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## Association of SARS-CoV-2 Genomic Load with Outcomes in Patients with COVID-19

Since its recognition, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused 31.2 million cases of coronavirus disease (COVID-19) worldwide (1). The surge in infections has overwhelmed the healthcare systems, and identifying patients who have a high risk for poor outcomes is critically important (2). Host factors have been associated with mortality (3–7), whereas the data on the association of viral factors with COVID-19 outcomes remain conflicting (8–11). We aimed to study the association of SARS-CoV-2 genomic load in nasopharyngeal samples with clinical outcomes. We used the cycle threshold (Ct) value, the number of amplification cycles needed to yield a positive fluorescent signal in a real-time reverse transcription–polymerase chain reaction (RT-PCR), as a surrogate for viral load.

### Methods

We conducted a retrospective cohort study at the New York University Langone Medical Center, a tertiary academic medical center in New York City. We evaluated all patients who presented to the emergency department between March 31, 2020, and April 10, 2020, with clinical and radiographic findings of viral pneumonia and positive screening for SARS-CoV-2 who required hospitalization. We excluded patients who were tested more than 24 hours into the admission, as our goal was to study the association of the genomic load at the time of admission to the hospital with patient outcomes.

The qualitative Cepheid Xpert Xpress SARS-CoV-2 assay was used for in-house diagnosis of COVID-19 (12). This assay

detects two nucleic acid targets, namely, N2 and E, and reports the Ct values. The Ct values provide a semiquantitative measure of genomic load, with an inverse relationship between the genomic load and Ct value (13). The N2 target is specific for SARS-CoV-2, whereas the E nucleic acid can also be found in SARS-CoV-1. A positive assay result implies that either N2 and E or N2 target alone were detected, whereas detection of the E nucleic acid alone is considered a presumptive positive result (the latter were excluded from this study).

The primary study outcome was the association of the genomic load in patients admitted to the hospital with COVID-19–related pneumonia with disease outcomes. We used a composite outcome of death or discharge to hospice care and use of mechanical ventilation or extracorporeal membrane oxygenation. All patients were followed up until April 30, 2020. The Charlson Comorbidity Index (CCI) and the pneumonia severity index (PSI) were calculated. Patients were divided into five classes based on the PSI, with a higher class at the time of admission being associated with worse outcomes (14). The duration of symptoms before presentation was also extrapolated.

We categorized Ct values into the following three SARS-CoV-2 genomic load groups based on tertiles: low ( $\geq 34.2$ ), intermediate (27.7–34.2), and high ( $\leq 27.7$ ). We compared the patients in the three genomic load groups on the basis of demographic characteristics, body mass index (BMI), smoking history, CCI, comorbidities, immunosuppressive diseases, duration of symptoms, and the PSI using the  $\chi^2$  test. A multivariate logistic regression analysis was performed to examine the association of the SARS-CoV-2 genomic load with the primary composite outcome adjusted for patient demographics, BMI, smoking history, comorbidities, transplant status, PSI, and duration of symptoms. The marginal method was used to estimate the probability of the composite outcome among patients with low, intermediate, and high genomic loads when all the other variables were fixed at their means (15). All calculations were performed using the Stata version 14.2 software package (Stata Corporation). A *P* value of less than 0.05 was considered statistically

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**Author Contributions:** I.M.Z. and M.E.A.-R. conceptualized the study. I.M.Z., P.J.P., A.B., K.I., and S.A.W. collected the data. I.M.Z. and F.N.Z. conducted the analysis. All authors participated in interpretation of data, drafting of the work; final version of the manuscript was approved by all authors.

