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# SARS-CoV-2 cycle threshold (Ct) values predict future COVID-19 cases

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ABSTRACT

*Aim:* Anticipating local surges in COVID-19 cases has predominantly been based on observation of increasing cases. We sought to determine if temporal trends in SARS-CoV-2 Cycle threshold (Ct) values from clinical testing were predictive of future cases.

*Methods:* Data were collected from a large, safety-net hospital in Los Angeles, California. Ct values for all SARS-CoV-2 detections by the GeneXpert system (Cepheid) between October 2020 to March 2021 were analyzed.

*Results:* A total of 2,114 SARS-CoV-2-positive samples were included. Cases increased dramatically in December 2020, peaking the first week of January, before returning to pre-surge numbers by mid-February. Ct values fell during this same period, with values in December and January (25.6 ± 7.8 and 27±7.9, respectively) significantly lower than those of the other months (30±9.3 to 37.7 ± 6.3). Average weekly Ct values for all patients negatively correlated with the number of tests run two weeks in the future ($r$= -0.74, $p$<0.0001), whereas Ct values for asymptomatic patients negatively correlated most strongly with total number of tests performed one month later ($r$= -0.88, $p$<0.0001). Predictive modeling using these Ct values correctly predicted whether cases would increase or decrease 65% of the time for a subsequent surge (May-July 2021).

*Conclusions:* During the largest COVID-19 surge in Los Angeles to date, we observed significantly lower Ct values (representing higher levels of viral RNA) suggesting that increased transmission of COVID-19 was temporarily associated with higher viral loads. Decreasing Ct values appear to be a leading indicator for predicting future COVID-19 cases, which can facilitate improved hospital-level surge planning.

## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread quickly around the world since its emergence in late 2019, giving rise to the current pandemic of coronavirus disease 2019 (COVID-19). The gold standard for diagnosing SARS-CoV-2 infection is reverse transcriptase polymerase chain reaction (RT-PCR) or transcription mediated amplification (TMA) assays. [1] Results are usually reported with a binary output (i.e. detected/not detected or positive/negative), but a qualitative indication of the amount of viral RNA present can be inferred from the cycle threshold (Ct) value. This represents the PCR cycle at which fluorescence reaches the threshold for detection, such that the lower the Ct value, the higher the amount of viral RNA detected.

Many factors influence the amount of RNA detected (e.g. specimen quality and type, extraction method, etc.) and Ct values are not directly comparable between assays. [2, 3] Nevertheless, lower Ct values have been shown in some studies to correlate with disease severity and to be predictive of progression to severe disease. [4–8] Lower Ct values are also associated with a higher probability of positive viral culture [9, 10], with one study showing a 32% reduced probability of culture positivity for each one unit increase in Ct value [10] Although lower Ct values may be prognostic for poorer outcomes among hospitalized patients, low Ct values are also observed in asymptomatic individuals who collectively account for up to 30% of COVID-19 cases. [11, 12] Importantly, Ct values also change over the course of infection, with a nadir around the time of symptom onset and subsequent increase in values as the infection progresses. [13, 14]

Several studies have shown that SARS-CoV-2 Ct values have changed over the course of the pandemic on a population level and that such population-level changes can be used to predict future cases. [15–17] Many of these studies rely on large datasets from multiple institutions and testing facilities in each region, comparing population-level Ct values to city, county, or state-wide case counts. Using data from previously tested clinical specimens at a single institution, we sought to

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determine if temporal trends in SARS-CoV-2 Ct values were predictive of future COVID-19 cases at an individual hospital-level. We additionally sought to determine if the distinction between symptomatic and asymptomatic Ct values altered the relationship with future COVID-19 cases. The ability to better predict future cases on an institutional level could potentially facilitate improved planning and resource utilization, as well as more judicious use of asymptomatic testing.

