RESEARCH ARTICLE

Insights into COVID-19: Linking Cycle Threshold with Symptoms, Severity, and Mortality

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Abstract

Aim and background: Due to the high human-to-human transmissibility of coronavirus disease-19 (COVID-19), it has gained immense global recognition and had a devastating impact. Because of the novel nature of disease, various predisposing factors contributing to disease severity and mortality remain doubtful. This study was performed to determine the association between cycle threshold (CT) value for RT-PCR COVID-19 and severity of the disease to emphasize the role of CT value in patient management, as a lot of emphasis was being laid on reporting of CT values to the clinicians. The association between clinical symptoms and CT values was also determined in addition to its association with mortality.

Methods: The study was conducted for a period of 18 months from January 2021 till June 2022. It included 212 COVID-19-positive patients who were diagnosed by RT-PCR test for COVID-19. Informed consent and history of the patients were recorded along with their clinical parameters. Data was analyzed statistically using a two-tailed *t*-test and the Chi-square test.

Results: Although a significant association was seen between CT value and symptoms, the severity of the disease was not found to be significantly associated with CT value. Also, no statistically significant association was found between CT value and mortality due to the disease.

Conclusion: Although CT value is indirectly related to the viral load, it should have no impact on patient management as the immune system shows a different response in every individual.

Clinical significance: Our study adds valuable insights to this evolving landscape, emphasizing the importance of considering multiple variables in comprehensively understanding the relationship between CT values and COVID-19 severity.

Keywords: Association, Coronavirus disease-19, Cycle threshold value, Mortality, Severity, Symptoms.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a novel viral illness termed new coronavirus disease-19 (COVID-19). It spread at a high pace all over the world after the first case of this viral infection was detected by the end of December 2019 in Wuhan, Hubei Province, China.[1] Due to the high human-to-human transmissibility of this illness, it has gained immense global recognition and had a devastating impact, killing more than six million people.[2] Despite the disease typically being mild, it has the potential to get worse and result in life-threatening conditions like pneumonia, respiratory distress, and multiorgan failure.[3] Fever, sore throat, cough, dyspnea, anosmia, anxiety, headache, arthralgia, mental problems, hair loss, and gastrointestinal problems are the main symptoms.[4] Therefore, medical professionals were striving diligently to determine which symptoms were more closely related to the severity of the disease.[3] It has been established that coexisting illnesses, including diabetes, cancer, and cardiovascular disease, predispose the patients to severe COVID-19 outcomes by altering viral-host dynamics and immune responses that cause life-threatening infections.[5] The real-time reverse transcription polymerase chain reaction (RT-PCR) is the confirmatory test for the detection of COVID-19. The cycle threshold (CT) value of a specimen represents a measurement of the amount of amplification that the target gene needs to achieve in order to cross a threshold level; thus, it is inversely associated with the load of virus in that sample.[6] There is currently a dearth of literature that links CT value to illness severity. Additionally, different findings have been observed regarding the same.[7] This has slowed the pace of reaching a final conclusion on the association between SARS CoV-2 CT value and disease severity. As a result, it would be extremely beneficial for therapy and patient care to anticipate the morbidity and risk of infection in patients upon diagnosis.[6] Thus, we aimed to assess the association between the CT value of COVID-19 and disease severity, along with the symptoms and mortality associated with the disease.

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Methods

Study Design and Participants

It was a cross-sectional study conducted at Sharda Hospital, Greater Noida, from January 2021 to June 2022. The hospital was requisitioned as a level-3 center for COVID-19. All patients positive for COVID-19 (by RT-PCR test) were included in the study. Patients positive by COVID antigen reports only were excluded from the study. Additionally, patients with incomplete history or incomplete

clinical records were excluded too. The study was approved by the University Ethics Committee (reference no. SU/SMS&R/76A/2022/63. Written consent and history from the patients was taken at the time of sample collection itself.

