

Impact of Severe Acute Respiratory Syndrome Coronavirus 2 Variants on Inpatient Clinical Outcome

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Background. Prior observation has shown differences in COVID-19 hospitalization risk between SARS-CoV-2 variants, but limited information describes hospitalization outcomes.

Methods. Inpatients with COVID-19 at 5 hospitals in the eastern United States were included if they had hypoxia, tachypnea, tachycardia, or fever, and SARS-CoV-2 variant data, determined from whole-genome sequencing or local surveillance inference. Analyses were stratified by history of SARS-CoV-2 vaccination or infection. The average effect of SARS-CoV-2 variant on 28-day risk of severe disease, defined by advanced respiratory support needs, or death was evaluated using models weighted on propensity scores derived from baseline clinical features.

Results. Severe disease or death within 28 days occurred for 977 (29%) of 3369 unvaccinated patients and 269 (22%) of 1230 patients with history of vaccination or prior SARS-CoV-2 infection. Among unvaccinated patients, the relative risk of severe disease or death for Delta variant compared with ancestral lineages was 1.30 (95% confidence interval [CI]: 1.11–1.49). Compared with Delta, the risk for Omicron patients was .72 (95% CI: .59–.88) and compared with ancestral lineages was .94 (.78–1.1). Among Omicron and Delta infections, patients with history of vaccination or prior SARS-CoV-2 infection had half the risk of severe disease or death (adjusted hazard ratio: .40; 95% CI: .30–.54), but no significant outcome difference by variant.

Conclusions. Although risk of severe disease or death for unvaccinated inpatients with Omicron was lower than with Delta, it was similar to ancestral lineages. Severe outcomes were less common in vaccinated inpatients, with no difference between Delta and Omicron infections.

Keywords. SARS-CoV-2; COVID-19; Delta variant; Omicron variant; inpatient outcomes.

In December 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineage B.1.1.7, now known as the Alpha variant, was identified as the first variant of concern [1]. Emerging SARS-CoV-2 variants continue to cause waves of infections and hospitalizations. Differences in the transmissibility and clinical severity of SARS-CoV-2 variants have the potential to greatly impact public health as large segments of the population simultaneously become infected and require hospitalization. By mid-January 2022, daily coronavirus disease 2019

(COVID-19) hospitalizations in the United States reached a new peak of 150 000 [2].

Omicron and Delta variants are more transmissible than earlier circulating SARS-CoV-2 lineages [3,4]. Compared with prior lineages, Alpha [5,6] and Delta [7–11] variants are associated with greater hospitalization risk and, for Delta, worse inpatient outcomes, but these findings have been limited by sample size and confounders [7,8,12]. Recent studies report decreased risk of hospitalization, severe illness, and death for Omicron compared with Delta variants [11,13–17], but limited data are available to describe the clinical trajectory of patients once hospitalized in context with previously circulating ancestral lineages [14,18].

Changing demographics, comorbidities, vaccination status, and therapeutics confound interpretation of the impact of SARS-CoV-2 lineage on COVID-19 severity. There remains a need to understand the clinical demands and outcomes of patients hospitalized with current variants. Therefore, we used a

Received 11 July 2022; editorial decision 23 November 2022; published online 19 December 2022

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Clinical Infectious Diseases® 2023;76(9):1539–49

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<https://doi.org/10.1093/cid/ciac957>

clinical registry to observe the impact of SARS-CoV-2 variants on clinical trajectory and outcome.

METHODS

Ethical Considerations and Data Availability

Research was conducted under Johns Hopkins Institutional Review Board protocol IRB00300364 with a waiver of consent. SARS-CoV-2 genomes were uploaded to the Global Initiative on Sharing All Influenza Data (GISAID) [19].

Setting and Data Source

The data source used for this study is JH-CROWN: The COVID Precision Medicine Analytics Platform Registry, a registry of electronic medical record (EMR) data from Johns Hopkins Medicine (JHM), which includes 5 acute-care hospitals in Maryland and the District of Columbia [20]. The EMR includes SARS-CoV-2 test results and vaccination records from the Chesapeake Regional Information System for our Patients (CRISP) [21] and other registries. Baseline comorbidities, including those to determine organ transplantation or immunocompromised status and Elixhauser score, were determined from International Classification of Diseases, Tenth Revision (ICD-10), codes [22,23]; conditions recorded in prehospitalization encounters or with start dates less than 48 hours after hospitalization were considered.

Cohort Composition and Outcome Determination

Cohort criteria aimed to include patients requiring inpatient care for COVID-19 and to exclude inpatients with insufficiently severe SARS-CoV-2 infections to independently warrant hospitalization. Inpatients with SARS-CoV-2 infection were identified based on positive JHM laboratory test results, record of positive SARS-CoV-2 test results from outside JHM recorded via CRISP, and identification by local infection control. Hospitalizations more than 14 days after diagnosis, more than 24 hours prior to diagnosis, and subsequent hospitalizations after an index hospitalization were excluded. Symptomatic COVID-19 requiring inpatient care was defined by a pulse oximetry recording of less than 95%, temperature of 38°C or greater, heart rate greater than 110 beats/minute, respiratory rate greater than 24 breaths/minutes, or use of supplemental oxygen within the first 24 hours of admission. Inpatients transferred from outside hospitals or admitted to surgical or psychiatric services were excluded.

Patients who received a dose of Ad26.COV2.S (Johnson & Johnson [Janssen]) more than 4 weeks or a second dose of mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) more than 2 weeks prior to hospitalization were classified as vaccinated; additional vaccine doses were not considered due to the small sample size. Prior SARS-CoV-2 infection was defined by a positive SARS-CoV-2 test more than 60 days or ICD-10 code more than 30 days prior to hospitalization indicating a

positive SARS-CoV-2 test or COVID-19. Unvaccinated patients with a history of prior SARS-CoV-2 infection were grouped with vaccinated patients for stratified analyses based on reports showing similar protective effects [24].

