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Effectiveness of the neutralizing antibody sotrovimab among high-risk patients with mild-to-moderate SARS-CoV-2 in Qatar

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ABSTRACT

Objectives: To estimate the real-world effectiveness of sotrovimab against severe, critical, or fatal COVID-19 in Qatar at a time in which most SARS-CoV-2 incidences occurred due to the BA.2 Omicron subvariant.
Methods: We conducted a matched case-control study among all individuals eligible for sotrovimab treatment per United States Food and Drug Administration guidelines in the resident population of Qatar. The odds of progression to severe forms of COVID-19 were compared in cases (treatment group) versus controls (eligible patients who opted not to receive the treatment). Subgroup analyses were conducted.
Results: A total of 3364 individuals were eligible for sotrovimab treatment during the study period, of whom 519 individuals received the treatment, whereas the remaining 2845 constituted the controls. The adjusted odds ratio of disease progression to severe, critical, or fatal COVID-19 comparing the treatment group to the control group was 2.67 (95% confidence interval 0.60-11.91). In the analysis including only the subgroup of patients at higher risk of severe forms of COVID-19, the adjusted odds ratio was 0.65 (95% confidence interval 0.17-2.48).
Conclusion: There was no evidence for a protective effect of sotrovimab in reducing COVID-19 severity in a setting dominated by the BA.2 subvariant.

Introduction

Several monoclonal antibodies against SARS-CoV-2 have been developed for the treatment of COVID-19 (Miguez-Rey *et al.*, 2022). One of these is sotrovimab, which significantly reduced the risk of COVID-19 hospitalization and death due to infection with pre-Omicron SARS-CoV-2 variants in a randomized clinical trial (Gupta *et al.*, 2021). The United States Food and Drug Administration (FDA)

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issued an emergency authorization to permit the use of sotrovimab for the treatment of mild-to-moderate COVID-19 in patients at high risk of progression to severe COVID-19 (US Food and Drug Administration, 2022). Following FDA guidelines, Qatar's Ministry of Public Health authorized the use of sotrovimab on October 20, 2021. Nonetheless, the efficacy of sotrovimab against Omicron (B.1.1.529) subvariants is in question (US Food and Drug Administration, 2022). We estimated the real-world effectiveness of sotrovimab against severe, critical, or fatal COVID-19 in Qatar at a time in which most incidences occurred due to the BA.2 Omicron subvariant.

Methods

Study population, data sources, and study design

The effectiveness of sotrovimab was investigated using a matched case-control analysis design among the resident population of Qatar. The study population included patients aged 12 years and older, weighing at least 40 kg, who tested positive for SARS-CoV-2 using real-time reverse transcription-quantitative polymerase chain reaction (PCR) testing or rapid antigen testing between October 20, 2021 and February 28, 2022 and who had at least one risk factor that increases their risk of severe COVID-19 progression per FDA guidelines (US Food and Drug Administration, 2022). No record of COVID-19 vaccination was also considered a risk factor for severe COVID-19 progression.

In compliance with Qatar's COVID-19 Home Isolation Service guidelines, all outpatient COVID-19 cases were screened for sotrovimab eligibility and, if eligible, were contacted by phone to offer sotrovimab. Clinical and disease outcome data were retrospectively collated for all individuals meeting the study eligibility criteria. Notably, Qatar has young and diverse demographics; of that, only 9% of its residents are aged ≥50 years, and 89% are expatriates from over 150 countries (Abu-Raddad et al., 2021a).

The cases (treatment group) included patients who received 500 mg over 30-minute infusions of sotrovimab within 7 days of their positive PCR or rapid antigen test. The controls were patients who were offered the treatment but opted not to receive it. Patients were excluded from the treatment group if they showed symptoms of severe COVID-19 (oxygen saturation level <90% or required oxygen supplements) before receiving sotrovimab. Patients were excluded from the control group if they showed signs or symptoms of severe COVID-19 within 7 days of diagnosis.

The cases and controls were exact-matched in a 1: 2 ratio by COVID-19 vaccination status, previous infection status, sex, age group, nationality, comorbidity count, and epidemic phase (Delta-dominated incidence vs Omicron-dominated incidence). Vaccination status and previous infection status of cases and controls were ascertained at the time of the positive PCR or rapid antigen test. The previous infection was defined as a positive PCR or rapid antigen test ≥90 days before the PCR or rapid antigen positive test under study (Abu-Raddad et al., 2021b; Kojima *et al.*, 2021). The primary outcome of this study was progression to severe, critical, or fatal COVID-19 among those treated with sotrovimab compared with untreated patients.

