Decreased Risk of Coronavirus Disease 2019–Related Hospitalization Associated With the Omicron Variant of Severe Acute Respiratory Syndrome Coronavirus 2

Jessica P. Ridgway,1 Samuel Tideman,2 Bill Wright,3 and Ari Robicsek2

1Department of Medicine, University of Chicago, Chicago, Illinois, USA, and 2Providence Research Network, Renton, Washington, USA

Among 134,223 patients with coronavirus disease 2019 (COVID-19), we assessed how risk of hospitalization changed at different intervals in the pandemic, controlling for prior COVID-19 immunity. In multivariable analysis, outpatients with COVID-19 during the Omicron–predominant time period had significantly lower odds of hospitalization compared to pre-Delta (adjusted odds ratio, 0.26 [95% confidence interval, .22–.32]).

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

The Omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with milder coronavirus disease 2019 (COVID-19) compared to previous variants [1–3]. It is unclear whether Omicron causes milder disease because it is inherently less virulent or because many infected individuals have prior immunity [1, 4]. To address this question, we assessed how the risk of hospitalization changed among patients with COVID-19 at different intervals in the pandemic, controlling for COVID-19 vaccination and prior known SARS-CoV-2 infection.

METHODS

We identified all symptomatic patients who tested positive for SARS-CoV-2 via nucleic acid amplification test (NAAT) at 1595 sites of care across 6 Western states in the Providence health network between 30 September 2020 and 7 January 2022.

RESULTS

A total of 134,223 patients were included in the study, including 90,503 patients tested in the outpatient setting and 43,720 patients tested in the ED. The mean age of patients was 41.8 years (standard deviation, 20.9 years), and 47% (63,124/134,223) were male. The racial and ethnic composition of the patient population was as follows: 55.7% (74,786/134,223) White, 22.9% (30,684/134,223) Hispanic, 4.2% (5,614/134,223) Black, 4.4% (59,555/134,223) Asian, and 12.8% (17,184/134,223) other race. One-quarter (25.3% [33,933/134,223]) of patients had received at least 1 dose of a COVID-19 vaccine, and 1.1% (1430/134,223) had a prior positive SARS-CoV-2 NAAT.

We excluded patients with a prior positive SARS-CoV-2 NAAT in the previous 90 days to avoid double-counting. We then followed patients through 21 January 2022 to assess our primary outcome: subsequent hospitalization with a COVID-19 diagnosis within 14 days. We collected demographic characteristics, care setting, vaccination status, and prior SARS-CoV-2 infections for all study patients. Patients were considered vaccinated if they received at least 1 dose of COVID-19 vaccine ≥14 days prior to their positive COVID-19 test. We chose to consider patients vaccinated even if they had only received 1 dose of a messenger RNA vaccine in order to account for all patients with any known prior vaccine-induced COVID-19 immunity.

To assess how hospitalization rates have changed over the course of the pandemic and in the face of different variants, we defined 3 key time periods for our analysis: pre-Delta (prior to 20 June 2021), Delta (20 June–18 December 2021), and Omicron (19 December 2021 or later, when Omicron accounted for >80% of cases in our region) [5].

We performed multivariable logistic regression to determine if the predominant SARS-CoV-2 variant at the time of positive SARS-CoV-2 test was associated with the outcome of COVID-19–related hospitalization, controlling for demographic characteristics, vaccination status, prior positive SARS-CoV-2 NAAT, and state. We stratified analyses based on location of care at the time of positive SARS-CoV-2 test (outpatient vs emergency department [ED]). This study was approved by the Providence Institutional Review Board.

Figure 1 describes how patient characteristics and hospitalization rates have changed for vaccinated and unvaccinated patients over the course of the pandemic. Vaccination rates were generally higher during the Omicron–predominant period compared to the Delta and pre-Delta time periods.
Regardless of vaccination status, patients’ unadjusted risk of hospitalization was lower during Omicron than in previous waves (5.1% [1520/30 052] vs 15.8% [8182/51 937] vs 16.7% [8714/52 234] for Omicron vs Delta vs pre-Delta, respectively).

In the multivariable analysis, patients with COVID-19 during the Omicron-predominant time period had significantly lower odds of hospitalization compared to patients in the pre-Delta time period (outpatients: adjusted odds ratio [aOR], 0.26 [95% confidence interval {CI}, .22–.32]; ED patients: aOR, 0.44 [95% CI, .42–.48]), even when adjusting for demographic characteristics, COVID-19 vaccination, and prior SARS-CoV-2 infection. Patients who had been vaccinated against COVID-19 also had lower odds of hospitalization (outpatients: aOR, 0.30 [95% CI, .26–.34]; ED patients: aOR, 0.69 [95% CI, .64–.73]). Patients who had previously tested positive for SARS-CoV-2 had no significant difference in hospitalization compared to patients who had not previously tested positive for SARS-CoV-2 (outpatients: aOR, 0.59 [95% CI, .26–1.34]; ED patients: aOR, 0.87 [95% CI, .67–1.13]). Variables associated with increased odds of hospitalization included male sex (outpatients: aOR, 1.18 [95% CI, 1.07–1.31]; ED patients: aOR, 1.35 [95% CI, 1.29–1.40]) and older age as measured in 1-year increments (outpatients: aOR, 1.06 [95% CI, 1.06–1.06]; ED patients: aOR, 1.05 [95% CI, 1.05–1.05]) (Supplementary Table 1).

