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A CYCLE THRESHOLD VALUE-BASED EPIDEMIC PROGNOSTICATION TO MONITOR LONG-TERM EPIDEMIOLOGIC TRENDS OF SARS-COV-2 VIRUS

Dr. Aditi Munmun Sengupta*	Research Scholar, Department of Physiology, University of Calcutta; Medical Officer, CK Birla Hospitals, Dept. of Critical Care, Kolkata. *Corresponding Author
Dr. Diptendu Chatterjee	Associate Professor, Department of Anthropology, University of Calcutta; Deputy Registrar, University of Calcutta
Prof. Bibhuti Saha	Professor And Head, School of Tropical Medicine, Kolkata

ABSTRACT The real-time reverse transcription-polymerase chain reaction (RT-PCR) is considered as the sensitive proof for detecting the viral infection of the SARS-CoV-2 virus obtained from respiratory samples. The quantitative values for the analysis are beneficial for estimating the transmissibility of people who test positive for SARS-CoV-2. This can be further achieved by analyzing the samples by semiquantitative means through the interpretation of the cycle threshold (Ct) values of RT-PCR that represent the first cycle of PCR at which a detectable signal appears during the assays. The Ct value shows a correlation between high viral load and disease infectiousness, which is observed with other respiratory viruses, including the influenza B infection and rhinovirus infection. Hence, the present study aims to analyze the surveillance of COVID-19 to monitor longer-term epidemiologic trends and trends in deaths due to COVID-19. In order to achieve this aim, the present review was reported to the preferred reporting items for systematic reviews and meta-analysis statements (PRISMA) for analyzing the Ct value-based epidemic predictions and to monitor long-term epidemiologic trends of SARS-CoV-2 virus. Total 33 studies have been finalized for finding out the results of the study. The epidemiologic parameter and a representative of the surveillance data for reporting to the World Health Organization were fulfilled by analyzing the systematic review and meta-analysis of the selected study. Moreover, the evaluation of the impact of the pandemic on the health care system and society was achieved by analyzing the studies mentioned here.

KEYWORDS : COVID-19, Cycle threshold value, PCR, SARS-CoV-2, Viral load

INTRODUCTION

The affected individuals from the COVID-19 pandemic have been observed with respect to the severity of disease evolving with no symptoms, the requirement of intensive care, and fatal outcomes. The new coronavirus infection caused by SARS-CoV-2 has been diagnosed using laboratory methods that involve the real-time reverse transcription-polymerase chain reaction (RT-PCR) (Tang et al., 2020). The real-time reverse transcription-polymerase chain reaction (RT-PCR) is considered as the sensitive proof for detecting the viral infection obtained from respiratory samples. The RT-PCR allows the qualitative analysis of the samples as nasopharyngeal swabs are observed to cause difficulty in standardizing. However, the quantitative values for the analysis would be beneficial for estimating the infectiousness of people testing positive for SARS-CoV-2. This can be further achieved by analyzing the samples by semiquantitative means through the interpretation of the cycle threshold (Ct) values of RT-PCR. A Ct value represents the first cycle of PCR at which a detectable signal appears during the assays. Hence, the number of amplification cycles required for targeting the sample gene to increase the threshold level is represented by the RT-PCR. Additionally, it can be said that the Ct value is inversely proportional to the viral load and has been considered as an indirect method toward the quantification of the copy number of the viral RNA in the present sample. The Ct value is often influenced by the dynamics of the RT-PCR assay being used for detection of infection along with the involvement of the factors responsible for the amplification efficiency of the sample being tested.

The Ct value shows a correlation between high viral load and disease severity which is observed with other respiratory viruses involving the influenza B infection or rhinovirus infection (Granados et al., 2017; Li et al., 2010). Recent studies concerning SARS-CoV-2 have shown a relationship between the lower RT-PCR Ct value and mortality rate of the patients being admitted in the hospitals (Magleby et al., 2020; Pujadas et al., 2020). It has been revealed from the analysis that the viral load of SARS-CoV-2 shows variations during the infection in the presymptomatic stage. Hence, the time at which the symptoms occur during the infection has been considered as an important factor for a low Ct value representing a high viral load.