**Table 1.** Association of SARS-CoV-2 genomic load with patient characteristics

Patient characteristics	Low Genomic Load (n = 107)	Intermediate Genomic Load (n = 103)	High Genomic Load (n = 104)
Age, yr, n (%)			
18–44	14 (13.1)	10 (9.7)	13 (9.6)
45–64	52 (48.6)	35 (34.0)	38 (36.5)
≥65	41 (38.3)	58 (56.3)	53 (50.9)
Race, n (%)			
White	44 (41.1)	54 (52.4)	42 (40.4)
Black	11 (10.3)	12 (11.7)	18 (17.3)
Hispanic	11 (10.3)	10 (9.7)	14 (13.5)
Other/Unknown	41 (38.3)	25 (24.6)	30 (28.8)
Sex, M, n (%)	68 (63.6)	65 (63.1)	72 (69.2)
Obesity (BMI ≥ 30), n (%)	44 (41.1)	39 (37.9)	34 (32.7)
Smoking (current/former), n (%)	21 (20.2)	30 (29.1)	21 (20.2)
Any pulmonary comorbidity, n (%)	15 (14.0)	23 (22.3)	12 (11.5)
Transplant, <sup>†</sup> n (%)	2 (1.9)	4 (3.9)	15 (14.4)
CCI, <sup>*†</sup> n (%)			
Low	58 (54.2)	41 (39.8)	35 (33.7)
Medium	33 (30.8)	28 (27.2)	36 (34.6)
High	16 (15.0)	34 (33.0)	33 (31.7)
Symptoms for ≤7 d, <sup>†</sup> n (%)	47 (43.9)	63 (61.2)	68 (65.4)

Definition of abbreviations: BMI = body mass index; CCI = Charlson Comorbidity Index; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

\*Low CCI 1–2, Medium CCI 3–4, High CCI ≥5.

<sup>†</sup>Statistically significant.

significant. This study was approved with a waiver of informed consent by the New York University Institutional Review Board.

## Results

Of the 457 patients who presented to our emergency department with positive for SARS-CoV-2 between March 31, 2020, and April 10, 2020, 314 met the inclusion criteria and were included in the final analysis. Among the included patients, the median age was 64 years (interquartile range [IQR], 54–72 yr), 205 (65.3%) were male, 140 (44.6%) were white, and the median BMI was

28.3 (IQR, 25.1–32.3). In terms of comorbidities, the median CCI was 3 (IQR, 1–5), and 117 patients (37.3%) were obese (i.e., BMI ≥30 kg/m<sup>2</sup>). In addition, 50 patients (15.9%) had at least one pulmonary comorbidity, 72 (23.5%) were active or former smokers, 21 (6.7%) were transplant recipients (20 solid organ transplantations and one hematopoietic stem cell transplantation) and four had human immunodeficiency virus (three of them virologically suppressed). The median duration of symptoms before presentation was 7 days (IQR, 5–10 d). Nine patients were classified in class I based on their PSI (2.9%), 78 were classified in class II (24.8%), 84 were classified

**Table 2.** Association of SARS-CoV-2 genomic load with patient outcomes

Patient characteristics	Low (n = 107)	Intermediate (n = 103)	High (n = 104)
Fever, n (%)	78 (72.9)	79 (76.7)	77 (74.0)
CRP, n (%)			
≤80	35 (32.7)	35 (34.0)	37 (35.6)
80–160	38 (35.5)	34 (33.0)	36 (34.6)
≥160	34 (31.8)	34 (33.0)	31 (29.8)
Pulmonary severity index, <sup>*</sup> n (%)			
I–II	41 (38.3)	25 (24.3)	21 (20.2)
III	28 (26.2)	29 (28.2)	27 (26.0)
IV–V	38 (35.5)	49 (47.5)	56 (53.8)
Death, <sup>*</sup> n (%)	8 (7.5)	9 (8.7)	21 (20.2)
Composite outcome, <sup>*†</sup> n (%)	17 (15.9)	21 (20.4)	36 (34.6)

Definition of abbreviations: CRP = C-reactive protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

\*Statistically significant.

<sup>†</sup>Composite outcome = death or discharge to hospice or intubation or extracorporeal membrane oxygenation.

in class III (26.8%), 102 were classified in class IV (32.5%) and 41 were classified in class V (13%).

