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Original Research Article

A Study on the Correlation between Cycle Threshold (Ct) Value and Clinical Severity in Patients Admitted with COVID-19 in the First and Second Waves of the COVID Pandemic

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Abstract:

Introduction: The standard test of real time (RT) PCR in the diagnosis of Coronavirus disease 19 (COVID-19) are reported based on the cycle threshold (Ct) value. The Ct value being inversely proportional to the viral load, limited studies have proved its relation to clinical severity.

Aim: The study aimed at evaluating the correlation of Ct value with clinical severity for COVID-19 and its comparison of baseline characteristics with the two waves of the pandemic.

Materials and Methods: The clinical parameters of all symptomatic COVID-19 patients positive by Truenat RT-PCR test and admitted to the hospital during the first and second waves were evaluated.

Results: Among 183 patients, early testing with a mean duration of 3.6 days after onset of symptoms had higher viral load content when compared to testing at 4.6 days after onset of symptoms (p-0.003). There were no significant association observed between COVID severity, oxygen requirement, co-morbidities, outcome, wave and viral load. When compared with the two waves, a significant association was observed with age, symptom categories and presence of comorbidities.

Conclusion: The Ct values of Truenat RT-PCR alone do not have a role in commenting the clinical severity among symptomatic COVID-19 patients. It can offer an opportunity to the clinicians to take extra precautions during the early stage of the disease to prevent favourable disease transmission. The first wave of COVID-19 being of longer duration, many older patients with comorbidities were infected when compared with the second wave.

Keywords: Corona virus disease-19 (COVID-19), Cycle threshold, clinical severity, viral load, Truenat Real Time Reverse Transcription polymerase chain reaction (PCR) test.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) broke out in early December 2019 [1]. It has been more than three years into the pandemic, the disease is ongoing and is no longer considered as a public health emergency of international concern.

The standard test for the molecular diagnosis of COVID-19 is by Real Time duplex Reverse Transcription Polymerase Chain Reaction (RT-PCR) [2]. In clinical practice, the SARS-CoV-2 RT-PCR test reports as positive or negative using a specific threshold for Cycle threshold (Ct) values. The Ct value is defined as the number of amplification cycles required for the fluorescent signal of the target gene to cross the threshold. This is a semiquantitative measure that aids in the broad categorization of viral genetic material in patient samples into low, medium and high. The SARS-

CoV-2 viral load is inversely proportional to the Ct values. A lower Ct value corresponds to a high viral load, thereby indicating a higher level of infectiousness. It has been suggested previously that the viral load of SARS CoV-2 plays an important role in determining the disease severity and increased infectivity, but limited data can establish its relation [3]. The peak concentrations of SARS CoV-2 RNA in nasopharyngeal swab reaches maximum within seven days of onset of symptoms [4]. However, Ct value depends on multiple factors like type of sample, technical competence of the person who is collecting sample, temperature of transportation, the date of sample collection from the duration of onset of illness and the kit used for molecular testing. In view of the observations, Indian Council of Medical Research (ICMR) has recommended further studies to look at Ct value correlation with clinical severity [5].

Many studies have evaluated the relationships among SARS-CoV-2 viral load and clinical severity and it points towards a positive correlation, mortality and disease progression [3, 6, 7]. Since the declaration of COVID-19 as a pandemic by the World Health Organisation (WHO) on March 11, 2020, India had witnessed three waves, with concerns about varying severity and mortality. So far the literature is sparse regarding the correlation of viral load and clinical severity in the region. In this context, the study is primarily aimed to find the correlation between Ct value and clinical severity and also to compare the baseline characteristics between the first two waves of the pandemic.

Materials & Methods

Study design & settings: This prospective cross-sectional study done during the period of March 2020 to July 2021 in a private medical college hospital in Kerala, India. The study was approved by the Institutional Ethics Committee (IEC Study No. IEC/2021/08/233) and informed consent from the patients were received for data collection.

Inclusion criteria: All symptomatic admitted COVID-19 patients, positive in Truenat RT-PCR test with Ct value of orf1a target gene between 10 and 32 were included in the study irrespective of age. Those patients whose RT-PCR test positivity within seven days of onset of symptoms was included in the study. The possible symptoms of COVID-19 included were fever, sore throat, cough, and shortness of breath, runny nose, nausea or vomiting, diarrhea, new loss of taste or smell, headache, fatigue or body aches.

Exclusion criteria: The COVID-19 patients who were referred in for expert care or referred out to other tertiary care centres were excluded from the study. All asymptomatic patients who were accidentally detected as positive for COVID-19 and patients who were sent for home isolation were also excluded from study.

