Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Risk of severe clinical outcomes among persons with SARS-CoV-2 infection with differing levels of vaccination during widespread Omicron (B.1.1.529) and Delta (B.1.617.2) variant circulation in Northern California: A retrospective cohort study

Jacek Skarbinski,[a,b,c,d]* Mariah S. Wood,[a] Tyler C. Chervo,[a] Jeffrey M. Schapiro,[d] Eric P. Elkin,[a] Emily Valice,[a] Laura B. Amsden,[a] Crystal Hsiao,[a] Charles Quesenberry,[a] Douglas A. Corley,[a,d] and Lawrence H. Kushi[a]

[a]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA
[b]Department of Infectious Diseases, Oakland Medical Center, Kaiser Permanente Northern California, Oakland, CA, USA
[c]Physician Researcher Program, Kaiser Permanente Northern California, Oakland, CA, USA
[d]The Permanente Medical Group, Kaiser Permanente Northern California, Oakland, CA, USA

The Lancet Regional Health - Americas 2022;12: 100297
Published online 16 June 2022
https://doi.org/10.1016/j.lana.2022.100297

Summary

Background The incidence of and risk factors for severe clinical outcomes with the Omicron (B.1.1.529) SARS-CoV-2 variant have not been well-defined.

Methods We conducted a retrospective cohort study to assess risks of severe clinical outcomes within 21 days after SARS-CoV-2 diagnosis in a large, diverse, integrated health system.

Findings Among 118,078 persons with incident SARS-CoV-2 infection, 48,101 (41%) were during the Omicron period and 69,977 (59%) during the Delta (B.1.617.2) period. Cumulative incidence of any hospitalization (2.4% versus 7.8%; adjusted hazard ratio [aHR] 0.55; 95% confidence interval [CI] (0.51-0.59), with low-flow oxygen support (1.6% versus 6.4%; aHR 0.46; CI 0.43-0.50), with high-flow oxygen support (0.6% versus 2.8%; aHR 0.47; CI 0.41-0.54), with invasive mechanical ventilation (0.1% versus 0.7%; aHR 0.43; CI 0.33-0.56), and death (0.2% versus 0.7%; aHR 0.54; CI 0.42-0.70) were lower in the Omicron than the Delta period. The risk of hospitalization was higher among unvaccinated persons (aHR 8.34; CI 7.25-9.60) and those who completed a primary COVID-19 vaccination series (aHR 1.72; CI 1.49-1.97) compared with those who completed a primary vaccination series and an additional dose. The strongest risk factors for all severe clinical outcomes were older age, higher body mass index and select comorbidities.

Interpretation Persons with SARS-CoV-2 infection were significantly less likely to develop severe clinical outcomes during the Omicron period compared with the Delta period. COVID-19 primary vaccination and additional doses were associated with reduced risk of severe clinical outcomes among those with SARS-CoV-2 infection.

Funding National Cancer Institute and The Permanente Medical Group

Keywords: COVID-19; Omicron variant; SARS-CoV-2

Introduction

Since the emergence and rapid spread of the Omicron (B.1.1.529) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, data from South Africa, Great Britain, and the United States have suggested that SARS-CoV-2 infection with the Omicron variant is associated with lower risks of severe COVID-19 requiring hospitalization, respiratory support, or death.[1–11] However, the risk of severe COVID-19 among persons with comorbidities associated with severe disease and the impact of varying levels of vaccination in reducing the risk of severe clinical outcomes in diverse,

*Corresponding author at: Department of Infectious Diseases, 3600 Broadway, Oakland, CA 94611, USA.
E-mail address: jacek.skarbinski@kp.org (J. Skarbinski).

Research in context

Evidence before this study

Prior studies have shown reduced risk of severe clinical outcomes associated with SARS-CoV-2 infection with the Omicron variant, but detailed understanding of the risk factors for severe clinical outcomes with the Omicron variant have not been well-defined.

Added value of this study

In this retrospective cohort study of 118,078 persons with SARS-CoV-2 infection, the risks of hospitalization, hospitalization with invasive mechanical ventilation and death were significantly lower during a period with Omicron variant circulation compared with a period with Delta variant circulation.

COVID-19 primary vaccination and additional doses were associated with reduced risk of severe clinical outcomes among those with SARS-CoV-2 infection during the Omicron period.

Implications of all the available evidence

SARS-CoV-2 infection with the Omicron variant is associated with ~50% lower risk of severe clinical outcomes compared to the Delta variant.

community-based populations is unclear.[2,5,12–15] Understanding which persons with SARS-CoV-2 infection are at highest risk of developing severe clinical outcomes is needed to identify persons who might benefit from outpatient therapies such as extra vaccine doses and monoclonal antibody treatments or remdesivir, which have logistical or supply constraints.[16]

To address these data gaps, we conducted a retrospective cohort study of persons with nucleic-acid amplification test (NAAT)-confirmed SARS-CoV-2 infection during time periods with predominant Omicron or Delta (B.1.617.2) variant circulation and assessed risks of severe clinical outcomes in the 21 days after positive test date in a large, diverse, integrated, community-based health system that closely approximates the demographics of the underlying census population. The aims of these analyses are to: 1) assess the risk of severe clinical outcomes among persons with SARS-CoV-2 infection during periods of Omicron versus Delta variant circulation; 2) identify risk factors for severe clinical outcomes among persons with SARS-CoV-2 infection during periods of Omicron versus Delta variant transmission; and 3) assess the risk of severe clinical outcomes among persons with varying vaccination status for COVID-19 during periods of Omicron versus Delta variant circulation.

Methods

Setting

Kaiser Permanente Northern California (KPNC) is an integrated health system that serves over 4.5 million members in Northern and Central California and provides comprehensive preventive and curative care in inpatient and outpatient settings across 266 medical offices and 21 hospitals. Members receive most clinical services, including laboratory testing, outpatient, and inpatient care in KPNC facilities. Members have similar sociodemographic characteristics to the population of Northern and Central California.[17] SARS-CoV-2 NAAT for outpatients and hospitalized patients are conducted at the regional laboratory or local hospital laboratories using various platforms.

Study design

We conducted a retrospective cohort study of persons with NAAT-confirmed SARS-CoV-2 infection during time periods with predominant Omicron or Delta variant transmission and assessed severe clinical outcomes within 21 days of first positive NAAT in a large integrated health system. The main exposure of interest was SARS-CoV-2 infection during time periods of predominant Omicron variant and Delta variant transmission. Data were obtained from the KPNC Virtual Data Warehouse, a common data model into which standardized data are extracted from clinical and administrative databases including an integrated electronic health record database (Epic, Verona, WI, USA), and from other sources.[18,19] The study was approved by the KPNC Institutional Review Board with waivers of the requirement for informed consent.

Inclusion criteria

We included all persons with an incident NAAT-confirmed SARS-CoV-2 infection from July 5 to November 30, 2021 or December 18, 2021 to January 7, 2022 who were KPNC members for at least one year prior to SARS-CoV-2 diagnosis. To meet inclusion criteria, patients had to have SARS-CoV-2 detected by NAAT of a nasopharyngeal or oropharyngeal specimen. Incident infection was defined as the first NAAT-confirmed SARS-CoV-2 infection during the study period or a subsequent NAAT-confirmed SARS-CoV-2 infection that was >90 days from any prior documented infection. The index date was defined as the date of NAAT-confirmed SARS-CoV-2 infection.

Primary exposure: ascertainment of predominant SARS-CoV-2 variant transmission during the Omicron and Delta time periods

Ascertainment of the predominant variant during specific time periods was assessed using two data sources.

