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Change in Effectiveness of Sotrovimab for Preventing Hospitalization and Mortality for At-risk COVID-19 Outpatients During an Omicron BA.1 and BA.1.1-Predominant Phase

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Highlights

- Omicron BA.1 or BA.1.1-infected adult outpatients were administered sotrovimab
- Sotrovimab did not to reduce hospitalization compared to all untreated patients

- Sotrovimab may reduce hospitalization rates in highest risk outpatient subgroups
- Sotrovimab treatment benefit during Delta was markedly attenuated in Omicron BA.1

ABSTRACT

Objectives: Sotrovimab effectively prevented progression to severe disease and mortality following infection with pre-Omicron SARS-CoV-2 variants. We sought to determine whether sotrovimab is similarly effective against SARS-CoV-2 Omicron variant infection.

Methods: Observational cohort study of non-hospitalized adult patients with SARS-CoV-2 infection from December 26, 2021 to March 10, 2022, using electronic health records from a statewide health system. We propensity matching patients not receiving authorized treatment for each patient treated with sotrovimab**.** The primary outcome was 28-day hospitalization; secondary outcomes included mortality. We also propensity matched sotrovimab-treated patients from the Omicron and Delta phases. Logistic regression was used to determine sotrovimab effectiveness during Omicron and between variant phases.

Results: Of 30,247 SARS-CoV-2 Omicron variant infected outpatients, we matched 1,542 receiving sotrovimab to 3,663 not receiving treatment. Sotrovimab treatment was not associated with reduced odds of 28-day hospitalization (2.5% versus 3.2%; adjusted OR 0.82, 95% CI 0.55, 1.19) or mortality (0.1% versus 0.2%; adjusted OR 0.62, 95% CI 0.07, 2.78). Between phases, the observed treatment odds ratio was higher during Omicron than during Delta (OR 0.85 vs. 0.39, respectively; interaction p=0.053).

Conclusions: Real-world evidence demonstrated sotrovimab was not associated with reduced 28-day hospitalization or mortality among COVID-19 outpatients during the Omicron BA.1 phase.

Keywords: real-world evidence, monoclonal antibody, COVID-19

BACKGROUND

With fluctuating rates of transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), neutralizing monoclonal antibody (mAb) products such as sotrovimab for outpatients who have recently tested positive for SARS-CoV-2 have been critical, evidence-based treatments to mitigate the impact of COVID-19 surges on the health care system and improve COVID-19 outcomes among high-risk individuals.(CDC 2021; Aggarwal et al. 2022; Ganesh et al. 2021; Huang et al. 2021; Jarrett 2021; O'Horo et al. 2022; Razonable et al. 2021) Several mAb products received emergency use authorization (EUA) from the US Food and Drug Administration(NIH 2020) based on Phase II/III randomized clinical trials conducted earlier in the pandemic. These trials generally demonstrated efficacy towards reduced hospitalization and disease severity among high-risk outpatients,(Dougan et al. 2021; Gupta et al. 2022; Weinreich et al. 2021) but little data from randomized trials is available to inform mAb efficacy against rapidly evolving variants including Omicron lineages.(Lynch et al. 2021) As such, analysis of contemporary real-world data sufficiently robust to evaluate important clinical differences is critical to evaluate treatment effectiveness and inform policy and practice decisions, as we and others have successfully done.(Huang et al. 2021; O'Horo et al. 2022; Ganesh et al. 2021; Razonable et al. 2021; Jarrett 2021)

We previously used a real-world data platform to report on sotrovimab effectiveness during the Delta variant pandemic phase,(Aggarwal et al. 2022) adding to the evidence generated from the COMET-ICE trial that found a significant reduction in risk of a composite endpoint of all-cause hospitalization or death following sotrovimab treatment.(Gupta et al. 2022) Following

the revoking of EUAs for other authorized mAbs in January 2022, sotrovimab was the only available mAb for outpatient treatment briefly during an early Omicron phase. However, a marked reduction in sotrovimab *in vitro* neutralization against Omicron BA.2 and its sublineages (Iketani et al. 2022; Takashita, Kinoshita, et al. 2022) led to the sotrovimab EUA being fully revoked when Omicron BA.2 sub-variant prevalence was estimated to be greater than 50% in all HHS U.S. regions (April 5, 2022). Yet, data evaluating sotrovimab effectiveness against Omicron BA.1 or BA.1.1 in a broad population of high-risk outpatients remains lacking. Furthermore, recent studies in immunocompromised solid organ transplant recipients suggest a benefit of sotrovimab in reducing severity of illness following early administration after SARS-CoV-2 infection during the Omicron BA.1 phase.(Solera et al. 2022; Chavarot et al. 2022)

