



# The many clinical advantages of reporting the cycle threshold (Ct) value

Giuseppe Lippi<sup>1</sup>, Mario Plebani<sup>2</sup>

<sup>1</sup>Section of Clinical Biochemistry and School of Medicine, University of Verona, Verona, Italy; <sup>2</sup>Department of Medicine-DIMED, University of Padova, Padova, Italy

Correspondence to: Prof. Giuseppe Lippi. Section of Clinical Biochemistry, University Hospital of Verona, Piazzale L.A. Scuro, 10, 37134 Verona, Italy. Email: giuseppe.lippi@univr.it.

Submitted Mar 02, 2022. Accepted for publication Mar 17, 2022.

doi: 10.21037/atm-22-1104

View this article at: <https://dx.doi.org/10.21037/atm-22-1104>

There is ongoing debate on advantages and limitations of reporting the cycle threshold (Ct) values in clinical specimens testing positive for severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) mRNA. In a recent document published authored by Rhoads *et al.* on behalf of the College of American Pathologists (CAP) Microbiology Committee Perspective (1), the authors concluded that caution shall be used in interpreting the Ct values of SARS-CoV-2 testing. Although we substantially agree that using this means for expressing SARS-CoV-2 viral load in diagnostic samples carries some technical drawbacks, we would like to briefly emphasize here the many other important clinical implications that Ct values reporting may have in coronavirus disease 2019 (COVID-19) diagnostics.

Several lines of evidence now confirm that the Ct value is a significant predictor of emergence and progression of local SARS-CoV-2 outbreaks. This has been clearly demonstrated by Yin *et al.* (2), who showed that the trends of Ct values predict epidemic trajectories in terms of future mean daily positive tests, as well as by Penney *et al.* (3), who demonstrated that the trend of Ct values in SARS-CoV-2 positive samples significantly predicts incident COVID-19 hospitalizations. Besides these important epidemiological implications, mounting evidence reveals that monitoring routine Ct values of SARS-CoV-2 by means of accurate and standardized molecular assays may have substantial clinical implications. To summarize the most important

findings, Shah *et al.* conducted a meta-analysis of studies which explored the association between SARS-CoV-2 viral load and outcome of COVID-19 (4), concluding that patients with low Ct values (i.e., typically <25), display an over 2-fold and a nearly 3-fold higher risk of developing severe COVID-19 illness and death, respectively, compared to those with higher Ct values. In another critical review of the literature, Rao and co-authors concluded that Ct values of SARS-CoV-2 RNA may even anticipate unfavourable changes in some laboratory biomarkers, which are predictive of adverse clinical outcome in patients with SARS-CoV-2 infection (5). Finally, Abu-Raddad *et al.* demonstrated that systematic assessment of Ct values in patients with COVID-19 vaccine breakthrough are highly predictive of SARS-CoV-2 infectiousness, thus enabling more appropriate planning and establishment of public preventive measures (6).

In conclusion, although we are aware that several pre-analytical (i.e., specimen collection, preservation, storage, transportation, preparation, inactivation and RNA extraction), analytical (e.g., analytical sensitivity and interfering substances, usage of different gene targets and diverse amplification and detection techniques) and post-analytical (e.g., calibration, test results interpretation, correlation with viral load) aspects may bias the importance of reporting the Ct values in SARS-CoV-2 positive samples (7), we firmly believe that the clinical advantages of using accurate and standardized molecular assays fit for this purpose may ultimately offset the limitations (*Table 1*).

**Table 1** Potential clinical advantages of reporting the Ct value in clinical specimens testing positive for SARS-CoV-2

Predicts emergence and progression of SARS-CoV-2 outbreaks
Predicts the risk of developing severe/critical forms of COVID-19 illness
Predicts SARS-CoV-2 infectiousness, even in patients with vaccine breakthrough

Ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Annals of Translational Medicine* for the series “Column in Laboratory Medicine”. The article did not undergo external peer review.

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroupp.com/article/view/10.21037/atm-22-1104/coif>). The series “Column in Laboratory Medicine” was commissioned by the editorial office without any funding or sponsorship. GL serves as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International

**Cite this article as:** Lippi G, Plebani M. The many clinical advantages of reporting the cycle threshold (Ct) value. *Ann Transl Med* 2022;10(7):427. doi: 10.21037/atm-22-1104

License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Rhoads D, Peaper DR, She RC, et al. College of American Pathologists (CAP) Microbiology Committee Perspective: Caution Must Be Used in Interpreting the Cycle Threshold (Ct) Value. *Clin Infect Dis* 2021;72:e685-6.
2. Yin N, Dellicour S, Daubie V, et al. Leveraging of SARS-CoV-2 PCR Cycle Thresholds Values to Forecast COVID-19 Trends. *Front Med (Lausanne)* 2021;8:743988.
3. Penney JA, Jung AW, Koethe BC, et al. Utility of the cycle threshold in anticipating the next phase of the coronavirus disease 2019 (COVID-19) pandemic. *Infect Control Hosp Epidemiol* 2022. [Epub ahead of print]. doi:10.1017/ice.2022.41.
4. Shah VP, Farah WH, Hill JC, et al. Association Between SARS-CoV-2 Cycle Threshold Values and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. *Open Forum Infect Dis* 2021;8:ofab453.
5. Rao SN, Manissero D, Steele VR, et al. A Systematic Review of the Clinical Utility of Cycle Threshold Values in the Context of COVID-19. *Infect Dis Ther* 2020;9:573-86.
6. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Relative infectiousness of SARS-CoV-2 vaccine breakthrough infections, reinfections, and primary infections. *Nat Commun* 2022;13:532.
7. Lippi G, Simundic AM, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). *Clin Chem Lab Med* 2020;58:1070-6.