Procedure

RT-PCR for COVID-19

Diagnosis for COVID-19 was done by performing RT-PCR in the biosafety level-II cabinet at the virology laboratory, Microbiology Department, Sharda Hospital.

Extraction of viral RNA from nasopharyngeal and oropharyngeal swabs was done manually using QIAamp Viral RNA Mini Kit, Germany. The amplification of extracted RNA was performed by using the COVID-19 RT PCR Kit from Biogenix Inc. Pvt. Ltd., targeting the specific sequence that is conserved and encodes the ORF 1ab gene and the nucleoprotein N gene.

Grouping of CT Values

The CT values were arbitrarily categorized into three groups as:

- Group I: ≤20 (low)
- Group II: >20–30 (medium)
- Group III: >30–35 (high)

Categorization of disease severity

The clinical parameters were recorded, and the patients were categorized into three groups of clinical severity according to the guidelines laid by the Ministry of Health and Family Welfare, Directorate General of Health Services, Government of India.[8]

Statistical Analysis

The collected data were configured into the Excel sheet and was evaluated with SPSS-21 software. Numbers and percentages were used to represent categorical variables. The Chi-square test was used for intergroup and categorical comparisons as appropriate. The *p*-value for finding the association between illness severity and CT value was calculated using a two-tailed *t*-test, 0.05 of which was taken to be insignificant.

Results

The study included 212 COVID positive patients, with 72.6% being males and 27.4% being females. Table 1 shows the demographic characteristics of the study population.

Since the hospital was mandated as a level III designated COVID center, the majority of the study population was comprised of admitted/IPD patients, with only a small population of 20 (9%) being from OPD and the rest 192 (91%) from IPD.

The clinical symptoms and signs with which the patients presented are depicted in Figure 1, where fever, sore throat, and headache were the most common symptoms.

The categorization of patients into different grades of clinical severity showed that maximum patients, 107 (50%), belonged to the severe category, followed by 71 (34%) in the moderate category, and the least, i.e., 34 (16%) in the mild category.

On grouping the patients based on CT values, 31.3% of them were found to be in the low CT value group, i.e., high viral load; the majority (59.4%) were in the moderate CT group, and the least in the high CT group, i.e., 9.4%. The mean CT value of each group is shown in Table 2.

The relationship between CT value and clinical presentation was investigated and discovered to be significant for all symptoms (Table 3). This shows that the plethora of symptoms increases with lower CT values or greater viral loads. However, there was no statistically significant relation between diarrhea and CT value.

The distribution of patients of varying severities into different CT value groups has been shown in Table 4. No statistically significant correlation between the CT value and the severity of clinical disease was observed.

Table 1: Demographic profile of the patients

Parameter	*Frequency (n)*	*Percentage (%)*
Gender		
Males	154	72.6
Females	58	27.4
Age (years)		
≤30	10	4.7
31–60	118	55.7
>60	84	39.6
Smokers	91	42.9
Non-smokers	121	57.1

