Diagnostic outcomes with SARS-CoV-2 serologic and molecular testing in a symptomatic/asymptomatic population: experience at a regional medical center

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Abstract

Background

Frequently, molecular reverse-transcriptase polymerase chain reaction (RT-PCR) tests come with time and resource constraints. Here, we examined whether serology could quickly identify individuals with coronavirus disease 2019 (COVID-19) presenting to hospital emergency rooms and for elective surgeries to prevent further spread of the virus.

Methods

Serology and RT-PCR test results for 726 hospital presenters were compared.

Results

Of 614 asymptomatic antibody-nonreactive patients, all were RT-PCR–negative. Of 16 symptomatic antibody-reactive patients, 12 were RT-PCR–positive at presentation and an additional 2 were previously RT-PCR-positive.

Conclusions

Initial automated serology testing along with symptomology may be useful for identifying COVID-19, and particularly for rapidly ruling out COVID-19 in low-prevalence populations.

Introduction

Emerging in China in late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly throughout the world, causing the coronavirus disease-2019 (COVID-19) pandemic. Currently, clinical laboratories mainly use molecular (reverse transcriptase-polymerase chain reaction [RT-PCR]), antigen and serologic testing to determine the presence of current and previous infection with the virus.[1,2] Frequent, widespread testing, as well as quick turnaround times, are required for timely diagnosis and patient management. However, many laboratories struggle to meet the demand for RT-PCR testing due to resource constraints.[1] RT-PCR–based diagnostic testing for the management of SARS-CoV-2 infection can lead to prolonged turnaround times of up to 1 week in cases where testing is not available and therefore outsourced. This delay in testing or test result transmission may have serious health implications for patients with respect to diagnosis, follow-up treatment, and isolation strategies. Automated serology assays are easier to use, have quicker turnaround times, and allow for frequent and widespread testing, but are not sensitive enough early after infection.[1,3]

Some studies in asymptomatic hospital healthcare workers have used serology as an initial rapid test to be followed by RT-PCR.[4] Other studies have found positive serology in asymptomatic subjects who tested negative by RT-PCR.[5] Here, given the resource limitations for molecular testing at some regional institutions, we explored whether benefit could be derived from initial rapid serology testing of symptomatic and unsuspected asymptomatic patients in a hospital setting when compared to RT-PCR results.

Materials and Methods

Blood samples were collected from July 13 through September 5, 2020, from 726 adult patients who presented to a regional medical center in New Mexico, United States (U.S.) for emergency medical care or prior to their scheduled surgery. All patients were assessed for signs and symptoms of SARS-CoV-2 infection, such as acute respiratory distress, dry cough, sore throat, fatigue, fever, chills, body aches, shortness of breath, or loss of taste and smell. Those showing signs and symptoms consistent with COVID-19 were considered symptomatic, while all other patients were considered asymptomatic. All patient samples were assessed with the Siemens Healthineers Atellica® IM SARS-CoV-2 Total (COV2T) assay* (Siemens Healthineers, Tarrytown, NY, U.S.), a fully automated chemiluminescent immunoassay that detects IgG and IgM antibodies to the spike protein of SARS-CoV-2 in serum and plasma,[6] and by multiple different RT-PCR molecular tests. The samples were tested with the serology and RT-PCR tests at the same time. The COV2T assay has received emergency use (EUA) authorization status in the U.S. and has met the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) Target Product Profile (TPP) criteria for both sensitivity and specificity.[6] This was a retrospective analysis that did not require ethical approval.

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Results

The data collected represent eight possible clinical outcomes (Table 1). A flowchart representation of data starting with patient symptomology status is shown in Figure 1. At the time of sample collection, the prevalence of COVID-19 in this population was estimated to be low, at 2.2% (16/726).

Table 1. Frequency distribution of eight different clinical outcomes using patient symptomology for COVID-19, serology, and molecular testing.

