

Utilization of laboratory-based COVID-19 test results

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Abstract

During the coronavirus disease 2019 (COVID-19) pandemic, COVID-19 testing is crucial, as it enables early detection and halting the spread of infection throughout the community. Real-time reverse-transcriptase polymerase chain reaction (Real-time RT-PCR) testing is the predominant method for COVID-19 testing, and the cycle threshold value (Ct value) is used to determine COVID-19 positivity. There are many ongoing studies using Ct value, and the present study aims to examine time series distribution during the pandemic using Ct values at the national level and analyze the association with time-varying reproduction number (Rt) to discuss the utilization of laboratory-based COVID-19 test results. We used Real-time RT-PCR results collected by Seegene Medical Foundation from the index case in Korea in February 2020 to January 2022 in Korea. The distribution of daily Ct value (*RdRp/S* target) was examined, and it was compared with the daily count of newly diagnosed cases and Rt to determine the usability of Ct values. Moreover, time lag was applied to the daily count of newly diagnosed cases to analyze the association between Ct values and Rt. During the COVID-19 pandemic, Ct values declined in general, while viral load increased progressively. After Ct values dropped markedly, the number of newly diagnosed cases rose substantially, and the association analysis also confirmed that the daily count of newly diagnosed cases declined with increasing Ct values. The time series trend of the Ct values was also similar to that of Rt, a classic marker used as a predictor of the trends of the pandemic, and when compared to the actual count of newly diagnosed cases, Ct values can be used to predict new diagnoses earlier than Rt. The fact that the Ct values were more sensitive to a substantial rise of new COVID-19 cases than Rt was in the early days of the pandemic also support this. We examined the potential of Ct values as a predictor of new COVID-19 cases in real-time using nationally collected Ct value data. Further, we proposed the use of Ct values as an index reflecting the degree of viral load, so the findings of this study can be used as valuable evidence to support public health decisions for response and resource distribution.

Utilization of laboratory-based COVID-19 test results

laboratory-confirmed COVID-19

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ABSTRACT

During the coronavirus disease 2019 (COVID-19) pandemic, COVID-19 testing is crucial, as it enables early detection and halting the spread of infection throughout the community. Real-time reverse-transcriptase polymerase chain reaction (Real-time RT-PCR) testing is the predominant method for COVID-19 testing, and the cycle threshold value (Ct value) is used to determine COVID-19 positivity. There are many ongoing studies using Ct value, and the present study aims to examine time series distribution during the pandemic using Ct values at the national level and analyze the association with time-varying reproduction number (Rt) to discuss the utilization of laboratory-based COVID-19 test results.

We used Real-time RT-PC results collected by Seegene Medical Foundation from the index case in Korea in February 2020 to January 2022 in Korea. The distribution of daily Ct value (*RdRp/S* target) was examined, and it was compared with the daily count of newly diagnosed cases and Rt to determine the usability of Ct values. Moreover, time lag was applied to the daily count of newly diagnosed cases to analyze the association between Ct values and Rt.

During the COVID-19 pandemic, Ct values declined in general, while viral load increased progressively. After Ct values dropped markedly, the number of newly diagnosed cases rose substantially, and the association analysis also confirmed that the daily count of newly diagnosed cases declined with increasing Ct values. The time series trend of the Ct values was also similar to that of Rt, a classic marker used as a predictor of the trends of the pandemic, and when compared to the actual count of newly diagnosed cases, Ct values can be used to predict new diagnoses earlier than Rt. The fact that the Ct values were more sensitive to a substantial rise of new COVID-19 cases than Rt was in the early days of the pandemic also support this.

We examined the potential of Ct values as a predictor of new COVID-19 cases in real-time using nationally collected Ct value data. Further, we proposed the use of Ct values as an index reflecting the degree of viral load, so the findings of this study can be used as valuable evidence to support public health decisions for response and resource distribution.

1 INTRODUCTION

In South Korea, the first case of COVID-19 was confirmed on January 20, 2020, and the government established its response measures based on aggressive testing, tracing, and quarantine and isolation. Of these strategies, aggressive testing is at the core for preventing the spread of infection through the community by enabling early detection of infection, and to facilitate testing, the government launched many screening testing sites, implemented mobile sample collection teams and mobile health examination services, continually increased diagnostic testing counts, and added COVID-19 to the existing respiratory disease surveillance system. As a result, mass COVID-19 tests were done with quick turnaround times, and the government performed tracing, enforced quarantine, and provided treatment based on the test results; for this, South Korea was considered to have done well in COVID-19 control compared to other countries (Lee, 2020).

In South Korea, COVID-19 tests are primarily performed via the 2019 Novel coronavirus Real-time reverse-transcriptase polymerase chain reaction (Real-time RT-PCR) to detect viral genes, and upper airway and lower airway samples are generally used. The assay is designed to detect two or three regions of SARS-CoV-2 genes that encode nucleocapsid (*N*), envelope (*E*), or spike (*S*) proteins or RNA-dependent RNA polymerase (*RdRp*) gene. Of various results generated by Real-time RT-PCR, cycle threshold (Ct) values, which is the number of cycles of amplification required to cross a certain threshold, are used to determine COVID-19 positivity. A sample is deemed positive when the Ct value of the target gene is equal to or smaller than the cutoff. Because this value can also be understood as the viral load, a lower Ct value is interpreted as a higher viral load.