## Methods

### *Study site*

The study site was a large (>600 bed), public, safety net hospital in Los Angeles County. The study period included specimens collected for SARS-CoV-2 clinical testing between October 1, 2020 and March 31, 2021, and between May 4, 2021-July 31, 2021. This study was approved by the University of Southern California health sciences campus institutional review board (HS-20–00,429).

### *Specimen collection and testing*

Patients admitted to our hospital were tested for the presence of SARS-CoV-2 using flocked nasopharyngeal (NP) swabs in Universal Transport Medium (UTM). Testing of symptomatic Emergency Department (ED) patients was performed using either NP or anterior nares (AN) swabs collected in UTM. Non-emergent pre-procedural/pre-surgical screening was not included as this was performed using the Aptima SARS-CoV-2 assay (Panther System, Hologic, Marlborough, MA) which does not provide Ct values. Patients who tested positive previously were excluded from re-testing within the subsequent 90-day period.

Several different SARS-CoV-2 assays were used by our laboratory during the study period, with testing routed by the laboratory to a given assay based on the test indication selected upon provider ordering i.e., "admit, symptomatic", "admit, asymptomatic", "outpatient", etc. as well as test kit reagent availability. Between October-1 and December 21, 2020, specimens from symptomatic and asymptomatic patients were tested with either the Xpert Xpress SARS-CoV-2 Assay (Cepheid, Sunnyvale, CA) or the Simplexa COVID-19 Direct Kit (Diasorin Molecular, Cypress, CA). From December 22 to March 31, 2021 testing of symptomatic patients was performed using the Xpert Xpress SARS-CoV-2/Flu/RSV assay (Cepheid). Asymptomatic admission testing was performed using the Xpert Xpress SARS-CoV-2 Assay (night shift) or the Simplexa COVID-19 Direct Kit (day and evening shifts). From May 4 to July 31, 2021 testing of symptomatic patients was performed using the Xpert Xpress SARS-CoV-2/Flu/RSV assay (Cepheid), with asymptomatic admission testing performed using the Xpert Xpress SARS-CoV-2 Assay. Both Xpert assays were run on the Infinity and XVI systems. During the first study period, a lack of intra-assay comparability of Ct values was observed between the Diasorin Liason MDX instruments in our laboratory (data not shown) and Simplexa results were therefore excluded from the analysis.

### *Data set*

Ct values for SARS-CoV-2 detections by both Xpert assays were obtained from the Infinity and XVI instruments. The Xpert Xpress SARS-CoV-2 assay includes Ct values for the e-gene and N2 region, and the lowest Ct value >0 was used for this analysis. The Xpert Xpress SARS-CoV-2/Flu/RSV assay uses the same e-gene and N2 targets but reports out a single Ct value that corresponds to the lowest Ct value >0. Comparability of Ct values between the Infinity and XVI instruments was determined as part of assay clinical validation, as well as during biannual verification of reproducibility between instruments and assays. Given that Ct values were comparable between the two instruments, data was both was included in analyses.

### *Statistical analysis*

Statistical analyses were performed using Microsoft Excel, XL STAT (Addinsoft USA, New York, NY). Data were were tested for normality using Shapiro-Wilk test and QQ-Plots. One way ANOVA testing was used to compare monthly average Ct values. Correlations between Ct values from different patient populations and total cases were acquired using Pearson's test. An alpha of 0.05 was used for all tests. A predictive model for future cases was created by doing a simple linear regression analysis on data from the Ct values of all detections between October 1, 2020, and March 31, 2021. This analysis is displayed in Supplemental Figure 1 (Supplemental Data). The linear regression model fitted from these data were then applied to Ct values collected between May 4, 2021 and July 31, 2021 and compared to future cases to validate this model.