We defined the Delta predominant period from July 5-November 30, 2021 using data from an ongoing whole genome surveillance system. KPNC is a partner in COVID-Net with the California Department of Public Health and submits all NAAT-confirmed SARS-CoV-2 specimens to the COVID-Net; a subset of specimens undergoes whole genome sequencing.[20] From July 5 to November 30, 2021, 69,977 specimens were submitted for sequencing, 15,211 (21.7%) underwent sequencing and 13,470 (19.2%) had reported lineage results. Of the 13,470 specimens with valid results, 12,990 (96.4%) were consistent with Delta variant infection (Figure 1). We defined the Omicron variant period from December 18, 2021 to January 7, 2022. The Omicron variant has a Δ69-70 amino acid deletion in the spike protein which has been associated with failures in polymerase chain reaction probes targeting the spike gene but a retained ability to detect probes targeting the Orf1ab and nucleocapsid genes; thus, the Omicron variant can be detected based on spike gene target failure (SGTF) on the ThermoFischer TaqPath COVID-19 combo kit.[21] From December 18, 2021 until January 7, 2022, 13,344 (27.7%) of 48,101 total specimens were tested for SGTF, and SGTF was identified in 12,476 (93.5%) of 13,344 specimens.

Outcome measures

The primary outcome measures were clinical outcomes of increasing severity including 1) any hospitalization; 2) hospitalization with low-flow oxygen support defined as low-flow oxygen delivery via nasal cannula, simple mask, reservoir mask, partial rebreather or nonrebreather; 3) hospitalization with high-flow oxygen support or non-invasive positive pressure ventilation (NIPPV) defined as high-flow oxygen delivery via high-flow nasal cannula, oxygen tent, reservoir mask or nonrebreather or NIPPV defined as use of a continuous

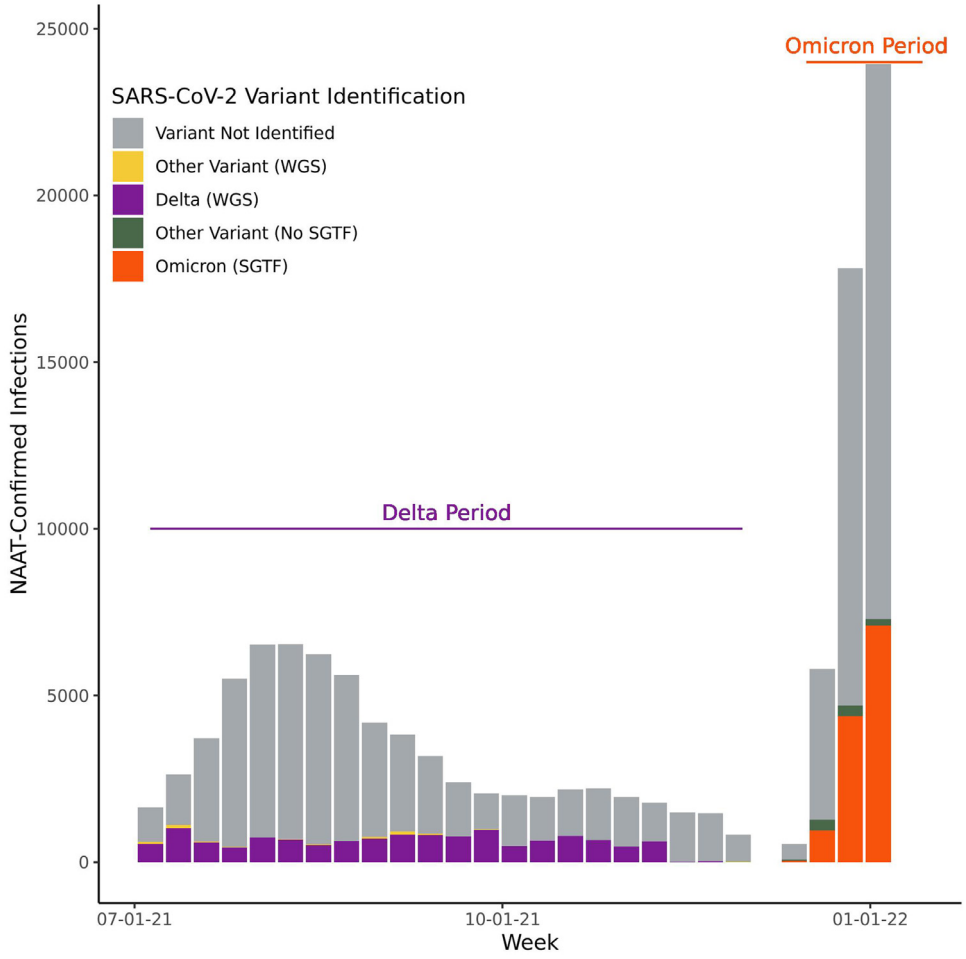

Figure 1. SARS-CoV-2 infections per week in Northern California during time periods of predominant Omicron SARS-CoV-2 variant (December 18, 2021-January 7, 2022) and Delta SARS-CoV-2 variant (July 5, 2021-November 30, 2021) transmission in Northern California, stratified by whole genome sequencing (WGS) or spike gene target failure (SGTF) testing and results.

positive airway pressure, bilevel positive airway pressure or auto-adjusting positive airway pressure device; 4) hospitalization requiring invasive mechanical ventilation (IMV) defined as positive pressure ventilation via an endotracheal or tracheostomy tube; and 5) death. Individuals could experience more than one of these outcomes during the 21-day follow-up period. Persons were followed for up to 21 days from date of NAAT-confirmed SARS-CoV-2 diagnosis and outcomes were assessed via data abstraction from the electronic medical record.

Other exposures of interest

Other exposures of interest included demographic characteristics (age, sex, race/ethnicity), body mass index, Charlson comorbidity index score[22] and individual Charlson comorbidities, prior infection defined as NAAT-confirmed SARS-CoV-2 infection >90 days prior to index date, and receipt of COVID-19 vaccination prior to index date. Individual Charlson comorbidity categories were reclassified into the following: 1) atherosclerotic cardiovascular disease includes persons with prior myocardial infarction, congestive heart failure, peripheral vascular disease and prior cerebrovascular event; 2) diabetes includes persons with diabetes with and without end-organ damage; 3) cancer includes persons with solid tumor with localized or metastatic disease, leukemia and lymphoma. We assessed receipt of all doses of COVID-19 vaccines (BNT162b2 [Pfizer/BioNTech], m-RNA-1973 [Moderna/National Institutes of Health] or Ad.26.COV2.s [Janssen] prior to index date. Receipt of the vaccine was obtained from the electronic health record or from the California Immunization Registry [CAIR]; all vaccine providers in the state are required to report vaccine administration to CAIR within 24 hours of administration. COVID-19 vaccination status was classified as: 1) Completed primary series, which includes persons who received one dose of Ad.26.COV2.s or 2 doses of BNT162b2 or m-RNA-1973; 2) Completed primary series plus an additional dose, which includes persons who completed a primary series and received at least one addition dose of any COVID-19 vaccine (Ad.26.COV2.s, BNT162b2 or m-RNA-1973); 3) Other, which includes persons who received one dose of either BNT162b2 or m-RNA-1973, another vaccine product, or an unapproved combination of vaccines; 4) unvaccinated, which includes persons who have not received any COVID-19 vaccine. We also assessed receipt of anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab) prior to hospital admission. These medications can be used under United States Food and Drug Administration Emergency Use Authorization and are recommended for the treatment of SARS-COV-2 infection in the outpatient setting.[23] Similarly, we assessed receipt of treatment for COVID-19 during hospitalization, including intravenous remdesivir, dexamethasone and tocilizumab.

Statistical analysis

We assessed the relative risk of each severe clinical outcome among persons with SARS-CoV-2 infection during the Omicron period versus the Delta period in the 21 days after initial NAAT-confirmed SARS-CoV-2 diagnosis. Persons were followed until the outcome of interest, an outcome more severe than the outcome of interest, 21 days after index date, or the end of the data collection period on January 20, 2022. Individuals could contribute to analyses for more than one outcome. We assumed that the multiple clinical severity events of low flow oxygen, high flow oxygen, invasive mechanical ventilation, and death that a patient with SARS-Cov-2 diagnosis might experience during the same hospitalization are independent of each other. As a result, each patient could contribute to one or more of the clinical severity outcomes analyses. For example, 205 patients that had consecutively experienced all four clinical severity events from low flow oxygen to death in the same hospitalization are included in all four clinical severity outcomes cox regression analyses (see *Supplemental Table* 1).

