



Coronavirus disease 19 positivity after negative results from six consecutive tests

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On March 11, 2020, the World Health Organization declared the novel coronavirus (COVID-19) outbreak a global pandemic, and it has spread to more than 200 countries. Approximately 2–5% of COVID-19 cases result in death due to massive alveolar damage and progressive respiratory failure (1). Because the 2019 novel coronavirus (2019-nCoV) is highly infectious, patient isolation is important for preventing secondary infections (1). For management of COVID-19, accurate diagnosis is essential. Real-time polymerase chain reaction (RT-PCR) is recommended as the final confirmatory test by the World Health Organization, as it helps identify the presence of the virus itself. Currently, RT-PCR is the standard diagnostic technique used by countries worldwide (2). However, clinicians in many hospitals have reported false-negative RT-PCR results (3). Here, we raise awareness on false-negative PCR results for 2019-nCoV by reporting a related case.

An 86-year-old woman, with a history of chronic kidney disease, diabetes, hypertension, and major depressive disorder visited the emergency room (ER) of our university hospital complaining of general weakness for 2 days. Upon arrival at the ER, her O₂ saturation was 70%. Her other vital signs were as follow: blood pressure, 100/50 mmHg; heart rate, 70 beats/min; body temperature, 35.4 °C; and respiratory rate, 20 breaths/min. Her initial laboratory test results from the ER were as follows: white blood cell count, 2.75k/ μ L (differential neutrophil and lymphocyte counts, 83.4% and 11.0%, respectively), and C-reactive protein level, 20.027 mg/L. Initial chest X-ray (CXR) showed severe

haziness in both lung fields (*Figure 1A*). A pharyngeal swab was performed, and RT-PCR (Allplex™ 2019-nCoV Assay, Seegene®, South Korea) for 2019-nCoV yielded negative results. The patient was intubated and received ventilator support. On the next day, CXR revealed aggravated haziness (*Figure 1B*), and chest computed tomography (CT) showed multifocal ground glass opacities with a crazy paving appearance in both lung fields (*Figure 1C*). RT-PCR for 2019-nCoV was repeated and yielded negative results again. Treatment with 10 g of Piperacillin/Tazobactam intravenous daily was started empirically. On hospital day 3, a third RT-PCR for 2019-nCoV was carried out and yielded negative results. Because the diagnosis of COVID-19 was not confirmed, the patient was admitted to the non-isolated intensive care unit (ICU) for further management. Once transferred on hospital day 3, a fourth RT-PCR for 2019-nCoV was carried out and yielded negative results. Although the RT-PCR tests repetitively yielded negative results, COVID-19 could not be completely ruled out because COVID-19 was prevalent and CT findings suggested viral pneumonia. Therefore, the patient was started on 800 mg of Lopinavir/Ritonavir (Kaletra) and 200 mg of Hydroxychloroquine sulfate (Oxiklorin) per oral daily from hospital day 3. On hospital day 4, the fifth and sixth RT-PCR tests were performed, both yielding negative results. However, on hospital day 5, a seventh RT-PCR test for 2019-nCoV yielded positive results. Consecutively, an eighth RT-PCR test on hospital day 5 also yielded positive results. Eventually, the patient was diagnosed as having COVID-19 and moved to an isolated ICU. Considering the



Figure 1 The chest radiograph and computed tomography images. (A) The anteroposterior (AP) chest X-ray (CXR) taken upon presentation to the emergency room reveals severe haziness in both lung fields. (B) The AP CXR on the second hospital day showed aggravated haziness. (C) Chest computerized tomography, coronal and axial images, revealing multifocal ground glass opacities with crazy paving appearance in both lung fields.

fatality rate of COVID-19, specifically among patients with underlying disease, the other patients in the non-isolated ICU had been exposed and put at risk for developing COVID-19. Fortunately, during the following two weeks, any patients admitted to the non-isolated ICU and any workers in the non-isolated ICU admitted in non-isolated ICU were not diagnosed as a COVID-19. On hospital day 13, the patient recovered and was moved to an isolated general ward. She continued receiving Hydroxychloroquine sulfate (Kaletra was stopped after 8 days) treatment.

The diagnosis of COVID-19 is confirmed by RT-PCR

(2-4). Although the sensitivity of RT-PCR has not been clearly determined, it is known to be around 70–80% (3,4). Therefore, the false negative rate per RT-PCR test may range from 20 to 30%. Additionally, most RT-PCR kits use only 2–3 primers for *2019-nCoV* gene detection. Considering that 2019-nCoV is prone to mutation, diagnosis relying on only a few primers may be one of the reasons for the false-negative results.

Importantly, negative RT-PCR results may lead to COVID-19 patients not being isolated. Therefore, transmission of 2019-nCoV to other people can occur,

potentially causing mass infection. Considering this, clinicians should be aware of the possibility of false-negative PCR results for 2019-nCoV. Chest CT is reported to have a high sensitivity for COVID-19 diagnosis (3). Therefore, clinicians should make a diagnosis of COVID-19 on the basis of chest CT findings and clinical features as well as RT-PCR results. When RT-PCR results are negative but image findings and symptoms are indicative of COVID-19, we recommend isolating patients from other people and performing repeat RT-PCR tests with close observation of the patients' symptoms.

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Footnote

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consent was obtained from the patient for publication of this study and any accompanying images.

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