One of the recommendations from Germany for patients who are detected with COVID-19 till the end of November has revealed that patients having Ct values >30 need not quarantine themselves if the occurrence of symptoms has been observed for 10 days or more (Kleist et al., 2020). The analysis evaluating the Ct value depended on the detection of infection rate and viability of SARS-CoV-2 in cell culture assays 8 days after the occurrence of symptoms (Bullard et al., 2020; Young et al., 2020; Wolfel et al., 2020). One of the studies has revealed that almost 8.3% of the cases with the SARS-CoV-2 infection have found Ct values >35 and the residents of the nursing facility were presymptomatic, representing positive viral culture despite Ct values >30 (Singanayagam et al., 2020; Kimball et al., 2020). This further shows that the infection rate of SARS-CoV-2 does not entirely depend upon the Ct value, but rather on the sampling time during the infection, the quality of nasopharyngeal swabs, the nucleic acid extraction method, and the protocol followed for the RT-PCR. The recommendation in Germany has been modified for using laboratory cut-offs of the Ct value consisting of viral preparation with approximately 1 million copies of per ml RNA of SARS-CoV-2 (Ade et al., 2021). The lower Ct value represents the rate of infection.

The World Health Organization (WHO) has implicated guidance for the surveillance of COVID-19 among humans which is caused by SARS-CoV-2. The suspected and probable cases of COVID-19 are being detected as per the recommendations of WHO involving diagnostic tests. The surveillance approaches have been implicated among the member states for COVID-19 national surveillance. The national surveillance for COVID-19 has encouraged the public authorities toward reducing the transmission of COVID-19 by limiting the rate of mortality and morbidity. New cases of COVID-19 should be identified and the data should

be evaluated for the relevant epidemiological analysis within 24 h of diagnosis. Furthermore, the national authorities have declared COVID-19 as a necessary, notifiable disease with the implication of immediate reporting. The surveillance system should be quite active to make the high-risk populations safe. All levels of the healthcare system are tracked by the surveillance systems with contact tracing at the community level. The infection of SARS-CoV-2 needs to be included as a mandatory scenario for reporting within the healthcare surveillance system among the countries with the necessary reporting systems. The number of COVID-19 deaths should be reported immediately as well. The routine analysis reports are distributed at reporting sites within the surveillance system which is made available to the public through government websites.

The COVID-19 pandemic has evolved several concerns in the public, administrative, and healthcare sectors. The transmission of SARS-CoV-2 and the report concerning its impact highlights the healthcare service-providers and healthcare professionals who are at risk and are considered as the major bearers of the infection. The inadequate facilities of healthcare equipment during the COVID-19 pandemic have increased the exposure of outpatient departments and operating rooms to the affected patients and healthcare providers causing cross-contamination. The WHO is responsible for implicating the guidelines for managing the patients and healthcare workers that have contributed toward the healthcare system.

MATERIALS AND METHODS
The present review was reported using the preferred reporting items for systematic reviews and meta-analysis statements (PRISMA).

Research Questions
According to the research objectives of the study that focuses on contributing toward the surveillance of COVID-19 to monitor longer-term epidemiologic trends and monitor trends in COVID-19 deaths, some of the specific research questions that will be effective in analyzing the research study have been illustrated below:
• What are the major impacts of the COVID-19 pandemic on the health care system and society?
• What do you mean by COVID-19 surveillance?
• How is the surveillance of COVID-19 analyzed?
• How are the epidemiological trends of the COVID-19 pandemic determined?
• How does the surveillance of COVID-19 monitor the epidemiological trends and COVID-19 deaths?
• What is the cycle threshold value (Ct)?
• How can the surveillance of COVID-19 be evaluated in terms of the cycle threshold value (Ct)?
• Can the surveillance of COVID-19 with a threshold value (Ct) be represented as an epidemiologic drift?

Research Objectives:
The main aim of the study is to focus on contributing toward the surveillance of COVID-19 to monitor the longer-term epidemiologic trends and trends in COVID-19 deaths. The following are the objectives that will be helpful in determining the major aim of the study:
• To contribute in the surveillance of COVID-19 to monitor the longer-term epidemiologic trends and trends in COVID-19 deaths
• To conduct the surveillance of COVID-19 as an epidemiologic parameter and a representative of surveillance data for reporting to the WHO
• To evaluate the impact of the pandemic on the healthcare system and society.

