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CLINICAL FEATURES AND LABORATORY DIAGNOSIS TOOL FOR EMERGING CORONA VIRUS (COVID-19): A REVIEW

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ABSTRACT

Corona virus disease 2019 (COVID-19) is a viral pneumonia disease with a severe outbreak in Wuhan, China, in December 2019, which is caused by coronavirus-2 (SARSCoV-2) with severe acute respiratory syndrome. There have been tremendous advances in in-vitro diagnostic (IVD) assays for corona virus disease 2019 (COVID-19). The initial diagnostic of COVID-19 is based on the test of Sputum, Blood and SWAB of throat and nose. The main IVD assays used for COVID-19 based on real-time reverse transcriptase polymerase chain reaction (RT-PCR) that takes a few hours but shortened to minimum of 45 hr. Another method of interest is the point-of-care (POC) molecular assay that decreased the assay duration to just 5 min and has been approved by the United States Food and Drug Administration (USFDA) under emergency use authorization (EUA). A range of serology immunoassays (IAs) have also been developed that complement the molecular assays for the diagnosis of COVID-19. The most prominent IAs are automated chemiluminescent IA (CLIA), ELISA, and rapid lateral flow IA (LFIA), which detect the immunoglobulin produced in persons in response to SARS-CoV-2 infection i.e, immunoglobulin (IgM) and immunoglobulin (IgG). In this review, we provide a brief introduction of the general features of SARS-CoV-2 and discuss various diagnostic method of COVID-19, which may be helpful in offering novel insights and potential therapeutic targets for eradiating the SARS-CoV-2 infection

INTRODUCTION:

Novel coronavirus which was later known as coronavirus disease 2019 (COVID-19) by the WHO on the February 11, 2020, has rapidly increased in pandemic scale which developed through bats. The outbreak that began in Wuhan, Hubei Province, China, in December 2019 has now spread throughout China and to 216 other countries and territories and globally 1 991 562 confirmed (76647) and 130 885 deaths (7875) case reported. On the same day, the international virus classification commission announced that the novel coronavirus was named as severe acute respiratory syndrome coronavirus2 (SARS-CoV-2). It was found that coronavirus have caused three epidemic diseases i.e, COVID-19, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The World Health Organization (WHO) announced that COVID-19 was listed as the Public Health Emergency of International Concern (PHEIC), meaning that it may have risks to multiple countries and requires a coordinated international response. [1,3,4,5,6] Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people those over 60 years old, people with low immunity and those with some medical problems like cardiovascular

disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness.[4, 5] The COVID-19 virus spreads through droplets of saliva or discharge from the nose when an infected person coughs or sneezes. At this time, there are no specific vaccines or treatments for COVID-19. However, there are many ongoing clinical trials evaluating potential treatments, but Hydroxychloro quinine which is an anti malarial drug proven effective against the virus. [4,5]

The substantial outbreaks of COVID-19 infections at the beginning of the 21st century have highlighted the necessity for readily available, accurate and fast diagnostic testing tools. The laboratory diagnostic methods for human coronavirus infections have evolved progressively, with the development of novel assays as well as the availability of updated tests for emerging ones. These assays are simple, fast and safe, are gradually replacing the conventional gold standards and can be used in the local hospitals and clinics bearing the burden of identifying and treating patients. [2,4,5] The review tries to explain the molecular immune pathogenesis, virology and diagnosis of COVID-19 and provide a reference for the drug development of SARS-CoV-2 infection.

Virology of SARS-CoV-2

Coronavirus is a type of virus that causes upper respiratory tract illness. This may lead to inflammation of respiratory tract and the buildup of mucus and fluids in the airway of the lungs (pneumonia). Coronaviruses are believed to be transmitted in most instances from person-to-person through inhalation or deposition on mucosal surfaces of large respiratory droplets. Other routes have also been implicated in the transmission of coronaviruses, such as contact with contaminated person and inhalation of aerosols, produced during aerosol generating procedures Coronaviruses are enveloped viruses with a single-stranded RNA genome. Coronaviruses belong to the family Coronaviridae which includes four genera, Alpha coronavirus, Beta coronavirus, Delta coronavirus and Gamma coronavirus. Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a beta coronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but in a different clade. [10, 11, 12,19]

Properties of Coronaviruses

● Corona virus is pleomorphic spherical of 80 to 220 nm (coronaviruses) and disc, kidney, or rod shaped up to 120 to 140 nm.

● Envelope with large, widely spaced club-shaped peplomers.

● Tubular nucleocapsid with helical symmetry.

● Linear, plus sense ssRNA genome 27 to 33 kb, capped, polyadenylated, infectious, untranslated sequences at each end.

● Three or four structural proteins: nucleoprotein (N), peplomer glycoprotein (S), transmembrane glycoprotein (M) and sometimes hemagglutinin-esterase (HE).

