUCTION

COVID-19 is a contagious disease caused by the coronavirus that causes severe acute respiratory syndrome. COVID-19 was first identified at the end of 2019 and the disease has since spread far and wide, resulting in an on-going pandemic. The causative agent of COVID-19 is SARS-CoV-2 which showed 79% similarity to SARS-CoV which was the causative agent for serve acute respiratory syndrome and 51.8% similarity with MERS-CoV the causative agent of Middle East Respiratory Syndrome (MERS) [1]. It was 87.6% similar with bat induced SARS therefore it was predicted that it was passed from bats to humans. Patients with COVID-19 presented with a variety of complaints, the most common of which were fever, cough, exhaustion, shortness of breath and loss of smell and taste [2]. A few uncommon symptoms are related to gastrointestinal system *i.e.* vomiting and diarrhoea; headache was also noted in a few percent of cases [3]. Therefore, a need for a fast, easy, as well as precise analysis in the direction of making a diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections was needed as soon as possible [4]. Presentation traits of the rapid SARS-CoV-2 antigen detection test ought to be evaluated and compared with the gold standard Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests for the conclusion of Corona Virus Disease (COVID-19) cases was widely used. As the virus mutated the sensitivity of the RT-PCR test changed but even though it was reduced the most practical test for detection of COVID-19 was still RT-PCR. The clinical route and viral detection time in mild or asymptomatic coronavirus disease 2019 (COVID-19) patients are unknown. The alleged low indicative sensitivity of upper respiratory specimens for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) makes it easier said than done to confirm COVID infection.

In a study comparing the rapid SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) antigen detection test and the real-time RT-PCR test for detection of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) in respiratory specimens during March-May 2020, found that the rapid assay for SARS-CoV-2 antigen detection showed comparable sensitivity and specificity with the real-time RT-PCR assay. Thus, there is a potential use of this rapid and simple SARS-CoV-2 antigen detection test as a screening assay.

Clinicians typically make a diagnosis of respiratory infection by viruses such as SARS-CoV-2 through undeviating recognition of viral nucleic acid or protein in respiratory tract specimens [5]. To clinically differentiate between COVID and other viral infection is near impossible as the symptoms are almost similar but the mortality and transmission of COVID is much higher than average viral infection. Pulmonary fibrosis caused by COVID-19 is also a very severe and has resulted in multiple fatalities. The two most repeatedly used tools to do this are Nucleic Acid Amplification Tests (NAATs) such as the polymerase chain reaction and Rapid Antigen based tests. When the COVID-19 pandemic began, RT-PCR tests were the first to be urbanized and broadly deployed.

NAATs such as RT-PCR detect viral RNA. A positive result is highly explicit for the presence of viral nucleic acid; however, it does not make a distinction between viable and non-viable virus. Thus, a positive test does not essentially indicate that a person is infectious and requires isolation.

A variety of gene targets are obtainable across different assays, including the envelope gene, the nucleo capsid gene, the ORF 1ab gene and the spike gene. Most assays are considered to detect two or more gene targets to improve their reliability.

A NAATs clinical sensitivity is affected by the assay's limit of detection, the time since infection begin and sample type. Because patients with symptoms have a propensity to present prior in their infection course, there is increased test sensitivity in symptomatic people relative to asymptomatic people. Now a day's anterior nares and saliva are primary sampling sites as the traditional nasopharyngeal samples are troublesome for the patient, but the nasopharynx is the most preferred site for sample collection.

A study to find specificity and sensitivity of RT-PCR in China found that the specificity was 0.988 and the sensitivity was found to be 0.777 [6]. According to this same study it is suggested that 2nd RT-PCR negative is required to bring the possibility of disease below 5%. The data can be different for different versions of RT-PCR; the current pandemic has led to rapid development of various rapid diagnostic tools.

