

CASE REPORT

False-negative SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) is an Important Consideration for Patient Management and Infection Prevention: A Case Report from The Louisville COVID-19 Epidemiology Study

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Abstract

We report a case of false negative SARS-CoV-2 RT-PCR on nasopharyngeal swab. Treating clinicians and infection preventionists should maintain a high suspicion for COVID-19 in the appropriate clinical setting despite negative test results. Utilization of chest CT should be strongly considered in the diagnostic work-up for suspected COVID-19, particularly in areas with limited RT-PCR availability.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic. [1] National and local governments have issued shelter at home and social distancing measures aimed at reducing the number of infected at any given time so as to not overwhelm healthcare facilities. [2,3] This strategy has been referred to as “flattening the curve.” To effectively flatten the curve, consideration should be given to the potential for false-negative testing. Typical findings on chest computed tomography (CT) have been described for patients with COVID-19 and may be a useful tool in identifying patients at high risk for false-negative testing. [4] This case describes the role of chest CT in identifying a patient at high risk for false-negative testing and management strategies.

Case report

A 67-year-old female presented to the emergency department (ED) on March 4, 2020 with complaints of shortness of air, severe fatigue, productive cough, body aches, sneezing, fever, nausea, and diarrhea for the past 5 days. No active disease was seen on a chest x-ray. A nasopharyngeal (NP) swab was taken and found negative for influenza A and B by PCR. The patient was diagnosed with an acute upper respiratory tract infection and discharged home with a prescription for azithromycin and albuterol. Five days later the patient returned to the ED with complaints of worsening shortness of air with exertion, chills, fatigue, decreased appetite, nausea, diarrhea, back pain, and productive cough. She denied recent travel, however she did note that she attended a concert on February 28, 2020 with her sister. Additionally, the patient reported she lives in close contact with her sister and aunt who were experiencing identical symptoms. An NP was obtained for testing by the BioFire® FilmArray® (BioFire Diagnostics, Salt Lake City, UT, USA) respiratory pathogen panel which returned negative for bacterial and viral targets. Despite a lack of known community spread at the time, there was concern for COVID-19 given the appearance of a cluster outbreak with the patient, her sister, and her aunt. A CT angiogram of the chest (**Figure 1**) demonstrated “multiple small and moderate size areas of focal ground glass infiltrate scattered within the central and peripheral aspects of both

Recommended Citation:

Song, Matthew; Wilde, Ashley M.; Moore, Sarah E.; Bohn, Brian C.; Patross, Clayton J.; Denham, Bryan; Schulz, Paul; Ramirez, Julio A. (2020). “False-negative SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) is an Important Consideration for Patient Management and Infection Prevention: A Case Report from The Louisville COVID-19 Epidemiology Study,” *The University of Louisville Journal of Respiratory Infections*: Vol. 4, Iss. 1, Article 43.

Received Date: May 5, 2020

Accepted Date: June 16, 2020

Published Date: July 6, 2020

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Funding Source: The author(s) received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

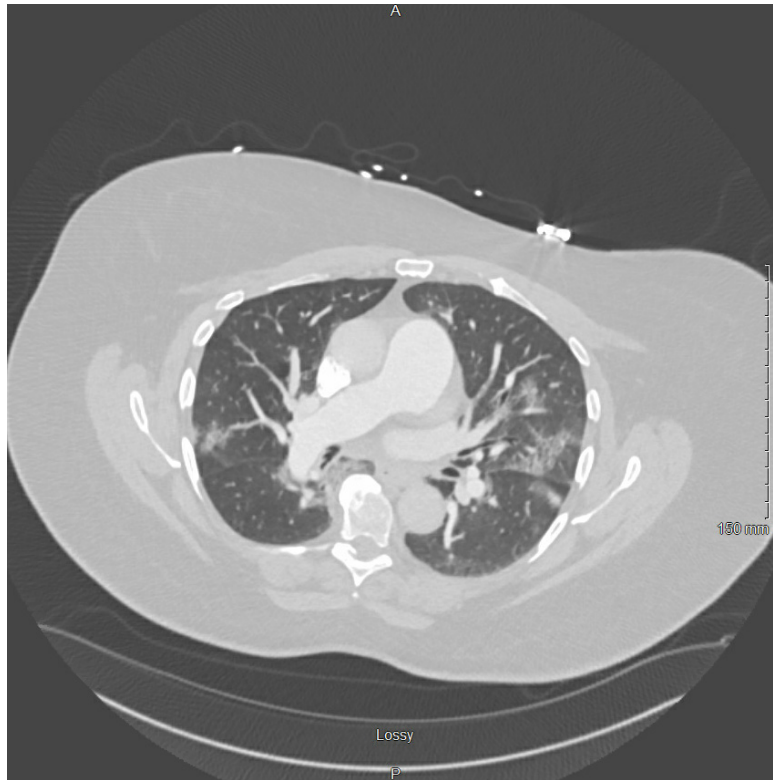


Figure 1. CT angiogram of the chest, March 9, 2020.

