SARS-CoV-2 Cycle Thresholds, Poverty, Race, and Clinical Outcomes

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ABSTRACT

Background: Poverty and high viral load are associated with worse outcomes among COVID-19 patients.

Methods: We included patients admitted to Froedtert Health between March 16 and June 1, 2020. SARS-CoV-2 viral load was proxied by cycle-threshold values. To measure poverty, we used Medicaid or uninsured status and residence in socially disadvantaged areas. We assessed the association between viral load and length of stay and discharge disposition, while controlling for demographics and confounders.

Results: Higher viral load was associated with longer length of stay (coefficient -0.02; 95% CI, -0.04 to 0.01; $P = 0.006$) and higher likelihood of death (coefficient -0.11; 95% CI, -0.17 to -0.06; $P < 0.001$). Poverty, residence in disadvantaged areas, and race were not.

Discussion: This study confirms a relationship of viral load with in-hospital death, even after controlling for race and poverty.

INTRODUCTION

The current gold standard for diagnosis of coronavirus disease 2019 (COVID-19) is the reverse transcriptase-polymerase chain reaction (RT-PCR) test. This test provides a cycle threshold (Ct) value, a proxy indicator of viral load.[1] Evidence suggests that viral load is higher in patients with more severe clinical presentations, on the first day of symptoms, and in fatal cases.[2,3]

Another poor prognostic factor among patients with COVID-19 is poverty, as shown by our research group[4] and others.[5,6] Specifically, we found that poverty is associated with requiring intensive unit care, even when controlling for race/ethnicity, age, body mass index, and comorbid conditions. Given that poverty is likely a proxy for nonclinical issues (ie, reduced access to care, housing density, and/or essential worker status), we were interested in the extent to which poverty accounted for the relationship between viral load and clinical outcomes. Therefore, the purpose of this study was to examine the association between SARS-CoV-2 viral load and clinical outcomes while adjusting for poverty and race among COVID-19 patients.

METHODS

Setting, Study Design, and Testing Methodology

This cross-sectional study was performed at Froedtert Health and the Medical College of Wisconsin (FH and MCW) and included all consecutive, unique patients hospitalized for at least 24 hours with a positive SARS-CoV-2 RT-PCR test between March 16 and June 1, 2020 (Figure). The study was approved by MCW's Institutional Review Board and a waiver of informed consent was granted.

COVID-19 tests were performed at FH and MCW's microbiology laboratory (Wisconsin Diagnostic Laboratories) using the Centers for Disease Control and Prevention's (CDC) methodology for RT-PCR tests (n = 107), Roche Molecular Systems

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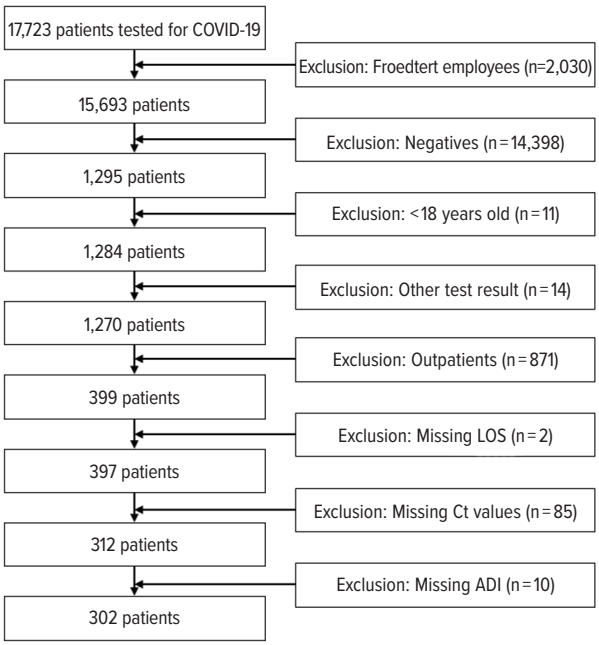
Figure. CONSORT flow diagram.



Abbreviations: LOS, length of stay; Ct, cycle threshold; AD, area disadvantage index.