## Results

### *Ct values fell during winter surge*

A total of 2114 SARS-CoV-2-positive specimens (hereafter referred to as cases) were detected by the Xpert Xpress assays between October 1, 2020 and March 31, 2021. Weekly cases began to rise beginning in November 2020, peaking the week of December 27th with a total 291 cases (Fig. 1). Cases subsequently declined returning to pre-surge case numbers by mid-February 2021. An inverse pattern was seen for weekly average SARS-CoV-2 Ct values, with values beginning to decrease in November to a nadir Ct=24.4 the week of December 20, 2020. As the number of cases fell, the weekly average Ct value reciprocally rose to levels similar to those seen before the surge. When averaged over the course of the month, Ct values were significantly lower in December and January (25.6 ± 7.8 and 27±7.9, respectively) than those in October (32.4 ± 8), November (30±9.3), February (31.7 ± 8.3), and March (37.7 ± 6.3) (Fig. 2). Monthly median Ct values were similar to monthly means, with the exception of March having a left skew suggesting the mean was influenced by a small number of patients with lower Ct values (Supplemental Table 1).

### *Ct values correlate with future case numbers*

To assess whether Ct values themselves predicted future caseloads at our hospital, we performed a linear regression analysis comparing weekly average Ct values with the number of cases the same week of sampling, and in subsequent weeks. When compared temporally, the average weekly Ct values for all tests performed negatively correlated with the number of cases occurring two weeks after specimen collection ($r = -0.75$, $p < 0.0001$) (Supplemental Figure 1).

We next performed a sub-analysis of Ct values among patients who were categorized as symptomatic or asymptomatic. Ct values for patients symptomatic at the time of testing most closely negatively correlated with the number of cases performed the week of collection ($r = -0.85$, $p < 0.001$) (Supplemental Figure 2). In contrast, Ct values from asymptomatic patients negatively correlated most strongly with total number of cases performed one month later ($r = -0.89$, $p < 0.0001$) (Supplemental Figure 3). The temporal correlation of weekly average Ct values, for all groups, with current and future weekly cases are shown in Supplemental Figure 4.

### *Correlation can be used to estimate future trends in case loads*

Finally, as a proof of concept, we leveraged the correlation between Ct values and future case numbers to predict future cases of COVID-19 at our hospital. Utilizing a linear regression model generated from the Ct values of all cases between October 1, 2020, and March 31, 2021 (Supplemental Figure 1), we analyzed data from specimens collected between May 4, 2021 and July 31, 2021 to validate forecasting estimates (Fig. 3, Table S2). The Pearson correlation between observed data

