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The relationship between the severity of pulmonary involvement in the CT scan of patients with Covid-19 and the threshold cycle of SARS-CoV-2

Mahdi Niknazar [1], Saeid Amel Jamehdar[2], Majid Khadem-Rezaiyan[3], Zahra Ataee[4*]

[1]Mashhad University of Medical Sciences, Mashhad, Iran
[2] Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Department of Community Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Introduction: There is no clear relationship between the threshold cycle of COVID-19 and the severity of pulmonary involvement in the CT scan of patients.
Methods: This study was conducted on 254 patients. The number of cycles of the threshold virus was extracted. The severity of pulmonary involvement was categorized based on each lobe's participation percentage, which was determined by a CT scan. The relationship between the CT number and the participation in the CT scan was measured.
Results: The patients with COVID-19 included 158 (62.2%) men and 96 (37.8%) women with a mean age and standard deviation of 60.99 ± 17.78 years. The average threshold cycle (CT Value) was 5.912 ± 19.38; its minimum and maximum were 9 and 36.
The percentage of proper lung involvement was 46.7±29%, and the percentage of left lung involvement was 47.8±29.8%. The number of people without conflict is 6 (2.4%), with mild conflict at 39 (15.4%), moderate at 65 (25.6%), and severe at 144 (56.7%). The number of people without involvement of the right lobe is 11 (4.3%), score 1, 42 (16.5%), score 2, 75 (29.5%), score 3, 51 (20.1%), involvement Score 4, 75 (29.5%). The number of people without left lobe involvement is 12 (4.7%), score 1, 46 (18.1%), score 2, 71 (28%), score 3, 48 (18.9%), involvement Score 4, 77 (30.3%).
Conclusion: With the increase in lung involvement, the threshold cycle has decreased, indicating the inverse relationship of the threshold cycle with the severity of disease involvement.

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Introduction

Coronaviruses are a significant group of pathogens affecting both humans and animals. In late 2019, reports emerged from Wuhan, a city in Hubei Province, China, regarding a surge in respiratory illness and viral pneumonia cases. This novel virus was subsequently identified as the causative agent. The rapid spread of this respiratory disease led to an epidemic in China, with cases soon reported in other countries. In February 2020, the World Health Organization (WHO) officially named the disease COVID-19. By March 2020, WHO declared it a pandemic and called for global action to detect and contain the virus (1). Genome sequencing studies revealed a close relationship between COVID-19 and another coronavirus known as Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) (2). The COVID-19 pandemic has posed significant challenges to healthcare systems worldwide.

Iran was one of the first countries to report numerous cases of COVID-19, initially in the city of Qom and later in other cities, starting in late

***Corresponding author**: Dr. Zahra Ataee, Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Email: ataeez@mums.ac.ir
Doi: 10.22038/RCM.2025.82951.1511

February. COVID-19 affects multiple organ systems, with respiratory involvement being the most common. The severity of respiratory symptoms can range from being asymptomatic to severe respiratory failure, which can lead to death (1).

