SARS-CoV-2 Omicron Variant is as Deadly as Previous Waves After Adjusting for Vaccinations, Demographics, and Comorbidities

Zachary Strasser (zstrasser@mgh.harvard.edu)
Massachusetts General Hospital https://orcid.org/0000-0002-4846-6059
Aboozar Hadavand
Minerva University
Shawn Murphy
Massachusetts General Hospital https://orcid.org/0000-0002-1905-8806
Hossein Estiri
Harvard Medical School https://orcid.org/0000-0002-0204-8978

Brief Communication

Keywords:

Posted Date: May 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1601788/v1

SARS-CoV-2 Omicron Variant is as Deadly as Previous Waves After Adjusting for Vaccinations, Demographics, and Comorbidities

Zachary H. Strasser MD, MBI, MBA[1,2], Aboozar Hadavand PhD[3], Shawn N. Murphy MD, PhD[1,2]*, Hossein Estiri PhD[1,2]*

[1.] Massachusetts General Hospital, Boston, MA; [2.] Harvard Medical School, Boston, MA; [3.] Minerva University, San Francisco, CA

*** co-senior authors**

Abstract Word Count: 148
Word Count: 1,999 [Abstract, Main:1,503; References: 496]

Corresponding Author: Zachary H. Strasser, MD
Postal address: MGH Laboratory of Computer Science, 50 Staniford Street, Suite 750, Boston, MA 02114, USA.
E-mail: zstrasser@mgh.harvard.edu

Abstract

The B.1.1.529 (Omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has previously been reported as more transmissible, but less severe than other SARS-CoV-2 variants. To test this assumption, we linked state-level vaccination data with quality-controlled electronic health records from a large healthcare system, including 13 hospitals, in Massachusetts, USA. We then performed a weighted case-control study to compare risks of hospital admission and mortality across the SARS-CoV-2 waves in over 130,000 COVID patients. Although the unadjusted rates of hospital admission and mortality appeared to be higher in previous waves compared to the Omicron period, after adjusting for confounders including various demographics, Charlson comorbidity index scores, and vaccination status (and holding the healthcare utilization constant), we found that the risks of hospitalization and mortality were nearly identical between periods. Our analysis suggests that the intrinsic severity of the Omicron variant may be as severe as previous variants.

Main

The B.1.1.529 (Omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported as more transmissible, but less severe, than previous variants in a variety of locations including South Africa, Scotland, England, and Canada.[1–4] However, understanding the intrinsic severity of Omicron is challenging.[5] A number of confounding factors affecting severity in COVID-19 have changed since the start of the pandemic and may continue to change. The confounding factors include the initiation of new vaccines and therapeutics,[6] implementation of various public health strategies,[7] variations in vulnerability that can be proxied in demographic factors,[8] and differences in healthcare utilization practices across institutions and time. Any comparison between SARS-CoV-2 variants without adequately

adjusting and controlling for important confounders that may change over time such as vaccination status and healthcare utilization, can mislead both the public and medical experts of the true danger of the variant. It could also lead to mistrust among the public and poor choices by health policy experts.

To reduce different confounding biases for comparing the severity of the Omicron variant versus previous variants, we applied a causal modeling approach -- using inverse probability of treatment weighting (IPTW) – to linked data from Massachusetts state-wide vaccine registry and curated outcomes and longitudinal electronic health records from the Mass General Brigham (MGB). The use of these data sources in this study were approved by the MGB Institutional Review Board with a waiver of informed consent. MGB is one of the largest healthcare systems in the United States providing care for approximately 1.5 million patients annually in the New England region. The choice of a multi-hospital network healthcare system allows for holding the healthcare utilization factor constant, and the hospital systems under MGB followed similar procedures.

Various methods can control for confounding in observational studies, including multivariable regression,[9] stratification,[10] and propensity-score matching methods.[11] IPTW, a type of propensity-score weighting method, has become more popular recently for assessing causal relationships in medicine.[12] We chose IPTW as our model for quantifying COVID-19 severity for several reasons. First, the propensity score-based method, in general, can summarize many covariates to a single covariate, which is helpful given the large number of covariates in our COVID-19 model. Second, compared with other propensity-score matching techniques, unmatched individuals are not discarded from an IPTW analysis. This increases the effective sample size.[13] Additionally, multiple

weighting formulations have been introduced to address different issues such as extremely large weights. These formulations can help find different treatment effects depending on the context.[14]

Across the MGB system, 148,876 patients had a positive polymerase chain reaction (PCR) between December 1st, 2020 and February 28th, 2022. 131,174 COVID-19 patients met the inclusion and exclusion criteria for the study. Table 1 shows the key demographics for this patient cohort separated into unique COVID-19 waves. In each of the waves more of the cases were women than men (ranging from 57.8% to 61.5%). The patients infected in the Winter 20'-21' period were older (47.4 ± 21.2) compared to later periods. The number of non-whites infected decreased in the latter two waves compared to the first two. The Charlson comorbidity index scores are similar across the four periods. However, in the Winter 20'-21' period, there were less patients having a score of 0, and more with a score greater than 4. As would be expected, given the introduction of vaccinations during the Winter 20'-21' period, the percentage of patients vaccinated changed substantially with each subsequent period. The first two periods have very few patients infected with SARS-CoV-2 having had a previous vaccination. Whereas in the later periods a greater percentage of the infected have been vaccinated.