The large Omicron wave exponential growth phase in Qatar started on December 19, 2021 and peaked in mid-January 2022 (Abu-Raddad *et al.*, 2022; Altarawneh *et al.*, 2022; Chemaitelly *et al.*, 2022a). Accordingly, infections diagnosed before December 19, 2021 were classified under the Delta-dominated incidence phase. Infections diagnosed on December 19, 2021 or thereafter were classified under the Omicron-dominated incidence phase. During the Omicron wave, >70% of incident cases were BA.2 infections (Abu-Raddad *et al.*, 2022; Altarawneh *et al.*, 2022; Chemaitelly *et al.*, 2022a). The remaining cases were mostly BA.1 cases, with only marginal Delta incidence.

Classification of case severity (acute care hospitalizations) (2021), criticality (intensive care unit hospitalizations) (2021), and fatality (2021) followed the World Health Organization (WHO) guidelines, and assessments were made by trained medical personnel independent of study investigators and using individual chart reviews, as part of a national protocol applied to every hospitalized COVID-19 patient.

Every hospitalized patient with COVID-19 underwent an infection severity assessment every 3 days until discharge or death. Individuals who progressed to severe, critical, or fatal COVID-19 were classified based on their worst disease outcome, starting with death (2021), followed by critical disease (2021), and then severe disease (2021). The study database was linked to the national COVID-19 severity, criticality, and fatality database to ascertain disease outcomes for every individual included in this study.

COVID-19 severity, criticality, and fatality classification

Severe COVID-19 disease was defined per WHO classification as a person infected with SARS-CoV-2 with oxygen saturation of <90% on room air and/or respiratory rate of >30 breaths/minute in adults and children aged >5 years (or ≥60 breaths/minute in children aged <2 months, ≥50 breaths/minute in children aged 2-11 months, or ≥40 breaths/minute in children aged 1-5 years) and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs) (2021). Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report (2021).

Critical COVID-19 disease was defined per WHO classification as an individual infected with SARS-CoV-2 with acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or noninvasive) or vasopressor therapy (2021). Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report (2021).

COVID-19 death was defined per WHO classification as a death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (*e.g.,* trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (*e.g.,* cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19. The detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report (2021).

Statistical analysis

The characteristics of treatment and control groups were described using frequency distributions and measures of central tendency. Group comparisons were performed using standardized mean differences, with a value of <0.1 indicating adequate matching (Austin, 2009).

The adjusted odds ratios (AORs) comparing odds of progression to severe, critical, or fatal COVID-19 in the treatment versus the

Table 1
Baseline characteristics of cases and controls.

Characteristics	Eligible study population	Eligible cases and controls			Matched cases and controls[a]		
	N = 3364 N (%)	Sotrovimab N = 519 N (%)	Controls N = 2845 N (%)	SMD[b]	Sotrovimab N = 345 N (%)	Controls N = 583 N (%)	SMD[b]
Median age (IQR) - years	40 (33-46)	44 (35-58)	40 (33-45)	0.63[c]	40 (32-50)	39 (33-46)	0.20[c]
Age (years)							
<40	1618 (48.1)	199 (38.3)	1419 (49.9)	0.64	169 (49.0)	302 (51.8)	0.07
40-59	1561 (46.4)	204 (39.3)	1357 (47.7)		147 (42.6)	241 (41.3)	
≥60	185 (5.5)	116 (22.4)	69 (2.4)		29 (8.4)	40 (6.9)	
Sex							
Male	1286 (38.2)	215 (41.4)	1071 (37.6)	0.08	124 (35.9)	195 (33.5)	0.05
Female	2078 (61.8)	304 (58.6)	1774 (62.4)		221 (64.1)	388 (66.6)	
Vaccination status[d]							
Unvaccinated	811 (24.1)	153 (29.5)	658 (23.1)	0.19	116 (33.6)	199 (34.1)	0.04
Two doses	1953 (58.1)	298 (57.4)	1655 (58.2)		191 (55.4)	314 (53.9)	
Three doses	600 (17.8)	68 (13.1)	532 (18.7)		38 (11.0)	70 (12.0)	
Prior infection status[d]							
No	3083 (91.7)	478 (92.1)	2605 (91.6)	0.02	327 (94.8)	554 (95.0)	0.01
Yes	281 (8.4)	41 (7.9)	240 (8.4)		18 (5.2)	29 (5.0)	
Nationality							
Qatari	1496 (44.5)	159 (30.6)	1337 (47.0)	0.34	103 (29.9)	186 (31.9)	0.06
Craft and manual worker nationalities[e]	771 (22.9)	144 (27.8)	627 (22.0)		83 (24.1)	127 (21.8)	
Other nationalities	1097 (32.6)	216 (41.6)	881 (31.0)		159 (46.1)	270 (46.3)	
Comorbidity count							
None	370 (11.0)	58 (11.2)	312 (11.0)	0.56	42 (12.2)	78 (13.4)	0.05
1	1848 (54.9)	186 (35.8)	1662 (58.4)		151 (43.8)	250 (42.9)	
2	860 (25.6)	167 (32.2)	693 (24.4)		105 (30.4)	181 (31.1)	
≥3	286 (8.5)	108 (20.8)	178 (6.3)		47 (13.6)	74 (12.7)	
Epidemic phase[f]							
Delta-dominated incidence	460 (13.7)	198 (38.2)	262 (9.2)	0.72	112 (32.5)	152 (26.1)	0.14
Omicron-dominated incidence	2904 (86.3)	321 (61.9)	2583 (90.8)		233 (67.5)	431 (73.9)	

