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Laboratory diagnosis of SARS COV-2: A mini review.

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Abstract

Real Time Reverse Transcriptase (RT-PCR) has been the gold standard for the diagnosis of COVID 19 infection. However the limitations of the method are false negative results, inability of the method to detect the infection in the early stage, variable results with different samples, variable results when done in different intervals, expensive instrumentation, need for well trained personnel and so on. So, it is the need for the hour to develop a device/method that is sensitive, can detect the cases at the early stage, cost effective, portable so that it will be very useful in resource limited settings. Lab on a chip could be the one such technology.

Keywords: SARS COV-2, Diagnosis, Reverse transcriptase PCR.

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Introduction

The coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection [1]. The World Health Organization (WHO) used the term 2019 novel coronavirus to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December 2019. The WHO announced that the official name of the 2019 novel coronavirus is coronavirus disease (COVID-19) [2]. Current reference name for the virus is severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Susceptibility to this infection seems to be associated with age, gender and other associated co-morbid conditions [3]. COVID-19 has been declared as a Public Health Emergency of International Concern by the WHO [4]. Recently, study on the early transmission dynamics of COVID-19 has reported human-to-human spread of the infection [5]. Therefore, it is very essential to diagnose COVID-19 infection precisely so that isolation and treatment can be done effectively.

Diagnostic approaches for the detection of SARS COV-2 infection

Currently, the real-time reverse transcriptase polymerase chain reaction (RT-PCR) amplification of the viral RNA is considered as the "gold standard". However, initial results of RT-PCR, in the early phase of infection is not always positive in COVID-19 infection [6,7]. In such situations, chest computed tomographic (CT) images could play an important role to detect the lesions in the lung parenchyma in suspected patients. However lung pathology may not be reflected in CT images as well irrespective of whether RT-PCR is positive or negative [6-9].

Hao et al. [10] described clinical features of atypical 2019 novel coronavirus pneumonia with an initially negative RT-PCR assay [10]. Along with false negative results, other major constraint for implementing RT-PCR as a routine screening technique in India appears to be its high cost per test and time duration required.

Li reported data of 610 hospitalized patients from Wuhan, clinically diagnosed with COVID-19 during the 2019 outbreak. They found that the RT-PCR results performed at different points of time were variable. They also found a potentially high false negative rate of RT-PCR testing for SARS-CoV-2 in hospitalized patients, clinically diagnosed with COVID-19 [11]. Fluctuating results of RT-PCR may be due to insufficient viral load in the specimen, laboratory error during sampling, or improper sample transportation methods [12].

It must be appreciated that no matter how accurate and fast testing methods are used in the laboratory, the diagnosis of viral pneumonias caused by SARS- COV-2 involves collecting the correct specimen from the patient at the right time. SARS-COV-2 has been detected from a variety of upper and lower respiratory sources including throat, nasal nasopharyngeal, sputum, and bronchial fluid [13-16]. Wang et al have just reported that the SARS- COV-2 RNA was detected only in 32% of OP swabs, which was significantly lower than that in NP swabs (63%) [17].

The main IVD assays used for COVID-19 employ real-

time reverse transcriptase polymerase chain reaction (RT-PCR) that takes a few hours. But the assay duration has been shortened to 45 min by Cepheid. Abbott has developed a point of care molecular assay that decreased the assay duration to just 5 min. Most molecular tests have been approved by the United States Food and Drug Administration (FDA) under emergency use authorization (EUA) and are Conformite Europeenne (CE) marked.

