Alpha to Omicron: Disease Severity and Clinical Outcomes of Major SARS-CoV-2 Variants

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Background. Four severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants predominated in the United States since 2021. Understanding disease severity related to different SARS-CoV-2 variants remains limited.

Method. Viral genome analysis was performed on SARS-CoV-2 clinical isolates circulating March 2021 through March 2022 in Cleveland, Ohio. Major variants were correlated with disease severity and patient outcomes.

Results. In total 2779 patients identified with either Alpha (n = 1153), Gamma (n = 122), Delta (n = 808), or Omicron variants (n = 696) were selected for analysis. No difference in frequency of hospitalization, intensive care unit (ICU) admission, and death were found among Alpha, Gamma, and Delta variants. However, patients with Omicron infection were significantly less likely to be admitted to the hospital, require oxygen, or admission to the ICU ($\chi^2 = 12.8$, $P < .001$; $\chi^2 = 21.6$, $P < .002$; $\chi^2 = 9.6$, $P = .01$, respectively). In patients whose vaccination status was known, a substantial number had breakthrough infections with Delta or Omicron variants (218/808 [26.9%] and 513/696 [73.7%], respectively). In breakthrough infections, hospitalization rate was similar regardless of variant by multivariate analysis. No difference in disease severity was identified between Omicron subvariants BA.1 and BA.2.

Conclusions. Disease severity associated with Alpha, Gamma, and Delta variants is comparable while Omicron infections are significantly less severe. Breakthrough disease is significantly more common in patients with Omicron infection.

Keywords. COVID-19; SARS-CoV-2; clinical severity; Delta; Omicron; variant.

There have been over 80 million coronavirus disease 2019 (COVID-19) cases (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infections) in the United States since early 2020 [1]. The resolution of the initial B.1 lineages in late winter 2020, was followed with the rise of the Alpha "UK variant" lineage (B.1.1.7). The Alpha variant remained dominant through that spring and summer until its subsequent replacement by the Delta variant (B.1.617.2, AY.*) in the fall. During this time, Beta and Gamma variants sporadically circulated in addition to several less-common lineages (Eta, Kappa, Iota, and Lambda). Most recently, the Omicron (B.1.1.529, BA*) variant emerged in December of 2021, quickly supplanting Delta, and this variant continues to circulate throughout the United States [2]. Within Omicron, several sublineages have been recognized and designated as BA.1 through BA.5. Circulating lineages are classified into 4 groups (variant of high consequence [VOHC], variant of concern [VOC], variant of interest [VOI], and variant being monitored [VBM]) [3]. Variants whose circulation achieves significant and sustained reduction are downgraded from VOC and VOI to VBM.

Understanding disease severity related to different SARS-CoV-2 variants remains limited. As part of the Ohio Department of Health (ODH) SARS-CoV-2 surveillance, we performed weekly genome analysis of SARS-CoV-2, sampling clinical isolates circulating in northeast Ohio. Focusing on the major circulating variants (Alpha, Gamma, Delta, and Omicron), we correlated disease severity and patient outcomes. Improved understanding of viral strains that alter disease outcomes is important for clinical risk stratification and may provide important clues to the complex virus-host relationship.

METHODS

Specimen Selection

Specimens positive for SARS-CoV-2 by nucleic acid amplification performed at the Cleveland Clinic from 11 March 2021 through 22 March 2022 were identified. A representative sampling was selected weekly for sequencing and lineage determination. Specimens either positive through antigen screening, reporting an indeterminate result, or obtained from locations other than the nasopharynx were excluded. While diagnostic

modalities evolved throughout the pandemic, reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal samples has been the primary diagnostic modality throughout the study period at our institution. Positive specimens with cycle threshold (Ct) values >30 were excluded due to poor quality sequencing reads occurring in such specimens. Selection preference occurred in specimens with S-gene dropout at the beginning of Alpha and Omicron waves as a function of screening quality control. Selection also included samples requested by ODH and local departments of health for analyzing breakthrough infections, and by request of medical providers. Such requests were infrequent (<5%). Most samples identified with Alpha and Gamma variants were included. Delta variant circulation dominated much of the study period and represented >50% of all sequenced samples. As such, a subset of Delta isolates was utilized instead of the entirety to prevent bias through overrepresentation.