**DISCUSSION**

In a large multicenter study, the SARS-CoV-2 Omicron variant was associated with significantly decreased odds of hospitalization compared to previous variants, even after controlling for COVID-19 vaccination status and prior positive SARS-CoV-2 test. Notably, we found that unvaccinated outpatients with COVID-19 during the Omicron-predominant time period were 72% less likely to require hospitalization than those during the Delta-predominant time period (0.8% vs 2.9%),
respectively). These findings may be explained by lower virulence of the Omicron strain, increased natural immunity in the population, or a combination of these influences. While our study controlled for vaccination status and known prior SARS-CoV-2 infection, there were likely a large number of missed prior SARS-CoV-2 infections in the study population. These missed cases could occur if patients were tested for SARS-CoV-2 outside our healthcare network (eg, at another facility or at home) or did not undergo testing. Later in the pandemic, patients may be more likely to have had prior undiagnosed SARS-CoV-2 infections, resulting in higher levels of immunity to SARS-CoV-2 during the Omicron-predominant time period.

Other studies have similarly found 40%–65% lower hospitalization rates among patients with the Omicron variant compared to the Delta variant [3, 6–8]. While our study assessed risk for hospitalization among patients in the outpatient or ED settings, prior studies among patients already hospitalized with COVID-19 have found lower risk of intensive care unit admission and death with the Omicron variant compared to the Delta variant of SARS-CoV-2 [1, 9].

Vaccination remains important: During the Omicron-predominant period, we found that unvaccinated outpatients had more than double the hospitalization rate (0.8% vs 0.3%) compared to vaccinated outpatients. Preliminary studies have reported that current COVID-19 vaccines have decreased effectiveness for preventing infection with the Omicron variant [10]. However, our data suggest that vaccination remains protective against severe COVID-19 during Omicron predominance.

Study limitations include possible hospitalization at outside healthcare facilities, but we limited our sample to locations associated with nearby Providence hospitals, and this limitation should not affect our calculation of the relative difference in admission rates between variants. We may be missing vaccination data for some patients vaccinated at outside healthcare facilities, resulting in their incorrect classification as “unvaccinated.” However, our healthcare facilities routinely verify vaccination status from patients and state registries during outpatient appointments and at hospitalization. Availability of COVID-19 testing may have changed over the course of the study period, potentially impacting study findings. For example, if people with mild illness were more likely to undergo SARS-CoV-2 testing and receive a COVID-19 diagnosis later in the pandemic, this could result in a lower measured hospitalization rate during the Omicron phase. Finally, we did not sequence SARS-CoV-2 specimens to identify variants, but rather inferred variant based on the predominant variant in the region at the time of testing.

In conclusion, in a large multicenter cohort study, we found that the Omicron variant of SARS-CoV-2 is associated with milder disease in both vaccinated and unvaccinated individuals.

**Supplementary Data**

Supplementary materials are available at Open Forum 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**

Patient consent. A waiver of consent was granted by the Providence Institutional Review Board, given that the study posed no more than minimal risk.

Potential conflicts of interest. All authors: No reported conflicts of interest.

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.

**References**

1. Maslo C, Friedland R, Toubkin M, et al. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. JAMA 2021; 327:583–4.
2. Christie B. Covid-19: early studies give hope Omicron is milder than other variants. BMJ 2021; 375:n3144.
3. Fergusson N, Ghani A, Hinsley W, Volz E. Hospitalisation risk for Omicron cases in England. Imperial College London. 2021. https://www.imperial.ac.uk/media/imperial-college/medicine/mrc-gida/2021-12-22-COVID19-Report-50.pdf. Accessed 15 February 2022.
4. Bhattacharyya RP, Hanage WP. Challenges in inferring intrinsic severity of the SARS-CoV-2 Omicron variant. N Engl J Med 2022; 386:e14.
5. Centers for Disease Control and Prevention. Variant proportions: COVID data tracker. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 14 January 2022.
6. Sheikh A, Kerr S, Woolhouse M, McMenamin J, Robertson C; EAVE II Collaborators. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland [manuscript published online ahead of print 22 April 2022]. Lancet Infect Dis 2022. doi:10.1016/S1473-3099(22)00141-4.
7. 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 [Preprint]. Postemb online 11 January 2022. doi:10.1101/2022.01.11.22269045.
8. Nyberg T, Ferguson N, Nash S, 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. Lancet 2022; 399:1303–12.
9. Modes ME, Directo MP, Melgar M, et al. 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; 71:217–23.
10. Rossler A, Riepler L, Bante D, et al. SARS-CoV-2 Omicron variant neutralization in serum from vaccinated and convalescent persons. N Engl J Med 2022; 386:698–700.