Severe COVID-19 was defined as respiratory support with high-flow nasal cannula, noninvasive positive-pressure ventilation, or mechanical ventilation [25]. The primary outcome was severe disease or death within 28 days of hospital presentation, chosen because severe COVID-19 onset occurs within this time frame for nearly all patients who develop severe disease [20]. Patients who were discharged alive and without record of death were assumed to survive through day 28 without severe disease.

SARS-CoV-2 Whole-Genome Sequencing

Whole-genome sequencing (WGS) surveillance was performed on remnant positive SARS-CoV-2 clinical samples, chosen irrespective of hospitalization status with priority for samples with cycle threshold values less than 20. RNA was extracted using Chemagic 360 (Perkin Elmer). Whole-genome sequencing was performed on the Oxford Nanopore GridION using the V3 primer ARTIC SARS-CoV-2 sequencing protocol or NEBNext ARTIC SARS-CoV-2 Companion Kit (VarSkip Short SARS-CoV-2 #E7660-L). Each WGS run pooled 94 samples plus a negative and positive control [26]. Alignment and variant calling were performed with the artic-ncov2019 medaka protocol [27]. Questionable mutations were visually inspected. Clades were determined using Nextclade [28] and lineages with Pangolin COVID-19 Lineage Assigner [29]. Sequencing results with insufficient depth and coverage for clade and lineage assignment were excluded.

Variant Inference

The rapid spread of novel variants after local introduction defines periods when a single viral clade dominates community transmission. Using our health system's WGS surveillance, we determined the rolling 2-week distribution of viral lineages classified as follows: Alpha, Delta, Omicron, ancestral lineages (emerging before Alpha), and other [30]. When the rolling 2-week average identified 95% or greater of WGS results as a single variant, patients without WGS results who were diagnosed on that day were inferred to have dominant lineage infections.

Statistical Methods

Propensity score weighting was used to infer the causal effect of variant on outcomes. This approach infers the outcomes that might be observed if the entire cohort were infected with 1 variant (eg, Delta) as compared with another (eg, Omicron), or the average treatment effect of a particular variant. Only pre-infection baseline clinical features were considered as covariates in regression and propensity models to avoid adjustment for intermediate variables in the causal pathway from the variant to outcomes that would bias estimates of the variants'

effects. Admission clinical characteristics known to be severe COVID-19 risk factors, including vital signs, ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen ($\text{SpO}_2:\text{FiO}_2$), basic laboratory values, and inflammatory markers, were reported by variant [23].

Propensity for a particular variant was assessed using gradient boosted logistic regression using the R *twang* package [31]. Weighted regression models were fit using the *survey* package [32]. Propensity models included age, sex, body mass index (BMI), Elixhauser score [33], and history of organ transplantation or immunocompromised status. Age, sex, BMI, and a composite comorbidity score were chosen for model inclusion due to their known association with illness severity [20]. Organ transplantation or immunocompromised status was chosen a priori for model inclusion as it is not included in the Elixhauser score [33] as well as observations of poor outcomes and variable response to vaccination in this population [34,35].

Log binomial regression assessed the average treatment effect on the risk difference and relative risk scales. Models estimated remdesivir use, steroid use, and hypoxia at presentation, reported by $\text{SpO}_2:\text{FiO}_2$. The probability of surviving and remaining free of severe disease was assessed using the Kaplan–Meier estimator. Convergence, positivity, and balance were assessed in propensity score analyses.

Sensitivity analysis restricted to patients with confirmed variants was performed using age, sex, and Elixhauser score to determine propensity scores. The association of vaccination or prior SARS-CoV-2 infection with severe disease was limited to patients with Omicron or Delta infections and assessed using

a Cox proportional hazard model adjusted for baseline clinical features, variant, and the interaction of variant and history of vaccination or prior SARS-CoV-2 infection.

RESULTS

Patient Population

From 1 September 2020 to 7 May 2022, 7586 adults were hospitalized within 2 weeks of COVID-19 diagnosis; 271 patients transferred from other hospitals and 236 admitted to surgical or psychiatric services were excluded (Supplementary Figure 1). Among 7079 remaining patients, 6095 (86%) with vital-sign abnormalities of tachycardia ($n = 2249$, 37%), tachypnea ($n = 3028$, 50%), fever ($n = 2126$, 35%), hypoxia ($n = 4815$, 79%), or supplemental oxygen requirement ($n = 3978$, 65%) were considered for inclusion.

Whole-Genome Sequencing Results and Variant Inference

For 386 of 613 (63%) study days, a single lineage accounted for 95% or more of the rolling 2-week average (Figure 1 and Supplementary Figure 2), including ancestral lineages (139 days), Delta (125 days), and Omicron (122 days). Among 6260 patients meeting inclusion criteria, WGS results were available for 1311 (22%) inpatients; variant was inferred for an additional 3288 (54%) inpatients. Confirmed or inferred variant data were available for 3369 of 4616 (73%) patients without a prior history of SARS-CoV-2 vaccination or infection and 1147 of 1369 (84%) vaccinated or previously infected patients. Inferred variant matched WGS data for 789 of 813 (97%) patients with results