Library Preparation and Sequence Data Analysis
Next-generation sequencing libraries of SARS-CoV-2–positive nasopharyngeal samples were prepared with Illumina COVIDSeq Test kit according to the manufacturer's recommendation and as described in our previous report [4, 5]. The limit of detection was determined to be 1000 copies per mL [6]. Data analysis was performed with a bioinformatics pipeline that was developed in house. Sequence reads were mapped to reference genome Wuhan-Hu-1 (NC_045512.2) using Burrows-Wheeler Aligner (version 0.7.15). Variant calling was performed with both Freebayes (version 1.3.4) and LoFreq (version 2.1.5) [7, 8]. We filtered single-nucleotide variants at 10% and insertion-deletion mutations at 5% allele frequency. Various quality controls removed any failed samples. Data quality was ensured by monitoring mapping quality, Phred score, and manual review. Mutations were manually reviewed with Integrative Genome Viewer (version 2.11.0) to remove any artifacts. Identified mutations were further annotated with snpEff (version 4.0e) [9]. Variant classification was performed with Pangolin program [10]. Derived genomes with related information were deposited into the Global Initiative on Sharing All Influenza Data (GISAID) database (with PLMI as tag in virus name) [11]. GISAID accession numbers for nucleotide sequences are available upon request.

Clinical Outcomes
Clinical outcomes were obtained from the Cleveland Clinic COVID-19 Registry [12]. This registry includes demographic, laboratory, and clinical data from patients tested for SARS-CoV-2 at Cleveland Clinic. Registry variables included demographics, comorbidities, medications, presenting symptoms, treatment, and disease outcomes. Capture of detailed research data was facilitated by the creation of standardized clinical templates implemented across the health care system.

Data were extracted using previously validated automated feeds from electronic health records (EPIC; EPIC Systems Corporation), manually by a study team trained on uniform sources for the study variables, and via natural language processing algorithms created to facilitate data abstraction at scale [13]. Manual chart review was performed for those patients with missing data elements. Study data were collected and managed using REDCap electronic data capture tools hosted at the Cleveland Clinic [13, 14]. Aberrant laboratory values, occurring within 21 days of hospitalization, were manually collected. Death was defined as demise occurring within 30 days of COVID-19 diagnosis. Vaccination status was confirmed through a combination of occupational health and safety software (ReadySet), electronic health record (EPIC), and ODH data. Full vaccination was defined as receiving 2 doses (Moderna/Pfizer) or 1 dose (Johnson and Johnson). Partial vaccination was defined as receiving 1 vaccination of either Moderna or Pfizer. Breakthrough infection was defined as SARS-CoV-2 infection ≥14 days following completion of vaccination series. Patient data analyzed in this study from Alpha, Gamma, and Delta infections occurred prior to Centers for Disease Control and Prevention (CDC) recommendations for use of booster immunization [15] whereas the majority of patients with Omicron were eligible to receive booster immunization. As such, receipt of a booster immunization is not included in our definition of full vaccination.

This study was approved by the Cleveland Clinic Institutional Review Board (IRB) and Institutional Biosafety Committee. A waiver of patient consent was provided by the IRB for use of residual samples.

Univariate Analysis
For clinical outcomes analysis, continuous variables were described using median and range; categorical variables were described using frequency and percentage. Demographics and clinical characteristics were compared between patients in different virus groups by using ANOVA, t test, or Kruskal-Wallis tests for continuous variables and Fisher exact or Pearson χ^2 tests for categorical variables. PRISM 8.4.3 software (GraphPad Software) was used for univariate analyses.

Multivariate Analysis
To assess the impact of demographic variables, comorbidity, vaccination status, and virus lineage on clinical outcomes, we performed logistic regression analyses and built 2 different models with hospitalization as the primary outcome (dependent variable). The first model took all the input data, regardless of vaccination status. The second model only considered patients with breakthrough infections. The independent variables considered included age, sex, comorbidity, vaccination status, and virus lineage. Seven conditions were considered for comorbidity: smoking history, asthma, diabetes,

hypertension, coronary heart disease, heart failure, and cancer. Vaccination status in model 1 was captured as unvaccinated, partially vaccinated, or fully vaccinated. Impact of treatment (remdesivir, steroids) is not incorporated into the multivariate analysis as hospitalization is the outcome variable that is commonly determined before initiation of such treatment. In terms of lineage, samples were Alpha, Delta, Omicron, and Gamma. The first model included all the 2779 samples while the second model only included the 776 fully vaccinated samples. We first built a full model by including all the variables and performed variable elimination iteratively by removing the least significant variable one at a time, based on the P value (Wald test) of its coefficient, until all the variables were significant at P value of .05. Sexand vaccination status (for model 1) were added back if they were eliminated earlier to check whether they would be significant. We further performed variance-based sensitivity analysis and calculated the first-order sensitivity index for each variable in the final model based on the Monte Carlo method [16]. We also investigated the potential interactions between virus lineage and all other variables in the final model. For model 2 with fully vaccinated patients, the number of days from the date of vaccination completion to the date of infection (vaccination-infection interval) was also included in the model.

