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Review Article

Evaluation of Diagnostic Modalities for SARS-Cov-2: A Review Study

Roghayeh Sheervalilou[1], Jamal Ahmadzadeh[2], Sahel Alavi[3], Kazhal Mobaraki[2], Saman Sargazi[4], Milad Shirvaliloo[5], Ali Golchin[6], Ali Yekanlou[6], Sahar Mehranfar[7*]

[1]Pharmacology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Epidemiologist, Social Determinants of Health Research Center, Urmia University of Medical Sciences, Urmia, Iran
[3]School of Nursing, Gerash University of Medical Sciences, Gerash, Iran
[4]Cellular and Molecular Research Center, Resistant Tuberculosis Institute, Zahedan University of Medical Sciences, Zahedan, Iran
[5]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[7]Department of Genetics and Immunology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Abstract

Background and aims: *In* late December 2019, a cluster of progressive pneumonia-like respiratory syndromes broke out in Wuhan, China. As the number of cases continued to rise, the 2019 coronavirus disease (COVID-19) has been declared a global public health emergency. The causative agent, i.e., SARS-CoV-2, is a highly contagious strain, which has resulted in the rapid worldwide outbreak of COVID-19. COVID-19 is an overwhelmingly transmissible disease that requires early and accurate diagnosis for proper and timely treatment of suspected cases.

Materials and Methods: In order to access the scientific documentation and evidence related to the subject published during 2019 to 2021, English keywords including "COVID-19", "SARS-CoV-2", "Diagnosis", "Immunoglobulin G (*IgG*)", "Immunoglobulin M (*IgM*)", and 'Polymerase Chain Reaction (PCR)" were searched in Medline, PubMed, and Google Scholar databases and Persian versions of these keywords were also looked for in Jihad-e Daneshgahi's Scientific Information Database (SID) and Iranian Journals database (Magiran)

Results: With respect to diagnosis, serum antibody assays, nucleic acid sequencing, and radiologic evaluation are among the most reliable methods to rule out the disease in suspicious cases. This review is a synopsis of the pathogenesis of coronavirus, which will mainly focus on the diagnostic methods, as well as laboratory changes in immunoglobulins, polymerase chain reaction results, and computed tomography (CT) findings.

Conclusion: Early diagnosis matters in that it not only contributes to the prevention of further transmission of the virus by asymptomatic carriers but also paves the way for clinicians to accurately choose the best therapeutic approach depending on the status of the patients.

Keywords: COVID-19, SARS-CoV-2, Diagnosis, Immunoglobulin G (*IgG*), Immunoglobulin M (*IgM*), Polymerase Chain Reaction (PCR)

***Corresponding Author:**
Sahar Mehranfar,
Department of Genetics and Immunology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran.
Tel: +98- 9144454610;
Fax: +98-4432240642;
Email: dr_sahar21@yahoo.com

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Introduction

A class of enveloped, positive-sense single-stranded RNA viruses, namely coronaviruses (CoV), which can be commonly isolated from different animal species, cause adverse effects in the respiratory, neurological, and enterohepatic systems of human beings. CoVs are recognized as important pathogens due mostly to their widespread global distribution and high infectivity.[1]

During 2002-2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) led to an outbreak in Guangdong, China, which resulted in the infection of 8000 patients and 774 cases of death in 37 countries. During 2012-2013, a novel strain of CoVs was first reported in Saudi Arabia, which was duly named Middle East respiratory syndrome coronavirus (MERS-CoV). This new strain resulted in fewer confirmed cases, albeit higher fatalities, with 2,494 confirmed cases and 858 deaths.[2,3] The current SARS-CoV-2 outbreak in 2020 initially presented with clinical signs of idiopathic pneumonia in Wuhan, China. After a while, nucleic acid sequencing and laboratory findings detected the culprit as a new strain of CoV.[4]

As expected, several similarities and discrepancies have been reported in the incidence, clinical signs, and the treatment for SARS, MERS, and COVID-19.[3,5] Unlike its predecessors, SARS-CoV-2 is spreading at a much faster rate and can even result in asymptomatic infections.[6] According to R0 values, COVID-19 is more infectious than SARS and MERS. Generally, the aged and/or immunocompromised individuals are at extreme risk of developing severe disease. Despite the odds, no medication has been approved for COVID-19.[1] Some clinical features of SARS-CoV, MERS-CoV, and SARS-CoV-2 are summarized in Table 1.

