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Research Brief

Utility of the cycle threshold in anticipating the next phase of the coronavirus disease 2019 (COVID-19) pandemic

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Since the onset of the coronavirus disease 2019 (COVID-19) pandemic in 2019, methods of accurate diagnostic testing have evolved rapidly.[1] The primary method of diagnosis of COVID-19 is real-time reverse transcriptase polymerase chain reaction (rRT-PCR) detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which amplifies and detects viral genetic sequences with fluorescence signals increasing proportionally to the quantity of amplified nucleic acid present.[2] This assay enables approximate quantification of viral RNA expressed as the cycle threshold (Ct), or the number of cycles required to amplify the viral RNA to a detectable level.[2] The Ct value is inversely related to viral load, and it is estimated that every 3.3 increase in Ct value is reflective of a 10-fold reduction in viral load at the time of testing.[2] As with other testing, results are affected by factors such as collection technique and transport time.

Epidemiologic monitoring and forecasting of the COVID-19 pandemic have been based on the rates of hospitalization, reported incident cases, and case-fatality rates. These data are often flawed due to the impacts of various testing practices and delays in reporting.[3,4] Recent studies have evaluated the use of Ct values as a more accurate method for estimating the epidemiologic trajectory of this pandemic.[5,6] Preliminary data suggest that when Ct values are higher, the epidemic appears to be in a waning phase, whereas when Ct values are trending lower, the epidemic may be growing.[5,6]

We examined the association between Ct values from specimens collected over time at a tertiary-care emergency department with weekly state hospitalizations to evaluate the utility of using Ct to estimate epidemiologic trends and anticipate the next phase of the pandemic.

Methods

Population

In this retrospective analysis, we collected Ct values of patients who presented to the Tufts Medical Center Emergency Department, a tertiary-care facility in Boston, Massachusetts, between March 20 and July 13, 2020. We included Ct data from all patients who tested positive for SARS-CoV-2 on a nasopharyngeal (NP) swab. This study was approved by Tufts Health Sciences Institutional Review Board and was granted exempt status.

SARS-CoV-2 PCR testing

Testing was performed using the Abbott M2000 SARS-CoV-2 assay. This assay is an rRT-PCR dual target assay for the RNA polymerase (RdRp) and N genes of the SARS-CoV-2 virus.[7] This assay has high sensitivity (93%) and specificity (100%) for SARS-CoV-2[8] and provides Ct values. The analytic time, or the time between specimen receipt in the laboratory and result, was 8 hours with a median turnaround time (ie, time between specimen receipt and provider notification) of 12–16 hours.

Statistical analysis

Weekly median Ct values were compared using the Pearson correlation coefficient to median weekly incident hospitalizations due to SARS-CoV-2 infection in Massachusetts, obtained from the Massachusetts Department of Public Health (DPH).[9] The previous week's data were published each Tuesday.[9] Data on incident hospitalizations due to SARS-CoV-2 infection were not available prior to May 9, 2020, and all available data were included in the analysis. The statistical analysis was performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC).

Results

Cycle threshold data were available from 342 samples. The median Ct value was plotted against median weekly incident SARS-CoV-2 related hospitalizations in Massachusetts (Fig. 1a). We detected a statistically significant inverse correlation between median Ct value and median incident hospitalizations: Pearson correlation coefficient −0.76 (95% CI, −0.93 to −0.29; $P < .05$) (Fig. 1b).

Discussion

Our study revealed a significant inverse correlation between median weekly Ct values and weekly incident hospitalizations for SARS-CoV-2 infection in Massachusetts.

