Open Forum Infectious Diseases

MAJOR ARTICLE

Pretest Symptom Duration and Cycle Threshold Values for Severe Acute Respiratory Syndrome Coronavirus 2 Reverse-Transcription Polymerase Chain Reaction Predict Coronavirus Disease 2019 Mortality

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Background. The relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and patient symptom duration in both in- and outpatients, and the impact of these factors on patient outcomes, are currently unknown. Understanding these associations is important to clinicians caring for patients with coronavirus disease 2019 (COVID-19).

Methods. We conducted an observational study between March 10 and May 30, 2020 at a large quaternary academic medical center in New York City. Patient characteristics, laboratory values, and clinical outcomes were abstracted from the electronic medical records. Of all patients tested for SARS-CoV-2 during this time (N = 16 384), there were 5467 patients with positive tests, 4254 of which had available cycle threshold (Ct) values and were included in further analysis. Univariable and multivariable logistic regression models were used to test associations between Ct values, duration of symptoms before testing, patient characteristics, and mortality. The primary outcome is defined as death or discharge to hospice.

Results. Lower Ct values at diagnosis (ie, higher viral load) were associated with significantly higher mortality among both in- and outpatients. It is interesting to note that patients with a shorter time since the onset of symptoms to testing had a worse prognosis, with those presenting less than 3 days from symptom onset having 2-fold increased odds of death. After adjusting for time since symptom onset and other clinical covariates, Ct values remained a strong predictor of mortality.

Conclusions. Severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction Ct value and duration of symptoms are strongly associated with mortality. These 2 factors add useful information for clinicians to risk stratify patients presenting with COVID-19.

Keywords. cycle threshold values; outcomes; SARS-CoV-2; symptom duration.

Approximately 20% of patients with coronavirus disease 2019 (COVID-19) will require hospitalization, and a subset will have severe manifestations such as acute respiratory distress syndrome and a hyperinflammatory state [1–5]. Much of the morbidity and mortality of COVID-19 has been attributed to the hyperinflammatory state that develops approximately day 7–10 after infection in a subset of patients and appears to lead to worse outcomes [6]. It is of critical importance to understand which patients presenting to care with COVID-19 will decompensate.

Reverse-transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab is the most common test for detecting acute, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The results of the RT-PCR are reported out as positive or negative, but the cycle threshold (Ct) value has not commonly been reported to providers. The Ct values are inversely related to viral loads—the lower the Ct value, the higher the viral load. A correlation between high viral load and disease severity is seen with other respiratory viruses such as influenza B infection or rhinovirus infection [7, 8]. Recent studies of SARS-CoV-2 have shown a relationship between lower RT-PCR Ct value and mortality in admitted patients [9, 10]. However, SARS-CoV-2 viral load is thought to fluctuate over the course of the infection, beginning with the presymptomatic stage. Therefore, the duration of symptoms

Received 20 October 2020; editorial decision 29 December 2020; accepted 2 January 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab003

may be an important factor that has not been considered yet in the relationship of low Ct values (high viral load) as predictors of outcome.

Understanding Ct values as a viral load proxy, variations in the inpatient and outpatient settings, and how the duration of symptoms before testing affects the association between Ct values and mortality is critical. Taking advantage of systematically collected data on symptoms, we examined the association between Ct values, symptom duration, and mortality in a large cohort of in- and outpatients with COVID-19 at New York-Presbyterian Columbia University Irving Medical Center, New York City.

METHODS

Patient Population

This observational study was conducted at an academic quaternary care medical center located in Northern Manhattan. Patients of all ages were included who tested positive by SARS-CoV-2 RT-PCR nasopharyngeal test for either viral target between March 10 and May 30, 2020. Testing was performed using either high-throughput automated cobas 6800 (Roche Molecular Systems, Branchburg, NJ) or the rapid Xpert Xpress SARS-CoV-2 test on the Infinity platform (Cepheid, Sunnyvale, CA). Both tests detect 2 viral targets in SARS-CoV-2; cobas 6800 in the ORF1ab nonstructural region and the envelope gene and Xpert Xpress in the nucleocapsid and envelope genes. Due to its rapid turnaround time, the Xpert Xpress test was used preferentially to screen women presenting to Labor and Delivery and for patients in the emergency room. Both tests were used per manufacturer recommendations under US Food and Drug Administration Emergency Use Authorization [11–13]. Per manufacturer recommendations, the limit of detection for a positive test is a Ct level of 40 for the cobas 6800 test and 45 for the Xpert Xpress test. To obtain Ct values, reports were generated directly from the instruments. These were scanned, and a database of Ct values was created using optical character recognition. Of the 5467 patients with positive tests, Ct values could be obtained for 4254. For the purpose of this study, the Ct value for target 1 (ORF1ab for cobas 6800 test and nucleocapsid for Xpert Xpress) was used for further analysis because these are the SARS-CoV-2-specific targets that do not cross-react with other seasonal coronaviruses.

