Review Article

Reporting SARS-CoV-2 viral load from upper respiratory tract specimens in the post-emergency phase: a narrative review

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Background and Objective: Although coronavirus disease 2019 (COVID-19) is no longer considered a global health emergency, it remains an important threat because of the persistently high number of infections, hospitalizations, and fatalities caused by repeated waves of new variants. Identifying factors that can aid in clinical decision making and public health interventions to mitigate the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) must hence be prioritized. Therefore, we present here a narrative review to discuss the drawbacks and emphasize the important advantages of continuing to report the viral load in upper respiratory tract specimens in individuals with SARS-CoV-2 infection.

Methods: This narrative review discusses the drawbacks and, in particular, highlights the important advantages of continuing to report viral load in upper respiratory tract specimens collected from individuals infected with SARS-CoV-2 after the global emergency phase has ended.

Key Content and Findings: Measurement of SARS-CoV-2 viral load (i.e., most commonly the cycle threshold) in upper respiratory tract specimens is subject to several limitations, the most important of which is poor interlaboratory comparability, especially when different nucleic acid amplification tests are used. Nevertheless, routine determination and reporting of viral load in persons with SARS-CoV-2 infection may have some important advantages. These essentially include the association with a number of epidemiologic, biologic, and clinical aspects, as this measure can predict disease severity, population epidemic, future public health burden, emergence of new variants, individual infectivity and shedding kinetics, as well as the risk of developing long-COVID.

Conclusions: Routine viral load determination and reporting in patients with SARS-CoV-2 infection could offer significant advantages that may outweigh the current technical limitations.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); viral load; cycle threshold (Ct)

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Introduction

Background

In May 2023, the World Health Organization (WHO) has decided to revise the status of the ongoing coronavirus disease 2019 (COVID-19) pandemic, by declaring the end of the global health emergency (1). Although this news was greeted with immense relief by policymakers, health care workers, and even by the worldwide population, COVID-19 remains a global health threat due to the still remarkable number of documented infections, hospitalizations and related deaths, primarily caused by repeated waves of new variants characterized by sufficient antigenic diversity to escape previous natural, vaccine-elicited or hybrid immunity (2). Thus, continuous monitoring of evolution and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a paradigm for the so-called "new normal", which will be characterized by an unpredictably long coexistence with this new virus (3).

Rationale and knowledge gap

Although it is now undeniable that a number of preventive measures, such as vaccination, isolation of infected people, improving ventilation, washing and sanitizing hands, and wearing face masks, etc., are effective tools that could be considered to prevent or limit severe outbreaks of COVID-19, the role of the clinical laboratory should not be ignored or even neglected (4). According to its conventional definition, viral load is traditionally used to define the amount of virus present in a clinical sample. In current practice of SARS-CoV-2 diagnostics, viral load is assayed in upper respiratory tract specimens using molecular biology techniques [particularly nucleic acid amplification techniques (NAATs)], where the final result of measurement, the cycle threshold (Ct), reflects the number of amplification cycles required to reach a threshold of detectable amount of genomic viral material (i.e., RNA for SARS-CoV-2) (5). In other words, a low Ct value reflects a high concentration of viral genetic material, while a high Ct value reflects a low concentration of viral genetic material (*Figure 1*). From a biological perspective, low Ct value is hence associated with high value of plaque forming units (PFU)/mL in viral culture, whilst high Ct value mirrors low value of PFU/mL in the viral culture (6). Nevertheless, the question as to whether the Ct value is analytically reliable, as well as epidemiologically and clinically valid is still open.

Objectives

The goal of this narrative review is to discuss the drawbacks and especially emphasize the important advantages of continuing to report the viral load in upper respiratory tract specimens collected from individuals infected with SARS-CoV-2 after the global emergency phase has passed. We present this article in accordance with the Narrative Review reporting checklist (available at https://jphe.amegroups.com/article/view/10.21037/jphe-23-98/rc).