Many recent studies have utilized Ct values in their investigation, primarily the association between Ct values and demographic factors (Ade et al., 2021; Chung et al., 2021), disease severity (Bustos et al., 2021), and mortality rate (Miller et al., 2021; Waudby-West et al., 2021). However, these studies are limited in the fact that they used positive COVID-19 samples from small regions or Ct values from hospitalized patients.

On the other hand, studies have also utilized Ct values in predicting future infection transmission trends

and monitoring infectious diseases. During an epidemic, investigating the transmission trend and predicting the size of outbreaks present valuable data for devising response measures against the epidemic. Currently, time-varying reproduction number (R_t) is used as an index for predicting the trends of an epidemic. However, R_t is dependent on the number of confirmed cases, and one key shortcoming of the index is that it cannot provide real-time prediction of the size of an epidemic due to the delay between the latent period of a disease and reporting of confirmed cases. To overcome such limitation of R_t , a few studies showed that large population distributions of Ct values can be used to predict epidemic trends (Lin et al., 2022; Yin et al., 2021). Furthermore, some studies added distributions of Ct values to the existing R_t calculation to generate more accurate predictions and compared their predictive accuracies (Alizon et al., 2022; Hay et al., 2021). However, these studies utilized Ct values collected from a short period or simply modeled their results using Ct values obtained through a simulation, and the said studies also analyzed the correlation between Ct values and prevalence, such as number of severe cases of infection, as opposed to the incidence rate.

Therefore, this study aims to investigate the long-term time series distribution of Ct values from nationally representative data and analyze the associations with the number of new cases and R_t trends to discuss the use of laboratory-based COVID-19 test results.

2 METHODOLOGY

Real-time RT-PCR results were obtained from the Seegene Medical Foundation. The assays used were divided into different periods. In the early stages, emergency use assays (Allplex 2019-nCoV (SARS-CoV-2) Assay, *E*, *RdRP*, *N* gene target (February 7, 2020 to December 13, 2020)) were used, and official assays (Allplex SARS-CoV-2 Assay, *E*, *RdRP/S*, *N* gene target (December 14, 2020 to January 31, 2022)) were used thereafter. The data was of upper airway samples collected from February 2020 to January 2022 from the collected specimens, Ct values from a total of 296,347 specimens that tested positive with *RdRP/S* as the target gene were used. The daily median Ct values were computed to determine the time series trends, and the category-specific distributions of Ct values were also examined. In addition, Ct values were compared against the number of new cases and R_t trends to determine their associations. Data for new cases and R_t were obtained from the Korea Disease Control and Prevention Agency (KDCA) for the period between January 20, 2020 (date of index case) to January 2022.

Time series trends and associations were analyzed for the total time and by four COVID-19 waves. The COVID-19 waves were defined by the KDCA; the first, second, and third waves were primarily mass outbreaks in a particular region, while the fourth wave was characterized by community-wide outbreaks facilitated by contacts throughout the community. The first wave is from January 20, 2020 to August 11, 2020. There was a total of 14,660 confirmed cases (daily average 71.5), and the fatality rate—defined as the ratio of confirmed cases to number of deaths—was 2.1%. The major routes of infection were a religious facility and health care facility in a non-metropolitan area. The second wave was from August 12, 2020 to November 12, 2020. There was a total of 13,280 confirmed cases (daily average 142.8), and the fatality rate was 1.66%. During this wave, small and medium-sized outbreaks occurred in religious facilities and demonstrations in the metropolitan area. The third wave was from November 13, 2020 to July 6, 2021. There was a total of 133,600 confirmed cases (daily average 566.1), and the fatality rate was 1.16%. Mass outbreaks occurred in correctional facilities, health care facilities, and religious facilities primarily in the metropolitan area. The fourth wave was from July 7, 2021 to January 31, 2022. There was a total of 684,068 confirmed cases (daily average 3,273.1), and the fatality rate was 0.69%. New patients were concentrated in the metropolitan area and large cities, and the cases surged markedly compared to previous waves due to several factors, including the diminished vaccine effectiveness, domination of the Delta variant, and emergence of the Omicron variant (Yang et al., 2022).

For the association analysis, we applied a time lag between Ct values and new cases and R_t for a detailed analysis of the two indices. The data were analyzed using the SAS 9.4 software (SAS Institute, Inc.).

3 RESULTS

In South Korea, a total of four COVID-19 waves occurred between January 20, 2020 to January 31, 2022.

We examined the distributions of daily Ct values, new cases, and Rt and analyzed their associations for the entire period and by the periods of four COVID-19 waves.

During the entire period, Ct values declined in general, indicating an increased viral load over time. In terms of the new cases, the number of new cases surged after a substantial drop of Ct values. During the first wave, the number of new cases rose rapidly at a point in which Ct values decreased, and Ct values increase gradually and subsequently declined with a rapid drop prior to the onset of the second wave. During the second wave, the number of new cases surged after the Ct values hit bottom, and Ct values rose gradually and subsequently dropped, with a marked decline until the onset of the third wave. During the third wave, the number of new cases also surged after the Ct values hit bottom, and the Ct values rose substantially and then rose again. During the fourth wave, the Ct values remained high with a smaller degree of change compared to that in previous periods, and although the number of new cases increased when Ct values decreased, the degree of increase in the number of new cases was very large (Figure 1).