To provide additional data on sotrovimab effectiveness against Omicron SARS-CoV-2, including immunocompromised patients and other high-risk subgroups, we used our real-world data platform to assess the impact of sotrovimab treatment on hospitalization and mortality among outpatients with early symptomatic COVID-19 infections during a SARS-CoV-2 Omicron BA.1 and BA.1.1 predominant phase in Colorado (December 26, 2021 to March 10, 2022).(CDPHE 2021; ISPOR 2021; Angus 2020; Wynia et al. 2022)

METHODS

Study Oversight and Data Sources

We conducted a propensity-matched observational cohort study, as part of a statewide implementation/effectiveness pragmatic trial, in a collaboration between University of Colorado researchers, University of Colorado Health (UCHealth) system leaders, and the Colorado Department of Public Health and Environment (CDPHE). The study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent. We obtained

data from the electronic health record (EHR; Epic, Verona, WI) of UCHealth, the largest health system in Colorado with 13 hospitals around the state and 141,000 annual hospital admissions, using Health Data Compass, an enterprise-wide data warehouse. EHR data were merged with state-wide data on vaccination status from the Colorado Comprehensive Immunization Information System and mortality from Colorado Vital Records.

Patient Population

Our primary cohort was patients diagnosed with SARS-CoV-2 infection between December 26, 2021 and March 10, 2022. Based on Colorado state-wide data (CDPHE 2021) SARS-CoV-2 infections due to the Omicron variant made up at least 96% of overall cases by 12/26/2021. As an update on previously published work,(Aggarwal et al. 2022) a second cohort was selected between October 1, 2021 to December 11, 2021 when the Delta variant made up at least 99% of overall cases to be able to investigate potential changes in sotrovimab effectiveness between the Delta and Omicron phases. All patients had at least 28 days of follow-up. Patients were identified by either a positive SARS-CoV-2 test (by polymerase chain reaction or antigen) or by the date of mAb administration if the date of the SARS-CoV-2 positive test was missing.

For our primary cohort, we excluded patients who received a medication order for any antiviral treatment except sotrovimab within 10 days of the positive SARS-CoV-2 test (**Supplement**, **Appendix Figure 1**); thus we included only patients who were untreated (N = 31,187) or who were treated with sotrovimab (N = 1,683). We excluded patients who were missing both a positive SARS-CoV-2 test date and a mAb administration date (N = 605), those who were already in the hospital or who were hospitalized on the same day as the positive test (N = 2,009), and if more than 10 days had elapsed between the SARS-CoV-2 test and mAb administration (N = 9). We did not exclude patients based on EUA eligibility due to the lack of consistently available comprehensive EHR data for all patients. After exclusions, the cohort

included 28,584 untreated patients and 1,663 sotrovimab-treated patients. We applied the same exclusions to a second cohort from the Delta variant dominant phase, resulting in 8,901 untreated patients and 556 sotrovimab-treated patients (**Supplement, Appendix Figure 2**).

Outcomes

The primary outcome was all-cause hospitalization within 28-days of the SARS-CoV-2 positive test. Secondary outcomes included all-cause 28-day mortality and 28-day Emergency Department (ED) visit rate. For both hospitalization and ED visit, we used the index visit. For hospitalized patients, we evaluated disease severity based on the maximum level of respiratory support required, rate of intensive care unit (ICU) admission, hospital and ICU length of stay (LOS) in survivors, and in-hospital mortality.

Variable Definitions

We used EHR data to identify all outcomes of interest. A hospitalization was defined as any inpatient or observation encounter. ED visits were defined as any visit to the ED, with or without an associated hospitalization. We estimated disease severity on an ordinal scale with the maximum level of respiratory support used at an encounter level with the following possible types (in ascending order): no supplemental oxygen, standard (nasal cannula/face mask) oxygen, high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV). In-hospital mortality was the highest level of disease severity. Due to small sample sizes, we also categorized disease severity as HFNC/NIV/IMV/Death vs. standard oxygen/no supplemental oxygen.

We determined presence and status of comorbid conditions based on previously described methods using the Charlson and Elixhauser Comorbidity Indices.(Aggarwal et al. 2022; Wynia et al. 2022) Immunocompromised status was further validated by manual chart reviews, and was categorized as not immunocompromised, mild, or moderate/severe, based on

U.S National Institutes of Health and Centers for Disease Control and Prevention guidelines (**Supplement**, **Appendix Table 1**).(NIH 2022; CDC 2022) We calculated the total number of comorbidities as the sum of the presence of diabetes mellitus, cardiovascular disease, pulmonary disease, renal disease, hypertension, and liver disease and classified as none, one, or two or more; we analyzed immunocompromised status and obesity as separate variables. We categorized vaccination status as the total number of vaccinations (0, 1, 2, or ≥ 3) administered prior to the date of the SARS-CoV-2 positive test.