Our findings are consistent with a prior mathematical model in which Ct values from a single cross-sectional sample were used to estimate the epidemic trajectory of SARS-CoV-2 cases.[5] That study demonstrated that by combining data from multiple cross sectional samples, population incidence can be estimated and longer-term incidence curves can be identified, without the use of more time and resource-intensive serologic surveillance

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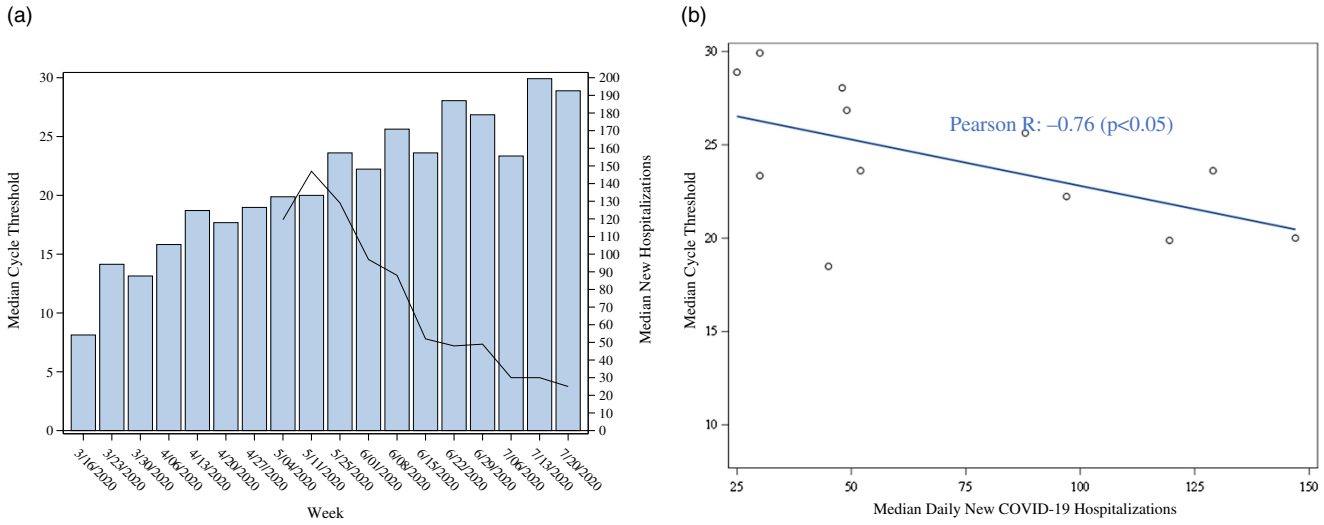

Fig. 1. Median Ct values by incident SARS-CoV-2 hospitalizations in Massachusetts. (a) Weekly median Ct values and incident hospitalizations due to SARS-CoV-2 infection. Bars represent median Ct for tests conducted during the week and the solid line represents the total new hospitalizations in MA during corresponding week. (b) Scatter plot of daily incident SARS-CoV-2 related hospitalization by median Ct with linear regression line and Pearson correlation statistic of −0.76 ($P < .05$). Note. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; rRT-PCR, real-time reverse transcriptase polymerase chain reaction; Ct, cycle threshold; COVID-19: coronavirus disease 2019.

studies.[5] The Pearson correlation coefficient in our study was similar to those of previous studies,[6] with an inverse relationship between Ct values and incident cases of SARS-CoV-2 hospitalization. Another study utilizing a larger number of Ct values showed a similar trend between Ct values and hospitalizations, with a Pearson correlation of −0.851 ($P < .001$).[10] Prediction modeling utilizing Ct values might provide a more reliable estimate, or useful adjunct, to assessing the epidemic trajectory of the SARS-CoV-2 virus than using data from existing surveillance systems without the reliability issues present with case-counting methods. Considering more complex disease transmission in the setting of vaccination and variants, developing more accurate epidemiologic models is vital to help guide distribution of resources.

The strengths of our study include the use of a reliable consistent SARS-CoV-2 rRT-PCR assay along with robust state hospitalization data collected by the Massachusetts DPH. Our study had several limitations. It was conducted over a relatively short period at a single institution utilizing a single diagnostic platform. This platform, however, has been shown to have analytic characteristics similar to those of other commonly used platforms and diagnostic assays.

In conclusion, SARS-CoV-2 viral loads, as estimated by Ct values generated with a rRT-PCR viral assay, are associated with changing epidemiologic characteristics. Increases in median Ct values preceded a drop in weekly hospitalizations due to SARS-CoV-2 infection across the state. These findings suggest that Ct values could be of use in epidemic predictive modeling, though more research is needed to assess the utility of this metric utilizing larger sample sizes and multiple cross-sectional samples.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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