PRISMA Methodology:
The surveillance data in the form of a Ct-based epidemiologic

curve from where the case fatality rate can be determined for showing epidemiologic trends of the SARS-CoV-2 virus were screened to monitor longer-term epidemiologic trends and trends in COVID-19 deaths while the infected patients were undergoing laboratory tests of the RT-PCR. The PRISMA analysis was done to identify, screen, and select the studies for a systematic literature review.
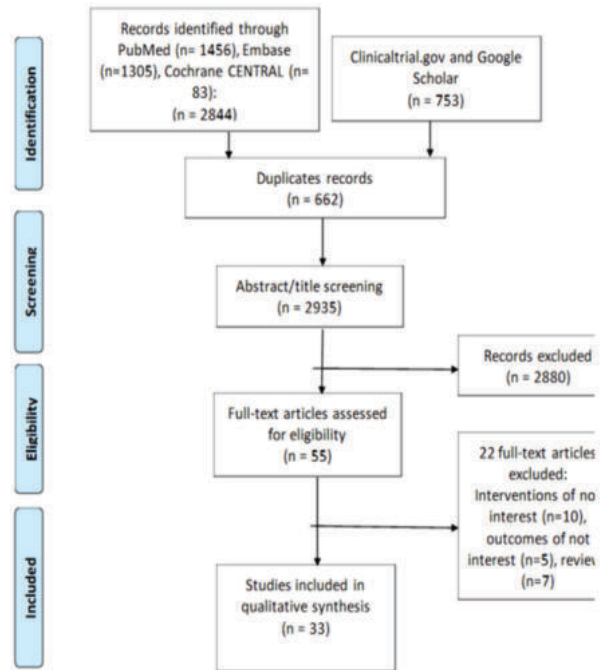

Figure 1: PRISMA flowchart for search methodology

Search Strategy:
Electronic databases were checked for research papers using the keywords 'COVID-19', 'Cycle threshold', "Real-time Reverse Polymerase Chain Reaction," "SARS-CoV-2," "novel coronavirus," "Symptom duration in COVID-19," "Laboratory testing of COVID-19," "Ct value for SARS-CoV-2," "viral load," etc. Different databases such as Embase, PubMed, Google Scholar, and the Cochrane library were screened and only randomized trial studies were taken into consideration in this systematic review. For instance; we searched PubMed, Embase, clinicaltrial.gov, Google Scholar, Cochrane Library for 2020, etc. to screen the surveillance data in the form of a Ct value-based epidemiologic curve from where the case fatality rate can be monitored to show epidemiologic trends of the SARS-CoV-2 virus. A PRISMA analysis was done to identify, screen, and select the studies for the systematic literature review. Total 2844 articles comprising 1456 articles from PubMed, 1305 articles from Embase, and 83 articles Cochrane library were screened. A total of 753 articles were screened from Clinicaltrial.gov and Google scholar.

Eligibility criteria
The study titles and research overview were identified and screened on an independent basis, and the studies which were not conforming to the topic were rejected. Following was the criteria for study inclusion and exclusion:

• **Criteria for study inclusion:**
The studies representing Ct value-based epidemiologic predictions from where the epidemic trend can be monitored were considered for the study. The epidemiologic parameter and a representative of surveillance data constituting the impact for reporting to the WHO were included in this study. Additionally, the data concerning the impact of the pandemic on the healthcare system and society were considered for the study.

Database: Medline <1950 to 2021 March 22>
Search Strategy:
1 "cycle threshold value"[all] OR "CT-value"[all] OR "CT value"[all] OR "cycle threshold"[all] OR
"CT-values"[all] OR "CT values"[all] OR "viral load"[all] OR "Viral Load"[Mesh]
2 ("coronavirus"[all] OR "COVID-19"[all] OR "covid 2019"[all] OR "COVID19"[all] OR "SARS-CoV-2"[all] OR
"SARS2"[all] OR "SARS-CoV-19"[all] OR "severe acute respiratory syndrome coronavirus 2"[all] OR "novel cov"[all]
OR "novel coronavirus"[all] OR "2019ncov"[all] OR "sars cov2"[all] OR "cov2"[all] OR "ncov"[all] OR
"coronaviridae"[all] OR "corona virus"[all])
1 AND 2
4 3 NOT ("animals"[Mesh] NOT "humans"[Mesh]))