From a biological viewpoint, high incidence of lymphopenia among patients with COVID-19 suggests that the virus might affect the lymphocytes, especially T-cells, in a manner similar to SARS-CoV.[7] SARS-CoV-2 particles are thought to spread through the respiratory epithelium by means of angiotensin-converting enzyme 2 (ACE2) receptors that are expressed on the ciliated bronchial epithelial cells. A massive infection can elicit generalized immune reactions like cytokine storm and induce hazardous alterations in the count and function of peripheral white blood cells.[3] COVID-19 is not restricted to one organ in the body but rather manifests with a broad spectrum of clinical features, ranging from septic shock and multi-organ dysfunction to no symptoms at all. Based on the severity of the disease, COVID-19 is commonly classified[8] as mild, moderate, severe, and critical types. Clinical features mostly include low-grade fever, shortness of breath, dry cough, lymphopenia, fatigue, diarrhea, and ground-glass opacifications on the chest computed tomography (CT).[9]

Similar to SARS, the incubation period of COVID-19 is approximately five days (2-14 days).[10] The diagnostic methods for accurate detection of COVID-19 have changed over time with increasing awareness of the pathophysiology of this disease. Today, serum immunoglobulin assays, nucleic acid sequencing, and chest imaging are recognized as the standard diagnostic methods.[11]

The definite diagnosis of COVID-19 is made once the oropharyngeal swab collected from a suspected case is confirmed to contain viral nucleic acid,[8,12] which is complemented by additional tests such as measuring the serum levels of Immunoglobulin M (IgM) and Immunoglobulin G (IgG) against the virus.[13] The serologic method has several advantages because it is simple to perform and yields a high sensitivity.[11] Quantitative real-time reverse transcriptase-polymerase chain reaction assay, or simply quantitative reverse transcription polymerase chain reaction (RT-qPCR), has been extensively used for detecting SARS-CoV-2 RNA in the respiratory secretions of suspected cases.[6] Based on available kits, this method offers a sensitivity of 45%-60%; therefore, repeated testing is recommended in the early stages of the disease.[14] CT is another diagnostic modality that can reveal the pathologic changes of lungs associated with COVID-19. CT as a widely available and cost-effective method can offer high sensitivity when performed and interpreted by experienced radiologists.[15,16]

Considering the prominent role of early diagnosis in the management of COVID-19, in this paper, we will present an in-depth review of COVID-19 diagnosis through IgG/M monitoring, PCR, and CT imaging.

COVID-19

Epidemiology

As reported earlier, the majority of people infected with COVID-19 were males with a mean age of 59 years (15-89 years). Besides, the mean incubation period of SARS-CoV-2 is approximately 4.8±2.6 days, ranging from 2 to 11 days.[17] There is not much data available concerning the typical chest CT imaging patterns of children infected with SARS-CoV-2.[18] As of February 15, 2020, COVID-19 pneumonia has resulted in a mortality rate of around 2%.[19] On February 12, an abrupt rise in new SARS-CoV-2 cases was due to a modified diagnosis method based on the 5th edition of national treatment guideline, a combination of SARS-CoV-2 nucleic acid test and clinical COVID-19 features.[6] Not surprisingly, COVID-19 cases who already had underlying diseases were more susceptible to severe disease and mortality.[20]

Biology

Coronaviruses belong to CoVs; order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, which include four genera: alpha coronavirus, beta coronavirus, delta coronavirus, gamma coronavirus, as well as multiple subgenera and species. Nidovirales are enveloped, non-segmented, positive-sense RNA viruses with a well-conserved genome that encodes numerous non-structural genes. Moreover, these viruses are characterized by multiple unusual enzymatic activities encoded within the replicase-transcriptase polyprotein, 3' nested sub-genomic mRNAs. Coronavirus virions are spherical, with diameters