We estimated crude and adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) using Cox proportional hazards models; each severe clinical outcome was modeled independently. To adjust for confounding, all models included sex, age, race/ethnicity, Charlson comorbidity index score and select comorbidities (atherosclerotic cardiovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, diabetes mellitus, cancer, renal disease), body mass index, prior infection with SARS-CoV-2, receipt of anti-SARS-CoV-2 monoclonal antibody treatment, and COVID-19 vaccination status. We assessed the proportional hazards assumption by testing for slopes in Schoenfeld residuals.[24]

We assessed risk factors for severe clinical outcomes among persons with SARS-CoV-2 infection including demographic characteristics, clinical comorbidities and COVID-19 vaccination status stratified by Omicron versus Delta period. We used Cox proportional hazards models as described above to assess interactions between risk factors and time period (Omicron versus Delta) to determine if risk factors for severe clinical outcomes differed between these periods.

All analyses used SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria).[25]

Role of funding source

The funders had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results

Among 118,078 persons with incident NAAT-confirmed SARS-CoV-2 infection who met inclusion criteria, 48,101 (41%) were in the Omicron period and 69,977 (59%) in the Delta period. The mean number of SARS-CoV-2 infections per day was substantially higher during the Omicron period (48,101 infections in a 21-day period or 2291.7 infections per day) versus the Delta period (69,977 infections during a 147-day period or 476.0 infections per day) (Figure 1; *Supplemental Table* 2).

Patient demographics, infection, and vaccination status for Omicron vs. Delta periods

Persons infected with SARS-CoV-2 during the Omicron period were more likely to be of Asian descent, have completed their COVID-19 vaccination primary series or completed a primary series and an additional dose, and have had a prior SARS-CoV-2 infection than persons infected with SARS-CoV-2 during the Delta period (see patient characteristics, Table 1).

Hospitalization for Omicron vs. Delta periods

The hospitalization rate (mean number of hospitalizations per SARS-CoV-2 infection per time period-day) was higher during the Omicron period (crude rate ratio 1.50; CI 1.41-1.60), reflecting the substantial burden of Omicron variant circulation on the health system (*Supplemental Table* 2). Overall, the crude percentages of persons who had a severe clinical outcome were significantly lower among persons with SARS-CoV-2 during the Omicron period than persons in the Delta period for any hospitalization (2.4% versus 7.8%), hospitalization with low-flow oxygen support (1.6% versus 6.4%), hospitalization with high-flow oxygen support or NIPPV (0.6% versus 2.8%), hospitalization with IMV (0.1% versus 0.7%), and death (0.2% versus 0.7%) (for all comparisons, P<0.01).

Persons hospitalized with SARS-CoV-2 infection during the Omicron period were significantly more likely to be older (median age 62 versus 59 years), to have a Charlson comorbidity index score ≥3, to have completed their COVID-19 vaccination primary series or completed a primary series plus an additional dose, and to have had a prior SARS-CoV-2 infection (Table 2; for all comparisons, P<0.01). Among hospitalized persons with SARS-CoV-2 infection, persons in the Omicron period were significantly less likely to require low-flow oxygen support (66% versus 82%), high-flow oxygen support or NIPPV (26% versus 36%), or IMV (6.0% versus 9.6%), or receive treatment with remdesivir (57% versus 74%) or dexamethasone (57% versus 80%) (for all comparisons, P<0.01).

In our primary analysis, persons with SARS-CoV-2 infection during the Omicron period compared with the Delta period had significantly lower risk of any hospitalization (aHR 0.55; CI 0.15-0.59), hospitalization with low-flow oxygen support (aHR 0.46; CI 0.43-0.50), hospitalization with high-flow oxygen support or NIPPV (aHR 0.47; CI 0.41-0.54), hospitalization with IMV (aHR 0.43; CI 0.33-0.56), or death (aHR 0.54; CI 0.42-0.70) in the 21 days after SARS-CoV-2 diagnosis adjusting for demographics, comorbidities, COVID-19 vaccination status, prior infection status and receipt of outpatient anti-SARS-CoV-2 antibody treatment (Table 3; Figure 2). In adjusted models, independent risk factors associated with increased risk of all severe clinical outcomes included age ≥40 years, male sex, Asian compared with White race/ethnicity, renal disease, body mass index ≥35 kg/m^2, and not having been vaccinated for COVID-19 compared with having completed a primary series plus an additional dose.

Vaccination status and outcomes for Omicron vs. Delta periods

The risk of a severe clinical outcome varied significantly by vaccination status during both the Omicron and Delta periods (p-interaction <0.01 for all comparisons). Persons who were unvaccinated had the highest risk in both periods, followed by a significantly lower risk among those who had completed a primary series only, followed by a further significantly lower risk among those who completed both a primary series and an additional dose in the Omicron period. Only persons who were unvaccinated were significantly more likely to experience severe clinical outcomes compared with persons who complete a primary series plus an additional dose in the Delta period (*Supplemental tables* 3-7). Demographic (age, sex) and clinical characteristics (Charlson comorbidity index score, select comorbidities, body mass index) were associated with increased risk of severe clinical outcomes in both the Omicron and Delta periods; the magnitudes of these associations were similar during the Omicron and Delta periods, suggesting that individual-level risk factors for severe clinical outcomes have not changed substantially between the Omicron and Delta periods.

Influence of sex, age, and race/ethnicity for Omicron vs. Delta periods

The risk of a severe clinical outcome varied significantly by sex during both the Omicron and Delta periods (*Supplemental Tables* 3-7). For example, during both periods, male compared with female patients were at a greater risk for both hospitalization with IMV (aHR 2.21; CI 1.33-3.68 during Omicron and 1.71; CI 1.43-2.04 during Delta) and for death (aHR 2.29; CI 1.47-3.59 during Omicron and 2.01; CI 1.66-2.43 during Delta).

In contrast, differences in risk for many severe clinical outcomes by race/ethnicity differed during the

