Correlates of Omicron SARS-CoV-2 viral load: diagnostic and clinical implications

Simon D. Pollett[1,2], Stephanie A. Richard[1,2], Anthony Fries[3], Allison Malloy[4,5], Anuradha Ganesan[1,2,4], Jeffrey Livezey[4,5], David Saunders[6], Nikhil Huprikar[4], Rupal M. Mody[7], Katrin Mende[1,2,8], David A. Lindholm[6,8], Catherine M. Berjohn[1,6,9], Julia S. Rozman[1,2], Milissa U. Jones[10], Christopher J. Colombo[6,11], Rhonda E. Colombo[1,2,6,11], David Tribble[1], Mark P. Simons[1], Brian K. Agan[1,2], Timothy H Burgess[1]

[1]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [2]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA, [3]U.S. Air Force School of Aerospace Medicine, Dayton, Ohio, USA, [4]Walter Reed National Military Medical Center, Bethesda, MD, USA, [5]Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA [6]Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [7]William Beaumont Army Medical Center, El Paso, TX, USA, [8]Brooke Army Medical Center, San Antonio, TX, USA, [9]Naval Medical Center San Diego, San Diego, CA, USA, [10]Tripler Army Medical Center, Honolulu, CA, USA, [11]Madigan Army Medical Center, Joint Base Lewis McChord, WA, USA

Background

Omicron SARS-CoV-2 infections are associated with less frequent olfactory sensory loss and a predominance of pharyngitis symptoms compared to prior variants, with proposed diagnostic implications. We examined whether such symptomology predicts a higher RNA abundance in the oropharynx. We further investigated how age, symptom-day, vaccination history and clinical severity correlate with viral load to inform clinical prognostication and transmission modeling. We leveraged the Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study which enrolled participants with sequence-confirmed Omicron from December 2021.

Methods

Study population: The EPICC study is a longitudinal cohort with the primary goal of exploring the short- and long-term impact of SARS-CoV-2 infection in US Military Health System (MHS) beneficiaries enrolled at 10 military treatment facilities. Omicron-infected cases for this analysis were derived from 9 sites. Demographic and clinical characteristics were measured with interviews and surveys. Biospecimen collection included respiratory swab collection after enrollment and repeat blood collection over one year.

SARS-CoV-2 genotyping: Respiratory swab specimens were collected and sent for SARS-CoV-2 PCR testing. SARS-CoV-2 positive specimens were sent for SARS-CoV-2 whole genome sequencing using NexteraXT library kits. Libraries were run on the Illumina NextSeq 550 sequencing platform and the Pango classification tool was used for genotype classification. Genotypes were aggregated into BA.1 or BA.2-like lineages.

Quantification of SARS-CoV-2 RNA abundance: qPCR was performed on study samples using the SARS-CoV-2 (2019-nCoV) CDC qPCR Probe Assay research-use-only kit.

Statistical methods: Demographic and clinical characteristics were summarized for sequence-confirmed SARS-CoV-2 Omicron cases. We compared the age, Charlson comorbidity index (CCI), and vaccine history for hospitalized and non-hospitalized Omicron cases. Median log10 N1 SARS-CoV-2 RNA GE/reaction (a proxy for viral load) were compared by anatomical swab site locations using the Kruskall-Wallis test. Multivariable linear regression models were fit to estimate the association between of anatomical swab site on SARS-CoV-2 RNA abundance, adjusting for sampling time, vaccine history, illness severity and age. Model fit was evaluated using AIC and BIC.

Results

Table 1. Characteristics of n = 125 Omicron SARS-CoV-2 infections in U.S military health system beneficiaries

	Hospitalized (N=17)	Outpatient (N=108)	p value
Age (years)			
Median (Q1, Q3)	55.2 (43.3, 66.6)	37.8 (29.4, 47.2)	< 0.012
Min - Max	35.4 - 85.4	1.1 - 86.6	
Sex			
Male	10 (58.8%)	59 (54.6%)	0.751
Female	7 (41.2%)	49 (45.4%)	
Race			
Asian	0 (0.0%)	6 (5.6%)	
Black	4 (23.5%)	13 (12.0%)	
Hispanic or Latino	3 (17.6%)	23 (21.3%)	0.471
Other	2 (11.8%)	6 (5.6%)	
White	8 (47.1%)	60 (55.6%)	
Maximum severity			
Asymptomatic	0 (0.0%)	3 (2.8%)	
Outpatient	0 (0.0%)	38 (35.2%)	
Outpatient, limited activity	0 (0.0%)	67 (62.0%)	
Hospitalized, no O^2	5 (29.4%)	0 (0.0%)	–
Hospitalized, conventional O^2	9 (52.9%)	0 (0.0%)	
Hospitalized, high flow O^2	3 (17.6%)	0 (0.0%)	
Lineage			
BA.1-like	17 (100.0%)	98 (90.7%)	
BA.2-like[a]	0 (0.0%)	8 (7.4%)	0.431
BA.1/BA.2[b]	0 (0.0%)	2 (1.9%)	
Number of COVID-19 vaccine doses			
0	3 (17.6%)	9 (8.3%)	
1	1 (5.9%)	2 (1.9%)	0.441
2	8 (47.1%)	56 (51.9%)	
3	5 (29.4%)	41 (38.0%)	
CCI, median (Q1, Q3)	3.0 (1.0, 5.0)	0.0 (0.0, 0.0)	< 0.012
Probable reinfection[c]	1 (5.9%)	10 (9.3%)	0.651
Maximum observed N1 viral RNA abundance (median GE/reaction, IQR)	3894.3 (527.5, 30870.8)	3089.0 (156.6, 47630.5)	0.96
Maximum observed N2 viral RNA abundance (median GE/reaction, IQR)	2622.3 (253.9, 47023.6)	2306.1 (192.6, 38994.9)	0.87