Abbreviation: IQR, Interquartile range; SMD, standardized mean difference.
[a] Cases (individuals who received the sotrovimab treatment) were exact-matched with up to two controls (individuals who did not receive the sotrovimab treatment) by vaccination status, prior infection status, sex, age group, nationality group, comorbidity count, and epidemic phase. The final sample size thus includes cases that could be matched either to two controls or only to one control. This resulted in small differences between the groups.
[b] SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD <0.1 indicates the optimal balance in matching.
[c] SMD is for the mean difference between groups divided by the pooled standard deviation.
[d] Vaccination status and prior infection status were ascertained at the time of infection.
[e] These include Bangladeshis, Indians, Nepalese, Pakistanis, Sri Lankans, and Sudanese due to large proportions of these nationals being craft and manual workers.
[f] Before December 19, 2021 incidence in Qatar was dominated by the Delta variant, whereas starting from December 19, 2021 incidence was dominated by the Omicron variant.

control group and associated 95% confidence intervals (CIs) were derived using conditional logistic regression, factoring the matching in the study design.

The analysis was repeated, including only the subgroup of patients at higher risk of severe forms of COVID-19. The latter included only individuals who were immunocompromised (recipients of solid organ or hematopoietic stem cell transplant, patients receiving chemotherapy or immunosuppressive treatments, patients with severe immunodeficiency, and patients with HIV), unvaccinated individuals, those aged ≥75 years, and pregnant women. All analyses were also repeated by restricting them to only the Omicron-dominated epidemic phase.

An additional analysis was conducted in which associations with severe, critical, or fatal COVID-19 were investigated using multivariable logistic regression to include all individuals eligible for sotrovimab treatment. AORs and associated 95% CIs were derived.

P-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata software, version 17.0, (Stata-Corp., College Station, TX, USA).

Oversight

The Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards approved this retrospective study with a waiver of informed consent. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supplementary Table 1).

Results

Of 3364 individuals with documented SARS-CoV-2 infection who met sotrovimab treatment eligibility during the study period, 519 individuals consented and received the treatment. These constituted the treatment group. The remaining 2845 individuals who did not receive the treatment constituted the controls. A total of 345 individuals in the treatment group were exact-matched in a 1: 2 ratio to 583 individuals in the untreated control group.

Table 1 shows the baseline characteristics of study participants before and after matching. The median age was 40 years (interquartile range 32-50) in the matched treatment group and 39 years (interquartile range 33-46) in the matched control group. Less than 9% of cases were aged ≥60 years. Patients were of diverse nationality backgrounds and were predominantly vaccinated females. Most study participants were infected during the Omicron wave. A total of 64 and two of the individuals in the matched treatment group had a record of a hospitalization encounter in an acute care bed and an intensive care unit bed, respectively, at any time between their SARS-CoV-2-positive test and

Table 2
Baseline characteristics of the subgroup of patients at higher risk of severe forms of COVID-19[a].