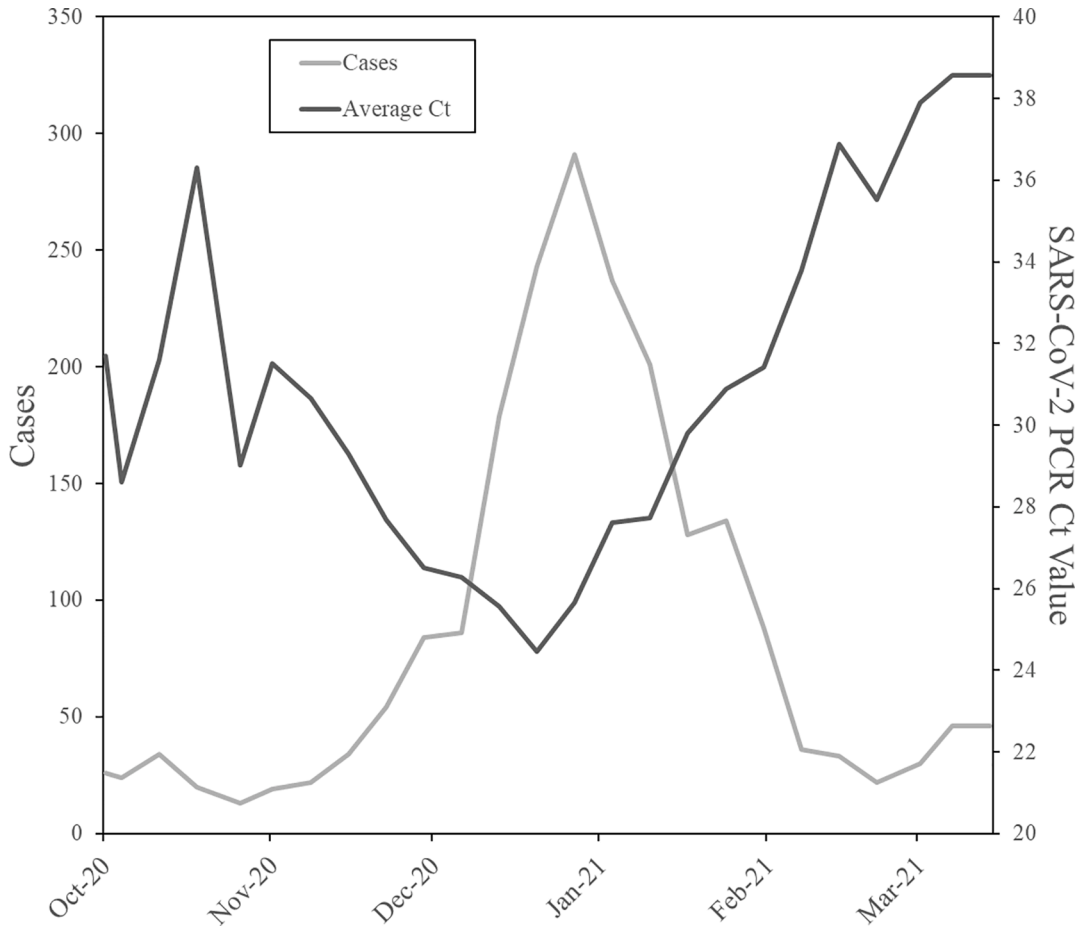


**Fig. 1.** Number of positive tests per week and weekly average Ct. During winter surge (December and January), average Ct values dropped dramatically representing higher viral loads in clinical specimens.

and the predictive model was 0.6 and the root mean square error (RMSE) was 70 cases. This method correctly predicted whether cases would increase or decrease 65% of the time, performing better when cases had dramatic increases (>30% increase in number of cases) which were captured 82% of the time.

## Discussion

The ability of Ct values to predict future COVID-19 cases at a single institution has not been thoroughly investigated. As the number of COVID-19 cases surged at our hospital during the winter months of 2020, there was a corresponding decrease in Ct values indicative of higher quantities of viral RNA. This is consistent with observations of decreasing Ct values during COVID-19 surges in other studies and suggests that aggregate Ct values may provide an indirect indication of the overall viral load in the exposure environment at a population level. [18–20]

We observed a strong, negative correlation between aggregate Ct values and future case numbers, with weekly-average Ct values most closely correlated with case numbers two weeks in the future. This is consistent with trends observed in other, population-level studies showing similar negative correlations between Ct values and COVID-19 cases. [21–23] This relationship is theorized to arise from increasing Ct values over the course of an infection. [24] During a growing pandemic more individuals will have been recently infected and thus will have lower average Ct values. When a pandemic is waning, a higher proportion of individuals will be farther along in their infections and thus have higher Ct values. [16]

When we investigated this association in subgroups based on the presence of symptoms, Ct values had a divergent temporal association with future cases. For symptomatic patients, average weekly Ct values negatively correlated most strongly with the total number of cases the same week of collection. However, for asymptomatic patients, Ct values were most strongly associated with total number of cases observed one month in the future, suggesting that low Ct values among asymptomatic individuals may be a stronger leading indicator for future surges in COVID-19 cases and thus hospital admissions.