Objective

- To provide brief introduction about diagnosis of COVID-19
- To explain the mechanism of RT-PCR tests and antigen/antibody detection tests in brief
- Prolonged SARS-CoV-2 detection
- Results of mild and moderate cases

LITERATURE REVIEW

Diagnosis of COVID-19

COVID can be diagnosed by various methods such as diagnosis based on clinical findings, diagnosis using nucleic acid for example RT-PCR or by antigen or antibody based immunological assays such as ELISA. Diagnosis based on clinical findings is not accurate therefore clinical diagnosis of COVID is not a very reliable diagnostic method but can be used to select patient who need to undergo laboratory tests for diagnosis as access to diagnostic tests is not adequate compared to the demand in pandemic As the number of people to be tested is humongous and capacity to perform these tests is not sufficient when compared to the demand [7]. Therefore, clinically selecting individuals to undergo laboratory diagnosis COVID plays an important role towards managing this pandemic.

The laboratory diagnosis of COVID was done using immunological assays based on immunological reactions and RT-PCR tests which work on principal of detection of virus specific nucleic acids [8]. A combination of both RT-PCR and immunological assays are proved to be better at diagnosis of COVID-19 as during the early and late phases of infection the viral load may not be sufficient to give a positive report therefore leading to a false negative report. During the end of reaction antibody based tests are more accurate as body produces antibodies to fight against the virus and these are easily detectable even after the infection has entered late stages. The advantage of antigen tests over antibody-based tests is that the body takes time to produce antibody, therefore in early phase of infection antibody-based tests will not be useful enough but antigen tests can be used. One more advantage that immunological assays have over molecular methods such as RT-PCR is that molecular methods have a need for highly trained personnel as well as a certified laboratory along and not just that but the sampling is also complicated compared to immunological assays and the time taken to produce results is also more for molecular methods, due to these points it is essential to use immunological assays to increase the speed of screening the population so that the spread of infection can be slowed down.

Mechanism of RT-PCR

The sample which is collected is from sites where the virus is usually found in body and then the collected samples are treated using various chemicals and enzymes to remove every Impurities and contents of cell except for the RNA, this RNA will be from both the individual's own cells as well as viral RNA. This RNA is then used to produce DNA through the process known as reverse transcription with the help of enzymes, these

strands of DNA produced is then paired with pre-made DNA fragments which are complimentary to viral DNA. This mixture is then used by RT-PCR machine to form multiple identical copies of the DNA by undergoing cycles of reaction, after each cycle the number is doubled. 35 cycles are the most common number of cycles performed by a RT-PCR machine, after each cycle the machine calculate the amount of Florence emitted by contents and when a certain level is reached then it gives result as positive otherwise the result is negative [8]. The number of cycles required to give a positive result is also a measure to estimate the severity of infection.

Mechanism of immunological assays

These tests use immunological reactions between antigen or antibodies specific to the COVID virus to detect their presence. These are not the best diagnostic tools for detection of viral infection but have other advantages and uses [9]. These advantages are that antigen and antibody are more stable than RNA therefore it's easier to handle them while transport and before tests. The antigen-based tests traps virus or its protein while the antibody based tests capture the antibodies produced by body against the infection [10]. Both these tests use a probe to report the findings. They are also used in combination with molecular methods to reduce false negative results.

Multi tired approach towards diagnosis of COVID and screening of at-risk population

There are various methods to diagnose COVID-19 and there are also tests which are very fast, easy and affordable but they cannot be considered as diagnostic because the chances of false negative results is also high in them when compared to other tests. But using just the gold standard tests for diagnosis as well as screening of COVID is impossible as the RT-PCR which is considered a gold standard for diagnosis of COVID requires a lot of time when compared to rapid tests which make it not a good choice for screening, it also requires nasopharyngeal swab which is an aerosol generating procedure due to which it increases the risk to health care workers [11]. As it is an aerosol generating procedure the health care staffs requires additional protective equipment which in case of pandemic was already in short supply. Therefore to tackle the pandemic and increase the speed of screening of population for COVID infection so as to identify the at risk population at early stage and curb the spread of disease as soon as possible rapid diagnostic tests such as immunological assays are used, although they are not that specific but as a screening too they are very useful as they are cheaper, faster and do not require any trained staff to collect the sample their use is very crucial for controlling the spread of disease. Rapid assay was greatly used during the pandemic for screening of population, at airports as well as public places. Those who tested positive in these rapid assays were then tested using RT-PCR.

