European Review for Medical and Pharmacological Sciences 2020; 24: 4548-4553

Current practice and potential strategy in diagnosing COVID-19

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Abstract. – OBJECTIVE: To summarize the current practice and potential strategy in diagnosing coronavirus disease 2019 (COVID-19).

MATERIALS AND METHODS: PubMed, Web of Science were systematically searched using terms including "COVID-19", "SARS-CoV-2" and "2019-nCoV". After removing duplicates, we then identified articles, letters and commentaries regarding diagnosing COVID-19.

RESULTS: Here we summarized relatively mature diagnostic methods like nuclear acid test and computed tomography. Besides, new aspects regarding these detection methods like suitable specimens for nuclear acid test, possible use of 18F-FDG PET/CT were also reported. Especially, we also presented several novel techniques for diagnosing COVID-19 like lung ultrasound.

CONCLUSIONS: Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) by National Health Commission is recommended to follow as it provides detailed diagnostic procedures using currently available tools. We suggest clinicians further explore the saliva's utility as a specimen for nuclear acid test and the use of lung ultrasound.

Key Words:
COVID-19, Diagnosis, Nuclear acid test, CT image, IgM-IgG test.

Introduction

In December 2019, a new type of coronavirus broke out in Wuhan and spread rapidly in China. Later, other regions around the world soon reported confirmed cases. In February 2020, the coronavirus study group of the International Committee on Taxonomy of Virus named the virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As of March 16, 2020, the virus has infected more than 80,000 people in China and more than 90,000 in other countries, posing a significant threat to global public health security[1].

SARS-CoV-2 is a single-stranded RNA virus that belongs to the coronavirus β genus, structural proteins of which include S proteins, N proteins, M proteins, and E proteins[2]. Its infecting procedure shares a great similarity with SARS-CoV[2,3]. By binding to the angiotensin-converting enzyme 2 receptor on the outside membrane, the virus gradually fuses into the host cell, causing great damage to its original function.

This novel coronavirus is mainly transmitted by aerosol like respiratory droplets generated during coughing and sneezing by symptomatic patients[4]. Caution is due here since asymptomatic patients in incubation period can also help its transmission. Besides, the median incubation period is 6.4 days, ranging from 2.1 days to 11.1 days[5]. This long period can cause great trouble in containing this widely-spread pandemic. Failing in restraining international transportation resulted in a surge in the number of suspected and confirmed infections globally. To slow down its spread and eventually contain it, accurate, rapid and convenient screening and diagnostic methods are of great significance. Here we summarized current practice and potential strategies in diagnosing COVID-19. This brief review may be of help to clinicians who work in fever clinics or perform screening in public areas.

Diagnosis

Clinical Features

At the early onset of this pandemic disease, a report from Hubei initially summarized clinical characteristics of 138 patients[6]. The authors found that the most common symptoms were fever (98.6%), fatigue (69.6%) and dry cough (59.4%) and that elderly patients were more likely to progress into a severe stage and later be transferred to intensive care units. Recently, Spiteri et al[7]

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reported 20 cases of COVID-2019 in European region, clinical manifestations of which share some similarity with those of patients reported from Wuhan. Fever was also found to be the most common syndrome (n=20; 52.63%), followed by cough (n=14; 36.84%), weakness (n=8; 21.05%) and headache (n=6; 15.79%).

Laboratory Examination

Blood samples of suspected patients were routinely collected when they entered the hospital. Indexes like white blood cell count and concentrations of C-reactive protein were then detected. Lippi et al[8] summarized several abnormal laboratory manifestations in COVID-19 infected people. They recommended some possible indexes for identifying suspected patients like increase in CRP concentration and decrease in both leukocytes and lymphocytes.

Nuclear Acid Test

Real time reverse-transcription poly chain reaction (RT-PCR), the usual detection method for common respiratory virus is also the primary diagnostic means for 2019-nCoV[9,10]. However, current positive rates of this test can vary greatly, depending on types of the specimens and gene fragments used.