Table 1. Clinical Features of SARS-CoV and MERS-CoV, SARS-CoV-2

Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Estimated Reproductive Number	2.68	2-5	>1
Host of virus	Bats are natural hosts, pangolins are intermediate hosts, and humans are terminal hosts	Chinese horseshoe bats are natural hosts, masked palm civets are intermediate hosts, and humans are terminal hosts	Bats are natural hosts, dromedary camels are intermediate hosts, and humans are terminal hosts
Transmission mode	Human-to-human through fomites, physical contact, aerosol droplets, nosocomial transmission, zoonotic transmission	Human-to-human through aerosol droplets, opportunistic airborne transmission, nosocomial transmission, fecal-oral transmission, zoonotic transmission	Respiratory transmission, zoonotic transmission, nosocomial transmission, limited human-to-human transmission, aerosol transmission
Average incubation period (days)	6.4	4.6	5.2

ranging between 100 and 160 nm.[21] These viruses have been isolated from bats and show high sequence homology with isolates from humans, suggesting that bats are natural hosts and reservoirs of this virus.[3]

HCoV-19 has a spike protein (S protein), an envelope protein (E), a membrane protein (M), and a nucleocapsid protein (N protein). Among these proteins, the N-protein is the most abundant one, which is relatively conserved among different coronaviruses; hence, it is frequently used as a diagnostic antigen.[22] With regard to genetic properties, coronavirus is comprised of two strains from Alphacoronavirus (HCoV-229E and HKUNL63) and four from Betacoronavirus subfamily (HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV).[23]

As long single-stranded RNA viruses, human coronaviruses appear to spread via human to human. The genome of human SARS-CoV-2 matched the typical CoVs and consisted of more than ten open reading frames (ORFs). The first ORF, ORF1a/b, processes into two large viral polyproteins. The other ORFs of SARS-CoV-2 encode the main structural proteins.[24] It is believed that SARS-CoV-2 spreads from person to person through respiratory droplets. SARS-CoV-2 can also spread via other routes of infection (i.e., close contact) if the virus persists on surfaces; however, it is not clear whether these routes are required for the distribution of the virus. SARS-CoV-2 binds to ACE2 receptors on type II pneumocystis [25] during entry into cells. Several pieces of evidence suggest that SARS-CoV-2 might change over time, or simultaneously, there may be more than one strain of the virus in circulation.[26]¶

Clinical Manifestations

Basically, Human COVs present with either pulmonary or extrapulmonary signs. COVID-19 cases are clinically categorized into four types: mild, normal, severe, and critical, according to "Diagnosis and Treatment Plan for Novel Coronavirus Pneumonia" (Fifth Edition).[27] The majority of COVID-19 cases present with early symptoms of headache, high fever (39°C), and abnormal respiratory features, including cough and changes in breathing pattern. The virus passes through the nasal and larynx mucous membranes, and at that point, it enters the lungs via respiratory tract and subsequently spreads to peripheral blood to cause viremia. Then, SARS-CoV-2 adheres to ACE2 receptors that are highly expressed in various organs (e.g., lungs, heart, kidneys, and gastrointestinal tract). The principal pathogenesis of SARS-CoV-2 infection is viremia and severe pneumonia combined with acute cardiac injury.[17]

Besides early symptoms, digestive manifestations were widely reported in COVID-19 patients with mild disease severity.[28] In more severe cases, SARS-CoV-2 could cause kidney failure and even death.[29] In addition to respiratory symptoms, fever, cough, diarrhea, and fatigue were widely seen in COVID-19 patients, whereas the chest pain and muscle ache were less commonly reported.[30] Although fever, headache, and myalgia are often reported in COVID-19 patients after 4 to 5 days, respiratory symptoms develop several days after the onset of initial symptoms.[31] In an immunocompetent individual, these COVs could clinically manifest with self-limiting upper respiratory infections and common colds, whereas in an elderly and immunocompromised host, they can severely infect the lower respiratory tract. SARS-CoV-2-positive RT-PCR results have also been reported for asymptomatic patients from Croatia and Thailand.[32]