RESULTS

Between 11 March 2021 and 22 March 2022, viral genome analysis was performed on nasopharyngeal specimens from 7117 patients positive for SARS-CoV-2. During this time, 69 distinct lineages were identified [10]. Major variants included Alpha (1360/7117, 19.1%), Gamma (134/7117, 1.9%), Delta (3722/7117, 52.3%), and Omicron (1840/7117, 25.9%), and represented 99.1% (7056/7117) of all identified isolates (Figure 1). During the initial weeks of the study, there was predominant circulation of SARS-CoV-2 Alpha variant isolates followed by a minor cocirculation with SARS-CoV-2 Gamma. However, a rapid reduction in Alpha and Gamma was observed in late July with a complete replacement by SARS-CoV-2 Delta lineage by early August. Subsequently, the introduction of Omicron variant quickly replaced the Delta variant over a 3-week period in December. By the end of the study, all circulating isolates belonged to SARS-CoV-2 Omicron variant. The remainder of study isolates (61/7117, 0.9%) included previous variants of interest Epsilon and Beta (0.8% and 0.03% respectively). No isolates were identified belonging to Kappa, Iota, Eta, or Lambda.

A total of 2779 (39.0%) samples had patient demographic, clinical, and outcome data retrieved from the COVID-19 registry. Study patients included 1144 (41.1%) men, 1828 (65.7%) white, with a median age of 39.5 years (interquartile range [IQR], 27.5–55.8; Table 1). Comorbidities were seen in the majority of patients (57.1%) with smoking history, hypertension, and asthma being the most prevalent (26.9%, 26.4%, 14.9%,

respectively). While patients within Alpha, Gamma, and Delta lineages were comparable (Supplementary Table 1), those identified with Omicron had significantly fewer pulmonary comorbidities including smoking history, and chronic obstructive pulmonary disease (ANOVA $P < .001$ and $P < .001$, respectively). Omicron-infected patients were also significantly older (42.5 years [IQR, 31.4–58.1] vs 38.6 years [IQR, 26.0–54.4]; t test $P < .001$). Paralleling rising vaccination rates within the community, the percentage of breakthrough infections increased over time (Alpha, 37/1153 [3.2%] vs Delta, 218/808 [26.9%]; $\chi^2 = 236.4$, $P \le .001$) with a substantial rise in breakthrough infections following the introduction of the Omicron variant (Delta, 218/808 [26.9%] vs Omicron 513/696 [73.7%], $\chi^2 = 327.6$, $P \le .001$). No sex differences were seen between major variant groups. Additionally, none of the patients included in this study received postexposure or outpatient interventions associated with reduced hospitalization and clinical severity including bamlanivimab, casirivimab, paxlovid, or molnupiravir.

Clinical outcomes were evaluated by lineage (Table 2). A total of 288 patients (10.3%) required hospitalization, of whom 71 (2.6%) required admission to the intensive care unit (ICU), and 28 (9.7% of admitted, 1.0% overall) died. For Alpha, Gamma, and Delta variants, the frequency of hospitalization, ICU admission, and death was comparable regardless of lineage (Supplementary Table 2) by univariate analysis. Similarly, none of these 3 variants showed differences in need for oxygen or ventilatory support. Conversely, patients with Omicron were significantly less likely to be admitted to the hospital (41/696 vs 247/2083; $\chi^2 = 20.2$, $P < .001$). Similarly, patients infected with Omicron were significantly less likely to require oxygen or be admitted to the ICU (24/696 vs 150/2083; $\chi^2 = 12.8$, $P < .001$ and 7/696 vs 64/2083; $\chi^2 = 9.2$, $P = .002$, respectively). Also, less medical therapy was utilized in Omicron-infected individuals (24/696 vs 188/2083; $\chi^2 = 23.3$, $P < .001$) whereas antiviral and steroid therapy was employed equally among Alpha, Gamma, and Delta patients ($\chi^2 = 0.7$, $P = .72$). Death was infrequent in all groups and no differences in mortality were identified between variant types ($\chi^2 = 3.8$, $P = .28$). Patient laboratory values were compared among SARS-CoV-2 groups (Figure 2). White blood cell (WBC) and absolute lymphocyte count (ALC) was significantly elevated in Omicron compared to other variants (ANOVA $P = .01$ and $P = .006$, respectively) whereas no differences in WBC nor ALC were detected among Alpha, Gamma, and Delta (ANOVA $P = .36$ and $P = .28$, respectively). Additionally, C-reactive protein (CRP) was diminished in patients infected with either Delta or Omicron strains. While ferritin levels were significantly diminished in Omicron patients, there were substantially fewer tests performed on Omicron-infected patients, likely causing an artificial skewing of the analysis.