SARS-CoV-2 Nucleic Acid Test (n=68), and Cepheid Xpert Xpress SARS-CoV-2 tests (n=127).[7]

Combined nasopharyngeal/oropharyngeal swabs were collected using a dual swab system and placed into viral transport media. The CDC SARS-CoV-2 assay was performed by extracting RNA using the eMag (bioMerieux) according to the manufacturers' product insert. RT-PCR was performed according to CDC protocol.[7] Roche Molecular Systems SARS-CoV-2 Nucleic Acid test and Cepheid Xpert Xpress SARS-CoV-2 test were performed and interpreted in accordance with emergency use authorization protocols (Doc Rev 3.0 and 2.0).[7]

Viral load, measured by Ct values, was obtained by direct interrogation of laboratory testing equipment. To harmonize viral loads obtained from different platforms and to ensure that the choice of Ct target did not influence our results, we included indicators for the test type in all multivariable analyses.

Variable Definitions

Information on acute care length of stay (LOS) and post-acute discharge disposition were obtained from electronic medical records. Discharge disposition was classified into 3 mutually exclusive categories: discharged home (with or without home health care), discharged to a skilled nursing facility, or death. We obtained demographic characteristics (age, sex, race), symptoms on admission (presence of fever, cough, shortness of breath, sore throat, diarrhea, nausea, vomiting, or abdominal pain, changes in mental status, and olfactory changes or taste changes), comorbidities (hypertension, diabetes, chronic heart disease, chronic lung disease, and chronic kidney disease), primary and secondary health insurance, body mass index (BMI), and smoking history. Race was based on self-reported data, where individuals were classified as African-American, White, Hispanic, or Other (Native Hawaiian or Pacific Islander, Native American or Alaska Native, and Asian).

In the absence of individual-level information on income, we used lack of health insurance or enrollment in Medicaid as our individual-level indicator of poverty. Finally, the patients' address of residence was obtained using the ZIP code lookup tool, as previously described.[4] Their 9-digit ZIP codes were then used to classify individuals as living in socially disadvantaged areas based on a score of 7 or higher on the Area Deprivation Index (ADI).[4]

Statistical Analysis

For descriptive analysis, patients were stratified into 2 groups based on the distribution of Ct values seen in the study. Specifically, patients with Ct values <26 were defined as having high viral loads, while those with Ct values ≥26 were defined as having low viral loads. Categorical variables were described as count (percentage) and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]). Pearson's chi-square test was used to compare categorical variables, Student *t* test for means, and Mann-Whitney-U test for medians. In the multivariable analyses, viral load was analyzed as a continuous variable.

LOS, a continuous variable, was analyzed using linear regression techniques applied to the logarithmic transformation of the dependent variable to minimize the influence of outliers. For discharge disposition—an unordered 3-category variable—we used a multinomial logistic regression. All analyses were conducted in Stata version 16 (StataCorp) and SPSS (version 24.0; SPSS Inc., Chicago, IL). To adjust for longitudinal effects of community spread, we stratified our observation period by weeks, including it as an independent variable.

RESULTS

A total of 302 patients were hospitalized for COVID-19 during the study period. Table 1 shows summary statistics for the cohort. Overall, 161 (53.3%) patients were male and 172 (57%) were ≥60 years old. Slightly over half were poor as measured by having Medicaid or no health insurance (n=156, 51.7%). The mean BMI was 31.9 (SD 9.1), and 124 (41.1%) patients reported having a history of smoking. The median hospital LOS was 6 days (IQR 3-11). Regarding discharge disposition, 54 (17.9%) patients died, 199 (65.8%) were discharged home, and 49 (16.2%) were discharged to nursing homes.

Patients with high viral loads (ie, Ct values ≤26) were older (65.6 [SD 16] vs 56.7, [SD 19]; $P<0.001$) and were more likely to be poor (81 [SD 57%] vs 75 [SD 46.9%]; $P=0.078$) than those with low viral loads. Patients with high viral loads also experienced a greater acute care LOS (8 [IQR 4-13] vs 5 [IQR 2-8];

$P<0.001$) and were more likely to die (39 [SD 27.5%] vs 15 [SD 9.4%]; $P<0.001$) than those with low viral loads.