Similar to other coronavirus pneumonias like SARS that is caused by a coronavirus as well as MERS, COVID-19 can lead to acute respiratory distress syndrome (ARDS).[33] Estimated frequency of symptoms observed to date indicates that 50-80% of COVID-19 patients present with cough, 69.6% have fatigue, 20%-40% experience dyspnea, and most importantly, 85% of the cases show fever.[34]

In a systematic review study, it has been shown that the most frequent symptoms of COVID-19 patients are fever, cough, and dyspnea; however, some young infected cases presented with no symptoms.[35] In another systematic review and meta-analysis including 656 patients, fever (88.7%), cough (57.6%), and dyspnea (45.6%) were the most commonly reported symptoms.[3] Table 2 summarizes some case reports on the clinical presentation of COVID-19.

Diagnosis

General Laboratory Findings

In patients with COVID-19, elevated prothrombin time, lactate dehydrogenase (LDH), D-dimer, alanine aminotransferase (ALT), amylase, C-reactive protein (CRP), total bilirubin and BUN/creatinine, creatine kinase (CK), ferritin, and normal or low procalcitonin have been frequently reported laboratory findings.[26]

Basically, the immune response of T helper (Th) cells plays a pivotal role in adaptive immunity following the recognition of viruses. After detection of the virus by antigen-presenting cells (APC) such as dendritic cells (DCs), these cells release cytokines and generate a microenvironment that is necessary for direct T-cell responses. Moreover, the production of virus-specific antibodies is mediated by $CD4^+$ T-cells, which activate the T-dependent B-cells.[36,37] Besides, significant changes in numerous serum cytokines were found in patients with COVID-19 infection. During the initial stages of COVID-19 infection, a significant decrease in CD4 and CD8 lymphocytes can also be observed. Increased levels of interleukin IL-2, IL-7, IL-10, granulocyte colony-stimulating factor) GCSF), interferon gamma-induced protein 10 (IP-10(, MCPI (monocyte chemotactic protein 1), MIPIA (macrophage inflammatory protein alpha), and TNF-α (tumor necrosis factor-a) have been reported in patients in the intensive care unit as well.[1] In addition, leukopenia, lymphopenia (+80%), and thrombocytopenia have been seen in patients with COVID-19.[26]

In a systematic review and meta-analysis by Zhao et al including 19 related studies, elevated CRP, D-dimer, and

Table 2. Case Reports on the Clinical Presentation of COVID-19

Study/Region	Study Type/ Medical Team	Patient/Gender/Age	Diagnostic Test	Inclusion Criteria	Test Results
Li et al, April, 2020 China	Retrospective study/ Yichang Central People's Hospital	22 pediatric subjects; 12 males and 10 females; median age: 8 years	RT-PCR HRCT	Epidemiological history: either travel/residence history in Wuhan or exposure history to patients with fever from Wuhan suffering from respiratory symptoms within 14 days before the onset of illness; positive detection of COVID-19 by RT-PCR	The most prevalent presenting symptoms were fever (64%) and cough (59%).
Guan et al, February 2020 China	Retrospective study / Guangzhou	1,099 subjects; 639 males and 460 females; median age: 47 years	RT-PCR	The initial cases were diagnosed as having 'pneumonia of unknown etiology,' based on the clinical manifestations and chest radiology after exclusion of the common bacteria or viruses associated with community-acquired pneumonia. Epidemiological history: either travel/residence history in Wuhan or exposure history to patients with fever from Wuhan suffering from respiratory symptoms within 14 days.	Fever (87.9%) and cough (67.7%) were the most prevalent symptoms, whereas diarrhea (3.7%) and vomiting (5.0%) were rare.
Shi et al, April, 2020 China	Retrospective study/ two hospitals in Wuhan	81 subjects; 42 males and 39 females; median age: 42.5 years	NGS RT-PCR	Patients with confirmed COVID-19 pneumonia, and who underwent serial chest CT scans	Frequently observed symptoms at onset were fever (73%) and dry cough (59%), dizziness (2%), diarrhea (4%), vomiting (5%), headache (6%), and generalized weakness (9%).