As the number of COVID-19 cases continued to rise, healthcare professionals faced the challenge of identifying and treating infected individuals. Accurate assessment of disease severity remains crucial for clinical management and implementing measures to prevent the rapid progression of the disease. Initially, due to the lack of a definitive diagnostic test, the diagnosis of COVID-19 relied on a combination of clinical, laboratory, and imaging findings. However, the standard method for diagnosing COVID-19 became real-time reverse transcription polymerase chain reaction (RT-PCR). In this method, a sample is taken from the patient's upper respiratory tract to detect the presence of viral nucleic acids. If the virus is present, nucleic acid quantity is measured using the cycle threshold (Ct) parameter, which refers to the number of amplification cycles required to generate detectable fluorescence signals. It is generally believed that a lower Ct value indicates a higher viral load, which correlates with increased disease severity and a higher likelihood of transmission to others (1, 3). However, there is still limited understanding of the relationship between the severity of lung involvement on CT scans and the cycle threshold (Ct) of SARS-CoV-2, the virus responsible for COVID-19. Imaging studies in COVID-19 patients commonly utilize chest X-rays or CT scans. Among these, CT scans are more sensitive for detecting lung involvement. In addition to clinical indicators of disease severity, the extent of lung involvement observed on CT scans can also provide valuable prognostic information. Several studies have highlighted the role of CT imaging in diagnosing and managing COVID-19 patients (4, 5). CT findings, such as ground-glass opacity and consolidation, indicate COVID-19 infection (6). Furthermore, some studies suggest that CT scanning may be more sensitive than PCR testing in diagnosing COVID-19 (7, 8). However, the severity and extent of pulmonary involvement, as observed on CT scans, may vary among COVID-19 patients (9). Therefore, it is essential to investigate the relationship between CT scan findings and SARS-CoV-2 cycle threshold (Ct) values, as this could provide valuable insights into disease progression and severity. The Ct value is a quantitative measurement used in PCR tests to assess the viral load in a patient's respiratory sample (10). It has been suggested that lower Ct values are associated with higher viral loads and more severe symptoms. In other words, there is an inverse correlation between viral load and Ct value, with lower Ct values reflecting more severe disease and a higher likelihood of transmission (11-13). However, the relationship between Ct values and disease severity and the degree of lung involvement has not been consistent across different studies, and discrepancies have been observed in some cases.

However, the relationship between the Ct value and the severity of lung involvement, as observed on CT scans, has not been widely evaluated. A more accurate understanding of the relationship between disease severity and the extent of lung involvement could enhance clinical decision-making. Evaluating CT findings and clinical symptoms would make it easier and more reliable to manage patients based on the severity of their lung involvement.

This study investigates the relationship between CT scan findings and Ct values in COVID-19 patients. The Ct value is a well-established criterion for assessing viral load and disease severity, which can provide valuable insights into the need for early intervention and treatment strategies. In clinical practice, determining the prognosis and formulating treatment plans based on the severity of lung involvement observed in CT scans and the viral load indicated by the Ct value plays a crucial role in patient management and recovery. Thus, understanding these two factors' correlations could significantly enhance decision-making in managing COVID-19 patients.

Material and Methods

This cross-sectional study was conducted from early 2019 to April 2021 at Imam Reza Hospital in Mashhad, Iran. The study protocol was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) (IR.MUMS.MEDICAL.REC.1400.51).

According to the National Guidelines for the Diagnosis and Treatment of COVID-19, patients who required hospitalization were those who met the following criteria:

Patients exhibiting symptoms consistent with COVID-19, accompanied by dyspnea, hypoxemia ($SpO2 < 90\%$), or a respiratory rate (RR) > 24 breaths per minute.

Patients with a decreased level of consciousness.

Patients with hypotension (systolic blood pressure < 90 mmHg).

