Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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General review

COVID-19 paraclinical diagnostic tools: Updates and future trends

Tamim Alsuliman[a,*], Rand Sulaiman[b], Sawsan Ismail[c], Micha Srour[d], Ali Alrstom[e]

[a] Service d'hématologie, hôpital Saint-Antoine, AP-HP Sorbonne Université, 75012, Paris, France
[b] Department of Genetics, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation
[c] Department of Pathology, Faculty of Medicine, Tishreen University, Lattakia, Syria
[d] Service maladie du sang, centre hospitalier universitaire de Lille, 59000, Lille, France
[e] Department of Infectious Diseases, Faculty of Medicine, Damascus University, Damascus, Syria

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ABSTRACT

Motivation: COVID-19 is one of the most widely affecting pandemics. As for many respiratory viruses-caused diseases, diagnosis of COVID-19 relies on two main compartments: clinical and paraclinical diagnostic criteria. Rapid and accurate diagnosis is vital in such a pandemic. On one side, rapidity may enhance management effectiveness, while on the other, coupling efficiency and less costly procedures may permit more effective community-scale management.
Methodology and main structure: In this review, we shed light on the most used and the most validated diagnostic tools. Furthermore, we intend to include few under-development techniques that may be potentially useful in this context. The practical intent of our work is to provide clinicians with a realistic summarized review of the essential elements in the applied paraclinical diagnosis of COVID-19.

Contents

* Corresponding author at: Service d'hématologie, hôpital Saint-Antoine, AP-HP Sorbonne Université, 184 Rue du Faubourg Saint-Antoine, 75012, Paris, France.
E-mail address: Dr.tameemsoliman@gmail.com (T. Alsuliman).

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Introduction

In December 2019, an increasing number of pneumonia cases appeared in Wuhan, Hubei State in China. Thorough analytical studies, accomplished by epidemiologists, demonstrated that the spread of the disease might be related to Wuhan South China Seafood Market [1]. Dedicated in-depth studies, using high-throughput sequencing, revealed a new beta-coronavirus that was called 2019 novel coronavirus (2019- nCOV) [2]. In January 2020, the World Health Organization (WHO) renamed the virus as SARS-COV-2 and the disease as COVID-19 [3].

Despite the attempts to limit the spread of the virus within the city, it rapidly disseminated to other states in China, which may be due to the movement preceding lunar Chinese New Year [4]. Within weeks, the infection had spread to many other countries worldwide.

By January 20th, many countries, including Japan, South Korea and Thailand had reported their first cases. The next day the first case was confirmed in the USA. The virus continued to spread until its first case was recorded in the Philippines (February 2nd), France (February 14th), Iran (February 21 st). By February 23th, the first case appeared in Italy, then many countries through Europe reported their first cases [5].

Considering the largely increasing cases throughout the world, world health organization (WHO) has announced a global pandemic on March 12th, 2020 [6]. As of May 23th at 15:00 Eastern European Summer Time, COVID-19 has affected 209 countries, with more than (5 105 881) confirmed cases and (333 446) deaths [7].

Coronaviruses (COVs) comprise a heterogeneous group of enveloped, positive sense and single-stranded RNA viruses owned their names due to 9–12 nm long surface spikes that look like a corona (equal to crown in Latin). They can cause many diseases, including respiratory, gastrointestinal, heart and neurological pathologies with variable severity among animals and humans [8].

Depending on the available data, bats may be the initial hosts of COVID-19. It may be transmitted to humans through pangolin [9] or other wild animals [2] confronted at the Huanan seafood market then disseminated through human to human transmission. Current data showed an incubation period of 3 days (with a range of 0–24 days) with a high probability of asymptomatic transmission [10].

The severe acute respiratory syndrome (SARS) was considered the first pandemic infection related to coronavirus. It started in China between 2002 and 2003, due to a new SARS-CoV coronavirus. It disseminated to 29 countries in 2003 due to the travel movement throughout the world, affecting 8098 patients with a case-fatality rate of 9.6%, and then SARS disappeared. Nosocomial transmission of SARS-CoV was common. Bats were considered as the primary reservoir, although unproven as the actual source while the intermediary source was considered civet cats in the wet markets in Guangdong [11].

The second coronavirus-related outbreak was the Middle East Respiratory Syndrome (MERS), which was caused by MERS-CoV. MERS appeared in April 2012 and was first identified in humans in the Kingdom of Saudi Arabia (KSA). The contact with camels or camel products is considered to be the cause of human infection. MERS continued to emerge and reemerge. Between 2012 and December 2019, a total of 2465 laboratory-confirmed cases of MERS-CoV infection, including 850 deaths (34.4% mortality), were reported from 27 countries [12].

COVID-19 outbreak brings back memories of the Spanish Flu Pandemic in 1918–1920, which was caused by H1N1 strain of the influenza virus. This pandemic had caused over fifty million deaths worldwide (The mortality rate ranged between 10% and 20%) [13].

