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Journal
Journal of Clinical Microbiology, 59(7)

ISSN
0095-1137

Authors
Murad, Douglas
Chandrasekaran, Sukantha
Pillai, Ajaya
et al.

Publication Date
2021-06-18

DOI
10.1128/jcm.00431-21

Peer reviewed

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

VIROLOGY

SARS-CoV-2 Infection Detection by PCR and Serologic Testing in Clinical Practice

Douglas Murad,[a] Sukantha Chandrasekaran,[b] Ajaya Pillai,[c] Omai B. Garner,[b] Christopher T. Denny[d]

[a]Department of Medicine/Department of Information Services and Solutions, David Geffen School of Medicine at UCLA, University of California at Los Angeles Medical Center, Los Angeles, California, USA

[b]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, California, USA

[c]UCLA Health Information Technology, Los Angeles, California, USA

[d]Division of Hematology/Oncology, Department of Pediatrics, Gwynne Hazen Cherry Memorial Laboratories, Jonsson Comprehensive Cancer Center, Molecular Biology Institute, University of California, Los Angeles, California, USA

ABSTRACT Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be diagnosed by PCR during acute infection or later in their clinical course by detection of virus-specific antibodies. While in theory complementary, both PCR and serologic tests have practical shortcomings. A retrospective study was performed in order to further define these limitations in a clinical context and to determine how to best utilize these tests in a coherent fashion. A total of 3,075 patients underwent both PCR and serology tests at University of California, Los Angeles (UCLA), in the study period. Among these, 2,731 (89%) had no positive tests at all, 73 (2%) had a positive PCR test and only negative serology tests, 144 (5%) had a positive serology test and only negative PCR tests, and 127 (4%) had positive PCR and serology tests. Approximately half of the patients with discordant results (i.e., PCR positive and serology negative or vice versa) had mistimed tests in reference to the course of their disease. PCR-positive patients who were asymptomatic or pregnant were less likely to generate a detectable humoral immune response to SARS-CoV-2. On a quantitative level, the log number of days between symptom onset and PCR test was positively correlated with cycle threshold (C_T) values. However, there was no apparent relationship between PCR C_T and serologic (arbitrary units per milliliter) results.

KEYWORDS COVID-19, PCR, SARS-CoV-2, diagnostics, serology

Clinical lab testing has played a central role in the management of the ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the most basic level, being able to reliably identify individuals that are acutely infected with this virus is an essential prerequisite to all patient-level care. In this regard, detection of viral RNA by means of PCR-based assays has proven to be a robust strategy (1). By targeting multiple regions of the viral genome, a high level of specificity for SARS-CoV-2 can be attained. Furthermore, it is estimated that many PCR-based assays can detect as few as 1,800 copies per ml of the virus, making it the current gold standard to which all alternative SARS-CoV-2 diagnostic systems are compared (2).

As impressively as PCR-based assays can perform, there are practical and inherent limitations to this platform. From a technical perspective, because PCR relies on exponential amplification of nucleic acid targets, reaction conditions must be stringently controlled to maintain reproducibility. This requires trained personnel and instruments that are primarily found in centralized clinical laboratories. Implementation of SARS-CoV-2 PCR diagnostic systems in point-of-care settings has been more challenging (1) and may be unfeasible for home-based testing.

Citation Murad D, Chandrasekaran S, Pillai A, Garner OB, Denny CT. 2021. SARS-CoV-2 infection detection by PCR and serologic testing in clinical Practice. J Clin Microbiol 59: e00431-21. https://doi.org/10.1128/JCM.00431-21.

Editor Yi-Wei Tang, Cepheid

Address correspondence to Christopher T. Denny, cdenny@mednet.ucla.edu.

Received 27 February 2021
Returned for modification 2 April 2021
Accepted 23 April 2021
Accepted manuscript posted online 26 April 2021
Published 18 June 2021

The clinical nature of the SARS-CoV-2 infection itself imposes additional restrictions. PCR can most effectively diagnose patients that have been infected by SARS-CoV-2 when they are actively shedding the virus or viral components. This estimated 7- to 10-day window of opportunity usually begins 2 days before patients become symptomatic and extends for a highly variable time afterwards (3). In the estimated 20 to 40% of patients that have few or no symptoms, optimizing the timing of PCR testing to fall within the interval of viral shedding has been very difficult (4, 5).