Characteristic	All, N = 118,078 n (%)	Omicron period, N = 48,101 n (%)	Delta period, N = 69,977 n (%)	p-value[2]
Age, years[1]	37 (23, 52)	37 (24, 51)	37 (22, 53)	0.002
Age, years				<0.001
0-17	21,208 (18%)	7,339 (15%)	13,869 (20%)	
18-39	43,310 (37%)	19,285 (40%)	24,025 (34%)	
40-49	19,588 (17%)	8,352 (17%)	11,236 (16%)	
50-59	15,907 (13%)	6,694 (14%)	9,213 (13%)	
60-69	10,662 (9.0%)	3,946 (8.2%)	6,716 (9.6%)	
70-79	4,967 (4.2%)	1,681 (3.5%)	3,286 (4.7%)	
80+	2,331 (2.0%)	699 (1.5%)	1,632 (2.3%)	
Sex				<0.001
Female	64,416 (55%)	27,280 (57%)	37,136 (53%)	
Male	53,662 (45%)	20,821 (43%)	32,841 (47%)	
Race/Ethnicity				<0.001
LatinX/Hispanic Ethnicity	33,047 (28%)	13,428 (28%)	19,619 (28%)	
Black/African Descent	12,564 (11%)	5,321 (11%)	7,243 (10%)	
Asian Descent	17,221 (15%)	9,564 (20%)	7,657 (11%)	
White/European or Middle Eastern Descent	46,118 (39%)	15,876 (33%)	30,242 (43%)	
Other/Unknown	9,128 (7.7%)	3,912 (8.1%)	5,216 (7.5%)	
Charlson co-morbidity index scores				<0.001
Missing (no visits in prior year)	10,836 (9.2%)	3,769 (7.8%)	7,067 (10%)	
Score 0	80,886 (69%)	33,837 (70%)	47,049 (67%)	
Score 1	15,119 (13%)	6,285 (13%)	8,834 (13%)	
Score 2	4,760 (4.0%)	1,857 (3.9%)	2,903 (4.1%)	
Score 3+	6,477 (5.5%)	2,353 (4.9%)	4,124 (5.9%)	
Chronic obstructive pulmonary disease	12,718 (11%)	5,218 (11%)	7,500 (11%)	0.5
Diabetes	10,334 (8.8%)	4,031 (8.4%)	6,303 (9.0%)	<0.001
Atherosclerotic cardiovascular disease	8,141 (6.9%)	2,832 (5.9%)	5,309 (7.6%)	<0.001
Renal disease	3,820 (3.2%)	1,389 (2.9%)	2,431 (3.5%)	<0.001
Cancer	1,938 (1.6%)	739 (1.5%)	1,199 (1.7%)	0.019
Rheumatologic disease	972 (0.8%)	364 (0.8%)	608 (0.9%)	0.036
Dementia	599 (0.5%)	196 (0.4%)	403 (0.6%)	<0.001
Body mass index, kg/m^2				<0.001
<25	35,300 (33%)	14,849 (34%)	20,451 (32%)	
25-29.9	31,284 (29%)	13,122 (30%)	18,162 (29%)	
30-34.9	21,781 (20%)	8,696 (20%)	13,085 (21%)	
35-39.9	10,328 (9.6%)	4,050 (9.2%)	6,278 (10.0%)	
≥40	8,370 (7.8%)	3,304 (7.5%)	5,066 (8.0%)	
COVID-19 vaccination				<0.001
None	49,690 (42%)	10,635 (22%)	39,055 (56%)	
Complete primary series	52,310 (44%)	24,608 (51%)	27,702 (40%)	
Completed primary series + additional dose	11,983 (10%)	11,347 (24%)	636 (0.9%)	
Other (partial/mixed/other)	4,095 (3.5%)	1,511 (3.1%)	2,584 (3.7%)	
Prior SARS-CoV-2 infection	3,499 (3.0%)	2,786 (5.8%)	713 (1.0%)	<0.001
Anti-SARS-CoV-2 antibody outpatient treatment[5]	1,130 (1.0%)	222 (0.5%)	908 (1.3%)	<0.001
Severe clinical outcomes				
Any hospitalization	6,624 (5.6%)	1,169 (2.4%)	5,455 (7.8%)	<0.001
Hospitalized with low flow oxygen support	5,256 (4.5%)	773 (1.6%)	4,483 (6.4%)	<0.001
Hospitalized with high flow oxygen support or non-invasive mechanical ventilation	2,282 (1.9%)	302 (0.6%)	1,980 (2.8%)	<0.001
Hospitalized with invasive mechanical ventilation	591 (0.5%)	70 (0.1%)	521 (0.7%)	<0.001
Died	561 (0.5%)	83 (0.2%)	478 (0.7%)	<0.001

Table 1 *(Continued)*

Characteristic	All, N = 118,078 n (%)	Omicron period, N = 48,101 n (%)	Delta period, N = 69,977 n (%)	p-value[2]
Testing for SARS-CoV-2 variant				
Whole genome sequencing confirmed Delta variant, n/N (%)	12,990/13,470 (96.4%)	0[3]	12,990/13,470 (96.4%)	
Whole genome sequencing confirmed Omicron variant, n/N (%)	6/13,470 (0.04%)	0[3]	6/13,470 (0.04%)	
Spike gene target failure confirmed probable Omicron infection, n/N (%)	12,476/13,344 (93.5%)	12,476/13,344 (93.5%)	0[4]	

***Table 1*: Characteristics of persons with SARS-CoV-2 infection in Northern California stratified by time periods of predominant Omicron SARS-CoV-2 variant (December 18, 2021-January 7, 2022) and Delta SARS-CoV-2 variant (July 5, 2021-November 30, 2021) transmission.**

[1] Median (IQR); n (%).
[2] Wilcoxon rank sum test; Pearson's Chi-squared test.
[3] No valid lineage results available for Omicron time period.
[4] Spike gene target failure not tested prior to Omicron time period.
[5] Treatment with bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab.

Characteristic	All, N = 6,624 n (%)	Omicron period, N = 1,169 n (%)	Delta period, N = 5,455 n (%)	p-value[2]
Age, years[1]	59 (43, 72)	62 (42, 76)	58 (44, 72)	<0.001
Age, years				<0.001
0-17	81 (1.2%)	24 (2.1%)	57 (1.0%)	
18-39	1,253 (19%)	244 (21%)	1,009 (18%)	
40-49	924 (14%)	108 (9.2%)	816 (15%)	
50-59	1,184 (18%)	159 (14%)	1,025 (19%)	
60-69	1,225 (18%)	220 (19%)	1,005 (18%)	
70-79	1,003 (15%)	175 (15%)	828 (15%)	
80+	954 (14%)	239 (20%)	715 (13%)	
Sex				0.064
Female	3,339 (50%)	618 (53%)	2,721 (50%)	
Male	3,285 (50%)	551 (47%)	2,734 (50%)	
Race/Ethnicity				<0.001
LatinX/Hispanic Ethnicity	1,756 (27%)	266 (23%)	1,490 (27%)	
Black/African Descent	904 (14%)	181 (15%)	723 (13%)	
Asian Descent	670 (10%)	171 (15%)	499 (9.1%)	
White/European or Middle Eastern Descent	3,036 (46%)	508 (43%)	2,528 (46%)	
Other/Unknown	258 (3.9%)	43 (3.7%)	215 (3.9%)	
Charlson co-morbidity index scores				<0.001
Missing (no visits in prior year)	431 (6.5%)	56 (4.8%)	375 (6.9%)	
Score 0	2,567 (39%)	375 (32%)	2,192 (40%)	
Score 1	1,045 (16%)	165 (14%)	880 (16%)	
Score 2	660 (10.0%)	113 (9.7%)	547 (10%)	
Score 3+	1,921 (29%)	460 (39%)	1,461 (27%)	
Chronic obstructive pulmonary disease	1,421 (21%)	297 (25%)	1,124 (21%)	<0.001
Diabetes	1,891 (29%)	390 (33%)	1,501 (28%)	<0.001
Atherosclerotic cardiovascular disease	2,135 (32%)	484 (41%)	1,651 (30%)	<0.001
Renal disease	1,265 (19%)	311 (27%)	954 (17%)	<0.001
Cancer	408 (6.2%)	83 (7.1%)	325 (6.0%)	0.14
Rheumatologic disease	166 (2.5%)	33 (2.8%)	133 (2.4%)	0.4
Dementia	346 (5.2%)	93 (8.0%)	253 (4.6%)	<0.001
Body mass index, kg/m^2				<0.001
<25	1,268 (19%)	282 (24%)	986 (18%)	

Table 2 *(Continued)*

Characteristic	All, N = 6,624 n (%)	Omicron period, N = 1,169 n (%)	Delta period, N = 5,455 n (%)	p-value[2]
25-29.9	1,797 (27%)	311 (27%)	1,486 (27%)	
30-34.9	1,626 (25%)	262 (23%)	1,364 (25%)	
35-39.9	889 (14%)	136 (12%)	753 (14%)	
≥40	998 (15%)	167 (14%)	831 (15%)	
COVID-19 vaccination				<0.001
None	4,237 (64%)	472 (40%)	3,765 (69%)	
Complete primary series	1,914 (29%)	476 (41%)	1,438 (26%)	
Completed primary series + additional dose	248 (3.7%)	184 (16%)	64 (1.2%)	
Other (partial/mixed/other)	225 (3.4%)	37 (3.2%)	188 (3.4%)	
Prior SARS-CoV-2 infection	149 (2.2%)	52 (4.4%)	97 (1.8%)	<0.001
Anti-SARS-CoV-2 antibody outpatient treatment[3]	74 (1.1%)	14 (1.2%)	60 (1.1%)	0.8
Severe clinical outcomes				
Hospitalized with low flow oxygen support	5,256 (79%)	773 (66%)	4,483 (82%)	<0.001
Hospitalized with high flow oxygen support or non-invasive mechanical ventilation	2,282 (34%)	302 (26%)	1,980 (36%)	<0.001
Hospitalized with invasive mechanical ventilation	591 (8.9%)	70 (6.0%)	521 (9.6%)	<0.001
Died	473 (7.1%)	75 (6.4%)	398 (7.3%)	0.3
Receipt of COVID-19 treatment				
Remdesivir	4,701 (71%)	662 (57%)	4,039 (74%)	<0.001
Dexamethasone	5,056 (76%)	667 (57%)	4,389 (80%)	<0.001
Tocilizumab	1,017 (15%)	153 (13%)	864 (16%)	0.018

***Table 2*: Characteristics of persons hospitalized after SARS-CoV-2 infection in Northern California stratified by time periods of predominant Omicron SARS-CoV-2 variant (December 18, 2021-January 7, 2022) and Delta SARS-CoV-2 variant (July 5, 2021-November 30, 2021) transmission.**

[1] Median (IQR); n (%).