The median Ct values were compared by COVID-19 wave. The median Ct value was the highest (31.71) in the first wave and decreased over time, with the lowest value (21.27) in the fourth wave (Figure 2).

By categories of Ct values, the percentage of Ct values < 25 increased whenever the number of new cases surged during the first, second, and third waves. However, during the fourth wave, the percentage of Ct values < 25 remained high regardless of the number of new cases (Figure 3).

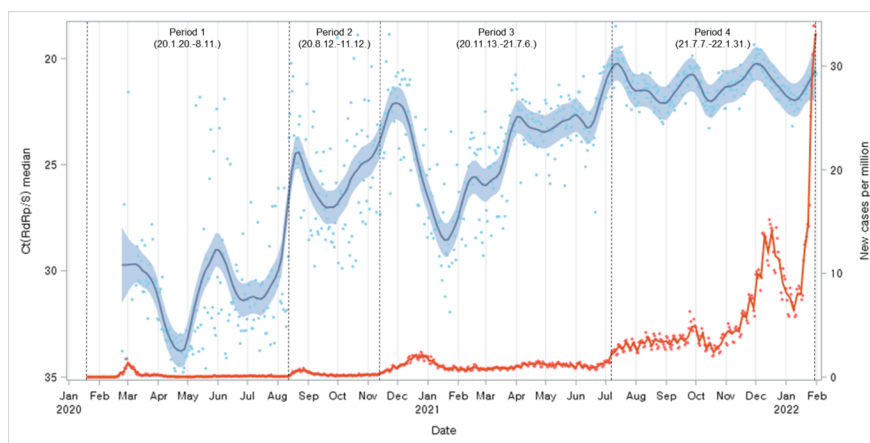


Figure 1. Distributions of Ct values and new cases per million population

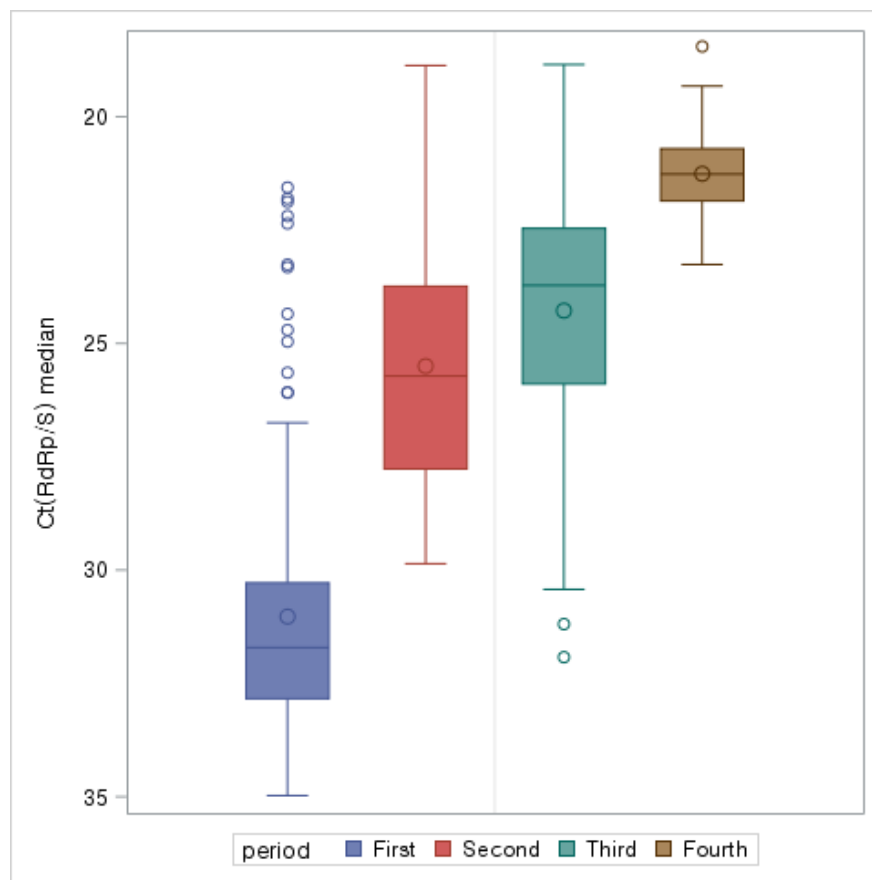


Figure 2. Median Ct values by COVID-19 wave

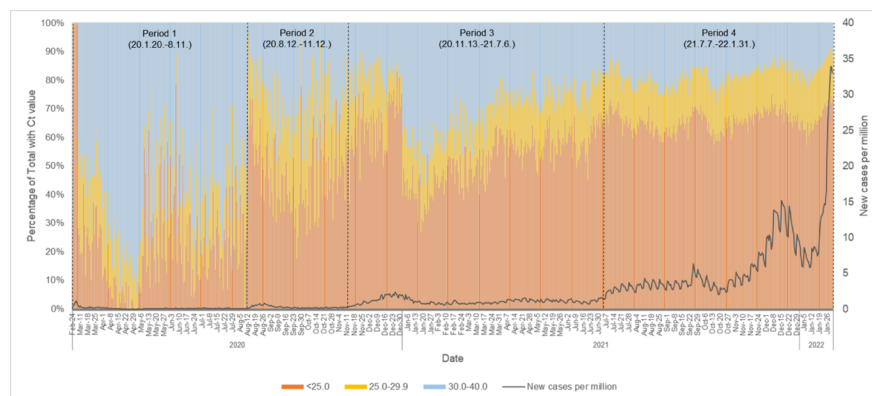


Figure 3. Percentages of different Ct value categories

Before comparing Ct value trends and Rt trends, we compared Rt trends with number of new cases. The number of new cases increased at a point in which Rt rose substantially. By period, there was a marked increase of new cases when Rt rose significantly during the first and second waves, but during the third and fourth waves, Rt remained largely stable despite the number of new cases surging (Figure 4).

