D J Med Sci 2023;9(2):88-94
doi: 10.5606/fng.btd.2023.51

Florence Nightingale

Review

SARS-CoV-2: A microbiological perspective on characteristics and diagnosis

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ABSTRACT

Early detection and rapid management are crucial to improve survival in coronavirus disease 2019 (COVID-19) patients, and after two years of the pandemic, many efforts have been made for early detection. Considering that COVID-19 patients may show no signs and symptoms that can distinguish COVID-19 from other infective or non-infective diseases, the use of rapid microbiological techniques is a key factor. These techniques have been developed to rapidly detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and prevent viral spread and transmission. However, recent data on the clinical, radiological, and laboratory characteristics of COVID-19 during hospitalization may help physicians to suspect SARS-CoV-2 infection early and distinguish it from other etiologies. Information on clinical features and microbiological techniques will be crucial in the coming years when endemic circulation of SARS-CoV-2 will likely be associated with clusters of infection. This review aims to compile the microbiological features and diagnostic methods of the SARS-CoV-2 virus, which is thought to have cause the strongest pandemic in the world, in the light of the literature.

Keywords: COVID-19, microbiological diagnosis, SARS-CoV-2.

Coronaviruses (CoVs) belong to the family Coronaviridae under the order Nidovirales, and they are further divided into four main genera; alpha (α), beta (β), gamma (γ), and delta (δ). The seventh and most recent member of the β-CoVs in the CoV family is named 2019-nCoV (severe acute respiratory syndrome CoV-2; SARS-CoV-2), which caused the first outbreak in the city of Wuhan, China. It has been reported that most of the initial cases were frequent visitors to the Huanan South China Seafood Market in Wuhan.[1-4] This review aims to compile the microbiological characteristics and diagnostic methods of the SARS-CoV-2 virus based on the literature.

Received: June 21, 2021
Accepted: September 09, 2021
Published online: August 29, 2023

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Cite this article as:
Tahmaz A, Dindar Demiray EK. SARS-CoV-2: A microbiological perspective on characteristics and diagnosis. D J Med Sci 2023;9(2):88-94. doi: 10.5606/fng.btd.2023.51.

MICROBIOLOGY OF SARS-COV-2

Coronaviruses are a family of viruses that have the ability to infect humans and many other species. Beaudette and Hudson[5] first identified CoV in chickens in 1937. Human coronavirus (HCoV) infection was first reported in a patient with the common cold in 1960.[6] When examined for their genomic characteristics, these viruses belong to the family Coronaviridae and the subfamily Orthocoronavirinae. Within the subfamily Orthocoronavirinae, there are four genera, and subsequently, several subgenera referred to as α, β, γ, and δ.

In humans, CoVs can cause a range of symptoms, from flu-like symptoms to more severe respiratory infections, especially affecting the respiratory system. Symptoms such as fever, muscle pain, shortness of breath, cough, and diarrhea are commonly observed, particularly in cases with zoonotic transmission. Currently, there are seven known types of CoVs that can infect humans: Among them, α-CoVs (HCoV-229E and HCoV-NL63) and β-CoVs (HCoV-HKU1 and HCoV-OC43) have been known for some

time, while more recently identified ones include Middle East respiratory syndrome (MERS-CoV), SARS-CoV, and most recently, coronavirus disease 2019 (COVID-19).[7,8]

Coronaviruses are non-segmented, positive-sense, single-stranded, enveloped ribonucleic acid (RNA) viruses. They directly code for various structural and non-structural proteins. They are known to have the largest genome among RNA viruses, ranging from 27 to 32 kilobases in length.[9,10] The structural proteins of CoV include nucleocapsid (N), envelope (E), membrane (M), hemagglutinin-esterase (HE) glycoprotein, and spike (S) protein. The name 'corona' was given to these viruses due to protrusions found on their surface, which resemble a crown or halo.[11,12]

The envelope is surrounded by glycoprotein spikes. It encloses the genome within the N. Viral RNA replication continues through a cascade initiated and terminated in the host cytoplasm by binding to a leader sequence of RNA polymerase. HCoV-229E, HCoV-NL63, and SARS-CoV encode four genes, respectively coding for S, M, N, and E proteins; HCoV-OC43 and HCoV-HKU1 also have another gene that codes for the HE protein.[8,11]