Other variables of interest included treatment status, categorical age in years, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of comorbidities, vaccination status, and cohort week (**Table 1, 2**). In the statistical models, Medicare and private/commercial were collapsed into one category due to collinearity of Medicare with age (**Supplemental Methods**).

Statistical Analysis

Omicron only analysis

We used nearest neighbor propensity matching with logistic regression to match patients with treatment status as the outcome. The propensity model included age, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of other comorbid conditions, number of vaccinations, and week in the study (categorical) **(Supplemental Methods)**. We removed 67 sotrovimab-treated patients who had missing covariate data and lost an additional 54 in the matching process. We assessed the achieved balance using a threshold of <0.1 for the standardized mean differences (SMD) and achieved a ratio of 2.38:1 (3,663:1,542) untreated to treated patients in the final cohort. Patients missing a SARS-CoV-2 positive test date

(56.9%) had their test date randomly imputed based on the distribution of observed time to mAb treatment, as previously done.(Aggarwal et al. 2022)

We used Firth's logistic regression to assess associations between binary outcomes (28-day hospitalization, 28-day mortality, and 28-day ED visits) and treatment. Firth's logistic regression (R package logistf V 1.24) addresses issues with low event rates and complete separation.(Georg Heinze 2020) Each multivariable model included all variables of interest as outlined in the previous section. We included cohort week as a continuous, linear term in all adjusted models and constructed cumulative incidence curves to visually assess the trend across time from SARS-CoV-2 positive date to 28-day hospitalization by treatment status. We also analyzed in-hospital secondary outcomes related to severity of respiratory disease in a descriptive manner.

We focused on five subgroup analyses of clinical interest: age (<65 years vs. ≥65 years), immunocompromised status (binary and tri-level), number of comorbid conditions (≥2 vs. <2), number of vaccinations (≥3 vs. <3), and time of study in the Omicron phase (Early vs. Late). We estimated the treatment effect for each subgroup using interaction models. We adjusted each model for all variables included in the primary model.

We performed two sensitivity analyses (**Supplement, Appendix Tables 6-9**). We repeated the primary analysis including only patients for whom we could verify their EUA eligibility based on available EHR data. We also repeated the primary analysis using a different SARS-CoV-2 positive test date imputation method that imputed a 10-day difference from the observed mAb administration date (the maximum difference allowed by the EUA).

Omicron and Delta analysis

To compare the effect of sotrovimab treatment during Omicron- or Delta-predominant COVID-19 phases, we developed a second propensity-matched analysis cohort. First, to address imbalances in treatment cohorts due to mAb supply, sotrovimab-treated patients during the Omicron-predominant phase were nearest-neighbor propensity-matched to sotrovimab-treated patients in Delta-predominant phase based on a logistic regression with variant as the outcome. Matching variables included age, sex, race/ethnicity, obesity, immunocompromised status, number of comorbid conditions, number of vaccinations, and insurance status. Then we propensity matched mAb-matched sotrovimab-treated patients to untreated patients stratified by variant using nearest-neighbor matching based on a logistic regression with treatment status as the outcome and the same covariates previously described.

We fit Firth's logistic regression models with all-cause 28-day hospitalization as the outcome. For the primary analysis, the model was stratified by variant and included all variables of interest. A second analysis combined both cohorts and added a treatment-variant interaction to the logistic regression model along with the adjustment variables. The second model allowed us to formally test if the effect of treatment differed statistically between the Delta and Omicron cohorts **(Supplemental Methods)**.

All statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing).(Team 2020)

RESULTS

Characteristics of sotrovimab-treated and untreated cohorts in the primary cohort

Of 30,247 patients with SARS-CoV-2 infection in the full primary cohort, 1,663 subjects received mAbs and 28,584 patients did not (**Supplement**, **Appendix Table 2**). In the full primary cohort, the sotrovimab-treated group generally reflects EUA criteria for mAb use. Those

treated were older (44.3% were age ≥65 years vs. 11.4% in untreated group), more likely to be obese (30.5% vs. 16.5%), be immunocompromised at any severity level (40.5% vs. 12.9%), or have one or more comorbid conditions (71.9% vs. 37.6%). Particularly early in the Omicron phase, the relative number in the sotrovimab treated group was lower as compared to the untreated group, due to a surge in cases outpacing available mAb treatment. Propensity matching eliminated clinically meaningful differences in matching variables between groups, resulting in 1,542 sotrovimab-treated patients propensity matched to 3,663 untreated patients (**Supplement, Appendix Figure 1**).