Characteristics	Eligible cases and controls			Matched cases and controls[b]		
	Sotrovimab N = 340 N (%)	Controls N = 1043 N (%)	SMD[c]	Sotrovimab N = 295 N (%)	Controls N = 533 N (%)	SMD[c]
Median age (IQR) - years	40 (32-56)	37 (30-44)	0.54[d]	39 (32-53)	36 (30-44)	0.40[d]
Age (years)						
<75	308 (90.6)	1,031 (98.9)	0.38	287 (97.3)	525 (98.5)	0.08
≥75	32 (9.4)	12 (1.2)		8 (2.7)	8 (1.5)	
Sex						
Male	100 (29.4)	274 (26.3)	0.07	71 (24.1)	118 (22.1)	0.05
Female	240 (70.6)	769 (73.7)		224 (75.9)	415 (77.9)	
Condition						
Malignancy						
No	286 (84.1)	888 (85.1)	0.03	253 (85.8)	429 (80.5)	0.14
Yes	54 (15.9)	155 (14.9)		42 (14.2)	104 (19.5)	
Organ/stem cell transplant						
No	304 (89.4)	1004 (96.3)	0.27	263 (89.2)	510 (95.7)	0.25
Yes	36 (10.6)	39 (3.7)		32 (10.9)	23 (4.3)	
Immunosuppressive treatment						
No	256 (75.3)	969 (92.9)	0.50	225 (76.3)	493 (92.5)	0.46
Yes	84 (24.7)	74 (7.1)		70 (23.7)	40 (7.5)	
Severe immunodeficiency						
No	338 (99.4)	1035 (99.2)	0.02	294 (99.7)	530 (99.4)	0.03
Yes	2 (0.6)	8 (0.8)		1 (0.3)	3 (0.6)	
HIV						
No	339 (99.7)	1042 (99.9)	0.04	294 (99.7)	532 (99.8)	0.03
Yes	1 (0.3)	1 (0.1)		1 (0.3)	1 (0.2)	
Pregnancy						
No	246 (72.4)	830 (79.6)	0.17	202 (68.5)	383 (71.9)	0.07
Yes	94 (27.7)	213 (20.4)		93 (31.5)	150 (28.1)	
Vaccination status[e]						
Unvaccinated	153 (45.0)	658 (63.1)	0.37	141 (47.8)	263 (49.3)	0.04
Two doses	145 (42.7)	287 (27.5)		118 (40.0)	211 (39.6)	
Three doses	42 (12.4)	98 (9.4)		36 (12.2)	59 (11.1)	
Prior infection status[e]						
No	312 (91.8)	953 (91.4)	0.01	276 (93.6)	502 (94.2)	0.03
Yes	28 (8.2)	90 (8.6)		19 (6.4)	31 (5.8)	
Nationality						
Qatari	116 (34.1)	483 (46.3)	0.26	93 (31.5)	166 (31.1)	0.06
Craft and manual worker nationalities[f]	74 (21.8)	159 (15.2)		62 (21.0)	101 (19.0)	
Other nationalities	150 (44.1)	401 (38.5)		140 (47.5)	266 (49.9)	
Epidemic phase[g]						
Delta-dominated incidence	104 (30.6)	172 (16.5)	0.34	85 (28.8)	142 (26.6)	0.05
Omicron-dominated incidence	236 (69.4)	871 (83.5)		210 (71.2)	391 (73.4)	

Abbreviation: IQR, Interquartile range; SMD, standardized mean difference.

[a] These include immunocompromised individuals (solid organ or hematopoietic stem cell transplant recipients, patients receiving chemotherapy or immunosuppressive treatments, patients with severe immunodeficiency, and HIV patients), unvaccinated individuals, those ≥75 years of age, and pregnant women.

[b] Cases (individuals who received the sotrovimab treatment) were exact-matched with up to two controls (individuals who did not receive the sotrovimab treatment) by vaccination status, prior infection status, sex, age group, nationality group, and epidemic phase. The final sample size thus includes cases that could be matched either to two controls or only to one control. This resulted in small differences between the groups.

[c] SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD<0.1 indicates the optimal balance in matching.

[d] SMD is for the mean difference between groups divided by the pooled standard deviation.

[e] Vaccination status and prior infection status were ascertained at the time of infection.

[f] These include Bangladeshis, Indians, Nepalese, Pakistanis, Sri Lankans, and Sudanese due to large proportions of these nationals being craft and manual workers.

[g] Before December 19, 2021 incidence in Qatar was dominated by the Delta variant, whereas starting from December 19, 2021 incidence was dominated by the Omicron variant.

the end of the study. The corresponding numbers for the untreated control group were 27 and zero, respectively. Most hospitalization encounters were unrelated to COVID-19 severity, for dispensing of treatment, or out of caution as part of a proactive approach to prevent the progression of the disease. Table 2 shows baseline characteristics of the subgroup at higher risk of severe forms of COVID-19 before and after matching. The matched study groups were overall well balanced in the different analyses (Tables 1 and 2).

The AOR of progression to severe, critical, or fatal COVID-19, comparing those treated to those untreated, was 2.67 (95% CI 0.60-11.91) (Table 3). This analysis was not possible when the timeframe was restricted to the Omicron-dominated epidemic phase because there were no cases of severe, critical, or fatal COVID-19 among the untreated controls (Table 3).

In the analysis including only the subgroup of patients at higher risk of severe forms of COVID-19, the AOR was 0.65 (95% CI 0.17-2.48; Table 3). Restricting this analysis to the Omicron-dominated epidemic phase yielded an AOR of 0.88 (95% CI 95% CI: 0.16-4.89) (Table 3).

In the additional analysis using multivariable logistic regression on the full sample, the AOR of progression to severe, critical, or fa-

Table 3
Association of sotrovimab treatment with COVID-19 infection severity in matched treatment and control groups.