Data Collection

For all presenting patients, electronic health records data extracted for this analysis included demographics, vital signs, laboratory results, admission, discharge, and transfer dates, medication administrations, procedure codes (current procedural terminology codes), and current and historical *International Classification of Disease* (ICD-9 and ICD-10) codes extracted from the clinical data warehouse. The first laboratory value and vital sign measurement for the index visit were obtained from patient flow sheets. Initial oxygen requirement was measured by oxygen rank severity score with 0 indicating no supplemental oxygen requirement and 4 indicating need for mechanical ventilation. A subset of consecutive charts was manually reviewed starting with the first patient testing positive for SARS-CoV-2 to our institution. The dataset was further enriched with manually abstracted data entered into a REDCap database that included the date of symptom onset and presenting symptoms. Symptoms and symptom duration were part of the hospitals' COVID-19 admission tools. All data were merged using RStudio.

Patient Consent Statement

Before initiation of data collection, approval for the study was obtained from the Columbia University Irving Medical Center Institutional Review Board (IRB). The requirement for obtaining written informed consent was waived by the IRB.

Study Design

We conducted a cohort analysis to examine the association between the Ct value on the first positive PCR and subsequent patient outcome. The primary endpoint was death or discharge to hospice by the time the final data set was assembled (August 20, 2020). Analyses included both in- and outpatients adjusting for demographic factors and comorbidities (available from the data warehouse). Analyses restricted to inpatients were done adjusting for the data on demographic factors and comorbidities available from the data warehouse as well as for reported duration of symptoms before presentation and laboratory parameters, which were largely not available for outpatients.

Statistical Analysis

Descriptive statistics were reported including counts with percentages, medians, and their interquartile ranges (IQRs) and box-and-whisker plots. The Wilcoxon rank-sum test was used to compare groups for continuous variables, and χ^2 test was used for categorical variables. To estimate associations between mortality and other covariates including Ct values, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. Final multivariable models included all covariates that were associated with the outcome at $P < .05$ or which influenced the magnitude of the Ct value associations by more than 10%. Linear regression was used to describe associations between Ct values and duration of symptoms before presentation. All statistical analyses were performed in SAS version 9.4 (Cary, NC).

RESULTS

Clinical Characteristics of Cohort

Between March 10 and May 30, 2020, 16 384 patients had SARS-CoV-2 tests performed at our institution and 5467 tests were

positive for SARS-CoV-2. Of these, 4254 (78%) had Ct values available for analysis (Figure 1). There were differences in the ascertainment of Ct values by admission status resulting in differences in the age, race/ethnicity, and outcome distributions between the 2 groups (Supplementary Table 1). Of the 4254 patients with positive tests, the majority was obtained on the cobas 6800 (n = 3808) and the remainder on the Xpert Xpress (n = 450).

Patient demographic and clinical characteristics are summarized in Table 1. The median age was 62 (IQR, 45–74 years) and 2244 (53%) were male. The median age was 63 (IQR, 47–75) for inpatients and 60 (IQR, 44–72) for outpatients. Patients were racially and ethnically diverse with 1557 (37%) and 950 (22%) identifying as Hispanic/Latinx or black Non-Hispanic, respectively. Of the 4254 patients with positive tests, 1946 (46%) were outpatients and 2308 (54%) required admission with 573 (13% of total) requiring intensive care unit (ICU) level care during admission. Patients who were admitted differed in age, race/ethnicity, and frequencies of comorbidities from those who were not admitted (Table 1).

Cycle Threshold Value and Poor Outcome in Both Inpatients and Outpatients

Among 4254 patients with available Ct values, 542 (13%) met the primary outcome of death or discharge to hospice, almost all of whom had been admitted. The small number of nonadmitted patients who died were recorded to have died in the emergency room. In admitted patients, who died, the median time to death after positive test was 7 days (IQR, 3–17 days). The median Ct value and IQR for the whole sample was 27.8 (22.5–32.1). In contrast to the hypothesized direction, inpatients had higher Ct values (median, 28.6; IQR, 23.1–32.5) than outpatients (median, 26.9; IQR, 21.8–31.6) ($P < .0001$) (Table 1).

In the cohort overall (in- and outpatients combined), a lower median Ct value (24.7; IQR, 20.9–29.8) was seen in

