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Evaluation of RT-PCR Cycle Threshold Values of SARS-CoV-2 and Epidemiological Datas of COVID-19 Patients

SARS-CoV-2'nin RT-PCR Döngüsü Eşik Değerlerinin ve COVID-19 Hastalarının Epidemiyolojik Verilerinin Değerlendirilmesi

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Abstract

Aim COVID-19 infection is diagnosed by RT-PCR. In the RT-PCR test, results are interpreted according to the cycle threshold (Ct) values, provide indirect measurements of viral load. In this study we aimed to evaluate the relationship between Ct values and demographics datas and sypmtoms of patients.

Material and Method The nasopharyngeal swab of the patients suspectedof COVID-19 were collected and tested by RT-PCR for SARS-CoV-2. Demographics, medical history, timelines for exposure and symptoms of the patients diagnosed as COVID-19 by RT-PCR were obtained from the hospital information system.

Results Total of 619 patient result was enrolled in the study. Ct values were determined as 24.74 (20.95-27.64) for 18> years-old and 22.85 (20.14-26.22) ≥18 years-old, there was no statistically difference according to the age among Ct values. Hypertension was the most common comorbid disease (13.3%) among COVID-19 patients. A positive correlation was detected among the onset of the symptoms and Ct values, Ct values were lowest (corresponding to a higher viral RNA concentration) soon after symptom onset. Patients who had fever, headache, muscle-joint pain significantly had lower Ct values were than patients who did not have these sypmtoms.

Conclusion As a result it was detected that Ct values were lower soon after the occurence of the symptoms. It is important to early testing for SARS-CoV-2 among persons who have respiratory symptoms, and isolation of them when their viral load and transmission rate is higher.

Keywords COVID-19, cycle treshold value, epidemiology, SARS-CoV-2.

Özet

Amaç *COVID-19 enfeksiyonu, RT-PCR ile teşhis edilmektedir. Döngü eşiği (Ct) değerlerine göre yorumlanan RT-PCR testi sonuçları viral yükün indirekt ölçümlerini sağlar. Bu çalışmada hastaların demografik özellikleri ve semptomları ile Ct değerleri arasındaki ilişkiyi değerlendirmeyi amaçladık.*

Gereç ve Yöntem *COVID-19 şüphesi olan hastaların nazofaringeal sürüntüleri toplandı ve SARS-CoV-2 için RT-PCR ile test edildi. RT-PCR ile COVID-19 tanısı alan hastaların demografik bilgileri, tıbbi öyküleri, maruziyet zaman çizelgeleri ve semptomları hastane bilgi sisteminden elde edildi.*

Bulgular *Toplam 619 hasta sonucu çalışmaya dahil edildi. Ct değerleri 18> yaş için 24,74 (20,95-27,64) ve 22,85 (20,14-26,22) ≥18 yaş olarak belirlendi, Ct değerleri arasında yaşa göre istatistiksel olarak fark yoktu. Hipertansiyon, COVID-19 hastalarında en sık görülen yandaş hastalık (%13,3) oldu. Semptomların başlangıcı ile Ct değerleri arasında pozitif bir korelasyon saptandı, Ct değerleri semptom başlangıcından hemen sonra en düşüktü (daha yüksek bir viral RNA konsantrasyonuna karşılık gelir). Ateş, baş ağrısı, kas-eklem ağrısı olan hastalarda Ct değerleri, bu semptomları olmayan hastalara göre anlamlı olarak daha düşüktü.*

Sonuç *Sonuç olarak semptomların ortaya çıkmasından kısa bir süre sonra Ct değerlerinin daha düşük olduğu tespit edildi. Solunum yolu semptomları olan kişilerde SARS-CoV-2 için erken test yapılması, viral yük ve bulaşma hızlarının yüksek olduğu zamanlarda izole edilmesi önemlidir.*

Anahtar Kelimeler *COVID-19, döngü eşik değeri, epidemiyoloji, SARS-CoV-2.*

INTRODUCTION

Coronaviruses cause disease in humans and animals. Four (human coronaviruses 229E, NL63, OC43 and HKU1) coronaviruses typically infect only the upper respiratory tract and cause mild infections.[1]

