Covid-19 positive test cycle threshold trends predict covid-19 mortality in Rhode Island

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Abstract

The cycle thresholds (Cts) at which reverse transcriptase polymerase chain reaction (rtPCR) tests for covid-19 become positive are intimately associated with both viral load, and covid-19 infectiousness (i.e., ability to culture live virus). Clinical data indicate lower Cts—and hence larger viral loads—independently predict greater covid-19 mortality when patients are hospitalized for symptomatic covid-19 pneumonia. We merged public covid-19 mortality data from the Rhode Island Department of Health with a de-identified dataset of n=5036 positive rtPCR test Cts from the Rhode Island Department of Health State Laboratory to explore the potential relationship between positive covid-19 test Ct distribution trends, and covid-19 mortality in the state of Rhode Island, from March through early to mid-June, 2020. Mean daily covid-19 positive test Ct data were compiled, and 7-day rolling average covid-19 mortality was offset by 21-days, given the lag between infection and death. We divided the Ct data into three strata, >32, 28-32, and <28, which were operationally defined as "not infectious," "maybe infectious," and "infectious," respectively. Between late March and June, mean daily Ct values rose linearly (R-squared=0.789) so that by early June, as the covid-19 pandemic ebbed in severity, all means reached the noninfectious (Ct >32) range. Most notably, this May-June trend for Cts was accompanied by a marked, steady decline in Rhode Island's daily covid-19 mortality. Our results suggest that monitoring, and public reporting of mean population covid-19 test Cts over time is warranted to gauge the vacillations of covid-19 outbreak severity, including covid-19 mortality trends.

Introduction

The cycle thresholds (Cts) at which reverse transcriptase polymerase chain reaction (rtPCR) tests for covid-19 become positive are intimately associated with both viral load, and covid-19 infectiousness (i.e., ability to culture live virus).[1,2] An rtPCR covid-19 assay system developed at the Harvard University/ Massachusetts Institute of Technology Broad Institute,[3] currently determining covid-19 "positivity" at 108 northeastern universities—including Rhode Island's major colleges[4]—described this *exponential* relationship:[3] *"…the Ct values correlated strongly with the logarithm of (covid-19) RNA concentration (R-squared > 0.99), with the observed range from Ct =12 cycles to Ct = 38 cycles corresponding to viral loads ranging from ~1.9 billion copies/mL to 8 copies/mL, respectively*

Additional clinical data indicate lower Cts—and hence larger viral loads—independently predict greater covid-19 mortality when patients are hospitalized for symptomatic covid-19 pneumonia, or other manifestations of being heavily infected by the virus.[5] Conversely, a study which recorded Cts of patients, serially, during their hospitalization for diagnosed covid-19 pneumonia, reported that increasing Cts were accompanied by decreasing disease severity (Sequential Organ Failure Assessment; SOFA) scores.[6] We explored the potential relationship between positive covid-19 test Ct distribution trends, and covid-19 mortality in the state of Rhode Island, between March and June, 2020.

Methods

Public covid-19 mortality data from the Rhode Island Department of Health COVID-19 Data Tracker,[7] were merged with a de-identified dataset of n=5036 positive rtPCR test Cts obtained through an Access to Public Records Act request to the Rhode Island Department of Health State Lab (RISHL). Standard rtPCR SARS-CoV-2 assay methodology targeting the nucleocapsid genes N1 and N2 was employed by the RISHL.[8] Mean daily covid-19 positive test Ct data were compiled, and 7-day rolling average covid-19 mortality was offset by 21-days, given the lag between infection and death. We divided the Ct data into three strata, >32, 28-32, and <28, which were operationally defined as "not infectious," "maybe infectious," and "infectious," respectively, consistent with prior reports[1,2], including a pooled analysis of six studies[1].

Results

Between late March and June, mean daily Ct values rose linearly (Figure 1.; R-squared=0.789) so that by early June, as the covid-19 pandemic ebbed in severity, all means reached the non-infectious (>32) range. Most notably, Figure 2. depicts how this May-June trend for Cts was accompanied by a pronounced, steady decline in Rhode Island's daily covid-19 mortality,

Discussion

An analysis evaluating the infectiousness of patients hospitalized with covid-19 reported that ***only*** viral loads > 10 million copies/mL, equivalent to Cts ≤ 25, were associated with isolation of infectious virus from the respiratory tract.[9] A complementary systematic review published 12/3/30 by the Oxford University Center for Evidence-Based Medicine confirmed that covid-19 rtPCR testing patient sample Cts >30 (mean from 6-studies) are associated with an inability to culture live virus, i.e., are non-infectious.[1]