The characteristics of sotrovimab-treated and untreated patients in the matched primary cohort are presented in **Table 1**. Overall, the age distribution was similar with approximately 40% aged ≥65 years, 60% female, 80% Non-Hispanic white, and 50% with private/commercial insurance. Hypertension (49%) and pulmonary disease (35%) were the most common comorbid conditions. Notably, 51% vs. 55% of untreated and sotrovimab-treated patients had received three or more vaccine doses at the time of infection, and 25% vs. 22% had not received any vaccine doses, respectively. The mean time from positive SARS-CoV-2 test to administration of sotrovimab treatment was 3.0 days (SD 1.8) in patients with a positive test date in the EHR.

Hospitalization and Mortality

Sotrovimab treatment was not associated with a lower rate of 28-day hospitalization compared to matched untreated controls: 39 (2.5%) vs. 116 (3.2%), adjusted OR (aOR) = 0.82 (95% CI 0.55-1.19; p = 0.29) (**Table 2, Figure 1**). Covariates that were associated with increased odds of 28-day hospitalization included age ≥ 65 (p = 0.04), obesity (p = 0.02), moderate/severe immunocompromised status (p < 0.001), and two or more other comorbid conditions (p < 0.001) (**Supplement, Appendix Table 3**). Having received two (p = 0.03) or ≥ three (p < 0.001)

vaccine doses were both associated with reduced hospitalization in comparison to having zero vaccine doses.

Rates of all-cause 28-day mortality were not statistically different, with one death in the sotrovimab-treated group (0.1%) as compared to seven deaths (0.2%) in the untreated group (aOR 0.62, 95% CI 0.07-2.78) (**Table 2**). ED visit rates were also similar between groups, 93 of 1542 (6.0%) in sotrovimab-treated, and 224 of 3663 (6.1%) in untreated (aOR 1.03, 95% CI 0.79-1.32).

Severity of Hospitalization

Among hospitalized patients, 6 of 39 (15.4%) in the sotrovimab-treated group required high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV) or died in the hospital, compared to 33 of 116 (28.4%) in the untreated group (**Table 2, Figure 2**). There also was a higher proportion of sotrovimab-treated patients who did not require oxygen (35.9% vs. 17.2%). The average hospital length of stay (LOS) for sotrovimab-treated patients was 5.2 (+/- 6.8) days in comparison to 7.3 (+/- 7.7) days in the untreated group. 4 of 39 (10.3%) sotrovimab-treated patients required ICU admission, as compared to 20 of 116 (17.2%) untreated patients. Collectively, these data appear to suggest a lower severity of disease among hospitalized sotrovimab-treated patients, although the sample sizes were too low for valid statistical inference.

Sensitivity Analysis

Neither restricting the primary cohort to only patients meeting EUA eligibility criteria based on available EHR data or using a more conservative imputation method for missing date of positive SARS-CoV-2 test materially changed the key results and scientific conclusions (**Supplement, Appendix Tables 6-9**). Sotrovimab-treated participants removed due to missing co-variate data

or lost after additional matching were not appreciably different than the primary matched cohort (**Supplement, Appendix Table 10**).

Sotrovimab treatment effect in subgroups

During the Omicron phase, sotrovimab treatment was associated with a lower odds of 28-day hospitalization in older patients (age ≥ 65 years) as compared to no antiviral treatment (OR 0.52, 95% CI 0.30-0.92) (**Figure 3**), a finding significantly different than the sotrovimab treatment effect in patients < 65 years (OR 1.42, 95% CI 0.82 – 2.04; interaction p = 0.01). In addition, sotrovimab treatment was more likely effective in immunocompromised, compared to not immunocompromised patients (OR 0.63, 95% CI 0.38-1.04 versus OR 1.40, 95% CI 0.76-2.50; interaction p = 0.04). Reassigning patients that were classified as immunocompromised only because of a tumor or cancer with or without metastases from a moderate-severe immunocompromised state to a mild immunocompromised state did not change the results (not shown). Sotrovimab treatment was also significantly different in patients with two or more comorbid conditions, compared to zero or one comorbid conditions (OR 0.65, 95% CI 0.42- 1.01 versus OR 2.52, 95% CI 1.05-6.09; interaction p = 0.007). Treatment effect results for all subgroups are shown in the Supplement (**Appendix Table 4**).

Sotrovimab treatment effect in Omicron and Delta phases

Compared to treated patients during the Delta phase, treated patients in the Omicron phase were on average older, more white, more obese, more immunocompromised, had more comorbid conditions, and had been vaccinated with more doses (data not shown). After propensity matching (**Supplement, Appendix Figure 2**), these differences were no longer clinically meaningful or statistically different (SMDs <0.1). In the combined analysis across Omicron and Delta phases, the observed treatment odds ratio for preventing 28-day hospitalization was higher

during Omicron than during Delta predominance (OR 0.85 vs. 0.39, respectively; interaction p=0.053; **Supplement, Appendix Table 5**). Though the composition of the propensity-matched cohort for the Omicron versus Delta analysis was different than for the primary Omicron analysis, the observed sotrovimab treatment odds rate was similar (0.85 versus 0.82).