Study group	Severe/critical/fatal[a] COVID-19	Mild/asymptomatic infection	Adjusted odds ratio (95% CI)
Main analysis			
Controls[b]	3	580	1.00
Sotrovimab[b]	4	341	2.67 (0.60-11.91)
Subgroup analysis[c]			
Controls[d]	8	525	1.00
Sotrovimab[d]	3	292	0.65 (0.17-2.48)
Restricting analyses to Omicron-dominated epidemic phase			
Main analysis			
Controls[b]	0	431	1.00
Sotrovimab[b]	2	231	-[e]
Subgroup analysis[c]			
Controls[d]	4	387	1.00
Sotrovimab[d]	2	208	0.88 (0.16-4.89)

[a] Severity (2021), criticality (2021), and fatality (2021) were defined according to the World Health Organization guidelines.
[b] Cases and controls were exact-matched one-to-two by vaccination status, prior infection status, sex, age group, nationality group, comorbidity count, and epidemic phase. Matching factors are described in detail in Table 1.
[c] Subgroup analysis was performed on a subsample that includes only immunocompromised individuals (solid organ or hematopoietic stem cell transplant recipients, patients receiving chemotherapy or immunosuppressive treatments, patients with severe immunodeficiency, and HIV patients), unvaccinated individuals, those ≥75 years of age, and pregnant women.
[d] Cases and controls were exact-matched 1:2 by vaccination status, prior infection status, sex, age group, nationality group, and epidemic phase. Matching factors are described in detail in Table 2.
[e] CIs could not be estimated through conditional logistic regression because of zero events among controls.

tal COVID-19, comparing those treated to those untreated, was 1.80 (95% CI 0.61-5.29) (Table 4). In the subgroup analysis restricted to only patients at higher risk of severe forms of COVID-19, the AOR was 1.33 (95% CI 0.44-4.05) (Table 5).

Discussion

There was no evidence of reduced risk of severe forms of COVID-19 among individuals who received sotrovimab treatment per the FDA guidelines. This was also true for the subgroup of patients at higher risk of severe forms of COVID-19. These findings contrast with the effectiveness observed in a randomized control trial and other studies (Aggarwal *et al.*, 2022; Gupta *et al.*, 2021; Gupta *et al.*, 2022; Huang et al., 2022; Ong *et al.*, 2022) but agree with another study that found no evidence of a protective effect (ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group 2022). These findings may be explained by the fact that most infections during the study occurred during the Omicron wave and were predominantly due to BA.2 (Abu-Raddad *et al.*, 2022; Altarawneh *et al.*, 2022; Chemaitelly *et al.*, 2022a). Recent evidence demonstrated lower neutralizing activity of sotrovimab against the Omicron variant and particularly against BA.2 (Takashita et al., 2022a,b). The FDA has recently blocked the use of sotrovimab in regions where BA.2 is dominant (US Food and Drug Administration, 2022). An alternative explanation is that those who consented and received the treatment may have perceived a need for this treatment because of poorer underlying health, thereby biasing the effectiveness of the treatment.

This study has limitations. Although the sample size was not small, it was not sufficient to precisely measure a small effect, given that we had to adjust the analysis for other factors that affect the severity of COVID-19, including age, vaccination, previous infection, comorbidities, and infection variant status. With the decreased efficacy of sotrovimab against BA.2, larger study samples may be needed to see the reduced effect size. It is possible that many patients declined sotrovimab treatment due to a perception of lower severity of Omicron infections.

Most of the study participants were vaccinated. Vaccination substantially reduces the severity of infection (Chemaitelly *et al.*, 2021; Chemaitelly *et al.*, 2022b), thereby potentially confounding the results or affecting the study's statistical precision to observe an effect. Vaccinated individuals may not benefit from sotrovimab treatment. All patients in our study were outpatients; thus, it is not likely that the lack of evidence of effectiveness could have been due to an inferior efficacy of sotrovimab treatment for inpatients.

Omicron, which resulted in a massive wave, was by far the largest of all waves in Qatar (Abu-Raddad *et al.*, 2022; Altarawneh *et al.*, 2022; Chemaitelly *et al.*, 2022a), and the study duration overlapped with this wave. With the lower severity of Omicron infections (Butt et al., 2022a,b), most COVID-19 hospitalizations during this time were with COVID-19 rather than because of COVID-19. The use of hospitalization as a marker of COVID-19 severity can lead to bias in studies assessing the effectiveness of interventions, particularly after Omicron emergence (Feikin *et al.*, 2022; Stowe *et al.*, 2022). Therefore, COVID-19 case severity was not assessed using records of hospitalization but using the specific criteria for case severity (2021), criticality (2021), and fatality (2021) per WHO guidelines, whcih is a key strength of this study. Every hospitalized patient with COVID-19 underwent an infection severity assessment per WHO guidelines every 3 days until discharge or death.