Database: Cochrane Central Register of Controlled Trials up to March 22
Search Strategy:
1 "cycle threshold value"[all] OR "CT-value"[all] OR "CT value"[all] OR "cycle threshold"[all] OR "CT-values"[all] OR
"CT values"[all] OR "viral load"[all] OR "Viral Load"
2 ("coronavirus"[all] OR "COVID-19"[all] OR "covid 2019"[all] OR "COVID19"[all] OR "SARS-CoV-2"[all] OR "SARS2"[all]
OR "SARS-CoV-19"[all] OR "severe acute respiratory syndrome coronavirus 2"[all] OR "novel cov"[all] OR
"novel coronavirus"[all] OR "2019ncov"[all] OR "sars cov2"[all] OR "cov2"[all] OR "ncov"[all] OR
"coronaviridae"[all] OR "corona virus"[all])
1 AND 2

Database: Embase <1974 to March 22, 2021>
Search Strategy:
1 "cycle threshold value"[all] OR "CT-value"[all] OR "CT value"[all] OR "cycle threshold"[all] OR "CT-values"[all] OR
 "CT values"[all] OR "viral load"[all] OR "Viral Load"
2 ("coronavirus"[all] OR "COVID-19"[all] OR "covid 2019"[all] OR "COVID19"[all] OR "SARS-CoV-2"[all] OR "SARS2"[all]
 OR "SARS-CoV-19"[all] OR "severe acute respiratory syndrome coronavirus 2"[all] OR "novel cov"[all]
OR "novel coronavirus"[all] OR "2019ncov"[all] OR "sars cov2"[all] OR "cov2"[all] OR "ncov"[all]
OR "coronaviridae"[all] OR "corona virus"[all])
1 AND 2

Grey literature sources: clinicaltrial.gov, and Google Scholar up to March 22, 2021
Search Strategy:
All possible combinations among search terms from each of the following domains were manually created and searched
 Only a single term from each domain was used in any combination.

Figure 2: Search Strategies

- **Criteria for study exclusion:**
The studies with the absence of Ct value, no case of fatality rate, no data and follow-up procedure regarding laboratory testing, and absence of epidemiologic parameter and a representative of surveillance data were excluded from the given study.

Study selection
The relevant studies were selected by initiating a search strategy in two stages. Firstly, the articles with appropriate topics were independently involved with the process of screening using important keywords related to this study and the necessary information was extracted. All available titles and abstracts were identified and scanned by them for the considered studies to meet the inclusion criteria. Second, full-text articles were thoroughly investigated by the reviewers independently. Papers that had cited these articles were also identified through PubMed (https:// pubmed. ncbi. nlm. nih. gov/),Cochrane Library (https://www.cochranelibrary.com/), Embase(https://www.embase.com/login), Google Scholar (https://scholar.google.com/), and Clinicaltrial.gov to identify potentially relevant articles subsequent to primary research. After study selection, any disagreements were mutually discussed, and a consensus was made before the inclusion of the study in this review.

Data extraction
Studies that fulfilled the inclusion criteria were processed for data extraction. The primary focus of the review was the analysis of surveillance data in the form of a Ct value-based epidemiologic prognosis from where the cases can be monitored to show the epidemiologic trends of the SARS-CoV-2 virus. The secondary outcome included the epidemiologic parameter and a representative of surveillance data for an impact for reporting to the WHO. The extracted data included the following study characteristics: the name of the first author,

year of publication, total number of participants (sample size), analyzed Ct value, clinicopathological features, diagnosis and laboratory testings, follow-up period, summary of the analyzed result, and prognostic significance involved.

RESULTS AND DISCUSSION
This systematic review included 33 studies and analyzed surveillance data in the form of a Ct value-based epidemiologic course. In the present study, we explored the case fatality rate of COVID-19 for showing epidemiologic trends of the SARS-CoV-2 virus. Epidemiologic parameters and a representative of surveillance data with an impact for reporting to the WHO will be associated with the Ct value of RT. It was seen in all the studies that the epidemiologic curve was directly related to the case fatality rate and surveillance data with an impact for reporting to the WHO regarding epidemiologic trends of the SARS-CoV-2. COVID-19 surveillance has led a major impact on the health care system and society. In order to justify the surveillance of COVID-19 for monitoring longer-term epidemiologic trends and trends in COVID-19 deaths, various studies have been screened out showing variations in the Ct value by implicating the laboratory testing which has been represented in the given study.