● Genome encodes 3 to 10 further non-structural proteins, including the RNA-dependent RNA polymerase enzyme made up of subunits cleaved from two polyproteins translated from the 5′-end.

● Replicates in cytoplasm, genome is transcribed to full length negative sense RNA, from which is transcribed a 3′-coterminaI nested set of mRNAs, only the unique 5′ sequences of which are translated.

● Virions are assembled and bud into the endoplasmic reticulum and Golgi cisternae, release is by exocytosis.

● Variant viruses arise readily, by mutation and recombination, and the use of different receptors influences the host range exhibited Future direction. [17, 18]

SYMPTOMS: These symptoms of the virus may appear **2-14 days after exposure** (based on the incubation period of MERS-CoV viruses).

Common symptoms include:

- Fever
- Tiredness
- Dry cough.

Other symptoms include:

- Aches and pains
- Sore throat
- Very few people will report diarrhoea, nausea or a runny nose.
- Shortness of breath(Trouble breathing)
- Persistent pain or pressure in the chest
- Confusion or inability to arouse
- Bluish lips or face
- Hypotension [3,4,5, 16]

FOR INITIAL DIAGNOSTIC TESTING FOR COVID-19

- A swab test: Take a special cotton swab and sample inside of the throat or nose.
- A nasal mid-turbinate (NMT) swab collected by a healthcare professional or by onsite self-collection (using a flocked tapered swab).
- An anterior nares (nasal swab; NS) specimen collected by a healthcare professional or by onsite self-collection (using a flocked or spun polyester swab).
- A nasal aspirate: Inject a saline solution into your nose, then remove the sample with gentle suction.
- Collecting and testing upper respiratory tract Specimens i.e, nasopharyngeal and oropharyngeal (OP) specimen.
- A tracheal aspirate: A thin, lighted tube called bronchoscope incorporated into the lungs and the sample is drawn for the testing.
- A sputum test: Sputum is a variation of mucus from your lungs that can be coughed out or sampled from the nose with a swab.
- Blood test- The collected sample will be analyzed for the virus, either through a blanket test for all variants of the corona virus (including regular flu) or through a specialized gene sequencing test that locates the marker for the novel corona virus.
- Testing lower respiratory tract specimens, if available.
- Staining and microscopic analysis of fixed smears
- Examination of viral cultures
- Oxygenation should be assessed by peripheral saturation or by arterial blood gas test [5,6,7,20,21]

Specimen collection

- For Lower respiratory tract

  - **Bronchoalveolar Lavage**

    Collect 2-3 mL of sample into a sterile, leak-proof, screw-cap sputum collection cup or in a sterile dry container.

  - **Sputum**

    Rinse the mouth of the patient with water and then expectorate deep cough sputum directly into a sterile, leak-proof, screw-cap sputum collection cup or in a sterile dry container. [5,6,7]

- For Upper respiratory tract

  - **Nasopharyngeal (NP) swab/ Oropharyngeal (OP) swab**

    Use only of synthetic fiber swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden shafts, as they may contain chemical substances that inactivate some viruses and inhibit PCR testing. Place swabs immediately into sterile tubes containing 2-3 mL of viral transport media.

  - *Nasopharyngeal swab:* Insert a swab into nostril parallel to the palate. Swab should reach depth equal to distance from nostrils to

outer opening of the ear. Leave swab in place for several seconds to absorb secretions. Slowly remove the swab while rotating it. A single polyester swab with a plastic shaft should be used for sampling of both nares

- *Oropharyngeal swab (throat swab):* Swab the posterior pharynx, avoiding the tongue.
- NMT swabs should be placed in a transport tube containing either viral transport medium, Amies transport medium, or sterile saline.
- If both NP and OP swabs both are collected, they should be combined in a single tube to maximize the test sensitivity and limit testing of resources.[5,6,7]

Storage: The specimens are stored at 2-8°C for up to maximum of 72 hours after collection. If a delay in testing or shipping is expected, store specimens at -70°C or below.[6,7]

Shipping: Specimens must be packaged, shipped, and transported according to the current edition of the International Air Transport Association (IATA). Store specimens at 2-8°C and ship overnight to testing center on ice pack. Label each specimen container with the patient's ID number (e.g., medical record number), unique specimen ID (e.g., laboratory requisition number), specimen type (e.g., serum) and the date the sample was collected. [6,7]

