RESEARCH LETTER

COVID-19 Disease Severity in Persons Infected With Omicron BA.1 and BA.2 Sublineages and Association With Vaccination Status

Infection with the SARS-CoV-2 Omicron variant is associated with less severe disease compared with the Delta variant.[1-3] Two main Omicron sublineages—BA.1 and BA.2—have variable geographic distribution. In Qatar, BA.1 was initially predominant but was quickly replaced by BA.2 as the predominant sublineage. This study sought to determine and compare the severity of SARS-CoV-2 infection among persons infected with these sublineages.

Methods | The study was approved by the institutional review boards of the Hamad Medical Corporation, Weill Cornell Medicine–Qatar, and Qatar University. A waiver of informed consent was granted because of the retrospective nature of the data retrieval. This retrospective cohort study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Using the national COVID-19 database in Qatar, we identified all COVID-19 infections diagnosed between December 19, 2021, and February 6, 2022, in adults (≥18 years). We matched each patient with BA.1 infection with a patient with BA.2 infection, including by age, sex, nationality, comorbidities, and vaccination status. Additional analyses were conducted after excluding all persons with a prior documented infection and all vaccinated persons. The primary outcome was COVID-19 case severity, criticality, and fatality using the World Health Organization guidelines[4,5] as assessed by trained medical personnel who reviewed the patients' medical charts.

Based on national surveillance data, infections between December 19, 2021, and February 6, 2022, were classified as Omicron infections. The BA.1 sublineage infection was proxied as S-gene target failure (SGTF) using the TaqPath COVID-19 Combo Kit (Thermo-Fisher Scientific) while BA.2 sublineage was proxied as a non–SGTF.

Results | From 24 301 total cases of BA.1 and 125 687 of BA.2, we were able to form 20 812 matched pairs of patients (median age [IQR], 35.0 [28.0-44.0] years; 47.9% women; 85.5% with no comorbidities). Of this final sample, 18.7% of patients were unvaccinated and 8.8% had received a booster dose in each group. Severe, critical, or fatal outcomes were recorded in 33 (0.2%) of patients with BA.1 and 36 (0.2%) of those with BA.2 (P = .25; **Table 1**). All patients with BA.1 and 35 of 36 (97.2%) with BA.2 were among those who had not received a booster dose (Table 1). In conditional logistic regression analyses accounting for exact matching, vaccination with 2 vaccine doses more than 3 months prior to infection (adjusted odds ratio [aOR], 0.22; 95% CI, 0.13-0.36) or with a booster dose (aOR, 0.02; 95% CI, 0.00-0.14) were associated with a significantly lower risk of any composite severe, critical, or fatal outcomes. Prior natural infection was not associated with a lower risk of these outcomes (aOR, 0.29; 95% CI, 0.04-2.14; **Table 2**); stratification by the sublineage yielded similar results.

We repeated the analyses after excluding those with prior documented SARS-CoV-2 infection and those who were vaccinated. The results mirrored our primary analyses, with a lower risk among the vaccinated, particularly among patients who had received a booster dose.

Discussion | The findings of this study provide reassurances at multiple levels. First, 99.8% to 99.9% of patients infected with either the BA.1 or BA.2 sublineages experienced no symptoms or mild disease. Second, there was no difference in the severity of illness between BA.1 and BA.2 sublineages infections. Among individuals who had received a booster vaccine dose, only 1 person experienced any severe, critical, or fatal outcome.

Table 1. Summary of Disease Outcomes (WHO Definition) of the 2 SARS-CoV-2 Omicron BA.1 and BA.2 Sublineages, Overall and Stratified by Vaccination Status

	Overall			No booster vaccine			Booster vaccine		
	% (95% CI)			% (95% CI)			% (95% CI)		
Disease outcome/status	BA.1 (n = 20 812)	BA.2 (n = 20 812)	*P* value[a]	BA.1 (n = 18 971)	BA.2 (n = 18 971)	*P* value[a]	BA.1 (n = 1841)	BA.2 (n = 1841)	*P* value[a]
Mild/asymptomatic	20 779 (99.8)	20 776 (99.8)	.17	18 938 (99.8)	18 936 (99.8)	.26	1841 (100.0)	1840 (99.9)	NA
Severe	24 (0.1)	28 (0.1)		24 (0.1)	27 (0.1)		0	1 (0.1)	
Critical	6 (<0.1)	4 (0.0)		6 (<0.1)	4 (<0.1)		0	0	
Death	3 (<0.1)	4 (0.0)		3 (<0.1)	4 (<0.1)		0	0	
Composite[b]	33 (0.2)	36 (0.2)	.25	33 (0.2)	35 (0.2)	.50	0	1 (0.1)	NA

Abbreviations: NA, not applicable; WHO, World Health Organization.