Anti-SARS-CoV-2 antibody tests were developed to address these temporal limitations. By assaying for host immune response to this virus, which would be expected to last weeks to months (6, 7), the diagnosis of SARS-CoV-2 infection could be made retrospectively. However, in comparison to PCR assays, serologic test platforms have more variables that need to be addressed in their development, including (i) selection of target viral antigens, (ii) development of monoclonal reagents, and (iii) implementation of detection technologies. As a result, there has been greater performance variability across different anti-SARS-CoV-2 antibody tests than had been seen with SARS-CoV-2 PCR platforms (8).

In this paper, we present a retrospective study on the effectiveness of both PCR and serologic testing platforms to diagnose SARS-CoV-2 infection. To limit possible confounding variation due to different testing platforms, the study population was limited to patients that were tested in-house at University of California, Los Angeles (UCLA), clinical labs. Our goal was that by analyzing this "real-world" experience, the strengths and shortcomings of PCR and serologic testing in diagnosing SARS-CoV-2 infection would come to light, and strategies to best utilize these potentially complementary tests could be formulated.

MATERIALS AND METHODS

Testing data. Specimens for SARS-CoV-2 PCR and anti-SARS-CoV-2 antibody tests were collected by trained UCLA health care practitioners at UCLA outpatient testing sites and clinics as well as inpatient wards before 11 August 2020 and processed within 24 h at UCLA laboratories. Test result data were extracted directly from the relational database provided by the electronic medical record (EMR) vendor. Data for patients with at least one PCR test and one antibody test were retained for analysis. External lab results shared from other institutions or analyzed at third-party laboratories were discarded because the underlying quantitative results were not available for review. For each positive PCR test, the results in cycle threshold values (C_T) were obtained directly from the instrument and averaged to produce a composite C_T value. PCR C_T values came from three different RT-PCR platforms (CDC SARS-CoV-2 RT-PCR assay, Simplexa SARS-CoV-2 direct real-time RT-PCR assay, and the TaqPath SARS-CoV-2 RT-PCR assay). A previous study showed a difference in C_T values of less than 3 between the assays and a negligible difference in C_T values between viral gene targets on the same assay (9). For antibody tests (SARS-CoV-2 IgG from DiaSorin), the result in arbitrary units (AU) per milliliter was obtained directly from the EMR relational database. While the threshold value for a clinically positive antibody test was set at 15 AU/ml, lower values that were above the sensitivity limit of the instrument were also recorded. For any patient with multiple PCR tests or multiple antibody tests, the PCR test with the minimum cycle threshold and the antibody test with the maximum number of AU per milliliter were flagged.

Patient classification. Given the likelihood of multiple tests corresponding to individual patients, aggregation was performed on the level of each unique patient. If the patient had any positive PCR tests, they were labeled as P^+; otherwise, they were P^-. Similarly, if the patient had any positive antibody tests, they were labeled as G^+; otherwise, they were G^-. Patients were then classified according to the four possible combinations of these two labels, that is, G^-P^-, G^-P^+, G^+P^-, or G^+P^+.

Interval analysis. The first analysis was designed to elucidate appropriate time intervals between individual PCR and serology tests by leveraging the fact that individual patients often had multiple PCR tests over time. Thus, it was the sole analysis that was performed at the level of the individual test. All of the remaining analyses relied upon aggregated, patient-level PCR and serology result classifications. First, for every patient with at least one positive serology result, that is, the G^+P^- and G^+P^+ populations, the time intervals between any PCR tests and the first positive serology test were calculated. These intervals were rounded to the nearest day. Then, two separate histograms were created with respect to testing interval, one for all positive PCR tests and one for all negative PCR tests. These two plots were then stratified by the patient's classification, that is, whether they had ever had a positive PCR result. Visual appearance of the histograms and proportion of tests before and after various time interval cut points were compared between the negative PCR tests from G^+P^- patients and any of the PCR tests from G^+P^+ patients. A similar analysis was then performed to compare the distribution of time intervals between PCR and serology tests for all patients with at least one positive PCR result. These distributions were then stratified by whether the patient had ever had a positive serology test, that is, whether they were G^-P^+ or G^+P^+. Differences in the visual appearance of the histograms were again compared.