Breakthrough infections were identified in 776/2779 (27.9%) patients (Table 3). Of these, 512 (65.4%) received Pfizer vaccination, 230 (29.4%) received Moderna, and 27 (5.2%) received
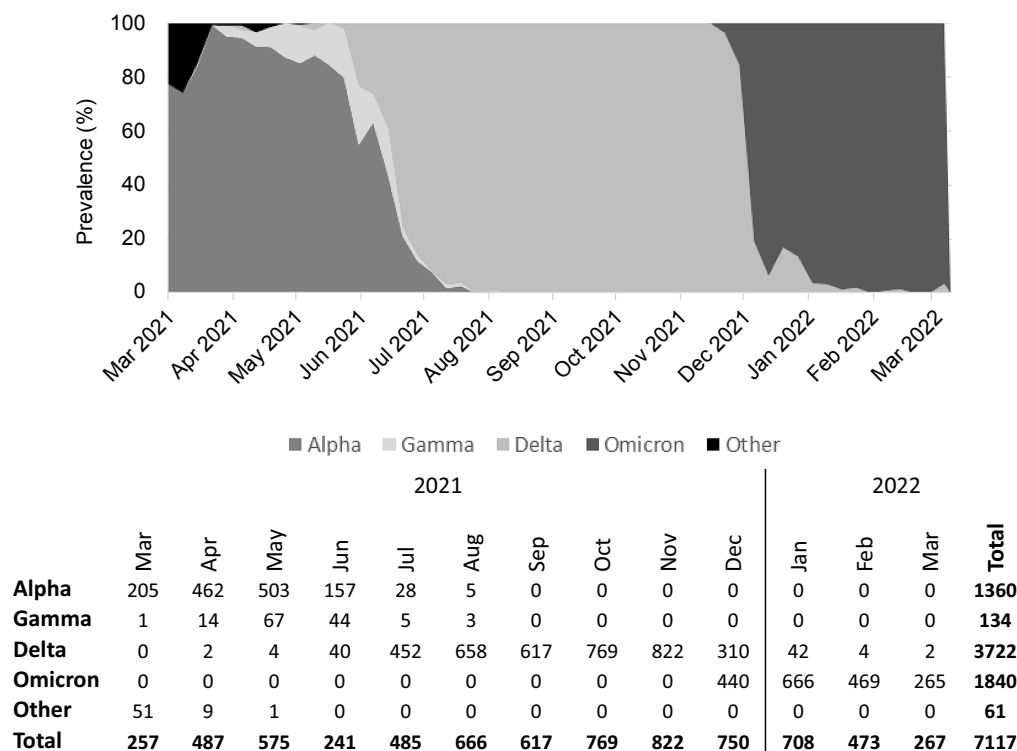
	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Total
Alpha	205	462	503	157	28	5	0	0	0	0	0	0	0	**1360**
Gamma	1	14	67	44	5	3	0	0	0	0	0	0	0	**134**
Delta	0	2	4	40	452	658	617	769	822	310	42	4	2	**3722**
Omicron	0	0	0	0	0	0	0	0	0	440	666	469	265	**1840**
Other	51	9	1	0	0	0	0	0	0	0	0	0	0	**61**
Total	**257**	**487**	**575**	**241**	**485**	**666**	**617**	**769**	**822**	**750**	**708**	**473**	**267**	**7117**

Figure 1. Weekly prevalence of major severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) over the study period (11 March 2021 through 22 March 2022). Isolates of screened clinical samples were determined and categorized into variant groups. Isolates that did not categorize into the 3 major variant groups (eg, epsilon, lambda, etc.) were designated as other. Weekly prevalence for each variant is displayed and raw totals are quantified.

Johnson and Johnson. The remainder (7, 0.9%) did not have vaccine manufacturer recorded. Of breakthrough infections with the Omicron variant, 221/513 (43.1%) had received a booster immunization ≥14 days prior to infection (median interval booster to infection 62.5 days; IQR, 44.0–79.0). In patients with breakthrough infections, 73 (9.4%) required hospitalization, 18 (2.3%) required ICU care, and 13 (1.7%) died. Patients with breakthrough infections requiring hospitalization commonly (67/73, 91.8%) had comorbid conditions. Breakthrough hospitalizations were significantly more common in patients infected with Delta and Omicron compared to Alpha and Gamma variants (25/808 and 32/696 vs 37/1153 and 2/122, respectively; χ^2 = 16.7, $P < .001$). Additionally, increased oxygen use was more common in patients in breakthrough hospitalizations with Delta and Omicron variants ($\chi^2 = 11.5$, $P < .001$). However, no difference in breakthrough ICU admissions, ventilator use, nor deaths were recognized between groups. Among Omicron subvariants (Supplementary Tables 3 and 4), BA.1 and BA.2 subvariants has comparable outcomes including hospitalization (39/626 vs 2/70; $\chi^2 = 1.2$, $P = .27$), oxygen use (22/626 vs 2/70; $\chi^2 = 0.7$, $P = .78$), ICU admission (7/626 vs 0/70; $\chi^2 = 0.8$, $P = .38$), and death (3/626 vs 0/70; $\chi^2 = 0.4$, $P = .57$). Similar findings were seen in analysis of breakthrough infections in Omicron subvariants (Supplementary Table 5).