Methods

We conducted a free literature search in the literature in science, medicine, and public health to define the potential limitations and advantages of reporting viral load in upper respiratory tract specimens from individuals with SARS-CoV-2 infection (*Table 1*). We began by searching for the terms "viral load" or "cycle threshold" and then expanded the search to include other terms that might help identify the drawbacks and clinical utility of reporting viral load in health care contexts, such as "disease or illness severity", "epidemics", "public health", "variants", "infectivity", "contagiousness", "shedding" and even "long-COVID". All articles found were in English, all but one were peer-reviewed, and came from academic institutions and government reports. The search was straightforward because viral load was studied in several articles and was linked to several important epidemiologic and clinical endpoints. Based on this literature search, we were able to identify a number of limitations and strengths associated with reporting the viral load of SARS-CoV-2 in the post-emergency phase of the COVID-19 pandemic.

Key content and findings

Potential drawbacks in reporting the Ct value

The Association for Diagnostic and Laboratory Medicine (ADLM) has conducted an in-depth analysis of the analytical and technical limitations of SARS-CoV-2 NAAT (7), and currently advises against the use of Ct values for the management of COVID-19 patients, citing a number of potential drawbacks to routine reporting of viral load (i.e., the Ct value) in upper respiratory tract specimens (*Table 2*). Most of these reasons are certainly sound, and include inappropriate procedures for patient preparation, specimen collection, storage, and transport; variable time interval

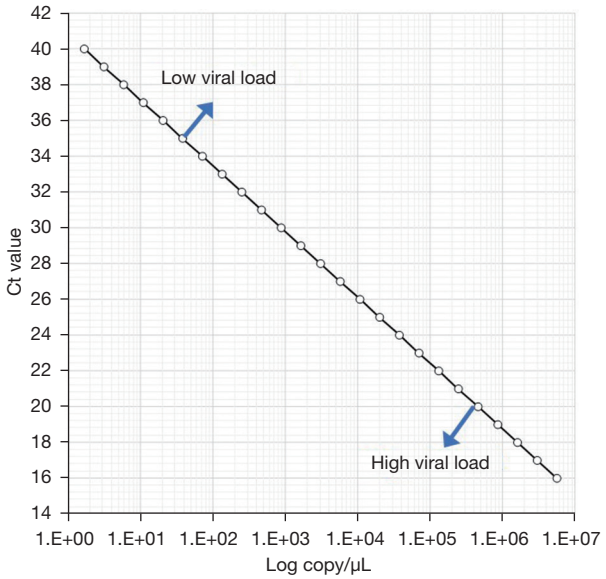

Figure 1 Linear correlation between the Ct value and the concentration of SARS-CoV-2 in upper respiratory tract specimens. Ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1 The search strategy summary

Items	Specification
Date of search	05 September 2023
Databases and other sources searched	PubMed; Scopus
Search terms used	"Cycle threshold", "Ct", "viral load", "SARS-CoV-2", "COVID-19"
Timeframe	Up to 05 September 2023
Inclusion criteria	Data limited to viral load in patients with SARS-CoV-2 infection
Selection process	G.L. and C.M. selected articles together

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

between patient infection and viral load determination; heterogeneous methods of specimen preparation for testing; presence of inhibitory or interfering substances; use of different gene targets (for type and number); use of fluorescent dyes for detection; effects of different variants; inadequate use of reference materials (i.e., insufficient standardization), use of heterogeneous detection thresholds, variable range of reportable measures, and insufficient comparability within and between instruments (7). The

Table 2 Drawbacks and potential advantages of measuring the viral load of SARS-CoV-2 in the post-emergency phase

Drawbacks
• Inappropriate patient preparation
• Inappropriate collection, storage and transportation of specimens
• Time passed between patient infection and viral load assessment
• Heterogeneity in sample preparation
• Presence of inhibitory or interfering substances
• Different gene targets
• Heterogeneity in fluorescent dyes
• New variants
• Poor standardization
• Heterogenous detection thresholds
• Variable range of reportable values
• Poor within- and between-instrument comparability
Advantages
• Prediction of disease severity
• Prediction of population epidemics
• Prediction of future healthcare burden
• Prediction of emergence of new variants
• Prediction of infectivity
• Prediction of shedding kinetics
• Prediction of long-COVID

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID, coronavirus disease.

