COVID-19 revolution: a new challenge for the internist

Diagnostic dilemmas in COVID-19 patient

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ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, *etc.*. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with the diagnosis of COVID-19.

The coronavirus infection disease 2019 (COVID-19) pandemic is a global health emergency of our time. To date, the virus has spread to every continent except Antarctica. The diagnosis of COVID-19 is mainly based on typical symptoms; normal or reduced peripheral white blood cell count, or reduced lymphocyte count; bilateral involvement on chest radiographs; exposure to infected patients, and confirmed by positive nucleic acid test of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from numerous types of specimens. The common symptoms of COVID-19 are fever, cough, myalgia or fatigue, expectoration, dyspnea. In addition, a part of patients reports anosmia and ageusia, headache or dizziness, and in a lower percentage of cases, gastrointestinal symptoms with diarrhea, nausea, and vomiting. Severe complications include pneumonia, acute respiratory distress syndrome, acute cardiac injury, shock, and multi-organ failure. A systematic review of the literature on the clinical features of COVID-19 showed the onset of dyspnea 6 days after the appearance of flu-like symptoms.[1,2]

The definite diagnosis of coronavirus disease 2019 (COVID-19) is based on the positive result of virological testing as the virus isolation and the polymerase chain reaction (PCR) from the nasopharyngeal and oropharyngeal swab. The probability of false-negative results on real-time-PCR (RT-PCR) using samples from the upper respiratory tract is 100% on the day of exposure, decreasing to 38% when symptoms begin roughly 4 days later and then to 20% at 3 days after symptoms start.[3]

The result of the swab can largely be influenced by variables such as the accuracy of the sampling method and the adequate amount of the rhino-pharyngeal secretion in the sample.

Early detection of COVID is essential for treatment and management, and it is especially true for severe patients.

Some cases of COVID-19 pneumonia with initially negative oropharyngeal and nasopharyngeal swabs (also 5) have been diagnosed later by other types of specimens, including bronchoalveolar lavage fluid (BALF), anal, stool, and urine swabs.[3-5]

On the contrary, antibody testing is not useful in the setting of an acute disease. The immunoglobulin (Ig) M antibody and IgG antibody against SARS-CoV-2 in plasma samples were tested using a qualitative *lateral flow immunoassay* (*LFIA*) test or quantitative ELISA and chemiluminescence immunoassay. IgM appears between the 5th and 10th day after the onset of symptoms and the IgG between the 12th and 14th day after the onset of symptoms. These tests can give false-positive and false-negative results. The reasons for the false-negative LFIA test may be due, in the first place, to too low concentrations of antibodies. When the IgM and IgG levels are below the detection limit (not yet determined) of this rapid test, the test result is negative. Another cause of a false-negative qualitative or quantitative test may be the difference in individual immune response and antibody titer. The absence of detection of antibodies (not yet present in an individual's blood due to the delay that physiologically connotes a humoral response compared to viral infection) through qualitative and quantitative serological tests does not exclude the possibility of an infection in progress early or asymptomatic and relative risk of contagiousness of the individual. In the studies carried out, the SARS-CoV-2-positive plasma did not show any cross-reactivity with other coronaviruses except for SARS-CoV.[6-9]

However, a combination of antibody tests and RT-PCR could be beneficial for the diagnosis of COVID-19 in patients with late symptoms compared to the time of infection due to the late appearance of the antibodies. A study by Guo et al. conducted on antibody titer in confirmed and probable cases showed a significantly increased identification rate of positive cases (98.6%) by combining the IgM ELISA with RT-PCR for each patient compared to the single RT-PCR test (51.9%).[8] In patients with gastroenteric symptoms, fecal samples should be tested to exclude a potential alternative route of transmission.[10]

A multicenter observational cohort study conducted in 25 hospitals in Shanghai revealed upon multivariate analysis that the main independent risk factors for early identification of COVID-19 patients were the history of epidemiological exposure, fatigue, blood cell count, whites less than 4×10^9 for L, lymphocyte count less than 0.8×10^9 for L, the opacity of ground glass and bilateral lung disease at computed tomography (CT).[11]

Since the beginning of the 2020 pandemic, a high prevalence of low lymphocyte and eosinophil count has been noticed in COVID-19 patients. In different cohorts of patients, lymphopenia has been documented in 31-83% and eosinopenia in 53-86% of cases.[12-17] The association of lymphopenia with fever or respiratory symptoms and CT findings typical of COVID-19, or the association of decreased lymphocyte count (while the total white blood count is normal or decreased) with just one of the other two criteria in a patient with substantial epidemiological risk factors, have been proposed as indications for managing and eventually treating the patient as if he/she was positive for a real-time PCR test.[18] Regarding eosinopenia, a retrospective study that examined symptomatic patients who visited a clinic in Wuhan found a sensitivity of 74.7% and a specificity of 68.7% for COVID-19 diagnosis, while the combination of low eosinophil count and elevated high sensitivity C-reactive protein yielded a sensitivity of 67.9% and specificity of 78.2%.[12] However, attention is warranted because lymphopenia is highly prevalent in some populations, such as elderly patients admitted to a medical ward for any reason,[19] potentially lowering the specificity of this laboratory finding. Lymphopenia is associated with malnutrition,[20] aging,[21] bacterial infection, trauma, steroid use.[22] Other white blood cells, such as eosinophils, are highly variable in their quantity even in healthy populations, thus limiting their diagnostic role. One study carried out on a small number of pneumonia patients in China during the COVID-19 pandemic found no significant difference between COVID-19 pneumonia and other kinds of pneumonia regarding lymphocyte count; however, alanine aminotransferase (ALT), aspartate aminotransferase (AST), g-glutamyltransferase, and lactate dehydrogenase (LDH) elevation was more frequent in COVID-19 patients.[23] Another study carried out on a larger number of patients admitted to an emergency room in Northern Italy found significant differences in differential white blood cell count, AST, ALT, and LDH between those who were positive for a real-time PCR test and those who were not. The study calculated an empirical threshold for AST and ALT that allowed the identification of 70% of either COVID-19-positive or -negative patients.[24]