The differing lag times between symptomatic and asymptomatic patients could represent different temporal associations of Ct values with different aspects of a growing epidemic, increases in cases and in turn increases in hospitalizations which tend to occur 6–12 days after symptom onset. [25] Utilizing data collected nationwide in Belgium, it was found that Ct values from all tests correlated with mean daily positive tests, with a lag of 17 days. [22] In contrast, a large study looking at population level data for a large metropolitan area in the United States found that hospitalizations correlated with median Ct values collected 33 days prior. [23] Other predictive methods utilizing qPCR data such as wastewater monitoring of SARS-CoV-2 display a similar pattern. Trends in wastewater levels of viral RNA precede changes in the total case numbers of a community by 4–10 days. [26] Similar to what is seen with Ct values in clinical specimens, trends in levels of SARS-CoV-2 RNA in wastewater precede increases in hospitalizations by a longer duration, up to 3 weeks in advance. [27]

Different characteristics of asymptomatic patient populations could also be contributing to differences seen in when Ct values. Symptomatic individuals represent an oftentimes self-selected population that developed symptoms and subsequently presented to the hospital for care. Overall spread in the community may be better characterized by the

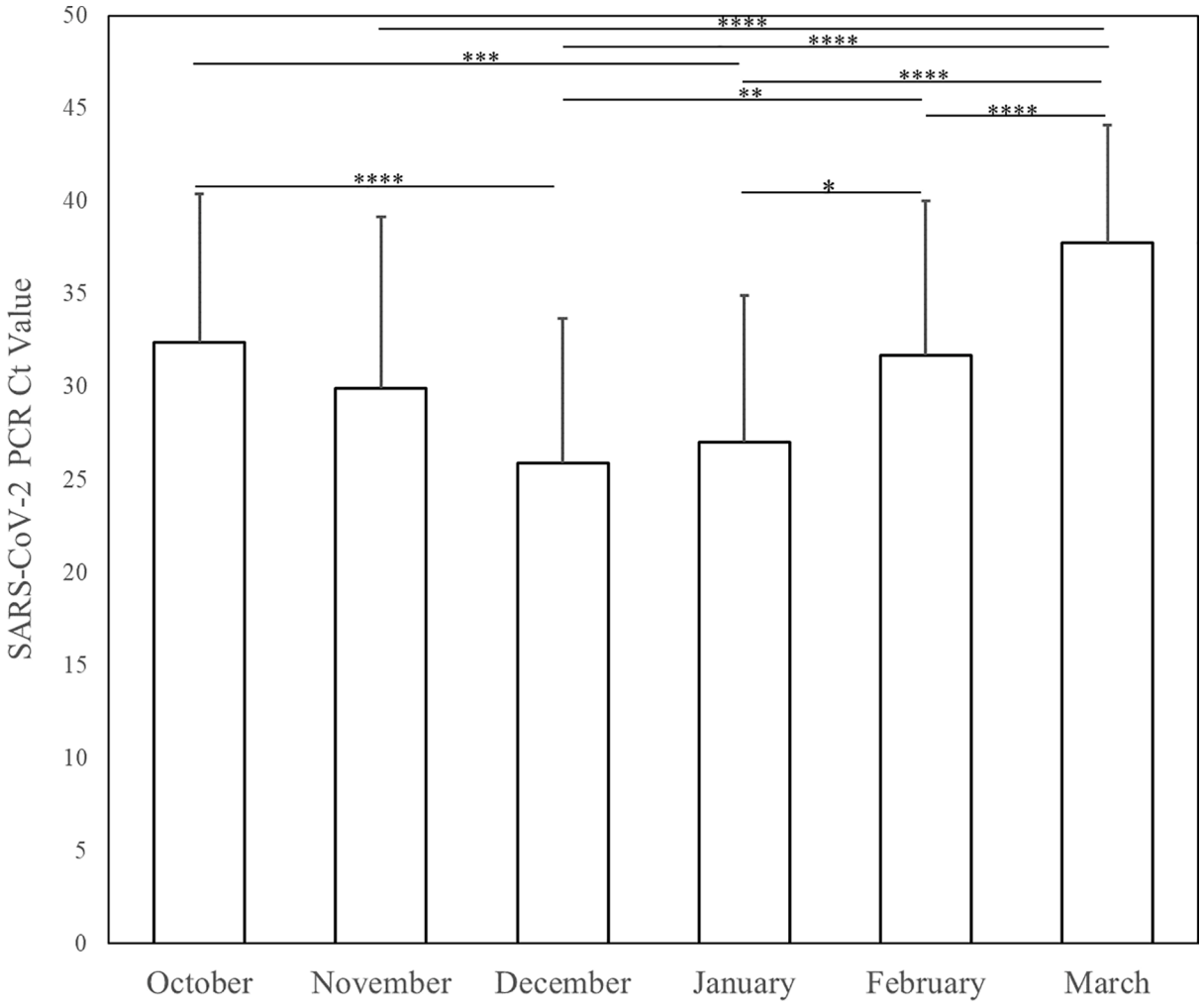


**Fig. 2.** Average Ct values per month. The months of December 2020 and January 2021 were significantly lower than months preceding and following. One-way AVOVA testing (*$P$<0.05, **$P$<0.01,***$P$<0.001, ****$P$<0.0001).

more random selection represented by the asymptomatic group in our study. Additionally, there are inherent differences both in the viral dynamics and in the behaviors of asymptomatic and symptomatic individuals. While time to peak viral loads have been shown to be similar between the two groups, symptomatic individuals can take significantly longer to clear their infection which may increase the proportion of late infections detected and included in the analysis. [28] Additionally, since viral levels in symptomatic individuals peak around the onset of symptoms, several days prior to hospital admission, a sizeable proportion of these patients would be tested during the clearance phase of their