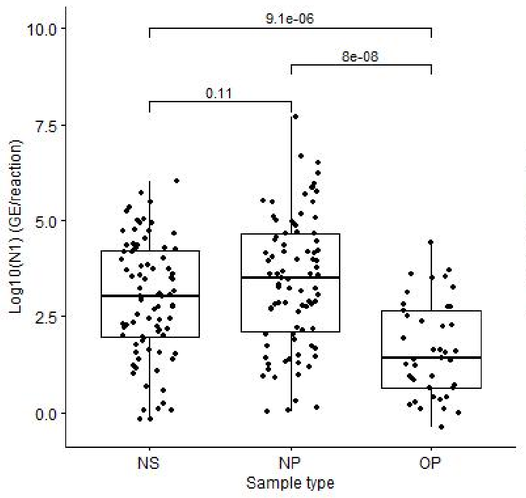
[a]BA.2, BA.2.10, BA.2.3 and BA.2.9
[b]n = 1 dual infection (BA.1.20/BA.2.3), n = 1 BA.1/BA.2 recombinant
[c]90 days or more since last positive SARS-CoV-2 PCR test
GE/reaction = genome equivalent/reaction
CCI = Charlson Comorbidity Index

Table 2. Correlates of log10 SARS-CoV-2 (N1) RNA abundance among n = 125 cases with Omicron infection

	β (StDev)[d]
Anatomical site of swab[a]	
Nasal	-0.54 (0.19)**
Oropharyngeal	-1.74 (0.23)***
Age category (years)[b]	
18-44	0.52 (0.50)
45-64	0.79 (0.54)
65+	1.02 (0.66)
Days post symptom onset	-0.05 (0.01)***
Prior COVID-19 vaccination[c]	0.37 (0.48)
Illness severity (outpatient)	0.12 (0.38)

[a]Compared to nasopharyngeal swab
[b]Compared to age < 18 years
[c]Compared to no vaccination or partial vaccination
[d]Model included age, anatomical site of swab, vaccination history, days post symptom onset, and illness severity
***p < 0.001; **p < 0.01; *p < 0.05

Figure 1. Log10 SARS-CoV-2 RNA N1 abundance by anatomical compartment in n = 125 cases with Omicron infection. NS = nasal swab, NP = nasopharyngeal swab, OP = oropharyngeal swab. P-values are indicated.



Results (continued)

We analyzed 125 sequence-confirmed Omicron cases. The median age was 38.8 years. 87% were vaccinated and 13.6% cases were hospitalized. Of those n = 100 cases completing an enrollment symptom survey, 24% described loss of smell or taste, 72% described nasal congestion, and 62% described sore throat. The median RNA abundance was lowest in OP swabs ($p < 0.001$) (**Fig 1**). Linear regression confirmed that OP sampling was associated with lower viral load ($p < 0.001$), and NP sampling was associated with the highest viral load (**Table 2**). We further noted that symptom-day was an independent correlate of viral load. There was a trend to older ages having a higher viral load but this was not statistically significant. Neither hospitalization nor vaccination status were associated with viral load in multivariate models (**Table 2**).

Conclusions

We noted prevalent sore throat symptoms and infrequent sensory loss in Omicron cases. Despite this, viral load was highest in NP/NS collected swabs as has been noted in pre-Omicron variants. These findings would not support a diagnostic approach which preferentially uses OP swabs, as was speculated early in the Omicron epidemic. In this study, we noted a higher RNA abundance in NP versus NS compartments, with potential diagnostic implications. Further study of RNA abundance, as well as live viral load, by upper respiratory compartment should be undertaken with future SARS-CoV-2 variants to ensure optimal clinical diagnostics. We note a trend toward age-dependent RNA abundance, and this should be examined in larger sample sizes. Finally, we estimate Omicron SARS-CoV-2 RNA abundance decay rates (by symptom day) which may be useful for SARS-CoV-2 transmission modeling.

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Correspondence

Dr. Simon Pollett, Associate Science Director, IDCRP
spollett@idcrp.org