TABLE 1 Patient counts and demographics for those who underwent both PCR and serology testing, by patient class[a]

Parameter	Value for cohort				
	G^-P^- ($n = 2,731$)	G^+P^- ($n = 144$)	G^+P^+ ($n = 127$)	G^-P^+ ($n = 73$)	All ($n = 3,075$)
Age, median (IQR)	48.3 (35.5–70.0)	51.23 (36.3–62.1)	50.5 (38.9–61.5)	49.0 (33.9–64.2)	48.6 (35.5–61.3)
Sex, no. (%)					
Female	1,404 (51.4)	73 (50.7)	72 (56.7)	37 (50.7)	1,586 (51.6)
Male	1,327 (48.6)	71 (49.3)	55 (43.3)	36 (49.3)	1,489 (48.4)

[a]G^-P^-, no positive PCR tests or serology tests; G^+P^-, at least one positive serology and no positive PCR tests; G^+P^+, at least one positive PCR and one positive serology test; G^-P^+, no positive serology tests and at least one positive PCR test. IQR, interquartile range.

For both analyses, manual chart review was performed to identify specific clinical features that varied between the stratified groups.

Patient comorbidities and immunocompromised status. All patient diagnoses recorded prior to the first PCR test were extracted. These diagnoses' ICD-10 codes were utilized to abstract the presence of Elixhauser comorbidities (10) and immunocompromised status (11) for each patient. Differences in mean AHRQ (Agency for Healthcare Research and Quality)-weighted Elixhauser score across each of the four test result groups was tested with analysis of variance (ANOVA). Differences in the percent presence of any underlying immunocompromising disease were compared across each of the four test result groups with Fisher's exact test. These comparisons were repeated among the subset of patients for whom the final relevant serology test occurred at least 12 h after the first relevant PCR test.

Association and agreement between PCR and serology. The second analysis measured the association and agreement between PCR and serology results. From this point onward, all analysis were performed at the level of the individual patient. Association was assessed by computing the odds ratio of having at least one positive serology result for patients with at least one positive PCR result. The adjusted measure of agreement between any positive PCR and serology results was calculated with Cohen's kappa.

Patient class and asymptomatic or pregnancy status. A number of focused chart reviews were then performed on distinct frequency clusters seen in the histograms. Namely, an assessment of the rate of asymptomatic status was compared between serology-positive patients with and without a positive PCR test (i.e., G^+P^+ and G^+P^-) occurring at least 1 day prior. Additionally, the rate of both asymptomatic status and pregnancy status were compared between PCR-positive patients with and without a positive serology test (i.e., G^+P^+ and G^-P^+) with appropriate timing intervals. Asymptomatic status was ascribed if there was no evidence of symptoms from manual review of clinical notes. Pregnancy status was determined in a similar manner.

Symptom duration and PCR quantitative results. In order to address whether the number of days between symptom onset and PCR testing was predictive of the quantitative result from PCR testing, all patients with a determinable symptom onset date and a subsequent positive PCR test were extracted from the patient classes that had been constructed (that is, G^-P^+ and G^+P^+). The number of days between symptom onset and PCR testing with a minimum C_T value was charted for each patient against the minimum C_T value. Log transforms of both axes were trialed to assess for best fit of an ordinary least-squares regression.

PCR and serology results' quantitative relationship. Finally, the quantitative relationship between C_T and number of AU per milliliter was assessed by ordinary least-squares regression values for all patients in the G^-P^+ and G^+P^+ cohorts. Given that many patients had multiple PCR and serology tests, the single tests for each patient resulting in minimum C_T and maximum AU values per milliliter, respectively, were utilized. Given the concerns about the effect of symptom onset and test timing on this relationship, three separate stratifications were performed by tertiles of days between symptoms and PCR test, days between symptoms and serology test, and days between PCR and serology test.