The S protein is the characteristic spike-like structure on the virus surface, which allows the virus to attach to the host cell through receptor binding and membrane fusion. It contains S1 and S2 subunits, where the S1 protein binds to the host cell receptor, and the S2 protein is responsible for membrane fusion. The S protein stimulates neutralizing antibodies and serves as the main antigen and target for cytotoxic lymphocytes. The N-terminal domain of S proteins binds to angiotensin-converting enzyme 2 (ACE-2) receptors on the host cell.[8,13]

The M protein is an envelope protein that protrudes from the outer surface of the envelope along with the N protein, and it plays a role in virus assembly, release, and gaining antigenic properties of virions. It contains three transmembrane domains. It enhances the folding and binding of virions (complete virus particles) to the N, shaping the membrane. The M protein is involved in stabilizing the N protein and maintaining the formation and continuity of the nucleocapsid-RNA complex. This protein renders the host cell susceptible to the virus. It activates the interferon-beta pathway through a toll-like receptor-dependent mechanism.[8,14]

Nucleocapsid protein is involved in regulating viral RNA synthesis and interacts with the M protein during virus budding. Additionally, during the immune system's efforts to eliminate the virus, the N protein acts as an interferon antagonist. It also serves as an antigen for cytotoxic T lymphocytes.[15]

Hemagglutinin-esterase is only found in β-CoVs. The hemagglutinin component is located on the envelope and enables the virus to attach to receptors containing sialic acid on the surface of the host cell, facilitating the initial adsorption of the virus to the membrane. It is believed that the E protein is essential for the virulence of the virus. It plays a role in bringing virions together within the cell and in the process of virus budding and release from the cell. When the E protein is not detected in the virus, it has been observed that the viral load is lower during the course of the disease. Non-structural proteins (nsp) found in the CoV genome have various functions, including RNA transcription, protein synthesis, and modification:[12]

1. Papain-like protease (PL-pro); plays significant roles in correcting virus replication and suppressing the host's natural immunity.[16]
2. 3C-like main protease (3CL-pro); also known as nsp5. It directly facilitates the maturation of nsps in the virus's life cycle.[17]
3. RNA-dependent RNA polymerase (RdRp); In CoVs, nsp12 is a conserved protein. This protein, which is an RNA-dependent RNA polymerase, is considered the most crucial enzyme in the replication/transcription complex.[18]

MICROBIOLOGICAL DIAGNOSTIC METHODS

The current pandemic period has once again emphasized the importance of laboratory diagnosis in the control of infectious diseases. Rapid and accurate diagnosis is crucial for implementing early isolation measures to limit the spread of the

pandemic. Additionally, early diagnosis allows for prompt initiation of treatment before the clinical condition progresses, leading to a decrease in morbidity and mortality.[19]

Sample collection and transportation

Healthcare personnel tasked with collecting samples (such as Infectious Diseases and Clinical Microbiology specialists, Medical Microbiology specialists, or personnel from Infection Control Committees and Nurses) should receive training from experienced teams regarding infection control measures, the use of personal protective equipment, appropriate sample collection, proper storage of samples, and their transport conditions.[8]

Collecting appropriate samples at the right time, using the correct method, and from the appropriate body area is crucial for the diagnosis of COVID-19. High viral load can be detected in samples taken within 5-6 days after the onset of symptoms. Samples are collected from the mucosa of the upper and lower respiratory tracts. For higher diagnostic success, the first oropharyngeal (OP) swab is taken to represent the upper respiratory tract, followed by nasopharyngeal (NP) sampling using the same swab, which should be transported in a viral transport medium. The presence of a gag reflex during OP swab collection and the patient's tearing up during NP sampling indicate proper sample collection.[19-21] In cases of more severe respiratory tract disease, sputum, endotracheal aspirate samples, and bronchoalveolar lavage samples can be used. However, it should be noted that there may be a higher risk of transmission in such cases. These samples should be sent directly to the microbiology laboratory without using transport media.[20,21]

Diagnostic tests

In classical virology diagnostics, there are three types of diagnostic tests: cell culture, serology, and molecular detection methods. Virus isolation is mentioned under biosecurity level-3 conditions. However, for diagnostic purposes, the World Health Organization (WHO) does not recommend virus culture and isolation.[22] Currently, there are two valid and up-to-date test methods for the diagnosis of COVID-19.[21]

