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Fluctuating RT-PCR CT values: A case series

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Abstract

Real-Time Reverse Transcriptase Polymerase Chain Reaction (r RT-PCR) has been the main diagnostic tool for SARS-CoV-2 infection since the early stages of the COVID-19 pandemic and a positive test enables the clinicians and public health professionals to quickly isolate the patient and prevent spread of the disease. The presence of viral RNA confirms SARS CoV-2 and the Cycle Threshold (Ct) values may give a rough estimate of viral load. Theoretically, the Ct value is inversely proportional to the amount of genetic material (RNA) in the starting sample and lower Ct values is generally associated with high viral load. Some experts assume that high viral load is directly correlated with increased infectiousness and severity of disease and suggest using Ct value or calculating viral load in decision-making. As per the policy, dated 14th June 2020, National Health Strategic Command Group in Qatar recommends using RT-PCR Ct value as a key determinant for decision on admission, discharge and isolation. The objective of this case series is to show that Ct values vary as the course of infection progresses, hence cannot be used as a reliable marker to take clinical decisions or even public health actions such as quarantine/ isolation. All six confirmed COVID19 cases showed fluctuating RT-PCR Ct values throughout the course of illness. The Ct value was higher in the beginning of the course of infection, depicting low viral load and later in the course the Ct value dropped indicating higher viral load. The Ct value decreased as symptoms developed or worsened. There is a high probability that patients in early symptomatic stage may show a high Ct value which may subsequently change and thus management will change. In such cases, the high Ct values will give a false sense of security and thus have an impact on the containment of spread of infection to others. Hence, it is not recommended to rely on numerical Ct values for determining infectiousness of COVID-19 patients and deciding patient management protocols since the Ct value an indirect marker of viral load, changes over the course of infection.

Keywords: fluctuating CT values; COVID-19; SARS CoV-2; RT-PCR CT values.

Introduction

Real-Time Reverse Transcriptase Polymerase Chain Reaction (r RT-PCR) has been the main diagnostic tool for SARS-CoV-2 infection since the early stages of the COVID-19 pandemic. This test confirms SARS CoV-2 by early detection of viral genome in clinical samples. There is a fluorescence signal in the test which increases proportional to the amount of amplified nucleic acid enabling accurate quantification of RNA in the sample. The cycle threshold or Ct value of a RT-PCR reaction is the number of cycles at which fluorescence of the PCR product is detectable over and above the background signal. If the fluorescence reaches a specified threshold within a certain number of PCR cycles (Ct value), the sample is declared positive. A COVID-19 testing laboratory needs to specify a Ct cut-off, which is the maximum number of PCR cycles for each test. A higher Ct cut-off means more patients are likely to receive positive diagnosis which causes an unnecessary burden and cost on already strained health care systems due to the COVID19 pandemic. And vice versa, a lower Ct value cut-off means, that more patients may be missed and there is a higher chance for COVID-19 infections to spread in the community [1]. Many PCR assays involve Ct value 40 as cut off to consider the test positive, allowing detection of even very few starting RNA molecules [2]. The National laboratory in Qatar under Hamad Medical Corporation (HMC), considering significant local and international evidence, adopted a cut off Ct value of 40 and anybody with Ct > 40 were considered negative. [3]

A positive test enables the clinicians and public health professionals to quickly isolate the patient and prevent spread of the disease. It is being assumed by some researchers / clinicians that high viral load directly correlates with increased infectiousness and severity of disease [4,5]. Ct values may give a rough estimate of viral load. Theoretically, the Ct value is inversely proportional to the amount of genetic material (RNA) in the starting sample and lower Ct values generally correlate with high viral load [6]. The National Health Strategic Command Group (NHSCG) in Qatar, recommends using PCR test Ct value as a key determinant for decision on admission, discharge and isolation. Any patient with RT-PCR Ct value >33 is considered non infectious and if he/she has symptoms, he/she were isolated in isolation facilities for 14 days from diagnosis whereas if the patient with Ct >33 was asymptomatic, they were advised to self-isolate in their homes [3].