[a] Estimated using the McNemar test.

[b] Severe, critical, or fatal outcomes.

Table 2. Multivariable Logistic Regressions With Outcome Disease Status (WHO Definition) as Dependent Variable, Overall and Stratified by the BA.1 and BA.2 Sublineages

Variable	Composite (severe/critical/fatal) outcome vs no outcome, aOR (95% CI)		
	Any sublineage[a]	BA.1 sublineage[b]	BA.2 sublineage[b]
Vaccination status at time of infection (comparator: not vaccinated)			
1 Dose	NA	NA	NA
Dose 2 ≤3 mo before infection	0.90 (0.12-7.01)	1.73 (0.21-14.42)	NA
Dose 2 >3 mo before infection	0.22 (0.13-0.36)	0.22 (0.11-0.46)	0.21 (0.10-0.42)
Dose 3	0.02 (0.00-0.14)	NA	0.03 (0.00-0.26)
Prior infection (comparator: no)	0.29 (0.04-2.14)	0.33 (0.04-2.46)	NA
Age (comparator: 18-29 y)			
30-39 y	0.92 (0.13-6.56)	NA	1.77 (0.16-19.71)
40-49 y	4.21 (0.84-21.18)	4.81 (0.50-46.82)	3.31 (0.33-33.22)
50-59 y	11.51 (2.48-53.50)	24.03 (2.95-195.99)	3.35 (0.31-35.88)
≥60 y	50.13 (11.17-225.82)	62.80 (7.65-515.38)	33.34 (3.81-291.54)
Male sex (comparator: female)	1.53 (0.92-2.52)	1.28 (0.62-2.65)	1.80 (0.89-3.65)
Nationality (comparator: Qatari)			
Foreign worker nationalities[c]	0.79 (0.39-1.62)	0.95 (0.36-2.52)	0.65 (0.23-1.89)
Other nationalities	0.58 (0.31-1.09)	0.59 (0.23-1.46)	0.59 (0.24-1.41)
Comorbidities, No. (comparator: 0)			
1	2.43 (0.90-6.53)	1.80 (0.46-6.92)	3.94 (0.90-17.41)
≥2	7.08 (3.48-14.38)	4.28 (1.71-10.73)	14.30 (4.45-45.95)

Abbreviations: aOR, adjusted odds ratio; NA, not applicable; WHO, World Health Organization.

[a] Conducted to account for exact matching of BA.1 and BA.2 sublineages.

[b] Multivariable logistic regression was conducted.

[c] Craft and manual workers predominantly from Bangladesh, India, Nepal, Pakistan, Sri Lanka, and Sudan.

This study's data set was derived from the Qatar National COVID-19 database with complete polymerase chain reaction testing and vaccination records. Outcomes were obtained from individual medical charts by trained independent reviewers. However, BA.1 and BA.2 sublineage ascertainment was based on proxy criteria—presence or absence of SGTF using the TaqPath Kit.[6] Some Omicron infections may have been misclassified as Delta infections, but this is unlikely because Delta incidence was low during the study.

In conclusion, SARS-CoV-2 infection with the Omicron variant sublineages BA.1 and BA.2 was rarely associated with severe, critical, or fatal disease. There is no discernable difference in severity of BA.1 vs BA.2 infections. Risk of severity is further mitigated by vaccination, particularly the receipt of a booster dose.

Adeel A. Butt, MBBS, MS
Soha R. Dargham, MS
Peter Coyle, MD
Hadi M. Yassine, PhD, MSc
Abdullatif Al-Khal, MD
Abdul-Badi Abou-Samra, MD, PhD
Laith J. Abu-Raddad, PhD

Author Affiliations: Hamad Medical Corporation, Doha, Qatar (Butt, Coyle, Yassine, Al-Khal, Abou-Samra); Department of Medicine, Weill Cornell Medicine, New York, New York (Butt); Department of Population Health Sciences, Weill Cornell Medicine, New York, New York (Butt, Dargham, Abu-Raddad); Infectious Disease Epidemiology Group, Weill Cornell Medicine–Qatar, Doha, Qatar (Dargham, Abu-Raddad); World Health Organization Collaborating Center for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine–Qatar, Doha, Qatar (Dargham, Abu-Raddad); Biomedical Research Center, Qatar University, Doha, Qatar (Yassine).