Argyropoulos et al. (2020) have shown the correlation of initial viral load among patients suffering from SARS-CoV-2 with related outcomes and symptoms. The patients from the US have been investigated for showing correlations between the viral load of SARS-CoV-2 and related parameters involving symptom severity, analysis of admission rate and discharge rate of the patients, stay duration in hospitals, admission in the ICUs, duration of the oxygen provided, and overall survival from a tertiary care center among 205 patients in New York City. Quantitative PCR was used for analyzing the viral load from the patients' samples. The algorithms and regression models revealed that the obtained viral load was

found to be lower among hospitalized patients when compared with non-hospitalized patients. Higher VL showed a correlation with a shorter time from the symptoms' occurrence in all patients and hospitalized patients only with a shorter hospital stay. The results revealed a higher shedding risk among less symptomatic patients. Further, the association between VL with patients having a history of cancer has been revealed.

Aron et al. (2020) have shown presymptomatic infection of SARS-CoV-2 with its transmission among skilled nursing facilities. Two serial point-prevalence surveys were done among the residents undergoing nasopharyngeal and oropharyngeal testing for SARS-CoV-2. RT-PCR was used for analyzing the viral culture and symptoms from 14 days of infection were recorded. Asymptomatic residents were tested positive and were again tested after 7 days. Residents with SARS-CoV-2 infection were categorized as symptomatic with typical symptoms of cough and cold along with shortness of breath with only atypical symptoms. The Ct value of the viral culture showed that the median Ct value for presymptomatic residents was 23.1. A 26% mortality rate was observed. Hence, the rapid spread of SARS-CoV-2 infection was seen among the residents from nursing facilities.

Azzi et al. (2020) have used saliva as a reliable tool for detecting SARS-CoV-2 strain. The saliva of infected patients suffering from COVID-19 was taken for analysis through RT-PCR and the analyzed results were compared with their clinical and laboratory data. A positive report in saliva and correlation of clinical data and the cycle threshold as a semiquantitative indicator of viral load was considered. All the patients showed positive results and among all, only two patients showed positive salivary results on the same days when their pharyngeal or respiratory swabs showed conversion. Hence, this result reveals that COVID-19 diagnosis cannot be limited to only qualitative detection, but is also involved in providing relevant information regarding the clinical disease among the patients.

Bullard et al. (2020) have aimed for the prediction of SARS-CoV-2 infection rate from the diagnostic samples. The respiratory samples from the patients of COVID-19 were taken within 8 days of the occurrence of symptoms and RT-PCR laboratory testing was conducted that resulted in the Ct value ≥ 24. This Ct value revealed that the patients lacked the infection rate of SARS-CoV-2 in the clinical and community perspectives.

Calle et al. (2020) have revealed the impact of viral load during the admission of patients with COVID-19 with respiratory failure in the hospitals. Nasopharyngeal samples of the infected patients were used for the analysis of RT-PCR. The obtained Ct value among patients during admission was found as high viral load (Ct < 25), intermediate viral load (Ct: 25–30), and low viral load (Ct > 30). Age, gender, sex, comorbidities, and laboratory markers were used for analyzing the cause of respiratory failure. The results revealed that a Ct value < 25 was associated with a higher risk of respiratory failure during admission. Hence, the prediction concerning respiratory failure among COVID-19 patients can be measured by assessing the viral load with Ct value during admission in hospitals.

Chen et al. (2020) aimed for showing the association of SARS-CoV-2 viral load (RNAaemia) with the interleukin 6 (IL-6) level among critical cases of COVID-19 patients. The clinical and laboratory data of critical COVID-19 patients were taken along with the determination of serum viral load and IL-6 levels. The results revealed that RNAaemia was diagnosed only in the critical COVID-19 patients which reflected the severity of the disease. Also, the level of IL-6 increased among critically ill COVID-19 patients. Hence, RNAaemia showed a correlation with the increased IL-6 level among COVID-19 patients.