[2] Wilcoxon rank sum test; Pearson's Chi-squared test.

[3] Treatment with bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab.

Omicron and Delta periods (*Supplemental Tables* 3-7). During the Delta period, for example, compared with non-Hispanic Whites, there were higher risks of hospitalization with IMV and death for patients who were Hispanic (aHR 1.57; CI 1.27-1.95 and 1.36; CI 1.08-1.72, respectively) and Asian (aHR 2.6; CI 1.91-3.54 and 2.15; CI 1.56-2.98, respectively). In contrast, during the Omicron period, these same comparisons for IMV and for death were not statistically different or inverse for patients who were Hispanic (aHR 0.52; CI 0.25-1.05 and 0.74; CI 0.42-1.29, respectively) or Asian (aHR 1.03; CI 0.48-2.21 and 0.39; CI 0.16-0.95, respectively). No significant differences were found for comparisons with Black patients for either period for these severe outcomes; Black patients were at an increased risk for any hospitalization and for any hospitalization with low-flow oxygen support during the Delta but not during the Omicron periods (*Supplemental Tables* 3-7).

Discussion

This analysis provides several key insights into the risks of severe clinical outcomes associated with the Omicron variant SARS-CoV-2 infection. First, we found that despite a higher number of diagnosed infections per day during the Omicron period, persons with SARS-CoV-2 infection during the Omicron period were significantly and substantially less likely to progress to severe clinical outcomes, including hospitalization and death. Second, persons hospitalized during the Omicron period with SARS-CoV-2 infection were significantly and substantially less likely to require higher intensity oxygen support or receive SARS-CoV-2 inpatient treatment than persons with SARS-COV-2 infection during the Delta period. Third, persons who received any COVID-19 vaccination were significantly and substantially less likely to experience severe clinical outcomes compared with those who did not receive a vaccination, during both the Omicron and Delta periods, and an additional dose was associated with a further significant and substantial reduction in risk. Fourth, the risk factors for severe clinical outcomes remained similar during the Omicron and Delta periods and include factors such as increasing age, overall comorbidity score, and certain comorbidities such as diabetes, atherosclerotic cardiovascular disease and obesity.

The risk of all severe clinical outcomes is significantly lower for persons with SARS-CoV-2 infection during the Omicron period. Our findings are similar to those that have been previously reported.[1-9] However,

Characteristic	Any Hospitalization		Hospitalization with low-flow oxygen support		Hospitalization with high-flow oxygen support or NIPPV		Hospitalization with invasive mechanical ventilation		Death	
	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)
Time period										
Delta,	5,445	1.0	4,483	1.0	1,980	1.0	521	1.0	398	1.0
July 5, 2021-Nov 30, 2021	(7.8%)		(6.4%)		(2.8%)		(0.7%)		(0.7%)	
Omicron,	1,169	0.55	773	0.46	302	0.47	70	0.43	83	0.54
Dec 18, 2021-Jan 7, 2022	(2.4%)	(0.51, 0.59)	(1.6%)	(0.43, 0.5)	(0.6%)	(0.41, 0.54)	(0.1%)	(0.33, 0.56)	(0.2%)	(0.42, 0.7)
Age, years										
0-17	81	0.12	39	0.09	16	0.13	3	0.11	2	0.2
	(0.4%)	(0.1, 0.16)	(0.2%)	(0.07, 0.13)	(0.1%)	(0.08, 0.21)	(0.0%)	(0.04, 0.37)	(0.0%)	(0.05, 0.87)
18-39	1,253	1.0	812	1.0	285	1.0	52	1.0	18	1.0
	(2.9%)		(1.9%)		(0.7%)		(0.1%)		(0.0%)	
40-49	924	1.61	778	2.07	360	2.69	85	3.49	35	4.23
	(4.7%)	(1.48, 1.76)	(4.0%)	(1.87, 2.29)	(1.8%)	(2.3, 3.15)	(0.4%)	(2.47, 4.95)	(0.2%)	(2.36, 7.59)
50-59	1,184	2.67	1,023	3.6	494	5	134	7.36	74	11.2
	(7.4%)	(2.46, 2.9)	(6.4%)	(3.27, 3.97)	(3.1%)	(4.3, 5.81)	(0.8%)	(5.3, 10.22)	(0.5%)	(6.56, 19.12)
60-69	1,225	3.94	1,042	5.5	521	8.23	164	13.66	94	19.65
	(11.5%)	(3.6, 4.3)	(9.8%)	(4.97, 6.09)	(4.9%)	(7.04, 9.63)	(1.5%)	(9.78, 19.06)	(0.9%)	(11.51, 33.57)
70-79	1,003	5.86	831	8.32	370	11.77	111	17.27	133	45.8
	(20.2%)	(5.27, 6.52)	(16.7%)	(7.36, 9.39)	(7.4%)	(9.77, 14.19)	(2.2%)	(11.75, 25.37)	(2.7%)	(26.42, 79.38)
80+	954	10.99	731	15.13	236	16.16	42	14.16	205	127.58
	(40.9%)	(9.75, 12.39)	(31.4%)	(13.18, 17.37)	(10.1%)	(12.96, 20.14)	(1.8%)	(8.76, 22.86)	(8.8%)	(72.86, 223.39)
Sex										
Female	3,339	1.0	2,524	1.0	964	1.0	253	1.0	231	1.0
	(5.2%)		(3.9%)		(1.5%)		(0.4%)		(0.4%)	
Male	3,285	1.29	2,732	1.42	1,318	1.84	338	1.77	330	2.06
	(6.1%)	(1.23, 1.36)	(5.1%)	(1.34, 1.5)	(2.5%)	(1.69, 2.01)	(0.6%)	(1.49, 2.09)	(0.6%)	(1.73, 2.46)
Race/Ethnicity										
LatinX/Hispanic Ethnicity	1,756	1.24	1,394	1.24	620	1.36	154	1.41	123	1.24
	(5.3%)	(1.16, 1.31)	(4.2%)	(1.16, 1.33)	(1.9%)	(1.22, 1.5)	(0.5%)	(1.15, 1.72)	(0.4%)	(1, 1.53)
Black/African Descent	904	1.24	690	1.15	273	1.06	71	1.08	60	0.93
	(7.2%)	(1.15, 1.34)	(5.5%)	(1.06, 1.26)	(2.2%)	(0.93, 1.22)	(0.6%)	(0.82, 1.41)	(0.5%)	(0.7, 1.24)
Asian Descent	670	1.54	498	1.51	243	2.15	63	2.26	52	1.62
	(3.9%)	(1.41, 1.68)	(2.9%)	(1.36, 1.67)	(1.4%)	(1.86, 2.48)	(0.4%)	(1.69, 3)	(0.3%)	(1.19, 2.21)
		1.0		1.0		1.0		1.0		1.0