ADLM also points to a number of postanalytical problems that may affect the clinical validity of this measure, including the frequent discrepancy between Ct value and actual infectivity (i.e., a high but still detectable Ct value may reflect shedding of nonviable genetic material), the wide range of reportable units of measurement, and the potentially erroneous clinical interpretation of the Ct value. Although the major limitation may be due to poor comparability of Ct values obtained by different laboratories using different equipment, a reference standard (WHO 20/146) consisting of a SARS-CoV-2 isolate inactivated by acid heat is now available, and can be used for calibration and/or harmonization of NAATs specifically developed for SARS-CoV-2 RNA detection. Preliminary findings from

two separate studies demonstrate that the introduction of this reference material for recalibration of SARS-CoV-2 molecular assays has been effective in harmonizing test results by reducing the inter-assay variability to a clinically insignificant bias (8,9).

Potential advantages in reporting the Ct value

Without disregarding the above limitations, reporting the Ct values of SARS-CoV-2 measured in upper respiratory tract specimens also offers a number of potential benefits that may even outweigh the limitations, and that will be briefly summarized in the following section of the article (*Table 2*).

Prediction of disease severity

The relationship between viral load and illness severity in patients with SARS-CoV-2 infection has been already explored in several studies. Most of these were recently summarized in the meta-analysis by Shah *et al.* (10). In the four studies (n=2,347 patients) included in their analysis, the authors found that patients hospitalized for COVID-19 with Ct values below 25 [odds ratio (OR) =2.31; 95% confidence interval (CI): 1.70–3.13] or between 25–30 (OR =1.45; 95% CI: 1.06–1.97) exhibited an enhanced risk of developing more severe illness compared to those with higher Ct values. The mean Ct difference between patients with or without severe COVID-19 illness was 5.2 (95% CI: 3.3–7.1). A subsequent study was published by Waller *et al.* (11), which also showed that a high viral load (i.e., Ct value <30) at hospital admission was independently associated with the risk of developing severe COVID-19 illness (OR =15.3; 95% CI: 1.7–134) in multivariate regression analysis. Interesting evidence was also provided by the study of Ingberg *et al.* (12), who examined 286 patients hospitalized for COVID-19 and reported that Ct level on admission was significantly correlated with the risk of intensive care unit (ICU) admission or death [area under the curve (AUC): 0.643].

Prediction of population epidemics

Several lines of evidence attest that the viral load may be significantly associated with population epidemics. Specifically, Sala *et al.* published a systematic literature review, where they explored the correlation of the Ct value with COVID-19 epidemiological trends (13). The authors included 16 studies, all of which described an inverse correlation between SARS-CoV-2 Ct values and the epidemiologic trajectories of SARS-CoV-2 cases. In the eight studies that examined the incidence rates of new COVID-19 diagnoses across two epidemic waves, a significant prediction time was always found in terms of negative cross-correlation between Ct values and new daily cases, with the prediction time ranging from 1 to 3 weeks. Important support to the fact that the viral load can be useful in predicting the epidemic course of an outbreak was also provided by the recent study by Phillips *et al.* (14), which concluded that Ct values negatively correlated with new SARS-CoV-2 cases approximately 2 weeks after the outbreak, and that a predictive model based on Ct values can efficiently predict the evolution of an outbreak with 65% accuracy. Thus, it could be concluded that monitoring Ct value may provide useful information for anticipating subsequent waves of COVID-19 and for determining the most appropriate containment and management interventions.