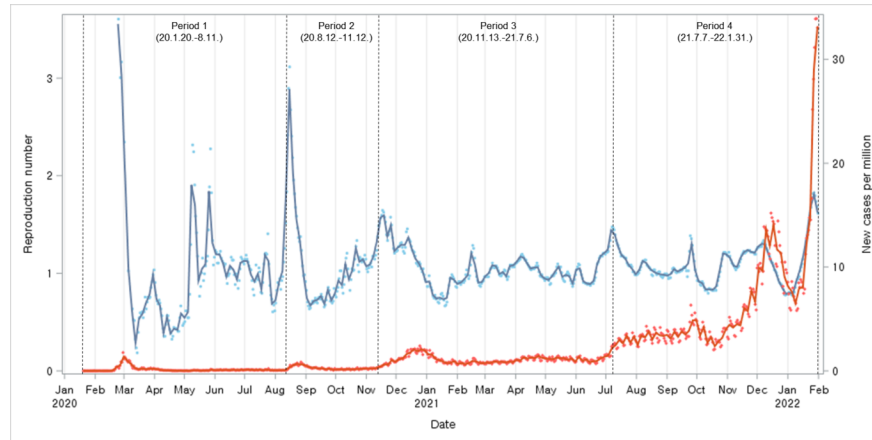


Figure 4. Distributions of R_t and new cases per million population

We compared Ct value trends and R_t trends. R_t rose when Ct values decreased, while R_t decreased when Ct values increased. However, while Ct values and R_t showed similar trends during the first and second waves in that both fluctuated dramatically, R_t did not change dramatically since the third wave (Figure 5).

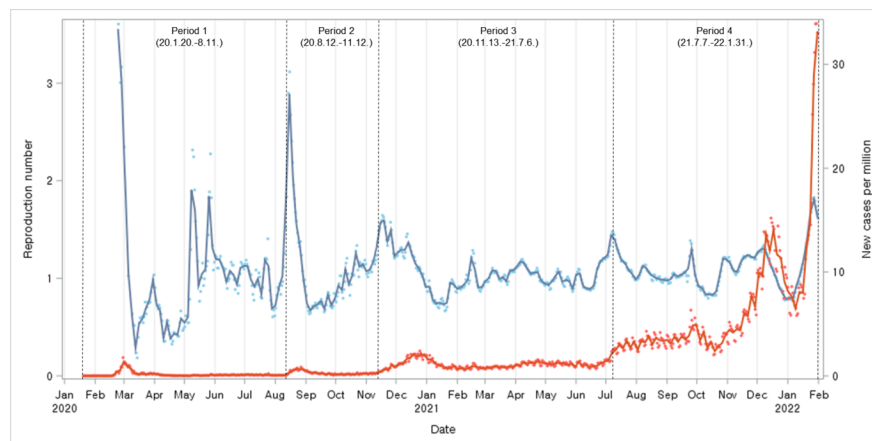


Figure 5. Distributions of Ct values and R_t

We analyzed the association between Ct values and number of new cases and between R_t and number of new cases. Both Ct values and R_t rose before a surge in new cases, so we analyzed the association in consideration of a time lag.

We performed a regression analysis to examine the association between daily Ct values and incidence per million population, and the time lag at which the two variables were most strongly correlated was 7 days. Thus, we analyzed the association between Ct values and incidence per million population seven days later, and the results confirmed a negative association between Ct values and number of new cases, where new cases decreased with increasing Ct values (Figure 6).