Choudhuri et al. (2020) revealed that the Ct value obtained from RT-PCR analysis of SARS-CoV-2 during admission in the hospitals associated with the mortality rate of the patients. The results revealed that the mean Ct value during admission was found to be high for the survivors when compared with the non-survivors. Also, increased Ct was associated with the decreased odds of in-hospital mortality.

Fa´ıco-Filho et al. (2020) have analyzed the association of the higher viral load of SARS-CoV-2 with the death rate. The viral load of SARS-CoV-2 was analyzed using the Ct value obtained by RT-PCR of nasopharyngeal swab samples. The outcome of the patients and disease severity were compared. The results showed severity as a mild disease for mild disease, moderate for the hospitalized ones, and severe for the ones being admitted to ICUs. The Ct values < 25 showed a high viral load, which was associated with mortality among hospitalized patients of COVID-19.

He et al. (2020) aimed for analyzing the temporal dynamics of viral shedding and transmission rate of COVID-19. RT-PCR reports of infected patients showed the highest viral load in throat swabs at the time of symptom onset. The cases were also found to show infection at the presymptomatic stage.

Huang et al. (2020) revealed the impact on health consequences of patients with COVID-19 for a longer duration who have been discharged from the hospital and identifying the associated risk factors for a particular disease severity. The results revealed that patients who survived from COVID-19 were facing issues of muscle weakness, insomnia, and anxiety or depression. The severely affected patients, during their stay in the hospital, suffered from severely impaired pulmonary diffusion capacities and abnormal chest imaging manifestations and are the major targeted population who need intervention for a longer period to recover from this illness.

Huang et al. (2020) have shown chronological changes of viral load among COVID-19 patients in Wuhan, China. Laboratory and clinical data were used for analyzing the epidemiological and clinical characteristics of the patients. The association between serial viral loads and illness severity was investigated. The results revealed that SARS-CoV-2 was at its peak for 2–4 days after admitting the patient to the hospital and later decreased after the treatment. The critically ill patients showed high viral loads when compared with the normal patients. The sputum showed a high viral load. Also, the rate of respiratory tract samples was positive and higher when compared with samples of the gastrointestinal tract. The viral load was negatively associated with blood routine and subsets of lymphocyte and was positively associated with laboratory features of the cardiovascular system.

Kimball et al. (2020) analyzed the asymptomatic and presymptomatic infections of SARS-CoV-2 among residents of a long-term care-skilled nursing facility of King County, Washington. Ct values have been used for detecting the rate of infection among the patients. The lower Ct value represented a high viral load. The typical symptoms include fever, cough, and shortness of breath. The atypical symptoms include chills, sore throat, increased confusion, nasal congestion, myalgia, dizziness, headache, nausea, and diarrhea.

Lesho et al. (2020) aimed for analyzing the temporal, spatial, and epidemiologic relationships of SARS-CoV-2 with the determination of Ct value. The results have clearly implicated that appropriate Ct values occurred during 9, 26, and 36 days after the onset of the symptoms. The RNA positivity was not influenced by race, gender, and corticosteroids. Initial Ct did not correlate with a requirement for admission or intensive care.

Liu et al. (2020) aimed to analyze the correlation between

dynamic changes in the nasopharyngeal viral load of patients infected with the new coronavirus causing pneumonia and lymphocyte count disease severity. The results have clearly revealed that SARS-CoV-2 RNA load in the nasopharynx is closely related to the severity of COVID-19. Also, Liu et al. (2020) aimed for viral dynamics in mild and severe cases of COVID-19.

Liu et al. (2020) analyzed 76 hospital admitted patients of Nanchang, China. Severe cases were classified by respiratory distress, oxygen saturation, ratio between partial pressure of oxygen and fractional concentration of oxygen in inspired air and severe disease complications, such as respiratory failure, mechanical ventilation, and septic shock or non-respiratory organ failure. The mean viral load of severe cases was around 60 times higher than that of mild cases, suggesting that higher viral loads might be associated with severe clinical outcomes. Thus, the results implicated that severe COVID-19 tends to have high viral load and a long virus- shedding period.

Liu et al. (2020) analyzed the clinical, epidemiological, laboratory, and radiological characteristics along with the determination of the biomarkers for the prediction of disease severity in 2019-nCoV-infected patients in Shenzhen, China. The results have shown a positive correlation of viral load from samples of the respiratory tract with the severity of lung disease.