Prediction of healthcare burden

Although predicting epidemiologic trends is certainly useful for managing an ongoing epidemic and/or pandemic, the anticipation of the relative burden of COVID-19 on the health care system is even more important, for a variety of clinical and economic reasons. The first evidence of an association between viral load and healthcare burden was published in the early phase of the pandemic in Italy (spring 2020) (15), when Clementi *et al.* showed that a substantial reduction in viral load among individuals diagnosed with SARS-CoV-2 infection was paralleled by a notable reduction in hospitalizations and ICU admissions for COVID-19. In a subsequent study, Dehesh *et al.* conducted a population-based longitudinal study (16), which found that the mean daily SARS-CoV-2 Ct value anticipated the occurrence of new positive cases (r=–0.34; P=0.016), COVID-19 related hospitalizations (r=–0.25; P=0.020), and COVID-19 related deaths (r=–0.26; P=0.015) by nearly 20–30 days. Similar evidence resulted from the study of Penney *et al.* (17), who reported a highly significant correlation between the Ct value in SARS-CoV-2 positive samples and incident hospitalizations (r=–0.76; P<0.05), thus confirming that the viral load of SARS-CoV-2 may provide important information for predicting the future pressure on healthcare.

Prediction of emergence of new variants

Predicting the emergence of new SARS-CoV-2 variants is a fundamental component of a COVID-19-containment

policy, as this aspect allows to establish proactive actions against the risk that a next wave of SARS-CoV-2 may offset population immunity, contributing to enhance the number of cases with severe illness. To this end, the recent study published by Harrison *et al.* (18) has provided important evidence showing that a paradigmatic reduction in mean gene *S* Ct values occurs approximately 6 to 29 days prior to the spread of a new variant in the population. Overall, mean gene *S* Ct levels were found to plateau or increase slightly approximately one month before the peak of incidence of new cases. However, genomic variants can lead to mismatches of primers/probes binding sites of existing polymerase chain reaction (PCR)-based assays due to suboptimal PCR amplification or PCR amplification failure. Therefore, an increase in Ct values may also be an alarming sign for the occurrence of mutant strains.

Prediction of infectivity

One of the most important implications of measuring the Ct value is to determine the individual risk of contagiousness of the infected person. A number of studies have been published on this important topic, some of which will be discussed in this section of the article. Jajou *et al.* studied 683 individuals with SARS-CoV-2 infection, in whom they measured the SARS-CoV-2 Ct value (19). Specifically, those classified as "SARS-CoV-2 transmitters" (i.e., index cases with at least one contact who tested positive) had significantly higher viral loads than non-transmitters (5.23 *vs.* 4.65 log10 copies/mL). Brown *et al.* conducted a large prospective study of 943 household contacts of SARS-CoV-2 index cases, for determining the possible correlates of transmission (20). Multivariable regression analysis revealed a significant association between viral load and transmission, with a 10-fold higher viral load associated with a 140% increased risk of contagion (OR =1.40; 95% CI: 1.07–1.85). A strong correlation between viral load of SARS-CoV-2 and infectivity was confirmed in the study by Bhavnani *et al.* (21), which showed that the risk of SARS-CoV-2 transmission was almost twice as high in individuals with higher viral load (i.e., >5 log10 copies/mL). Not surprisingly, the risk of household transmission was higher in patients with active cough than in those without, as it can be assumed that the former category of patients shed larger amounts of viral particles.

Prediction of shedding kinetics

The shedding kinetics is an important determinant of SARS-CoV-2 biology, because it may influence both disease duration and infectivity. Therefore, identifying potential predictors of duration of viral shedding would certainly be useful for the clinical decision making and for defining public health interventions which may be effective to curb SARS-CoV-2 transmission. In an interesting study, van Kampen *et al.* prospectively followed infectious SARS-CoV-2 shedding by viral cultures in 129 patients hospitalized with COVID-19 (22), and reported that a higher viral load (i.e., $>10^7$ RNA copies/mL) was an independent predictor of prolonged viral shedding in multivariate analysis (OR =14.7; 95% CI: 3.7–58.1). These results were confirmed in another study, which also showed that a lower value of SARS-CoV-2 Ct was associated with prolonged time before achieving viral clearance (P<0.001) (23). Taken together, these results suggest that viral load may be considered a critical factor in SARS-CoV-2 virus shedding (24).