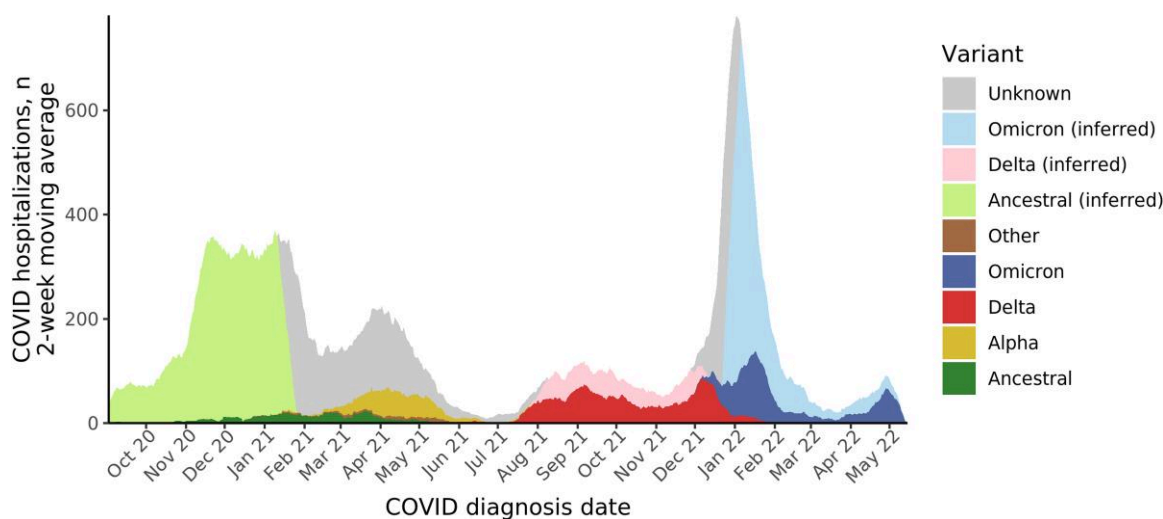


Figure 1. SARS-CoV-2 variants among hospitalized patients: 2-week moving average by date of COVID-19 diagnosis and variant. COVID-19–related hospitalizations with available confirmed SARS-CoV-2 variant results determined by WGS are shaded in darker colors. WGS surveillance of positive SARS-CoV-2 samples within Johns Hopkins Medicine was used to determine a community prevalence of SARS-CoV-2 variants (Supplementary Figure 2). During time periods when the 2-week moving distribution of variants reached 95%, variant was inferred for hospitalized patients who did not have WGS results. During periods when no single variant reached 95%, no inference of variant for patient without WGS was attempted. Abbreviations: COVID-19/COVID, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WGS, whole-genome sequencing.

Table 1. Demographics and Clinical Characteristics by Variant Among 3369 Unvaccinated Patients Hospitalized With COVID-19 Without a Prior History of SARS-CoV-2 Infection

Characteristics	All (N = 3369)	Ancestral (n = 2039)	Alpha (n = 201)	Delta (n = 546)	Omicron (n = 549)	Other (n = 34)
Age, years	62.0 (49.0–75.0)	65.0 (53.0–78.0)	59.0 (47.0–69.0)	55.0 (41.0–66.0)	61.0 (45.0–73.0)	61.0 (50.2–66.2)
Sex						
Female	1682 (49.9%)	1009 (49.5%)	104 (51.7%)	272 (49.8%)	279 (50.8%)	18 (52.9%)
Male	1687 (50.1%)	1030 (50.5%)	97 (48.3%)	274 (50.2%)	270 (49.2%)	16 (47.1%)
BMI, kg/m ²	28.5 (24.3–34.1)	28.5 (24.5–33.9)	29.8 (25.7–35.6)	29.1 (24.6–35.6)	26.8 (23.0–32.7)	31.8 (26.4–37.4)
Race/ethnicity						
Asian	155 (4.6%)	123 (6.0%)	6 (3.0%)	17 (3.1%)	8 (1.5%)	1 (2.9%)
Black	1253 (37.2%)	637 (31.2%)	128 (63.7%)	229 (41.9%)	245 (44.6%)	14 (41.2%)
Hispanic	374 (11.1%)	276 (13.5%)	7 (3.5%)	45 (8.2%)	45 (8.2%)	1 (2.9%)
Non-Hispanic White	1430 (42.4%)	908 (44.5%)	52 (25.9%)	231 (42.3%)	224 (40.8%)	15 (44.1%)
Other or unknown	157 (4.7%)	95 (4.7%)	8 (4.0%)	24 (4.4%)	27 (4.9%)	3 (8.8%)
Nursing home admission	217 (6.4%)	189 (9.3%)	2 (1.0%)	7 (1.3%)	19 (3.5%)	0 (0.0%)
Elixhauser score	5.0 (3.0–7.0)	5.0 (3.0–7.0)	5.0 (3.0–8.0)	4.0 (2.0–6.0)	5.0 (3.0–8.0)	4.0 (3.0–8.5)
Immunocompromised/transplant	287 (8.5%)	159 (7.8%)	34 (16.9%)	46 (8.4%)	46 (8.4%)	2 (5.9%)
Diabetes	1348 (40.0%)	843 (41.3%)	87 (43.3%)	182 (33.3%)	223 (40.6%)	13 (38.2%)
Cardiovascular disease	1611 (47.8%)	1015 (49.8%)	98 (48.8%)	199 (36.4%)	286 (52.1%)	13 (38.2%)
Chronic pulmonary disease	1104 (32.8%)	678 (33.3%)	74 (36.8%)	155 (28.4%)	185 (33.7%)	12 (35.3%)
Malignancy	947 (28.2%)	617 (30.3%)	63 (31.3%)	112 (20.5%)	143 (26.1%)	12 (35.3%)
Pregnant	25 (0.7%)	12 (0.6%)	2 (1.0%)	7 (1.3%)	4 (0.7%)	0 (0.0%)
SpO ₂ :FiO ₂ ratio	435.0 (275.0–459.0)	430.0 (277.0–454.0)	435.0 (287.0–459.0)	430.0 (258.0–454.0)	444.0 (293.0–464.0)	442.0 (336.0–459.0)
Pulse	99.0 (86.0–113.0)	97.0 (84.0–111.0)	102.0 (90.0–113.0)	104.0 (88.0–116.0)	101.0 (86.0–115.0)	93.5 (85.0–107.2)
Respiratory rate, breaths/minute	20.0 (18.0–27.0)	21.0 (18.0–27.0)	20.0 (18.0–26.0)	21.0 (18.0–27.0)	20.0 (18.0–26.0)	21.0 (18.0–27.5)
Temperature, °C	37.2 (36.8–37.9)	37.2 (36.8–38.0)	37.3 (36.8–38.2)	37.1 (36.7–37.9)	36.9 (36.6–37.5)	37.5 (37.0–38.2)
White blood cell count	6.7 (5.0–9.2)	6.6 (5.0–9.1)	6.3 (4.8–8.3)	6.2 (4.7–8.6)	7.8 (5.5–10.7)	6.0 (3.9–6.8)
GFR, mL/minute per 1.73 m ²	70.0 (45.0–94.0)	67.0 (44.0–91.0)	64.0 (37.0–92.0)	82.0 (54.0–99.0)	69.0 (46.8–99.0)	83.0 (63.5–90.0)
CRP level, mg/L	6.2 (2.6–11.6)	6.2 (2.5–11.4)	5.8 (3.0–11.5)	7.4 (3.5–12.6)	5.4 (1.8–11.4)	3.5 (1.3–10.1)
IL-6 level, pg/mL	28.5 (11.4–62.8)	27.0 (11.3–59.0)	17.8 (10.7–53.8)	31.1 (11.3–93.0)	77.2 (30.5–98.4)	36.5 (26.4–11 026.9)