Data analyzed from the United Kingdom's National Covid-19 Infection Survey revealed a significant impact of calendar time on the prevalence of rtPCR positives at a Ct <30: markedly fewer during mid-July to early August, versus the month of May, through mid-June, 2020.[6] Moreover, investigators from the Bronx Montefiore Medical Center have reported lower hospital admission covid-19 rtPCR Cts were independently associated with increased covid-19 inpatient mortality.[5] Specifically, Cts <22.9 (the lowest quartile), multivariable-adjusted for age, sex, body-mass index, hypertension, and diabetes, were associated with ~4-fold greater covid-19 mortality risk, versus Cts >32.4 (the uppermost quartile).[5] Using a comparable cutpoint, *a priori*, i.e., Cts >32,[2] we externally validated these findings by demonstrating that statewide Rhode Island covid-19 mortality dropped precipitously from March to June, 2020, as mean covid-19 positive test Cts from our RISHL sample rose above 32.

Conclusion

Our results suggest that monitoring, and public reporting of mean population covid-19 test Cts over time is warranted to gauge the vacillations of covid-19 outbreak severity, including covid-19 mortality trends.

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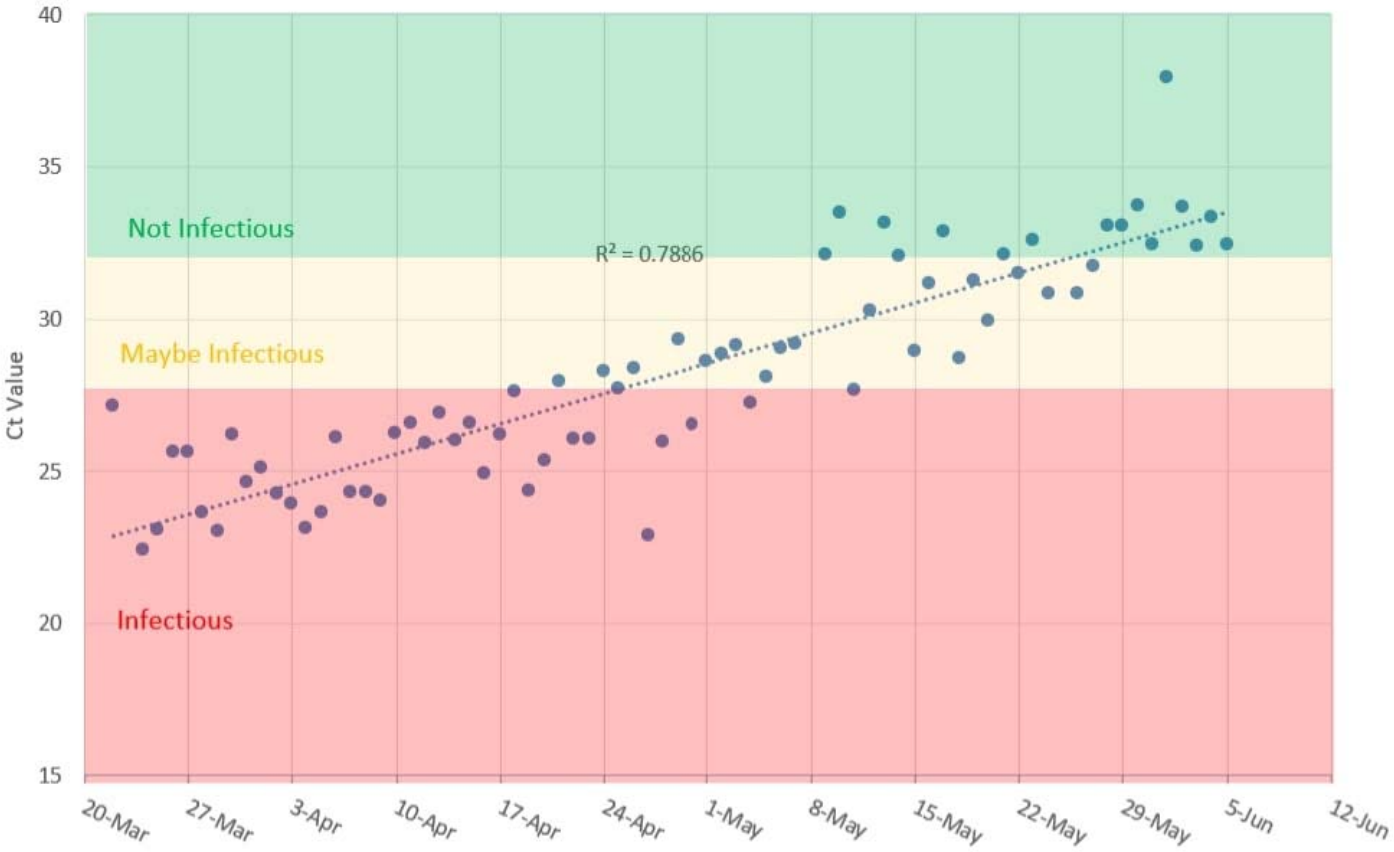
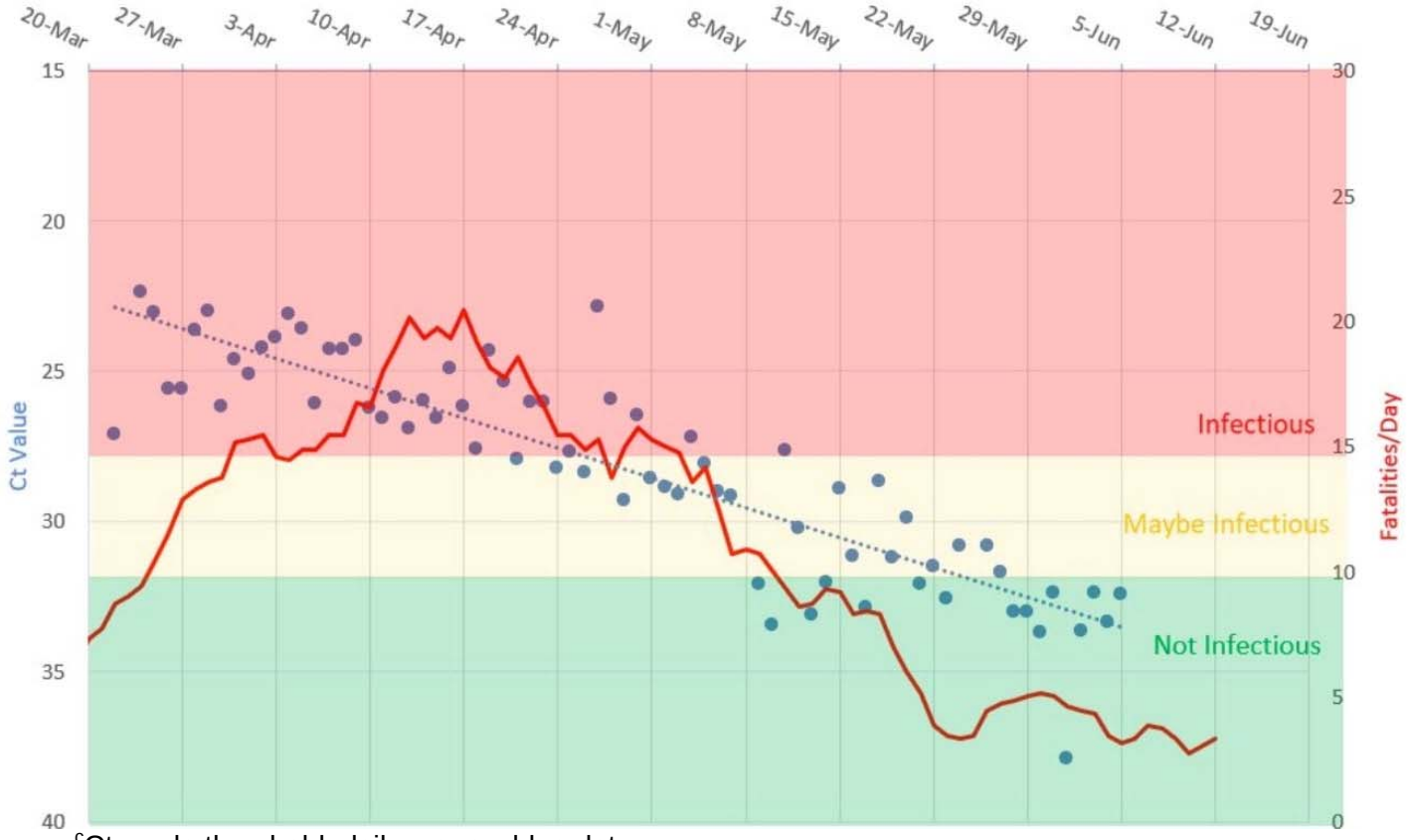
Figure 1. Covid-19 rtPCR[a] mean daily Ct[b] values, March-June, 2020



[a]rtPCR= reverse transcriptase polymerase chain reaction
[b]Ct=cycle threshold, daily means; blue dots

Figure 2. Covid-19 rtPCR positive test mean daily Ct values[c], and covid-19 deaths[d]



[c]Ct=cycle threshold, daily means; blue dots
[d]21-day offset for 7-day rolling average of deaths; red line curve