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Research

Diagnosis of SARS-CoV-2: A Review on the Current Scenario and Future Outlook

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ABSTRACT

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has undoubtedly created an emerging disease of topmost public health priority spilling throughout the globe. The diagnosis currently relies on a multiplex of criteria including the epidemiology, clinical manifestations and *in vitro* diagnostics. Presently, the real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) is considered as the most reliable assay for the detection of SARS-CoV-2 and is being supplemented by other auxiliary tests, including serology and radiology. Many of these molecular and immunological tests have been validated by the Indian Council of Medical Research (ICMR) and the Food and Drug Administration (FDA) and commercial kits have been introduced in the field. But, considering the sensitivity and specificity based shortcomings and the lacunae in monitoring the spread of the virus, there is an immense need to develop integrated smart devices based on novel, safe, rapid and accurate diagnostic techniques and implement them on a large scale to curb this outbreak in the country and the world as a whole.

Keywords: 3D genomic technology; Chromatin conformation; Hi-C

INTRODUCTION

In the last two decades, the coronaviruses (CoV) have become the major pathogens of emerging respiratory disease epidemics such as the severe acute respiratory syndrome (SARS) in 2002 (China) and the Middle East respiratory syndrome (MERS) in 2012. The most recent outbreak of a novel coronavirus in the timeline began in 2019 with published literature tracing the first report of symptomatic individuals in Wuhan, China, in the form of pneumonia of unknown etiology. The International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoV) [1].

The SARS-CoV-2 is a positive-sense, single-stranded RNA virus which belongs to the genus Betacoronavirus of the Coronaviridae family (order Nidovirales). The WHO has designated the disease caused by this novel CoV as coronavirus disease 2019 (COVID-19) and it was declared as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020 and a pandemic on March 11, 2020 [2]. Till date, a total of 67,03,095 cases have been reported globally to be positive for SARS-CoV-2 with a case fatality rate of approximately 5.86 percent [3], while in India, there are 2,27,029 confirmed cases with a case fatality rate of 2.80 percent as on 4th June, 2020 [4]. Among the various strategies which are being followed to contain the spread of this highly contagious virus in human population throughout the globe, there is an urgent need for prompt and intensive testing of suspected cases to diagnose SARS-CoV-2 so that quarantine measures can be taken and further spread of infection can be controlled.

Diagnosis of SARS-COV-2

Clinical diagnosis of SARS-CoV-2 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations, such as CT scan, nucleic acid detection, blood culture and immunological techniques (Point-of-care

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Testing (POCT) of IgM/IgG, Enzyme-Linked Immunosorbent Assay (ELISA).

History

A detailed history should be taken from the persons suspected to be infected with SARS-CoV-2, including the residence, travel, smoking and underlying comorbidities. The details of the important risk factors which should be recorded for suspicion of SARS-CoV-2 infection include the following: Fever and at least one respiratory manifestation such as cough or dyspnea KNTGGG, [5].

History of travel or residence in a geographical region reported to have community transmission of the SARS-CoV-2 during the 14 days prior to the onset of symptoms [5]. Close contact with a suspected or confirmed person infected with SARS-CoV-2 during the 14 days prior to the onset of symptoms [5]. People aged 65 years and older are at higher risk of severe illness [6]. People with underlying health conditions i.e. comorbidities (e.g. chronic respiratory disease, cardiovascular disease, immune compromised, obesity, diabetes, renal or liver disease, cancer) are at higher risk for severe illness [6,7]. Smokers are having 1.91 times the odds of progression in the severity compared to those who have never smoked [8].

Severe disease and higher mortality has been seen in the male sex [9-11] Testing certain asymptomatic individuals may also be important for infection control purposes (for e.g., in congregate settings where COVID-19 cases have been identified, prior to time-sensitive surgical procedures, and prior to time-sensitive aerosol-generating procedures if PPE (personal protective equipment) supplies are limited, and in hospitalized patients at locations where prevalence is high) [12].

Clinical manifestations

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic or paucisymptomatic forms to clinical conditions characterized by respiratory failure, to systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes [1]. The prodromal symptoms on the initial presentation include fever, myalgia, cough and sore throat, which can become severe, and patients can flinch with shortness of breath and respiratory failure [3]. The incubation period for COVID-19 is thought to be within 14 days following exposure [4]. Based on a modeling study from China, it has been estimated that symptoms develop in 97.5 percent of infected individuals within 11.5 days, with a median of 5.1 days [7].

The clinical pictures of patients with COVID-19 induced sepsis have multiorgan involvement. These signs and symptoms include respiratory manifestations such as severe dyspnoea and hypoxamia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopeania. The reference for the evaluation of multiorgan damage and the related prognostic significance is the Sequential Organ Failure Assessment (SOFA) score, which predicts ICU mortality based on lab results and clinical data [5].