DISCUSSION

During a SARS-CoV-2 Omicron BA.1 and BA.1.1 variant-predominant phase in Colorado, sotrovimab was not associated with a lower incidence of the primary outcome of 28-day all-cause hospitalization. In addition, it was likely that the sotrovimab treatment benefit observed during the Delta phase of the pandemic (Aggarwal et al. 2022) was markedly attenuated during this Omicron phase. However, the lower confidence boundary of 0.55 during the Omicron phase makes us interpret these results with caution. Notably, COVID severity metrics including all-cause or hospital mortality, hospital length of stay, as well as higher levels of respiratory support via HFNC, NIV, or invasive mechanical ventilation all trended in the direction of sotrovimab benefit, but were underpowered and did not reach statistical significance. Coupling hospital severity data with a possible benefit from sotrovimab treatment among key high-risk subgroups (age ≥ 65 years, immunocompromised status, ≥ 2 comorbid conditions), it is possible that sotrovimab retained some benefit in improving outcomes during the Omicron BA.1 / BA.1.1 phase, though this effect was likely attenuated compared to the effect observed during the Delta phase.

By evaluating a predominantly Omicron BA.1 sublineage cohort, our findings do not fully support observed sotrovimab neutralization of BA.1 variants *in vitro*,(Cameroni et al. 2021) though perhaps a lower sotrovimab neutralization potency against Omicron/BA.1 and Omicron/BA.1.1 as compared to ancestral strains and prior variants of concern made our clinical

findings more predictable.(Iketani et al. 2022; Takashita, Kinoshita, et al. 2022) Further, with ineffective *in vitro* sotrovimab neutralization against Omicron BA.2 (Iketani et al. 2022; Takashita, Kinoshita, et al. 2022) and among newer Omicron subvariants,(Yamasoba et al. 2022; Takashita, Yamayoshi, et al. 2022) as well as a clinical observation that sotrovimab did not mitigate disease progression during a BA.2 Omicron dominant phase,(Zaqout 2022) our findings do support the statements by the NIH guidelines committee (NIH 2021) and FDA (FDA 2022) that sotrovimab should not be recommended as a current outpatient treatment against COVID-19 among the general population of outpatients that meet EUA criteria. However, with a signal towards potential sotrovimab benefit in patients ≥ 65 years old, moderately/severely immunosuppressed,(Solera et al. 2022; Chavarot et al. 2022) or with multiple comorbid conditions, some caution should be taken before removal of potentially effective treatments in the highest risk individuals, particularly depending on broad availability of alternate treatment options for infected outpatients or in higher risk subgroups. In addition, re-consideration for use of sotrovimab and other mAbs against future variants of concern based on *in vitro* neutralization potency is warranted.

Our results are of practical importance for policymakers and clinicians because they provide updated data to support treatment prioritization in the setting of multiple antiviral treatment options yet limited supply and infusion capacity. As such, it is crucial to rapidly measure and report real-world effectiveness of each treatment against each clinically relevant SARS-CoV-2 variant.(NASEM 2021)

Limitations

This study has several limitations. Even though we used statewide data for mortality and vaccination status, hospitalizations were collected only within a single health system. In addition, this health system is geographically limited to one US state with relatively low racial and ethnic

minority representation, though it serves both urban and rural populations through academic and community hospitals. If untreated patients were less likely to be seen in this health system and more likely to be hospitalized elsewhere, this may bias our results toward the null. We also relied on EHR data, including manual chart reviews, which may have missing or inaccurate information about the presence of chronic conditions.(Bennett et al. 2021) Collectively, these factors might have limited our ability to detect the impact of sotrovimab treatment.

We only collected 28-day hospitalization and mortality data, and therefore we cannot comment on sotrovimab effects over a longer phase after SARS-CoV-2 infection. However, our prior study would suggest that 28-day and 90-day data yield similar hospitalization and mortality results.(Wynia et al. 2022) In the current study, propensity scoring appropriately matched sotrovimab-treated and untreated patient groups across multiple variables, but unmeasured confounders may remain. Our EHR data does not contain patient level information on SARS-CoV-2 variants, including quantification of anti-SARS-CoV-2 antibody(s) or viremia duration that may be relevant to understand treatment responsive characteristics among the highest risk individuals, including those that are severely immunocompromised. Notably, during Colorado's Delta phase more than 99% of sequenced SARS-CoV-2 was Delta variant and during Colorado's Omicron phase it was more than 96% of Omicron BA.1/BA.1.1.(CDPHE 2021)

Finally, this study occurred while our health system's sotrovimab distribution criteria changed due to implementation of austere measures, and as such, patients who received sotrovimab may have differed over the course of the study. We accounted for this by doing a subgroup analysis of early (12/26/21 – 2/5/22) and late (2/6/22 – 3/10/22) infection periods. Though we observed a similar sotrovimab effect in each period (**Figure 3)**, it is notable that hospitalization rates among sotrovimab-treated and untreated groups appeared lower during the late period.