Visualizations and statistical analysis. All visualizations and statistical analyses were performed using JMP, version 14 (SAS Institute Inc., Cary, NC). This study was exempted from review by the institutional review board of University of California, Los Angeles.

RESULTS

SARS-CoV-2 PCR status correlates with anti-SARS-CoV-2 IgG detection. In order to determine potential relationships between PCR detection of SARS-CoV-2 viral shedding and development of anti-SARS-CoV-2 IgG, patients that had at least one of these tests performed were retrospectively identified. Recognizing the potential variability associated with anti-SARS-CoV-2 serologic testing, we restricted this population to those that had only in-house testing performed at UCLA Healthcare clinical labs. The study interval extended through 10 August 2020.

Since both tests return a binary positive/negative result, this patient cohort can be subdivided into a 2-by-2 matrix representing the possible outcome combinations of the two tests (Table 1). For those patients that had multiple occurrences of the same

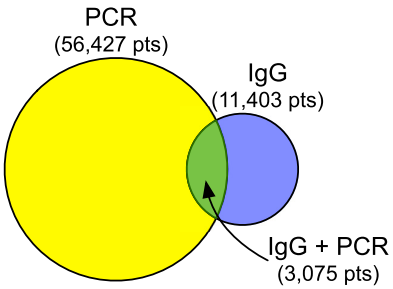

FIG 1 Intersection of PCR and serology tests for patients tested at UCLA. The yellow circle represents the number of patients that received at least one SARS-CoV-2 PCR test during the study period. The blue circle represents the number of patients that underwent at least one SARS-CoV-2 serology test during the study period. The intersection of the yellow and blue circles represents the number of patients that underwent both tests at any time during the study period.

test, a single positive result would categorize the patient as positive even if subsequent tests were negative.

During the study period, a total of 56,427 patients had at least one PCR test and 11,403 patients had at least one anti-SARS-CoV-2 IgG test (Fig. 1). In these two populations, there were 3,075 patients that had both tests performed, with each patient falling into one of the four aforementioned classes (Table 1).

Among patients with at least one PCR and one serology test, there was a strong correlation between the results of the two diagnostic tests. As a measure of association, the odds ratio of a positive serology test for individuals with a positive PCR test compared to a negative PCR test was 32.99 (95% confidence interval [CI], 23.64 to 46.03). The proportion of observed agreement between the two tests was 92.9%. The adjusted measure of agreement (Cohen's kappa) between the two tests was 92.4%.

Anti-SARS-CoV-2 IgG–PCR test interval analysis suggests a finite window of opportunity to detect SARS-CoV-2 viral shedding by PCR. Of the two outlier subgroups, the anti-SARS-CoV-2 IgG-positive, PCR-negative (G^+P^-) subgroup represents a SARS-CoV-2-infected cohort that had been missed by viral shedding assays. The development of measurable anti-SARS-CoV-2 antibodies generally comes later in the course of this infection, at a time when many patients have ceased to shed virus or virus components. Therefore, in order for viral shedding to be detected, a PCR test would have to have been performed at a sufficient time before the positive anti-SARS-CoV-2 IgG test but after the patient had been infected. It is possible that a proportion of the G^+P^- cohort consisted of patients who underwent PCR testing outside this interval.

To assess what fraction of this cohort could be due to mistimed PCR testing, the distribution of anti-SARS-CoV-2 IgG-to-PCR test intervals in the G^+P^- cohort was compared to that in the anti-SARS-CoV-2 IgG-positive, PCR-positive (G^+P^+) cohort (Fig. 2). For each cohort, the time between each PCR and the first positive anti-SARS-CoV-2 IgG result and measurement was calculated. These time intervals were then subdivided depending on whether the PCR result was positive or negative, and frequencies of each interval were determined.