Data are presented as median (IQR) or no. (%). Vital signs and laboratory results are the first observation within 36 hours of hospital admission. Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GFR, glomerular filtration rate; IL-6, interleukin 6; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂:FiO₂, ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen.

Table 2. Demographics and Clinical Characteristics by Variant Among 1230 Patients Hospitalized With COVID-19 With a History of SARS-CoV-2 Infection or Vaccination

Characteristics	All (N = 1230)	Ancestral (n = 26)	Alpha (n = 15)	Delta (n = 295)	Omicron (n = 891)	Other (n = 3)
Age, years	69.0 (57.0–79.8)	57.0 (50.8–69.8)	59.0 (54.0–70.5)	68.0 (59.0–80.0)	69.0 (57.0–80.0)	74.0 (65.5–82.5)
Sex						
Female	564 (45.9%)	11 (42.3%)	8 (53.3%)	143 (48.5%)	400 (44.9%)	2 (66.7%)
Male	666 (54.1%)	15 (57.7%)	7 (46.7%)	152 (51.5%)	491 (55.1%)	1 (33.3%)
BMI, kg/m ²	27.1 (23.1–32.6)	28.4 (25.3–33.5)	26.5 (21.3–34.6)	28.4 (24.4–33.8)	26.7 (22.8–32.0)	32.0 (29.2–33.5)
Race/ethnicity						
Asian	54 (4.4%)	3 (11.5%)	1 (6.7%)	15 (5.1%)	35 (3.9%)	0 (0.0%)
Black	396 (32.2%)	8 (30.8%)	9 (60.0%)	88 (29.8%)	290 (32.5%)	1 (33.3%)
Hispanic	74 (6.0%)	6 (23.1%)	1 (6.7%)	11 (3.7%)	56 (6.3%)	0 (0.0%)
Non-Hispanic White	658 (53.5%)	8 (30.8%)	4 (26.7%)	170 (57.6%)	474 (53.2%)	2 (66.7%)
Other or unknown	48 (3.9%)	1 (3.8%)	0 (0.0%)	11 (3.7%)	36 (4.0%)	0 (0.0%)
Vaccinated	1181 (96.0%)	3 (11.5%)	9 (60.0%)	291 (98.6%)	876 (98.3%)	2 (66.7%)
Prior SARS-CoV-2 infection	83 (6.7%)	23 (88.5%)	6 (40.0%)	10 (3.4%)	43 (4.8%)	1 (33.3%)
Nursing home admission	83 (6.7%)	2 (7.7%)	0 (0.0%)	12 (4.1%)	69 (7.7%)	0 (0.0%)
Elixhauser score	6.0 (4.0–9.0)	6.5 (5.0–10.5)	8.0 (5.0–10.5)	6.0 (4.0–9.0)	6.0 (4.0–9.0)	3.0 (2.0–6.5)
Immunocompromised/transplant	238 (19.3%)	6 (23.1%)	5 (33.3%)	67 (22.7%)	159 (17.8%)	1 (33.3%)
Diabetes	564 (45.9%)	13 (50.0%)	7 (46.7%)	147 (49.8%)	397 (44.6%)	0 (0.0%)
Cardiovascular disease	793 (64.5%)	13 (50.0%)	9 (60.0%)	187 (63.4%)	582 (65.3%)	2 (66.7%)
Chronic pulmonary disease	502 (40.8%)	16 (61.5%)	7 (46.7%)	124 (42.0%)	354 (39.7%)	1 (33.3%)
Malignancy	512 (41.7%)	11 (42.3%)	10 (66.7%)	137 (46.6%)	353 (39.7%)	1 (33.3%)
Pregnant	4 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	3 (0.3%)	0 (0.0%)
SpO ₂ :FiO ₂ ratio	449.0 (328.0–464.0)	449.0 (354.0–464.0)	435.0 (240.5–449.0)	444.0 (339.0–459.0)	449.0 (326.5–464.0)	357.0 (353.0–396.0)
Pulse	96.0 (82.0–111.0)	97.5 (87.5–112.0)	99.0 (94.0–109.5)	93.0 (80.5–108.0)	98.0 (82.0–112.0)	102.0 (82.5–122.5)
Respiratory rate, breaths/minute	20.0 (18.0–24.0)	21.0 (18.0–25.8)	20.0 (18.0–34.0)	20.0 (18.0–24.0)	20.0 (18.0–24.0)	18.0 (17.0–21.0)
Temperature, °C	36.9 (36.6–37.4)	37.1 (36.6–38.2)	36.9 (36.6–37.9)	37.0 (36.6–37.7)	36.8 (36.5–37.3)	37.2 (36.5–37.9)
White blood cell count	7.6 (5.5–10.7)	6.0 (4.6–9.4)	5.0 (3.3–6.3)	7.0 (5.4–9.3)	7.9 (5.7–11.2)	4.2 (3.9–4.7)
GFR, mL/minute per 1.73 m ²	63.0 (37.0–89.0)	67.0 (39.5–96.0)	59.0 (43.0–104.5)	61.0 (37.0–87.0)	64.0 (37.0–87.5)	80.0 (69.5–91.0)
CRP level, mg/L	4.2 (1.3–10.9)	3.3 (1.7–13.9)	5.9 (3.5–6.9)	5.5 (2.0–11.9)	3.6 (1.0–10.2)	4.2 (4.0–4.5)
IL-6 level, pg/mL	42.4 (22.5–77.4)	51.4 (34.7–82.5)	166.7 (90.6–242.8)	44.7 (28.6–60.5)	33.0 (20.0–86.1)	–