The death toll associated with COVID-19 highly surpasses the other two coronaviruses SARS-CoV and MERS-CoV, and the outbreak is still ongoing, which represents a considerable threat to global public health and economies [14].

As for many respiratory viruses, diagnosis relies on two main compartments: clinical manifestations as fever, fatigue, dry cough, dyspnea, and gastrointestinal symptoms, while the paraclinical diagnostic tools vary between the Polymerase chain reaction (PCR) and computed tomography (CT) [15]. Rapid and accurate diagnosis is vital in such a pandemic. From one side, rapidity may enhance management effectiveness and accelerate the application of more suitable isolation measures, leading to less contiguity. While, on the other hand, coupling rapidity with less costly procedures may permit, especially to low-income countries, more examinations to be applied, thus, faster and more effective community-scale management.

In this review, we will shed light on the established diagnostic methods which were applied to help manage the outbreak. Furthermore, we intend to include some under-development techniques that may be potentially useful in this context. The practical intent of our work is to provide a realistic perspective on the diagnosis of COVID-19, through reviewing different biological, radiological, and pathological aspects of this disease diagnosis.

To this end we searched for research articles, reviews, letters and other types of publications when needed. Research included major data bases and search engines, trying to include as much as possible of novel and high value information.

Biological diagnostic tools

Priorities for COVID testing

Most patients with confirmed COVID-19 have developed fever and symptoms of acute lower respiratory tract illness (dry cough, dyspnea).

The rapid global spread of the virus and the limited testing capacity may preclude testing all patients with suspected COVID-19. Therefore, it is crucial to set priorities and criteria for conducting confirmation laboratory tests.

High-priority individuals include hospitalized patients (especially critically ill patients with unexplained respiratory failure), symptomatic health care workers with features of respiratory illness, and symptomatic individuals who have underlying chronic health conditions or risk factors for severe disease [16].

Under-treatment or soon-to-be-treated cancer and autoimmune disorders patients may be at high risk for COVID-19 when receiving chemotherapy or immune- comprising treatments.

This group of high risk individuals may also include patients to-be-transplanted, both of organ and hematopoietic stem cell.

These patients must be screened using PCR before applying aforementioned treatments.

In case of test impossibility they should be put under quarantine for 14 days prior to treatment initiation [17–19].

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At least, patients who meet the testing criteria should undergo testing for SARS-CoV-2.

Economic burden of COVID-19 and PCR diagnosis cost

During such an outbreak, it is likely that preferences for specific activities will change with the outbreak. It seems that these changes will create a global economic burden.

In 2003, the SARS-CoV virus bought the world output down by $50 billion. Initial estimates indicate that the economic impact of the COVID-19 outbreak might be much more significant, maybe around $360 billion [20].

A year of lockdown will take down the globe's economy by approximately 22%, with a cost of $4.2 trillion. Furthermore, the high death toll of this pandemic is considered to be firstly a humanitarian disaster, but also an economic burden, as some estimate the value of the lost lives as 9.5$ million per life [21].

In many low and middle-income countries, COVID-19 test cost exceeds government per head health spending. This may impose restrictions on the applicability of the test to all. For example, in some countries, each test costs around $75, whereas the health per head expenditure is around (34 $) [22].

Even for some high-income European countries, with a testing cost around 135 euros and a limited capacity per laboratory, only the individual suspected to have the infection with specific criteria may be accepted to conduct the test, of where the necessity to find simpler and more affordable diagnostic tools [23].

RT-PCR testing in COVID-19

Due to the high infection rate, rapid and accurate diagnostic methods are urgently needed to identify, isolate and treat patients as soon as possible, which reduces mortality and spread the risk of infection in the population.

Laboratory-confirmed SARS-CoV-2 infection requires the detection of viral nucleic acid in respiratory tract samples by the use of real-time reverse-transcription polymerase chain reaction (rRT-PCR) assay. Whereas clinical/radiological diagnosis is based on symptoms, exposures, and chest imaging [24].

The significance of rRT-PCR assay is demonstrated by the fact that it is currently considered the most determining factor for hospitalization decisions and isolation for individual patients [25].

However, it has not yet been determined whether it can be considered as the gold standard for early diagnosis. But most guidelines, such as NHS guidance for COVID 19 testing, preferred this molecular assay for screening/testing technique [26].

Targets for RT-PCR assay

Highly conserved and abundantly expressed genes are considered as attractive targets of SARSCoV-2 RT-PCR assays, such as, the structural spike (S) and nucleocapsid (N) genes, and the nonstructural RNA-dependent RNA polymerase (RdRp) gene, and the open reading frame ORF1ab which encodes a replicase polyprotein 1ab required for viral RNA replication and transcription [27].

A study conducted by Chu et al. described two RT-PCR assays to detect ORF1b and N regions of the viral genome separately. Results reported that these assays are sensitive and specific to only sarbecoviruses. Furthermore, the N gene RT-PCR assay was found to be more sensitive in detecting 2019-nCoV RNA in different respiratory samples (sputum and throat swab) [28].