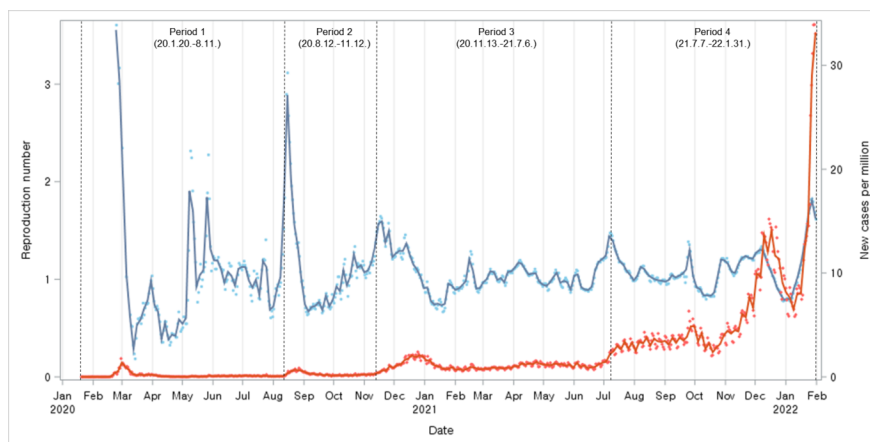
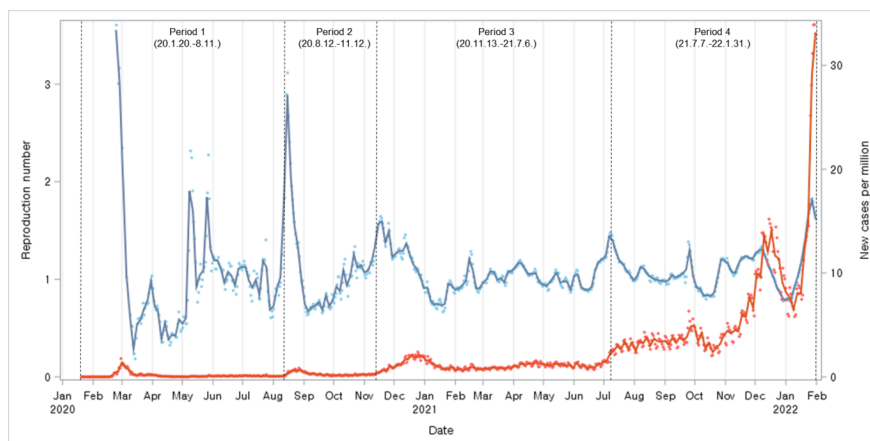
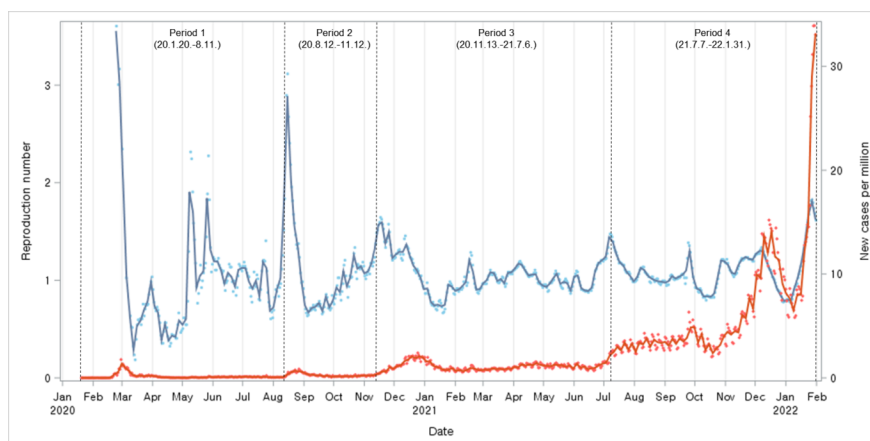
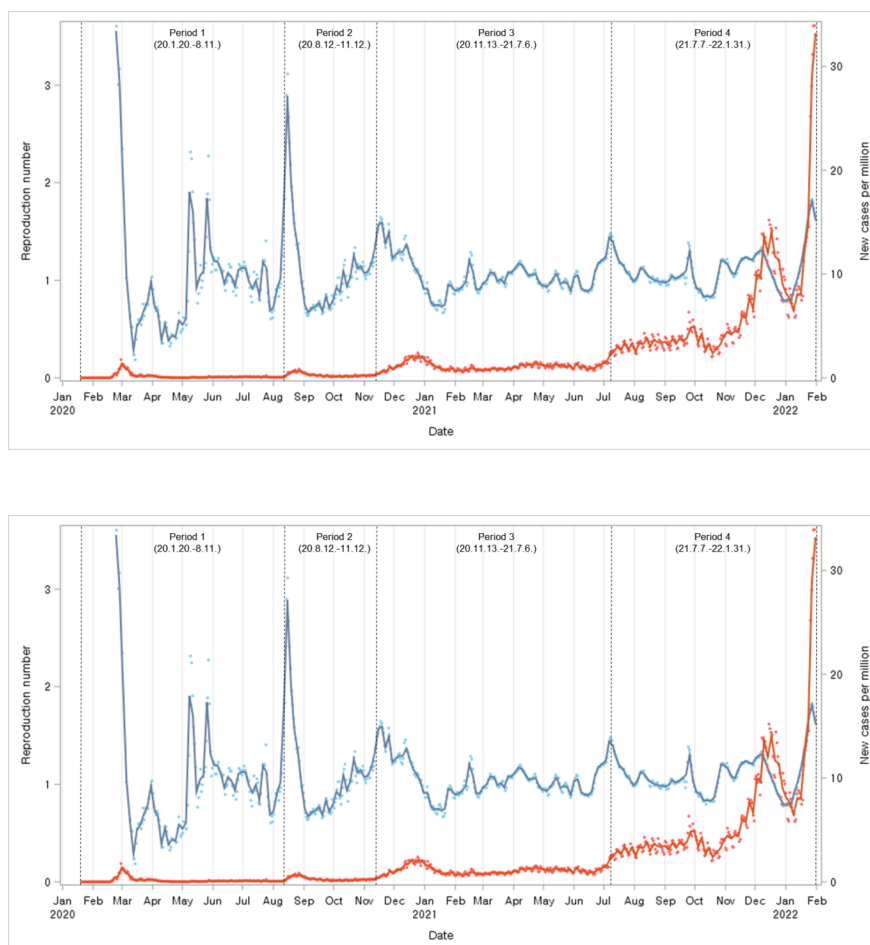


Figure 7. Association between Ct values and number of new cases

We analyzed the association between Ct values and new cases by COVID-19 wave. During all four waves, new cases declined with increasing Ct values. The time lags differed across the four waves, with 7 days in the first wave, 4 days in the second wave, 7 days in the third wave, and 3 days in the fourth wave (Figure 7).