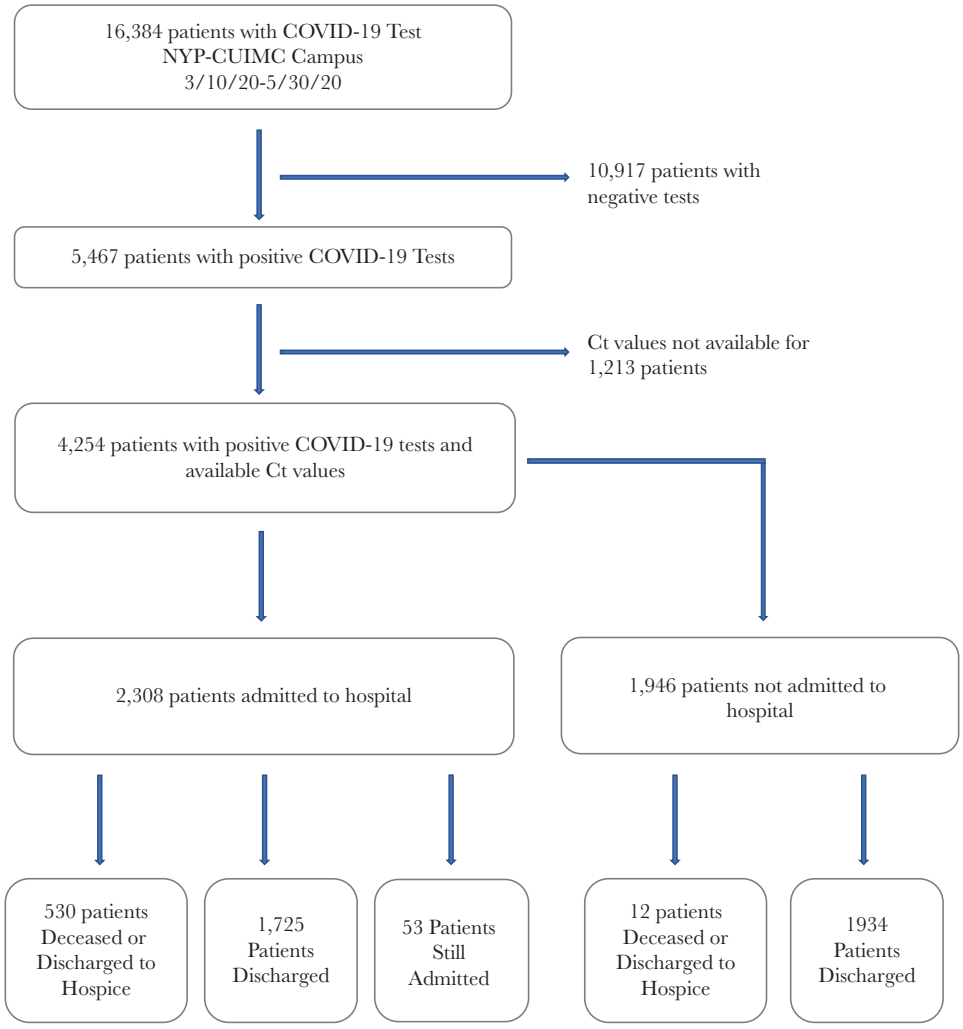

Figure 1. Study cohort. Cycle threshold (Ct) value indicated Ct from reverse-transcription polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2. The Ct value for initial test. Patients still admitted as of August 20, 2020. COVID-19, coronavirus disease 2019; CUIMC, Columbia University Irving Medical Center; NYP, New York Presbyterian Hospital.

Table 1. Persons Testing Positive Between March 10 and May 30, 2020 by SARS-CoV-2 RT-PCR Nasopharyngeal Test With Available Cycle Threshold Values by Admission Status

Characteristics	Admitted (N = 2308)	Not Admitted (N = 1946)	Total (N = 4254)
		Median (p25–75)	
Cycle threshold (Ct) value target 1	28.6 (23.1 – 32.5)	26.9 (21.8–31.6)	27.8 (22.5–32.1)
	N (%)	N (%)	N (%)
Sex			
Male	1237 (54)	1007 (52)	2244 (53)
Female	1071 (46)	939 (48)	2010 (47)
Age in Completed Years			
0–19	96 (4)	41 (2)	137 (3)
20–44	431 (19)	459 (24)	890 (21)
45–54	267 (12)	269 (14)	536 (13)
55–64	424 (18)	406 (21)	830 (20)
65–74	477 (21)	357 (18)	834 (20)
75–84	363 (16)	266 (14)	629 (15)
>85	250 (11)	148 (8)	398 (9)
Race/Ethnicity			
Hispanic/Latinx	1193 (52)	384 (20)	1577 (37)
Black Non-Hispanic	350 (15)	600 (31)	950 (22)
White Non-Hispanic	283 (39)	442 (23)	725 (17)
Asian	15 (18)	70 (4)	85 (2)
Other/Unknown/Declined	467 (20)	450 (23)	917 (22)
Highest Level of Care			
ICU	573 (25)		573 (13)
Admitted not ICU	1735 (75)		1735 (41)
Outpatient		1738 (89)	1738 (41)
Discharged from ER		208 (11)	208 (5)
Primary outcome			
Death	512 (22)	11 (1)	523 (13)
Discharged to hospice	18 (1)	1	19
Discharged home	1725 (75)	1934 (99)	3659 (86)
Still intubated	28 (1)	0	28 (<1)
Still in hospital (not intubated)	25 (1)	0	25 (<1)
Comorbidities			
Hypertension	1319 (57)	260 (13)	1579 (37)
Coronary artery disease	359 (16)	71 (4)	430 (10)
Diabetes	835 (36)	144 (7)	979 (23)
Kidney Disease	456 (20)	52 (3)	508 (12)
Liver Disease	121 (5)	44 (2)	165 (4)