It is recommended to use specific primers and probes in the ORF1ab and N gene regions. When both targets test positive, the case would be considered a confirmed infection with COVID-19 [29,30].

The cycle threshold values (Ct-value) of rRT-PCR determine the copy number of SARS-CoV-2 RNA in a specimen. A Ct-value of less than 37 is defined as a positive test, and a Ct-value of 40 or more is defined as a negative test. A medium viral load is defined when Ct-value of 37 to less than 40, and may require confirmation by repeating the test [30].

In a study conducted by Chan et al., three novel RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2 were developed. Then, these assays were compared to each other and to that of the reported RdRp-P2 assay, which is used in many laboratories in Europe.

Among these three novel assays, the COVID -19 -RdRp/Hel assay had the lowest limit of detection and the highest analytical sensitivity at 95% detection probability. Furthermore, the COVID-19 RdRp/Hel assay was significantly more sensitive than the established RdRp-P2 assay for the detection of viral RNA in both respiratory tract specimens (nasopharyngeal aspirate/swab or throat swab) and non-respiratory tract specimens (saliva, and plasma), as it detected viral RNA in 15.4% additional specimens that were tested negative by the RdRp -P2 assay. In contrast, there was no significant difference in the sensitivity of the two assays for sputum and feces/rectal swabs.

Exclusivity testing showed that COVID-19 -RdRp/Hel assay did not cross-react with other human SARS-CoV, whereas the RdRp-P2 assay showed cross-reactivity with SARS-CoV in cell culture. This is because the probes of RdRp/Hel assay were developed to contain 7–9 nucleotide differences with those of human SARS-CoV, whereas the probe of the RdRp-P2 assay contained only three nucleotide differences [31].

The Charité algorithm (Berlin, Germany) uses a two-step assay to confirm COVID-19 infection. The first step is a line-screening assay that detects the envelope (E) gene of subgenus Sarbecovirus. The second step is a confirmatory assay, a SARS-CoV-2 specific RT-PCR assay that targets RdRp. Cross-reactivity with alphacoronaviruses and betacoronaviruses was not detected [32].

Another method established by the University of Hong Kong to detect subgenus Sarbecovirusu uses N-gene screening assay followed by a confirmatory Orf1b assay. Positive patients should be considered as SARS-CoV2 confirmed cases, as none of the sarbecoviruses have been previously detected in humans, and SARS was eliminated in humans as the last reported human SARS case was detected in 2004 [33].

Correlation between disease progression and rRT-PCR results

A retrospective study was conducted by Chen et al., with a total of 249 patients diagnosed with COVID-19. Results showed that the clinical progression of COVID-19 in patients presented two phases. The first phase was represented by fever, cough, fatigue and other systemic symptoms. In the course of this phase, upper respiratory specimens were tested by RT-PCR for viral RNA and the majority of the patients showed positive results for SARS-CoV-2. In the second week of the disease progression, symptoms began to relieve in most of the patients. In parallel, half of the patients showed PCR negative results with their upper respiratory tract samples. The estimated median duration to negative reverse-transcriptase PCR tests of upper respiratory tract samples was 11 days.

A proportion of 2.8% of patients had a story of direct contact with confirmed COVID-19 cases. These patients were asymptomatic, with positive RT-PCR results in their throat-swab samples. In these asymptomatic patients, PCR turned out to be negative two days [1–3] after admission [34].

Specimens

It is strongly thought that involving various specimens from multiple sites could lower false negatives and improve sensitivity. An

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important issue is how and where to collect samples for testing. Actual guidelines (as the current public health England guidance) [35] suggest samples from the upper respiratory tract. The question remains whether there is a significant difference in sensitivity between nasopharyngeal (NP, nasal) or oropharyngeal (OP, throat). Throat swabs may appear to be uncomfortable for patients and could induce coughing, while lingual swabs are more comfortable, and some consider that they can achieve comparable results.

The total positive rate of rRT-PCR for throat swab samples has been reported to be about 30%–60% at initial presentation [25,36].

A cohort study conducted by Ye et al. showed that the positive rate of throat swabs (44.0%) is higher than that of lingual swabs (36.3%) for the detection of COVID-19. This difference was only seen when the samples were taken by a single experienced nurse. These results indicate that standardized sampling by the same nurse could improve the detection rate [37].

Another cohort by Yang et al. examined 205 throat swabs and 490 nasal swabs in 213 hospitalized COVID-19 patients. It was reported positive test rates in favor of the Nasopharyngeal specimen or nasal swabs, in both mild and severe cases, and at different time points of illness onset (day 0–7, 8–15 and >15). Unfortunately, no significance calculation was performed. These results contrast with another German smaller study by Wolfel et al., conducted on 9 COVID-19 patients, with no discernible difference in viral loads or detection rates when comparing nasal and throat swabs [38].