Data are presented as median (IQR) or no. (%). Vital signs and laboratory results are the first observation within 36 hours of hospital admission. Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GFR, glomerular filtration rate; IL-6, interleukin 6; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂:FiO₂, ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen.

during a period of single lineage dominance. During Omicron community dominance, 355 of 374 (95%) patients with available WGS results had the Omicron variant, including 84 of 94 (89%) patients with severe disease. Omicron subvariants included BA.1 (n = 293), BA.2 (n = 69), and BA.2.12.1 (n = 27).

Clinical and Demographic Features

Among 3369 patients without prior SARS-CoV-2 vaccination or infection, the median age was 62 years (interquartile range [IQR]: 49–75 years) (Table 1) and 1687 (50%) were male. Vaccinated or previously infected patients were older (median age: 69 years; IQR: 57–80 years; $P < .001$) and had more comorbidities (median Elixhauser score: 6 [IQR: 4–9] compared to 5 [IQR: 3–7]) (Table 2). Among patients without a prior history of SARS-CoV-2 vaccination or infection, those infected with ancestral lineages were older than other groups (median age: 65 years [IQR: 53–78] compared to 58 years [IQR: 43–70]). The proportion of patients who were Black was higher in Alpha (64%), Delta (42%), and Omicron (45%) variant groups than in ancestral lineages (31%).

The presenting SpO₂:FiO₂ was higher for unvaccinated patients with Omicron infections (median: 444; IQR: 293–464) compared with patients with Delta (median: 430; IQR: 258–454) and ancestral lineage (median: 430; IQR: 277–454) infections. Among 2554 (76%) unvaccinated patients with C-reactive protein (CRP) recorded less than 36 hours after admission, patients with Omicron infections had lower (5.4; IQR: 1.9–11.4) and Delta patients had higher (7.4; IQR: 3.5–12.6) median CRP compared with patients with ancestral lineage infections (6.2; IQR: 2.5–11.4).

Inpatient Outcomes, Patients Without a History of SARS-CoV-2 Vaccination or Prior Infection

Among patients without a history of SARS-CoV-2 vaccination or prior infection, 977 (29%) developed severe disease or death

within 28 days of hospitalization (median time to event: 0.45 days; IQR: 0.07–2.35 days), including 583 (29%) ancestral, 66 (33%) Alpha, 179 (33%) Delta, 140 (26%) Omicron, and 9 (27%) other variant group infections (Table 3 and Supplementary Table 1). By 28 days of follow-up, almost all patients were discharged or developed severe disease; only 12 (<1%) patients remained hospitalized without having developed severe disease. There were 541 (16%) unvaccinated patients who required mechanical ventilation or died by day 28 (median time to event: 2.8 days; IQR: 0.5–7.6 days) (Supplementary Figure 3). By day 28, there were 182 (9%) ancestral, 9 (4%) Alpha, 46 (8%) Delta, 41 (7%) Omicron, and 3 (9%) other patients who died (median time to death: 9.9 days; IQR: 5.1–173 days).

Average treatment effect models estimated a 28-day probability of severe disease or death by variant group of 0.28 for ancestral, 0.35 for Alpha, 0.36 for Delta, and 0.26 for Omicron infections (Table 4; model balance shown in Supplementary Table 2 and Supplementary Figure 4). Figure 2A plots the inverse probability weighted risk of severe disease or death by variant over the course of hospitalization. The relative risk of developing severe disease or death within 28 days for the Delta variant compared with ancestral lineages was 1.3 (95% confidence interval [CI]: 1.12–1.51). Compared with the Delta variant, the 28-day relative risk of severe disease or death for Omicron was .72 (95% CI: .59–.88) and compared with ancestral lineages was .94 (.78–1.11). Compared with ancestral lineages, the weighted mean presenting SpO₂:FiO₂ for the Delta variant was lower by 21.53 (95% CI: –35.26 to –7.8). Patients with Delta infections were more likely to receive remdesivir (relative risk: 1.12; 95% CI: 1.02–1.22) and patients with Omicron infections were less likely to receive steroids (relative risk: .88; 95% CI: .82–.95) than patients with ancestral lineage infections. A sensitivity analysis of 2610 unvaccinated patients that

Table 3. Severe Disease or Death by Day 28 of Hospitalization Among Hospitalized Unvaccinated Patients Without a Prior History of SARS-CoV-2 Infection

	All Patients (N = 3369)	No Severe Disease or Death by Day 28 (n = 2392)	Severe Disease or Death by Day 28 (n = 977)	P
Variant, inferred or confirmed				.067
Ancestral	2039 (60.5%)	1456 (71.4%)	583 (28.6%)	
Alpha	201 (6.0%)	135 (67.2%)	66 (32.8%)	
Delta	546 (16.2%)	367 (67.2%)	179 (32.8%)	
Omicron	549 (16.3%)	409 (74.5%)	140 (25.5%)	
Other	34 (1.0%)	25 (73.5%)	9 (26.5%)	
Variant, confirmed only				.236
Ancestral	141 (16.7%)	101 (71.6%)	40 (28.4%)	
Alpha	201 (23.8%)	135 (67.2%)	66 (32.8%)	
Delta	334 (39.5%)	216 (64.7%)	118 (35.3%)	
Omicron	136 (16.1%)	101 (74.3%)	35 (25.7%)	
Other	34 (4.0%)	25 (73.5%)	9 (26.5%)	

Data are presented as no. (%). Percentages in the first column are calculated by column; the remaining percentages are calculated by row. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

excluded inference of Alpha, Delta, and Omicron variants showed similar estimates for the relative risk of severe disease or death, but with wider CIs (Supplementary Table 3 and Supplementary Figure 5).