World Health Organization (WHO) declared COVID-19 infection caused by SARS-CoV-2virus as a pandemic on March 2020. SARS-COV-2 is a beta coronavirus that is closely related to SARS-CoV.[2,3] There were more than 767 million confirmed COVID-19 cases in the whole world, and more than 6 million people had died by July, 2023.[4]

The diagnosis of COVID-19 in both symptomatic patients and asympyomatic suspected individuals is most frequently based on the detection of SARS-CoV-2RNA from respiratory tract specimens. The standard molecular method for COVID-19 diagnosis is via real-time reverse transcription polymerase chain reaction (RT-PCR).[5] Several studies have compared the performance of available RT-PCR tests using a split specimen approach and report 96% to 100% positive agreement (proxy for sensitivity) based on consensus test results.[6,7] Lower sensitivity of 75% to 90% has been reported for a rapid point-of-care (POC) molecular test when compared to laboratory-based RT-PCR assays.[8-11]

Real-time RT-PCR cycle threshold (Ct) values represent the number of amplification cycles required for the target gene to exceed a threshold level. Ct values are related to viral load and can provide an indirect method of quantifying the copy number of viral RNA in the sample.[6] The relationship between viral load and Ct is inversely proportional. In a clinical setting, the results of SARS-CoV-2RT-PCR tests are usually reported qualitatively as a binary positive or negative result using a specified cut-off, either based on Ct or integrated by an automatic algorithm interpreting different parameters of the potential amplification.[7]

Qualitative RT-PCR tests do not measure the viral load within a sample, but Ct values offer a semi-quantitative assessment of viral RNA load as lower Ct values correspond to higher viral RNA concentrations. Ct values can be effected from some factors including reaction conditions and amplification efficiency. But it is known that an increase of 3.3 units in Ct value corresponds to 10-fold less target RNA under optimum conditions.[8] Ct values can use as an indirect indicator of relative viral load in diagnostic samples of persons tested for Sars-Cov-2.[9]

In this study we aimed to determine the relationships between Ct values and onset of symptoms, demographic factors, and symptoms among laboratory-confirmed COVID-19 cases.

MATERIAL and METHOD

Individuals in this study were patients who admitted to Ondokuz Mayis University Hospital Respiratory Infection outpatient clinic between October 2020 and November 2020 and tested positive for SARS-CoV-2 on a nasopharyngeal (NP) swab. Some questions on demographics, medical history, timelines for assesment of exposure were asked to the patients. Symptom assessments were conducted by physicians at the time of specimen collection.

NP specimens were collected by physicians. For participants who tested positive more than once during the investigation period, Ct values from only the first positive test were included. All specimens were tested at the Ondokuz Mayıs University Hospital Microbiology COVID-19 Laboratory using the Bio-speedy® SARS CoV-2 Double Gene RT-qPCR (Bioeksen, Turkey). This assay amplifies and detects two targets (ORF1ab and N) of the virus with a limit of detection 200 genome per mL. Vnat tubes were used for extraction. The human housekeeping gene target RNAse P (RP) was measured in each sample for use in normalization. Bio-rad CFX96 was used for amplification

Results were considered positive if signal was detected (Ct<38) for RP, ORF1ab and N genes. Ct values for am-

plification of both viral targets ORF1ab and N genes were analyzed.

The presence of symptoms at the time of sampling of NP swab were asked to the patients and recorded. The asked symptoms were; fever, cough, headache, loss of smell and taste, runny nose, shortness of breath, muscle-joint pain, weakness, diarrhea, and any other symptoms (chest pain, vomiting, sore throat, back pain). The presence of comorbid conditions, story of house-hold contacts, story of travel to abroad or contact with individual who came from abroad and whether he/she can be a health-care worker were also questioned. The hospitalization status of the patients were controlled by the hospital information system. The study was a retrospective study, patient consent was not taken.

Ethical approvel was taken from Ondokuz Mayıs University Medical Faculty Clinical Ethic Committe (B.30.2.ODM.0.20.08).

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin.

Statistical analysis

The compliance of the variables to normal distribution was examined by Kolmogorov-Smirnov/Shapiro-Wilk tests. The median and interquartile range were used for descriptive analysis. Variables and Ct values were compared using the Man-Whitney U test. The relationship between symptom onset time and Ct values was calculated using the Spearman test. Statistical tests for which $p<0.05$ were reported as statistically significant.