Magleby et al. (2020) analyzed the impact of the viral load of SARS-CoV-2 concerning the mortality among hospitalized patients of COVID-19. The characteristics of patients were compared using Ct value with viral load assessment as low, medium, and high. The results revealed that high viral load was determined as per the age, comorbidities, smoking status, and recent chemotherapy. The mortality rate was found to be 35% with high viral load, 17.6% with medium viral load, and 6.2% with low viral load. High viral load was independently associated with mortality and intubation.

Pujadas et al. (2020) contributed toward the prediction of mortality rate due to COVID-19 by assessing SARS-CoV-2 viral load. The results revealed that the variations in age, sex, race, and related diagnosed diseases presented an independent association between viral load and mortality. Moreover, the difference in survival probability between high viral load and low viral load was determined.

Ra et al. (2020) analyzed the assessment of viral load of SARS-CoV-2 infection from the upper respiratory tract among asymptomatic and mildly symptomatic patients. Questionnaire-based surveys in South Korea were used for determining the presence of symptoms. The result revealed that 36% of patients were asymptomatic and 64% of patients were symptomatic. Asymptomatic and symptomatic patients did not show significant differences in the mean Ct values. Hence, it was clearly implicated that almost one-fifth of the patients were asymptomatic without severe symptoms and their viral loads were comparable with symptomatic patients. More of the mildly symptomatic patients or asymptomatic patients showed persistent positive upper respiratory RT-PCR results during follow-up.

Ram-Mohan et al. (2020) analyzed the prediction of clinical deterioration and extrapulmonary complications from RNAaemia of SARS-CoV-2. Quantitative (qPCR) and digital (dPCR) PCR were used to quantify SARS-CoV-2 RNA from nasopharyngeal swabs of the affected patients. The patient symptoms, laboratory markers, and clinical outcomes, and oxygen requirements over time were determined. The role of RNAaemia in predicting clinical severity was also characterized. The results revealed that 23% of the patients had viral RNA detected in plasma by dPCR when compared to 1·4% by qPCR. The RNAaemic patients had more chances of

gaining disease severity. Hence, dPCR was more sensitive than qPCR for the detection of SARS-CoV-2 RNAaemia.

Salvatore et al. (2020) aimed at the epidemiological correlation of the Ct value using RT-PCR for detecting SARS-CoV-2. In order to study the relationship between the Ct values of viral RNA, demographic, clinical, and epidemiological characteristics were collected and analyzed. The results revealed that a low Ct value was determined after the onset of symptoms. Low Ct value was found among the patients within the age group of 18 years and those having upper respiratory symptoms. A high Ct value was found among patients with no symptoms.

Schwierzeck et al. (2020) aimed for determining the first nosocomial outbreak of SARS-CoV-2 among pediatric dialysis units. Epidemiological links were analyzed by patient interviews and chart reviews. Ct values of all positive cases were compared between symptomatic and asymptomatic cases. The results revealed a low Ct value among typical cases of COVID-19 representing high viral shedding.

Scola et al. (2020) aimed to detect viral load among discharged patients of COVID-19 from infectious disease wards. The results revealed that Ct value above 33–34 using our RT-PCR system and can be discharged from hospital care with strict confinement for non-hospitalized patients.

Shi et al. (2020) showed the correlation of viral load with serum biomarkers among COVID-19 cases. The SARS-CoV-2 viral loads from the pharyngeal swab, IgM anti-SARS-CoV-2, CRP, and serum amyloid A (SAA) from the serum of COVID-19 patients were measured on admission. The viral loads among positive IgM patients showed different trends among cases with different severity while IgM negative patients showed an increase in cases as per time and occurrence of symptoms.

Shlomai et al. (2020) analyzed the prediction of hypoxemia and disease outcome in admitted patients with COVID-19 from the nasopharyngeal viral load. Ct value of the admitted patients was correlated with the patients' clinical parameters. The age of the patients was correlated with the viral load. High viral load was found among the non-survivors and mechanically ventilated patients when compared to surviving non-intubated patients. Low viral load was independently associated with reduced risk for mechanical ventilation and mortality.