Abbreviations: HRCT, high-resolution computed tomography; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction

LDH, as well as decreased blood platelet and lymphocytes counts were markedly correlated to severe COVID-19. Similarly, increased CRP, myoglobin, aspartate aminotransferase (AST), and ferritin, and decreased hemoglobin were noted in Wuhan patients relative to those outside Wuhan.[20] In agreement with these findings, another meta-analysis has reported that the most common abnormal laboratory changes in COVID-19 patients include lymphopenia, elevated CRP, as well as increased AST and LDH. In this case, higher levels of angiotensin II also contribute to acute lung injury. Results of the study conducted by Rodriguez-Morales et al revealed that diminished albumin, increased CRP and LDH, lymphopenia, as well as higher ESR levels were the most common laboratory findings observed in a total of 2,874 positive COVID-19 cases.[3]

In the meantime, non-survivors are assumed to present with higher D-dimer, as well as longer PT and PTT associated with lower fibrinogen and antithrombin levels.[35] As shown in Table 3, there has been no consistent change in CRP levels among case reports as mildly increased CRP level has been observed in some case reports.[38] At the same time, a lower mean concentration of CRP was noted in asymptomatic patients confirmed with COVID-19.[19]

IgG/IgM Titers

Acute antibody responses to SARS-CoV-2 have been reported earlier in several papers.[39-41] Therefore, an immediate, simple, and precise diagnosis of suspected COVID-19 is essential for monitoring, management, and treatment of the patient. Although several methods are used in clinical practice, the diagnostic value of IgM and IgG has been relatively overlooked. In a related study, within 19 days after the onset of symptoms, almost all the patients tested positive for antiviral IgG, followed by seroconversion for IgG and IgM. The titers of both immunoglobulins plateaued within few days after seroconversion.[42] Rapid detection of SARS-CoV-2-specific IgM and IgG was shown to be associated with high specificity (100% for IgM and 99.2% for IgG), demonstrating that this assay is beneficial for determining previous virus exposure. Nevertheless, negative results may be unreliable during the first weeks after SARS-CoV-2 exposure.[43]

Rapid and simple point-of-care lateral flow immunoassays have been lately practiced for simultaneous detection of IgM and IgG antibodies against SARS-CoV-2 in symptomatic or asymptomatic humans infected with the virus at different stages.[44] Using a chemiluminescence-immunoassay method, Lin et al found that IgG testing was more reliable than IgM for identifying SARS-CoV-2 infections from the confirmed patients, reaching 82.28% sensitivity and 97.5% specificity.[23] In a study by Jia et al on 57 suspected COVID-19 patients, the positive rate for single detection was 60.61% (for IgM) and 5.45% (for IgG). However, the positive diagnostic rate of the combination of IgM and IgG detection was 72.73% in 33 patients with COVID-19 negative RT_PCT results and it was 87.50% in 24 patients with COVID-19 negative RT-PCT results.[11]

Nucleic Acid Detection: PCR

Nowadays, precise genome detection serves a substantial function in COVID-19 diagnosis. In this regard, RT-PCR is the primary technique for detection of SARS-CoV-2 nucleic acid. However, RT-PCR is a time- and labor-consuming method for monitoring the increasing number of suspected individuals and asymptomatic patients.[45] In January 2020, the first protocols of RT-PCR assays for specific amplification of SARS-CoV-2 RNA-dependent