Table 3 *(Continued)*

Characteristic	Any Hospitalization		Hospitalization with low-flow oxygen support		Hospitalization with high-flow oxygen support or NIPPV		Hospitalization with invasive mechanical ventilation		Death	
	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)
White/European or Middle Eastern Descent	3,036 (6.6%)		2,468 (5.4%)		1,034 (2.2%)		269 (0.6%)		303 (0.7%)	
Other/Unknown	258 (2.8%)	0.94 (0.82, 1.07)	206 (2.3%)	0.94 (0.81, 1.08)	112 (1.2%)	1.2 (0.98, 1.46)	34 (0.4%)	1.42 (0.99, 2.04)	23 (0.3%)	1.38 (0.9, 2.12)
Charlson Co-Morbidity Index Score										
Missing (no visits in prior year)	431 (4.0%)	1.28 (1.15, 1.42)	369 (3.4%)	1.34 (1.19, 1.5)	180 (1.7%)	1.39 (1.18, 1.63)	62 (0.6%)	2.23 (1.67, 2.98)	35 (0.3%)	2.71 (1.83, 4.03)
Score 0	2,567 (3.2%)	1.0	1,979 (2.4%)	1.0	860 (1.1%)	1.0	190 (0.2%)	1.0	89 (0.1%)	1.0
Score 1	1,045 (6.9%)	1.21 (1.1, 1.32)	846 (5.6%)	1.09 (0.98, 1.21)	396 (2.6%)	1.07 (0.92, 1.25)	99 (0.7%)	1.09 (0.8, 1.48)	77 (0.5%)	1.81 (1.28, 2.55)
Score 2	660 (13.9%)	1.45 (1.29, 1.64)	543 (11.4%)	1.29 (1.13, 1.47)	232 (4.9%)	1.11 (0.91, 1.36)	58 (1.2%)	1.06 (0.71, 1.59)	64 (1.3%)	2.07 (1.39, 3.07)
Score 3+	1,921 (29.7%)	1.88 (1.61, 2.19)	1,519 (23.5%)	1.54 (1.29, 1.84)	614 (9.5%)	1.3 (0.99, 1.71)	182 (2.8%)	1.62 (0.97, 2.69)	296 (4.6%)	3.02 (1.91, 4.76)
Chronic obstructive pulmonary disease	1,421 (11.2%)	1.13 (1.05, 1.21)	1,191 (9.4%)	1.31 (1.21, 1.42)	512 (4.0%)	1.39 (1.23, 1.57)	137 (1.1%)	1.33 (1.05, 1.69)	173 (1.4%)	1.2 (0.98, 1.47)
Diabetes	1,891 (18.3%)	1.22 (1.13, 1.32)	1,556 (15.1%)	1.3 (1.19, 1.42)	706 (6.8%)	1.37 (1.2, 1.57)	208 (2.0%)	1.48 (1.14, 1.93)	227 (2.2%)	1.15 (0.93, 1.43)
Atherosclerotic cardiovascular disease	2,135 (26.2%)	1.39 (1.27, 1.51)	1,684 (20.7%)	1.34 (1.22, 1.49)	669 (8.2%)	1.26 (1.09, 1.47)	193 (2.4%)	1.47 (1.11, 1.95)	314 (3.9%)	1.14 (0.88, 1.47)
Renal disease	1,265 (33.1%)	1.44 (1.31, 1.58)	990 (25.9%)	1.43 (1.29, 1.59)	398 (10.4%)	1.44 (1.23, 1.7)	113 (3.0%)	1.41 (1.04, 1.89)	201 (5.3%)	1.39 (1.09, 1.76)
Cancer	408 (21.1%)	1.26 (1.13, 1.41)	320 (16.5%)	1.3 (1.14, 1.48)	133 (6.9%)	1.36 (1.11, 1.66)	36 (1.9%)	1.24 (0.85, 1.81)	72 (3.7%)	1.62 (1.23, 2.14)
Rheumatologic disease	166 (17.1%)	1.21 (1.03, 1.41)	146 (15.0%)	1.37 (1.16, 1.63)	58 (6.0%)	1.41 (1.08, 1.85)	14 (1.4%)	1.18 (0.68, 2.04)	19 (2.0%)	1.18 (0.74, 1.89)
Dementia	346 (57.8%)	2.01 (1.78, 2.27)	250 (41.7%)	1.74 (1.5, 2)	76 (12.7%)	1.32 (1.02, 1.7)	13 (2.2%)	0.95 (0.53, 1.7)	74 (12.4%)	1.91 (1.45, 2.51)
Body mass index <25	1,268 (3.6%)	1.0	896 (2.5%)	1.0	308 (0.9%)	1.0	85 (0.2%)	1.0	156 (0.4%)	1.0

Table 3 (Continued)

Characteristic	Any Hospitalization		Hospitalization with low-flow oxygen support		Hospitalization with high-flow oxygen support or NIPPV		Hospitalization with invasive mechanical ventilation		Death	
	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)	n (%)	aHR (CI)
25-29.9	1,797 (5.7%)	1.09 (1.01, 1.18)	1,388 (4.4%)	1.17 (1.07, 1.27)	556 (1.8%)	1.28 (1.11, 1.48)	123 (0.4%)	0.91 (0.69, 1.21)	141 (0.5%)	0.78 (0.62, 0.99)
30-34.9	1,626 (7.5%)	1.39 (1.29, 1.5)	1,348 (6.2%)	1.56 (1.43, 1.71)	604 (2.8%)	1.94 (1.68, 2.25)	147 (0.7%)	1.48 (1.12, 1.96)	116 (0.5%)	1.07 (0.82, 1.38)
35-39.9	889 (8.6%)	1.7 (1.55, 1.86)	752 (7.3%)	1.98 (1.79, 2.2)	360 (3.5%)	2.68 (2.28, 3.14)	102 (1.0%)	2.39 (1.77, 3.23)	72 (0.7%)	1.59 (1.18, 2.14)
>=40	998 (11.9%)	2.54 (2.32, 2.78)	837 (10.0%)	2.96 (2.67, 3.28)	444 (5.3%)	4.53 (3.87, 5.31)	134 (1.6%)	4.11 (3.06, 5.51)	73 (0.9%)	2.37 (1.74, 3.22)
COVID-19 vaccination										
None	4,237 (8.5%)	8.34 (7.25, 9.6)	3,582 (7.2%)	9.88 (8.3, 11.76)	1,684 (3.4%)	13.71 (10.2, 18.42)	463 (0.9%)	11.65 (6.78, 20.02)	366 (0.7%)	12.18 (7.32, 20.26)
Complete primary series	1,914 (3.7%)	1.72 (1.49, 1.97)	1,343 (2.6%)	1.63 (1.37, 1.95)	473 (0.9%)	1.75 (1.29, 2.36)	97 (0.2%)	1.1 (0.63, 1.93)	152 (0.3%)	1.82 (1.08, 3.06)
Completed primary series + additional dose	248 (2.1%)	1.0	162 (1.4%)	1.0	53 (0.4%)	1.0	16 (0.1%)	1.0	18 (0.2%)	1.0
Other (partial/mixed/other)	225 (5.5%)	3.63 (3.01, 4.38)	169 (4.1%)	3.86 (3.08, 4.84)	72 (1.8%)	4.75 (3.28, 6.89)	15 (0.4%)	3.14 (1.51, 6.52)	25 (0.6%)	6.21 (3.3, 11.67)
Prior SARS-CoV-2 infection	149 (4.3%)	1 (0.85, 1.18)	76 (2.2%)	0.67 (0.53, 0.84)	21 (0.6%)	0.4 (0.26, 0.61)	3 (0.1%)	0.23 (0.07, 0.7)	10 (0.3%)	0.72 (0.38, 1.36)
Anti-SARS-CoV-2 antibody outpatient treatment	74 (6.5%)	0.33 (0.26, 0.41)	58 (5.1%)	0.31 (0.24, 0.41)	15 (1.3%)	0.21 (0.13, 0.35)	1 (0.1%)	0.05 (0.01, 0.37)	1 (0.1%)	0.04 (0.01, 0.31)

***Table 3*: Factors associated with severe clinical outcomes among persons with SARS-CoV-2 infection in Northern California, stratified by time periods of predominant Omicron SARS-CoV-2 variant (December 18, 2021-January 7, 2022, n=48,101) and Delta SARS-CoV-2 variant (July 5, 2021-November 30, 2021, n=69,977) transmission.**

aHR = adjusted hazard ratio using cox proportional hazards models to assess the association between SARS-CoV-2 infection during a period with predominant Omicron variant circulation versus predominant Delta variant circulation adjusted for demographics, clinical comorbidities and vaccination status.