SARS-CoV-2 Viral Load, Poverty, and Health Care Utilization

Table 2 shows the parameter estimates from our multivariable models. After controlling for race, socioeconomic status, and potential confounders (ie, age, sex, comorbidities, BMI, ADI), viral load was significantly associated with longer LOS (coefficient -0.02; 95% CI, 0.04 to -0.01; $P=0.006$). Patients with higher viral loads were also more likely to die during hospitalization (coefficient -0.11; 95% CI, -0.17 to -0.05 0.95; $P<0.001$). Neither poverty, residence in a disadvantaged area, nor race were associated LOS or in-hospital death. Viral load was not a significant predictor of discharge to a skilled nursing facility among those discharged alive from the hospital, but poverty was a significant predictor (coefficient 2.83; 95% CI, 1.18 to 4.49; $P<0.001$). Neither residence in a disadvantaged area nor race were significantly associated with discharge to a skilled nursing facility.

In addition to viral load, age ≥60 (coefficient 0.42, 95% CI, 0.16 to 0.67; $P<0.001$), male sex (coefficient 0.29; 95% CI, 0.07 to 0.50; $P<0.001$), and higher BMI (coefficient 0.02; 95% CI, 0.01 to 0.03; $P<0.001$) were independently associated with longer LOS. Relative to those discharged home, COVID-19 patients discharged to a nursing home were more likely to be 60 years or older (coefficient 1.97; 95% CI, 1.04 to 2.90; $P<0.001$), male (coefficient 0.87; 95% CI, 0.10 to 1.63; $P<0.001$), poor (coefficient 2.83; 95% CI, 1.18 to 4.49; $P<0.001$), and have 1 to 2 comorbidities (coefficient 0.29; 95% CI, 0.05 to 0.54; $P<0.001$).

DISCUSSION

In this cross-sectional study of hospitalized COVID-19 patients, we found that higher viral loads were associated with longer LOS and greater in-hospital mortality. Poverty, residence in a disadvantaged area, and race

Table 1. Characteristics of Patients Hospitalized for COVID-19, Overall and by Viral Load

Characteristics	Total N=302	High Viral Load N=142	Low Viral Load N=160	*P* value
Age (mean, SD)	60.89,18.22	65.61,16.05	56.71,19.03	<0.001
≥60 years old, N (%)	172 (57)	95 (66.9)	77 (48.1)	0.001
Sex: male, N (%)	161 (53.3)	71 (50)	90 (56.3)	0.28
Race, N (%)				
African-American/Black	177 (58.6)	78 (54.9)	99 (61.9)	0.22
White	84 (27.8)	46 (32.4)	38 (23.8)	0.09
Other	12 (4)	1 (0.7)	11 (6.9)	0.01
Hispanic, N (%)	29 (9.6)	17 (12)	12 (7.5)	0.19
Residence in socially disadvantaged area (ADI ≥7), N (%)	186 (61.6)	80 (56.3)	106 (66.3)	0.08
Poverty status: uninsured or Medicaid, N (%)	156 (51.7)	81 (57)	75 (46.9)	0.08
Comorbidities, N (%)				
None	59 (19.5)	32 (22.5)	27 (16.9)	0.216
1-2	131 (43.4)	54 (38)	77 (48)	0.077
≥3	112 (37.1)	56 (39.4)	56 (35)	0.426
Body mass index (mean, SD)	31.9 (9.1)	32.05 (9.81)	31.77 (8.53)	0.794
History of smoking/current smoker, N (%)	124 (41.1)	59 (41.5)	65 (40.6)	0.871
Days to symptoms onset (median, IQR)	2 (0-5)	1(0-4)	2 (1-7)	<0.001
Symptoms, N (%)				
Fever	103 (34.1)	53 (37.3)	50 (31.3)	0.266
Cough	197 (65.2)	95 (66.9)	102 (63.7)	0.57
Shortness of breath	124 (41.1)	58 (40.8)	66 (41.3)	0.94
Diarrhea, nausea, vomiting, abdominal pain	42 (13.9)	24 (16.9)	18 (11.3)	0.16
Other symptoms	173 (57.3)	77 (54.2)	96 (60)	0.31
Outcomes, N (%)				
Length of stay (median, IQR)	6 (3-11)	8 (4-13)	5 (2-8)	<0.001
Discharge disposition, N (%)				
Nursing home discharge	49 (16.2)	29 (20.4)	20 (12.5)	0.062
Home or other nonmedical setting discharge	199 (65.9)	74 (52.1)	125 (78.1)	<0.001
Death	54 (17.9)	39 (27.5)	15 (9.4)	<0.001