Period 1 (20.01.20-20.08.11.) Period 2 (20.08.12-20.11.12.)



Period 3 (20.11.13-21.07.06.) Period 4 (21.07.07-22.01.31.)

Figure 8. Association between Ct values and number of new cases by COVID-19 wave

We performed a regression analysis to examine the association between R_t and number of new cases. The time lag at which the two variables were most strongly correlated was 3 days. Thus, we analyzed the association between R_t and incidence per million population three days later, and the results confirmed a positive association between the two, where new cases increased with increasing R_t (Figure 8).

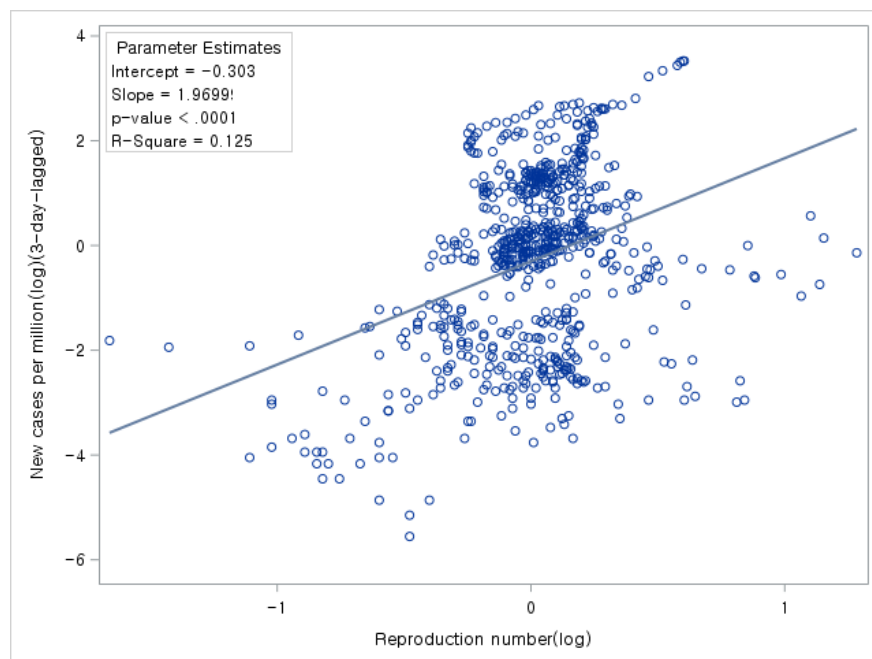
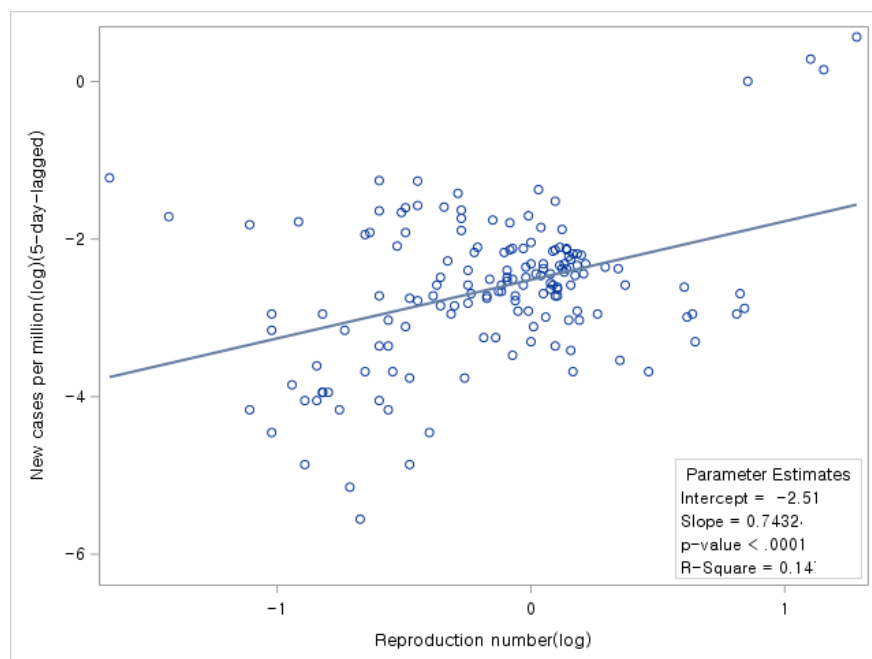
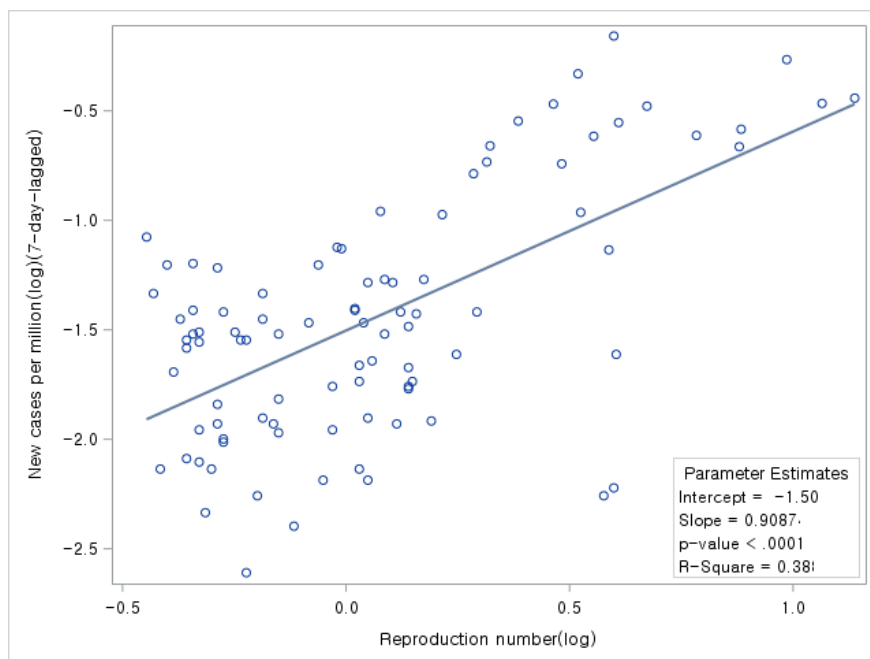


