LETTER TO THE EDITOR

Differing Sensitivity of COVID-19 PCR Tests and Consequences of the False-negative Report: A Small Observation

Sunil K Garg

Abstract

The world at large cannot afford to miss even a single case of COVID-19 because of its far-reaching consequences; therefore, the diagnostic development to achieve test with much higher sensitivity should be made available at a mass level as early as possible.

Keywords: COVID-19 infection, COVID-19 patient, Diagnosis test, SARS-CoV-2 RT-PCR.

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Purpose

To share our observations on six patients admitted to our hospital with signs, symptoms, and chest imaging findings consistent with the diagnosis of COVID-19. While their RT-PCR tests were consistently negative, they were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with multiplex PCR respiratory panel.

Summary

A 38-year-old woman was transferred to our hospital from another facility as a case of suspected COVID-19. Her four consecutive RT-PCR tests for COVID-19 were negative. She was admitted to the COVID unit for further management because of high clinical suspicion for COVID-19 based on her history of fever, cough, shortness of breath, chest X-ray, and CT findings.

We again requested a COVID-19 RT-PCR test along with an upper respiratory infectious multiplex PCR panel test given the possibility of other organisms, which tests for 17 respiratory viruses and 4 atypical bacteria. To our surprise, this time again her sample for COVID-19 was negative by RT-PCR while the sample for upper respiratory infectious multiplex PCR panel test that also consisted of SARS-CoV-2 was positive for COVID-19 and negative for other viruses and bacteria.

We repeated the sampling on another patient who was also highly suspected of COVID-19. This patient was also negative four times on RT-PCR. The COVID-management team wanted to transfer this patient to a non-COVID unit because of consecutive negative RT-PCR reports and the ongoing requirement of beds. The upper respiratory infectious multiplex PCR panel test was requested for him along with the sample for COVID-19 by RT-PCR pending a decision on shifting. In terms of results, the same thing happened. His COVID-19 report by RT-PCR was negative while his upper respiratory infectious multiplex PCR panel test was positive for SARS-CoV-2.

Thereafter, we repeated the upper respiratory infectious multiplex PCR panel test in four more patients (a total of 6 patients) and the findings were the same (Table 1). We included only those clinical COVID patients for upper respiratory infectious multiplex PCR panel test who were consistently negative with the routine RT-PCR except in the last patient. In our last patient, we conducted the upper respiratory infectious multiplex PCR panel test after only one negative RT-PCR test and the patient's second RT-PCR test was positive along with a positive upper respiratory infectious multiplex PCR panel test.

We did upper respiratory infectious multiplex PCR panel testing with the BioFire Respiratory Panel (RP) 2.1. RP 2.1 is a multiplex polymerase chain reaction (PCR) test intended for the simultaneous qualitative detection and differentiation of nucleic acids from multiple viral and bacterial respiratory organisms, including nucleic acid from SARS-CoV-2, in nasopharyngeal swabs obtained from patients suspected of respiratory infection consistent with COVID-19, and other respiratory tract infections. While BioFire respiratory 2.1 test received emergency use authorization in May 2020, it became the first COVID-19 diagnostic test granted marketing authorization using the de novo review pathway by FDA on March 17, 2021.[1]

These findings have several implications. As happened in our case, there was a plan to shift one of our patients to a non-COVID unit based on negative reports while the patient was a case of COVID-19. The non-COVID unit is an area where non-COVID patients are being treated and where healthcare professionals are not as much protected in PPE as in the COVID unit. The intake of such patients, those otherwise are highly suspected COVID-19 but consecutively negative RT-PCR, to non-COVID unit based on negative RT-PCR reports means putting both patients and

Department of Critical Care, NMC Healthcare, Dubai, United Arab Emirates

Corresponding Author: Sunil K Garg, Department of Critical Care, NMC Healthcare, Dubai, United Arab Emirates, Phone: 91-11-22334455, e-mail: sucare12@yahoo.co.in

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Table 1: Characteristic of patients and tests

Patient serial number	1	2	3	4	5	6
Duration of symptoms before hospitalization (days)	8–9	3	4	5	2	2
Presenting symptoms on hospitalization	Fever, pain abdomen, shortness of breath	Shortness of breath	Shortness of breath	Cough, fever and shortness of breath	Fever, cough, shortness of reath	Fever, cough, shortness of breath
Indication of ICU admission	Hypoxia, tachycardia, tachypnea	Hypoxia, tachypnea	Hypoxia	Hypoxia	Hypoxia	Hypoxia, tachypnea
RT-PCR	Negative	Negative	Negative	Negative	Negative	Positive (2nd report)
Number of times RT-PCR done	5	4	3	2	4	3
Multiplex PCR respiratory panel report	Positive	Positive	Positive	Positive	Positive	Positive
Number of times multiplex PCR respiratory panel done	1	1	1	1	1	1

healthcare professionals at risk in the non-COVID unit. Secondly, the cases of COVID-19 are reported and calculated based on positive reports only. Likely, many patients who have COVID-19 but tested negative may not be counted toward COVID cases or their death may not be recorded as COVID-19 mortality. Thirdly, due to the scarcity of medications, those patients who are tested positive get priority for medicines. It is very much likely that just because of false-negative (FN) reports of highly suspected COVID-19, such patients may not be the preferred candidate during medication allocation and distribution over those patients who have positive report despite their serious illnesses. This is with special regards to remdesivir and tocilizumab.

Studies of FN results from respiratory samples for SARS-CoV-2 are variable demonstrating FN rates ranging from 1% to 30%.[2] FN results can occur for numerous reasons, including suboptimal specimen collection, testing too early in the disease process, low analytic sensitivity, inappropriate specimen type, low viral load, or variability in viral shedding.[3–5] But positive report with one method and negative with another while the sample was taken at the same time rule out most of these variables of false negativity in our patients and support the better sensitivity of one over other.

Whether it is in a hospital or at a community level, we believe that the world at large cannot afford to miss even a single case of COVID-19 because of its far-reaching consequences in terms of community spread by asymptomatic or mildly symptomatic RT-PCR-negative individuals; therefore diagnostics development to achieve test with much higher sensitivity should be made available at a mass level as early as possible. Our observation has its limitation; hence, a large study is required to confirm or refute our findings.

Orcid

Sunil K Garg https://orcid.org/0000-0001-9710-8736

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