Abbreviations: ER, emergency room; ICU, intensive care unit; p, percentile; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

those patients who died or were discharged to hospice compared with those who survived (median, 28.2; IQR, 22.8–32.3) ($P < .0001$). In univariable analysis, patients with higher SARS-CoV-2 RT-PCR Ct values had lower odds of mortality (OR [for each unit change in Ct value] = 0.94; 95% CI, 0.93–0.96). Patients who died were also more likely to be male, older, admitted, and have comorbidities including, diabetes, hypertension, coronary artery disease, or kidney disease (Table 2). The association between lower Ct value and poor outcome was consistent across the 2 testing platforms. The association in those tested with cobas 6800 was OR = 0.94 (95% CI, 0.92–0.96) and in those tested with Xpert Xpress Infiniti OR = 0.90 (95% CI, 0.86–0.94).

In multivariable analysis, lower Ct value of positive SARS-CoV-2 RT-PCR test remained significantly associated with mortality (OR, 0.93; 95% CI, 0.91–0.95). Other factors that remained significantly associated with mortality in multivariable analysis were male sex, older age, and admission status (Table 2).

Outcomes stratified by admission status and Ct quartiles in the whole population are shown in Figure 2. Most noticeably in admitted patients, poor outcomes occurred more commonly if Ct values were in the first (Ct < 22.5) or second (22.5 < Ct < 27.8) quartile than if Ct values were in the third (27.8 < Ct < 32.1) or fourth quartile (Ct > 32.1). This gradient was even more pronounced for patients requiring ICU level

Table 2. Predictors of Poor Outcome (Death or Discharge to Hospice) in 4254 Persons With a Positive SARS-CoV-2 RT-PCR Nasopharyngeal Test

Predictors	Univariable Odds Ratio (95% Confidence Interval)	Multivariable[a] Odds Ratio (95% Confidence Interval)
Cycle threshold (continuous)	0.94 (0.93–0.957)	0.93 (0.91–0.95)
Sex (male vs female)	1.4 (1.16–1.67)	1.5 (1.19–1.89)
Age (completed years)	1.1 (1.06–1.07)	1.1 (1.07–1.09)
ICU vs not admitted	117.8 (65.24–212.83)	244.3 (131.02–455.63)
Admitted not ICU vs not admitted	32.1 (17.93–57.38)	39.1 (21.57–70.74)
Diabetes	3.4 (2.80–4.07)	
Coronary artery disease	3.4 (2.73–4.34)	
Hypertension	6.1 (4.989–7.50)	
Kidney disease	4.4 (3.51–5.39)	
Liver disease	1.1 (0.71–1.75)	

Abbreviations: ICU, intensive care unit; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Multivariable adjusted for the variables shown.

care. For ICU patients with Ct values in the first or second quartile, 51.2% and 51.0%, respectively, had a poor outcome. The frequency decreased to 22.8% for ICU patients with Ct values in the fourth quartile.

Cycle Threshold Value and Poor Outcome Among Inpatients

We then examined predictors of death or discharge to hospice in the 2308 persons with a positive SARS-CoV-2 RT-PCR nasopharyngeal test admitted to the hospital (Table 3). This analysis also included laboratory values and the reported duration of symptoms.

In univariable analysis, lower Ct value again was significantly associated with mortality (OR, 0.92; 95% CI, 0.90–0.93). In the multivariable analysis, adjusted for sex, age, level of care, time from symptom onset, and laboratory parameters, Ct value remained significantly associated with mortality (OR, 0.94; 95% CI, 0.91–0.96). It is interesting to note that presentation soon after symptom onset (<3 days) was associated with higher odds of mortality in both univariable and multivariable analysis. Additional variables that remained significantly associated with mortality in the multivariable analyses were male sex (OR, 1.46; 95% CI, 1.05–2.02), older age (OR [per year], 1.07; 95% CI, 1.06–1.08), and admission to ICU. Laboratory values that remained significantly associated with mortality in this model included elevated interleukin (IL)-6, elevated lactate dehydrogenase (LDH), and low platelet count.

Although lower Ct value was a strong predictor of poor outcome, there was no single Ct value cut off that could be used alone to achieve acceptable sensitivity and/or specificity for triage. The area under the curve of the receiver operating characteristic curve was 0.6537 (Supplementary Figure 1).

Duration of Symptoms and Cycle Threshold Values Are Associated With Mortality

We were able to ascertain the duration of symptoms before presentation among 1860 (81%) of the inpatients included in this analysis. Three with reported onset of symptoms only after the test were excluded. The median time from symptom onset to presentation was 6 days (IQR, 3–10 days) with 394 (21%) presenting <3 days after symptom onset and 820 (44%), 439 (24%), 105 (6%), and 99 (5%) presenting 3–7 days, 8–14 days, 15–21 days, and >21 days after symptom onset, respectively.