To et al. (2020) analyzed the serial respiratory viral load of SARS-CoV-2 in posterior oropharyngeal (deep throat) saliva samples from patients with COVID-19, and serum antibody responses. The results revealed that patients with COVID-19 had the highest viral load which accounted for the fast-spreading nature of this epidemic.

Trunfio et al. (2020) aimed for predicting the disease severity, survival, and six-month sequelae among symptomatic patients of COVID-19 by a diagnosis of SARS-CoV-2 by Ct value. The results revealed that even after controlling the SARS-CoV-2 virus, Ct value was still associated with COVID-19-related death, disease severity, number of signs, and symptoms.

Westblade et al. (2020) aimed at predicting the mortality of patients with or without cancer among hospitalized patients with COVID-19 being assessed by viral load. The results found that the mortality rate in hospitals was 38.8% among patients with high viral load, 24.1% among patients with a medium viral load, and 15.3% among patients with a low viral load. Patients with hematologic malignancies had higher median viral loads when compared with patients without cancer.

Xia et al. (2020) analyzed the epidemiological and initial

clinical characteristics of patients with family aggregation of COVID-19. Initial examination results of lower CD4+ lymphocyte counts and RT-PCR-CT values coupled with higher NLR may indicate the severity of COVID-19 infection for these family clusters.

Yu et al. (2020) aimed for analyzing the viral load of SARS-CoV-2 in sputum that shows association with the risk of COVID-19 progression. The results revealed that the viral load of the sputum in the lower respiratory tract tested at baseline was closely related to the severity of COVID-19. High viral load shows more severity toward COVID-19. Hence, antiviral treatment can reduce the risk of progression of mortality among patients with COVID-19.

Yuan et al. (2020) aimed for assessing viral load in the throat and anal swabs among infected children with COVID-19. The results revealed a significant difference and weak positive consistency among pediatric patients. Also, the viral loads from throats and anal swabs represented no significant difference and correlation.

Zheng et al. (2020) aimed at analyzing the dynamics of viral load and disease severity among patients who were infected from Zhejiang, China. The results of the Ct value revealed that the median duration of the virus in the respiratory samples of patients with severe disease was significantly longer than in patients with a mild disease. Virus duration was longer in patients older than 60 years and in patients who were male.

Zou et al. (2020) aimed at analyzing the viral load of SARS-CoV-2 in the upper respiratory specimens of patients who were infected. The result revealed a high viral load after symptom onset, with higher viral loads detected in the nose than in the throat. The viral load that was detected in the asymptomatic patient was similar to that in the patients with symptoms, which suggests the transmission potential of patients who were asymptomatic or minimally symptomatic.

CONCLUSIONS
The present study has followed a systematic literature review for analyzing the Ct value-based epidemic swing and to monitor long-term epidemiologic trends of the SARS-CoV-2 virus. All 33 studies reviewed have shown the analysis of Ct value by detecting the viral load through RT-PCR using the nasopharyngeal swabs as samples. Correlations between the viral load of SARS-CoV-2 and related parameters of the patients who were infected admitted in hospitals have been implicated in the study. Most of the studies showed that a higher viral load was found among patients who were critically ill during COVID-19 that further increased the mortality rate in the hospitals. Additionally, the detection of sputum for analyzing the viral load has been observed to be high in most cases. The low Ct value represents a high viral load, indicating that the patient is more prone toward the infection. The viral load among the patients showed variations as per age, gender, sex, comorbidities, and other related parameters like clinical, laboratory, radiological variables. Hence, the high viral load of SARS-CoV-2 showed an independent association with the mortality rate of patients with COVID-19. Hence, the discussed epidemiologic parameter and surveillance data mentioned in the above studies have a major impact on reporting to WHO for the control and prevention of the COVID-19 pandemic. Ct value-based segregation along with contact tracing is expected to be a useful measure for an early flattening of epidemic curve, which will consequently help in better utilization of preventive and curative resources and reducing death rates. The above studies have also shown the analysis of viral load among healthcare workers and the results have clearly implicated that the transmission rate of the virus entirely depends upon the Ct value and the healthcare workers are getting infected due to direct contact while treating the patients with COVID-19. Hence, apart from diagnostic methods CT value based,

isolation and quarantine are also preventive measures to control the transmission of the virus. In future the local and state officials can enact public health policies to foresee a pandemic surge and thereby suggest changes to existing interventions.

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