DIFFERENTIAL DIAGNOSIS

- **Most common**
- Because COVID-19 cannot be distinguished clinically from other pneumonias, history of contacts or travel serves as an important parameter.
- **Influenza**
- Includes fever, dry cough, and muscle pain; unlike with COVID-19, upper respiratory tract symptoms are common (coryza, sore throat)
- Elderly persons or those with significant symptoms often require hospitalization
- Mostly occurs in winter months in temperate climates
- Patients with severe disease may have abnormal chest radiographic findings suggesting influenzal pneumonia or secondary bacterial pneumonia. Positive result on rapid influenza diagnostic test confirms influenza diagnosis with high specificity during typical season; negative result does not rule out influenza –
- **Other viral pneumonias**
- Includes fever, dry cough, and dyspnea
- Physical examination
- Chest radiography usually shows diffuse patchy infiltrates
- Diagnosis is usually clinical; testing for specific viral causes (eg, respiratory syncytial virus, adenovirus) may be done
- **Bacterial pneumonia**
- Includes fever, cough, and dyspnea, pleuritic pain occurs in some cases
- Physical examination may find signs of consolidation (dullness to percussion, tubular breath sounds)
- Chest radiography usually shows lobar consolidation or localized patchy infiltrate. Sputum examination may find abundant polymorph nuclear leukocytes and a predominant bacterial organism
- Pneumococcal or legionella antigens may be detectable in urine; sputum culture may find those or other pathogens. [15,22]

ADVANCED DIAGNOSIS METHOD FOR COVID-19

Cell culture: Isolation of COVID-19 in cell culture is not routinely performed for diagnostic purposes due to the lack of permissive cell lines, time to results, labour and expertise requirements, and the lack of commercial antisera for confirmation of culture. Cell culture should not be performed for infectious cell cases in routine diagnostic laboratories for biosafety reasons. However,

virus isolation in cell cultures is critical to obtain isolates for characterization and to support the development of vaccines and therapeutic agents. [13]

Medical imaging

Chest imaging (eg, plain radiography, CT) may be beneficial to diagnose COVID-19 in infected individuals with a high clinical development of infection based on the risk factors and symptoms has shown abnormalities in most reported patients it usually shows bilateral involvement, varying from consolidation in more severely ill patients to ground-glass opacities in less severe and recovering pneumonia but it is not generally recommended for routine screening. [16, 17]

Direct viral tests:

Using real- time reverse transcription polymerase chain reaction (rRT-PCR). COVID-19 test can be done on respiratory samples obtained by various methods including naso-pharyngeal swab or sputum sample. Results are generally available within a few hours to 2 days. The RT-PCR test performed with throat swabs is only exposure in the first week of the disease. Later on the virus can disappear in the throat and it continues to multiply/grow in the lungs. For infected people tested in the second week, alternatively sample material can then be taken from the deep airways by suction catheter or coughing up material (sputum) can be used.[6,7,8,22]

Rapid tests:

Rapid tests are qualitative or semi-quantitative in vitro diagnostics tool (IVDs) designed to give a fast result. For COVID-19, rapid tests may take about 10-30 minutes until giving a result compared with about four hours for molecular tests. There are two types of COVID-19 rapid tests currently in use in hospital or in development: direct SARS-CoV-2 antigen detection and indirect antibody detection tests. Antigen detection tests detect the viral components present in a infectious person during the infection in samples like nasopharyngeal secretions. Antibody tests detect the antibodies that later appear in serum of a infectious person as part of the immune response against the virus. [8,9]

Immunoassays

Immunoassay have been developed and used for rapid detection of SARS-CoV-2 antigens or antibodies. These rapid point-of-care immunoassays are generally lateral flow assays. Such lateral flow assays have been developed for detecting antigens such as the SARS CoV-2 virus or for detecting antibodies (IgM and IgG] against COVID-19 infections. Rapid antigen lateral flow assays would theoretically provide the advantage of fast time to results and low-cost detection of SARS-CoV-2 but are likely to suffer from poor sensitivity. Monoclonal antibodies used specifically against SARS-CoV-2 have been under preparation, and several rapid antigen assays are being developed. [8,14,17, 22]

Serology

Serology measures the host response to infection and it is an indirect measure of infection that is best utilized retrospectively. Serological assays are not routinely used for diagnosis of COVID-19 infections due to the lack of commercial reagents. Serological assays are important in understanding the epidemiology of the virus including the asymptomatic infections. It has been particularly used for antibody detection in the diagnosis of emerging COVID-19, such as SARS-CoV and MERS-CoV. in the early phase of the disease infectious patients may not test positive for viral RNA, ,but retrospectively can be shown to have developed an immune response. When rapid antigen testing and/or molecular assays are neither available nor stable, serology can be used as a supplementary diagnostic tool. In China, six serology testing tool have received urgent approval from the National Medical Products Administration (NMPA) by 12 March 2020. Proper specimen handling and storage facility are important to maintain the integrity of specimens and the performance the serologic tests. [13, 14]