There was strong similarity between the anti-SARS-CoV-2 IgG-to-negative-PCR interval distributions from both the G^+P^- and G^+P^+ cohorts. In both groups, approximately 56% of PCR tests (92 of 162 for the G^+P^+ cohort; 119 of 212 for the G^+P^- cohort) were performed either on the same day or after the initial positive anti-SARS-CoV-2 IgG result was obtained, giving intervals with negative values. In contrast, the anti-SARS-CoV-2 IgG–PCR positive interval distribution from the G^+P^+ cohort was substantially shifted to the right, and intervals of 0 days or less accounted for only 11% (28 of 245) of all measurements.

The interval from symptom onset to first PCR test is prolonged in a subset of the anti-SARS-CoV-2 IgG-positive, PCR-negative cohort. Based on our anti-SARS-CoV-2 IgG–PCR test interval analysis, we reasoned that the G^+P^- cohort could be subdivided according to when they had their first PCR test. Seventy-seven of 144 (53%)

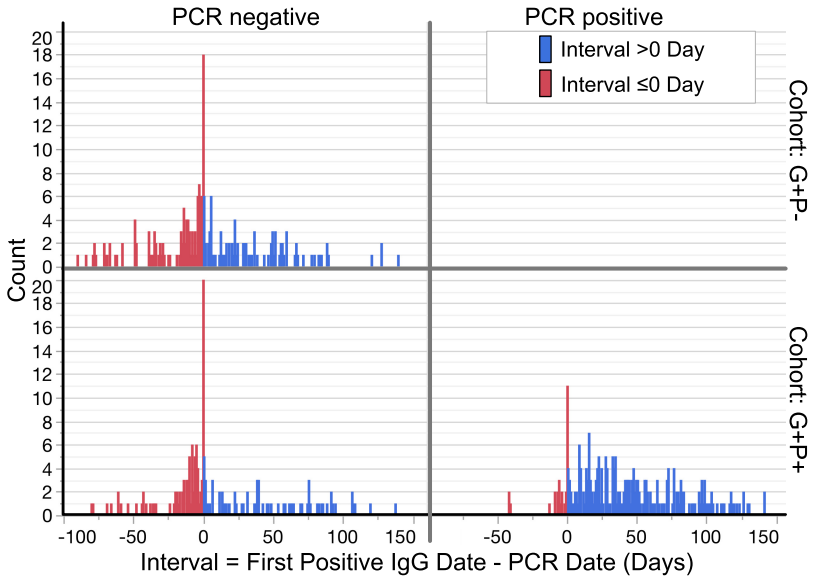

FIG 2 Histogram of interval between first positive serology and any PCR test for G^+P^- and G^+P^+ patients. The top row of histograms is restricted to tests from G^+P^- patients. Therefore, the top right histogram is empty and the top left histogram represents the distribution of intervals between each negative PCR test and first positive serology test. The bottom row of histograms is restricted to tests from G^+P^+ patients. The histograms of the interval between both negative PCR tests (bottom left) and positive PCR tests (bottom right) with respect to first positive tests are plotted.

patients had their first PCR test on the same day as or after they had their first positive anti-SARS-CoV-2 IgG test, greatly increasing the chance that PCR testing would be negative. Manual chart review was then performed for the remaining 67 patients to search for other factors that could account for why viral shedding was missed.

This subgroup was sequentially winnowed down depending on specific clinical features. Twelve patients were found to have had a previous positive SARS-CoV-2 PCR test either recorded in their history or performed by an outside lab. Seventeen patients either were asymptomatic or had a symptom onset date that could not be unambiguously determined from the medical record. In the remaining 38 patients, the median time from symptom onset to their first PCR test was 15 days. In contrast in the 106 patients from the G^+P^+ cohort where symptom onset could be determined, the median of this time interval was 5.5 days.