Table 3. Case Reports on the Laboratory Findings of Patients with COVID-19

Study/ Region	Study Type/ Medical Team	Patient/Gender/Age	Diagnostic Test	Inclusion Criteria	Test Results
Lin et al., March, 2020 China	Retrospective study/ Jiangxi Provincial People's Hospital	2 subjects; 2 males; median age: 47 years	RT-PCR	Positive detection of COVID-19 by RT-PCR and confirmed by CT imaging	Normal leukocyte count, normal or increased neutrophils, normal or decreased lymphocytes, elevated glucose, and normal or elevated C-reactive protein decreased AST
Li et al., April, 2020 China	Retrospective study/Yichang Central People's Hospital	22 pediatric subjects; 12 males and 10 females; median age: 8 years	RT-PCR HRCT	Epidemiological history, positive detection of COVID-19 by RT-PCR	Mildly increased CRP and ESR
Shi et al., April, 2020 China	Retrospective study/two hospitals in Wuhan	81 subjects; 42 males and 39females; median age: 42.5 years	NGS RT-PCR	Patients with confirmed COVID-19 pneumonia, and who underwent serial chest CT scans	Increased level of amyloid A protein in most of the COVID-19, lower mean concentrations of CRP and AST in asymptomatic patients
Jia et al., March, 2020 China	Retrospective study/Shenzhen Hospital	24 patients with positive and 33 patients with a negative nucleic acid test	RT-PCR	Epidemiological history, clinical manifestations, and laboratory findings	Reduced lymphocyte counts, increased hsCRP in COVID-19 patients

Abbreviations: AST, Aspartate aminotransferase; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; hsCRP, High-sensitive C-reactive protein; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction.

RNA polymerase (RdRp), envelope (E), and nucleocapsid (N) genes were released.[46] Although RT-PCR is the gold standard for COVID-19 diagnosis, this technique lacks enough sensitivity for the detection of low viral load present in test specimens. In many areas, RT-PCR kits are in short supply.[16] Although RT-PCR is not easily performed with the global shortage of testing kits, RT-PCR kits are variable and yield relatively low sensitivity; therefore, repeated testing may be necessary to ensure diagnosis, particularly early in the course of the infection,[14] reflecting the experience with MERS-CoV. In a study conducted by Alfaraj et al on 336 patients infected with MERS-CoV, approximately 89% of patients were positive for MERS-CoV after 1 swab, while 96.5% had positive results after 2 consecutive swabs and 97.6% had positive results after 3 swabs.[47]

A large body of evidence has recently shown the limitations of RT-PCR. First, more than 7 SARS-CoV-2 nucleic acid PCR tests are already available.[48] Second, it has been demonstrated that the samples taken from the upper respiratory tract show their highest viral loads almost three days after the onset of clinical symptoms. It has also been shown that nasal samples have higher viral loads than throat samples.[49] Zhang et al reported low sensitivity (30%-50%) of RT-PCR in single upper respiratory specimen testing.[48] Multiple factors have been suggested to explain the false-negative rate of this method. For instance, the variation of viral RNA sequences might affect the results of RT-qPCR. Concerning sampling procedures, it has been urgently suggested that sputum and bronchoalveolar lavage fluid collected from the lower respiratory tract of patients must be used for testing SARS-CoV-2 infection.[50]

Results of the study conducted by Long et al revealed that the sensitivity of initial RT-PCR was only 83.3%, and initially missed cases became positive for SARS-CoV-2 in the third round of RT-PCR tests after 8 days. This suggests that RT-PCR assay should be repeated in patients with typical chest imaging findings and initial negative RT-PCR results.[51] On the other hand, RT-PCR is a time-consuming technique since it often requires 5 to 6 hours, while chest imaging results can be obtained over a shorter period of time. Ai et al proposed a combinative approach of RT–PCR, CRISPR-based assay, and metagenomic next-generation sequencing (mNGS) for COVID-19 diagnosis. According to their findings, it might be advantageous to combine such molecular diagnostic techniques to rule out other pathogens for an accurate diagnosis of SARS-CoV-2.[52]

Chest Imaging: CT

Besides RT-PCR, initial attempts focused on the use of chest CT in the forefront of COVID-19 diagnosis.[53] Imaging can show the number, size (patchy, large block, nodular, lumpy, etc), density (ground glass density, paving stones-like change, consolidation, fibrosis, etc.), and distribution of these lesions.[54]