The number of detected cases were relatively higher in the winter months compared to the summer and spring. There were 36,682 detected cases in Winter 20' - 21', 10,281 in Spring 21', and 18,892 in the Delta period. Then during the Omicron wave the number of cases increased to 65,317. Despite the increased number of cases in the Omicron period, the hospitalization risk and mortality risk were lower than the other three periods. The hospitalization risk during the Omicron period was about 12.7 % of detected cases. Whereas the hospitalization risk in the other three periods varied between 14.2 % and 15.8 %. Compared with the Omicron period the risk of hospitalization

was lower for the Winter 20'-21' period (OR: 1.24, 95% CI: 1.19 - 1.29, $p < 0.01$), Spring 21' period (OR: 1.26, 95% CI: 1.19 - 1.33, $p < 0.01$), and Delta period (OR: 1.11, 95% CI: 1.06 - 1.17, $p < 0.01$). The in-hospital mortality risk among detected cases was also substantially lower during the Omicron period compared to the Winter 20'-21' period (OR: 1.85, 95% CI: 1.57 - 2.18, $p < 0.01$), Spring 21' period (OR: 1.40, 95% CI: 1.05 - 1.85, $p < 0.01$), and Delta period (OR: 1.60, 95% CI: 1.29 - 1.97, $p < 0.01$).

However, unlike the common perception of a less severe Omicron variant, after adjusting for confounding variables, the hospitalization risk of the Omicron period was actually very similar to the previous time periods. Compared with the Omicron period, the risk of hospitalization was lower in the Winter 20'-21' period (OR: 0.92, 95% CI: 0.89 - 0.95, $p < 0.005$). There was no detected difference when comparing adjusted hospitalization risk of Omicron to Spring 21' (OR: 1.10, 95% CI: 0.99 - 1.21, $p = 0.06$) or Omicron to Delta (OR: 1.00, 95% CI: 0.99 - 1.01, $p = 0.67$). Compared to the Omicron period, the risk of mortality was very similar to the Winter 20'-21' period (OR: 1.00, 95% CI: 1.00 - 1.01, $p = 0.4$) and Delta period (OR: 1.00, 95% CI: 1.00 - 1.01, $p = 0.08$). And compared to Spring 21', while Omicron had a statistically significant decreased risk of mortality, the adjusted odds ratio was nearly equivalent (OR: 1.00, 95% CI: 1.00 - 1.01, $p = 0.01$).

Our findings suggest that after accounting for confounders, the Omicron variant was as deadly as the previous SARS-CoV-2 waves. The hospitalization risk had a less consistent pattern, but after accounting for confounders, Omicron seems to have a slightly higher hospitalization risk than the Winter of 20' - 21', and slightly lower hospitalization risk than that of Spring 21'. There were changes in the distribution of sex, age, race, and comorbidity score between each of the waves.

Each of these factors have previously been associated with differences in severity of COVID-19.[15–17] After accounting for their changes, the significance of the severity seems to decrease. The vaccination covariate changed the most between waves. Previous studies have shown very clearly that vaccinations protect against the Omicron variant.[18–20] However, while a case-control matching study suggested Omicron may have less severe outcomes, such a studies suffers from small patient populations analyzed and that many patients are discarded in the analysis.[4] Our study incorporates vaccinations, comorbidities, demographics, and healthcare utilization, applies IPTW weighting matching, and shows severity is actually very similar between variants.

There are several limitations in this study. First, the vaccination status is based on the Massachusetts state level vaccine registry. Therefore, we may be underestimating the number of vaccinated patients and overestimating the number of unvaccinated patients in the more recent periods. Additionally, we counted cases as positive PCR SARS-CoV-2 tests. This likely undercounts the number of real SARS-CoV-2 infections since it does not include patients who had an at-home rapid test, visited a facility outside of MGB, or chose not to get tested. Despite this limitation, it is likely a consistent problem between periods. Finally, we considered all infections between December, 2021 to February, 2022 as representative of Omicron. However, there were likely other variants during these episodes that infected patients. Still, Omicron rapidly became the dominant strain.