Conclusion

This study of real-world data demonstrated sotrovimab treatment was not associated with reduced 28-day hospitalization among COVID-19 outpatients during the Omicron BA.1 variant phase, unlike the high effectiveness observed during the Delta phase. Outpatient sotrovimab treatment may have been beneficial in certain higher risk subgroups, and may reduce respiratory severity among those subsequently hospitalized, but larger cohorts would be necessary to further examine these observations.

FOOTNOTES

1) The authors do not have a commercial or other association that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)

2) This study was funded by the National Center for Advancing Translational Sciences of the United States National Institutes of Health [grant numbers UL1TR002525, UL1TR002535-03S3 and UL1TR002535-04S2].

3) This work has not been presented in part or in entirety at any meetings, and has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and the work aims for the inclusion of representative human populations. The study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent

4) This work was supported by the Health Data Compass Data Warehouse project (healthdatacompass.org).

5) Data sharing: Deidentified participant data and a data dictionary defining each field in the set, as well as a statistical analysis plan will be made available to others with publication with a signed data access agreement and approval by the project steering committee via communication with the corresponding author, for researchers to reproduce results.

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FIGURE LEGENDS

Figure 1. Cumulative Incidence Plots for All-Cause Hospitalization to Day 28 by Sotrovimab Treatment Status among Omicron BA.1 or BA.1.1 Infected Outpatients

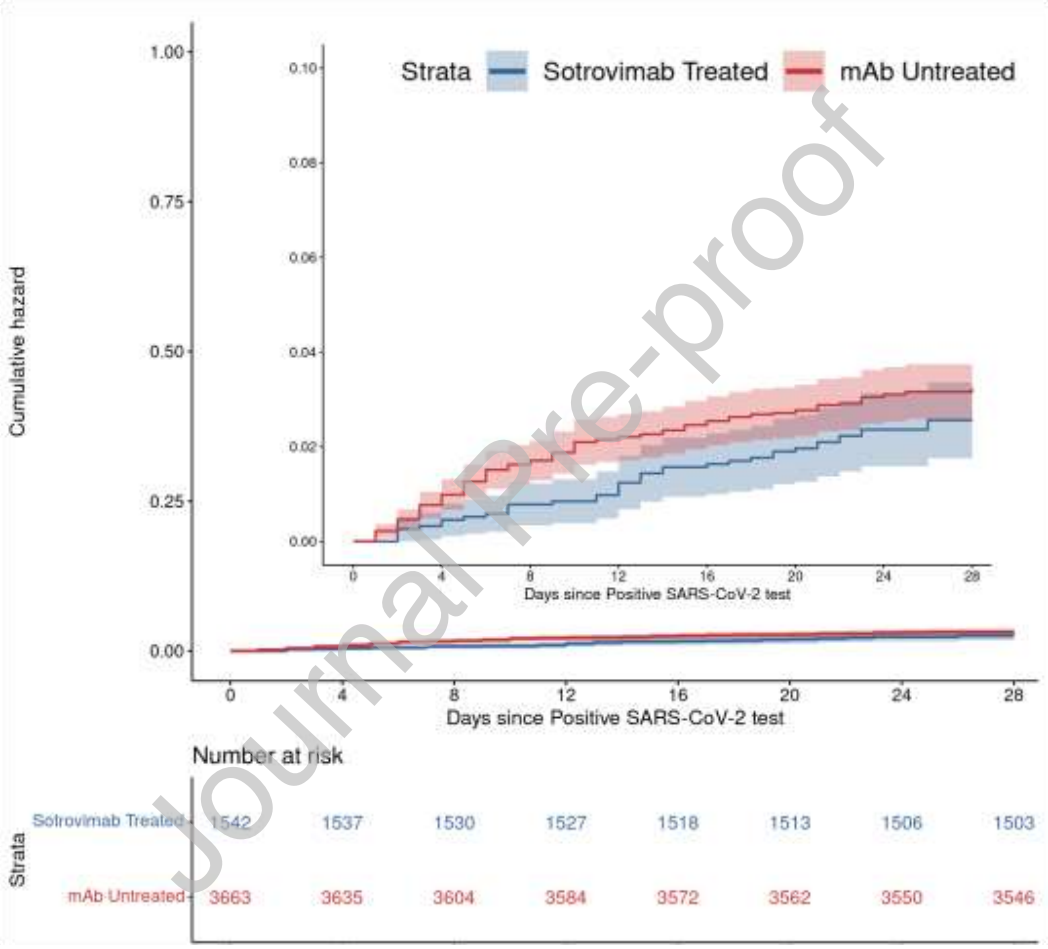

Figure 2. Severity of Hospitalization - Secondary Outcomes. The total sample size of the hospitalized subset is 155, of which 39 are in the Sotrovimab-treated group, and 116 are in the untreated group.