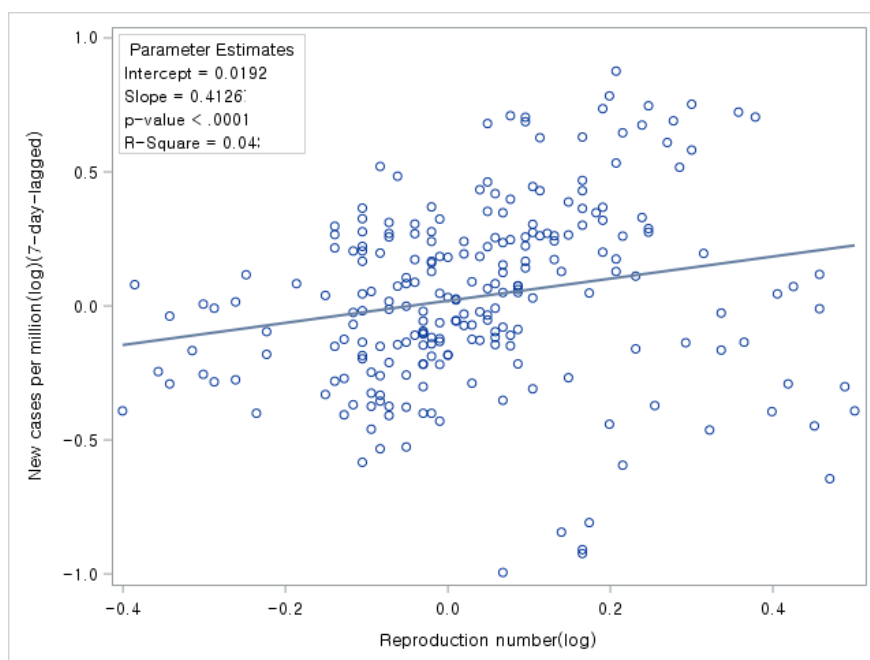
Figure 9. Association between R_t and number of new cases

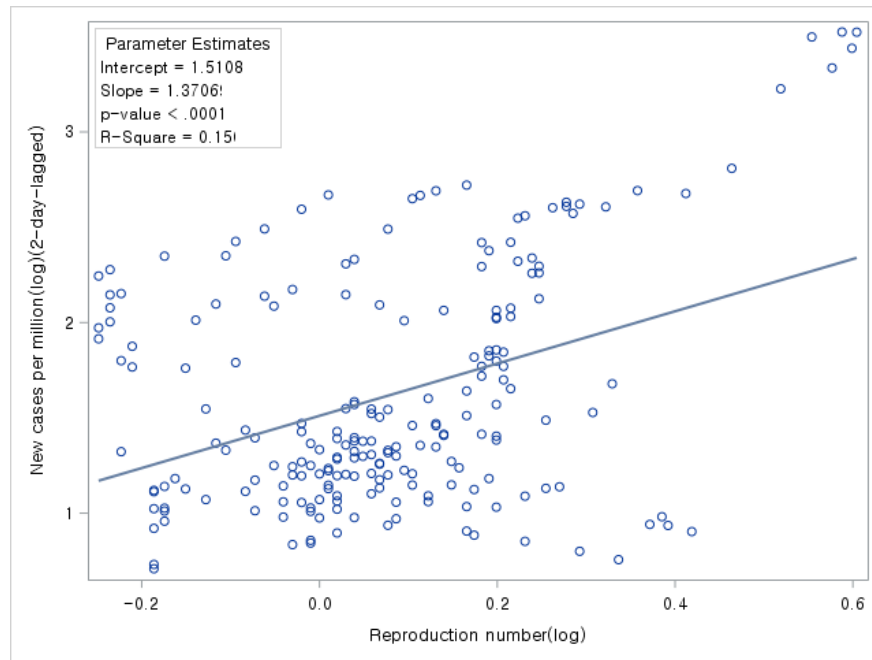
We analyzed the association between R_t and number of new cases by COVID-19 wave. During all four waves, new cases increased with increasing R_t . The time lags did not differ significantly across the four waves, with 5 days in the first wave, 7 days in the second and third waves, and 2 days in the fourth wave (Figure 9).