With the small proportion of Qatar's population aged ≥60 years (Abu-Raddad et al., 2021a), our findings may not be generalizable to countries in which elderly citizens represent a larger proportion of the population. The median age in the study samples was ≤40 years, and <10% of patients were aged ≥60 years, considerably younger than in other studies (Aggarwal *et al.*, 2022; Gupta *et al.*, 2021; Gupta *et al.*, 2022; Huang et al., 2022; Ong *et al.*, 2022). Such a relatively young age may alter the benefit of this treatment and confound the study results. As an observational study, investigated cohorts were neither blinded nor randomized, so unmeasured or uncontrolled confounding cannot be excluded.

In conclusion, there was no evidence for a protective effect of sotrovimab in reducing COVID-19 severity in a setting dominated by the BA.2 subvariant.

Table 4
Associations with COVID-19 infection severity in the full sample including all eligible individuals for sotrovimab treatment.

Predictors	Sotrovimab		Controls		Severe/critical/fatal[a] COVID-19 vs. mild/asymptomatic infection			
	Total sample	Severe/critical/ fatal[a] COVID-19	Total sample	Severe/critical/ fatal[a] COVID-19	Univariable regression analysis		Multivariable regression analysis	
	N (%)	N (%[b])	N (%)	N (%[b])	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Study group								
Control	-	-	2,845 (100.0)	10 (0.4)	1.00		1.00	
Sotrovimab	519 (100.0)	9 (1.7)	-	-	5.00 (2.02-12.37)	<0.001	1.80 (0.61-5.29)	0.288
Vaccination status[c]								
Unvaccinated	153 (29.5)	4 (2.6)	658 (23.1)	5 (0.8)	1.00		1.00	
Two doses	298 (57.4)	4 (1.3)	1,655 (58.2)	4 (0.2)	0.37 (0.14-0.95)	0.040	0.51 (0.17-1.57)	0.242
Three doses	68 (13.1)	1 (1.5)	532 (18.7)	1 (0.2)	0.30 (0.06-1.38)	0.122	0.35 (0.06-1.88)	0.219
Prior infection status[c]								
No	478 (92.1)	9 (1.9)	2,605 (91.6)	10 (0.4)	1.00		1.00	
Yes	41 (7.9)	0 (0.0)	240 (8.4)	0 (0.0)	1.00 (1.00-1.00)	-	1.00 (1.00-1.00)	-
Age (years)								
<40	199 (38.3)	2 (1.0)	1,419 (49.9)	5 (0.4)	1.00		1.00	
40-59	204 (39.3)	2 (1.0)	1,357 (47.7)	3 (0.2)	0.74 (0.23-2.34)	0.607	0.81 (0.24-2.70)	0.728
≥60	116 (22.4)	5 (4.3)	69 (2.4)	2 (2.9)	9.05 (3.14-26.10)	<0.001	5.68 (1.63-19.77)	0.006
Sex								
Male	215 (41.4)	4 (1.9)	1,071 (37.6)	4 (0.4)	1.00		1.00	
Female	304 (58.6)	5 (1.6)	1,774 (62.4)	6 (0.3)	0.85 (0.34-2.12)	0.728	0.75 (0.28-1.98)	0.558
Nationality								
Qatari	159 (30.6)	3 (1.9)	1,337 (47.0)	3 (0.2)	1.00		1.00	
Craft and manual worker nationalities[d]	144 (27.7)	2 (1.4)	627 (22.0)	0 (0.0)	0.65 (0.13-3.21)	0.593	0.70 (0.13-3.72)	0.678
Other nationalities	216 (41.6)	4 (1.9)	881 (31.0)	7 (0.8)	2.52 (0.93-6.82)	0.070	1.91 (0.65-5.60)	0.240
Comorbidity count								
None	58 (11.2)	0 (0.0)	312 (11.0)	4 (1.3)	1.00		1.00	
1	186 (35.8)	3 (1.6)	1,662 (58.4)	5 (0.3)	0.40 (0.12-1.33)	0.134	1.13 (0.29-4.41)	0.864
2	167 (32.2)	1 (0.6)	693 (24.4)	1 (0.1)	0.21 (0.04-1.17)	0.075	0.43 (0.06-2.82)	0.377
≥3	108 (20.8)	5 (4.6)	178 (6.3)	0 (0.0)	1.61 (0.43-6.12)	0.471	2.47 (0.44-13.85)	0.302
Epidemic phase[e]								
Delta-dominated incidence	198 (38.2)	4 (2.0)	262 (9.2)	5 (1.9)	1.00		1.00	
Omicron-dominated incidence	321 (61.8)	5 (1.6)	2,583 (90.8)	5 (0.2)	0.17 (0.07-0.43)	<0.001	0.35 (0.13-0.96)	0.041