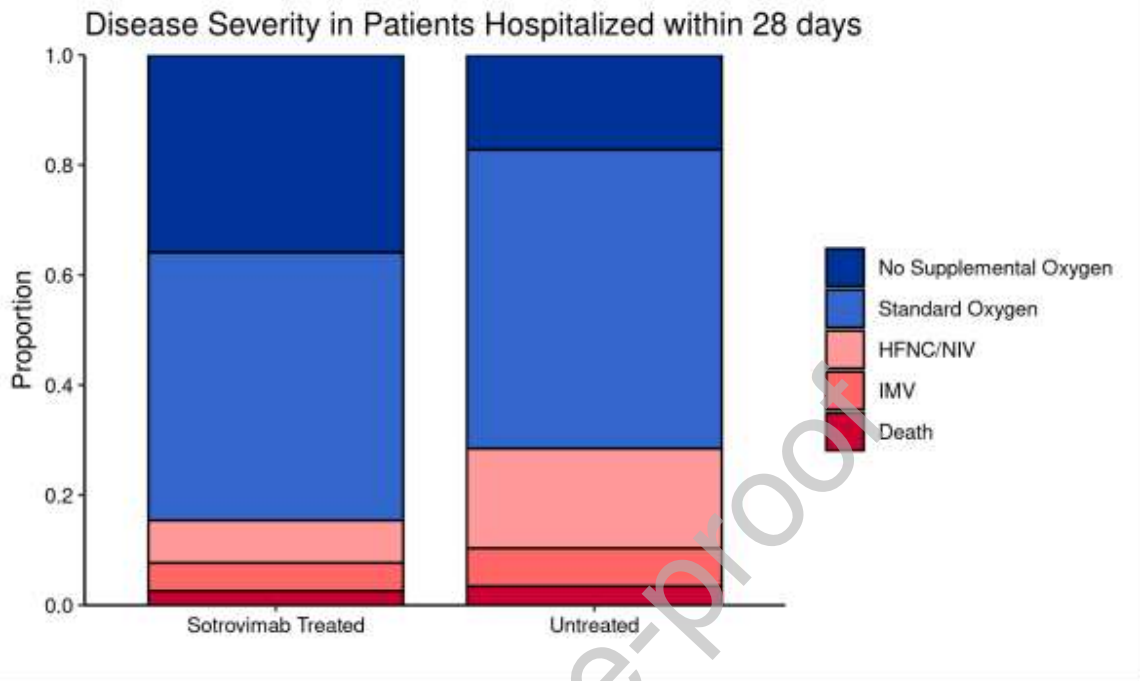

Figure 3. Forest Plot for Omicron BA.1 or BA.1.1 Infected Outpatient Subgroup Analysis.

Int = interaction, OR = odds ratio. The interaction terms for binary age greater or less than 65 years (p=0.012), binarized immunocompromised status (p=0.043), and binarized number of comorbidities (p=0.006) were significant.

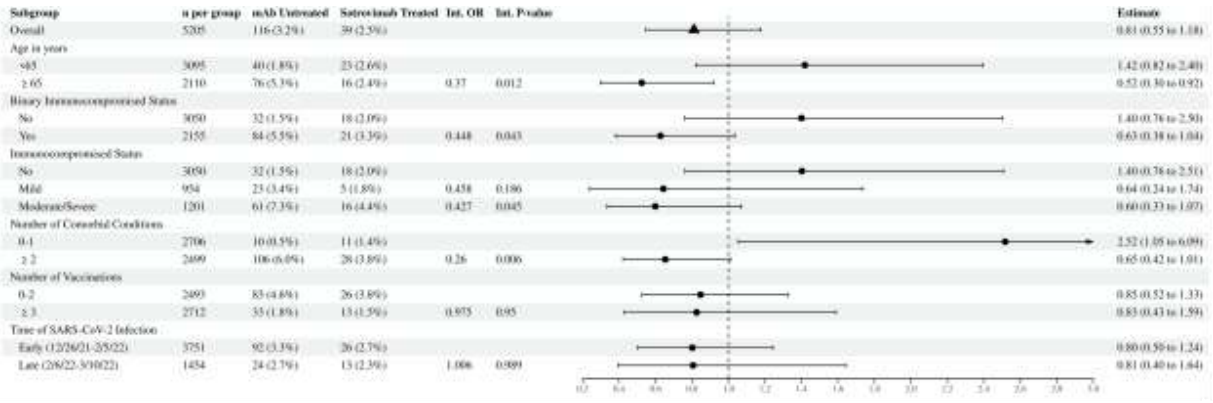

Table 1. Baseline Characteristics by Mab Treatment Status for Primary Matched Cohort