infection. [24] This delay from peak viral load at symptom onset to presentation at the hospital means that a greater proportion of early infections would likely be captured by populations containing more asymptomatic individuals. Since the predictive capacity of this method relies on the shifting distribution of cases at different stages of infection, increased sensitivity to early infections and reduced numbers of late infections may shift correlations between Ct values and hospitalizations farther into the future for datasets more heavily weighted with tests from asymptomatic individuals. Social factors such as participation in activities may make this group a more prominent driver of infections and thus a potentially better surrogate for measuring community spread. [29] To our knowledge at the time of writing, no other studies have investigated how the presence of symptoms can change correlations between Ct values and future cases. Further studies separating these patient populations are warranted to investigate the generalizability of these results.

As proof of concept, we utilized the correlation between average weekly Ct values and future cases to provide rudimentary insights into the near-future progression of COVID-19 cases. The introduction and subsequent dominance of the Delta variant into Los Angeles County in May 2021 as well as rising vaccination rates may have decreased accuracy of this approach. The Delta variant has been shown to have a shorter proliferation phase of infection, peaking sooner than prior variants. Vaccination status also can change infection dynamics by significantly reducing the clearance phase of infections and decreasing the total number of days where it is possible to detect the virus. [13] The changing dynamics caused by these two factors could potentially alter the proportion of early versus late infections detected, impacting how accurately a model based on very different dynamics can predict whether the pandemic is waxing of waning. Additionally, infections with the Delta variant are associated with higher viral loads (and thus lower Ct values) than infections with prior variants (i.e. viruses circulating with which the model was generated) which would cause this method to overestimate future number of cases. [13, 30] Despite these confounders, the general trend of increased future cases was still largely successfully captured.