Abbreviations: AOR, adjusted odds ratio; OR, odds ratio.
[a] Severity (2021), criticality (2021), and fatality (2021) were defined according to the World Health Organization guidelines.
[b] Proportion of those who progressed to severe, critical, or fatal COVID-19 among those in the predictor category.
[c] Vaccination status and prior infection status were ascertained at the time of infection.
[d] These include Bangladeshis, Indians, Nepalese, Pakistanis, Sri Lankans, and Sudanese due to large proportions of these nationals being craft and manual workers.
[e] Before December 19, 2021 incidence in Qatar was dominated by the Delta variant, whereas starting from December 19, 2021 incidence was dominated by the Omicron variant.

Table 5
Associations with COVID-19 infection severity in the subgroup of patients at higher risk of severe forms of COVID-19[a].

Predictors	Sotrovimab		Controls		Severe/critical/fatal[b] COVID-19 vs. mild/asymptomatic infection			
	Total sample	Severe/critical/ fatal[b] COVID-19	Total sample	Severe/critical/ fatal[b] COVID-19	Univariable regression analysis		Multivariable regression analysis	
	N (%)	N (%[c])	N (%)	N (%[c])	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Study group								
Control	-	-	1,043 (100.0)	9 (0.9)	1.00		1.00	
Sotrovimab	340 (100.0)	7 (2.1)	-	-	2.42 (0.89-6.53)	0.083	1.33 (0.44-4.05)	0.618
Vaccination status[d]								
Unvaccinated	153 (45.0)	4 (2.6)	658 (63.1)	5 (0.8)	1.00		1.00	
Two doses	145 (42.6)	3 (2.1)	287 (27.5)	3 (1.0)	1.26 (0.44-3.55)	0.668	1.52 (0.49-4.70)	0.468
Three doses	42 (12.4)	0 (0.0)	98 (9.4)	1 (1.0)	0.64 (0.08-5.10)	0.674	0.58 (0.07-5.16)	0.626
Prior infection status[d]								
No	312 (91.8)	7 (2.2)	953 (91.4)	9 (0.9)	1.00		1.00	
Yes	28 (8.2)	0 (0.0)	90 (8.6)	0 (0.0)	1.00 (1.00-1.00)	-	1.00 (1.00-1.00)	-
Age (years)								
<75	308 (90.6)	5 (1.6)	1,031 (98.8)	8 (0.8)	1.00		1.00	
≥75	32 (9.4)	2 (6.3)	12 (1.2)	1 (8.3)	7.46 (2.05-27.20)	0.002	6.92 (1.50-32.02)	0.013
Sex								
Male	100 (29.4)	2 (2.0)	274 (26.3)	4 (1.5)	1.00		1.00	
Female	240 (70.6)	5 (2.1)	769 (73.7)	5 (0.7)	0.61 (0.22-1.70)	0.348	0.61 (0.21-1.74)	0.357
Nationality								
Qatari	116 (34.1)	2 (1.7)	483 (46.3)	3 (0.6)	1.00		1.00	
Craft and manual worker nationalities[e]	74 (21.8)	2 (2.7)	159 (15.2)	0 (0.0)	1.03 (0.20-5.34)	0.973	1.22 (0.21-6.94)	0.822
Other nationalities	150 (44.1)	3 (2.0)	401 (38.4)	6 (1.5)	1.97 (0.66-5.92)	0.226	2.01 (0.62-6.57)	0.246
Epidemic phase[f]								
Delta-dominated incidence	104 (30.6)	4 (3.8)	172 (16.5)	4 (2.3)	1.00		1.00	
Omicron-dominated incidence	236 (69.4)	3 (1.3)	871 (83.5)	5 (0.6)	0.24 (0.09-0.66)	0.005	0.30 (0.10-0.88)	0.028

Abbreviations: AOR, adjusted odds ratio; OR, odds ratio.

[a] These include immunocompromised individuals (solid organ or hematopoietic stem cell transplant recipients, patients receiving chemotherapy or immunosuppressive treatments, patients with severe immunodeficiency, and HIV patients), unvaccinated individuals, those ≥75 years of age, and pregnant women.

[b] Severity (2021), criticality (2021), and fatality (2021) were defined according to the World Health Organization guidelines.

[c] Proportion of those who progressed to severe, critical, or fatal COVID-19 among those in the predictor category.

[d] Vaccination status and prior infection status were ascertained at the time of infection.

[e] These include Bangladeshis, Indians, Nepalese, Pakistanis, Sri Lankans, and Sudanese due to large proportions of these nationals being craft and manual workers.