The Ct values were higher with longer time between onset of symptoms and testing. This pattern was most noticeable among

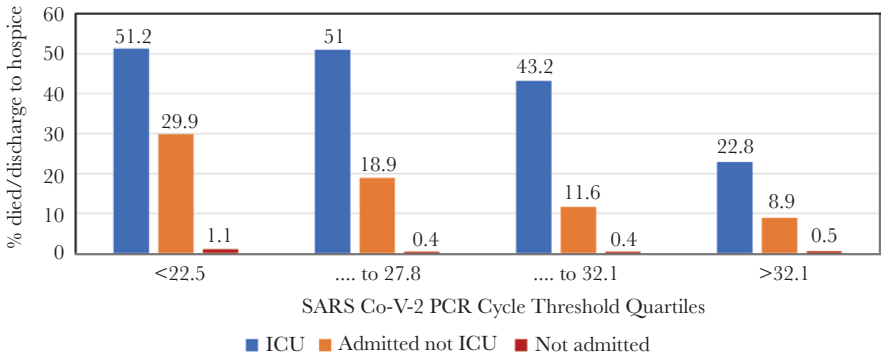

Figure 2. Frequency of death or discharge to hospice in 4254 patients by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cycle threshold value quartiles and admission status. ICU, intensive care unit.

Table 3. Predictors of Poor Outcome (Death or Discharge to Hospice) in 2308 Persons Admitted With a Positive SARS-CoV-2 RT-PCR Nasopharyngeal Test

Predictors	N	Univariable Odds Ratio (95% Confidence Interval)	N	Multivariable Odds Ratio (95% Confidence Interval)
Cycle threshold (continuous)	2308	0.92 (0.90–0.93)	1302	0.94 (0.91–0.96)
Sex (male vs female)	2308	1.4 (1.13–1.67)	1302	1.46 (1.05–2.02)
Age (completed years)	2308	1.1 (1.06–1.08)	1302	1.07 (1.06–1.08)
ICU vs not ICU	2308	3.7 (2.98–4.53)	1302	4.66 (3.29–6.60)
Oxygen severity rank (score 0–4)	2092	1.8 (1.66–2.04)		
Test <3 days after symptom start (vs ≥3 days)	1857	2.4 (1.86–3.00)	1302	1.89 (1.30–2.74)
Laboratory Parameter:				
C-reactive protein (mg/L) (log_{10})	1907	3.8 (2.86–4.93)		
Interleukin-6 (pg/mL) (log_{10})	1493	4.9 (3.80–6.36)	1302	2.8 (1.99–3.93)
Lactate dehydrogenase (U/L) (log_{10})	1872	10.6 (6.56–17.09)	1302	4.3 (2.02–9.09)
Ferritin (ng/mL) (log_{10})	1870	2.0 (1.60–2.50)		
Platelets ($\times 10^3/\mu L$) (log_{10})	2238	0.4 (0.23–0.61)	1302	0.3 (0.13–0.64)
White blood cell count ($\times 10^3/\mu L$) (log_{10})	2238	3.1 (1.95–4.82)		
International normalized ratio	1917	1.3 (1.12–1.64)		
Creatinine (mg/dL) (log_{10})	2177	4.4 (3.25–5.92)		

Abbreviations: ICU, intensive care unit; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

inpatients who survived (n = 1412), with an increase of 0.36 Ct units (95% CI, 0.3–0.43) per day after symptom onset to test; however, this was also observed in inpatients who died (n = 445) with an increase of 0.29 (95% CI, 0.17–0.40) per day (Figure 3). Figure 4 shows the median Ct values by time in days after symptom onset to presentation stratified by outcome. There was little increase in the presenting Ct by time since symptom onset until approximately 3 days, and thereafter Ct values increased with longer time since symptom onset.

As shown in Table 3, patients presenting <3 days after symptom onset had a more than 2-fold increased odds of death (OR = 2.4; 95% CI, 1.86–3.00) than those presenting later. On a continuous scale in days (>14 days recoded as =15), patients with longer time in days between symptom onset and

