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COVID-19 Clinical and Laboratory Diagnosis Overview

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Abstract

COVID-19 was identified in Wuhan, China in in December 2019, and rapidly spread worldwide, being declared global pandemic one month later on 30 January 2020. Since its emergence, COVID-19 has raised global concerns associated with drastic measures that were never adopted in any previous outbreak, to contain the situation as early as possible.

The 2019 novel corona virus (2019-nCoV) or SARS-CoV-2 is the causative agent of COVID-19. 2019-nCoV genetic sequence was rapidly identified within few days since the first reported cases and RT-PCR kits became available for COVID-19 diagnosis. However, RT-PCR diagnosis carries a risk of false-negative results, therefore additional serologic test are needed.

The most important approach in the battle against COVID-19 is rapid diagnosis of suspicious cases, timely therapeutic intervention and isolation to avoid community spread.

In this review, we summarize the clinical scenario that raises suspicion of COVID-19 and available laboratory diagnostics.

Key words: COVID-19, serology, RT-PCR, lab, clinical

Introduction

The 2019 novel corona virus (2019-nCoV)/SARS-CoV-2 sequence was first identified in January 2020, from bronchoalveolar lavage (BAL) samples of five patients in Wuhan, China, presenting with unusual respiratory symptoms; fever, cough, and dyspnea accompanied by complications of acute respiratory distress syndrome with diffuse lung opacities and consolidation detected in chest radiography. Next generation sequencing results revealed an unknown β-CoV strain with 79.0% nucleotide identity with the sequence of SARS-CoV, 51.8%

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identity with the sequence of MERS-CoV and 87.7% nucleotide identity with bat SARS-like CoV ZC45[1]. Therefore, it was announced that the 2019-nCoV is of bat origin. In fact, bats are the key reservoir of CoVs, and many human CoVs most probably have originated from bats [2,3]. The disease caused by 2019-nCoV/SARS-CoV-2 was named as corona virus disease 2019 (COVID-19) by the World Health Organization (WHO) [4].

On 30 January 2020, COVID-19 was declared by the WHO as a public health emergency of international concern (PHEIC) [5]. In 2005, the WHO gained the power to declare an international emergency [6], since then, international emergency was declared five times; H1N1 swine flu in 2009, the Ebola outbreak in West Africa in 2013, the polio outbreak in 2014, the Zika outbreak in 2016, and Ebola outbreak in the Democratic Republic of Congo in 2019 [6]. However, none of these previous emergencies led a worldwide pandemic [7]. Because of the rapid increase in number of COVID-19 cases and uncontrolled worldwide spread, it was declared by the WHO a pandemic [8]. As of May 1, 2020 the virus has infected 3 175 207 total confirmed cases with 224 172 deaths [9]. COVID-19 pandemic was associated with strict measures to contain the situation where many countries closed its borders associated with partial lockdown of most daily activities and social distancing. COVID-19 properties alert global concerns. The incubation period of COVID-19 is believed to be as long as 14 days, with potential asymptomatic transmission [10,11] in addition to being highly contagious and having higher transmissibility (R0: 1.4–5.5) than both SARS-CoV (R0: 2–5) and MERS-CoV (R0: <1) [12], although the mortality rate is lower 3.4% for COVID-19, compared to 10% for SARS-CoV and 34% for MERS-CoV (13-15).

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COVID-19 diagnosis:

Clinical presentation

The China National Health Commission proposed guidelines for initial diagnosis and disease severity triage into mild, severe, and critical categories. Around 70% to 80% of patients are mild, and 20% to 30% are severe or critical [16]. Table 1

Clinical diagnosis requires epidemic exposure, in addition to two clinical findings of the following: fever, radiographic features, normal or lowered white blood cells, or reduced lymphocyte count [16].

Real Time-PCR (PT-PCR)

The current diagnostic test for COVID-19 is RT- PCR assay [17]. It would not be possible to do PCR test to all suspected individuals, so the Centers for Disease Control and Prevention (CDC) released guidance for COVID-19 PCR testing were cases are prioritized [18]. Table 2

The recommended specimen for testing is lower respiratory tract specimen; *sputum and/or endotracheal aspirate or bronchoalveolar*. If not possible or in asymptomatic contacts, upper respiratory tract specimen; *nasopharyngeal and oropharyngeal swab or wash in ambulatory patients* is collected, with preference of combined nasopharyngeal swab and oropharyngeal swab collection (19).