Inpatient Outcomes, Patients With a History of Vaccination or Prior SARS-CoV-2 Infection

The 1230 inpatients with a history of vaccination or prior SARS-CoV-2 infection included 295 (35%) Delta, 891 (62%) Omicron, and 44 Alpha, Ancestral, or other lineage infections. There were 66 (23%) vaccinated patients with Delta and 194 (22%) vaccinated patients with Omicron who developed severe disease or who died within 28 days (Table 5 and Supplementary Table 4), with a median time to event of 0.5 (IQR: 0.08–3.24) days. By 28 days of follow-up, there remained 15 (1%) vaccinated persons hospitalized without having developed severe disease.

Among patients with Omicron and Delta infections, inpatients who were vaccinated or had a history of SARS-CoV-2 infection had less than half the 28-day risk of severe disease or death compared with unvaccinated inpatients (adjusted hazard ratio: 0.4; IQR: 0.3–0.54) (Supplementary Table 5). The adjusted 28-day risk of severe disease or death was similar between patients with Delta and Omicron variant infections (Figure 2B and Supplementary Figure 6). There were 35 (12%) patients with Delta and 113 (13%) patients with Omicron with a history of SARS-CoV-2 vaccination or prior infection who required mechanical ventilation or who died within 28 days of hospitalization (median time to event: 1.92 days; IQR: 0.18–7.59 days).

DISCUSSION

Leveraging on-site SARS-CoV-2 genomic surveillance and real-time EMR linkage, we report clinically relevant differences in severe disease risk among patients hospitalized with symptomatic COVID-19 by SARS-CoV-2 variant. Compared with previously circulating lineages, unvaccinated patients with the Delta variant were more likely to develop severe illness or death when adjusted for known risk factors for severe COVID-19. Although unvaccinated patients hospitalized with the Omicron variant had a lower risk of severe disease compared with those with the Delta variant, the risk of severe disease or death was similar compared with SARS-CoV-2 lineages that circulated earlier in the pandemic. Among vaccinated patients, there was no difference in the risk of developing severe illness between Delta and Omicron variants once patients were hospitalized.

The finding that unvaccinated individuals hospitalized with Omicron infections have a similar risk of severe disease compared with cases prior to the emergence of variants of concern undercuts public perception that Omicron is a mild disease. Outpatients with Omicron infections in prior reports had a

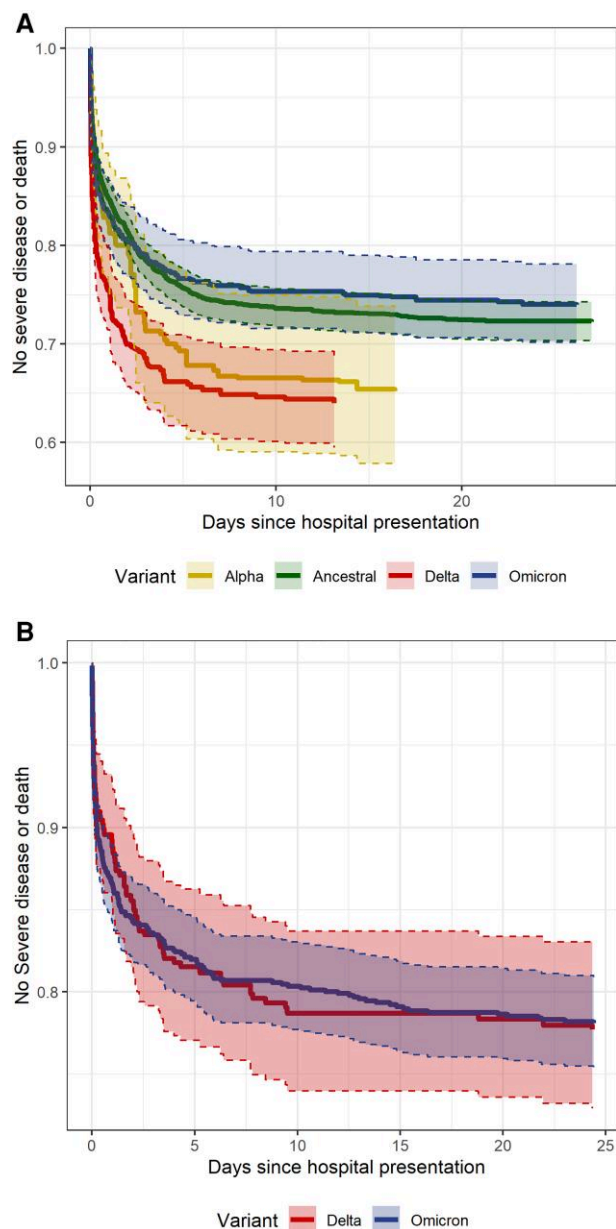


Figure 2. Inverse probability weighted risk of severe disease or death by days since hospital presentation and variant for patients hospitalized with COVID-19 including (A) 3207 unvaccinated patients without a prior history of SARS-CoV-2 infection and (B) 1159 patients with a history of SARS-CoV-2 infection or vaccination. The shaded area surrounding the estimate expresses 95% CIs bound by dashed lines. Among 3369 unvaccinated patients without a prior history of SARS-CoV-2 infection with available inferred variant data, 34 with other variants and 128 with missing BMI were excluded from the model. Among 1230 patients with a prior history of SARS-CoV-2 infection or vaccination with available inferred variant data, 44 with variants other than Omicron or Delta and 27 with missing BMI were excluded from the model. Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

0.2–0.5-fold risk of requiring hospitalization compared with those with Delta infections [11,14–16]. Once hospitalized, patients with Omicron in a South African cohort had a 0.3-fold risk of requiring oxygen therapy compared with patients with