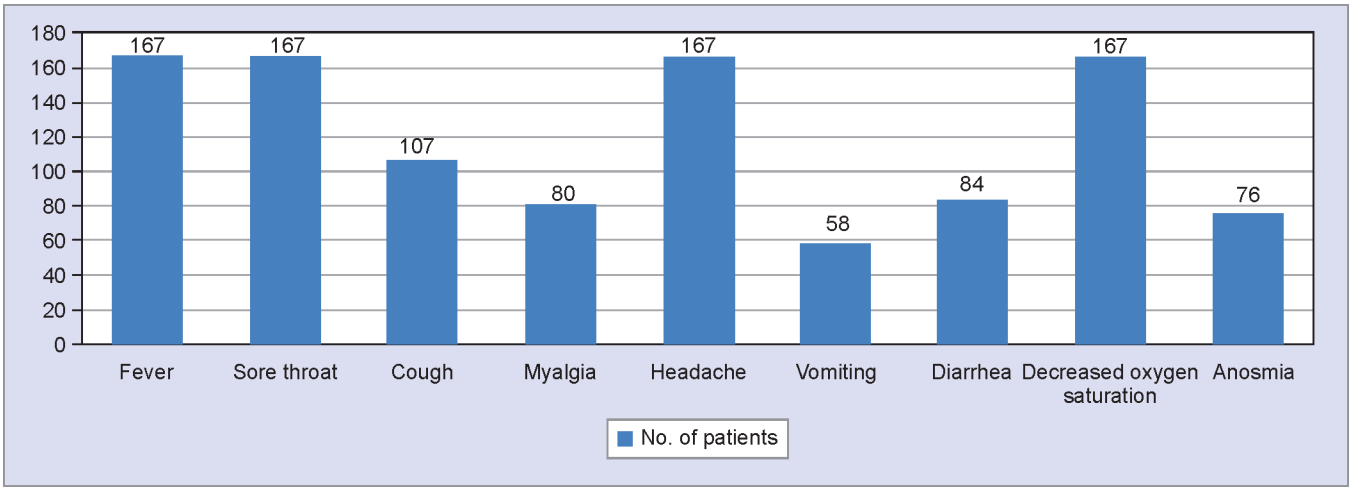

Fig. 1: Clinical parameters of study population

Table 2: Distribution of patients in different CT groups

Groups	*Cycle threshold value*	*No. of patients (n)*	*Percentage (%)*	*Mean CT value ± SD**
I	< 20 (low)	66	31.3	17.51 ± 1.67
II	21–30 (medium)	126	59.4	25.3 ± 2.66
III	>30–35 (high)	20	9.4	33.3 ± 1.14

*SD, standard deviation

Table 3: Association of CT value with clinical symptoms

Symptom	*Group I*	*Group II*	*Group III*	*p-value*
Fever	53 (80.3)	98 (77.8)	16 (80)	0.000
Sore throat	53 (80.3)	98 (77.8)	16 (80)	0.000
Cough	34 (51.5)	63 (50)	10 (50)	0.000
Myalgia	23 (34.8)	47 (37.3)	10 (50)	0.000
Anosmia	28 (42.4)	44 (34.9)	4 (20)	0.000
Headache	53 (80.3)	98 (77.8)	16 (80)	0.000
Diarrhea	19 (28.8)	54 (42.9)	11 (55)	0.104
Vomiting	16 (24.2)	35 (27.8)	7 (35)	0.000
Decreased oxygen saturation	50 (75.8)	101 (80.2)	16 (80)	0.000

Table 4: Association between CT value and disease severity

Disease severity	*Group I*	*Group II*	*Group III*	*p-value*
Mild	10	20	4	0.578
Moderate	26	41	4	
Severe	30	65	12	

Table 5: Patient distribution with change in CT value and symptomology

	Symptomatic improvement		
Change in CT value	Yes	No	*Total*
Nil	1	11	12
Increase	6	121	127
Decrease	7	46	53
Total	14	178	192

Among the 192 patients who were admitted in the ward/ICU, 169 patients succumbed to death, and only 23 patients could survive. The association between CT value and mortality came out to be statistically non-significant ($p = 0.355$). Hence, it can be deduced that high viral load/low CT value was not associated with deaths in COVID patients.

The CT value of admitted patients was recorded serially and their signs and symptoms watched to evaluate whether improvement or deterioration in clinical condition was related to any change in CT value. It was observed that after one week some patients had shown improvement in symptomatology despite the decrease, increase, or no change in CT value (Table 5).

The Chi-square test was used to calculate the relation between change in CT value and change in symptoms of patients, and it came out to be statistically non-significant with a *p*-value of 0.135. Considering this fact, we can say that CT value/viral load had no relation with change in symptoms, whether the condition of patients improved or worsened.