When all variables were evaluated together on multivariate logistic regression, for model 1, age, and having coronary artery disease increased the risk of hospitalization (Table 4 and Supplementary Table 6). Patients infected with Omicron and fully vaccinated were significantly less likely to be hospitalized ($P < .05$). Sensitivity analysis was performed based on Monte Carlo simulation [16]. The 4 variables in the final model (age, lineage, coronary artery disease status, and vaccination status) were considered. To generate realistic virus lineage and vaccination status, first, we performed random sampling with replacement from the true dataset and retained the date of diagnosis. The virus lineage and the vaccination status were sampled based on their respective distributions of that month from the whole dataset consisting of 7117 patients. Age was obtained by random sampling with replacement. Coronary artery disease status was sampled based on the proportion of patients with coronary artery disease. We understand that not all correlations among the variables were considered in our simulation because their relationships were hard to model. Based on our sampling strategy, we obtained 10 000 patients. Age is the most important variable explaining 64.4% of the observed variance (ie, the first-order sensitivity index), followed by lineage (18.1%), coronary artery disease (10.3%), and vaccination status (7.0%). We further checked potential interactions between virus lineage and other significant

Table 1. Demographic Data of SARS-CoV-2–Infected Patients by Variant

Characteristic	Total	Alpha B.1.1.7	Gamma P.1, P.1.1, P.1.2	Delta B.1.617.2, AY*	Omicron B.1.1.529, BA*	P Value
n	2779	1153 (48.8)	122 (5.2)	808 (34.2)	696 (25.0)	
Male	1144 (41.1)	485 (42.0)	44 (36.0)	339 (41.9)	276 (39.6)	.46
Median age, y (IQR)	39.5 (27.5–55.8)	38.5 (25.9–54.2)	35.9 (23.1–53.1)	39.0 (27.1–55.4)	42.5 (31.4–58.1)	<.001
Children, <18 y	213 (7.7)	103 (8.9)	12 (9.83)	83 (10.2)	15 (2.2)	<.001
Full vaccination prior to infection	776 (27.9)	37 (3.2)	8 (6.55)	218 (26.9)	513 (73.7)	<.001
Race/ethnicity						
White	1828 (65.7)	657 (56.9)	44 (36.0)	581 (71.9)	546 (78.4)	<.001
Black	711 (25.5)	388 (33.6)	65 (53.2)	159 (19.6)	99 (14.2)	<.001
Other	240 (8.6)	108 (9.4)	13 (10.6)	68 (8.4)	51 (7.3)	.4
Hispanic	139 (5.0)	68 (5.9)	9 (7.37)	38 (4.7)	24 (3.4)	.07
Any comorbidity	1589 (57.1)	697 (60.4)	66 (54.0)	476 (58.9)	350 (50.2)	<.001
Any pulmonary comorbidity	1014 (36.4)	502 (43.5)	48 (39.3)	329 (40.7)	135 (19.3)	<.001
Smoking	749 (26.9)	389 (33.7)	39 (31.9)	240 (29.7)	81 (11.6)	<.001
COPD/emphysema	126 (4.5)	57 (4.9)	6 (4.91)	36 (4.5)	27 (3.9)	<.001
Asthma	416 (14.9)	183 (15.8)	14 (11.4)	134 (16.5)	85 (12.2)	.05
Any cardiac comorbidity	766 (27.5)	320 (27.7)	27 (22.1)	220 (27.2)	199 (28.5)	.52
Hypertension	734 (26.4)	312 (27.0)	24 (19.6)	213 (26.3)	185 (26.5)	.04
Coronary artery disease	149 (5.36)	43 (3.7)	8 (6.55)	49 (6.1)	49 (7.04)	.01
Heart failure	109 (3.92)	46 (4.0)	9 (7.37)	34 (4.2)	20 (2.9)	.11
Any immune comorbidity	456 (16.4)	182 (15.7)	17 (13.9)	157 (19.4)	100 (14.3)	.04
Cancer	235 (8.5)	85 (7.4)	6 (4.91)	74 (9.2)	70 (10.0)	.09
Immune suppressive treatment	10 (0.4)	4 (0.3)	0 (0)	1 (0.1)	5 (0.7)	.24
History of transplant	31 (1.1)	17 (1.5)	3 (2.45)	6 (0.7)	5 (0.7)	.15
Other immunosuppressive disease	185 (6.7)	78 (6.8)	10 (8.19)	53 (6.6)	44 (6.3)	.89
Diabetes	307 (11.0)	133 (11.5)	14 (11.4)	79 (9.8)	81 (11.6)	.60

Data are No. (%) except where indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

variables in model 1. Omicron and coronary artery disease have strong interactions, which increase the risk of hospitalization (Supplementary Table 7). With the interaction term, the main effect of coronary artery disease is not significant anymore. The result may imply that although patients with Omicron are less likely to be hospitalized, patients with coronary artery disease have greatest risk of hospitalization when infected with Omicron.