Liu et al[11] collected laboratory results of 4,880 cases from Jan 22 to Feb 14 in Renmin Hospital of Wuhan University and found that the positive rate of tests based on nucleocapsid protein sequence was 40.81%. But in Wang et al[12], positive rate of test targeting at open reading form 1ab was reported to be 32.27%. As for different specimens, things were even more complicated. Recently, several researches investigated the biodistribution of COVID-19 in different tissues. It was found that, apart from excretion from respiratory tract, the virus can also be detected in blood[12], tears[13], oral fluids[14] and feces[12,15,16]. However, tests on feces, blood, tears only have positive rates measuring 29% (n=44), 1% (n=3) and 5% (n=1) respectively, which cannot satisfy the needs for accurate diagnosis[12,13]. Fortunately, saliva had a remarkable performance in serving as samples. In a diagnostic study, self-collected saliva of 91.7% of patients generated positive outcomes[14]. Despite the high positive rates, procedures for sampling saliva also involve less exposure chances, further guaranteeing clinicians' safety. However, the limited cases involved restrain its usage in practical settings. Thus, more relevant studies are urgently needed.

One of the limitations of RT-PCR is the time-consuming procedures involved in practical settings. Besides, its accuracy also needs great improvements. To satisfy the growing needs for a rapid and accurate NAT method for COVID-19, several researches were done and some of them generated rather promising outcomes. Pfefferle et al[17] described a new method, *cobas 6800* in detail. This integrated technology performed on a high-throughput platform allows less hands-on time while maintaining fast and reliable results. In another study, Chan et al[18] illustrated three novel real-time RT-PCR methods targeting at the RNA-dependent RNA polymerase, envelope and nucleocapsid genes from SARS-CoV-2. Of notice, this newly developed assay, entitled COVID-2019-RdRp/Hel, had a relatively lower limit of detection. Combined with the fact that saliva contained higher concentration of viral load[14], this technique may significantly reduce the false negative numbers and therefore limit the spread of SARS-CoV-2. Apart from real time RT-PCR, fluorescence quantitative PCR (FQ-PCR) was also proposed[19]. The report declared their experience of applying high-throughput sequencing to further the inconclusive result generated by the FQ-PCR.

Imaging Features

Computed Tomography

Though NAT is considered as the gold standard for COVID-19, abundant false positive cases indicate that another complimentary tool is needed. Computed tomography (CT) then acts as such tool[20,21]. This method was basically available in all sorts of medical institutions and can generate outcomes rapidly. Bilateral ground glass opacity was discovered in 98% of the suspected cases in one study[22]. A more detailed article reporting imaging features of different disease stages was available recently[23]. Patchy ground glass opacities in the peripheral areas with partial consolidation in the center were found in most of the common patients. Larger areas of opacities and consolidations can be discovered in severe patients. Of note, while one lesion can be absorbed under correct medical care, another novel lesion may soon appear in another area. This phenomenon may inform us of the necessity of repeated CT scanning for closely evaluating disease progression.

To evaluate its accuracy in identifying patients with COVID-19 from suspected groups, a report of 1,014 cases analyzed the correlation of chest CT and NAT[24]. Researchers discovered that the positive rate of CT test was much higher than that of RT-PCR. Attention is needed when clinicians interpret the results. 52% of 308 patients with negative RT-PCR but positive CT results were not considered as confirmed cases at last. That is to say, CT test is more likely to generate false positive outcomes, which may result in waste of medical resources. Worse still, the error can hardly be estimated as suspected patients with positive CT images may eventually be affected in hospitals full of genuine patients. Li et al[20] specially demonstrated its defect in differentiating COVID-19 from other viruses, partially explaining the high false positive rate. Besides, the accuracy of CT test depends greatly on the radiologist. In the research by Ai et al[24], we may notice that an expert with 12 years of experience was involved in the interpretation.

Lung Ultrasound

Apart from CT, lung ultrasound (US) was also recommended recently[25]. It was once reported to be superior to standard CT for evaluation of pneumonia or respiratory distress syndrome[26]. Peng et al[27] performed lung US on 20 patients and summarized five main clinical findings, including thickening of the irregular pleural line. Besides, a strong connection between ultrasonography findings and the disease stages was also reported. This indicates its great use in dynamically monitoring COVID-19 progression. *Chinese Critical Ultrasound Study Group* published *Critical-Ultrasound-based Recommendations on Severe COVID-19* recently, in which lung US findings and relevant managements were described in detail[28].