lungs” highly suggestive for COVID-19. An NP swab was obtained and sent to the University of Louisville research lab, which is a Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a certified high-complexity laboratory, for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR testing. The patient was placed in appropriate isolation per protocol and admitted to the hospital. The NP swab returned negative on hospital day 3. At this point, the patient’s sister and aunt had both been admitted and found to be positive for SARS-CoV-2. Therefore given continued high clinical suspicion for COVID-19 the patient remained in isolation and repeat nasopharyngeal and oropharyngeal (NP/OP) swabs and blood, serum, urine, and sputum were obtained and sent for testing. The repeat NP/OP, blood, serum, and urine returned negative but the sputum returned positive for SARS-CoV-2 by RT-PCR.

Discussion

The present case highlights the potential for false negative results for SARS-CoV-2 testing by RT-PCR. The implications of this should not be understated as it could potentially steer treating clinicians into incorrect diagnoses, resulting in sub-optimal patient management. Furthermore, false negative tests may result in premature discontinuation of appropriate hospital isolation or home quarantine thereby sabotaging ongoing efforts to “flatten the curve.”

There are multiple potential causes for false negative RT-PCR testing and include, but are not limited to, clinical test sensitivity, sampling error, site of infection, technical error, and human error. As there is no gold standard diagnostic available for COVID-19, the clinical sensitivity of the RT-PCR is currently unknown. Proper NP swab collection may be difficult depending on the experience of the collector and may also be further impeded by patient complaints of discomfort. It is unlikely sampling error occurred in our patient as the second upper respiratory tract sample was obtained by an infectious diseases physician with more than 15 years of experience. Positive lower respiratory tract specimens and negative upper respiratory tract, blood, serum, and urine specimens may have been a reflection of the site of infection as pneumonia was evident on chest CT. More research is needed to elucidate the association between specimen sensitivity and disease presentation. Technical errors with conducting RT-PCR in the lab may result in false negative testing, but no suspicion was reported. Lastly, human error may result in increased risk for false negative testing and may be amplified during the beginnings of a pandemic when new testing techniques are likely employed and volumes are expected to be high.

This report is not the first to highlight the variable positivity rate based on specimen source for SARS-CoV-2. In a

recent report, Wang et al reported their findings on 1070 specimens from 205 hospitalized patients with RT-PCR confirmed COVID-19 in China. They found that bronchoalveolar lavage resulted in the highest positive rates at 93% (14/15 specimens), followed by sputum with 72% (72/104 specimens). Nasal swabs and pharyngeal swabs had a 63% (5/8 specimens) and 32% (126/398 specimens), respectively. [5]

Furthermore, this case highlights the role of chest CT in diagnosing patients with COVID-19. Patients who present with COVID-19 display signs and symptoms that are non-specific and the additional information added by a chest CT may aid in determining the likelihood of COVID-19 prior to RT-PCR testing. This is in contrast with the American College of Radiology (ACR) recommendation against using CT as a screening tool or first line test for diagnosing COVID-19. [6] It should be noted that the ACR recommendation is predicated on the notion that RT-PCR testing is widely available, which may not be the case in all areas affected by the pandemic. The role of CT is further supported by Ai et al who examined 1014 patients suspected with COVID-19 in China. They found that chest CT had a sensitivity of 97% (95% CI: 95-98%) based on positive RT-PCR and that 48% of patients who had positive chest CT but negative SARS-CoV-2 RT-PCR were still considered highly likely cases based on a clinical criteria. [7] The role of CT may primarily be limited to the inpatient setting given logistical barriers.

In conclusion, negative SARS-CoV-2 RT-PCR should not be used solely to exclude the diagnosis of COVID-19. Chest CT is a highly useful tool in determining risk for false negative testing and should be considered by providers caring for those who are suspected with COVID-19. Chest CT may be particularly useful when RT-PCR availability is limited. Patients with a high clinical suspicion, despite negative testing, should remain in isolation while undergoing additional investigation and treatment.

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