RESULTS

A total of 619 patients who tested positive for SARS-CoV-2 were included in this analysis. A majority of those with a positive for SARS-CoV-2 were male (52.4%). The median age was 41.56±17.38. Ct values ranged from 13.98 to 36.63 (median, 31.16). Ct values were determined as 24.74 (20.95-27.64) for 18> years-old and 22.85 (20.14-26.22) ≥18 years-old.

The most common symptom among the patients were weakness (65.8%) and followed by muscle-joint pain (59.9%) and cough (51.5%) (Table 1).

Table 1. Distribution of symptoms of COVID-19 patients.

	n (%)
Weakness	407 (65.8)
Muscle-joint pain	371 (59.9)
Cough	319 (51.5)
Fever	205 (33.1)
Runny nose	189 (30.5)
Headache	303 (48.9)
Loss of smell and taste	189 (23.9)
Diarrhae	100 (16.2)
Shortness of breath	92 (14.9)

The 12% of the positive patients were healthcare workers. And 46.5% of the patients were mentioned that they had a contact with SARS-CoV-2 positive person. The 16.3% of the patient needed hospitalization during the infection.

Total of 220 (35.5%) patients comorbid diseases at the time of sample collection. Hypertension was the most common comorbid disease (13.3%) (Table 2).

Table 2. Comorbid diseases/status of the patients.

Comorbid diseases	n (%)
Hypertension	82 (13.3)
Diabetes Mellitus	60 (9.7)
Asthma	20 (3.2)
Hyperthyrodism	9 (1.5)
Hashimoto's thyroiditis	6 (1.0)
Allergic rhinitis	6 (1.0)
Organ transplantation	5 (0.8)
Chronic renal deficiency	4 (0.6)
Pregnancy	1 (0.2)
Total	187 (30.2)

The relationship between Ct values and the age was evaluated in two groups as patients under 18 years of age and above, and no significant difference was detected.

A positive correlation was detected among the onset of the symptoms and Ct values, it was observed that the Ct value increased as the number of symptom days increased. (spearman correlation test, p<0.001).

Patients who had fever significantly had lower Ct values than patients who did not have (median Ct values of 22.39 and 23.11, respectively; p=0.007). Similarly, Ct values were significantly lower among those reporting headache compared to those with no headache (median Ct values of 22.54 and 23.21, respectively; p=0.003). Additionally, median Ct values were lower among patients had muscle-joint pain compared to patients who did not have. However, median Ct values of patients who mentioned that had loss of smell and taste higher among than who did not report that symptoms (median Ct values 24.17 and 22.70, respectively; p=0.031). No statistically differences seen in median Ct values among the symptoms of cough, runny nose, shortness of breath, weakness and diarrhae who had these symptoms or not. There was no signficant difference for Ct values of being healthcare-worker or not and hospitalization or not (Table 3).

Table 3. Statistically significant associations between cycle threshold value and symptoms.

	Ct values of patients meeting symptom/status	Ct values of patients not meeting symptom/status	p
Fever	22.39 (19.63-25.47)	23.11 (20.33-26.91)	0.007
Cough	22.87 (20.04-26.40)	22.96 (20.30-26.29)	0.493
Headache	22.54 (19.73-25.53)	23.21 (20.37-27.26)	0.003
Loss of smell and taste	24.17 (21.22-26.87)	22.70 (19.97-26.12)	0.031
Runny nose	22.05 (20.14-25.42)	23.18 (20.18-26.74)	0.059
Shortness of breath	22.82 (20.04-26.49)	22.89 (20.22-26.23)	0.894
Muscle-joint pain	22.51 (20.04-25.57)	24.11 (20.69-27.61)	0.001
Weakness	22.87 (20.25-26.10)	22.90 (19.91-27.15)	0.646
Diarrhae	23.14 (20.66-26.72)	22.85 (20.11-26.22)	0.623
Health-care worker	24.24 (20.78-27.36)	22.81 (20.04-26.19)	0.059
Hospitalization	23.07 (19.75-27.32)	22.82 (20.21-26.12)	0.326

DISCUSSION

In this analysis, we examined associations between SARS-CoV-2 RT-PCR Ct values and epidemiological charecteristics of patients with confirmed COVID-19.