	Group (Serology/RT-PCR)	n (total n = 726)	Percent of Total
Symptomatic (13.9%)	**Reactive/positive**	**12**	**1.66**
	Reactive/negative	4	0.55
	Nonreactive/positive	3	0.41
	Nonreactive/negative	82	11.29
Asymptomatic (86.1%)	Reactive/positive	1	0.14
	Reactive/negative	10	1.38
	Nonreactive/positive	0	0
	Nonreactive/negative	**614**	**84.57**

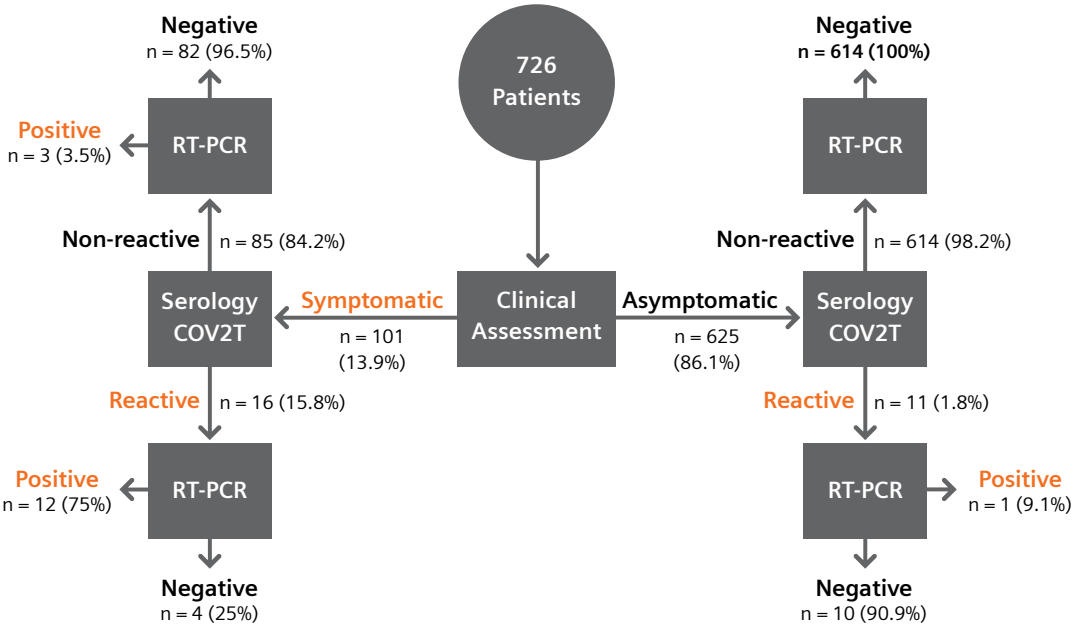

Figure 1. COVID-19 disposition flowchart. 726 patients were clinically assessed for signs and symptoms of COVID-19 at a regional medical center in New Mexico, U.S., from July 13 through September 5, 2020. The Atellica IM SARS-CoV-2 Total assay* was used for serology assessment, whereas a variety of different RT-PCR methods were used for molecular analysis.

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Discussion

Many laboratories throughout the world struggle with increased demand for COVID-19 testing. Reagent and supply shortages, complex workflows, and the need for highly trained medical technologists pose challenges for healthcare providers to accommodate increases in RT-PCR testing.[1] Molecular testing is highly sensitive and specific for the presence of SARS-CoV-2 RNA and considered diagnostic of COVID-19.[1] Conversely, serology antibody assays (typically detecting IgG or IgG and IgM antibodies to the virus) detect recent or prior infection and are widely available on central laboratory instrumentation and can accommodate large testing volumes. Automated serology assays are more cost-effective and provide faster turnaround times than molecular tests, especially when dealing with large patient populations (e.g., the typical turnaround time for an automated immunoassay analyzer is 30 minutes compared to a typical time to results of several hours for RT-PCR). In addition, serology assay sample collection and preparation procedures are less cumbersome and more reliable than RT-PCR procedures. Still, it takes the human body about 1–3 weeks post-infection to develop an active immune response that leads to the production of detectable levels of antibodies.[5] Consequently, antibody assays are more often used only to aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection.[2,3] While serology tests lack sensitivity compared to RT-PCR to identify patients during the earliest period after infection, recent evidence suggests that RT-PCR may lack in specificity for detection of live virus, leading to detection for weeks after infection due to remnant RNA.[7]

Here, we describe the relationship between SARS-CoV-2 serology and RT-PCR in conjunction with patient symptomology. Of eight possible clinical outcomes, two are of special interest: symptomatic antibody-reactive and asymptomatic antibody-nonreactive. Twelve (75%) of the 16 symptomatic patients with a reactive serology test result were also positive by RT-PCR. The remaining 4 (25%) had negative RT-PCR results, and half of those were previously RT-PCR–positive. The other two reactive symptomatic patients may have lacked detectable levels of viral RNA (due to timing and/or technical issues or other causes) but had developed an immune response, or had been infected previously and had symptoms for another reason. Healthcare providers may benefit from the quicker turnaround time of the automated immunoassay and the reliability of the serology result (i.e., to base their initial decisions on the reactive serology in conjunction with the patient's symptoms). Faster medical attention, such as recommendations for patient isolation or postponement of elective surgeries, may lead to improved outcomes, such as reduced wait times and decreased spread of the virus.