COVID-19 molecular testing: The test was performed using Truenat SARS CoV-2 assay, which was ICMR endorsed molecular test for COVID-19 diagnosis. The limit of detection (LoD) of the Truenat SARS CoV-2 assay was estimated to be 487 genome copies/mL as per manufacturer's instruction. The target sequences for SARS CoV-2 for the assay were E and orf1a genes. The oropharyngeal or nasopharyngeal swabs were collected from patients with less than seven days of onset of symptoms. The swabs were immediately transferred to the lysis buffer or transport medium (Trueprep AUTO Transport medium). The nucleic acid was extracted using Trueprep AUTO Universal Catridge based Prep kit and Trueprep AUTO device. The purified RNA was transferred to Truenat SARS-CoV-2 chip and the test was run in Truelab Uno Dx/Quattro PCR analyser. The patients for whom Truenat COVID-19 Real Time duplex RT-PCR tests for the semiquantitative detection of SARS CoV-2 RNA in nasopharyngeal swab specimen were included in the study. A cycle threshold (Ct) value >10 in orf1a gene is further categorized as 'High' (Ct: 10-20), 'Medium' (Ct: 20-25), 'Low' (Ct: 25-30) and 'Very Low' (Ct: 30-32) based on the viral load, as per manufacturer's instruction. For ease of statistical analysis, the categories were re-classified as High (Ct: 10-25) and Low (Ct: 25-32).

Antigen testing for COVID-19: The test was performed using Standard Q (SD Biosensor) antigen testing kit (ICMR endorsed). Antigen testing for COVID was performed at 5 days during hospitalisation. If the antigen test was positive, retesting was done every 48 hours till it turned negative.

Study procedure: The patient demographic details on age and gender were collected along with the clinical information on the presence of co-morbidities. The viral load was compared with various clinical parameters like clinical severity stages, clinical outcome, length of hospital stay, days to antigen test negativity and other parameters. Based on symptomatology, the patients were classified into three categories namely, Category A (mild sore throat/cough/rhinitis), Category B (Category A symptoms with fever or lung/heart/liver/kidney/ hypertension/neurological disease/haematological disorder/cancer/cardiovascular disease/on long term steroids/pregnancy/age more than 60 years) and Category C (breathlessness, hypotension, worsening of underlying chronic conditions). The clinical severity stages were mild, moderate and severe based on the state guidelines [8]. The Ct values were compared with those presented during first 3 days of symptoms and upto 7 days of

symptoms. The association of demographic and various clinical parameters were compared between the first and second waves of COVID-19.

Statistical analysis:

The association between Ct value with clinical severity and the baseline characteristics with COVID-19 waves were compared using Chi-square test. The length of hospital stay and the days to antigen testing negativity was compared with viral load by using Independent Sample T-test.

Results

Among 183 patients who were COVID-19 positive by RT-PCR testing, out of which 140 (76.5%) patients presented in the first wave and 43 (23.5%) patients in the second wave.

The demographic and clinical information of all the admitted patients with COVID-19 are presented in Table 1.

Table 1: Demographic and clinical information of COVID-19 patients (n=183)

Variable	Number	Percentage (%)
Age		
• 0-9	3	1.6
• 10-19	6	3.3
• 20-29	13	7.1
• 30-39	12	6.6
• 40-49	16	8.7
• 50-59	29	15.8
• 60-69	49	26.8
• 70-79	46	25.1
• 80-89	9	4.9
Gender		
• Male	115	62.8
• Female	68	37.2
Comorbidities		
• Diabetes Mellitus	95	51.9
• Hypertension	93	50.8
• Chronic obstructive pulmonary disease (COPD)	16	8.7
• Asthma	14	7.7
• Chronic kidney disease	29	15.8
• Liver disease	11	6
• Coronary artery disease (CAD)	35	19.1
• Cerebral vascular accident (CVA)	14	7.7
• Hypothyroidism	14	7.7
• Dyslipidemia	34	18.6

The mean age of the patients in the first wave was 59.17 years ± standard deviation (SD) of 17.42 with youngest patient being 11 years and oldest, 87 years old while 49.49 years ± SD 22.43, ranging from 1 and 86 years in the second wave. Among the patients, maximum number were in 60-69 age group (26.8%) and 62.8% were males. The most common comorbidities observed were diabetes mellitus (51.9%) and hypertension (50.8%). All the patients included in the study were symptomatic and time taken by the patients to turn up for Truenat testing for COVID was 3.9 days after the onset of symptoms. The association of various factors with the viral load are described in Table 2.