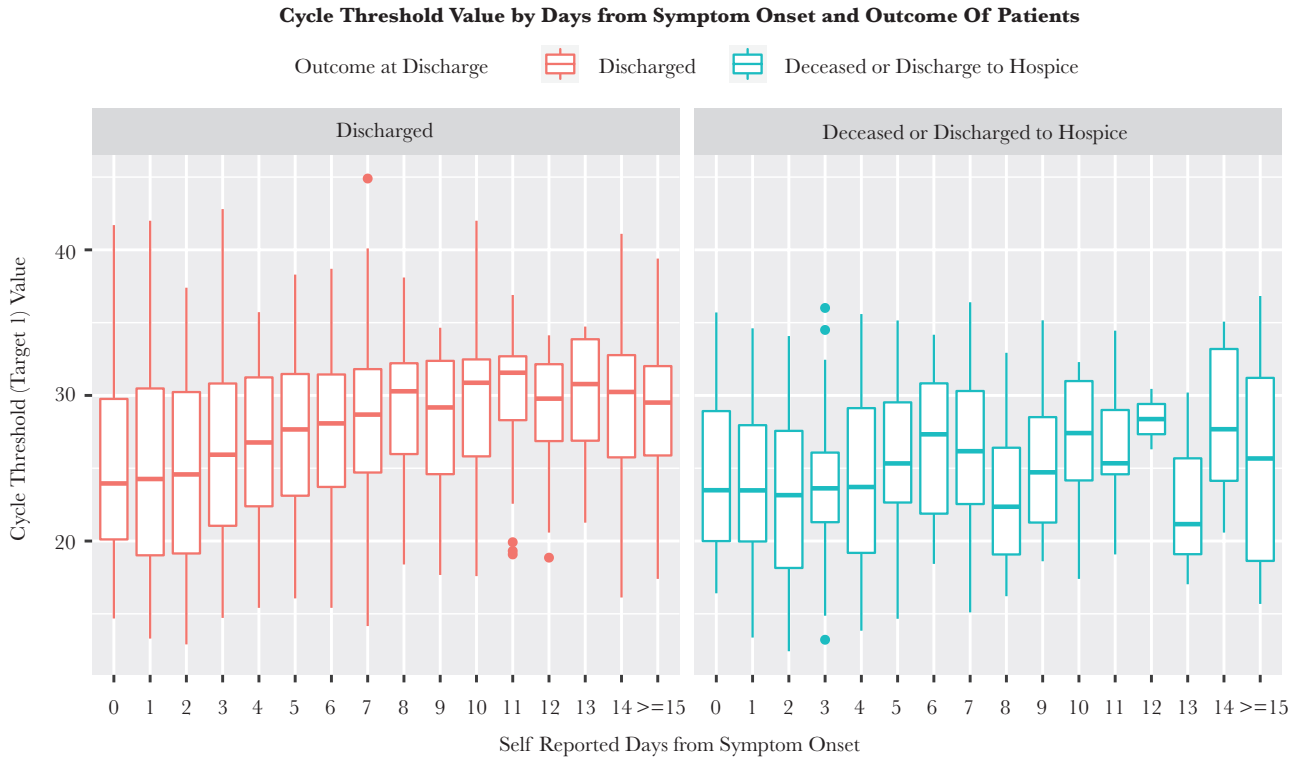

Figure 3. Box plots of cycle threshold (Ct) for target 1 of initial severe acute respiratory syndrome coronavirus 2 test by days since symptom onset to test among 1412 admitted patients who survived to discharge and 445 admitted patients who died or were discharged to hospice. Symptom duration before test was self-reported by the patient or family member who provided history upon presentation. Days from symptom onset ≤0 were excluded. Days from symptom onset >14 were categorized as ≥15.

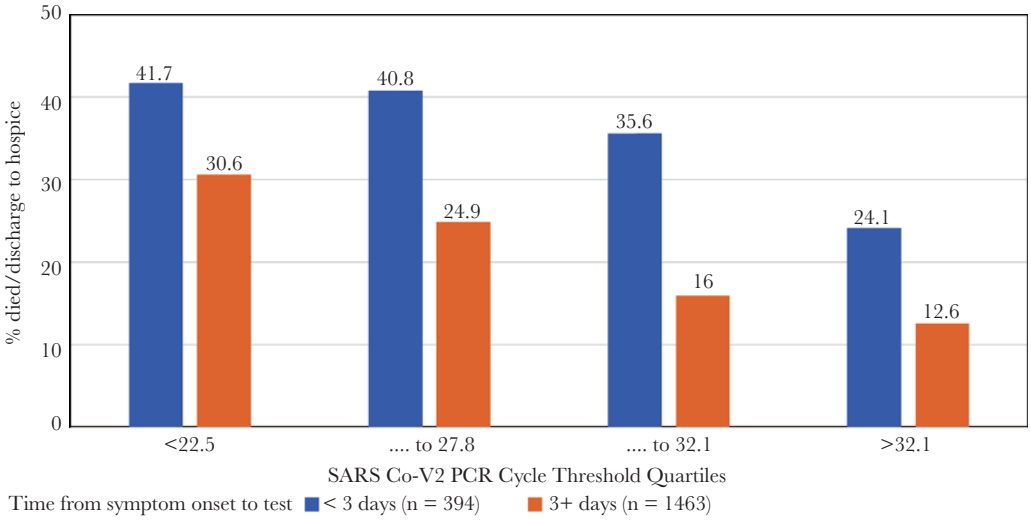

Figure 4. Frequency of death or discharge to hospice in 1857 admitted patients by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cycle threshold value quartiles and presentation <3 days or 3 or more days after symptom onset. PCR, polymerase chain reaction.

presentation had better outcomes (OR = 0.93; 95% CI, 0.91–0.95). Categorizing time after symptom onset into <3 days, 4–7 days, 8–14 days, and 15+ days showed odds of death relative to those presenting 8–14 days after symptom onset (group with the lowest odds of death) to be greatest in those presenting <3 days (OR, 3.1; 95% CI, 2.25–4.32) but still increased in those presenting 4–7 days (OR, 1.5; 95% CI, 1.12–2.04), and with a nonsignificant trend to be worse if presenting >14 days (OR, 1.3; 95% CI, 0.85–2.00) (Figure 3).