Real-time tracking of a pandemic's local trajectory is essential for resource allocation. Concerns over the potential for local surges in COVID-19 cases prompted many hospitals in the US to preemptively suspend elective procedures at various points. It is estimated that elective procedure cancellations led to deficits of $16.3-$17.8 billion per month in revenue and between $4-$5.4 billion per month in net income

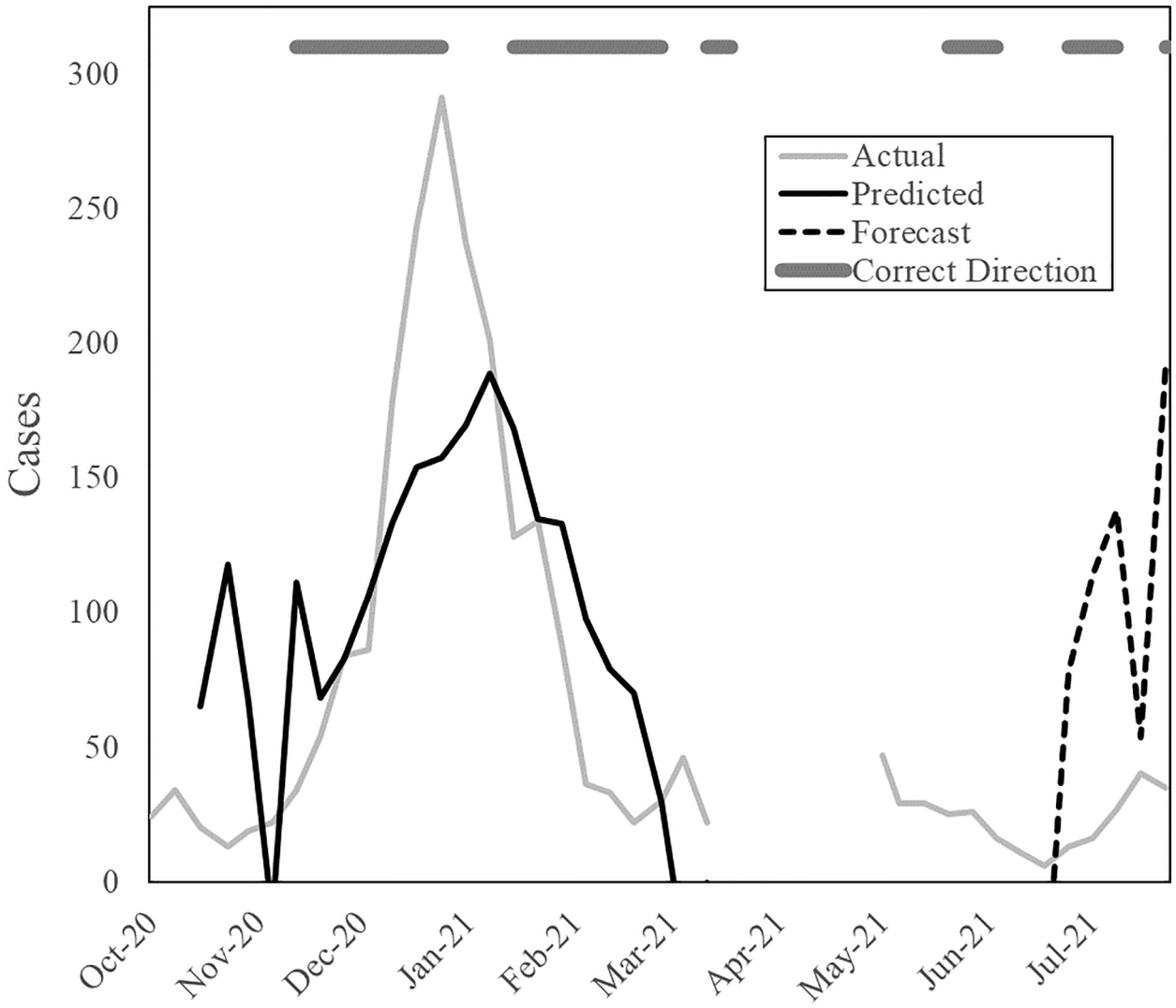


**Fig. 3.** Actual and predicted cases using using a linear regression model generated from pooled weekly Ct values. The thick line at top of chart represents times when the model correctly predicted the direction of weekly cases. Model was generated with Ct values of all COVI COVID cases between October 1, 2020, and March 31, 2021. Data collected from May 4, 2021 until July 31, 2021 were were used to validate the forecasting estimates.

for the US hospital system. [31] Institutional-level Ct value monitoring could be a potentially useful tool for informing key decisions e.g. surge staffing, preemptive suspension of elective procedures, etc. The current practice of waiting for an increase in local or institutional case counts to occur misses the opportunity to detect potential surges earlier in their course. Here, we observed that decreases in Ct values predicted future COVID-19 cases and have the potential to be a tool for anticipating future changes in institutional COVID-19 cases.