The anti-SARS-CoV-2 IgG-negative, PCR-positive cohort identifies a subset of patients with limited anti-SARS-CoV-2 humoral response. As with the G^+P^- group, a proportion of the anti-SARS-CoV-2 IgG-negative, PCR-positive (G^-P^+) cohort could be accounted for by ineffectual timing of when these tests were performed in the course of a patient's disease. To quantify this subset, an anti-SARS-CoV-2 IgG–PCR interval analysis was performed. A similar strategy was used, with the difference being that the first positive PCR test was used as the primary point of reference, since this measurement is the closest to each patient's time of active disease. Similar to before, the time between the first positive PCR and anti-SARS-CoV-2 IgG result was calculated. Time intervals were then subdivided depending on whether the anti-SARS-CoV-2 IgG result was positive or negative, and interval frequencies were determined.

Similar to our previous interval analysis, the interval distributions from the G^-P^+ group and the G^+P^+, IgG-positive subgroup were very different (Fig. 3). In the former, 42% (38/88 observations) of all anti-SARS-CoV-2 IgG measurements were made on the same day or before the first positive PCR result was obtained. In contrast 95% (162/170 observations) of anti-SARS-CoV-2 IgG tests in the G^+P^+, IgG-positive subgroup, were performed at least 1 day after the first positive PCR result was obtained. These data suggest that 51% (37 of 73) of the patients in the G^-P^+ cohort could have returned a negative anti-SARS-CoV-2 IgG result because of mistimed execution of this test.

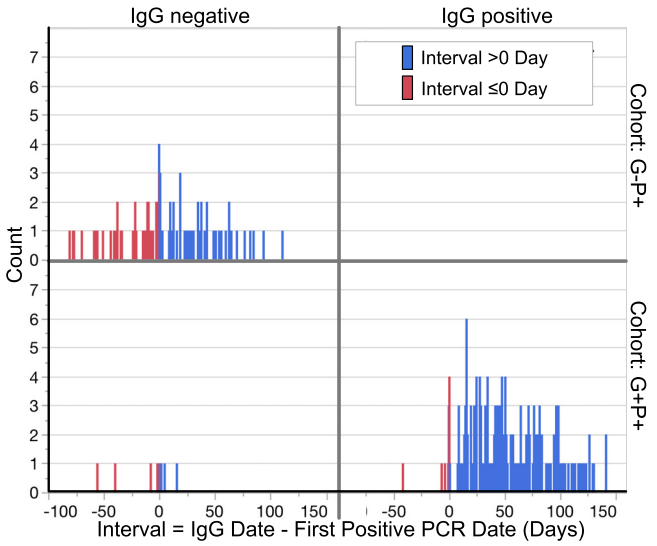

FIG 3 Histogram of interval between first positive PCR and any serology test for G^-P^+ and G^+P^+ patients. The top row of histograms is restricted to tests from G^-P^+ patients. Therefore, the top right histogram is empty and the top left histogram represents the distribution of intervals between each first positive serology test and negative serology test. The bottom row of histograms is restricted to tests from G^+P^+ patients. The histograms of the interval between the first positive PCR test and both negative serology tests (bottom left) and positive serology tests (bottom right) are plotted.

Manual chart review was performed for the remaining 49% (36 of 73 patients) of the G^-P^+ cohort with appropriate timing between PCR and serology test to identify specific clinical features that were more frequently found than in the G^+P^+ cohort. Most prominently, 33% (12 of 36) of the G^-P^+ group were asymptomatic. In comparison, 7% (8 of 114) of patients in the G^+P^+ cohort had low-level symptoms indistinguishable from their chronic medical conditions or were asymptomatic altogether (Fisher exact test P value < 0.001; odds ratio, 6.5; 95% CI, 2.2 to 20.6). Strikingly, among female patients between the ages of 11 and 50 whose positive PCR preceded serology testing by at least 1 day, 35% (6 of 17) in the G^-P^+ cohort were pregnant versus 5% (2 of 41) in the G^+P^+ group (Fisher's exact test P value = 0.006; odds ratio, 10.1; 95% CI, 1.5 to 115.9).