Table 2: Association of viral load with clinical parameters of COVID-19

Factors	High viral load (n=121, 66.1%)	Low viral load (n=62, 33.9%)	Total	Chi-square	p*-value
Clinical severity					
• Mild	61 (69.3%)	27 (30.7%)	88 (48.1%)	0.774	0.379
• Moderate-severe	60 (63.2%)	35 (36.8%)	95 (51.9%)		
Oxygen requirement					
• No oxygen support	76 (69.1%)	34 (30.9%)	110 (60.1%)	1.086	0.297
• With oxygen support	45 (61.6%)	28 (38.4%)	73 (39.9%)		
Comorbidities					
• Yes	90 (63.8%)	51 (36.2%)	141 (77%)	1.439	0.23

• No	31 (73.8%)	11 (26.2%)	42 (23%)		
Outcome					
• Improved	109 (65.3%)	58 (34.7%)	167 (91.3%)	0.617	0.432
• Expired	12 (75%))	4 (25%)	16 (8.7%)		
Wave					
• First	92 (65.7%)	48 (34.3%)	140 (76.5%)	0.044	0.834
• Second	29 (67.4%)	14 (32.6%)	43 (23.5%)		

* Chi-square test was used and p-value </= 0.05 was considered as significant

The median SARS-COV-2 RT-PCR Ct values of the 183 patients was 25.22 (IQR: 12.63-29.12) at admission. The median Ct value during the first 3 days of symptoms was 18.15 (high viral load) compared to 23.8 in up to day 7 of symptoms. The majority of patients were having high viral load at the time of admission (n=121, 66.1%). The average Ct value of high and low viral load categories was 14.54 and 29.03 respectively. Early testing with a mean duration of 3.6 days after onset of symptoms had higher viral load content when compared to testing at 4.6 days after onset of symptoms. This was statistically significant with a p-value of 0.003. There were no significant association observed between COVID severity, oxygen requirement, co-morbidities, outcome, wave and viral load.

Table 3 displays all other variables related to COVID. There was no significant association noted between lengths of stay with viral load. In a total of 109 (59.6%) patients, who were monitored with COVID antigen testing, the average days for test negativity was 8.4 days. There was no significant association with days of antigen testing negativity and viral load.

Table 3: Comparison of viral load with other variables related to COVID-19

Variable	Number	Mean	Standard deviation	T-value	p*-value
Length of hospital stay with viral load (n=183)					
• High viral load	121	9.38	5.9	2.807	0.096
• Low viral load	62	7.85	5.7		
Days to Antigen testing negativity (n=109)					
• High viral load	71	8.27	2.8	0.229	0.633
• Low viral load	38	8.58	3.9		

*T-test was used and p-value </= 0.05 was con-sidered as significant.

The association of baseline characteristics related to COVID was compared between two waves and displayed in Table 4. A significant association was observed with age, symptom categories and presence of comorbidities. Other parameters including gender, Ct value, duration of symptoms, length of stay, clinical severity, outcome, requirement of steroids and oxygen had no significant association.

Table 4: Association of various parameters with first and second wave of COVID-19

Parameter	First wave (n=140)	Second wave (n=43)	p*-value
Age	59.17 years	49.49 years	0.003
Gender			
• Male	91 (65%)	24 (55.8%)	0.276
• Female	49 (35%)	19 (44.2%)	
Ct value	21.09	20.58	0.662
Days of onset of symptoms	4.03	3.65	0.320
Length of hospital stay	9.35 days	7.28 days	0.042
Category based on symptoms			
• Category A	19 (13.6%)	12 (27.9%)	0.041
• Category B	102 (72.9%)	29 (67.4%)	
• Category C	19 (13.6%)	2 (4.7%)	
Clinical severity			
• Mild	64 (45.7%)	24 (55.8%)	0.385
• Moderate	53 (37.9%)	15 (34.9%)	
• Severe	23 (16.4%)	4 (9.3%)	
Presence of comorbidities			
• Yes	115 (82.1%)	26 (60.5%)	0.003
• No	25 (17.9%)	17 (39.5%)	

Requirement of systemic steroids			
• Yes	61 (43.6%)	14 (32.6%)	0.199
• No	79 (56.4%)	29 (67.4%)	
Requirement of Oxygen			
• Yes	59 (42.1%)	14 (32.6%)	0.262
• No	81 (57.9%)	29 (67.4%)	
Outcome			
• Improved	127 (90.7%)	40 (93%)	0.639
• Expired	13 (9.3%)	3 (7%)	

* P-value </= 0.05 was considered as significant

Discussion

The COVID-19 global pandemic was an unparalleled health emergency which had spread rapidly across multiple countries in early 2020. The RT-PCR has been the main diagnostic tool for COVID-19 infection and has enabled the clinicians to quickly isolate the patient. Theoretically, the Ct value is inversely proportional to the amount of genetic material or the viral load [9]. Although a qualitative reporting of results is sufficient for COVID-19 diagnosis, a semiquantitative value as in Truenat, can guide in infection control and clinical decisions. India witnessed the initial two waves of COVID-19, which peaked in September 2020 and March 2021. Our study evaluated the correlation between Ct value and clinical severity between the two waves. There was no significant association between Ct value and clinical severity, outcome, presence of comorbidities, length of hospital stay and days of antigen testing negativity in the present study. A significant association was only observed with age, presence of comorbidities and presence of comorbidities when the two waves were compared.