Molecular detection methods

Reverse-transcriptase polymerase chain reaction (RT-PCR) assay

The most commonly used test method for the detection of SARS-CoV-2 in routine practice today is nucleic acid amplification using RT-PCR. Nasopharyngeal, bronchoalveolar lavage (BAL), and anal swab samples are tested using PCR in appropriate viral transport carriers.[23,24]

The accuracy of the tests can vary depending on factors such as the sampled body region, the quality of the sample, the stage of the disease, the replicative stage of the virus, or the degree of virus clearance. The sensitivity of the test has been reported as follows: 32% in throat swab samples, 63% in NP swab samples, 72% in sputum samples, 93% in BAL samples, and 46% in fibrobronchoscope brush biopsies.[25,26] SARS-CoV-2 RNA has also been isolated from different samples, such as blood, feces, and urine. However, these samples are considered less reliable compared to respiratory samples.[8]

In real-time-PCR (rRT-PCR) tests, the detection of SARS-CoV-2, which has a positive-sense, single-stranded RNA genome, relies on targeting various structural and non-structural genes necessary for replication. The target genes include the S, E, M, and N proteins, as well as the RdRp and open reading frames, ORF1a and ORF1b, genes. PCR tests use these genes that are evolutionarily conserved, expressed, and show minimal cross-reactivity. The Centers for Disease Control and Prevention recommends working with two gene regions of the N protein, N1 and N2, and the human RNase P gene for screening. The WHO suggests using the E gene for screening and the RdRp gene region for confirmation in rRT-PCR tests. Both approaches have shown high analytical sensitivity and specificity, and no superiority has been detected between them. To prevent interference from genetic variations of the virus and cross-reactivity with endemic CoVs, at least two molecular targets are sought in the tests.[19,20,22]

In Türkiye, for the detection of SARS-CoV-2, the RdRp gene fragment is targeted using a one-step RT in combination with RT-qPCR. The RdRp gene-targeted kit used in routine practice in our country yields positive results only for

SARS-CoV-2. The kit has a detection limit of 5-6 copies of SARS-CoV-2 in the reaction. It has a reported specificity of 99.0% and an analytical sensitivity of 99.4%.[23]

The specificity of the rRT-PCR test is reported to be >95%, while its sensitivity ranges from 63% to 78%. If symptoms are present in a patient, a single negative rRT-PCR test result should not be conclusive, and a follow-up rRT-PCR test should be performed. Currently, there is insufficient evidence to use the defined viral load for monitoring disease severity or therapeutic response.[27] It is essential to evaluate patients based on their clinical, radiological, and other laboratory findings.[1,8] The diagnosis of RT-PCR is increased by 19% in the presence of fever. When considered in addition to computed tomography, the sensitivity increases from 79 to 94%, reducing the false-negative rates in RT-PCR due to lung involvement.[28,29]

Sequence analysis

Sequence analysis is one of the most comprehensive methods used for the identification of viral nucleic acids. The detailed genome sequence of SARS-CoV-2 was first recorded in the GenBank database under the accession number MN908947 by Wu et al.[30] on January 5, 2020. With the use of next-generation sequencing methods, detailed genomic base analysis of many viruses is being conducted. However, due to reasons such as the high cost, complexity compared to other methods, the need for experienced personnel, and the increased number of cases during the pandemic, the practical use of these existing new methods is not preferred. Nonetheless, conducting these studies effectively is essential for performing molecular epidemiological investigations of the virus, detecting genome mutations, and confirming suspicious rRT-PCR results.[29,31]

Serological tests

Antigen detection rapid diagnostic tests

The antigen test used as a rapid diagnostic test is based on the detection of viral proteins released by SARS-CoV-2 in clinical samples. The detected antigens indicate acute infection as they are produced only during virus replication. The effectiveness of the test can vary depending on factors such as the date the sample was taken, the viral load quantity, and the quality of the sample. One of the most significant advantages of these tests is their ability to provide rapid results. However, they can also produce false-positive results during the course of other CoV infections that cause the common cold and other bacterial infections. In cases where test results are considered negative but suspicious, they should be confirmed with another molecular test based on the patient's clinical condition.[32] Effective antigen detection tests can be considered as preliminary tests to efficiently identify individuals who may have had COVID-19 and reduce the need for other expensive molecular confirmatory tests. However, based on current data, the WHO does not recommend the use of antigen tests for disease diagnosis.[33]