Prediction of long-COVID

The persistence of SARS-CoV-2 infection and/or the presence of a virus reservoir in the human body are among the most important factors influencing the risk of developing long-COVID, since continued SARS-CoV-2 shedding from organs and tissues may contribute to perpetuate the direct and indirect viral injury (25). Girón Pérez *et al.* followed 70 COVID-19 patients who had recovered from acute infection for up to 3 months, after which time they were interviewed about residual symptoms with a survey (26). A highly significant correlation was observed between SARS-CoV-2 viral load and number of symptoms in the post-COVID-19 period (r=0.74; P<0.001). In another study, Su *et al.* conducted a longitudinal study of 309 COVID-19 patients, followed between diagnosis and convalescence occurring approximately 2–3 months after the acute SARS-CoV-2 infection (27). SARS-CoV-2 viral load in the convalescent phase was found to be significantly associated with the post-acute sequelae of COVID-19. In another preliminary investigation, Lu *et al.* studied 136 subjects who had recovered from the acute SARS-CoV-2 infection and were followed up for up to 8 months (28). Of note, the peak *N* gene viral load was associated with 30% higher risk [adjusted risk ratio (aRR) =1.30; 95% CI: 1.03–1.66] of developing post-acute sequelae of SARS-CoV-2 infection.

Conclusions

COVID-19 is no longer classified as a global health emergency but still causes a significant number of

infections, hospitalizations, and deaths. Identifying factors that can assist management and public health in containing SARS-CoV-2 transmission must therefore be considered a primary public health task.

There are certainly some preanalytical, analytical, and postanalytical limitations to the measurement of SARS-CoV-2 viral load (i.e., primarily Ct value) in upper respiratory tract specimens. In addition to preanalytical problems that may affect the collection and storage of swabs (different and/or inappropriate sampling techniques, unsuitable media, and/or conditions for transport and storage), one of the most important drawbacks is the poor interlaboratory comparability, especially when different assays are used, mainly because the reference standard WHO 20/146 still seems to be underutilized. Inappropriate interpretation of Ct values during the clinical course of the disease may also bias the clinical reasoning. Nevertheless, it is predictable that test results from different clinical laboratories using different NAAT platforms or even different techniques such as droplet digital polymerase chain reaction (ddPCR), which gives absolute count of viral copy number, will become increasingly comparable as secondary standards calibrated to WHO material and common international units (i.e., through conversion of Ct values to concentrations, e.g., log10 copies/mL) are adopted, as demonstrated in the study by Boan *et al.* (29).

In this optimistic scenario, routine viral load assessment and reporting in patients with SARS-CoV-2 infection could offer significant benefits that might even outweigh existing technical limitations. These advantages are large because the Ct value of SARS-CoV-2 is associated with a number of epidemiologic, biologic, and clinical aspects, as viral load can predict disease severity, population epidemic, future public health burden, emergence of new variants, individual infectivity and shedding kinetics, as well as the risk of developing long-COVID. Importantly, viral load in the nose and upper respiratory tract, where clinical samples are primarily collected, is highly heterogeneous in infected individuals. Interestingly, based on model studies (30,31), it has been shown that the time elapsed between cell infection and the onset of shedding, as well as the shedding rate of infectious virions, are absolutely critical for early infection. Therefore, further experimental tests following a nasal high titer infection test would help medical diagnostics to identify who is at enhanced risk of spreading the infection to the deep lung. However, further standardization processes would be needed to improve the clinical utility of reporting the Ct value. Although it is now highly likely that assessment of SARS-CoV-2 viral load would help identify individuals at higher risk for adverse outcome (32), its clinical relevance for identifying so-called super-spreaders is still debated in the current scientific literature, as demonstrated by Tian *et al.* (33), who showed that the individual viral load is not an efficient predictor of transmissibility.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jphe.amegroups.com/article/view/10.21037/jphe-23-98/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jphe.amegroups.com/article/view/10.21037/jphe-23-98/coif). The authors have no conflicts of interest to declare.

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

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