Despite the association between time since symptom onset and Ct values, in multivariable analysis, both time since symptom onset and Ct value were independent predictors of mortality regardless of whether time since symptom onset was treated as a continuous (OR, 0.94; 95% CI, 0.92–0.95) or categorical variable (OR = 0.94; 95% CI, 0.92–0.96). The association between the Ct value and subsequent prognosis was stronger in those presenting ≥3 days (OR = 0.92; 95% CI, 0.90–0.95) than those presenting <3 days (OR = 0.96; 95% CI, 0.93–0.99) (P = 0.04 for the interaction term). A gradient in the frequency of poor outcomes by quartile of the initial Ct value was most striking in those presenting >3 days after symptom onset but was still seen in those presenting <3 days after symptom onset (Figure 4). Associations between outcome and Ct values and symptom duration before testing remained consistent after adjusting for age; older age being a strong predictor of outcome (Table 3). Nevertheless, it should be noted that the low rates of outcome in the younger group limited our capacity to fully interrogate effect modification by age.

DISCUSSION

In this study, we observed a significant association between lower Ct values (and therefore higher viral load) and mortality in a large cohort of COVID-19 patients. We also found that reported symptom duration before testing was an independent predictor of outcomes. These findings provide important new insights into the role of duration of symptoms before presentation and its connection with both viral load and patient outcomes. Given the strong association between Ct values and mortality, Ct value on initial SARS-CoV-2 testing may be an important predictor of outcomes, especially for those patients being admitted to the hospital. Although Ct value is a strong predictor of poor clinical outcomes, our data does not find a clinically meaningful cutoff that could be used for triaging of patients. Duration of symptoms before presentation and Ct value on initial SARS-CoV-2 test are independent predictors of mortality and are potentially useful indicators of patient trajectory. Because no single value is predictive of a poor outcome, categories of Ct values such as quartiles could be used to triage patient's risk for decompensation. The Ct values were the lowest (viral load the highest) in the first 3 days of self-reported symptoms. Patients who presented earlier in their course and went on to either die or be discharged to hospice had lower Ct values than those who presented with similar symptom duration and survived.

A correlation between high viral load and mortality has been described in other viral infections, such as yellow fever virus and Ebola virus [14–16]. With Ebola virus and yellow fever virus, patients who present later to care tend to have higher viral loads and higher mortality. In this study, we observe the opposite with COVID-19, where patients who present early with high viral loads have a 2-fold increase risk of death. This is also in line with studies on transmissibility of the virus, which show that risk of transmission is highest in the first few days of symptoms, when viral loads are highest [17, 18]. Therefore, a patient

who presents with a low Ct value on their initial test may be on a trajectory to a poor outcome compared with someone who presents with a higher Ct value, even if both patients report similar symptom duration. It is possible that higher viral loads act as a trigger for the hyperinflammatory state seen in severe cases of COVID-19. Based on these data, Ct value and symptom duration could be used in conjunction with other factors that show an association with higher mortality, such as age >75, high IL-6, high LDH, and low platelets, to help guide the clinician's assessment of risk for poor outcome.

This study fills several important gaps in current knowledge on this topic. First, the role of symptom duration in outcomes and viral load is described for the first time. This information may not be readily available in other datasets but was systematically captured in our COVID-19 admission screens in the medical record. This cohort also includes both inpatients and outpatients as well as adult and pediatric patients. Outpatients and patients who were discharged from the emergency room have been largely excluded from prior studies on the role of Ct values in outcomes. Other strengths of this study include a large cohort with Ct values and definitive outcomes included for most patients. Furthermore, a range of race/ethnicity is represented in this cohort, including Hispanic and African American patients, who are disproportionately affected by the COVID-19 pandemic [19–21].

Several limitations need to be considered. This study was a single quaternary academic medical center during the peak of the major outbreak. This could limit its generalization to other patient populations, specifically those with lower circulating amounts of virus. However, as the pandemic continues and new hot spots emerge, this experience will provide useful information for these areas as they navigate their own surges. Data included in the study was limited to what is available in the electronic medical records, and errors can exist in both patient recall and/or provider documentation, especially around collection of symptom duration. Even with these issues, we were able analyze data from a large cohort of 4254 patients. Finally, management of patients changed over the course of the epidemic as new data, experimental therapeutics, and clinical trials became available. It is difficult to fully take into account how this constant change of treatment practices may have influenced patient outcomes.