Antibody detection tests

Another broad category of tests used in the diagnosis of COVID-19 is serological tests that detect immunoglobulin (Ig) M, IgA, IgG, and total antibodies in the blood. Serological tests are less complex compared to molecular tests. The antibody response to the infection depends on the host's immunity. Factors such as age, nutritional status, disease severity, underlying conditions affecting the immune system, and medications used can all play a role in the development of immunity. However, since immunity takes time to develop, antibody testing is not useful for diagnosing an acute illness. Serological tests can complement molecular tests by indicating whether an infection is acute or non-acute/serological response lagging, depending on the timing of symptoms. As immunity develops later, antibody tests may support molecular tests. In this context, rRT-PCR is currently used effectively in surveys but does not detect past infections. Concerns about cost-effectiveness and potential misuse during epidemic situations have been raised.[27,33,34]

With the current knowledge, there is still no clear consensus on whether previously infected and recovered individuals will partially catch SARS-CoV-2 in their future experiences or how long any protective immunity might last.[8]

Antibody tests for SARS-CoV-2 can be used for the following situations;

1. Contact tracing,

2. Serological surveillance at the local, regional, and national levels,
3. Diagnosis of individuals who have encountered the virus and may have acquired immunity,
4. Testing individuals with clinical/radiological findings but negative RT-PCR results for diagnostic purposes,
5. Identifying individuals with neutralizing antibodies for plasma therapy,
6. Evaluating the response to vaccination and determining the level of immunity in the community.[8,29]

In serological tests, the antigenic regions of the N and S proteins, which are structural components of SARS-CoV-2, are used. The N protein plays a crucial role in the virus's pathogenesis, replication, and RNA packaging. It is an important antigen for early diagnosis, and an increase in N protein can be detected in serum or urine samples of individuals with COVID-19, especially in the first 15 days of the disease. Due to its larger molecular structure, enzyme-linked immunosorbent assay (ELISA) offers convenience in detecting N protein antibodies. If the test detects antibodies against the N antigenic region, its sensitivity is higher compared to a test that detects antibodies against the S antigen.[35]

The S glycoprotein plays a role in the entry of the virus into host cells and is composed of two subunits, S1 and S2. The receptor-binding domain is found in the S1 subunit and is responsible for binding to the ACE-2 receptor. The amino-terminal end of the S1 subunit is considered the most variable and immunogenic antigen. On the other hand, the S2 subunit facilitates membrane fusion. The S protein is a crucial molecule used in serological studies, vaccine development, and research related to neutralizing antibodies. Cross-reactivity can be prevented by using tests that simultaneously utilize two antigens, which increases the sensitivity of detecting both IgM and IgG antibodies.[29,34,35]

Serological tests (immunoassay;IA) developed for the diagnosis of SARS-CoV-2 can be performed using whole blood, serum, plasma (EDTA or citrate), as well as respiratory and oral samples effectively. Some serological tests detect total Ig, while many of them can detect both IgG and IgM. The most prominent IAs are automated chemiluminescence IA (CLIA), manual ELISA, and rapid results providing lateral flow IA, all of which can detect both IgM and IgG. Lateral flow IA-based serological tests have been implemented as point-of-care (POC) applications. The effectiveness of POC tests may vary. The sensitivity of serological tests for SARS-CoV-2 ranges from 73 to 100%, and their specificity ranges from 99 to 100%. These tests are qualitative and only indicate the presence of antibodies.[29] For ELISA tests that detect IgM and IgG in the diagnosis of SARS-CoV-2, the sensitivity is reported to be between 77 to 83%, and the specificity is greater than 95%. In a study using the CLIA method, the sensitivity for IgM was found to be 48.1% with a specificity of 100%, and for IgG, the sensitivity was 88.9% with a specificity of 90.9%.[36] Another study by Pan et al.[37] demonstrated that IgM, IgG, and total antibody levels were highest after the 15th day of infection. In another study, it was reported that the accuracy of serological tests increased when serum samples were tested two weeks after the initial positive PCR test result.[38]

In conclusion, updates on various aspects of COVID-19, including diagnosis, treatment, vaccination, and more, continue to evolve as the number of cases and research in this field increase. It is crucial to keep track of current studies and stay updated with the latest developments.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Took part in the idea and design of the manuscript, ensuring the controls of the manuscript, collecting the data, analysing the data, writing the manuscript and literature review: A.T.; Took part in the conception and design of the manuscript, ensuring the controls of the manuscript, writing the manuscript and literature review: E.K.D.D.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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