Table 4. Clinical Outcomes and Features by Variant in an Average Treatment Effect Model Adjusted for Risk Factors for Severe COVID-19 Among Unvaccinated Patients With No Prior History of SARS-CoV-2 Infection

	Ancestral	Alpha	Delta	Omicron
Mean presenting SpO ₂ :FiO ₂	363.54 (358.31–368.77)	359.45 (339.73–379.17)	342.01 (329.32–354.7)	364.58 (353.48–375.68)
Mean difference	Ref	−4.09 (−24.49 to 16.31)	−21.53 (−35.26 to −7.8)	1.04 (−11.23 to 13.31)
28-Day risk of severe disease or death				
Estimate	0.28 (0.26–0.3)	0.35 (0.27–0.43)	0.36 (0.31–0.41)	0.26 (0.22–0.3)
Relative risk, ancestral as reference	Ref	1.26 (0.95–1.56)	1.3 (1.11–1.49)	0.94 (0.78–1.1)
Relative risk, Delta as reference	0.77 (0.66–0.89)	0.97 (0.74–1.26)	Ref	0.72 (0.59–0.88)
Risk difference, ancestral as reference	Ref	0.07 (−0.01 to 0.15)	0.08 (0.03–0.13)	−0.02 (−0.06 to 0.03)
Treatment with remdesivir				
Estimate	0.53 (0.51–0.55)	0.61 (0.53–0.69)	0.59 (0.54–0.64)	0.51 (0.46–0.55)
Relative risk, ancestral as reference	Ref	1.16 (1–1.31)	1.12 (1.02–1.22)	0.96 (0.87–1.06)
Treatment with dexamethasone				
Estimate	0.71 (0.69–0.74)	0.79 (0.73–0.85)	0.76 (0.72–0.8)	0.63 (0.58–0.67)
Relative risk, ancestral as reference	Ref	1.1 (1.01–1.2)	1.06 (1–1.13)	0.88 (0.81–0.94)

The average treatment effect model uses inverse probability weighting to estimate clinical features and outcomes if the entire cohort was composed of a single variant. Weighting was performed using risk factors for severe COVID-19 including age, sex, body mass index, Elixhauser comorbidity score, and presence of immunosuppression or history of transplantation. Values in parentheses represent the 95% confidence interval of the estimates. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ref, reference; SpO₂:FiO₂, ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen.

Table 5. Severe Disease or Death by Day 28 of Hospitalization Among Hospitalized Patients With a Prior History of SARS-CoV-2 Vaccination or Infection

	All Patients (N = 1230)	No Severe Disease or Death by Day 28 (n = 961)	Severe Disease or Death by Day 28 (n = 269)	<i>P</i>
Variant, inferred or confirmed				
Ancestral	26 (2.1%)	22 (84.6%)	4 (15.4%)	.686
Alpha	15 (1.2%)	10 (66.7%)	5 (33.3%)	
Delta	295 (24.0%)	229 (77.6%)	66 (22.4%)	
Omicron	891 (72.4%)	697 (78.2%)	194 (21.8%)	
Other	3 (0.2%)	3 (100%)	0 (0.0%)	
Variant, confirmed only				
Ancestral	6 (1.3%)	6 (100%)	0 (0.0%)	.378
Alpha	15 (3.2%)	10 (66.7%)	5 (33.3%)	
Delta	188 (40.4%)	138 (73.4%)	50 (26.6%)	
Omicron	253 (54.4%)	197 (77.9%)	56 (22.1%)	
Other	3 (0.6%)	3 (100%)	0 (0.0%)	

Data are presented as no. (%). Percentages in the first column are calculated by column; the remaining percentages are calculated by row. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Delta [15]. Other comparisons of Omicron to Delta infections have shown a 0.34-fold risk of intensive care unit (ICU) admission and a 0.31-fold risk of death [36,37]. Adjustment for unascertained prior infection and vaccination in some population-based cohorts reduces the magnitude of intrinsic severity estimate differences between Omicron and Delta variants [37,38]. Comparison of disease severity between Omicron and Delta alone overlooks the increased severity of the Delta variant compared with prior lineages that were responsible for millions of deaths. Using stricter criteria for cohort entry to exclude asymptomatic SARS-CoV-2 infection, we found a 0.72-fold risk of severe disease for patients with Omicron compared with Delta, but no significant difference compared with ancestral lineages.

Patients who were vaccinated or who previously had SARS-CoV-2 infection were less than half as likely as unvaccinated patients to develop severe disease in the Delta and Omicron era, and there was no difference in this risk by variant. We found that vaccinated patients requiring hospitalization were older and had more comorbidities. Vaccines remain largely effective in preventing COVID-19–related mortality and population-based surveillance continues to show a more than 5-fold protection against hospitalization [39–41].

Comparison of severe disease risk between variants is critical as the evidence base for understanding disease severity, therapeutic efficacy, and health system burden is primarily based on pre-Delta variant observations. The perception that healthy

persons hospitalized for COVID-19 are unlikely to require ICU-level care formed early in the pandemic underestimated their risk after the emergence of the Delta variant. As it is infeasible to re-evaluate every COVID-19 therapeutic each time a new variant emerges, data comparing severe disease risk by variant are necessary for clinicians to regauge the risks and benefits of COVID-19 therapeutics.

Study limitations include partial reliance on community prevalence to infer SARS-CoV-2 lineage and increased likelihood of unrecognized prior SARS-CoV-2 infection over the observation period. However, surveillance was performed locally with 97% concordance of inferred to confirmed variant. Model estimates from sensitivity analyses limited to confirmed variants were similar to primary analyses. Low-level co-circulation of the comparatively severe Delta variant during Omicron-dominant transmission may overrepresent Delta among hospitalized patients, especially the severely ill. Although inferred-confirmed variant concordance decreased to 95% during Omicron-dominant transmission, this misclassification biases against finding a severity difference between Omicron and Delta.