*Treatment with bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab as an outpatient.

Abbreviations: NIPPV = Non-invasive positive pressure mechanical ventilation.

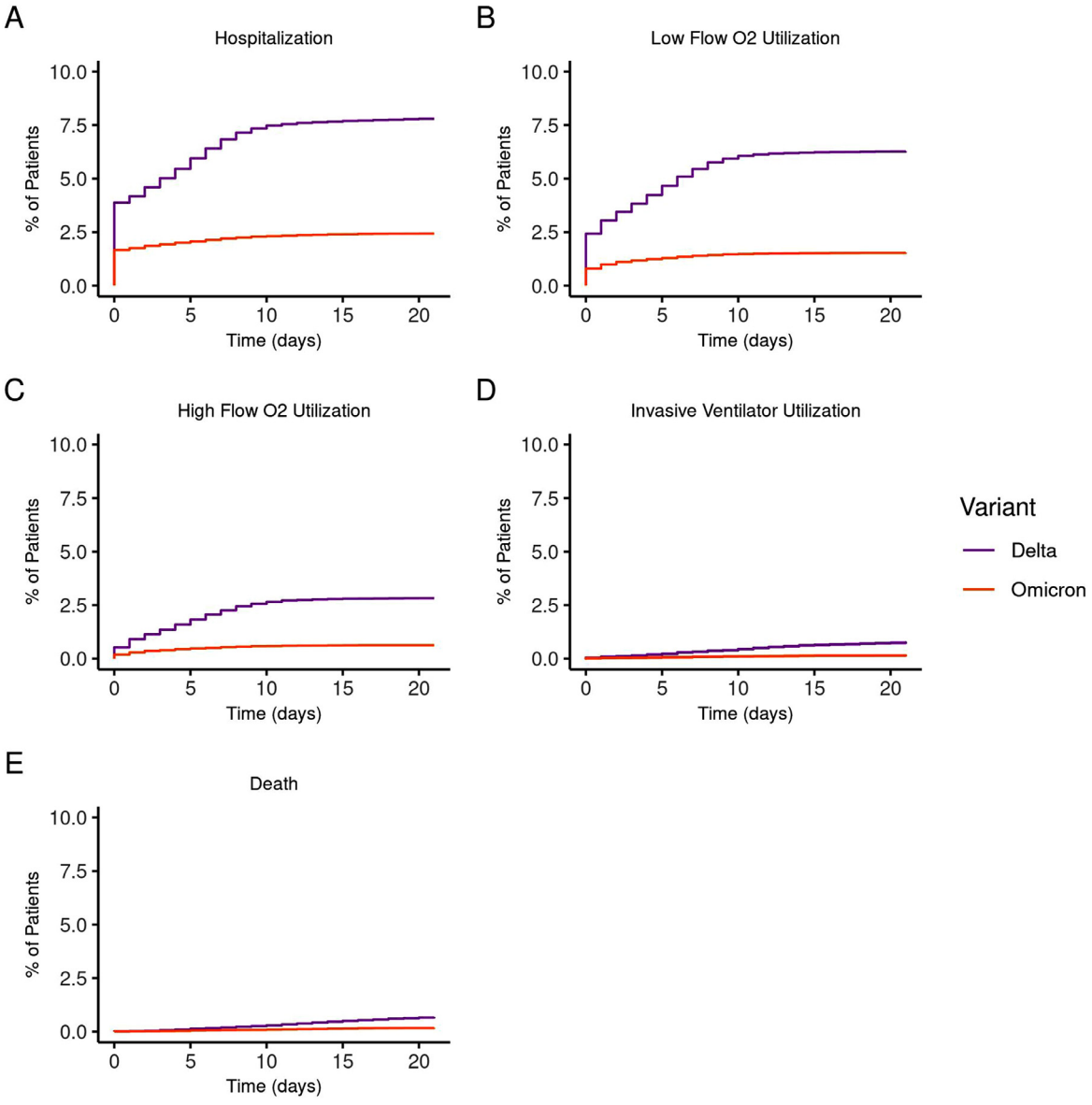

Figure 2. Cumulative incidence of severe clinical outcomes among persons with SARS-CoV-2 infection in Northern California stratified by time periods of predominant Omicron SARS-CoV-2 variant (December 18, 2021-January 7, 2022) and Delta SARS-CoV-2 variant (July 5, 2021-November 30, 2021) transmission.

all current work-to-date to elucidate the risk of severe clinical outcomes associated with the Omicron variant is based on persons diagnosed with SARS-CoV-2 infection and thus these estimates possibly overestimate the true risk of severe clinical outcomes, as persons with undiagnosed or unreported Omicron variant infection are excluded from the denominator.[26] Many health systems, including KPNC, test all persons for SARS-CoV-2 infection on admission to the hospital, and thus persons hospitalized with SARS-CoV-2 infection are unlikely to be undiagnosed or unreported, and the proportion of those hospitalized among those tested for the virus will be overestimated. Thus, the absolute risk of severe clinical outcomes among those with SARS-CoV-2 infection might be substantially lower than reported here or in other studies. During the Omicron period, this bias may be even more pronounced if SARS-CoV-2 is less likely to cause substantial symptoms and people with less severe symptoms are less likely to seek testing. The reduced risk of severe disease is also supported by biological studies. For example, prior studies have suggested the Omicron variant is less likely to infect the respiratory epithelium and thus less likely to cause lung injury.[27,28]

Our study also provides additional detail on key events during hospitalization and documents the reduced intensity of treatment in terms of COVID-19-specific inpatient therapies such as antivirals or immunomodulators as well as oxygen support. The reduced intensity of treatment further supports the reduced severity of Omicron versus Delta SARS-CoV-2 variant infection, but is balanced by the increased number of cases per day during the Omicron period, leading to an increased overall number of hospitalizations of persons with SARS-CoV-2 infection. The increased number of hospitalizations continues to put substantial strain on hospital resources even if intensity of treatment is lower during the hospitalization.

In our analyses, COVID-19 vaccination is associated with a lower risk of severe clinical outcomes during both the Omicron and Delta periods. Among those with SARS-CoV-2 infection, vaccinated persons are significantly less likely to develop severe clinical outcomes compared to those who are unvaccinated. Our analysis suggests a dose-response relationship, as those who have completed a primary series plus an additional dose had reduced risk of severe disease compared to those who received a primary series only; both groups had reduced risk compared to the unvaccinated. Interestingly, the reduced risk of severe clinical outcomes among those who received a primary series plus an additional dose is statistically significant during the Omicron period, but not the Delta period. Thus, vaccination, including additional doses, is a key strategy to reduce the risk of severe COVID-19 and is associated with significant protection for severe disease even among those who are infected with Omicron SARS-CoV-2 variant.[5,13-15,29-31] These data support the current recommendations for an additional or booster dose of COVID-19 vaccine.