With effect from 19th June 2020, considering significant local and international evidence, the NHSCG revised the protocol for the RT-PCR Ct cut off values and hence the national laboratory revised their reporting pattern of RT-PCR results, as those with Ct value>30 being categorized as Reactive and those with <30 as active [7,8]. The COVID-19 System Wide Incident Command Committee (SWICC) too revised the protocol for admission and discharge from isolation facility using the revised cut off for RT-PCR Ct values [8]. Those with Ct value <30 will be admitted in an isolation facility for 14 days from diagnosis. If asymptomatic they will be considered recovered and discharged home and advised home isolation for 7 more days. This 7 day of home recovery period has also been lifted recently. [8]

Both asymptomatic and mildly symptomatic cases can discontinue isolation after 14 days from diagnosis and there is no need to repeat PCR test for COVID-19 positive cases once confirmed positive. COVID-19 positive cases who are asymptomatic and have Ct value >30 and recommended self-isolation in their homes for 7 days from diagnosis and after which they are considered recovered and allowed to resume normal life. However, the symptomatic cases with Ct value >30 shall remain in an isolation facility for a week [8]. All close contacts of both positive and reactive cases with high-risk exposure would also be tested and quarantined for 14 days since the day of exposure even if the result is negative [8].

The objective of this case series is to show that Ct values vary as the course of infection progresses in a person, hence cannot be used as a reliable marker to take clinical decision-making process or even public health actions such as quarantine/ isolation. These are the first six cases that came to our notice in June 2020.

Summary of cases

Case I

A 29-year-old Filipino female who works as house maid was in close contact with a positive person in the same household and was swabbed and tested positive for COVID with a Ct value 36.49, indicating a low viral load. Though her Ct value was greater than 30 and she was asymptomatic, she was transferred a Quarantine facility with the family. After 5 days she started complaining of fever headache, intermittent cough, chest pain and loose stools. She was then admitted to CDC hospital, and she was re-swabbed after 10 days and the Ct value reduced to 29.065, probably indicating an increasing viral load. When her symptoms subsided, she was transferred back to the quarantine facility.

Case II

A 35-year-old Yemeni male who works in a ministerial office, presented to Primary Health Care Center with symptoms of sore throat of two days duration and with history of contact with a positive case and he tested negative. After a month he was tested again due to runny nose, thirst, taste & smell loss and resulted positive with Ct value of 31.69 (indicating low viral load) and when the test was repeated after 4 days the Ct value drastically dropped to 17.23 (indicating a high viral load).

Case III

A 37-year-old Qatari female, who is a homemaker had contact with a positive case, developed mild upper respiratory tract infection symptoms and tested positive with Ct value of 31.15 (indicating low viral load). After 2 weeks, the PCR was repeated, and the Ct value was 29.96 (indicating a high viral load).

Case IV

An asymptomatic 46-year-old obese Qatari female was tested for COVID after having contact with a positive case and resulted positive with Ct value of 32.7 (indicating low viral load). She is an asthmatic, a diabetic and a hypertensive. A week later she developed myalgia, dizziness and lethargy and progressed to productive cough with pleuritic chest pain when she was transferred from the quarantine facility to CDC hospital. She was admitted with COVID pneumonia and retested, when the Ct value had dropped to 25.2, indicating a higher viral load.

Case V

A 50-year-old Jordanian male, working as an engineer in the industrial area, the first hot spot area identified during the COVID-19 outbreak in Qatar, presented to the health facility mild cough, throat pain, diarrhea and body ache. He is a known case of epilepsy, hypertension and dyslipidemia and gave no history of contact with a COVID-19 positive person. He tested negative. Ten days later he presented again with cough and fever and tested positive with Ct value of 34.39, indicating a low viral load. He was transferred to a tertiary care hospital as a case of COVID pneumonia where he was retested the next day, and the Ct value had further dropped to 29.19 indicating an increasing viral load.

Case VI

A 27-year-old Qatari male, an asthmatic presented with dry cough and sore throat and malaise and was tested negative. Later he presented with history of contact with a COVID-19 positive person, at work and tested positive, with a Ct value of 33.35. Though asymptomatic at the time of first positive result, after a week he started feeling unwell and complained of tightness of chest, cough, sore throat and generalized body ache. On testing when he developed symptoms, the Ct value was found to be 21.5.

Discussion

Some experts suggest using RT-PCR Ct value or to calculate viral load which can help refine decision-making (shorter isolation etc) [9]. However, the evidence is not robust enough to definitively support this assumption. Ct values can allow physicians to identify patients most at risk for severe disease and death. It can also allow contact tracing teams to triage their efforts on patients with higher infectivity and reduce the need for isolation of close contacts of patients that are not infectious.