[f] Before December 19, 2021 incidence in Qatar was dominated by the Delta variant, whereas starting from December 19, 2021 incidence was dominated by the Omicron variant.

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Ethical approval

The Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards approved this retrospective study with a waiver of informed consent. The research was performed in accordance with relevant guidelines and regulations.

Author contributions

AZ, MAA, and ASO co-designed the study, led the database development, and co-wrote the manuscript. HC co-designed the study, performed the statistical analyses, and co-wrote the first draft of the article. LJA co-designed the study, led the statistical analyses, and co-wrote the first draft of the article. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and the writing of the manuscript. All authors have read and approved the final manuscript.

Data availability

The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. Aggregate data are available within the manuscript and its Supplementary Material. A limited dataset, including the cases and controls and their associated variables that were used in the analysis, can be made available for researchers upon request to the corresponding author of this study.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

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References

Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Al Kanaani Z, Al Khal A, Al Kuwari E, et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. Sci Rep 2021a;11:6233.

Abu-Raddad LJ, Chemaitelly H, Coyle P, Malek JA, Ahmed AA, Mohamoud YA, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. EClinicalmedicine 2021b;35.

Abu-Raddad LJ, Chemaitelly H, Ayoub HH, AlMukdad S, Yassine HM, HA Al-Khatib, et al. Effect of mRNA vaccine boosters against SARS-CoV-2 omicron infection in Qatar. N Engl J Med 2022;386:1804–16.

Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. N Engl J Med 2022a;386:995–8.

Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2. N Engl J Med 2022b;386:1475–7. doi:10.1056/NEJMc2201933.

ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022;22:622–35.

Aggarwal NR, Beaty LE, Bennett TD, Carlson NE, Davis CB, Kwan BM, et al. Real-world evidence of the neutralizing monoclonal antibody sotrovimab for preventing hospitalization and mortality in COVID-19 outpatients. J Infect Dis 2022. doi:10.1093/infdis/jiac206.

Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, et al. Effects of previous infection and vaccination on symptomatic omicron infections. N Engl J Med 2022;387:21–34.

Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009;38:1228–34.

Butt AA, Dargham SR, Loka S, Shaik RM, Chemaitelly H, Tang P, et al. COVID-19 Disease Severity in Children Infected with the Omicron Variant. Clin Infect Dis 2022a;75(1):e361–7. doi:10.1093/cid/ciac275.

Butt AA, Dargham SR, Tang P, Chemaitelly H, Hasan MR, Coyle PV, et al. COVID-19 disease severity in persons infected with the Omicron variant compared with the Delta variant in Qatar. J Glob Health 2022b;12:05032.

Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021;385:e83.

Chemaitelly H, Ayoub HH, Coyle P, Tang P, Yassine HM, HA Al-Khatib, et al. Protection of Omicron sub-lineage infection against reinfection with another Omicron sub-lineage. Nat Commun 2022a;13:4675.

Chemaitelly H, Ayoub HH, AlMukdad S, Coyle P, Tang P, Yassine HM, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. Nat Commun 2022b;13:3082.

Feikin DR, Abu-Raddad LJ, Andrews N, Davies MA, Higdon MM, Orenstein WA, et al. Assessing vaccine effectiveness against severe COVID-19 disease caused by omicron variant. Report from a meeting of the World Health Organization. Vaccine 2022;40:3516–27.

Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021;385:1941–50.

Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2022;327:1236–46.

Huang DT, McCreary EK, Bariola JR, Minnier TE, Wadas RJ, Shovel JA, et al. Effectiveness of casirivimab-imdevimab and sotrovimab during a SARS-CoV-2 Delta variant surge: a cohort study and randomized comparative effectiveness trial. JAMA Netw Open 2022;5(7). doi:10.1001/jamanetworkopen.2022.20957.

Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. Eval Health Prof 2021;44:327–32.

Miguez-Rey E, Choi D, Kim S, Yoon S, Săndulescu O. Monoclonal antibody therapies in the management of SARS-CoV-2 infection. Expert Opin Investig Drugs 2022;31:41–58.

Ong SWX, Ren D, Lee PH, Sutjipto S, Dugan C, Khoo BY, et al. Real-world use of sotrovimab for pre-emptive treatment in high-risk hospitalized COVID-19 patients: an observational cross-sectional study. Antibiotics (Basel) 2022;11:345.

Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. Nat Comm 2022;13:5736. doi:10.1038/s41467-022-33378-7.

United States Food and Drug Administration. Fact sheet for healthcare providers. Emergency use authorization (EUA) of sotrovimab, 2022; 2022 https://www.fda.gov/media/149534/download (accessed 1 February 2022).

World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. 2020. Available at: https://www.who.int/publications/m/item/international-guidelines-for-certification-and-classification-(coding)-of-covid-19-as-cause-of-death. Accessed May 31, 2021.