Prolonged SARS-CoV-2 detection and reversed RT-PCR results of mild or asymptomatic patients

Prolonged SARS-CoV-2 detection means that the patient is having his/her RT-PCR report positive for longer duration. With average time taken by patient to recover from COVID-19 being 11 days, the number of patients with RT-PCR report positive for more than 3 week or 21 days is also high [12,13]. According to a study conducted in Korea, almost 23% patients had RT-PCR report positive even after 3 weeks of being tested positive and 14% of the participants of this study tested positive even after 4 week of their initial positive report. In the same study it was found that the negative report of upper respiratory RT-PCR was reversed in 37.5% of patients. This proves that a single negative report of RT-PCR is not a proof that a patient is no more COVID positive. To prevent this from causing a catastrophic event two consecutive negative RT-PCR report is considered before discharge so as to bring false negative results below 5%. Upper respiratory swab remains positive for SARS-CoV-2 for a mean of 15.4 or 16.7 days, fecal swab was positive for almost 28 days [13]. Although the person was tested positive the viral load decreased considerably with time, also when the contact tracing was done, it was found that the spread was also very low by these patients with prolonged SARS-CoV-2 infection.

DISCUSSION

SARS-CoV-2 or COVID-19 pushed almost every country to its limits, not only health care infrastructure around the globe experienced overburdening but it also faced shortage of different equipment and materials which are essential to treat patients. For example, in India there was a shortage of oxygen, PPE kits, medicines, hospital beds, *etc*. The global import and export were also greatly affected, which led to shortage of various raw materials. The use of protective equipment such as masks and face shield as advised by government around the globe, led to shortage of masks even for health care workers. The diagnostic tools for covid were not something new; the existing RT-PCR test was designed for diagnosis of COVID-19, along with development of rapid diagnostic tests which were based on immunological reactions between antigen and antibody. Therefore 2 types of rapid tests were developed, namely antigen-based tests and antibody based tests. The antigen based tests were useful for early diagnosis and antibody testing required the body to form antibody therefore it was not useful for early diagnosis although it had different uses such as to calculate the percentage of population with antibody against COVID. The rapid diagnostic tests proved very helpful to screen the population as they were used for random sampling of individuals at various occasions and places such as airport, hospitals. The use of rapid testing reduced the load on RT-PCR labs so that they can be used by those who really need it, such as patient with symptoms, direct contact of patients. RT-PCR although being the gold standard for diagnosis of COVID-19 had many limitations, due to these limitations it was impossible to use them to screen at risk population. The

limitations of RT-PCR include requirement of laboratory, a reference for diagnosis which needs to be updated for different variant, various reagent and apparatus, trained staff, time required to obtain results, etc. Also, the RT-PCR false negative were common.

CONCLUSION

Many studies were performed to gather knowledge about COVID-19 infection and associated symptoms. In one of these studies it was found that in a fraction of mild as well as asymptomatic patients the duration of infection was found to be prolonged, which means that the duration of infection was more than 3 weeks and the reversal of RT-PCR results was also very common. The reversal in RT-PCR results were noticed in a little more than one-third of the participants of the study. And to tackle this problem 2 consecutive negative RT-PCR report was used as a criterion for discharge as with 2 conductive negative reports the chance of false negative was below 5%. Although the symptoms were mild, but the prolonged detection of SARS-CoV-2 lead to great mental instability in patients who were asymptomatic or had mild symptoms. COVID also led to development in various field related to healthcare such as development of new type of personal protective equipment which was more users friendly and mask made with new materials which were less harmful to nature, development of testing facility and many more fields. There's a lot to learn from COVID-19, the number of fatalities were huge and some of these lives could have been saved if there was better coordination between government and healthcare facilities and if the healthcare system was trained for pandemic beforehand as a precautionary measure.

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