Diagnosing COVID-19: "Did We Miss Anything?"

Moses M. Asaf[1], Eric D. Tenda[1,2]

[1] Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] National Heart and Lung Institute, Imperial College London, United Kingdom.

Corresponding Author:
Eric Daniel Tenda, MD. National Heart and Lung Institute, Imperial College London. South Kensington Campus, London, Greater London SW7 2AZ, United Kingdom.
email: ericdanieltenda@yahoo.com.

In late 2019, a mass of patients showing symptoms of a pneumonia-like disease of unknown origin emerged in Wuhan, China. Little did the world know it was the prelude of what would be a devastating pandemic. Samples were collected from these patients and the use of unbiased sequencing and subsequent isolation of the pathogen using human airway epithelial cells led to the discovery of a novel coronavirus, named 2019-nCoV by the World Health Organization (WHO) and Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses.[1,2] The disease caused by this virus is officially called the coronavirus disease 2019 (COVID-19).

Coronaviruses are enveloped RNA viruses that are spherical in shape with bulbous surface projections.[1,3] Currently, there are six known species of coronavirus that can cause various systemic diseases in humans.[1] Two of the six species of coronaviruses – Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – originated from animals and have caused outbreaks in the past with relatively high mortality rates.[4] SARS-CoV and MERS-CoV have been shown to possess the potential to cause severe and potentially fatal respiratory tract infections.[5]

SARS-CoV-2 is a highly transmissible beta-coronavirus that could infect humans by binding into the angiotensin-converting enzyme 2 (ACE2) receptor, the same receptor as SARS-CoV.[5] The genome sequence of SARS-CoV-2 has been found to share 79.5% identity to SARS-CoV and is 96.2% identical to a strain of bat CoV, raising the suspicion that bats may be the natural host and reservoir of SARS-CoV-2.[5] Pangolin is the most likely intermediate host of SARS-CoV-2 between bats and humans, based on preliminary data.[2]

From the discovery of SARS-CoV-2 in late 2019 until January 24, 2020, there had been 830 confirmed cases of COVID-19 in nine countries with 26 fatalities.[6] Since then, the virus has been spreading aggressively on a global scale, and the number of cases has grown exponentially. By March 12, 2020, 116 countries had been affected, and 118,000 confirmed cases had been reported.[7] In March 28, 2020, the Johns Hopkins Coronavirus Research Center database had confirmed a total of 615,519 cases of COVID-19 in 177 countries with 28,717 fatalities.

COVID-19 primarily manifests as an acute respiratory infectious disease, as shown by the clinical findings several recent studies have found. Generally, the most common symptoms found in COVID-19 patients include fever, dry cough, fatigue, expectoration, and malaise, with gastrointestinal symptoms such as diarrhea occurring infrequently or sporadically throughout the illness.[8-10] Though not yet well-documented, Li et al.[11] have suggested that ocular manifestations such as unilateral or bilateral conjunctivitis are still a possibility in COVID-19,

based on a previous report in Wuhan, where a healthcare worker donning full protective gear except goggles was infected, with unilateral conjunctivitis preceding the onset of illness. The spectrum of disease severity in COVID-19 varies from asymptomatic, mild, moderate, to severe and critical. In severe cases, COVID-19 patients could develop acute respiratory distress syndrome (ARDS), respiratory failure, sepsis, multiple organ failure, and death.[5,10] ARDS commonly develops on day 8 to 12 from the onset of illness.[9,10]

Recent studies have reported that white blood cell (WBC) count tends to be normal in most patients, though some experience a minor decrease in WBC.[5,10] Decreased total lymphocyte or lymphocytopenia is a common occurrence.[8,9] Increased coagulation activity marked by elevated d-dimer concentrations were also common, but significant elevation of greater than 1 mcg/ml is associated with poor prognosis.[8,10,12] Generally, marked alteration of coagulation parameters increase the risk of disseminated intravascular coagulation (DIC) and could subsequently lead to a poor patient outcome that results in death. Procalcitonin is an inflammatory marker that is not usually substantially increased in COVID-19 patients, and a gradual increase in concentration could indicate a bacterial superinfection or a superimposed bacterial infection.[13] However, another inflammatory marker, C-reactive protein (CRP), has generally been shown to increase and is directly proportional to disease severity and poor prognosis.[14,15] Other laboratory predictors of poor outcome include a higher sequential organ failure assessment (SOFA) score, which encompasses the respiratory (PaO2/FIO2), coagulation (platelets), cardiovascular (mean arterial pressure), hepatic (bilirubin), neurological (Glasgow comma scale), and renal (creatinine) systems, increased lactate dehydrogenase, and increased cardiac troponin.[10,13]