Bedside thoracic ultrasound (US) can be used for the early diagnosis and follow-up of patients with suspected or confirmed COVID-19 infection. US showed various B lines patterns (focal, multifocal, and confluent), subpleural consolidation, a thickened pleural line, and translobar consolidation with occasional air bronchograms. Pleural effusion is uncommon in COVID. Lung ultrasound is highly sensitive in detecting multiple lung pathologies, it allows monitoring of patients admitted to the 24-hour Intensive Care Unit and early

diagnosis of pneumothorax and lung thickenings from new-onset bacterial superinfection by adjusting therapy in real time.[25]

In a retrospective study conducted in China on a sample of patients with a confirmed molecular diagnosis of COVID-19 undergoing simultaneous US and chest CT from independent operators, USs were more sensitive than chest CTs in the diagnosis of a regional alveolar interstitial model (60% *vs* 38.5%), alveolar-interstitial syndrome (93.3% *vs* 68%), consolidation (38.9% *vs* 3%,) and pulmonary embolism (74.4% *vs* 15.6%).[26]

Chest CT images could play a vital role in detecting the lesions in the pulmonary parenchyma in patients that are suspected of COVID-19 infection and negative initial RT-PCR.

While traditional chest radiographs have very limited sensitivity in the early stages of the disease,[27] the first imaging manifestation visible in CT scan may appear before developing symptoms.[28]

The typical CT findings of COVID-19 are multiple sub-segmental or segmental ground-glass density shadows in both lungs, caused by honeycomb-like thickening of interlobular septa; the thinner the CT scan layers, the greater sensitivity is achieved in revealing these alterations. Less typical alterations found in CT scans are multiple, patchy consolidations of the lung or multiple consolidated nodes surrounded by ground-glass opacities. Classifying CT findings by correlating with disease progression, a staging system has been proposed, whose ultra-early stage (characterized by single, double, or scattered opacities) predates clinical manifestations.[28]

A retrospective study carried out on 87 patients with fever and suspected COVID-19 infection who were subjected to both PCR and chest CT found that in 36 patients that eventually resulted positive to the PCR test at the second or third round of investigation, 35 had CT findings, and only 30 were identified by PCR, at presentation, documenting a sensitivity of 97.2% for CT scan (*vs* 84.6% sensitivity in the first round of PCR testing). Among COVID-19 patients, 69.4% had multiple lesions and 30.6% a single lesion; peripheral distribution was significantly more common in COVID-19 patients (P=0.025) while consolidations (as opposed to ground-glass opacities) were more common (P=0.001) in the non-COVID-19 group.[29]

Not all studies have directed their attention on the same level of sensitivity. A systematic review of the literature[30] found that sensitivity ranged from 61% to 99% in 16 different studies, with the studies carried out in Wuhan, at the epicenter of the pandemic in China, having the greatest sensitivity (possibly because of the experience acquired by involved radiologists). Only two studies allowed reported specificity of the test, and it was low in both (25-33%); only three studies reported the number of cases in which PCR test was initially false negative; after combining them in 31 out of 36 cases, chest CT at presentation was positive. Besides, the methodology of studies that found high sensitivity for CT scan in COVID-19 has been questioned.[31]

In order to improve the diagnostic performance of CT scan, a scoring system was proposed following a study on 91 patients with suspected COVID-19, which distinguishes radiological features that are suggestive of COVID-19 from findings that are more common in different lung diseases (Table 1).[32]

According to the study, the cutoff values yielded a sensitivity of 56.67% and a specificity of 95.35% for a score > 4, a sensitivity of 100% and a specificity of 23.26% for a score > 0, and a sensitivity of 86.67% and a specificity of 67.44% for a score > 2.

In conclusion:

- The definite diagnosis of COVID-19 is based on the viral isolation or positive result of RT-PCR from oropharyngeal and nasopharyngeal swabs.
- The combination of antibody tests and RT-PCR could be very useful for diagnosing COVID-19 with late symptoms.
- When the RT-PCR test for swab was negative at an early stage, the chest images play an important role in diagnosis even in patients with mild symptoms. Based on clinical manifestations, laboratory findings, and chest CT images, the diagnosis of COVID-19 pneumonia can be made. The necessity of further microbiological examinations of a PCR-negative patient (*i.e.*, on lower respiratory tract) must be evaluated in each case according to the level of specificity of CT findings as rated by experienced radiologists and/or clinicians.

Table 1. Chest CT image features and Scores from Luo *et al.*[32]

Positive +1
Posterior part/lower lobe predilection
Bilateral involvement
Rounded ground-glass opacities
Subpleural bandlike ground-glass opacities
Crazy-paving pattern
Peripheral distribution
Ground-glass opacities +/– consolidation

Negative –1
Only one lobe involvement
Central distribution/peribronchovascular
Tree-in-bud sign
Bronchial wall thickening

Score 1, positive significant COVID-19 image features; Score –1, non-COVID-19 with viral pneumonia or community-acquired pneumonia of unknown cause image features.

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