For model 2 (breakthrough infections), the only factors that significantly increased the risk of hospitalization were age, having cancer, and heart failure. Following vaccination, neither Omicron nor Delta variants were associated with decreased risk of hospitalization. Increased vaccination interval prior to infection was associated with decreased hospitalization rate in patients with breakthrough infections (Supplementary Table 6). Sensitivity analysis shows that age has the largest first-order sensitivity index (62.4%), followed by cancer (18.4%) and heart failure (18.3%). The gap between second dose of vaccine and test date has least first-order sensitivity index (0.7%).

DISCUSSION

Since its introduction, numerous variants of SARS-CoV-2 have arisen [17, 18]. To date, variant emergence has predominantly been a stepwise, sequential replacement of preexisting strains by those with improved transmissibility [19, 20]. Our previous work demonstrated that replacement of existing variants by those having transmission advantages is often rapid [5]. This study details the circulation of 4 main variants across much of 2021 and early 2022. During this period, all were initially classified as VOC during their initial appearance and, with the exception of Omicron, currently no longer circulate.
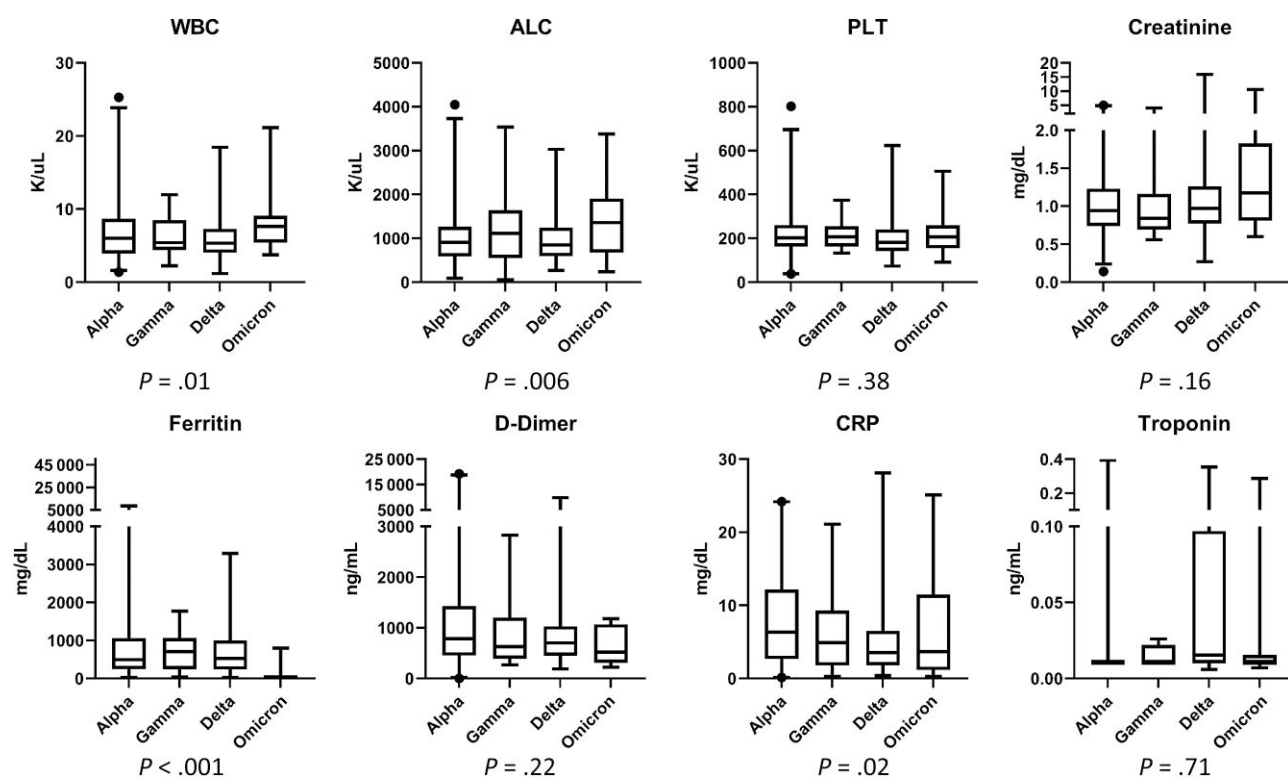
The acute upsurge of Omicron was different from previous transitions. The Omicron variant spread at a pace far exceeding previous viral strains with the United States, recording 1 million cases of COVID-19 in a single day [1]. While the Omicron genome has many unique changes separating it from previous lineages, several spike glycoprotein mutations are shared with previous variants including T478K, K417N, N501Y, N655Y, and P681H, which are associated with increased transmissibility and higher viral binding affinity for human angiotensin-converting enzyme 2 (ACE2) [21, 22]. Additionally, the significant alterations of the spike glycoprotein may allow this variant to partially escape natural or vaccine-induced immunity [23, 24]. Studies are finding that Omicron receptor binding domain (RBD) mutations can significantly change the binding pattern of known antibodies. The