Patients who continued to experience dehydration and food intolerance despite outpatient supportive treatments.
Patients at risk of complications from COVID-19, without shortness of breath or hypoxia, but with positive lung imaging findings based on clinical assessment and severity of lung involvement (14).
Patients meeting the hospitalization criteria outlined in the national guidelines were initially tested for COVID-19 and underwent a CT scan within 72 hours of admission.
The clinical records of all patients admitted to the hospital with a confirmed diagnosis of COVID-19, based on a positive PCR test, were reviewed. Eligible patients were those who had undergone a CT scan before the start of treatment, were over 16 years old, had no underlying lung disease, and whose PCR test and CT scan were conducted within 72 hours of each other. Data were extracted from the hospital's Health Information System (HIS). The virus's cycle threshold (Ct) value was determined using a PCR machine (Rotor-Gene Q, Germany), with real-time PCR conducted on nasopharyngeal and oropharyngeal swab samples. The results were recorded, extracted, and stored in the Central Laboratory database of Imam Reza Hospital.
The CT scan findings of the patient's lungs were extracted from the hospital's PACS system. The severity of pulmonary involvement was assessed based on the percentage of participation in each lobe and scored as follows: No involvement: score 0, Involvement 1-25%: score 1, Involvement 25-50%: score 2, Involvement 50-75%: score 3, and Involvement 75-100%: score 4.
The total score for each lobe ranged from 0 to 20, and the overall severity of lung involvement was categorized into four groups: no involvement (0), mild involvement (1-5), moderate involvement (6-10), and severe involvement (11-20). The relationship between the cycle threshold (Ct) value and the severity of pulmonary involvement was analyzed using SPSS version 26 software.
Referring to the study by Wei et al., which reported a correlation of 0.179 between the TSS score and CT value, the sample size was calculated using the correlation coefficient formula in the MadCalc software (version 19.8). With an alpha error of 0.05 and a power of 80%, the required sample size was calculated to be 242 participants. After accounting for a 5% dropout rate, the final sample size was 255 participants.
The necessary data were extracted during the study period, and after meeting the inclusion and exclusion criteria, data analysis was performed using SPSS version 26 software. The characteristics of the study participants were presented using appropriate statistical methods, with results displayed in tables and graphs. Quantitative variables were described using mean and standard deviation, while qualitative variables were described by frequency and percentage. To compare quantitative variables, the independent t-test was used for two groups (normal and abnormal laboratory values), and one-way ANOVA was used for three groups (normal, hypo, and hyper).
The relationship between quantitative variables was evaluated using Pearson's correlation coefficient. The relationship between qualitative variables was assessed using the Chi-square test, and Fisher's exact test was applied when necessary. The appropriate non-parametric test was used if the data did not follow a normal distribution. All tests were two-sided, and a significance level of less than 0.05 was considered statistically significant.

Result

From the beginning of 2019 to the end of April 2021, 254 confirmed COVID-19 patients were admitted to Imam Reza Hospital (AS) in Mashhad. Of these, 158 (62.2%) were men and 96 (37.8%) were women, with an average age of 60.99 ± 17.78 years. The minimum age was 16 years, and the maximum was 101 years.
The average cycle threshold (Ct) value was 5.912 ± 19.38, with a minimum of 9 and a maximum of 36.
Based on CT scan findings, the percentage of lung involvement was almost equal between the right and left lungs. The average participation rate of the right lung was 46.7 ± 29% (min = 0%, max = 95%), and the left lung involvement was 47.8 ± 29.8% (min = 0%, max = 95%).
Regarding the overall severity of lung involvement, six patients (2.4%) had no involvement, 39 (15.4%) had mild involvement, 65 (25.6%) had moderate involvement, and 144 (56.7%) had severe involvement.

Furthermore, 11 patients (4.3%) had no involvement of the right lung lobe, and 12 patients (4.7%) had no involvement of the left lung lobe. Notably, 50.4% of patients had at least grade 2 participation in the right lung, and 50.8% had at least grade 2 participation in the left lung (Table 1).

Table 1: Frequency of right and left lung involvement by grade

	Right lung		Left lung	
Involvement	Frequency (%)	Cumulative percentage	Frequency (%)	Cumulative percentage
0	11 (4.3%)	4.3%	12 (4.7%)	4.7%
1	42 (16.5%)	20.9%	46 (18.1%)	22.8%
2	75 (29.5%)	50.4%	71 (28.0%)	50.8%
3	51 (20.1%)	70.5%	48 (18.9%)	69.7%
4	75 (29.5%)	100.0%	77 (30.3%)	100.0%
Total	254 (100.0%)		254 (100.0%)	

As shown in Table 2, the threshold cycle (Ct) value was significantly different across the grades of lung involvement (p = 0.001). Patients with no lung involvement had the highest Ct value (25.00 ± 3.09), while patients with moderate participation had the lowest Ct value (20.62 ± 6.61). (Table 2)

Table 2: Comparison of Threshold cycle rate based on lung scan findings

Involvement	Number	Mean	standard deviation	95% confidence interval
No	6	25.00	3.098	21.75-28.25
mild	39	16.87	5.559	15.07-18.67
moderate	65	20.62	6.618	18.98-22.26
sever	144	19.26	5.471	18.36-20.17
total	254	19.38	5.912	18.65-20.11