In research conducted by Wang et al., the authors described the testing of COVID-19 in 1070 specimens from 205 infected patients using rRT-PCR. Investigators detected COVID-19 RNA in lung wash (14 of 15 samples; 93%), sputum (72 of 104; 72%), nasal swabs (5 of 8; 63 %), lung biopsy (6 of 13; 46 %), throat swabs (126 of 398; 32 %), feces (44 of 153; 29 %), and blood (3 of 307; 1 %). The 72 urine specimens all tested negative [39].

Notably, this raises concerns about "ruling out" COVID-19 based on combined pharyngeal and nasal swabs obtained at a single time point. Based on these limited available data and its quality, it's not possible to assess the sensitivity of each test and there is no enough data for performing both nasal and throat swabs. On the other hand, it may be recommended, when it's possible, to collect a lower respiratory tract specimen in the form of sputum, which appears to be the highly sensitive of all specimens (as a non-invasive exam) [40]. Sensitivity will also depend on technical issues related to testing performance, delay after illness onset and methods of sampling [39].

In most symptomatic COVID-19 patients, viral RNA may be detected in the nasopharyngeal swab as early as 1 day of symptoms initiation. This positivity starts to decline by week 3 and subsequently becomes undetectable [41], as shown in Fig. 1.

Live coronavirus sheds at high concentrations from the nasal cavity even in asymptomatic infected individuals, thus, it can be detected by PCR before symptoms initiation [42].

Stool sampling

Gastrointestinal symptoms, such as diarrhea, nausea and vomiting have been frequently reported in patients infected with SARS-CoV-2, sometimes alone or alongside other general or respiratory manifestations.

Many studies had confirmed the presence of the live virus in stool samples, thus, stool samples can also be diagnostic. Furthermore, it worth studying whether stool specimen collection may eventually reduce medical staff infections compared to respiratory swabs specimens.

A study conducted by Xiao et al. confirmed the presence of the virus in feces samples. Feces samples were positive for viral RNA and the cycle threshold values were 23.34 for the open reading frame 1lab gene and 20.82 for the nucleoprotein gene [43].

Regarding the collection of samples, it worth mentioning that PCR samples, in general, can be obtained by dacron or polyester flocked swabs and should reach the laboratory as soon as possible after collection [44].

A study conducted by Zhang et al. revealed that 35.7% of confirmed COVID-19 patients had a positive stool sample of viral nucleic acid. It was shown that the accuracy of fecal specimen detection may be equivalent to oropharyngeal swabs results [45].

Another publication by Zhang et al. enrolled three pediatric patients with mild COVID-19 infection. Results suggested the long existence of viruses in feces. All patients recovered soon with negative SARS-CoV-2 nucleic acid in throat swab specimens, while the three remained positive in the fecal specimens within 10 days after recovery and discharge [46].

Chen et al. found that 66.67% of laboratory-confirmed COVID-19 patients were tested positive for SARS-CoV-2 RNA in stool specimens. Furthermore, it was in consistency with Zhang et al. that the positivity of stool samples is not associated with the presence of gastrointestinal symptoms and the severity of illness. A proportion of 64.29% of patients remained positive for viral RNA in the feces after the pharyngeal swabs turned negative. Concerning the duration of viral shedding from the feces, it was found that it is 7 days [6–10] after negative conversion in pharyngeal swabs [47].

The long existence of viral RNA in feces indicate that the fecal-oral route may serve as an alternative infection route, and this suggested that the replication of virus in the gastrointestinal tract may not be consistent with that in the respiratory tract [47–49].

These finding raise concerns about whether patients with negative respiratory swabs are truly virus-free, or sampling of additional body sites is needed. Therefore, it may be important to routinely detect viral RNA in stool specimens of COVID-19 patients during the hospitalization and recovery stage, and to perform transmission-based precautions for patients until the negative conversion of viral RNA in feces. According to reports to date, no patients showed positive results for viral RNA in pharyngeal swabs reversibly after the anal swabs turned negative [47].

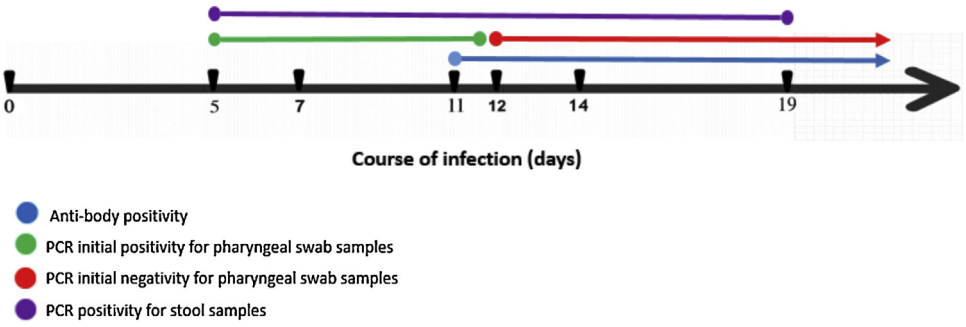

Fig. 1. PCR and antibody positivity in regard to the course of COVID-19 infection.