Period 1 (20.01.20-20.08.11.) Period 2 (20.08.12-20.11.12.)





Period 3 (20.11.13-21.07.06.) Period 4 (21.07.07-22.01.31.)

Figure 9. Association between R_t and number of new cases by COVID-19 wave

4 DISCUSSION

Since the first case of COVID-19 in the country on January 20, 2020, South Korea performed aggressive screening tests to ensure early detection of individuals who developed the infection and traced, quarantined, and treated patients as necessary, based on which it was considered to have done well in COVID-19 control compared to other countries. Aggressive COVID-19 testing was performed via Real-time RT-PCR, and the Ct value, which is the number of amplification cycles performed to cross a certain threshold, is used to determine positivity. This value can also be understood as viral load.

Recently, studies have expanded beyond the dichotomous use of Ct values for determining COVID-19 positivity or negativity and began to explore Ct values in relation to demographic characteristics, disease severity, and mortality rates. In addition, some studies have investigated the use of Ct values for predicting future epidemic trends and monitoring infectious diseases. Therefore, the present study aimed to examine the time series distribution of actual Ct values using nationally collected data and analyzed its association with the number of new cases and R_t trends to discuss the utilization of laboratory-based COVID-19 test results.

From January 20, 2020 to January 31, 2022, a total of four COVID-19 waves occurred in Korea. Hence, we analyzed the associations among daily Ct values, number of new cases, and R_t for the entire COVID-19 period and each COVID-19 wave. During the entire period, Ct values generally decreased, indicating an increased viral load over time. In relation to the number of new cases, the number of new cases surged after a substantial drop in Ct values. This reflects the fact that the number of new cases increases markedly after viral load is relatively increased. In terms of the different periods for COVID-19 waves, the average daily number of new cases was markedly higher during the second wave (142.8) than first wave (71.5), despite the fact that the cumulative number of cases was similar between the two periods, showing that the virus spreads more in a shorter period of time when Ct values are low.

When compared with R_t , which is used to predict incidence, the time series trends of R_t and Ct values were similar. However, when compared to the actual number of new cases, Ct values predicted new cases

earlier than R_t . Moreover, C_t values were more sensitive than R_t in predicting new cases before the later COVID-19 waves when the incidence rate skyrocketed.

We also compared C_t values against the emergence of variant viruses and launching of vaccination, which may contribute to changes in C_t values, but there were no significant changes in C_t values before and after these periods. The Alpha variant, discovered in late December 2020, had been the dominant variant until mid-July 2021, and the Delta variant became the dominant variant from July 2021 to end of December 2021. The Omicron variant was discovered in late November 2021 and became the dominant variant since. C_t values hit bottom in early December, before the emergence of the Alpha variant, and rose drastically until mid-January 2021. Then, C_t values again decreased until early July 2021, when the Delta variant emerged. Since the emergence of the Delta variant, C_t values remained high without marked changes. Although C_t values began to drop after February 26, 2021, when the vaccine rollout was begun, but the data shows that the timing of increase began to decline from before the initiation of vaccine rollout.

Our findings from the comparison of time series trends of C_t values obtained by analyzing nationwide data with trends of new cases show that C_t values can be used to predict future incidence rates and size of epidemic. Moreover, C_t values were found to predict the size of an outbreak more quickly than R_t , the classic predictor of epidemic trends. Furthermore, C_t values fluctuated more than R_t during the early days of the pandemic before the emergence of variants of concern, such as Delta and Omicron variants, highlighting its potential as an indicator sensitive to incidence rates. One limitation of this study is that our study data—although it was nationally collected data—only accounted for 40% of the total data and lacked test results for two out of 17 cities and provinces in Korea. However, there is a low risk of bias, as the data was collected through the same testing and sampling methods in a single diagnostic laboratory.

The findings show that C_t values can be used in the prediction of future outbreaks and determine viral load. Thus, these findings will serve as evidence supporting the use of C_t values to assist in public health decision making to determine the degree and timing of infection control responses as well as resource allocation, beyond simply using them for COVID-19 diagnostic purposes.

5 CONCLUSION

This study confirmed the potential of C_t values as a real-time indicator for future outbreaks by analyzing nationally collected C_t values. Furthermore, we found that the degree of the spread of virus differed depending on the C_t value even if the size of the outbreak was similar. Based on these findings, viral load and an indicator reflecting viral load could be presented alongside the number of new COVID-19 cases to facilitate public health decision making pertaining to infection control responses and resource allocation.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST STATMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) of Seoul National University (IRB No. E2207/001-002).

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