ANOVA test was used for comparison

As shown in Table 3, the threshold cycle was analyzed by gender and age, and there was no significant difference between the groups. (Table 3)

Table 3: Comparison of Threshold cycle rate based on gender and age

		Number	Mean	Standard deviation	P-value
Gender	Male	158	19.47	5.924	0.662
	Female	96	19.23	5.920	
Age	Lower than 60	106	19.38	6.160	0.999
	Higher than 60	148	19.38	5.748	

An Independent t-test was used to compare the two groups.

Discussion

This study included 254 confirmed COVID-19 patients, comprising 158 men (62.2%) and 96 women (37.8%). The average age of the patients was 60.99 ± 17.78 years, with a minimum age of 16 years and a maximum of 101 years.

The average cycle threshold (Ct) value was 5.912 ± 19.38, with a minimum value of 9 and a maximum value of 36.

Regarding the severity of lung involvement, six patients (2.4%) had no involvement, 39 (15.4%) had mild involvement, 65 (25.6%) had moderate involvement, and 144 (56.7%) had severe involvement. As observed, the majority of patients had severe pulmonary involvement.

The percentage of proper lung involvement in patients was estimated to be 46.7 ± 29% (min = 0%, max = 95%), while the percentage of left lung involvement was 47.8 ± 29.8% (min = 0%, max = 95%). The average rate of participation in both lungs was nearly equal.

There was no statistically significant difference in the average threshold cycle (Ct value) between men and women or between patients under and over 60.

In a similar study conducted by Karahasan Yagci et al. on 284 patients in Turkey in 2020, which aimed to investigate the severity of lung involvement on chest CT scans in PCR-positive patients and associated factors, the average Ct value was estimated to be 28.16 ± 3.5, which was higher than in the present study. This study found an inverse relationship between the Ct value of SARS-CoV-2 in nasopharyngeal samples and the severity of lung involvement in CT scans among all patients.

The threshold cycle (Ct value) was significantly lower in patients with greater intensity of lung involvement on chest CT scans, which is consistent with our study. The mean viral load was highest in patients with no CT involvement compared to those with mild, moderate, and severe involvement on chest CT scans (15).

A large study in the United States analyzed 4,428 positive RT-PCR samples, with an overall viral Ct range of 6.16–37.92 (16). Zeng et al. estimated viral loads in over 3,000 samples collected from 96 patients. They reported that patients with severe disease had significantly higher viral loads, which were higher in the early stages of the disease (17).

A sex-dependent increase in disease severity after infection with pathogenic coronaviruses has been reported for both SARS and MERS, and this has also been observed for SARS-CoV-2 (18). In the study by Zheng et al., it was found that the duration of the virus in men was significantly longer than in women, which helps explain the greater severity of the disease in men in terms of viral persistence. In addition to differences in immune status between men and women, this has also been associated with variations in hormone levels.

In this study, a correlation was found between age and the duration of the virus, which partially explains the higher rate of severe disease in patients over 60 years of age. Another factor is that older individuals have higher levels of angiotensin-converting enzyme 2 (ACE2) in their alveoli, which is believed to be a receptor for the new coronavirus (17).

In a Swedish study of 286 patients, Engberg et al. found that higher viral loads, as indicated by lower Ct values in nasopharyngeal samples and more extensive lung infiltrates on chest CT scans, were associated with an increased risk of ICU admission or death. The Ct value was beneficial for identifying high-risk patients, even those with less extensive pulmonary involvement (19).

This study also proposed a method for predicting the risk of ICU admission or death by combining the Ct value and chest CT score of hospitalized patients. For example, in this study, a patient with less than 25% CT scan involvement and a Ct value of 25 had the same risk for an adverse outcome as a patient with 25-50% CT scan involvement and a Ct value of 35, with both having an approximately 20% risk. Similarly, the estimated risk was approximately 50% for a patient with a Ct value of 28 and 25-50% involvement on a chest CT scan and a patient with a Ct value of 13 and more than 25% involvement on a chest CT scan. In contrast, all patients with more than 50% involvement in chest CT scans, regardless of Ct value, had a 50% risk of ICU admission or death (19).