Accepted for Publication: June 18, 2022.

Published Online: August 22, 2022. doi:10.1001/jamainternmed.2022.3351

Corresponding Author: Adeel A. Butt, MBBS, MS, Hamad Medical Corporation, PO Box 3050, Doha, Qatar (aabutt@hamad.qa).

Author Contributions: Drs Butt and Abu-Raddad had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Butt, Al Khal, Abou-Samra, Abu-Raddad.
Acquisition, analysis, or interpretation of data: Butt, Dargham, Coyle, Yassine, Abu-Raddad.
Drafting of the manuscript: Butt, Abu-Raddad.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Butt, Dargham, Abu-Raddad.
Administrative, technical, or material support: Butt, Al Khal, Abou-Samra, Abu-Raddad.
Supervision: Abu-Raddad.
Other–data related to identifying variants circulation: Yassine.

Conflict of Interest Disclosures: Dr Butt reported grants from Gilead Sciences to the institution, outside the submitted work. No other disclosures were reported.

Disclaimer: Data used in this study were collected as a part of the Qatar national COVID-19 response and was overseen by the Ministry of Public Health and Hamad Medical Corporation. Neither had a role in the analysis or interpretation of the data, preparation, review, or approval of the manuscript, nor the decision to submit the manuscript for publication. The views expressed in this article are those of the authors and do not necessarily represent official government views or policy of the State of Qatar or the Hamad Medical Corporation.

Additional Contributions: The authors are grateful for the leadership and assistance provided by the Ministry of Public Health in Qatar, the System-Wide Incident Command and Control Center, and the Business Intelligence Unit at Hamad Medical Corporation. We are also grateful for the dedicated frontline health care workers who have selflessly served and provided care and comfort to all patients in Qatar. We acknowledge the data, viral genome sequencing, and logistical efforts of the National Study Group for COVID-19 Epidemiology including Hebah A. Al Khatib, PhD, Gheyath K. Nasrallah, PhD, Houssein H. Ayoub, PhD (Qatar University); Srusvin Loca, BCA, Anvar H. Kaleeckal, MSc, Ali Nizar Latif, MD, Riyazuddin M. Shaik, MSc (Hamad Medical Corporation); Patrick Tang, MD, PhD (Sidra Medicine); and Roberto Bertollini, MD, MPH (Ministry of Public Health, Doha, Qatar). We also acknowledge the statistical and data management support of Hiam Chemaitelly, PhD, and administrative

support of Adona Canlas, BSc (Weill Cornell Medicine–Qatar, Cornell University). We are grateful for support from the Biomedical Research Program and the Biostatistics, Epidemiology, and Biomathematics Research Core, both at Weill Cornell Medicine–Qatar. We are also grateful for the Qatar Genome Program for supporting the viral genome sequencing. None of the additional contributors received any compensation for their contributions.

1. 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. doi:10.1016/S0140-6736(22)00017-4

2. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada. *JAMA*. 2022;327(13):1286-1288. doi:10.1001/jama.2022.2274

3. Danza P, Koo TH, Haddix M, et al. SARS-CoV-2 infection and hospitalization among adults aged ≥18 years, by vaccination status, before and during SARS-CoV-2 B.1.1.529 (Omicron) variant predominance: Los Angeles County, California, November 7, 2021-January 8, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(5):177-181. doi:10.15585/mmwr.mm7105e1

4. Seedat S, Chemaitelly H, Ayoub HH, et al. SARS-CoV-2 infection hospitalization, severity, criticality, and fatality rates in Qatar. *Sci Rep*. 2021;11(1):18182. doi:10.1038/s41598-021-97606-8

5. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Severity, criticality, and fatality of the SARS-CoV-2 Beta variant. *Clin Infect Dis*. 2021:ciab909. doi:10.1093/cid/ciab909

6. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 34. Accessed April 14, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050236/technical-briefing-34-14-january-2022.pdf