As of March 2, 2020, the WHO's interim guidance on laboratory testing for COVID-19 still recommends the use of nucleic acid amplification tests (NAAT), such as reverse-transcriptase polymerase chain reaction (RT-PCR), to screen suspect cases.[16] The specimens recommended to be collected are upper respiratory materials (nasopharyngeal and oropharyngeal swab) and/or lower respiratory materials (sputum/ endotracheal aspirate/bronchoalveolar lavage).[16] However, recent radiological studies concerning the remarkable sensitivity of chest computed tomography (CT) scan in diagnosing COVID-19 patients raises the question on whether or not chest CT should be a staple modality in diagnosing COVID-19.[17,18] Studies by Fang et al.[17] and Ai et al.[18] have found the sensitivity of chest CT in diagnosing COVID-19 to be 98% and 97% respectively. Subsequently, a subgroup of patients in the study of Ai et al.[18] showed positive chest CT scans prior or within 6 days of the initial positive RT-PCR results. Chest CT has even been shown to be a reliable screening tool in asymptomatic patients, as shown by the study of Shi et al.[19], substantiating the suggestion that asymptomatic patients could develop abnormalities in chest CT prior to the onset of symptoms. Patients with NCP generally show signs of bilateral subpleural ground-glass opacity, consolidation, and sometimes accompanied by the thickening of the interlobular septum often called a "crazy paving stone-like" pattern.[19,20] Several other studies also support the notion of using chest CT as a screening tool in subjects with negative RT-PCR results suspected with COVID-19 infection based on their exposure history and/or clinical symptoms.[17,18] RT-PCR is still a reliable diagnostic tool, although there are some factors that may compromise the efficiency. Those factors include improper sampling technique, varying detection rate due to different manufacturers, low viral load, and imperfect development of nucleic acid detection technology.[17] Overall, in the context of a rapidly needed emergency disease control like COVID-19, physicians should adjust and utilize their arsenal of diagnostic tools to find the balance between swiftness and accuracy, and chest CT might help to find that balance.

Another radiological modality as a possible screening or diagnostic tool for COVID-19 is the lung ultrasound (LUS). In LUS, COVID-19 is characterized by a patchy distribution of subpleural consolidation with associated areas of white lung.[21] LUS may be useful in healthcare facilities that may not have sophisticated

radiological or laboratory equipment necessary to diagnose COVID-19, as ultrasound devices are commonly more readily available than CT and RT-PCR test kits, especially in primary and secondary healthcare facilities. LUS may be useful in the emergency room setting and in monitoring disease progression in ICU patients using a ventilator, as the mobility of these patients are usually very limited and performing radiological examinations such as CT scan would be extremely difficult. LUS is also safer in terms of radiation exposure compared to CT and should be considered as a viable option in children suspected with COVID-19. Nonetheless, it should be noted that LUS is heavily dependent on a skilled operator, and different operators might have different interpretations based on their subjectivity. LUS operators should also be equipped with proper personal protective equipment (PPE) as they are in close proximity with suspected patients while conducting examinations.

Recently, the United States (US) Food and Drug Administration (FDA) has given an emergency use authorization (EUA) to Abbott Laboratories for the use of their product called the Abbott ID NOW COVID-19 test that runs on Abbott's ID NOW™ platform. This lightweight and portable assay device is claimed to be "fastest available molecular point-of-care test for novel coronavirus", and can deliver positive results in a mere five minutes and negative results in 13 minutes by targeting the RdRP Gene of the virus. If this claim is substantiated and could perform with high sensitivity and specificity, this product could significantly help healthcare workers in diagnosing COVID-19, which subsequently would enhance response time for management and isolation, and overall help lessens the spread of COVID-19. Abbott Laboratories is expected to produce around 5 million tests in April, and deliver another 50,000 tests per day. If successful, the use of this rapid immunoassay test in the US could serve as a precedent for screening programs in other countries, including Indonesia.

Given these are what we currently comprehend about COVID-19, it is imperative for each physician on the frontlines to equip themselves with the latest diagnostic proficiency in order to tackle this challenge in an efficient manner. As different physicians in different healthcare facilities face different circumstances, the use of adaptive and structured diagnostic method is essential in identifying the most appropriate management strategy, preventing poor prognosis and outcome, and overall help reduces the spread of COVID-19.

Another issue worth addressing that could supplement efficient diagnosis in facing this challenge includes infrastructural improvements such as the establishment of an accessible real-time and transparent ICU information network between healthcare facilities where laboratory and radiological results could be accessed securely, and the establishment of adequate numbers of contemporary laboratories that could efficiently run RT-PCR tests in a designated region. Qualified healthcare workers should also be distributed evenly with sustainable working hours and sufficient equipment to ensure patient safety and their well-being. Understandably, addressing these issues will require sophisticated planning and execution will not be straightforward, but problem identification is always the first step in resolving any challenge.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from patients with pneumonia in china, 2019. N Engl J Med. 2020;382(8):727-33.
2. Del Rio C, Malani PN. COVID-19-new insights on a rapidly changing epidemic. JAMA. 2020.
3. Goldsmith CS, Tatti KM, Ksiazek TG, et al. Ultrastructural characterization of SARS coronavirus. Emerg Infect Dis. 2004;10(2):320.
4. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-92.
5. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11.
6. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel Coronavirus emerging in China — Key questions for impact assessment. New Engl J Med. 2020;382(8):692-4.
7. Hoseinpour Dehkordi A, Alizadeh M, Derakhshan P, Babazadeh P, Jahandideh A. Understanding epidemic data and statistics: A case study of COVID-19. arXiv. 2020:arXiv: 2003.06933.
8. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med.

2020.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
11. Li J-PO, Lam DSC, Chen Y, Ting DSW. Novel coronavirus disease 2019 (COVID-19): the importance of recognising possible early ocular manifestation and using protective eyewear. BMJ Publishing Group Ltd; 2020.
12. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–7.
13. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020.
14. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
15. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;00:1–12.
16. Organization WH. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. World Health Organization; 2020.
17. Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. 2020:200432.
18. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020:200642.
19. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425-34.
20. Zhao X, Liu B, Yu Y, et al. The characteristics and clinical value of chest CT images of novel coronavirus pneumonia. Clin Radiol. 2020;75(5):335-40.
21. Soldati G, Smargiassi A, Inchingolo R, et al. Is there a role for lung ultrasound during the COVID-19 pandemic? J Ultrasound Med. 2020.