CONCLUSIONS

Taken together, this study supports a role for use of Ct values from SARS-CoV-2 testing and history of symptom duration as useful tools to help predict which patients presenting with COVID-19 may have worse outcomes. Patients at particularly high risk for poor outcomes include those presenting early in their disease course with low Ct values. These parameters add value to other variables, such as inflammatory markers, older age, and oxygen requirements, that contribute to poor outcomes and should also be considered when attempting to triage patients. Current antiviral treatments for COVID-19, such as remdesivir, offer minimal benefits and have been plagued by availability shortfalls [22, 23]. As more effective antivirals become available, it will be important to target them to patients in the viral phase of the illness when they will likely be most effective. Utilizing Ct values in the context of symptom duration can help providers predict who is at higher risk for decompensation and help guide the use of antivirals. Additional studies are needed to determine all predictors of poor outcomes in COVID-19; however, the reporting of Ct values from SARS-CoV-2 RT-PCR testing in conjunction with history of symptom duration can be used by providers as another tool to risk stratify patients and prioritize resources.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Figure 1. Receiver operating characteristic curve for the SARS-Co-V2 RT-PCT cycle threshold (Ct) value to predict poor outcome (death or discharge to hospice) among 2308 admitted patients.

Acknowledgments

We acknowledge the data in the COVID-CARE database based at New York Presbyterian Hospital/Columbia University Irving Medical Center, Division of Infectious Diseases.

Author contributions. E. H. M., J. Z., and A.-C. U. contributed to conceptualization. E. H. M., J. Z., D. C., L. K., and A. C.-U. contributed to methodology. J. Z., D. C., and L. K. contributed to formal analysis. J. Z., J. L. S., D. A. G., and S. W. contributed to data curation. E. H. M. and A. C.-U. contributed to writing the original draft. E. H. M., J. Z., D. C., M. K. A., M. S., N. M., M. E. S., M. T. Y., L. K., and A. C.-U. contributed to writing, review, and editing. A.-C. U. supervised the work. E. H. M., A. C.-U., J. Z., and M. E. S. contributed to funding acquisition.

Financial support. Funding for M. E. S. and J. Z. was provided by National Institute of Allergy and Infectious Diseases ([NIAID] Grant 5UM1AI069470) and supplement to the award. Funding for E. H. M. was provided by NIAID Grant 5T32AI100852-08.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ **2020**; 369:m1996.
2. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet **2020**; 395:1763–70.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA **2020**; 323:1239–42.
4. Jeremy AW, Gold KKW, Christine M, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19—Georgia. MMWR Morb Mortal Wkly **2020**; 69:545–50.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **2020**; 395:497–506.
6. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal. J Heart Lung Transpl **2020**; 39:405–7.

7. Granados A, Peci A, McGeer A, Gubbay JB. Influenza and rhinovirus viral load and disease severity in upper respiratory tract infections. J Clin Virol **2017**; 86:14–9.
8. Li CC, Wang L, Eng HL, et al. Correlation of pandemic (H1N1) 2009 viral load with disease severity and prolonged viral shedding in children. Emerg Infect Dis **2010**; 16:1265–72.
9. Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019 [Published online ahead of print 30 June 2020]. Clin Infect Dis **2020**;ciaa851. doi:10.1093/cid/ciaa851
10. Pujadas E, Chaudhry F, McBride R, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. Lancet Respir Med **2020**; 8:e70.
11. Center for Disease Control. CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT PCR diagnostic panel. **2020**. https://www.fda.gov/media/134922/download. Accessed 2 July 2020.
12. FDA. Xpert Xpress SARS-CoV-2 instructions for use. **2020**. https://www.fda.gov/media/136314/download. Accessed 3 July 2020.
13. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant **2020**; 20:1800–8.
14. Fitzpatrick G, Vogt F, Moi Gbabai OB, et al. The contribution of Ebola viral load at admission and other patient characteristics to mortality in a Médecins Sans Frontières Ebola case Management Centre, Kailahun, Sierra Leone, June–October 2014. J Infect Dis **2015**; 212:1752–8.
15. Hartley MA, Young A, Tran AM, et al. Predicting ebola severity: a clinical prioritization score for ebola virus disease. PLoS Negl Trop Dis **2017**; 11:e0005265.
16. Kallas EG, D'Elia Zanella LGFAB, Moreira CHV, et al. Predictors of mortality in patients with yellow fever: an observational cohort study. Lancet Infect Dis **2019**; 19:750–8.
17. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med **2020**; 382:1177–9.
18. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med **2020**; 26:672–5.
19. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med **2020**; 382:2372–4.
20. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with covid-19. N Engl J Med **2020**; 382:2534–43.
21. Richardson S, Hirsch JS, Narasimhan M, et al.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA **2020**; 323:2052–9.
22. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med **2020**; 383:1813–26.
23. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19—interim WHO solidarity trial results [Published online ahead of print 2 December 2020]. N Engl J Med **2020**;NEJMoa2023184. doi:10.1056/NEJMoa2023184