Limited diagnostic utility of SARS-CoV-2 serologic testing in symptomatic PCR negative patients

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To the Editor:

Several studies have advocated for the routine use of SARS-CoV-2 serologic testing to diagnose and manage patients with symptoms concerning for COVID-19 (1). The broad use of serology for this purpose is tempting given that variability in specimen type, collection technique, and time from symptoms all reduce the sensitivity of molecular methods for SARS-CoV-2 (2). However, guidelines from the CDC and the IDSA suggest the use of serologic testing only to support the diagnosis of COVID-19 in individuals with high clinical suspicion that repeatedly test negative by diagnostic methods (3,4). Nonetheless, studies have demonstrated improved sensitivity of paired molecular and serological testing relative to molecular testing alone (1). In contrast, limited studies are available in the published literature assessing the utility of serology for the diagnosis of SARS-CoV-2 in PCR negative, symptomatic patients at presentation.

The purpose of this study was to assess the utility of SARS-CoV-2 serologic testing for diagnosing patients upon admission that were negative by molecular testing. Remnant specimens were collected from patients presenting to the Barnes Jewish Hospital ED between 08/29/2020 and 09/19/2020 that tested negative for SARS-COV-2 RNA by nasopharyngeal swab collected within 4 hours of presentation. Patients were tested for SARS-CoV-2 RNA due to clinical suspicion for COVID-19 or as a standard of care screen for hospital admission. Symptomatic patients were defined as those with respiratory symptoms, (i.e shortness of breath), cough, fever, loss of taste or smell, headache, and sore throat. This study was approved by the Washington University Institutional Review Board (IRB# 202007097). Remnant EDTA plasma specimens were obtained from 393 patients within 12h of admission. Patients were adjudicated as symptomatic (n =171), asymptomatic (n = 174), or unknown symptoms/altered mental status

(AMS) (n = 48) based on physician encounter notes. Specimens were analyzed with the Abbott SARS-CoV-2 IgG immunoassay on an Abbott Architect i2000. Using the manufacturer suggested cut-off (1.4 S/CO) for a positive, 14 of 393 patients were positive for antibodies to SARS-CoV-2 (seropositivity rate of 3.6%) (**Figure 1**), 6 of which were from patients with previous RT-PCR-confirmed COVID-19 infection. Among patients without previously diagnosed COVID-19, the seropositivity rate in symptomatic patients was 1.2% (2/171), in patients with AMS was 4.3% (2/46), and in asymptomatic patients with no known previous COVID-19 diagnoses was 2.6% (4/170). The seropositivity rate among symptomatic patients presenting ≥ 14 days after symptom onset was 0% (0/67), 7-13 days was 5% (1/20), and for patients < 7 days was 2.1% (1/47). Among the 4 patients with AMS that were serologically positive, 2 were previously diagnosed by PCR.

These results imply relatively low diagnostic utility of SARS-CoV-2 serologic testing in patients presenting to the ED with symptoms consistent with COVID-19 infection but negative by molecular testing. While the CDC and IDSA state that serological testing is an adjunct for diagnosis in patients outside of the PCR window, these results imply that this is rare scenario clinically. Furthermore, studies have demonstrated low sensitivity of serologic testing <14d after symptom onset (5). If serological testing was broadly implemented, 2 of 393 patients would have been identified as novel SARS-CoV-2 cases. Both patients were considered high risk cases and only 1 was removed from contact precautions. Furthermore, both had a relatively mild hospital course and were discharged within 1 week. One limitation of this study was the use of a single serological assay as opposed to an orthogonal approach (4). However, given the symptomatic

nature of the majority of the patients coupled with the high specificity of the Abbott assay (5), the PPV in this patient population was likely satisfactory.

In conclusion, we demonstrate low diagnostic utility of SARS-CoV-2 serological testing for identifying novel cases of acute SARS-CoV-2 infections in the ED after a negative PCR test. In contrast to claims for the ubiquitous use of SARS-CoV-2 serological testing and in congruence with guidelines from the CDC (3,4), serological testing should be reserved for patients with high pre-test probability of a positive result that are at least 14 days from symptom onset.

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REFERENCES

1. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clin Infect Dis 2020;71:2027-34.
2. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. Ann Intern Med 2020;173:262-67.
3. CDC. Interim Guidelines for COVID-19 Antibody Testing [Accessed Nov 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
4. Hanson KE, Caliendo AM, Arias CA, Englund JA, Hayden MK, Lee MJ, et al. IDSA Guidelines on COVID-19 Serologic Testing (online ahead of print). Clin Infect Dis 2020 ; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1343/5904785
5. Tang MS, Hock KG, Logsdon NM, Hayes JE, Gronowski AM, Anderson NW, et al. Clinical Performance of Two SARS-CoV-2 Serologic Assays. Clin Chem 2020;66:1055-62.

FIGURE LEGEND

Figure 1. SARS-CoV-2 seroprevalence in patients presenting to the ED with clinical suspicion of COVID-19 that tested negative by SARS-CoV-2 PCR. **A.** Results using the manufacturer suggested cutoff (1.4 S/CO, dotted line), segregated by symptom status at time of presentation. Triangles represent patients with previous diagnosis, circles represent patients with no previous diagnosis of COVID-19.