Abbreviations: ADI: area disadvantage index; IQR: interquartile range; ICU, intensive care unit.
Patients with Ct values <26 were categorized as having high viral loads, while those with Ct values ≥26 as low viral load.

Table 2. Multivariate Analysis of Length of Stay, Death, and Discharge Disposition Among COVID-19 Positive Patients

	Length of Stay Coefficient (95%)	Discharge Disposition (Relative to Discharge Home)	
		Death Coefficient (95% CI)	Nursing Home Coefficient (95% CI)
Viral load	**-0.02[a] (-0.04 to -0.01)**	**-0.11[a] (-0.17 to -0.05)**	-0.02 (-0.08 to 0.03)
Health insurance			
Medicaid or uninsured	0.05 (-0.24 to 0.33)	0.93 (-0.12 to 1.97)	**2.83[a] (1.18-4.49)**
Medicare	-0.07 (-0.42 to 0.28)	0.85 (-0.29 to 1.98)	1.13 (-0.60 to 2.85)
Age ≥60 years	**0.42[a] (0.16 to 0.67)**	**1.46[a] (0.60 to 2.32)**	**1.97[a] (1.04 to 2.90)**
Sex: male	**0.29[a] (0.07 to 0.50)**	0.22 (-0.48 to 0.92)	**0.87[**] (0.10 to 1.63)**
African American/Black	-0.09 (-0.34 to 0.15)	0.19 (-0.61 to 0.98)	-0.71 (-1.56 to 0.14)
1-2 comorbidities	0.06 (-0.01 to 0.13)	0.01 (-0.22 to 0.24)	**0.29[a] (0.05 to 0.54)**
Body mass index	**0.02[a] (0.01 to 0.03)**	0.03 (-0.01 to 0.07)	-0.02 (-0.06 to 0.02)
Days to symptoms onset	-0.001 (-0.02 to 0.02)	-0.04 (-0.11 to 0.04)	-0.09 (-0.18 to 0.01)
Area disadvantage index	-0.02 (-0.05 to 0.03)	-0.02 (-0.14 to 0.11)	-0.06 (-0.19 to 0.08)
Week block	-0.007 (-0.07 to 0.06)	0.13 (-0.07 to 0.34)	-0.01 (-0.24 to 0.23)

Viral load was measured by cycle threshold values.
[a]Indicates statistical significance at $P \leq 0.05$.

were not associated with increased LOS or mortality when viral load was included in the model. Although patients who were discharged to a nursing home had higher viral loads, poverty rather than viral load was a significant predictor of nursing home discharge.

Studies have explored the relationship between SARS-CoV-2 viral loads and in-hospital clinical outcomes.[2,3,8] Similar to our findings, others found an association between viral load and mortality after adjusting for race, age, and other variables. Our study builds upon the existing literature, as we found that high viral load was still associated with mortality, even after adjusting for poverty, residence in a disadvantaged area, and race. We also noted an association between viral load and LOS while controlling for sex, age, race, and other demographic variables—a finding that is inconsistently reported in the literature.[9,10]

Our study has several limitations. The research was performed at a single health system over a relatively short study period, and therefore may not be generalizable to other areas. The SARS-CoV-2 test samples were taken at different points during each patient's clinical course and measured by different platforms. These issues, however, are unlikely to have influenced our findings as analyses of the number of days from onset of symptoms to the day of testing indicated no association between these 2 variables (data not shown). Additionally, we controlled for test type in our multivariable models.

In conclusion, viral load, measured indirectly by Ct values, was independently associated with in-hospital death—even after controlling for race and poverty. Although these socioeconomic factors increase the likelihood of COVID-19 infection, they do not influence the effect of viral load on clinical outcomes.

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