In the present study, the mean age of the patients in the first and second waves was 59 years and 49 years, respectively. A similar age group was reported in other studies and systematic reviews [10, 11]. During analysis, more males (62.8%) were found to be positive when compared with females and similar findings were observed in other studies in India [12, 13]. In a meta-analysis study performed on COVID-19, the commonest comorbidities were hypertension, diabetes and cardiovascular diseases [14]. In the present study, the five commonest comorbidities observed in COVID-19 were diabetes (51.9%), hypertension (50.8%), CAD (19.1%), dyslipidemia (18.6%) and chronic kidney diseases (15.8%) which were similar to other studies [14, 15].

The SARS CoV-2 virus can be detected for a median of 20 days after symptom onset, but the infectiousness may decline significantly after 8 days of symptom onset [4, 16]. The present study has included only patients in whom the virus was detected by RT-PCR technique in less than 7 days of onset of symptoms. The viral loads of SARS CoV-2 varies during the course of infection, the highest viral load (low Ct values) have been reported in the first week of illness [17-19]. In our study, the average Ct value of those patients presented with less than 3 days of symptoms was lower than when compared with the other group with 4 to 7 days duration. The Ct value correlated with the duration of symptoms. Although a qualitative RT-PCR test result is sufficient for the diagnosis of COVID, Ct values may be important in predicting the stage of the disease.

Although many studies have reported a positive correlation between clinical severity and Ct values, the viral load or Ct value were not significantly different for mild and moderate-severe cases of COVID in our study [3, 20-23]. Westblade et al in their study noted that the in-hospital mortality rate was significantly higher in high viral load COVID patients with or without hematological malignancies [20]. Trunfio et al had controlled the confounding factors (the analysed gene, the time from COVID-19 onset to swab collection and the adopted assay) and observed a positive correlation of Ct value with mortality, disease severity and the persistence of sequelae at 6 months [21]. Rajyalakshmi B et al observed a positive correlation of Ct value with increased Intensive care unit (ICU) admission, mortality and increased length of ICU stay in their study in India [23].

No association was observed for Ct value (viral load) with the oxygen requirement, presence of comorbidities, mortality and the two waves in the present study. There was no correlation for Ct value (viral load) and the mean duration of antigen testing negativity and duration of hospital stay in our present study. A lack of correlation between SARS CoV-2 Ct value and clinical outcomes was observed in many other studies across the world [24, 25]. The Ct value for a specimen depends on the method of collection of samples, and it may vary between different kits, target genes and the different runs of the same kit [25].

We had also studied the difference of baseline characteristics of COVID-19 patients in the first and second waves. The mean age of COVID patients in the first and second wave was 59.17 years and 49.49 years respectively (p-0.003). Also,

the length of hospital stay was significantly higher in the first wave when compared with the second wave (9.35 Vs 7. 28 days, p-0.042). The COVID patients in category C was significantly lower in the second wave when compared with the first wave (p-0.041). The first wave witnessed a significantly large number of COVID patients with comorbidities when compared with the second wave (82.1% Vs 60.5%, p-0.003). The most common comorbidities for COVID patients in the first wave were diabetes mellitus, hypertension and CAD when compared with second wave in the study by Tendulkar et al [13]. However, the mean age of the patients and the duration of hospital stay in first and waves were very similar in their study.

Limitations:

Our study has limitations including small sample size, as we had adjusted the possible confounding factors of a single RT-PCR assay, single target gene and days of onset of COVID-19 symptoms and sample collection. Despite such limitations, to our knowledge, this would be first study assessing the correlation between Ct values and clinical severity and their comparison in the two waves of COVID for symptomatic patients.

Conclusion:

We conclude that SARS CoV-2 Ct values of Truenat RT-PCR alone do not have a role in commenting the clinical severity among patients with symptomatic COVID-19. The Ct value can offer an opportunity to the clinicians to take extra precautions during the early stage of the disease to prevent favourable disease transmission. The first wave of COVID-19 being of longer duration, many older patients with comorbidities were infected and with a prolonged hospital stay. However, there is no significant difference between the two waves for various baseline characteristics including gender, clinical severity, outcome, requirement of steroids and oxygen.

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