Table 2. Comparison of Clinical Outcomes Among Major SARS-CoV-2 Variants

Outcome	Total	Alpha B.1.1.7	Gamma P.1, P.1.1, P.1.2	Delta B.1.617.2, AY.*	Omicron B.1.1.529, BA*	P Value
Total	2779	1153	122	808	696	
Hospitalized	288 (10.3)	129 (11.1)	15 (12.2)	103 (12.7)	41 (5.9)	<.001
ICU admission	71 (2.6)	31 (2.7)	4 (3.3)	29 (3.6)	7 (1.0)	.01
Oxygen	174 (6.3)	76 (6.6)	11 (9.0)	63 (7.8)	24 (3.4)	.002
High-flow oxygen	50 (1.8)	24 (2.1)	2 (1.6)	20 (2.5)	4 (0.6)	.004
Noninvasive ventilation	38 (1.4)	21 (1.8)	2 (1.6)	12 (1.5)	3 (0.4)	.09
Mechanical ventilation	31 (1.1)	15 (1.3)	0 (0)	11 (1.4)	5 (0.7)	.37
Steroids	192 (6.9)	100 (8.7)	10 (8.2)	75 (9.3)	22 (3.2)	<.001
Remdesivir	174 (6.3)	75 (6.5)	7 (5.7)	68 (8.4)	7 (1.0)	<.001
Any O$_2$	159 (5.7)	76 (6.6)	11 (9.0)	63 (7.8)	24 (3.4)	.002
Any ventilation	45 (1.6)	25 (2.2)	2 (1.6)	17 (2.1)	6 (0.9)	.19
Any medical Treatment	210 (7.6)	100 (8.7)	10 (8.2)	78 (9.7)	24 (3.4)	<.001
Death	28 (1.0)	15 (1.3)	2 (1.6)	8 (1.0)	3 (0.4)	.28

Data are No. (%).
Abbreviations: ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 2. Comparison of laboratory abnormalities among different SARS-CoV-2 variants. Box and whiskers plot displaying first through 99th percentile results among patients infected with 1 of the 4 major SARS-CoV-2 variants. Horizontal lines represent mean value. P values for ANOVA performed at a significance level of .05 is displayed. Abbreviations: CRP, C-reactive protein; PLT, platlets; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cells; ALC, absolute lymphocyte count.

combination of E484A, K417N, and Y505H is thought to make Omicron substantially disruptive to known anti–SARS-CoV-2 antibodies [25]. However, Omicron contains unique spike mutations not observed in previous strains (N764K, D796Y, N856K, Q954H, N969K, and L981F). Recent reports demonstrate that

Omicron has altered spike cleavage efficiency and reduction in transmembrane serine protease 2 (TMPRSS2)-mediated entry, resulting in weaker cell fusion and syncytial formation compared to Alpha and Delta variants [25, 26]. Lastly, Omicron isolates are less effective in inhibiting host interferon response from

Table 3. Comparison of Clinical Outcomes in Breakthrough Infections Among Major SARS-CoV-2 Variants

Outcome	Total	Alpha B.1.1.7	Gamma P.1, P.1.1, P.1.2	Delta B.1.1.519, AY.*	Omicron B.1.1.529, BA*	P Value
Total	2779	1153	122	808	696	
Fully vaccinated	776 (27.9)	37 (3.2)	8 (6.6)	218 (26.9)	513 (73.7)	<.001
Breakthrough hospitalization	73 (2.62)	14 (1.2)	2 (1.6)	25 (3.1)	32 (4.6)	<.001
Breakthrough ICU admission	18 (0.64)	7 (0.6)	0 (0)	8 (1.0)	3 (0.4)	.42
Oxygen	43 (1.54)	8 (0.7)	1 (0.8)	17 (2.1)	17 (2.4)	.01
High-flow oxygen	13 (0.46)	5 (0.4)	0 (0)	6 (0.7)	2 (0.3)	.49
Noninvasive ventilation	12 (0.43)	5 (0.4)	0 (0)	5 (0.6)	2 (0.3)	.68
Mechanical ventilation	11 (0.39)	5 (0.4)	0 (0)	5 (0.6)	1 (0.1)	.45
Any O_2	35 (1.25)	8 (0.7)	1 (0.8)	17 (2.1)	17 (3.3)	.01
Any ventilation	13 (0.46)	5 (0.4)	0 (0)	7 (0.9)	2 (0.4)	.32
Breakthrough death	13 (0.5)	7 (0.6)	1 (0.8)	4 (0.5)	1 (0.2)	.50

Data are No. (%).