No difference in average comorbidity score or immunocompromised proportion was detected among patients in the four test result cohorts. The above analysis suggests that specific clinical features or patient states could play a role in their ability to generate an anti-SARS-CoV-2 humoral response. This prompted the question of what degree the observed outlier cohorts (G^+P^- and G^-P^+) could be due to a generalized increase in patient cumulative comorbidities or immunocompromised status. To address this, Elixhauser comorbidity scores were generated for all 3,075 patients, and their distribution across test result groups was assessed (see Tables S1 and S2 in the supplemental material). No significant difference in average comorbidity was found across the four different cohorts (ANOVA P value = 0.12). When only the 1,314 patients for which relevant serology testing occurred at least 12 h after PCR testing, there was also no detectable difference in average comorbidity across groups (ANOVA P value = 0.86). Similarly, the distribution of patients with an immunocompromising disease among the four cohorts was not significantly different in the total (3,075 patients) or the appropriately timed (1,314 patients) populations (Fisher exact test of independence two-sided P values of 0.18 and 0.53, respectively).

In symptomatic individuals, the quantitative result from PCR is associated with the number of days since symptom start. Both SARS-CoV-2 PCR and anti-SARS-CoV-2 IgG tests are quantitative assays that return cycle threshold values (C_T) or concentrations (AU per milliliter), respectively. These values are then indexed to test-specific thresholds in order to be reported as qualitative results (e.g., positive/negative). As in the above

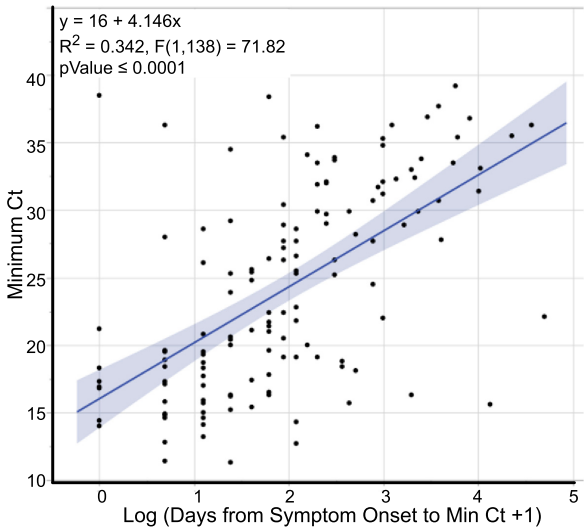

FIG 4 Linear-log relationship between the number of days since symptom onset and quantitative result from PCR testing. One hundred forty patients having determinable symptom onset dates and positive PCR tests were included from the pool of patients that underwent both PCR and serology testing.

analyses, we investigated to what extent SARS-CoV-2 PCR and anti-SARS-CoV-2 IgG quantitative values could be associated with clinical features at the individual-patient level. Intervals between PCR and serology test were calculated using the dates of the PCR test with minimum C_T value and the serology test with the maximum number of AU per milliliter. Of the 200 individuals with at least one positive SARS-CoV-2 PCR result and any SARS-CoV-2 serology result, there were 140 with a determinable symptom onset date.

Using these subjects, the relationship between the minimum C_T value from any positive tests and the log of the number of days of symptoms preceding said testing was analyzed. Due to the need for log transformation, 1 day was added to each testing interval. Results from ordinary least-squares regression (Fig. 4) were suggestive of a positive relationship between days since symptom onset and PCR C_T value (linear-log F-test P value < 0.0001; $R^2 = 0.34$). Given the inverse relationship between C_T value and viral load, we observed an expected decrease in viral load with increasing time since symptom onset.

Development of anti-SARS-CoV-2 IgG response quantitatively does not correlate with relative viral load detected by PCR. The next question related to whether the value (AU per milliliter) from serology testing could be predicted from the quantitative result of PCR testing. Patients with at least one detected PCR result followed at least 1 day later by a detected serology result were included. One hundred thirty-five such patients were identified. Simple bivariate linear regression between the untransformed and log-transformed values of the two variables was insignificant (Fig. S1).