Reliance on EMR data likely undercounted the cohort prevalence of prior SARS-CoV-2 infection. A longitudinal serosurvey suggests that unreported SARS-CoV-2 is common [42], which may convey increasing unrecognized immunity that underestimates the intrinsic severity of recently emerging variants [43]. Unrecognized prior SARS-CoV-2 infection in our cohort may bias towards underestimating Omicron severity, likely greatest for Omicron to ancestral lineage comparisons given the shorter interval between Delta and Omicron waves. Our focus on hospitalized patients does not report differences in intrinsic severity between variants and benefits of vaccination conveyed by reducing hospitalization risk. However, our cohort provides a comparison of variant severity within the frame of reference of clinicians providing inpatient COVID-19 care. Differences in patient characteristics and care patterns may limit the generalizability of our findings. Defining symptomatic COVID-19 by vital sign abnormalities likely includes patients hospitalized for exacerbation of chronic medical conditions temporally related to a positive SARS-CoV-2 test and misses others with subtle symptoms. A limited sample size may have failed to detect a small, severe disease risk difference between the Omicron variant and ancestral lineages.

Study strengths include strict, objective inclusion criteria for symptomatic COVID-19, detailed clinical information from the EMR, extensive WGS results, and robust causal inference methods. Our findings show that, for vaccinated patients who are hospitalized with COVID-19, their risk of severe disease or death is low—reduced by half compared to unvaccinated patients—and equally low for both Omicron and Delta

infections. Despite the comparatively lower risk of hospitalization for Omicron infections, for unvaccinated patients who require hospitalization there remains a risk of severe disease nearly equivalent to the pre-Delta waves of COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Acknowledgments. The authors acknowledge the Johns Hopkins Precision Medicine Analytics Platform (PMAP) and Core for Clinical Research Data Acquisition (CCDA) for preparing the EMR data for analysis. This study was only possible with the efforts of the Johns Hopkins Clinical Microbiology Laboratory and clinicians and staff caring for patients with COVID-19.

Disclaimer. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the sponsors.

Financial support. Support for this work was provided by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), to the Johns Hopkins Center of Excellence in Influenza Research and Surveillance (HHSN272201400007C), and the NIH RADx-UP initiative (R01DA045556-04S1), and with the National Institute on Drug Abuse to the HIV Prevention Trials Network Laboratory Center (UM1AI068613), National Heart, Lung, and Blood Institute, NIH, and National Institute of Biomedical Imaging and Bioengineering, NIH, to the NIH RADx-Tech program (3U54HL143541-02S2 and U54EB007958-12S1), Centers for Disease Control and Prevention (contract number 75D30121C11061), Maryland Department of Health, the Johns Hopkins University President's Fund Research Response, the John Templeton Foundation, the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, John Hopkins inHealth, and the Johns Hopkins Precision Medicine Initiative. R. B. also reports support for this work from the Food and Drug Administration, paid to their institution. S. L. Z. also reports the following support for this work: U54CA260492-01 (S. Klein; paid to their institution); NIH/National Cancer Institute, Johns Hopkins Excellence in Pathogenesis and Immunity Center for SARS-CoV-2 (JH-EPICS) (30 September 2020–31 August 2022); 90077243 (Rosen) Scleroderma Research Foundation Trajectory Modeling (1 October 2017–30 June 2020).

Potential conflicts of interest. The Maryland Department of Health collaborates for research with BioRad, Hologic, and DiaSorin. J. B. has equity/entitlement to future royalties in miDiagnostics. B. T. G. is a member of the Food and Drug Administration (FDA) Pulmonary-Asthma Drug Advisory Committee and a board member of the Society of Bedside Medicine and has received consulting fees from Janssen Research and Development, LLC (related to vaccine trial case adjudication); Gilead Sciences, Inc (related to COVID therapeutics); and Atea Pharmaceuticals, Inc (related to COVID therapeutics). R. B. is a consultant for Merck & Co and Hologic. R. B. also reports royalties or licenses from emocha Health, support for attending meetings and/or travel from Hologic, and participation on a Data Safety Monitoring Board or Advisory Board for Merck. H. H. M. reports the following grants or contracts unrelated to this work: National Institutes of Health (NIH) UM1AI0686, NIH UM1 AI068613-14, NIH R01 DA045556-04S1, NIH 3U54HL143541-02S2, NIH 4UH3CA211396-03, and NIH R01 CA243393 and receipt of equipment, materials, drugs, medical writing, gifts, or other services related to research contract from BioRad, DiaSorin, and Hologic. D. C. G. reports grants or contracts unrelated to this work from Illumina, Inc; IDbyNDA, Inc; and Fisher Center Discovery Program, Johns Hopkins; consulting fees from bioMerieux, Inc; and payment or honoraria for lectures, presentations, speaker's

bureaus, manuscript writing, or educational events from the American Association of Clinical Chemistry and Pan American Society of Clinical Virology. A. G. reports unrelated grants or contracts from NIH and Unitaid and the Centers for Disease Control and Prevention (CDC); participation on an NIH/NIAID Advisory Council and Indo US Science Technology Governing Board; and roles on the IMPAACT Network TB Scientific Committee and World Health Organization (WHO) MDR TB Guidelines Committee. M. L. R. reports grants or contracts unrelated to this work from Critical Path Institute/FDA, paid to their institution. S. L. Z. reports the following grants or contracts unrelated to this work: 1R01AR073208-01 (Shah) (1 April 2018–31 March 2023), NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Autoantibodies Define Scleroderma Subgroups with Distinct Relationships to Cancer; UL1TR003098 (Ford) (1 June 2019–30 April 2024), NIH/National Center for Advancing Translational Sciences (NCATS), Johns Hopkins Institutional Clinical and Translational Science Award. S. L. Z. also reports a role as Co-Director for Data Science, JHM inHealth Precision Medicine (paid to their institution). These conflicts of interest are being managed by the Johns Hopkins University in accordance with its conflict-of-interest policies. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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