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT is a technology that can reflect changes in metabolic and functional states in patients while observing pathogenic structures of lesion sites. Qin et al[29] reported clinical findings gained by ^{18}F-FDG PET/CT. Ground-glass opacities showed a high tracer uptake of ^{18}F-FDG. Besides, the image firstly suggested that COVID-19 may cause lymphadenitis. However, a letter against its use for diagnosis was published[30]. One reason is the complex procedure needed would be unpractical in most clinical settings, and the other reason is the risk of disease spreading due to the long period it takes.

Immunological Examinations

When combined together, detection methods mentioned above are of help in identifying infected patients in clinical settings. Nevertheless, containing COVID-19 demands detection methods with large scale screening and field detection ability, neither of which is satisfied by etiological detection or medical imaging technology.

Fortunately, a qualified method was successfully developed[31]. This novel technique uses lateral flow immunoassay to detect IgM and IgG antibodies against COVID-19 in human blood samples simultaneously. Apart from the short period, both sensitivity and specificity are also remarkably high. It may suggest its potential use as a diagnostic tool for rapid screening in public area like airport, station, etc. Of notice, this technique can only tell whether the subject is infected recently instead of the current conditions.

Prospects

The paragraph above illustrated the results obtained from different specimens. Current samples used in clinical settings are mainly nasal or pharyngeal swabs, which usually generate positive rates only measuring 40% or so[11]. However, we may notice a study discovering that saliva showed a remarkable performance in RT-PCR tests[14]. We therefore recommend researchers to focus on this utility and further explore the accuracy of NAT detecting this specimen.

Notably, though blood and tears did not seem to be of interest during diagnostic procedures, they were reported to have a strong relationship with specific clinical manifestations. Chen et al[32] reported a group of 58 cases. Patients with detectable viral RNA in blood all gradually developed to a severe stage. The only sample of tear that yielded positive results was collected from a patient with conjunctivitis[13]. Nevertheless, inherent defects in both studies resulted in these unconvincing statements. More researches are still needed for further illustrations.

Besides, lung US also seemed to be a promising technology available in most clinical settings with ability to provide rapid outcomes[25]. Of notice, this technique was also reported to

have several limits[27]. For example, it can not detect pathological changes that are deep in the lung and therefore CT would still be of necessity. ^{18}F-FDG PET/CT proposed by Qin et al[29] may not be available in clinical use due to its inherent defects. However, as it can reveal abnormal metabolic and functional manifestations of COVID-19, it may serve as an investigation tool for the time being.

As for the immunological test described, we believe that it can be of great help in countries with urgent needs for rapid screening to contain the spread of COVID-19. Of note again, IgM-IgG test is not able to test the current health condition of patients, it can only inform us whether the patient was infected recently[31]. Thus, it should only be used in field detection to identify suspected or confirmed patients and may not serve as an indicator in discharge criteria.

We here recommend the *Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment* (7th edition) published by National Health Commission, in which diagnosis procedures were given in great detail[21]. Briefly, the procedures can be divided into two separate parts. To determine whether one is a suspected patient, epidemiological history or clinical symptoms are needed. Exposure history involves any form of body contact with confirmed cases within 14 days and clinical features include symptoms like fever, CT images with signs mentioned above and laboratory examination showing decrease in both leukocytes and lymphocytes. One with exposure history can be considered as a suspected patient if any two of the clinical features show up, but only when an exposure-free patient represents all three clinical features can he be suspected. Later, samples from a suspected patient will run NAT and serology test. When any of NAT and IgM-IgG test generates positive result, he or she will be confirmed and receive further treatments.

Lately, America, Australia, Iran and Italy all reported a tremendous increase in confirmed cases recently, among which Italy is now the most serious region attacked by SARS-CoV-2[1]. There was a growing concern that COVID-19 will rapidly spread the European continent among the public, which caused great panic and influenced the economic hugely[33]. Timely and firm measures shall be taken to contain the COVID-19 before it causes more damaging results. To achieve this goal, timely diagnosis is of great significance. We hope this review will help those who are fighting at the frontline and the containment of this pandemic.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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