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Brief Communication

No correlation between Ct values and severity of disease or mortality in patients with COVID 19 disease

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ABSTRACT

There are several reports of Ct values of RT PCR assays for COVID 19 being associated with disease severity and infectivity. We studied the correlation between Ct values and disease severity and mortality at our hospital . All patients with RT PCR diagnosed COVID 19 illness admitted at the study site and for whom Ct values were available were included in the study. The patients with mild disease had significantly lower Ct values than patients with severe disease but had also been tested significantly earlier in the illness than those with severe disease. The patients who died had significantly lower Ct values than patients who survived but here again they had significantly shorter duration of symptoms before testing. We therefore recommend that the time of testing since onset of symptoms should be controlled for while correlating Ct values with disease severity.

1. Introduction

Currently available RT PCR methods for diagnosis of COVID 19 are able to give an estimate of the viral load [1]. The cycle threshold (Ct) values of the PCR reaction correlate inversely with the viral load; low Ct values indicate high viral loads and vice versa [2]. Furthermore, higher viral loads have been seen to correlate with disease severity and infectivity [3,4]. We therefore studied the correlation of the Ct value of RT PCR for COVID 19 with severity of disease and mortality in patients admitted with COVID 19 at our hospital.

2. Methods

This was a retrospective study conducted at a tertiary care hospital in Mumbai, India. The study evaluated all patients admitted with a RT PCR confirmed diagnosis of COVID 19 at the study site between 23rd March and 30th June 2020. The patients for whom testing were done at the study site and for which Ct values were available were included for analysis. Testing was done by Real Star SARS-CoV-2 kit by Altona Diagnostics, Germany. The patient population was segregated into those with severe disease (saturation $\leq$ 93% on room air at any point in the hospital stay) and those with non severe disease. The Ct values of the study patients were categorized as high (Ct 31–40), moderate (21–30) and low (11–20). The Ct values were compared between the patients with severe disease and mild disease and in patients of severe disease between those that died and those that survived. The time duration in days between onset of illness and day of testing was also compared between the groups. Testing for normality of data was done by Kolmogorov Smirnov test. Testing for statistical significance between the groups for categorical variables was by chi square test, for mean values by unpaired *t*-test and for median values by Kruskal Wallis test. A p value less than 0.05 was considered statistically significant.

3. Results

During the period between 23rd March and 30th June 2020, a total of 219 patients were admitted to the study site with a RT PCR diagnosis of COVID 19. Of these, 130 patients had severe disease (defined as pulse oximetry saturation $\leq$ 93% in room air) and the rest 89 had non severe/mild disease. Cycle threshold values of 54/89 patients with mild disease and 112/130 with severe disease were available for analysis. The distribution of the Ct values and duration of illness prior to testing is depicted in Table 1. It shows significantly lower Ct values of patients with mild disease compared to those with severe disease. However the duration of illness prior to testing (summarized as median since data was not normally distributed) was significantly shorter in the group with mild

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Table 1
Distribution of Ct values in patients with mild and severe disease.

Median duration of symptoms before testing	Mild disease (n = 54)	Severe disease (n = 112)	Significance testing
	3 days	5 days	P = 0.02 (Kruskall Wallis test)
Ct 11–20	29 (54%)	35 (31%)	Chi square statistic 7.7, p = 0.02
Ct 21–30	17 (31%)	52 (46%)	
Ct 31–40	8 (15%)	25 (22%)	

disease (3 days) as compared to those with severe disease (5 days). Of the 113 patients with severe disease, 56 had died, 55 had been discharged and 2 had been transferred to other hospitals. . The Ct values of patients who died were significantly lower than those who survived (Table 2). However the duration of illness prior to testing (summarized as median since data was not normally distributed) in patients who died was significantly shorter (3 days) than those who survived (5 days).

4. Discussion

In our small study we could not demonstrate any correlation between Ct values and severity of disease. Though patients with mild disease had lower Ct values and possibly higher viral loads they had also been tested earlier (median 3 days) than those with severe disease (median 5 days). However in patients with severe disease the Ct values of those who died were significantly lower than those who survived; but at the same time these patients had shorter duration of symptoms before testing (median 3 days as against 5 days). While it is difficult to draw conclusions from these results, it appears that time since onset of symptoms has a stronger relationship with the Ct values as compared to the severity of disease.

Literature supports correlation of Ct values aka viral load and severity of disease. In a very recent publication, Magleby et al. studied Ct values of 678 patients with COVID 19 in New York [3]. In-hospital mortality was 35% with a high viral load (Ct < 25; n = 220), 18% with a medium viral load (Ct 25–30; n = 216), and 6% with a low viral load (Ct > 30; n = 242; P < 0.001). The risk of intubation was also higher in patients with a high viral load (29%), compared to those with a medium (21%) or low viral load (15%; P < 0.001). Zheng and Liu et al. from China have also reported higher viral loads and longer persistence of the virus in patients with severe disease as compared to those with mild disease [5,6]. However many other studies have not explored this relationship of Ct values with disease severity [7,8]. Similarly studies have not found any difference between viral loads as determined by Ct values between symptomatic and asymptomatic patients. [9].

Recently the ability of Ct values to reflect the true viral load has been questioned [10]. Experts state that the Ct values for a specimen vary between different kits and techniques (including target genes, primers and threshold fluorescence values) and Ct values may vary between different runs of the same kit · [10] The Ct value also depends on the method of collection of the sample and hence there may be variation in Ct values between two different samples obtained from the same person on the same day and run on the same kit. The Ct values also depend on the timing of sample collection in relation to onset of symptoms; samples collected earlier in the illness will have lower Ct values than those collected later in the illness [11]. Therefore, the time of sampling since onset of illness has to be controlled while comparing Ct values between mild and severe disease. Our study proves the same point.

The other utility of the Ct value is in determining infectivity wherein patients with Ct values of more than 24 may be considered non infectious

Table 2
Distribution of Ct values in patients with severe disease who died and who survived.

Median days of symptoms before testing	Survived (n = 56)	Died (n = 55)	Significance testing
	5 days	3 days	P = 0.02 (Kruskall Wallis test)
Ct 11–20	12 (21%)	24 (44%)	Chi square statistic 6.3 p = 0.04
Ct 21–30	30 (54%)	22 (40%)	
Ct 31–40	14 (25%)	9 (16%)	

[4]. However, with most guidelines moving away from repeat tests to take decisions about de isolation, this utility of the Ct value is also losing value·[12].

Despite all this, all clinicians should look at Ct values in all patients with COVID 19 infection to better understand the dynamics of the disease. The Indian Council of Medical Research has also recommended the same· [13] Better ways of estimating the viral load of COVID 19 and further exploration of the relationship between viral loads with viable virus and disease severity/infectivity are needed. Till then, decisions about predicting severity of disease should be based on clinical parameters including age, comorbidities and laboratory parameters including the absolute lymphocyte count, C reactive protein levels and D- Dimer levels rather than the Ct value.

Declaration of competing interest

None.

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