Recent studies have shown that approximately 96% of COVID-19 cases manifest with chest CT abnormalities, including multiple bilateral and peripheral ground-glass opacity (GGO) with or without consolidation,[55] frequently with a rounded spherical morphology and a peripheral lung distribution.[56] Previously, it was observed that lung lesions of patients infected with SARS progressed rapidly, producing "white lungs" characterized by diffuse infiltration of both lungs. On the contrary, lung lesions in patients with COVID-19 infection are comparably mild and might be wrongly diagnosed as common viral infections or bronchopneumonia.[57] There were apparent similarities between chest CT imaging patterns of COVID-19 and SARS infections. To name a few, both subpleural GGO and consolidations are prevalent and mainly observed in bilateral subpleural areas while other features such as cavities, pleural effusion, and enlarged lymph nodes are hardly seen. However, within the absorption phase of pneumonia, more severe interstitial fibrosis was discovered in patients with SARS.[27]

Upon performing a systematic review of case reports and case series, Tahvildari et al reported that CT images of 80% of confirmed COVID-19 patients displayed GGO patterns, while 69% of patients presented with bilateral lung involvement.[58] Another systematic review and meta-analysis including a total of 2,874 positive COVID-19 patients showed that 68.5% of lung lesions were GGOs, 25% of the lesions were unilateral and 72.9% of them were bilateral.[3] Table 4 represents some case reports performed on COVID-19 patients focusing on their CT findings.

Multiple reports published to date have outlined the higher sensitivity of chest imaging in early detection

Table 4. Case Reports on the CT Findings of Patients with COVID-19

Study/Region	Study Type/ Medical Team	Patient/Gender/Age	Diagnostic Test	Inclusion Criteria	Test Results
Gao et al., April, 2020 China	Retrospective study / Zhejiang Hospital	6 subjects; 1 male and 5 females; median age: 40±10 years	RT-PCR HRCT	Patients were positive for 2019 novel coronavirus nucleic acid via laboratory testing of respiratory secretions	About 33.3% of patients had bilateral lung involvements, 66.7% had single-lung involvement, and 83.3% had ground-glass opacities
Shi et al., April, 2020 China	Retrospective study/ two hospitals in Wuhan	81 subjects; 42 males and 39 females; median age: 42.5 years	NGS RT-PCR	Patients with confirmed COVID-19 pneumonia, and who underwent serial chest CT scans	The prevalent pattern of CT abnormality discovered was GGO (65%), bilateral (79%), peripheral (54%), and ill-defined (66 [81%]) opacification.
Wang et al., March, 2020 China	A Longitudinal Study/ Isolation wards of Union Hospital	90 subjects; 33 males and 57 females; median age: 45 years	RT-PCR	At least one positive RT-PCR result obtained before or after admission; at least 1 CT scan showed lung abnormalities before or after admission	45 to 62% of patients with COVID-19 infection presented with ground-glass opacities in different periods. Following 12-17 days of illness, the mixed patterns were more frequent, while irregular linear opacity peaked on illness days 6-11. They also found that most of the lesions were bilateral and subpleural.
Li et al., March, 2020 China	Retrospective study/ Yichang Central People's Hospital	22 pediatric subjects; 12 males and 10 females; median age: 8 years	RT-PCR	Epidemiological history: either travel/residence history in Wuhan or exposure history to patients with fever from Wuhan suffering from respiratory symptoms within 14 days before the onset of illness; and positive detection of COVID-19 by RT-PCR	The most prevalent CT abnormalities observed were mixed ground-glass opacity and consolidation lesions (36%), consolidations (32%), and GGO (14%). About 68% of these lesions were multilobar, presented with an average of three lung segments involved.
Pan et al., June 2020 China	Retrospective study/ Union Hospital	21 pediatric subjects; 6 males and 15 females; aged: 25-63 years	RT-PCR	Epidemiological history: either travel/residence history in Wuhan or exposure history to COVID-19 patients; clinical manifestations (fever, imaging characteristics of pneumonia, and/or normal or decreased white blood cell count or decreased lymphocyte count); and positive detection of COVID-19 by RT-PCR	CT scans showed ground-glass opacities (75%), increased crazy-paving pattern (53%) and total CT score after 8 days; consolidation (91%) after 9-13 days and a peak in the total CT score after 14 days followed by a decrease in the total CT score without crazy-paving pattern.
Long et al., June 2020 China	Case-control study/ Yichang Yiling Hospital	36 COVID-19 subjects; 20 Males and 16 Females; Median age: 44.8±18.2; and 51 yrs control subjects; 26 Males and 25 Females; Median age: 47.1±18.8	RT-PCR	Patients with a fever of > 38℃ and COVID-19 pneumonia suspicion (b) who underwent both thin-section CT of the chest and RT-PCR examinations.	Except for 30.6% of patients with a single lesion, the majority of patients had more multiple CT abnormalities.
Guan et al., February, 2020 China	Retrospective study / Guangzhou	1,099 subjects; 639 Male and 460 Females; Median age: 47 yrs	RT-PCR	The initial cases were diagnosed as having 'pneumonia of unknown etiology,' based on the clinical manifestations and chest radiology after exclusion of the common bacteria or viruses associated with community-acquired pneumonia. Epidemiological history: either travel/residence history in Wuhan or exposure history to patients with fever from Wuhan suffering from respiratory symptoms within 14 days.	The most frequent patterns on CT images were ground-glass opacity (50.0%) and patchy bilateral shadowing (46.0%).
Lin et al., March, 2020 China	Retrospective study/ Jiangxi Provincial People's Hospital	2 subjects; 2 Males; Median age: 47 yrs	RT-PCR	Positive detection of COVID-19 by RT-PCR and confirmed by CT imaging	Multiple regions of patchy consolidation and small ill-defined GGO with indistinct border in both lungs, small ill-defined ground-glass opacities in both lower lung lobes