Measuring severity of the new variant can be challenging given there are so many confounders that have changed since the start of the pandemic. Still the large difference of the unadjusted risk of hospitalization and mortality between the Omicron period and that of other periods, and that

difference decreasing after adjusting for differences in waves is important for highlighting that variants remain dangerous entities.

Acknowledgments

No financial or in-kind support was provided for the conduct of the study.

Author Contributions

All authors contributed to the study design. HE extracted the data. ZS and HE cleaned and analyzed the data with the guidance of AH. ZS drafted the initial manuscript. All authors revised the manuscript for critical content and clarity and approved it. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests Statement

The authors declare no competing interests.

Table 1: Demographics and health status across four temporal waves of patients infected with SARS-CoV-2

		12/2020 - 2/2021 (Winter 20' - 21') (N = 36,682)	3/2021 - 6/2021 (Spring 21') (N = 10,281)	7/2021 - 11/2021 (Delta) (N = 18,894)	12/2021 - 2/2022 (Omicron) (N = 65,317)
Female sex (%)		58.3	58.1	57.8	61.5
Age (yr.)		47.4 ± 21.2	41.2 ± 21.1	43.2 ± 22.2	41.1 ± 21.6
Nonwhite race (%)		28.1	29.0	20.4	26.6
Charlson Comorbidity	0 (%)	58.3	64.5	63.3	63.4
	1-3 (%)	32.1	27.9	29.2	29.0
	>4 (%)	9.7	7.6	7.5	7.60
Vaccine Status	No vaccine (%)	99.9	96.1	70.1	38.2
	Partial Vaccination (%)	0.1	1.1	1.9	2.9
	Full Vaccination (%)	-	2.8	26.1	33.3
	Full Vaccination with Booster (%)	-	-	1.8	25.6

Table 2: Severity outcome across four temporal waves of SARS-CoV-2

	Infected	Hospital Admissions n (%)	OR[b] (95% CI)	Adjusted[c] OR[b] (95% CI)	Mortality[a] n (%)	OR[b] (95% CI)	Adjusted[c] OR[b] (95% CI)
12/2020 - 2/2021 (Winter 20' - 21')	36,682	5,732 (15.6)	1.24 (1.19 - 1.29)	0.92 (0.88 - 0.96)	303 (0.83)	1.85 (1.57 - 2.18)	1.00 (.99 - 1.00)
3/2021 - 6/2021 (Spring 21')	10,281	1,622 (15.8)	1.26 (1.19 - 1.33)	1.09 (0.99 - 1.21)	64 (0.62)	1.40 (1.05 - 1.85)	1.01(1.00 - 1.01)
7/2021 - 11/2021 (Delta)	18,894	2,683 (14.2)	1.11 (1.06 - 1.17)	1.00 (0.99 - 1.01)	134 (0.71)	1.60 (1.29 - 1.97)	1.01 (0.99 - 1.02)
12/2021 - 2/2022 (Omicron)	65,317	8,322 (12.7)	-	-	313 (0.48)	-	-

[a] in-hospital, 30-day mortality

[b] compared to Omicron [95% CI]

[c] adjusted refers to covariates weighted to balance for confounding bias and the model controlling for the covariates.

References

1. Wolter, N. *et al.* Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet* **399**, 437–446 (2022).
2. Sheikh, A., Kerr, S., 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).
3. Ferguson, N., Ghani, A., Hinsley, W., Volz, E. & On behalf of the Imperial College COVID-19 Response Team. Report 50: Hospitalisation risk for Omicron cases in England. (2021) doi:10.25561/93035.
4. Ulloa, A. C., Buchan, S. A., Daneman, N. & Brown, K. A. Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada. *JAMA* **327**, 1286–1288 (2022).
5. Bhattacharyya, R. P. & Hanage, W. P. Challenges in Inferring Intrinsic Severity of the SARS-CoV-2 Omicron Variant. *N. Engl. J. Med.* **386**, e14 (2022).
6. Rosenberg, E. S. *et al.* Covid-19 Vaccine Effectiveness in New York State. *N. Engl. J. Med.* **386**, 116–127 (2022).
7. Banholzer, N. *et al.* Estimating the effects of non-pharmaceutical interventions on the number of new infections with COVID-19 during the first epidemic wave. *PLoS One* **16**, e0252827 (2021).
8. Venkatesan, P. The changing demographics of COVID-19. *Lancet Respir Med* **8**, e95 (2020).
9. Alexopoulos, E. C. Introduction to multivariate regression analysis. *Hippokratia* **14**, 23–28 (2010).
10. Zhang, Z., Zhang, H. & Khanal, M. K. Development of scoring system for risk stratification in clinical medicine: a step-by-step tutorial. *Ann Transl Med* **5**, 436 (2017).

11. Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav. Res.* **46**, 399–424 (2011).
12. Chesnaye, N. C. *et al.* An introduction to inverse probability of treatment weighting in observational research. *Clin. Kidney J.* **15**, 14–20 (2022).
13. Stuart, E. A. Matching methods for causal inference: A review and a look forward. *Stat. Sci.* **25**, 1–21 (2010).
14. Li, F., Morgan, K. L. & Zaslavsky, A. M. Balancing Covariates via Propensity Score Weighting. *Journal of the American Statistical Association* vol. 113 390–400 (2018).
15. Spagnolo, P. A., Manson, J. E. & Joffe, H. Sex and Gender Differences in Health: What the COVID-19 Pandemic Can Teach Us. *Ann. Intern. Med.* **173**, 385–386 (2020).
16. Estiri, H. *et al.* Predicting COVID-19 mortality with electronic medical records. *NPJ Digit Med* **4**, 15 (2021).
17. Raharja, A., Tamara, A. & Kok, L. T. Association Between Ethnicity and Severe COVID-19 Disease: a Systematic Review and Meta-analysis. *J Racial Ethn Health Disparities* **8**, 1563–1572 (2021).
18. Abu-Raddad, L. J. *et al.* Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. *N. Engl. J. Med.* (2022) doi:10.1056/NEJMoa2200797.
19. Collie, S., Champion, J., Moultrie, H., Bekker, L.-G. & Gray, G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. *N. Engl. J. Med.* **386**, 494–496 (2022).
20. Chandrashekar, A. *et al.* Vaccine protection against the SARS-CoV-2 Omicron variant in macaques. *Cell* (2022) doi:10.1016/j.cell.2022.03.024.

Methods

Study Population

The clinical data in this study comes from patients seen at Mass General Brigham (MGB). The vaccination data comes from the Massachusetts vaccine registry. This is a diverse population in the northeastern United States (New England region). MGB is one of the largest healthcare systems in the United States providing care for approximately 1.5 million patients annually in the New England region.

Study Design

The study was approved by MGB's IRB board Protocol # 2020P001063. The study was exempt from the requirement for informed consent from the patients, owing to the retrospective design.

Inclusion/Exclusion Criteria

We included all patients who had a positive SARS-2-CoV polymerase chain reaction (PCR) test between December 1st, 2020 and February 28th, 2022, anywhere across the MGB healthcare system. To increase the likelihood that we have enough information from a patient to compute their comorbidity history and capture their outcomes in follow up care within the MGB system providers, we required a minimum data floor threshold of at least two diagnosis records, six months apart, in the three years prior to their SARS-CoV-2 infection. State wide-vaccination records were then linked to the local MGB data repository.

Feature Engineering

Then we tabulated the covariates for each patient. The Charlson comorbidity index score was calculated in R by extracting International Classification of Diseases, Version 10 (ICD-10) codes and using the Rpackage "comorbidity" to calculate the Charlson scores for each patient. The vaccination status was categorized into one of four groups- "No Vaccine", "First Dose Only"

(representing the first dose of Modern or Pfizer BioNTech), “Fully Vaccinated” (representing the second dose of Moderna or Pfizer and BioNTech), or “Fully Vaccinated with Booster” (representing any of the vaccines with an additional booster given). The racial category was based on one of four categories including “White”, “Black or African American”, “Asian”, or “Other/Unknown”.

Modeling Approach

Given that the Omicron variant became the dominant strain in the northeastern United States between December 2021 and February 2022, we considered SARS-CoV-2 infections during this time frame to be representative of an Omicron infection. The hospitalization risk (hospital admissions over cases) and mortality risk (in-hospital deaths over cases) were then calculated. We first performed Fisher's exact test with 95% confidence intervals to calculate odds ratios comparing the hospitalization and mortality risks of each period to the Omicron period. A two-sided P value of less than 0.05 was considered to indicated statistical significance in all analyses. Then, to reduce the confounding bias, we classified patients based on age, Charlson comorbidity index score, vaccination status, ethnicity/race, and gender and estimated weights that balance the covariates (using inverse probability weights from propensity score), the treatment effect (using a survey-weighted generalized linear model) and corresponding confidence intervals (using profiled log-likelihood). Observations were weighted based on an estimated probability of receiving the treatment (i.e., four COVID-19 variants). The method is inverse probability of treatment weighting (IPTW). These weights helped achieve a more balanced sample across the covariates for determining the adjusted odds ratios. R version 3.6.3 was used for the data modeling and analysis.

Software and Code

R statistical software version 3.6.3 (R Foundation) was used for analysis. The code for analysis is available at https://github.com/ZackS13/omicron_severity.git

Data Availability

The data was extracted from Mass General Brigham's COVID-19 Data Mart Enclave. Due to privacy regulations and per institutional and IRB approvals for this study, the patient level data cannot be shared.