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कल्याण मंत्रालय, भारत सरकार

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Evidence Based Advisory on Correlation of COVID-19 Disease Severity with Ct Values of the Real Time RT-PCR Test

Real Time Reverse Transcription Polymerase Chain Reaction (Real Time RT-PCR) is the gold standard test for detection of SARS-CoV-2. This test enables early detection of viral genome in clinical samples. A positive test enables the clinicians and public health professionals to quickly isolate the patient and prevent spread of the disease. 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. 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 load¹. It is being assumed by some researchers / clinicians that high viral load directly correlates with increased infectiousness and severity of disease^{2,3}. However, the evidence is not robust enough to definitively support this assumption. Recent discussions about guiding the clinical decision-making process based on the Ct values of RT-PCR test reported by laboratories has several limitations⁴.

ICMR has discussed the issue of correlating COVID-19 disease severity with Ct values and accordingly deciding on patient management protocol, with a panel of esteemed laboratory experts. Following are the consolidated recommendations of the ICMR "Expert Group":

- There are no reliable studies to definitively prove a direct correlation between disease severity / infectiousness and Ct values. Viral load does not have much role in patient management.
- Ct values differ from one kit to the other. Comparability of Ct values among different kits is a challenge as our labs are using a mixed basket of kits now with different Ct cut-offs and different gene targets.
- Ct values also depend on how the sample has been collected. A poorly collected sample may reflect inappropriate Ct values. Besides, Ct values are also determined by technical competence of the person performing the test, calibration of equipment and pipettes and analytical skills of the interpreters.
- Ct values between nasal and oropharyngeal specimens collected from the same individual may differ.
- Similarly, temperature of transportation as well as time taken from collection to receipt in the lab can also adversely impact Ct values.
- Samples from asymptomatic/mild cases show Ct values similar to those who develop severe disease.
- 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.
- Severity of COVID-19 disease largely depends on host factors besides the 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.



- Moreover, the RT-PCR test presently being conducted is qualitative in nature. Ct values may give a rough estimate of viral load. However, more specialized standards are required for quantitative assays which are currently unavailable for SARS-CoV-2.

In view of the above, it is not recommended to rely on numerical Ct values for determining infectiousness of COVID-19 patients and deciding patient management protocols.

References:

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