In order to investigate whether the quantitative relationship between the serology value (AU per milliliter) and C_T value was dependent on any of the time intervals between symptom onset, PCR testing, and serology testing, three separate stratified analyses were performed. There was no clear linear relationship between C_T value and serology value at any of the time strata between PCR and serology testing for the 135 of 200 patients with a detectable serology test, collected at least 1 day after a positive PCR test (Fig. S2). Similarly, stratification by tertiles of interval between symptom start and PCR test or serology test revealed no evidence of a linear relationship between C_T and number of AU per milliliter (Fig. S3 and S4).

DISCUSSION

Anti-SARS-CoV-2 antibody tests were never intended to supplant PCR-based testing but were meant to complement it. In this regard, the high correlation and positive agreement between these two tests is reassuring. Nevertheless, the number of patients that fell into the outlier (G^+P^- and G^-P^+) cohorts was higher than expected given the published performance of these assays (9). This suggests that these discordant results reflect clinical limitations of trying to use both tests in a coherent manner. Approximately half of the patients in both outlier cohorts had mistimed tests. For 53% of patients in the G^+P^- group, the SARS-CoV-2 PCR specimen was obtained at a time when they had ceased shedding virus. Similarly, for 51% of patients in the G^-P^+ cohort, the anti-SARS-CoV-2 antibody specimen was drawn before they had had sufficient time to mount a detectable antibody response. Better provider outreach and education could lead to improved utilization of these two diagnostic tests.

Comparison of the G^+P^- and G^+P^+ cohorts provides insight into optimal timing of anti-SARS-CoV-2 antibody and PCR testing over the course of an acute infection by this virus. Ideally, PCR testing should be performed within 7 days of symptom onset in order to capture active viral shedding. If it is and the result is negative, subsequent anti-SARS-CoV-2 antibody testing is also very likely to be negative and therefore uninformative.

The dramatic difference in the interval between symptom onset and first PCR result between the G^+P^- and G^+P^+ groups suggests that the anti-SARS-CoV-2 antibody test can be best utilized in scenarios where PCR testing came too late in the course of a patient's disease. Our data suggest that if PCR testing was performed 14 or more days from symptom onset and returned a negative result, the patient could still have been infected by SARS-CoV-2 even though active viral shedding had ceased. In this scenario, anti-SARS-CoV-2 antibody testing could identify these patients retrospectively.

While coordinate use of both anti-SARS-CoV-2 antibody and PCR tests should capture a greater number of patients that have been infected with SARS-CoV-2, it will still not identify them all. The G^-P^+ cohort highlights limitations of anti-SARS-CoV-2 antibody testing even when appropriately timed with respect to symptom onset and PCR testing. The finding of a 4.7-fold increase in asymptomatic patients is not surprising considering that anti-SARS-CoV-2 antibody titers have been associated with severity of symptoms (12). However, the increase in pregnancy in the P^+G^- cohort was unanticipated and suggests that the immunomodulatory effect of pregnancy could inhibit the formation of detectable anti-SARS-CoV-2 antibodies.

While we were able to identify relationships between anti-SARS-CoV-2 antibody and PCR qualitative test results, elucidating similar trends on a quantitative scale remained elusive. The inverse relationship between the time from symptom onset to first positive PCR and PCR C_T likely reflects falling viral load as the disease progresses. However, a similar relationship between PCR C_T and anti-SARS-CoV-2 antibody AU values could not be established. This may reflect the inherent variability in the antibody immune response to SARS-CoV-2 infection.

It is this immune response variability that has led anti-SARS-CoV-2 antibody testing to fall short of the initial hope of being able to comprehensively define those that have been infected by SARS-CoV-2. Given the very wide range in clinical manifestations of this disease, from asymptomatic to life-threatening, there is likely a significant subpopulation of patients that can rid themselves of the virus without having to generate measurable anti-SARS-CoV-2 antibodies. There is some evidence that adaptive cellular immune responses do occur in asymptomatic patients (13). These in theory could serve as biomarkers of SARS-CoV-2 infection, but testing for these in a clinical lab setting will be challenging.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

ACKNOWLEDGMENTS

C.T.D. is supported by NIH grant UL1TR001881.

We thank Sitaram Vangala, Associate Director of the UCLA Department of Medicine Statistics Core, for his generous analytic assistance.

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