Of the 314 included patients, 107 (34.1%) were categorized into the low, 103 (32.8%) into the intermediate, and 104 (33.1%) into the high SARS-CoV-2 genomic load category (Table 1). Patients with high genomic loads had higher CCI scores ( $P = 0.006$ ), were more likely to be transplant recipients ( $P < 0.001$ ), and had a significantly shorter duration of symptoms ( $P = 0.004$ ). The PSI was significantly higher in patients with high genomic loads ( $P = 0.03$ ). Transplant history (odds ratio [OR], 5.37; 95% confidence interval [CI], 1.15–25.0) and duration of symptoms (OR, 0.93; 95% CI, 0.88–0.97) remained significantly associated with high genomic load in multivariate analysis.

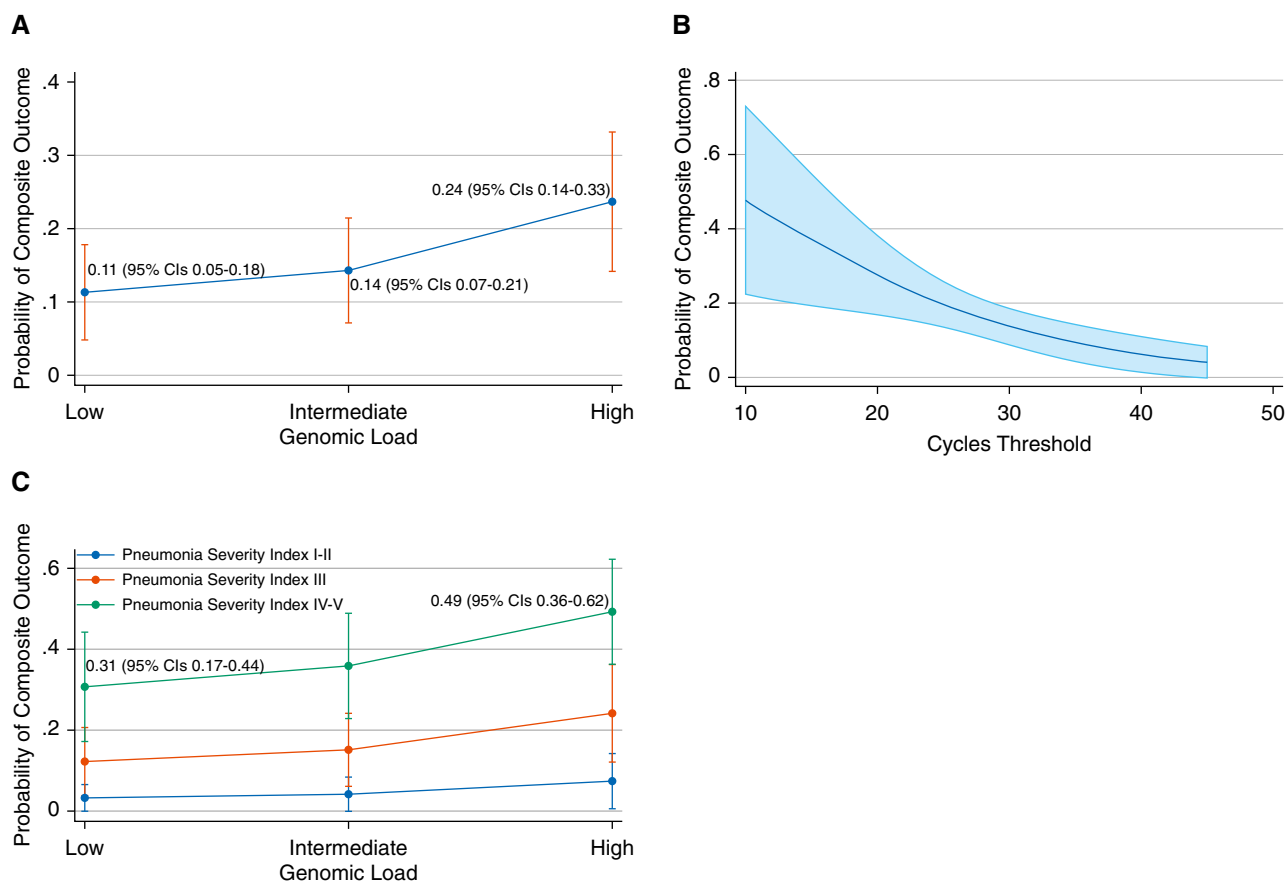
The follow-up period was a median of 25 days (IQR, 21–28 d). At the end of follow-up, the composite outcome was reached by 74 patients (23.6%). Median time to primary outcome was 3.5 days (IQR, 1–6 d). On the day of censoring, 309 patients (98.4%) had either reached the primary outcome or were discharged. Compared with patients with low genomic load, patients with high genomic load had a significantly higher unadjusted risk to die ( $P < 0.001$ ) and reach the composite outcome of death, intubation, or extracorporeal membrane oxygenation ( $P = 0.004$ ) (Table 2).