of COVID-19 in comparison with RT-PCR. This inconsistency resulted in suggesting that a CT scan could be more sensitive than RT-PCR.[14] Compared to RT-PCR, chest CT imaging might have some advantages. First of all, a CT scan can detect early lung lesions, and if performed by expert radiologists, it is able to yield high sensitivity. Besides, imaging techniques are widely available and economical. Jin et al developed an efficient artificial intelligence system for rapid diagnosis of COVID-19 with an accuracy as good as trained radiologists.[16] This deep convolutional neural network showed an accuracy of 94.98%, a sensitivity of 94.06%, and a specificity of 95.47% based on an independent dataset of 1255 cases.

Further tests revealed that only one radiologist was marginally more accurate than the developed diagnostic system.[16] Long et al reported the CT sensitivity of 97.2%, suggesting that this technique presents markedly higher sensitivity than initial RT-PCR (83.3%). Based on their observations, results of CT imaging would be more reliable since RT-PCR may produce initial false-negative results.[51]

As recommended by Wang et al, combining RT-PCR testing with clinical features should be used for accurate diagnosis of COVID-19 in order to facilitate the management of COVID-19 outbreak because some CT imaging features, including GGO and patchy shadows in bilateral lungs, have been reported in many "suspected" cases with negative RT-PCR results for the virus, making lung CT a non-specific diagnostic tool when used alone.[50]

Conclusion

COVID-19, the most catastrophic epidemic in recent memory, is spreading globally at an overwhelming rate. In the absence of specific medications or an effective vaccine, early diagnosis constitutes to be the pillar upon which all other therapeutic strategies lie. Besides timely diagnosis, factors associated with the evolution of the virus and the outcomes of treatment must be carefully addressed and investigated when a new infectious disease has emerged. Serum antibody assays, PCR, and CT are invaluable assets at our disposal that can greatly help reveal the presence and severity of the disease in suspected and confirmed cases, respectively. Early diagnosis matters in that it not only contributes to the prevention of further transmission of the virus by asymptomatic carriers but also paves the way for clinicians to accurately choose the best therapeutic approach depending on the status of the patients.

Ethical Approval

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