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Rapid detection and diagnosis of COVID-19

Rapid detection of SARS-CoV-2 is considered to be an urgent priority to contain this pandemic. The rRT-PCR is now used as the standard method to confirm the infection, but it may be considered as a time-consuming procedure. Samples testing must be carried out in central laboratories with advanced equipment. This leads to more time being consumed. Consequently, the time needed to get the results may take from some hours up to 2 or 3 days, depending on the country [20].

Loop-mediated isothermal amplification

Loop-Mediated Isothermal Amplification (LAMP) Assay is an isothermal nucleic acid amplification technique with high specificity, efficiency, and rapidity.

LAMP showed advantages over rRT-PCR, with simplified sample preparation and one single protocol. Hence, results can be obtained in less than an hour. Furthermore, the diagnostic sensitivity of tests based on LAMP-reaction assays was higher (>95%), compared to that in rRT-PCR.

During the Avian influenza pandemic, the LAMP assay showed success in the rapid detection of the H5N1 virus, as this assay was used in a point of care devices [20].

This may suggest that the LAMP assay could be a candidate for the point-of-care device application in the rapid detection of COVID-19.

Serological antibody assay

It is strongly thought that serological testing can be an approach in the surveillance of COVID-19. As it takes 1–2 weeks for positivity after the onset of infection. Serum samples were tested using the enzyme-linked immunosorbent assay (ELISA).

A study conducted by Zhao et al. enrolled a total of 173 confirmed cases of COVID-19 by the use of rRT-PCR on samples from the respiratory track reported that the seroconversion sequentially appeared for the total antibody (Ab), IgM and then IgG, with a median time of 11, 12 and 14 days, respectively. Besides, the presence of antibodies was < 40% among patients in the first week of illness, and then rapidly increased to 100.0%, 94.3% and 79.8%, respectively since day 15 after onset. This may conclude that the total antibody is more sensitive than IgM and IgG for detecting SARS-CoV-2 infection.

In contrast, the positive rate of RNA decreased from 66.7% (58/87) in samples collected before day 7 to 45.5% (25/55) during days 15 to 39. Thus, antibody detection can be an essential supplement to RNA detection during the illness course. Probably, combining RNA and antibody detections may significantly improve the sensitivity of pathogenic diagnosis for COVID-19 patients ($p < 0.001$), even in the early phase of 1-week since onset ($p = 0.007$).

Moreover, results revealed a correlation between clinical severity and antibody titer up from 2- week after illness onset, as higher titer of Ab was independently associated with a worse clinical outcome ($p = 0.006$) [50].

In cases where nucleic acid amplification test (NAAT) assay is negative and there is a strong doubt or epidemiological link to COVID-19 infection (travel to highly infected areas . . . etc.), paired serum samples (acute and convalescent-phase) could support the diagnosis. Cross-reactivity to other coronaviruses can be very challenging, but commercial and noncommercial serological tests are currently under development and evaluation [51].

Rapid Antibodies test (point-of-care test) lateral flow immunoassay

A simple point-of-care device was developed to detect IgM and IgG antibodies against the SARS-CoV-2 virus in blood samples within 15–20 min. This provides the possibility to identify a more significant number of infected patients, mainly, asymptomatic carriers to prevent virus spread.

Depending on clinical studies to validate the clinical efficacy uses, the overall testing sensitivity was 88.66% and specificity was 90.63%. This test is commercially available with 87% accuracy.

Furthermore, the IgM-IgG combined assay showed advantages over a single IgM or IgG test with better utility and sensitivity. It can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories [52].

This antibodies test could also have an impact, since it can be available for the massive population, on the lockdown strategy. So it can be used for massive immune confirmation, especially with asymptomatic or mildly symptomatic patients who no longer represent threats for others in case of seroconversion.

Rapid antigen testing (point-of-care-test): new and potential techniques

Because of the impact attributed to the point of care (POC) devices in terms of management of infections epidemics, several manufactures have made efforts to build devices for POC testing. The samples are ordinarily nasal or throat swab. Many POC devices use molecular testing (rapid PCR testing using nucleic acid fluorescent probes):

1) a cartridge in GeneXpert® machine (Cepheid®), results could be obtained within 45 min (as claimed); 2) a cartridge in m2000® machine (Abbott®): time to obtain results is approximately 13 min (as claimed); 3) a cartridge in vivalytic® machine (Bosch®), time to obtain results is 150 min (as claimed).

While on the Respi-strip® (Coris Bioconcept®) is an immune-based test, using monoclonal antibodies to nucleocapsid protein. This test's results can be obtained within 15 min (as claimed) [53–58].