Abbreviations: ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4. Significant Variables of Logistic Regression Results Using Hospitalization as the Dependent Variable

Model 1 Variables	Coefficient	P Value	Model 2 Variables	Coefficient	P Value
Intercept	−4.28	<.001	Intercept	−4.39	<.001
Age	0.05	<.001	Age	.05	<.001
Coronary artery disease	0.70	.001	Heart failure	1.17	.003
Omicron	−1.08	<.001	Cancer	1.10	.006
Vaccinated status	−0.36	.045	Vaccination to infection interval	−0.006	<.001
Log Likelihood Ratio (LLR) P value		9.67e−53	LLR P value		4.38e−23

mutation of genes associated with inhibition of host interferon response [27]. Reduced clinical severity likely results from multiple changes across the genome [28, 29].

We find those infected with Omicron are significantly less likely to become hospitalized. Similar reports of diminished severity associated with Omicron have also been published [26–28]. We find no difference in disease severity among the 3 previous variants (Alpha, Gamma, Delta) in univariate or multivariate analysis despite rising vaccination rates during 2021 [29]. However, the risk of hospitalization from breakthrough infections is significantly less in those with a higher vaccination to infection interval. This demonstrates the benefits of vaccination against SARS-CoV-2 variants. Additionally, with the exception of CRP, no significant variation in laboratory values was observed among Alpha, Gamma, and Delta groups. Conversely, Omicron-infected patients had less-severe changes in WBC, ALC, and perhaps ferritin. The reasons behind less-severe disease associated with Omicron are beginning to emerge. Studies now find lower viral loads in rodent lungs suggesting that Omicron does not replicate readily in the lower respiratory tract compared to the upper [30, 31]. Similar findings have been recognized in human lung organoids [32]. Further study of the mechanisms for diminished severity from Omicron infection are needed.

Our study contains several limitations. Our sampling paralleled the community outbreak where the majority of patients neither required hospitalization nor ICU care. Additionally, mortality was infrequent for all SARS-CoV-2 lineages. This adversely affects the power to discern outcomes between variants for low frequency/high severity events (ICU care, ventilation, mortality). Case-control studies comparing hospitalized versus nonhospitalized infections would better delineate the impact of virus lineage on severe outcomes. Also, while we show low hospitalization rates associated with Omicron, substantial numbers of hospitalizations continue to occur [1]. Further multicenter investigations are needed to detail both acute and postinfectious impacts of Omicron. It is possible that by excluding samples with low viral load (Ct value >30), applied to ensure accuracy of variant typing, we may underselect patients with less-severe disease. However, this exclusion was applied throughout the study period. Our data were influenced by sporadic requests by ODH and patient providers to sequence infected patients with history of full vaccination and therefore contains sampling bias. However, such requests were infrequent and spread across the study period. Additionally, our study did not capture those patients with previous history of SARS-CoV-2 disease when accounting for breakthrough infections. However, we hypothesize that the percent of individuals

with prior infection would increase over time parallel to vaccination status. Several studies have reported increased breakthrough infection with both Delta and Omicron lineages following resolution of natural disease [33]. Lastly, the most significant limitation of this study centers on our analysis over a prolonged study duration (March 2021 through March 2022). This time period saw substantial changes in many variables that impact clinical management including evolution of guidelines used for care [34], rise in prevalence of antibodies from both vaccination and infection (especially beginning December 2022 in association with the emergence of Omicron) [35–37], development of monoclonal treatment and postexposure prophylaxis [38, 39], as well as increases in testing accessibility allowing for more asymptomatic testing. These advancements in disease recognition and treatment in addition to the influence of natural or vaccine-induced immunity makes determination of the degree to which a specific variant alters clinical outcomes difficult. However, our study and others find a mitigation of disease severity in patients infected with Omicron, a difference that was not present among the prior 3 variants.

In conclusion, our study demonstrates dynamic shifts in SARS-CoV-2 variants during 2021 with Omicron supplanting Delta within weeks of introduction. Previous variants (Alpha, Gamma, Delta) were similar in severity and all were associated with higher hospitalization and oxygen use compared to Omicron. No differences in Omicron subvariant severity (BA1 vs BA2) were detected. SARS-CoV-2 variant assignment remains an important factor in understanding the epidemiology of this pandemic.

Supplementary Data

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

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