High viral loads in both upper and lower respiratory tract are detected 5 – 6 days of the onset of symptoms [20-23]. Lower respiratory tract specimens yielded highest viral loads for the diagnosis of COVID-19 [24]. As for upper respiratory tract specimens higher sensitivity of nasopharyngeal swabs (63%) was detected compared to oropharyngeal swabs (32%) [25].

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Available RT-PCR testing targets two genes in the virus genome; the E and RdRP genes. The E assay is specific for all SARS-CoV-related viruses, while the RdRP assay only detects the COVID-19 virus, the recommendation for laboratory confirmation of cases is to detect two different genetic targets E followed by RdRP [26]. However, in areas where COVID-19 virus is widely spread, positive RT-PCR test result requires detection of at least one target gene, with priority to the E gene being more sensitive [26]. It should be well clear that one or more negative results do not rule out the possibility of COVID-19 virus infection as false negative result in an infected individual may be caused by several factors; 1. Poor quality of the specimen, 2. Timing of specimen collection; late or very early in the infection, 3. Inappropriate specimen handling and/or and shipping, 4. Technical error in the test. It is recommended that if a negative result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens were collected, additional specimens should be collected and tested preferably from the lower respiratory tract. [27]

Serological Tests

Serological testing detects antigens and antibodies directed against the virus. Although there is fundamental need for serological tests for COVID-19, no tests are yet approved for COVID-19 diagnosis. There are no commercially available antigen tests for COVID-19 available at the time of writing. Several studies reported validation of serological tests for COVID-19 but most of them are conducted on small number of patients. As SARS-CoV2 belongs to the same family of β-Coronaviruses as those caused SARS and MERS outbreaks, it is expected to have similar antibody generation process [28] where there is a lag period of 14-28 days after the onset of illness till the antibodies appear in patients' serum [29]. In some people with COVID-19, disease

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confirmed by RT-PCR, weak, late or absent antibody responses have been reported [30-31]. The strength of antibody response is dependent on multiple factors as age, nutritional status, disease severity, and certain medications or infections that may suppress the immune system [30,31,32].

In March 2020, the FDA issued a policy that allows developers of certain serological tests to begin to market or use their tests once appropriate evaluation to ensure test validation are performed. The FDA issued this policy to allow early patient access to certain serological tests. Until 18 April 2020, four serological tests were issued an Emergency Use Authorization (EUA) intended for use by clinical laboratories [33]. Criteria for EUA was: 1.The SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus; 2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the product may be effective in diagnosing COVID-19, and that the known and potential benefits of the product when used for diagnosing COVID-19, outweigh its known and potential risks; and 3. There is no adequate, approved, and available alternative to the emergency use of the product [34].

It is recommended to use combined IgG&IgM antibody testing for more accurate results [28]. The average time for seroconversion in reported studies is 12 days, while positive RT-PCR is detected 5-6 days from the onset of symptoms, making antibody testing still inferior to RT-PCR in COVID-19 diagnosis but more likely used when RT-PCR is not available or accessible [35].

A sample of reported studies using different serological tests to detect antibodies against SARS-CoV-2, mentioning; the technique used, number of cases, test sensitivity to detect COVID-19 and the median number of days until seroconversion are summarized in table 3.

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Conclusion

COVID-19 available diagnostics puts the health authorities in challenging situation as diagnosis based on clinical symptoms alone is inaccurate, in addition to the presence of asymptomatic carriers and long incubation period of the virus. False negative RT-PCR results in infected patients adds to the challenge, necessitating the need for a rapid and sensitive technique to be available in most laboratories for swift detection of COVID-19 in order to limit spread and properly treat infected individuals. Available diagnostic tests alone are not enough to provide guaranteed diagnosis of COVID-19. Clinical suspicion of COVID-19 should be thoroughly taken in consideration even with negative test results to allow timely management of COVID-19, contain and limit the damage of current outbreak.