Procalcitonin changes in COVID-19 patients

Apparently, abnormally high values of procalcitonin (PCT) are associated with a 5-fold higher risk of more severe SARS-CoV-2 infection (OR, 4.76; 95% CI, 2.74–8.29). Furthermore, it seems that serial procalcitonin measurements may play a key role in predicting evolution towards a more severe form of the disease.

A possible explanation is that the production, sustainability and release of procalcitonin from extrathyroidal source is reinforced by (IL)-1β, tumor necrosis factor (TNF)-α and IL-6. At the same time, its synthesis is inhibited by interferon (INF)-γ, which is usually high in viral infection.

As a result, it has not to be surprising that procalcitonin concentration seems to be normal in non-complicated COVID-19 patients, while they tend to climb higher in more severe forms [59].

Development of a flow cytometric approach for COVID-19 diagnosis

In a recent publication SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells responses were measured in COVID-19 cases. Using flow cytometry, among other approaches, SARS-CoV-2-specific $CD4^+$T cell were seen in all COVID-19 cases, and $CD8^+$ T cell responses were seen in most, thus, flow cytometry could present a potential for COVID-19 diagnosis, alongside other potential laboratory indicators like PCT . . . etc.

It is worth noting the pre-existing SARS-CoV-2-crossreactive T cell responses in healthy donors, indicating some potential for pre-existing immunity in the human population [60,61].

Radiological tools in the service of COVID-19 diagnosis

While the rRT-PCR test plays a crucial role in the diagnosis of COVID-19, false-negative results have been recorded in the initial

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diagnosis, which highlights the importance of recruiting additional techniques in the diagnosis and management criteria. The National Health Commission of China has published the 6th version of the diagnosis and treatment program, which recommends the use of radiologic techniques in the diagnosis and management of SARS-CoV-2 infection [25,62].

In a study of Ai et al. results, shown in Table 1, demonstrated the high sensitivity of CT scan as a conventional, rapid and practical diagnostic method in screening and managing critical cases in epidemic areas. Also, 42% of cases eventually improved in follow-up scans before the turning of rRT-PCR results in negative, which recommends the use of a CT scan in the follow-up. However, the study revealed many limitations, including the low specificity due to the false-positive cases with the common imaging characteristics with other viral pneumonia [25].

In a recent retrospective study by Li et al. including 51 patients with COVID-19 and two other patients with adenovirus, all of them were diagnosed by rRT-PCR, a low rate (3,9%) of COVID-19 misdiagnosis was detected (missed cases). However, some CT features on the initial examination overlapped with CT features of SARS and MERS, including consolidation and septal thickening [63]. Another study on 51 patients by Fang et al. revealed 98% sensitivity of CT compared to 71% sensitivity of RT-PCR [64].

The most common CT features, according to multiple reported cases, were bilateral ground-glass opacities, patchy consolidation mainly located along with the bronchial bundle with reactive thickened adjacent pleura and mild bronchiectasis. No lymphadenopathy or pleural effusion was detected in these reports [65–68].

The study by Chung et al. revealed 21% with normal findings, 57% with ground-glass opacity, 29% with ground-glass opacity and consolidation. While 71% had two or more lobes involved, and 76% had bilateral disease [69].

Besides, a comprehensive review by the European Society of Radiology had defined CT features of COVID-19. The most common findings were Ground-Glass Opacity GGO (98%), multifocal patchy consolidation (up to 64%, considered as an indicator for disease progression), reticular pattern or thickened interstitial septa, crazy paving pattern which ends up from acute interstitial inflammatory and alveolar edema, bronchiolectasis which is defined as gelatinous mucous-filled bronchi on a background of the airless lung, pleural thickening, and fewer commonly pleural effusion, subpleural curvilinear lines, fibrosis, small bubble-like air-containing space or the bubble sign. Less common features were small multifocal nodules, Halo sign, which refers to nodules surrounded by ground glass, and atoll sign or reversed Halo sign, which is a focal Ground glass opacity (GGO) surrounded by ring-shaped consolidation [70,71].

Similar findings were described in another study on 99 patients with patchy bilateral GGO in 75% and unilateral involvement in 25% [72].

Furthermore, according to a retrospective study comparing CT features in deceased and recovered patients: air bronchogram and extensive multifocal consolidations were more common in the mortality group, which suggests a worse prognosis for these abnormalities [73].

In one of the retrospective cohort studies including 81 patients from Wuhan, the most common abnormal pattern on CT scan was GGO (65%), mainly involving the right lower lobe, with ill-defined margins (81%), air bronchograms (47%) and interlobular septal thickening (35%). Most of cases demonstrated bilateral involvement (79%), and peripheral distribution (54%) slightly predominating in the right lower lobe.

Less common features were bronchiectasis (11%), cystic changes (10%). Although previous cases didn't demonstrate features of lymphadenopathy or pleural effusion, this study included five patients with lymphadenopathy (6%) and four patients with pleural effusion (5%).