In the multivariate model, controlling for patient age, sex, BMI, CCI, smoking and transplant history, duration of symptoms,

and PSI, high genomic load remained an independent risk factor for the composite outcome (OR, 1.59;  $P = 0.02$ ). In addition, the duration of symptoms (OR, 0.93;  $P = 0.05$ ) and PSI at the time of admission (OR, 3.7;  $P < 0.01$ ) were also significantly associated with the composite outcome in multivariate analysis. The margins analysis indicated that the average probability of the composite outcome would be 24% (95% CI, 0.14–0.33) if everyone had a high genomic load compared with 11% (95% CI, 0.05–0.18) if everyone had a low genomic load (Figures 1A and 1B). Among patients with a high PSI, the expected probability of the composite outcome was 49% (95% CI, 0.36–0.62) for those with a high genomic load as opposed to 31% (95% CI, 0.17–0.44) for those with a low genomic load (Figure 1C).

## Discussion

We found that patients with a short duration of symptoms and high comorbidity index, as well as transplant recipients, were more likely to have a high SARS-CoV-2 genomic load at the time of hospital admission. The patients with high genomic load had a more severe clinical presentation and two times higher odds of dying or being intubated, independent of age, comorbidities, and severity of illness on presentation. Among patients with a severe clinical presentation at the time of hospital admission, patients with high genomic load were almost twice as likely to die or get intubated.



**Figure 1.** (A) Prediction of outcomes based on genomic load category. (B) Prediction of outcomes based on cycles threshold. (C) Prediction of outcomes based on genomic load and pneumonia severity index. CI = confidence interval.

The contribution of viral factors in disease severity is less understood, with conflicting evidence in the literature (9, 11, 16, 17). In our study, we examined the utility of genomic load from the upper respiratory tract in making inferences for the disease outcomes. Although still unclear, it is plausible that lower respiratory samples may be more closely associated with clinical outcomes than nasopharyngeal samples (18). However, the difficulty in obtaining such samples makes it unlikely that this will be of significant value in daily clinical practice. Current evidence suggests that there is active replication of SARS-CoV-2 in the upper respiratory tissues during the first 5 days after the onset of symptoms (19), a finding that correlates with our observation of higher genomic load in patients presenting within 7 days of symptom onset.

Limitations of this study should be acknowledged and arise primarily from its retrospective design. However, both the primary outcome and the genomic load are objective measures that would not be influenced by incomplete reporting. Second, this study relies on Ct values obtained through a single assay, and the generalizability of the outcomes across different RT-PCR methods should be examined. Next, variation in the technique of obtaining the nasopharyngeal swab or collection of the specimen at different phases of the respiratory cycle could potentially cause fluctuation in the genomic load detected by the assay.

In summary, we showed that SARS-CoV-2 genomic load is an independent predictor of adverse outcomes in patients admitted to the hospital with COVID-19–related pneumonia and that above and beyond age, comorbidities, and severity of illness on presentation, genomic load may be used to risk-stratify patients in an era in which appropriate triaging is of utmost importance.

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