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COMMENTARY

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Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak

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In December 2019 2019, a cluster of acute respiratory illness occurred in Wuhan, Hubei Province, China. This disease is now officially known as 2019 novel coronavirus disease (COVID-19) from World Health Organization, novel coronavirus pneumonia from Chinese Health Authorities, or SARS 2.0 from group discussions, caused by SARS-CoV-2 or 2019 nCoV.[1] Up to 15 February 2020, 66 581 cases have been confirmed along with 8969 suspected cases in the country and 37 914 confirmed cases in Wuhan. Internationally, cases have been reported in 24 countries and 5 continents. On 12 February, a sudden spike in new cases with COVID-19 (15 152 new cases) was due to changed diagnosis method according to the fifth edition of guidance,[2] combination of SARS-CoV-2 nucleic acid test and clinical COVID-19 features.

Quantitative real-time reverse transcriptase-polymerase chain reaction (RT-qPCR) assay has routinely been used for the detection of causative viruses from respiratory secretions and final pathogenic diagnostics of COVID-19. More than seven types of SARS-CoV-2 nucleic acid test kit have been developed and approved rapidly, while a large number of the "suspected" cases with typical clinical COVID-19 features and identical specific computed tomography (CT) images were not diagnosed. Unfortunately, due to an overwhelming situation in local hospitals, many "suspected" cases and diagnosed cases cannot efficiently be separated or treated. Recently, one patient was not confirmed by RT-qPCR testing for SARS-CoV-2 infection for the first three times within 3 weeks before bronchoalveolar lavage fluid (BALF) was acquired, results from both RT-qPCR and next-generation sequencing (NGS) testing were positive for SRAS-CoV-2. These largely affected efficiency to control viral spreading and outbreak. Indeed, several factors have been proposed to explain the inconsistency or the high false-negative rate (FNR).[3] For example, results from RT-qPCR testing using primers in the ORF1ab gene and N genes can be affected by the variation of viral RNA sequences. In terms of the natural history of the disease and viral load in different anatomic sites of the patients, sampling procedures largely contribute to high FNR. By estimate, FNR from one-time testing was as high as 30% to 50% in real COVID-19 cases.

It is urgent to rapidly optimize the quality of testing kit and standard operating procedure for the best testing of SARS-CoV-2 infection. Based on the sequence analysis of SARS-CoV-2 and ACE2 as a viral receptor, we urgently recommend that samples from the lower respiratory tract of the patients, including sputum and BALF, should be used for testing viral infection although nasopharyngeal swab is more commonly used and easier. Other factors or methods we should consider to further decrease high FNR include sample reagents (for example, TRIzol has been proved for the stability of RNA samples and can inactivate viruses), sample transport condition, and laboratory practice standard. Lastly, developing serum-based testing methods, for example, detection of SARS-CoV-2-specific immunoglobulin M from patients' sera.

Unlike SARS-CoV and MERS-CoV, SARS-CoV-2 is spreading faster, initially, COVID-19 may present without symptoms, or develop into fever, coughing, shortness of breath, pain in the muscles, and tiredness. As the SARS outbreak in 2003, some cases with COVID-19 may also develop into pneumonia and acute

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respiratory distress syndrome, which contributed about 9% of death from the patients with severe conditions. Previous studies have tested sensitivity and specificity for clinical diagnosis of severe acute respiratory syndrome (SARS).[3,4] The study showed a sensitivity of 0.96 and a specificity of 0.96 for SARS clinical diagnosis based on the SARS disease course.[3] In the fifth edition of diagnosis and treatment of COVID-19,[5] clinical diagnosis was proposed for the first time. This method has been used to define cases in Hubei province which have epidemiology history, clinical features (fever and/or respiratory symptoms, early onset of normal/decreased white blood cell count or decreased lymphocyte count) along with sign of pneumonia on chest CT scan/X-ray. As described in a latest preprint article with a large number of cases (1099 cases) with COVID-19, the most common clinical and radiographic features were summarized from a large number of cases with COVID-19.[6] Fever and cough were the most common symptoms, lymphopenia was very common on admission, severe cases appeared to have more prominent laboratory abnormalities. The most common patterns (76.4%) on chest CT were ground-glass opacity and bilateral patchy shadowing. The study also disclosed a case with a 24-day incubation period for the first time, which was claimed as a unique case by one of the coauthor.[6] These CT patterns have been found in many "suspected" cases with negative testing of SARS-CoV-2 viral RNA in hospitals in Wuhan, China.

As we learn more about SARS-CoV-2 and COVID-19, we began to realize the deficiency in the diagnosis based on sole detection of viral nucleic acid, diagnosis with a combination of RT-qPCR or NGS testing and clinical criteria may be more important for the management of the current outbreak in China, especially in Wuhan. Since the Chinese government launched an urgent policy for all diagnosed patients with COVID-19, there is no cost for all treatments from the COVID-19. This change would significantly facilitate sufficient management of the SARS-CoV-2 outbreak in Wuhan, especially increase patient compliance for quarantine and treatments.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

YW and HK contributed equally to this study. Conception or design of the work: YW, HK, and ZT; data collection: YW and HK; drafting the article: YW and HK; critical revision of the article: ZT and XL; final approval: YW, HK, XL, and ZT.

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REFERENCES

1. Gorbalenya AE, Baker SC, Baric RS, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses—a statement of the Coronavirus Study Group. https://doi.org/10.1101/2020.02.07.937862
2. Xi M, Wei Q, Qihua F, et al. Understanding the influence factors in viral nucleic acid test of 2019 novel coronavirus (2019-nCoV). *Chin J Lab Med*. 2020;43:E002.
3. Rainer TH, Chan PK, Ip M, et al. The spectrum of severe acute respiratory syndrome-associated coronavirus infection. *Ann Intern Med*. 2004;140(8):614-619.
4. Ho PL, Chau PH, Yip PSF, et al. A prediction rule for clinical diagnosis of severe acute respiratory syndrome. *Eur Respir J*. 2005;26:474-479.
5. National Health Commission of the People's Republic of China. Novel coronavirus pneumonia diagnosis and treatment protocol (5th edition, trial). Available from: http://www.nhc.gov.cn/yzygj/s7653p/202002/3b09b894ac9b4204a79db5b8912d4440.shtml. Accessed February 2, 2020.
6. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv*. 2020. https://doi.org/.org/10.1101/2020.02.06.20020974; https://www.medrxiv.org/content/10.1101/2020.02.06.20020974v1

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