A pediatric version of the score has also received validation [6] The septic shock is associated with increased mortality, circulatory, and cellular/metabolic abnormalities such as serum lactate level greater than 2 mmol/L (18 mg/dL) and persisting hypotension despite volume resuscitation [1]. Some laboratory findings associated with the critical illness include an exuberant inflammatory response, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated proinflammatory cytokines [7-8].

As per a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed infections, approximately 81 percent of patients presented with mild illness, 14 percent presented with severe illness, and 5 percent presented with a critical illness. The characteristics of the various forms are given below: Other complications include arrhythmias, acute cardiac injury, and shock. The onset of Guillain-Barré syndrome has also been reported 5 to 10 days after initial symptoms.

Smell and taste disorders (anosmia and dysgeusia) have also been reported in patients infected with SARS- CoV-2.Gastrointestinal symptoms (eg, nausea and diarrhea) have also been reported, sometimes even on initial presentation. The prevalence of diarrhea, nausea/vomiting, and abdominal pain have been reported to be 13, 10, and 9 percent, respectively [6]. Various other symptoms have also been reported, including headache, sore throat, and rhinorrhea [9] and conjunctivitis. In addition to such symptoms, there have also been reports of dermatologic findings, including maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis.

The clinical features which are apparent in the symptomatic SARS-CoV-2 infection have been depicted in Figure 1.

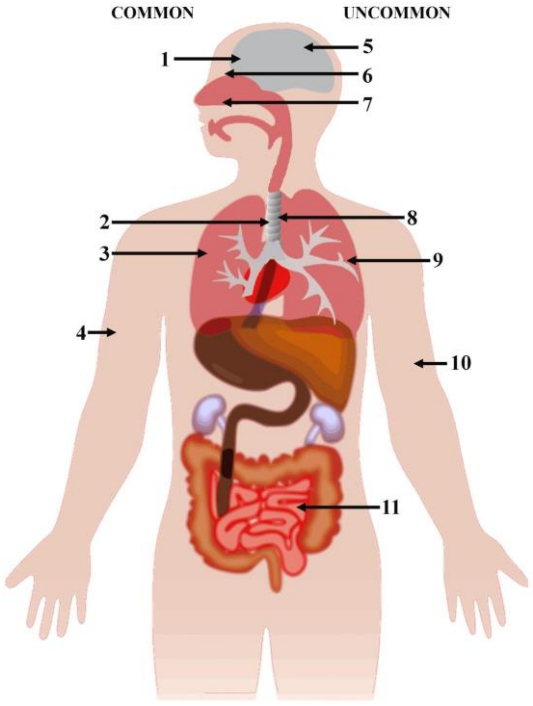

Figure 1: Clinical manifestations of symptomatic SARS-CoV-2 infection in human beings.

Commonly evident symptoms include fever, altered sense of smell and/or taste (1), cough, sputum expectoration, sore throat (2), dyspnoea (3), fatigue, myalgia (4), whereas the uncommon symptoms include confusion, dizziness, headache (5), conjunctivitis (6), rhinorrhoea, nasal congestion (7), haemoptysis (8), chest pain, bronchial breath sounds, tachypnoea, crackles/rales on auscultation (9), cutaneous manifestations, cyanosis (10), and gastrointestinal symptoms (11).

MATERIALS AND METHODS

Laboratory examinations which should be conducted in the patients suffering from a severe form of SARS-CoV-2 infection have been compiled in Table 1. Among these, the laboratory abnormalities which are most commonly found in patients with pneumonia include lymphopenia, leukocytosis, thrombocytopenia, elevated liver transaminases, elevated C-reactive protein, elevated lactate dehydrogenase, etc. apart from neutrophilia, decreased hemoglobin, decreased albumin and renal impairment [13]. In children, these are not common [4].

The collection of samples in adequate quantity by proper methods is essential for the accurate diagnosis of SARS-CoV-2 infection. Table 2 depicts the information on the collection and storage of samples from the presumably infected persons. If only one sample is to be collected, the nasopharyngeal swab is recommended [14].

For the patients which are asymptomatic or have mild manifestations, the nasopharyngeal and oropharyngeal swabs should be collected and placed in the VTM to increase sensitivity [6]. If the sample from the upper respiratory tract of patients is negative, especially in patients with severe disease, samples from the lower respiratory tract should be tested for confirmation. As the serological tests become available, the paired serum samples (acute and convalescent) can be collected. Additional samples like blood stool and urine may be collected, but the frequency of shedding of virus and hence the diagnostic value of such samples is still unknown. The samples should be transported to the laboratory at 2-8°C at -70°C on dry ice in case of delay. In the laboratory, samples can be stored at 2-8°C, but repeated freezing and thawing should be avoided.