Discussion

In the present study, we sought an association of CT value with symptoms, severity, and mortality in patients with COVID-19. In our study, the demographic features of 212 COVID-19 patients were described based on clinical classification and illness severity. Clinically, the majority of patients were categorized as having severe illness and had a moderate CT value. The most prevalent symptoms noted were fever, cough, and decreased oxygen saturation, which are in line with reports by Guan et al., who evaluated a group of 1099 COVID-19 patients in China, and Salma et al., who evaluated 202 patients in Saudi Arabia.[9,10] Our study unveiled a meaningful association between CT values in COVID-19 and the manifestation of various symptoms, with a notable exception in the case of diarrhea.[10–12] The significant correlation observed between lower CT values and the presence of typical COVID-19 symptoms, such as fever, cough, and shortness of breath, reinforces the notion that a higher viral load is often linked to more severe clinical presentations. However, the lack of a significant association with diarrhea in our findings raises intriguing questions about the specific viral dynamics related to gastrointestinal symptoms. It is conceivable that factors beyond viral load, such as host susceptibility and immune response, may play a more prominent role in determining the occurrence of diarrhea in COVID-19 cases. Our findings were similar to the results of the study conducted by Salvatore et al.[13] Our results, however, are not in agreement with various other studies, which do not show a link between viral CT values and the occurrence of symptoms.[14]

Cycle threshold value indirectly determines the viral load in a patient, which in turn seems to be associated with the level of severity of the disease. During the pandemic, a lot of emphasis was being laid upon the reporting of CT values to the clinicians so that they could decide the plan of management accordingly. As per the clinical parameters, we did not find a significant association between CT values and disease severity. Our outcomes align with those of Shah et al. and Al-Shareef et al., who were unable to identify a connection between CT levels and severity of disease in COVID-19 patients.[15,16] A number of other studies have also shown that the severity of clinical disease does not depend on the CT value and, hence, has no significance in determining the plan of treatment. Contrary to this, some studies have shown positive a association between the CT value and the degree of COVID severity.[17–19] This divergence in findings could be attributed to several factors. Firstly, the heterogeneity in study populations, including variations in demographics, comorbidities, and viral strains, may contribute to differences in outcomes. Additionally, the timing of sample collection in relation to the course of the disease could influence CT values, as viral loads may vary throughout the infection timeline. The diverse methodologies employed in different studies, such as the use of varying diagnostic platforms and protocols, may introduce variability in CT value determination. Moreover, the definition and categorization of COVID-19 severity can differ across studies, affecting the interpretation of results.

The relationship between the CT value and mortality was found to be non-significant, indicating that the deaths of patients due to COVID-19 were not linked to high viral loads or low CT values. In contrast to the findings of our study, a study done in the UK reported a significant association between initial CT value and mortality.[20]

It's important to note that while some studies have suggested a correlation between lower CT values and increased mortality, the relationship is complex and not universally consistent. The interpretation of CT values should be done in conjunction with a comprehensive clinical assessment, and decisions regarding patient management and prognosis should be based on multiple factors.[21,22]

Our study has few limitations. First, the study sample size was relatively small. A larger number of patient population could have given a wider reflection of our results. Secondly, we could not associate CT value with the onset of symptoms. Had it been so, we might have been able to make our study stronger and more impactful.

Conclusion

To conclude, we can say that although CT value is the proxy marker of viral load, the behavior of the immune system is still different for each human body. The associated factors, such as age, comorbidities, and access to healthcare amenities, as well as the nutritional status of the patients, may affect the response of the body to the virus and its multiplication, which may be different for all patients. Hence, considering CT value as the prognostic marker and deciding the treatment plan on its basis is not wise enough. However, studies still need to be done to improve the knowledge on every aspect, considering the fact that SARS-CoV- 2 is a novel virus.

Clinical Significance

Our study's nuanced findings contribute valuable insights to the evolving understanding of COVID-19 symptomatology and underscore the need for comprehensive exploration of the multifaceted aspects of this complex disease. The intricate interplay between viral dynamics, host factors, and clinical outcomes in COVID-19 necessitates a nuanced approach to research. Our study adds valuable insights to this evolving landscape, emphasizing the importance of considering multiple variables in comprehensively understanding the relationship between CT values and COVID-19 severity.

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