To monitor disease progression, it recommended to combine both serial viral load monitoring and antibody response as viral load found to be inversely related to serum antibody response [22].

Detection of antibody responses to COVID-19 in the population is important to aid vaccine development, and to add to our understanding of the extent of infection among individuals who passed asymptomatic and/or not identified during surveillance efforts. On the other hand, positive antibody testing doesn't guarantee safety from reinfection by COVID-19 or acquisition of herd immunity, and therefore shouldn't be considered as an excuse to ignore public health advice which may lead to increasing the risk of continued transmission.

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Table 1. COVID-19 severity triage

Mild	Severe	Critical
• fever, • respiratory sympmtoms, • pneumonia on chest radiography.	• **Need to meet one of the following criteria:** • respiratory distress, RR ≥ 30/minutes; • resting blood oxygen saturation ≤ 93%; or • arterial blood oxygen partial pressure (PaO2)/FiO2 ≤ 300 mm Hg.	• **Need to meet one of the following criteria:** • respiratory failure needing mechanical oxygenation; • shock; or • development of other organ failures, requiring intensive care unit care.

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Table 2. Priorities for testing according to CDC guidelines [18]	
Priority 1 ***Ensure optimal care options for all hospitalized patients, lessen the risk of nosocomial infections, and maintain the integrity of the healthcare system***	• Hospitalized patients • Symptomatic healthcare workers
Priority 2 ***Ensure that those who are at highest risk of complication of infection are rapidly identified and appropriately triaged***	• Patients in long-term care facilities with symptoms • Patients 65 years of age and older with symptoms • Patients with underlying conditions with symptoms • First responders with symptoms
Priority 3 *As resources allow, test individuals in the surrounding community of rapidly increasing hospital cases to decrease community spread, and ensure health of essential workers*	• Critical infrastructure workers with symptoms • Individuals who do not meet any of the above categories with symptoms • Health care workers and first responders • Individuals with mild symptoms in

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	communities experiencing high 2019-nCoV hospitalizations
Non-Priority	• Individuals without symptoms

Table 3. Serological tests data from reported studies

Technique	Number of cases	Antibodies tested	Seroconversion (median days)	Positive detection rate	Reference
Enzyme Immunoassay (EIA)	23	anti-NP IgM anti-NP IgG anti-RBD IgM anti-RBD IgG	>10	88% 94% 94% 100%	22
Immunofluorescence	31	IgM IgG	7-14		23
ELISA	173	Total (IgA, IgG, IgM) IgM IgG	11 14 12	93.1% 64.7% 82.7%	30
ELISA	140	IgA IgM IgG Combined IgA&IgM	8-14	93.3% 93.1% 77.9% 90.4%	36

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ELISA, and Chemiluminescence immunoassay (CLIA)		IgM IgG	10-12		37
Lateral flow immunoassay	58	IgM IgG Combined IgG&IgM		1.72% 3.45% 94.8%	38
Fluorescence Immunochromatographic assy	57	IgM IgG Combined IgG&IgM		60.61% 45.45% 72.73%	39
Immunofluorescence assays (IFA)	1	IgM IgG	9 20		40
Colloidal Gold Antibodies Test	38	IgM IgG	8	50.0% 92.1%	41
ELISA	109	IgM IgG	4-30	77.3% 83.3%	42
Chemiluminescent analytical system	37	IgM IgG	13 11	88% 100%	43
Iimmuno-chromatography	105	IgM IgG Combined IgG&IgM	8-14	78.6% 57.1% 83.3%	44

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Chemiluminescence immunoassay (CLIA)	43	IgM IgG	>5	48.1% 88.9%	45
ELISA	214	IgM IgG	>10	80.4% 82.2%	46
Chemiluminescence immunoassay (CLIA)	34	IgM IgG	14		47
ELISA	175	IgM IgG	10-15		48
ELISA	178	IgM IgG	>5	81% 100%	49
ELISA	179	Combined IgG&IgM	8-15	85.6%	50