RESULTS

Table 1: Laboratory findings associated with SARS-CoV-2 infection.

Test	Results	Relevance
Pulse oximetry	Low oxygen saturation (SpO_2 <90%) may be seen.	Recommended in case of respiratory distress and cyanosis. Although 'silent hypoxia and respiratory failure can also occur in patients without any symptoms of respiratory distress.
Arterial Blood Gas (ABG)	Low partial oxygen pressure may be seen.	Recommended in case of respiratory distress and cyanosis in patients having low oxygen saturation (SpO_2 <90%) to detect hypercarbia or acidosis.
Complete Blood Count (CBC)	Lymphopenia, leukocytosis, and thrombocytopenia are most commonly seen.	Lymphopenia, leukocytosis, and thrombocytopenia may serve as markers for early identification of severe disease associated with poor prognosis.
	Neutrophilia and decreased haemoglobin may be seen.	High neutrophil-to-lymphocyte ratio also indicates the risk for severe illness and poor prognosis.
Coagulation test	Elevated D-dimer and fibrinogen, prolonged prothrombin time	Non-survivors have been found to have significantly higher D-dimer levels, longer activated partial thromboplastin time and prothrombin time as compared to survivors.
Metabolic tests	Elevated liver transaminases; decreased albumin; renal impairment	Abnormalities in liver function may be more common in patients with SARS-CoV-2 infection as compared to other types of pneumonia.
Serum procalcitonin	May be elevated	May be elevated in case of secondary bacterial infection, more commonly in children. May be useful in limiting the overuse of antibiotics in SARS-CoV-2 related pneumonia.
Serum C-reactive protein	May be elevated	May be elevated in case of secondary bacterial infections, or in hyper inflammation. May serve as markers for early identification of severe disease.
Serum ferritin	May be elevated	Indicates the development of

		cytokine release syndrome.
Serumlactate dehydrogenase	May be elevated	Reported in 73% to 76% cases. May be more common in patients with SARS-CoV-2 infection as compared to other types of pneumonia.
Serum creatine kinase	May be elevated	Reported in 13% to 33% cases Indicates muscle or myocardium injury.
Serum troponin	May be elevated	Elevated in case of cardiac injury.

Table 2: Testing priorities for the diagnosis of SARS-CoV-2 infection.

Priority	Cases	Remarks
I	Hospitalized patients	Hospitalized patients to be provided with optimal care.
	Symptomatic healthcare workers	Risk of nosocomial infections to be reduced.
		Integrity of healthcare system to be maintained.
II	Symptomatic patients in long-term care facilities	Patients at higher risk of complications to be promptly identified.
	Symptomatic patients of 65 years age and older	
	Symptomatic patients with underlying health conditions	
	Symptomatic first responders	
III	Symptomatic infrastructure workers	Testing the community with rapidly increasing hospital cases (as per the available resources).
	Symptomatic individuals who are not in categories of I and II priority.	
	Health care workers and first responders	Ensuring the health of essential workers.
	Individuals with mild symptoms	
IV	Individuals without symptoms	Non-priority

DISCUSSION

In the present-day era of information and technology, smartphones equipped with the global positioning system (GPS) and internet is omnipresent, which can be efficiently exploited as the analysis and surveillance platform. Examples of such smart fitness devices that have already been anticipated in other diseases include the fit bit wearable device for influenza-like illness and iHealth Align device for blood glucose monitoring. In a remarkable move, the Aarogya Setu mobile App has been launched in India on 2nd April 2020, which enables Bluetooth based contact tracing and mapping of likely hotspots apart from disseminating the relevant information about SARS-CoV-2 [15]. Furthermore, there is a need for the development of an automated smartphone-based POC device equipped with the molecular and immunological tests based on the SARS-CoV-2 biomarkers so that the diagnosis as well as reporting of this highly communicable disease can transform to software-based analytics.

CONCLUSION

The SARS-CoV-2 has become a global pandemic defying the geographical borders and putting the lives of billions at risk, especially those at the extreme of ages and immune compromised. Diagnosis of the SARS-CoV-2 infection currently relies on a combination of epidemiological criteria, evident clinical manifestations and *in-vitro* diagnostic assays. Although there have been commendable advances in the diagnostic assays but, considering the sensitivity and specificity based disadvantages in the presently available diagnostics, it becomes imperative to highlight that the nations need to invest more in the research and smart integrated diagnostics so that safe, rapid and reliable technologies for the detection of SARS-CoV-2 can be developed and implemented in large scale for the accurate diagnosis and containment of this outbreak.

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