The age and Ct value correlation investigated in some studies. Singanayagam et al.[10] reported that there was no significant difference in Ct values (p = 0.12) across the different age groups. And Buchan et al.[11] also reported that SARS-CoV-2 RT-PCR Ct values are similar among different age groups, suggesting equivalent test performance irrespective of patient age. However in the study of Sargent et al.[12], young children (<5 years-old) had significantly lower median (interquartile range) Ct values (6.5 [4.8-12.0]), indicating that young children have equivalent or more viral nucleic acid in their upper respiratory tract compared with older children (5-17 years–old) and adults. In our study, there was no significant difference in Ct values of children (<18 years-old) and adults.

The viral load and onset of the symptoms takes interest. Presence of virus in the pharynx was found very high during the first week of symptoms.[13] And Ct values were reported significantly correlated with the symptom onset.[9] We found a positive correlation between the onset of the symptoms and Ct values, as the onset of the symptoms increases, increase in the Ct values was seen. While Ct values are not direct quantitation of viral load, these results suggest that viral RNA levels in the pharynx are highest soon after symptom onset.

Fever was found common symptom among SARS-CoV-2 positive individuals.[14,15] In a study the most common symptom among SARS-CoV-2 positive healthcare-workers was fever (55.4%).[16] In USA a web-based self survey among the COVID-19 patients indicated that cough and muscle pain were the most common symptoms at the day of testing.[17] In a meta analysis by Struff et al.[18] the diagnostic accuracy of signs and symptoms to determine if a person presenting in primary care or to hospital outpatient settings was investigated. They found data on 84 signs and symptoms and reported that most of the symptoms had very low sensitivity and high specificity, only cough (25 studies) and fever (7 studies) had a pooled sensitivity of at least 50% but specificities were moderate to low. In a study conducted in UK, in the 71.5% of the SARS-CoV-2 positive patients, cough and fever were the most common symptoms.[19] However in our study, most common symptom was weakness, followed by muscle-joint pain and cough. The most prevelant comorbidity were hypertension and diabetes mellitus, same as our study.[15,20]

The number of studies that investigated the relationship between symptoms/epidemiological data and Ct value is limited. In some studies they reported that there was no significant relationship between Ct value (viral load) and demographics, symptom status and comorbidities.[21-24] However, in an analysis, the viral load in the respiratory samples of the patients was higher during the initial stage of the disease and higher loads in patients with severe disease was seen.[14] In a study, data suggest that lower Ct values may be associated with worse outcomes and that Ct values may be useful in predicting the clinical course and prognosis of patients with COVID-19.[7] Salvatore et al.[9] reported that Ct values were significantly lower in patients who had respiratory symptoms and Ct values among participants reporting different symptoms did not vary by age group. In a study by Soeroto et al.[25] the association between the severity of the COVID-19 disease and Ct values was investigated and they stated that there was no significant difference in RT-PCR Ct value among mild, moderate, severe and critical groups measured in the second week of illness.[25]

Kurzeder et al.[26] developed a simple scoring system based on data available shortly after hospital admission including the Ct value had a high predictive value for death and they mentioned that the score may also be useful to estimate the likelihood for required.[26] In our study, we found that Ct values changed among the symptoms, significant

differences was determined for some symptoms like fever, headache, anosmia/ageusia, muscle-joint pain. Ct values were significantly correlated with onset of the symptoms. Age was not found related with the Ct values.

Our study has some limitations. This study is a single centre study, and investigate the SARS-CoV-2 PCR results of patients who admitted to COVID-19 outpatient clinic. And viral load can be effected by various factors. We mainly focused on symptoms and demographics of the patients and their correlation of Ct values.

It is imported to access to SARS-CoV-2 tests immediately for individuals who have respiratory symptoms or have high-risk exposure. And identifying such individuals when Ct values are lowest and degree of infectiousness is high, and isolation of them to prevent transmission.

Ethical Approval

Ethical approvel was taken from Ondokuz Mayıs University Medical Faculty Clinical Ethic Committe (B.30.2.ODM.0.20.08).

Declaration of Helsinki

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin (B.30.2.ODM.0.20.08).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.T.Ç., Design: Y.T.Ç., A.A., Data collection: Y.T.Ç., A.A, G.K., E.H.E., Analysis or interpretation: Y.T.Ç., O.Y., D.G.V., A.B. Liretarure search: Y.T.Ç., K.B. Writing: Y.T.Ç

Conflict of Interest

The authors declare that they have no conflict of interest.

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Informed consent

Retrospective study.

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