	Untreated N=3663)	Sotrovimab Treated (N=1542)
Age Group *		
18-44 years	997 (27.2%)	387 (25.1%)
45-64 years	1219 (33.3%)	492 (31.9%)
≥65 years	1447 (39.5%)	663 (43.0%)
Female Gender *	2231 (60.9%)	916 (59.4%)
Race/Ethnicity *		
Non-Hispanic White	2974 (81.2%)	1256 (81.5%)
Hispanic	391 (10.7%)	160 (10.4%)
Non-Hispanic Black	95 (2.6%)	41 (2.7%)
Other	203 (5.5%)	85 (5.5%)
Insurance Status *		
Private/Commercial	1878 (51.3%)	759 (49.2%)
Medicare	1581 (43.2%)	699 (45.3%)
Medicaid	110 (3.0%)	48 (3.1%)
None/Uninsured	3 (0.1%)	2 (0.1%)
Other/Unknown	91 (2.5%)	34 (2.2%)
Immunocompromised Status *		
None	2148 (58.6%)	902 (58.5%)
Mild	679 (18.5%)	275 (17.8%)
Moderate/Severe	836 (22.8%)	365 (23.7%)
Obesity*	1119 (30.5%)	483 (31.3%)
Number of Other Comorbid Conditions *		
None	998 (27.0%)	411 (26.7%)
One	914 (25.0%)	393 (25.5%)
Two or more	1761 (48.1%)	738 (47.9%)
Diabetes Mellitus	716 (19.5%)	371 (24.1%)
Cardiovascular Disease	1116 (30.5%)	446 (28.9%)
Pulmonary Disease	1295 (35.4%)	540 (35.0%)
Renal Disease	446 (12.2%)	268 (17.4%)
Hypertension	1812 (49.5%)	765 (49.6%)
Liver Disease	488 (13.3%)	235 (15.2%)
Number of vaccinations prior to SARS-CoV-2+ *		
0	898 (24.5%)	335 (21.7%)

1	182 (5.0%)	68 (4.4%)
2	726 (19.8%)	284 (18.4%)
3+	1857 (50.7%)	855 (55.4%)
Days to mAb Admin: mean (SD)	NA	3.004 (1.967)
Time (weeks)*		
12/26 - 1/1	704 (19.2%)	258 (16.7%)
1/2 - 1/8	353 (9.6%)	106 (6.9%)
1/9 - 1/15	382 (10.4%)	127 (8.2%)
1/16 - 1/22	500 (13.7%)	170 (11.0%)
1/23 - 1/29	393 (10.7%)	128 (8.3%)
1/30 - 2/5	442 (12.1%)	188 (12.2%)
2/6 - 2/12	291 (7.9%)	167 (10.8%)
2/13 - 2/19	211 (5.8%)	112 (7.3%)
2/20 - 2/26	181 (4.9%)	107 (6.9%)
2/27 - 3/5	116 (3.2%)	102 (6.6%)
3/6 - 3/10	90 (2.5%)	77 (5.0%)

* *Variables* used in the propensity matching. Abbreviations: mAb, monoclonal antibody.

Table 2. Primary and Secondary Outcomes by MAb Treatment Status for Primary Cohort

Outcome	Sotrovimab-Treated	Untreated	Adjusted OR	95% CI
Overall Sample Size	**N=1542**	**N=3663**		
All-Cause 28-day Hospitalization *(primary outcome)*	39 (2.5%)	116 (3.2%)	0.82	(0.55, 1.19)
All-Cause 28-day Mortality	1 (0.1%)	7 (0.2%)	0.62	(0.07, 2.78)
Any ED visit to Day 28	93 (6.0%)	224 (6.1%)	1.03	(0.79, 1.32)
Hospitalized Sample Size	**N=39**	**N=116**		
Hospital LOS days, mean (SD)	5.2 (6.8)	7.3 (7.7)	--	--
HFNC/NIV, IMV or Death	6 (15.4%)	33 (28.4%)	--	--
ICU Admission	4 (10.3%)	20 (17.2%)	--	--
ICU LOS days, mean (SD)	1.5 (0.58)	8.1 (14.04)	--	--

All regression models adjusted for age, sex, race/ethnicity, obesity, immunocompromised status, number of comorbidities, insurance status, and vaccination status. Abbreviations: mAb, monoclonal antibody; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; SD, standard deviation; HFNC, high flow nasal cannula; NIV, non-invasive ventilation

Conflict of interest

The authors do not have a commercial or other association that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)