Risk factors for severe clinical outcomes with SARS-CoV-2 infection have been well-described and have important clinical applications for identifying persons who might benefit from outpatient therapies to prevent severe outcomes or to prioritize receipt of these interventions when there are logistical or supply constraints; many recommended therapies (e.g., sotrovimab, nirmatrelvir/ritonavir) are in short supply.[16] This study confirms that the risk factors for severe COVID-19 among persons with SARS-CoV-2 infection have not changed substantially despite the emergence of the Omicron variant. Key risk factors continue to include age, certain comorbidities, obesity and vaccination status. Most importantly, as stated above, we found that vaccination status continues to reduce the risk of severe COVID-19 despite reports of immune evasion by the Omicron SARS-CoV-2 variant.[31]

This study has several key strengths. First, we used data from a large, integrated health system with over 4.5 million community-based members with access to robust and stable SARS-CoV-2 testing and COVID-19 vaccination programs. KPNC members receive almost all their healthcare in the system and thus we have almost complete ascertainment of clinical events, including hospitalizations and deaths, as well as demographics, comorbidities, and vaccination status. Testing and treatment practices are standardized throughout the health system and were stable during the study periods. Second, although we do not have complete sequencing data on all SARS-CoV-2 infections within KPNC, we have established mechanisms to understand SARS-CoV-2 variants circulating during each time period. Third, we have near complete ascertainment of recorded clinical risk factors for severe outcomes, allowing adjustment of our estimates by demographics, clinical characteristics, and vaccination status. The limitations of this analysis are: 1) we do not have complete sequencing or variant identification on all SARS-CoV-2 infections; there is a possibility for bias in these estimates if there are other SARS-CoV-2 variants circulating within KPNC during the selected time periods. 2) We use SGTF to define the Omicron period and although SGTF is closely associated with the Omicron variant, we do not have confirmation using whole genome sequencing within our system. However, our definition of the Omicron period, starting December 18, 2021, corresponds well with that used by the Centers for Disease Control and Prevention in their recent analyses of health care utilization comparing the Omicron period to earlier periods of the SARS-CoV-2 pandemic, in which they used December 19, 2021.[2] 3) In our analysis we assumed that the multiple clinical severity events experienced by a single patient during the same hospitalisation are independent of each other. This approach can overestimate the overall clinical severity of SARS-CoV-2 infection, however, it would equally affect the Delta and Omicron periods.

In summary, SARS-CoV-2 infection during the Omicron period is associated with significantly reduced severe clinical outcomes including hospitalization and death. COVID-19 vaccination including a primary series as well as primary series with additional dose reduce risk of severe outcomes even during the Omicron period and remains a key preventive strategy to reduce the risk of severe COVID-19. Lastly, risk factors for severe clinical outcomes remain similar during the Omicron period and include age, clinical comorbidities, obesity and vaccination status.

Contributors

All authors contributed to conceptual ideas and contributed to methodology, JS, MSW, EPE, TCC, EV, CQ, LHK contributed to formal analysis; JS, LHK contributed to writing and original draft preparation; all authors contributed to writing, reviewing, and editing the manuscript; and JS and LHK supervised the work.

Data sharing statement

De-identified data that underlie the results reported in this article will be made available upon reasonable request.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders or of Kaiser Permanente.

Funding

This study was supported in part by the National Cancer Institute Serological Sciences Network (SeroNet) grant U01 CA 260584 (Jacek Skarbinski, Douglas A Corley, and Lawrence H Kushi), and a Delivery Science Grant and the Physician Researcher Program of The Permanente Medical Group Delivery Science and Applied Research Program (Jacek Skarbinski).

Declaration of interests

All authors: No conflicts of interest identified. 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.

Acknowledgements

The authors are grateful to all Kaiser Permanente members without whom this study would not have been possible. In addition, we wish the acknowledge our partnership with the California Department of Health and participation in the California SARS-CoV-2 Whole Genome Sequencing Initiative (COVIDNet).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100297.

References

1 Ferguson N GA, Hinsley W, Volz E. Imperial College Report 50: *Hospitalisation risk for Omicron cases in England*, 2021. Updated 22 December. Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/.

2 Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in disease severity and health care utilization during the early Omicron variant period compared with previous SARS-CoV-2 high transmission periods - United States, December 2020-January 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):146–152.

3 Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. *medRxiv*. 2022.01.11.22269045; https://doi.org/10.1101/2022.01.11.22269045.

4 Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. *JAMA*. 2022;327(6):583–584.

5 Sheikh A KS, Woolhouse M, McMenamin J, Robertson C. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021. Available from: https://www.pure.ed.ac.uk/ws/portalfiles/portal/245818096/Severity_of_Omicron_variant_of_concern_and_vaccine_effectiveness_against_symptomatic_disease.pdf.

6 Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. *medRxiv*. 2021.12.24.21268382; https://doi.org/10.1101/2021.12.24.21268382.

7 US Centers for Disease Control and Prevention. First confirmed case of Omicron variant detected in the United States. 2021. [updated Updated 1 December, 2021. Available from: https://www.cdc.gov/media/releases/2021/s1201-omicron-variant.htm.

8 Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. *medRxiv*. 2022 2;2021.12.30.21268495. https://doi.org/10.1101/2021.12.30.21268495.

9 Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet*. 2022;399(10323):437–446.

10 Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399(10332):1303–1312.

11 Modes ME DM, Melgar M. Clinical characteristics and outcomes among adults hospitalized with laboratory-confirmed SARS-CoV-2 infection during periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) variant predominance — One Hospital, California, July 15 –September 23, 2021, and December 21, 2021–January 27, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:217–223.

12 Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant. *N Engl J Med*. 2022;386:1532–1546.

13 Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med*. 2022;386:494–496.

14 Garcia-Beltran WF, St. Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185(3):457–466.e4.

15 Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. *Nat Med*. 2022;28(5):1063–1071.

16 National Institutes of Health COVID-19 Treatment Guidelines. The COVID-19 treatment guidelines panel's interim statement on patient prioritization for outpatient anti-SARS-CoV-2 therapies or preventive strategies when there are logistical or supply constraints December 23, 2021. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/.

17 Gordon NP. Similarity of the adult Kaiser Permanente Membership in Northern California to the Insured And General Population in Northern California: statistics from the 2011 California Health Interview Survey, 2015.

18 Ross TR, Ng D, Brown JS, et al. The HMO research network virtual data warehouse: a public data model to support collaboration. *EGEMS*. 2014;2(1):1049.

19 Weeks J, Pardee R. Learning to share health care data: a brief timeline of influential common data models and distributed health data networks in U.S. health care research. *EGEMS*. 2019;7(1):4.

20 California Department of Health. California SARS-CoV-2 Whole Genome Sequencing Initiative. Available from: https://testing.covid19.ca.gov/covidnet/.

21 Scott L, Hsiao N-y, Moyo S, et al. Track Omicron's spread with molecular data. *Science*. 2021;374(6574):1454–1455.

22 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.

23 National Institutes of Health. COVID-19 Treatment Guidelines. 2022. Available from: https://www.covid19treatmentguidelines.nih.gov/.

24 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239–241.

25 R Core Team. R: A language and environment for statistical computing Vienna, Austria: R Foundation for Statistical Computing; 2021. Available from: https://www.R-project.org.

26 Institute of Health Metrics and Evaluation. COVID-19 results briefing: the United States of America January 21, 2022. Available from: https://www.healthdata.org/sites/default/files/files/102_briefing_United_States_of_America_4.pdf.

27 Abdelnabi R, Foo CS, Zhang X, et al. The omicron (B.1.1.529) SARS-CoV-2 variant of concern does not readily infect Syrian hamsters. *Antiviral Res*. 2022;198:105253.

28 Michael CWC, Kenrie PYH, John H, et al. SARS-CoV-2 Omicron variant replication in human respiratory tract ex vivo. *Sci Open*. 2022. https://doi.org/10.21203/rs.3.rs-1189219/v1.

29 Gozzi N, Chinazzi M, Davis JT, et al. Preliminary modeling estimates of the relative transmissibility and immune escape of the Omicron SARS-CoV-2 variant of concern in South Africa. medRxiv. 2022 .01.04.22268721; https://doi.org/10.1101/2022.01.04.22268721.

30 Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. *N Engl J Med*. 2022;386:492–494.

31 Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization of the SARS-CoV-2 Omicron variant. *N Engl J Med*. 2022;386:599–601.