Molecular methods

Random-amplification and deep-sequencing technique played a important role in identifying MERS-CoV and SARS-CoV-2. Deep sequencing molecular methods such as next generation sequencing and metagenomic next generation sequencing will continue to be needed to determine future mutations of SARS CoV-2 but are currently not used in diagnosing COVID-19 infections. Most of the molecular diagnostics being developed for the diagnosis of COVID-19 infections involve real-time RT-PCR assays. Current molecular method that detect the pandemic HCoVs require multiple sets of PCR oligonucleotides .This method is a supplemental diagnosis tool of pneumonia caused by SARS-CoV-2. This method uses molecules isothermal amplification followed by chip detection. Some molecular tool uses real-time PCR technique with hydrolysis probes. After extraction of nucleic acids, the extracts are transferred to a real-time PCR for nucleic acid amplification and detection. Three separate RT-PCR reactions target the N gene. One primer/probe set detects all beta coronaviruses, while two sets are specific for SARS-CoV-2. All the two assays must be positive to report SARS-CoV-2. For this method the Specimen types uses are upper and lower respiratory specimens (such as NP or OP swabs, sputum, lower respiratory tract aspirates, and nasopharyngeal wash/aspirate or nasal aspirate). Molecular methods include loop-mediated isothermal amplification, multiplex isothermal amplification followed by microarray detection. [13,14,17]

Real-time RT-PCR assays

A real-time RT-PCR method is recommended for testing of COVI-19. A major advantage of real-time RT-PCR assays is that amplification and analysis are done simultaneously in a closed system to minimize false positive results associated with amplification product contamination. Coronaviruses have a number of molecular targets within their positive-sense, single-stranded RNA genome that can be used for PCR assays. These include structural proteins, including envelope glycoprotein, spike, envelope, transmembrane, helicase, and nucleocapsid. In addition to these genes that encode structural proteins, there are species-specific accessory genes that are required for viral replication. These include RNA-dependent RNA polymerase, hemagglutinin-esterase, and open reading frames. In the United States, the CDC recommends two nucleocapsid protein targets [N1 and N2] while WHO recommends first line screening with the E gene assay followed by a confirmatory assay using the RNA-dependent RNA polymerase. The COVID-19- RNA-dependent RNA polymerase / helicase assay had the lowest limit of detection in vitro and higher sensitivity and specificity. However, it is likely that well-optimized targets will arise from a number of viral genomic locations since assay performance is usually done by the reagent design, not the target itself, since the viral genes are present in equal copy number. [14,15]

Antibody and plasma therapy: This therapy has been preliminary acquired favourable results in acute, severe SARS-CoV-2 patients. Usually, the generation of recombinant human monoclonal antibody (mAb) is a fairly straightforward path to neutralize SARS-CoV. CR3022, a SARS coronavirus- specific human monoclonal antibody, can bind potently with the receptor-binding domain (RBD) of SARS-CoV-2 and has the potential to be developed as candidate therapeutics of SARS-CoV-2 infections. Other monoclonal antibodies neutralizing SARS-CoV, such as m396, CR3014, could be an alternative for the treatment of SARS-CoV-2.[19]

CONCLUSION

The occurrence and development of SARS-CoV-2 depend on the interaction between the viral factor virus and a individual's immune system. Viral factors i.e, virus type, mutation, viral load, viral titer, and viability of the virus in vitro. The individual's immune system factors include genetics, age, gender, nutritional status, neuro endocrine-immune regulation, and physical status. These factors all contribute to whether an individual is infected with the virus or not, the duration and severity of the disease, and the reappearance of

infection. In the early stages of the pandemic, accurate diagnosis helps to control the spread of the disease. It is imperative to develop new, safe, accurate, fast, reliable and simple new technologies for detecting SARS-CoV-2. The importance of the laboratory diagnosis tool is to limit the spread as well as increase treatment of those patients who have a serious infection. This commentary has addressed current issues regarding various testing for SARS-CoV-2. This importance of repeated testing should the done to first screening out the positive cases and then use of appropriate treatment method to minimize the cases and to decrease the true mortality rate as well as other epidemiological markers. Finally, the importance of rapid development of integrated, random access, point-of-care molecular devices for the accurate diagnosis of SARS-CoV-2 infections cannot be overemphasized. These STAT tests will be very important for real-time patient management and infection control decisions, especially when other less infectious forms of pneumonia are present. These assays are safe, simple, fast and can be used in local clinics and hospitals who already have the needed instruments and who are responsible for identifying and treating such patients. Fast near-patient and POCT could help more efficiently decrease of suspected cases of novel coronavirus, helping to focus limited resources on enabling appropriate use of quarantine. A handful of diagnostics developers are now striving to bring fast SARS-CoV-2 tests to market as soon as possible, with hopes of ultimately assisting with the ongoing outbreak in the world.

Conflict of interest: Authors report no conflict of interest.

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