Several serological immunoassays have been developed by IVD companies for the detection of SARS- COV-2 viral proteins and antibodies in the serum or plasma. The most widely used biomarkers for the detection of SARS-CoV-2 infection in commercial immunoassays (rapid lateral flow immunoassay (LFIA) tests, automated chemiluminescence immunoassay (CLIA), manual ELISA, and other formats) are IgM and IgG antibodies produced in suspects from the 2nd week of viral infection. IgM can be detected in the patient samples from 10 to 30 days after SARS-CoV-2 infection, while IgG can be detected from 20 days onwards [18]. The IgM response occurs earlier than that of IgG, but it then decreases and disappears. On the other hand, IgG can persist after infection for a long time and may have a protective role. Apart from the molecular diagnostics, numerous LFIA based rapid POC tests have been developed by several companies, which enable the detection of IgM and IgG antibodies produced in suspects in response to SARS-COV-2 infection. One of the most prominent rapid tests is the COVID-19 test developed by BioMedomics, USA, which detects IgM and IgG antibodies in suspects in just 10 min [19]. It requires minimal sample volume, i.e. 20 μL of finger-pricked blood or 10 μL of serum/plasma. It does not require any instrument or trained staff and, thus, it can be employed at any place and time, especially in developing nations with limited healthcare resources and remote settings. The assay is ideal for primary healthcare workers for the rapid testing of COVID-19 suspects. Another prospective test is the SARS-CoV-2 rapid by Pharmacy AG, Germany [20], which employs only two drops of finger-pricked blood sample from the suspects and can provide results in 20 min. The results obtained by the rapid test correlated well with those achieved by RT-PCR. The most exciting advance is the DPP COVID-19 IgM/IgG test launched recently by Chembio Diagnostics, USA, which has already received FDA EUA. It is a POC rapid LFIA test that provides results in just 15 min using finger-pricked blood sample.

The accurate diagnosis of people infected with the SARS-COV-2 is essential to curb the global spread of COVID-19. However, the current RT-PCR based diagnostic assays are not robust, as they are still missing several infected cases [21-23]. Moreover, they can only be performed in well-equipped central laboratories by highly skilled analysts. Therefore, they are of limited utility and cannot be deployed widely, such as in developing nations, remote locations, and regions with decentralized laboratories. The delay in diagnosing people until after they have passed the disease onto many others is contributing to the continued global spread of COVID-19. The rapid LFIA and automated CLIA tests for IgM and IgG could complement the existing COVID-19 testing by RT-PCR. However, there is a need to stringently evaluate the clinical performance of commercial tests before they are used for the diagnosis of COVID-19.

The RT-PCR based lab on a chip, diagnostic devices may have a meaningful, positive impact on the provision of mass screening and treatment in campaigns to eliminate infectious disease. These campaigns have had limited success to date in combating COVID19 transmission, which has been linked to the inability of current field-based diagnostic tools to detect low level infections. Thus, the availability of easy-to-use, highly sensitive nucleic acid amplification tests, such as those provided by lab on a chip device, could potentially detect these missed cases and reduce the opportunity for transmission. This would have a significant impact on public health in areas where COVID-19 is highly prevalent.

Future Research Perspectives

Development of 'Lab on a chip' devices can deliver precision diagnostics for COVID 19 in low-resource, underserved settings with a sensitivity that is higher than that of the current diagnostic tests used in the field and with performance that is similar to that of a laboratory-based real-time PCR test. These diagnostic devices may have a meaningful, positive impact on the provision of mass screening and treatment in campaigns to eliminate infectious disease. Thus, the availability of easy-to-use, highly sensitive nucleic acid amplification tests, such as those provided by this device, could potentially detect these missed cases and reduce the opportunity for transmission. This would have a significant impact on public health in areas affected with COVID -19.It could also inform current thinking within governments and nongovernmental organizations concerning improvements in the effectiveness and cost-effectiveness of prophylactic approaches to control diseases (where new precise diagnostic tools are required to rapidly and accurately target where treatment is needed).

Conclusion

The Implications of lab on a chip devises from the patient's perspective would mean early diagnosis which forms the tenet of control of the disease by increasing the yield. Early diagnosis at community level would translate into application of efficient prevention mechanisms of spread of the infection. Early diagnosis will aid the clinician in providing timely treatment by reducing the morbidity and mortality due to SARS COV 2 infection.

Conflicts of Interest

None

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