However, many recent discussions have pointed out several limitations about Ct values of Rt-PCR guiding the clinical decision making [10]. According to some experts, precautions are needed when interpreting the Ct values of SARS-CoV-2 RT-PCR results [11]. RT-PCR may have suboptimal sensitivity, for instance because in early stages of COVID-19 infection, the viral load is below detection limit [12]. Accuracy of the reported Ct values also depend on technical factors like how the sample has been collected, technical competence of the person performing the test, calibration of equipment and pipettes and analytical skills of the interpreters, temperature of transportation as well as time taken from collection to receipt in the laboratory. Ct values between nasal and oropharyngeal specimens collected from the same individual may differ [12].

Patients in early symptomatic stage may show a high Ct value which may subsequently change as their disease progresses. In such cases, the initial high Ct values give a false sense of security that such patients are not infectious. Several studies observed increases in viral loads prior to clinical deterioration (particularly those based on lower respiratory tract specimens) with decreases in viral load observed prior to improvement of symptoms. Occasionally, samples from asymptomatic/mild cases show Ct values like those who develop severe disease because severity of COVID-19 disease largely depends on host factors besides viral load. Some patients with low viral load may land up in very severe disease due to triggering of the immunological responses. Hence, again high Ct value may give a false sense of security [13].

According to a recently published study, viral shedding may already begin 2-3 days before the appearance of the first symptoms [14]. In general, the highest viral loads from upper respiratory tract samples were observed at the time of symptom onset and for a few days after (generally within one week), with levels slowly decreasing over the next one to three weeks [15]. In general, viral loads from upper respiratory tract samples were observed to peak within a week of symptom onset and followed a relatively consistent downward trajectory, whereas viral loads from stool/ sputum samples were found to peak later in the disease (generally two to three weeks after symptom onset) and followed a more erratic pattern [16].

A case report of a 6-month-old infant, who was tested as part of contact tracing, noted no symptoms on admission to hospital, but a relatively high viral load (nasopharyngeal sample targeting ORF1ab-gene, peak viral load Ct value = 13.73). The viral load decreased over the next nine days, although it raised slightly when the child experienced a fever on day two of admission, before falling again once the fever resolved [17].

In the above case series, it is evident that the viral load at different time points of an infection is varying. The Ct value was higher in the beginning of the course of infection, depicting low viral load and later in the course the Ct value dropped indicating higher viral load. We can also see that the Ct value decreased as symptoms developed or worsened.

As per the revised SWICC policy on 28th June 2020, if a person is tested only once and they are classified as active / reactive and managed accordingly [8]. There is a high probability of these reactive cases becoming active category later in the course and thus management will change. Patients in early symptomatic stage may show a high Ct value which may subsequently change. In such cases, high Ct values will give a false sense of security. This will then have an impact on the containment of spread of infection to others.

Considering the recent evidence, HMC re-revised policy on 20th March 2021 states that all patients with an initial reactive test result should be reviewed and retested after 7 days to see if the symptoms have changed and whether the CT value is increasing or decreasing [18]. If the Ct value dropped to lower than 30 then the isolation was extended to another 14 days. If the Ct value on retesting, remains above 30 or turns negative then he/ she may end the isolation and continue with community engagement maintain all safety precautions and may rejoin work (if working) [18]. Further studies relating to SARS-CoV-2 detection and viral load at different time points of an infection, including in those without any symptoms, which will aid with the clinical interpretation of Real-Time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) test results.

Conclusion

Since the Ct value an indirect marker of viral load changes over the course of infection, it is not recommended to rely on numerical Ct values for determining infectiousness of COVID-19 patients and deciding patient management protocols.

Recommendation: Even if the Ct value is >30 on the initial RT-PCR it is always recommended to retest after 7 days to capture the different stages of infection and also ensure that if somebody is declared reactive, confirm he is in the later stages of infection before release from isolation; in order to curb the spread.

Declarations

Ethical consideration: A waiver of all the consent was obtained vide PHCC/DCR/2020/11/131, as this research involved reviewing the reports of those positive cases who have already recovered, involved no risk to the subjects. The data were collected from patient notes for the purpose of research in an anonymized way and information regarding collected data will be kept confidential.

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