This study's results in symptomatic antibody-reactive patients suggest that this approach (assessing serology along with clinical presentation) could be useful in hospitals with limited molecular testing capabilities. Reproducing these results in a larger sample size would provide greater statistical power and confidence in these data. Furthermore, all patients that were designated asymptomatic for COVID-19 and tested nonreactive for SARS-CoV-2 antibodies had negative RT-PCR results. Although concordance was 100%, the possibility of infection in asymptomatic, antibody-nonreactive patients cannot be ruled out within the first week post-infection, based on previous knowledge of asymptomatic prevalence and the seroconversion window of SARS-CoV-2 infection.

Additionally, of the 625 patients designated as asymptomatic, 11 (1.8%) were reactive for antibodies, and only 1 (9.1%) was positive by RT-PCR. Whether this individual had residual viral genetic material and antibodies from a previous infection or was incidentally found to be asymptomatic, RT-PCR–positive, and antibody-reactive could not be determined. The other 10 (90.9%) were negative by RT-PCR; prior infection could have occurred several weeks earlier, resulting in decreased viral load by the time of testing. Considering that asymptomatic patients may still spread disease and have positive serology,[4,8] these 11 patients could be instructed to take precautions and be reassessed. Conversely, some patients with a positive RT-PCR may have resolved the infection several weeks prior with nonviable RNA remnants still detectable.[7,9,10]

Also, whereas RT-PCR is a confirmatory test here, a negative RT-PCR test in patients designated as symptomatic and antibody-nonreactive for antibody may not completely exclude a patient from having COVID-19; this could depend on the viral load, timing of the RT-PCR test, (e.g., tested too early and/or did not seroconvert), or whether the individual was immunosuppressed. Alternatively, these patients could have other diseases that share symptoms with COVID-19, such as influenza. Regardless, these patients could also be instructed to take precautions and be reassessed. Indeed, three of these patients were RT-PCR–positive and likely had not developed detectable antibodies at the time of testing.

A strength of the data is that it supports the notion that negative serology performed on asymptomatic individuals in the study population of 726 would preclude RT-PCR testing or provide a faster initial clinical assessment on 614, or 614/726 = 85%, of the individuals. As mentioned, the COVID-19 RT-PCR positivity rate was relatively low (16/726 = 2.2%); therefore, the relevance of these results is perhaps greater when the positivity rate of the local population is low and/or when most patients are asymptomatic.

This study has some limitations. This was a retrospective study, so time of testing from symptom onset or infection was not available. However, this study is akin to surveilling the general population, where asymptomatic and symptomatic individuals may not know or have recorded the time since infection or onset of symptoms. Also, patient demographics for sex and precise age were not available. Another limitation is that results from the various RT-PCR tests might not be directly comparable.

In conclusion, assessing serology along with clinical presentation may lead to improved actionable outcomes. Notably, the data supports the utility of a protocol combining clinical assessment and serology (and no subsequent PCR) for asymptomatic patients in low-positivity areas (i.e., asymptomatic patients coming in for elective surgeries in areas that are not currently experiencing a large surge of new cases). These patients may benefit from quicker, appropriate isolation and medical attention. The benefits of serological testing on symptomatic patients appear less apparent. However, while antibody test results should not be taken in isolation or as a replacement for diagnostic RT-PCR, they may still serve as a valuable first indicator of the patient's COVID-19 status.

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Funding: This work was supported by Siemens Healthcare Diagnostics Inc..

Disclosure of interest: The authors report no conflict of interest. All authors are employees of Siemens Healthcare Diagnostics Inc.

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Published by Siemens Healthcare Diagnostics Inc. · Order No. 30-21-DX-602-76 · 03-2021 · ©Siemens Healthcare Diagnostics Inc., 2021