The study revealed that asymptomatic patients could also present with abnormalities on CT scan and that abnormalities showed a rapid increase within two weeks after symptom onset, followed by a gradual decrease in the third week.

These results highly suggested that the clinical course of the disease correlates with radiological evolution. However, these features were not specific for COVID-19, and they also present in pneumonia caused by other viruses and bacteria [74].

In a multi-center recent retrospective study on a total of 424 patients from China and the United States, radiologists compared CT abnormalities between COVID-19 and non-COVID-19 pneumonia.

Their results revealed that non-COVID-19 pneumonia was more likely to manifest with air bronchogram (23% compared to 14% for COVID-19), pleural thickening (33 vs. 15%), pleural effusion (39 vs. 4%), central with peripheral distribution (35 vs. 14%), and lymphadenopathy (10,2 vs. 2,7%). While COVID-19 pneumonia was more likely to manifest with GGO (91% vs 68% for non- COVID-19), fine reticular opacity (56% vs 22%), reverse halo sign (11% vs 1%), vascular thickening (59% vs 22%), and bilateral peripheral distribution (80% vs 57%) [75].

Another study by Dai et al. conducted another comparison of CT manifestations between COVID-19 pneumonia, other viral types of pneumonia and common bacterial pneumonia.

According to their findings, common bacterial pneumonia manifested with multiple consolidations involving lung parenchyma, with bronchial wall thickening and centrilobular nodules.

Table 1
Resuming the findings of some studies on the radiological diagnostic tools for COVID-19.

Author	N*	Type of the study	Radiologic Techniques	Conclusion
Ai et al	1014	Retrospective/comparison	CT	88% vs 59% **Sensitivity compared to RT-PCR**
Li et al	51	Retrospective/comparison	CT	96,1% **Sensitivity compared to RT-PCR**
Fang et al	51	Retrospective/comparison	CT	98% vs 71% **Sensitivity compared to RT-PCR**
Wong et al	64	Retrospective/comparison	CXR	69% VS 91% **Sensitivity compared to RT-PCR**
Chung et al	21	Retrospective/descriptive	CT	GGOs* 57%
Chen et al	99	Retrospective/descriptive	CT	GGOs 75%
Yuan et al	27	Prospective/descriptive	CT	GGOs 67% with lower zone involvement 96%
Shi et al	81	Retrospective/descriptive	CT	GGOs 65%
Bai et al	424	Retrospective/descriptive	CT	GGOs 91% for COVID-19 and 68% for other viral pneumonia
Dai et al	15	Retrospective/descriptive	CT	GGOs 93,3%

N: Number of patients - ●.
GGOs: Ground-Glass Opacities – ●.

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COVID-19 pneumonia was characterized by bilateral GGOs progressing massively during the clinical course, crazy paving pattern, diffuse consolidations and even white-lung appearance in the advanced stage, while other viral pneumonias had high-attenuation reticular patterns, Interstitial inflammation, atelectasis and localized pulmonary edema [76].

However, further studies are required in order to evaluate the accuracy of CT scan and to define its diagnostic role in COVID-19 patients, in complement to clinical and laboratory results.

Comparison of the diagnostic efficacy between CT and rRT-PCR

In such a pandemic, rapid and accurate diagnosis plays a vital role.

Coupling rapid detection with high sensitivity of viral infection may allow better control of viral spread and provides faster and more effective community-scale management.

According to results from recent studies, chest CT abnormalities have been identified in patients prior to the detection of viral RNA from upper respiratory specimens in endemic areas [15,25,64].

In a study of 1014 patients in Wuhan who underwent both rRT-PCR testing and chest CT for evaluation of COVID-19, investigators found that chest CT achieved higher sensitivity for the diagnosis of COVID-19 as compared with initial rRT-PCR from pharyngeal swab samples. Results, showed indicated that 59% of patients had positive rRT-PCR results, and 88% had positive chest CT scans.

In patients with negative rRT-PCR results, 75% (n = 308) had positive chest CT findings. Besides, analysis of serial rRT-PCR assays and CT scans was performed; the mean interval between the initial negative to positive rRT-PCR results was determined to be 5.1 ± 1.5 days, and the initial positive to the subsequent negative rRT-PCR result was 6.9 ± 2.3 days. Using rRT-PCR results as the reference standard, the sensitivity, specificity, and accuracy of chest CT in diagnosing COVID-19 were 97%, 25%, and 68%, respectively [25]. The low specificity may be related to other etiologies causing similar CT findings.

In consistency with the previous study, Fang et al. reported that the sensitivity of chest CT was higher than that of rRT-PCR (98% vs. 71%, respectively) [64].

In addition, a retrospective analysis conducted by Chunqin Long et al. showed that the sensitivity of CT examinations was 97.2% (35/36 patients were positive) at presentation, whereas the sensitivity of initial rRT-PCR was 84.6% (30/36 patients were positive). In the second rRT-PCR round, three patients had a positive result, and the other three were positive in the third round of rRT-PCR [15]. These findings indicate, among others, that rRT-PCR should be repeated to avoid misdiagnosis.