Though Ct values can be compiled from routine clinical testing by clinical microbiology laboratories, we do not believe that Ct values should be clinically reported on all patients. Studies have shown differences of up to five cycles when the same sample is tested by different assays. [32] Similarly, laboratory proficiency testing data show enormous variability in Ct values between laboratories, even when the same assay is used. [33] It is critical to note that Ct values are not viral loads, which are determined using quantitative assays that often normalize for specimen quality. Importantly, specimen quality dramatically impacts the Ct value obtained. [34] Neither does a high Ct value necessarily indicate the absence of infectious virus as Ct values vary over the infectious course and between specimen sources [35]. Additionally, viral loads are just one component of transmissibility along with contact pattern (e.g. duration of exposure, activity), the environment (e.g. ventilation) and host factors (e.g. age). [36] Nevertheless, useful population-level data can be derived from analyzing aggregate Ct value data.

Predictions generated from data like ours are likely less applicable to disease dynamics in the general population and may be more applicable to the dynamics seen at an individual hospital. Put another way, these data are a measure of epidemic dynamics in a given hospital's patient population, rather than the population generally. While these are undoubtedly related, demographics can inherently differ when, for instance, a hospital patient population consists disproportionately of people who are older or who have higher comorbidity rates. However, this distinction does not diminish the potential utility of these findings, as the financial and human burden of pandemics fall disproportionally on hospital systems. In theory, compiling large-scale data across multiple institutions or testing labs could be complicated by the fact that a wide number of clinical assays are in use, and Ct values are not necessarily comparable between assays even when the same gene is targeted. [37] It is therefore possible that aggregate Ct values in such a scenario could result in noise potentially complicating interpretation. Importantly, one of the few studies to assess this looked at single assay. [16] The impact of Ct values from multiple distinct assays and gene targets on regional surge prediction is currently unknown.

Other limitations of this study include that it is limited to a single hospital and assay manufacturer (i.e. Cepheid). Simplexa results were

not included in this study due to a lack of comparability in Ct values between our instruments during the study period. Interestingly, one study that found a lack of correlation between Ct values and clinical outcomes used the Simplexa assay. [38] In addition, bias could be introduced based on hospital-specific testing policies and algorithms, as well as shortages of testing supplies. While all inpatient admissions at our hospital were tested for SARS-CoV-2, only patients where there was a clinical suspicion for COVID-19 were tested in the Emergency Department. A similar selection bias would presumably be present at any institution testing for SARS-CoV-2, and so likely would not affect the applicability of our findings to other hospitals. Variation in specimen quality impacts the amount of viral RNA in each individual sample although is minimized with the large sample size and use of aggregate data in our analysis. Our study period encompasses the period when the Cal.20C variant was circulating locally. The impact, if any, of current or future variants on the kinetics of Ct value decreases is currently unknown.

In summary, the ability to easily estimate the relative burden of future COVID-19 cases in a hospital system would provide more guidance for better resource allocation. SARS-CoV-2 Ct values, which can be obtained from clinical testing, can provide additional information for individual hospitals to anticipate disease outbreaks and inform decisions to use resources more judiciously.

## Supplementary material

22.03.30-Supplement_COVID-19 Ct Paper.docx

## Conflict of Interest Statement

Dr. Butler-Wu has received consulting honoraria from Cepheid.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2022.105153.

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