In a review examining 25 studies, the majority found that viral load, most commonly measured by Ct value, was significantly associated with adverse outcomes. Notably, this result was also valid in studies with a sample size of over 500 participants (20, 21).

Theoretically, at least two explanations can be proposed for why a higher nasopharyngeal viral load is associated with worse outcomes. First, patients who eventually require intensive care or die may have sought healthcare earlier, such as frail individuals who struggle to manage symptoms at home and are at higher risk of severe illness.

As mentioned, peak viral load tends to occur earlier in the disease course; however, viral load has independent predictive value, and studies suggest that prior contact with healthcare is not the sole explanation.

However, it is essential to note that the duration of symptoms is a subjective measure, typically reported by the patient in the emergency room. Some of the explanatory value may be lost due to inaccurate patient recall, while the Ct value is a more objective and accurate measure of the duration of infection.

Second, sustained high viral loads may be a relevant trigger for immunopathology, leading to severe lung disease. Viral abundance in the lower airways has been shown to predict mortality. However, it remains unclear whether the high viral load observed at hospitalization results from a very high peak viral load at the onset of illness or whether an aberrant host response impairs viral clearance (19, 22).

It may be speculated that although SARS-CoV-2 viral load in nasopharyngeal swab samples is high in the early stages of COVID-19, it is not necessarily correlated with changes in chest CT findings. In the later stages of SARS-CoV-2 infection, viral load in nasopharyngeal swab samples decreases, viral load in lower respiratory tract samples increases, and chest CT changes become detectable. At this stage, sputum or other lower respiratory tract samples may be more reliable than nasopharyngeal swab samples (15).

In a study conducted by Rajyalakshmi et al. in India in 2021, which investigated the prognostic effect of threshold cycle (Ct value) in COVID-19 patients, it was found that lower Ct values were associated with an increased risk of ICU admission, mortality, shock, and longer ICU hospitalization. However, the results of this study did not show a statistically significant relationship between the Ct value and the severity of pulmonary involvement in the chest CT scan of the patients (23).

In another study conducted in Qatar in 2020 by Khaleed Jemmieh et al., it was stated that although RT-PCR Ct has good diagnostic value, its prognostic value appears unreliable (24).

This finding aligns with the suggestion of Farfour et al., who emphasized that infection prevention and control measures should be implemented in all suspected patients based on epidemiological, clinical, or radiological findings, and these measures should only be discontinued once the diagnosis is definitively ruled out (25).

Other factors associated with higher viral load, such as age and gender, have been reported in previous studies (26). However, none of these factors were statistically significant in the present study, which is consistent with the findings of Ingberg et al. (19).

The results of this research allow us to identify differences between hospitalized patients in our country and those in other parts of the world, ultimately leading to improved decision-making in managing COVID-19 patients. The findings of this study contribute to the existing knowledge about COVID-19 and provide valuable insights for developing more effective diagnostic and management protocols. Consequently, understanding the relationship between the intensity of involvement in CT scans and the threshold cycle of SARS-CoV-2 is crucial in combating the COVID-19 pandemic.

Conclusion

In most similar studies referenced, an inverse relationship between the threshold cycle and the severity of pulmonary involvement on the CT scan of COVID-19 patients has generally been concluded, but this could not be established in our study.

There was no statistically significant difference in the average threshold cycle between men and women or between individuals under and over 60.

In the hospital, disease prognosis and treatment management decisions are crucial in the recovery process. Therefore, investigating the relationship between the severity of lung involvement on the CT scan and the CT value (which reflects viral load and disease severity) can significantly contribute to patient management, prognosis prediction, and understanding of disease severity.

One of the limitations of our study was the lack of examination of concurrent infectious diseases during the patient's hospitalization, which is recommended for consideration in future studies.

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