The results of rRT-PCR tests must be cautiously interpreted, as it may be affected by various external factors, including sampling operations, specimens source, sampling timing (different periods of the disease development), and performance of detection kits. A number of factors could lead to a negative result in an infected individual, including poor quality of the specimen, containing insufficient patient material, the specimen was collected late or very early during the infection timeline, the specimen was not handled and shipped appropriately or because of technical reasons inherent in the test (e.g., virus mutation or PCR inhibition). In case of strong clinical or geographical doubt with a negative test, especially from upper respiratory tract sampling, a second test can be conducted, preferably from the lower respiratory tract [51].

The role of chest radiography (CXR)

Although CT has been well-recognized as the first-line radiologic investigation for COVID-19, recent studies by the American College of Radiology suggest using CXR as a first-line tool to decrease the risk of cross-contamination caused by CT suites as well as to minimize the economic burden in radiology departments and increase the availability of its service [77].

In a retrospective cohort study by Wong et al. on 64 patients with COVID-19 infection confirmed by rRT-PCR, CXR had a sensitivity of 69% compared to 91% for rRT-PCR and 97% for CT. The most common findings were bilateral peripheral consolidation with lower zone dominance, which showed its highest peak 10–12 days after symptom onset. Ground glass opacities were less common features. Interestingly, six patients in the study revealed chest x-ray abnormalities before confirming positivity on rRT-PCR. However, due to the low sensitivity of CXR compared to CT, further evidence is needed to support its use in the initial screening [78,79].

Pathological aspects of COVID-19: some essential issues

Few studies have recently revealed pathological characteristics of COVID-19 demonstrating the importance of histological diagnosis. However, to the best of our knowledge, no complete autopsy pathological report has been recorded yet. Xu et al. first autopsied the lung and extra-pulmonary organs of a deceased 50-year-old male who was diagnosed with COVID-19 infection associated with acute respiratory distress syndrome (ARDS). Their findings demonstrated end-stage diffuse injury [80].

Tian et al. reported early-stage changes when studying samples of biopsies from two patients who underwent surgical resection for lung adenocarcinoma while accidentally diagnosed with an early phase COVID-19 pneumonia [81].

Early pathological manifestations included proteinaceous exudate, pulmonary edema, inflammatory clusters with multinucleated giant cells, vascular congestion, reactive epithelial hyperplasia, and suspected viral inclusions while end-stage pathological changes included fibromyxoid exudate, diffuse alveolar damage, and hyaline membrane formation. In addition to the presence of atypical pneumocytes characterized by amphophilic granular cytoplasm, large nuclei and prominent nucleoli with no identified viral inclusions.

Both studies with a literature review of pathological features of Severe Acute Respiratory

Syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19, found that they share multiple pathological characteristics. However, subsequent systematic autopsy might better explain the clinic-pathological features of COVID-19 [80–82].

Recently, an interesting approved animal study was performed on golden Syrian hamsters that were inoculated with SARS-COV2 isolated from a laboratory-COnfirmed COVID-19 patient in Hong Kong. Several tissue organs were dissected and underwent histological examination. Tracheal tissue examination revealed epithelial desquamation with focal cilia loss and mononuclear infiltration, while microscopic examination of the infected lungs revealed the formation of hyaline membranes with mononuclear cell infiltration, large multinucleated syncytial bodies and alveolar lumens filled with cellular debris, hemorrhage. Also, the proliferation marker Ki67 was extensively expressed in bronchiolar cells demonstrating marked cellular proliferation.

Furthermore, multiple extra-pulmonary organ tissues were studied. Reduction in the spleen size was markedly observed with red and white pulp depletion and a decrease in the size and number of follicles. Pale eosinophilic lymph with sinus ectasia was observed in the mesenteric and bronchial lymph nodes. Interestingly, the intestinal mucosa was highly affected; demonstrating increased mononuclear cell infiltration in the lamina propria with massive necrosis in the epithelial cells.

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These pathological changes revealed a possible explanation of the extra-pulmonary symptoms of the disease [83].

Conclusion

The COVID-19 is a relatively new disease; thus, all opportunities must be explored in order to find the most effective mean of diagnosis, prevention and treatment.

These efforts may also benefit from new technologies, including molecular biology and radiology techniques, but maybe also from artificial intelligence medical applications [84].

Rapidity and accessibility may also represent important objectives for new researches.

Meanwhile, strict and well-applied measures of prevention and detection could help enhancing virus detectability [85].

Most importantly, the combination of well-conducted clinical examination with adequate laboratory tests and adapted radiological exams are still the most potent arsenal against this disease.

Declaration of Competing Interest

TA has received honorarium from Biotest France SAS. RS, SI, MS and AA declare no conflict of interests for this manuscript.

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