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Journal Pre-proof

Real-World Evidence of Neutralizing Monoclonal Antibodies for Preventing Hospitalization and Mortality in COVID-19 Outpatients

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DOI: https://doi.org/10.1101/2022.01.09.22268963) they are not currently under review at any other journal nor presented publicly.

KEYWORDS: COVID-19, monoclonal antibody, outpatient, delta variant, hospitalization, mechanical ventilation

ABBREVIATION LIST: CI, confidence interval; COVID-19, Coronavirus disease 2019; EHR, electronic health record; ED, emergency department; EUA, emergency use authorization; ICU, intensive care unit; LOS, length of stay; mAb, monoclonal antibody; OR, odds ratio; NNT, number-needed-to-treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation

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ABSTRACT

Background: Neutralizing monoclonal antibodies (mAbs) were authorized for treatment of COVID-19 outpatients based on clinical trials completed early in the pandemic, which were underpowered for mortality and subgroup analyses. Real-world data (RWD) studies are promising for further assessing rapidly-deployed therapeutics.

Research Question: Did mAb treatment prevent progression to severe disease and death across pandemic phases and based on risk factors including prior vaccination status?

Study Design and Methods: This observational cohort study included non-hospitalized adult patients with SARS-CoV-2 infection from November 2020-October 2021, using electronic health records from a statewide health system plus state-level vaccine and mortality data. Using propensity matching, we selected approximately 2.5 patients not receiving mAbs for each patient who received mAb treatment under emergency use authorization. The primary outcome was 28-day hospitalization; secondary outcomes included mortality and hospitalization severity.

Results: Of 36,077 patients with SARS-CoV-2 infection, 2,675 receiving mAbs were matched to 6,677 not receiving mAbs. Compared to mAb-untreated patients, mAb-treated patients had lower all-cause hospitalization (4.0% vs 7.7%; adjusted OR 0.48, 95%CI 0.38-0.60) and all-cause mortality (0.1% vs. 0.9%; adjusted OR 0.11, 95%CI 0.03-0.29) to day 28; differences persisted to day 90. Among hospitalized patients, mAb-treated patients had shorter hospital length of stay (5.8 vs. 8.5 days) and lower risk of mechanical ventilation (4.6% vs. 16.6%). Results were similar for preventing hospitalizations during the Delta variant phase (adjusted OR 0.35, 95%CI 0.25-0.50) and across subgroups. Number-needed-to-treat (NNT) to prevent hospitalization was lower for subgroups with higher baseline risk of hospitalization—e.g., multiple comorbidities (NNT=17) and not fully vaccinated (NNT=24) vs. no comorbidities (NNT=88) and fully vaccinated (NNT=81).

Interpretation: Real-world data revealed a strong association between receipt of mAbs and reduced hospitalization and deaths among COVID-19 outpatients across pandemic phases. RWD studies should be used to guide practice and policy decisions, including allocation of scarce resources.

High rates of coronavirus disease 2019 (COVID-19) transmission and illness persist, especially among unvaccinated individuals, as well as those with waning vaccine or infection-related immunity, such as older adults or those with certain chronic medical conditions.[1,2] Neutralizing monoclonal antibody (mAb) treatment provides immediate passive immunity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19. Several mAb products have received emergency use authorization (EUA) from the US Food and Drug Administration.[3] These authorizations were based on early Phase II/III randomized controlled trials that demonstrated reduction in a combined endpoint of hospitalization or death among high-risk outpatients with early symptomatic infection, though these trials were small in size with few deaths and conducted before the emergence of the Delta variant or widespread availability of vaccines against SARS-CoV-2.[4-6]

Once a promising therapeutic agent has been authorized for emergency use, it becomes more challenging to recruit patients into randomized controlled trials, as patients may seek active therapy and clinicians may view randomization to placebo as unethical.[7] Consequently, studies of mAbs following EUA have primarily been small observational trials, confirming reduced hospitalization rates but not large enough to detect a mortality benefit nor to assess any potential heterogeneity of mAb treatment effects by comorbid conditions or vaccination status.[8-10] The latter information could be especially useful in policymaking about how best to allocate limited access to mAb treatment during shortages.[11,12] Furthermore, no published studies have yet directly evaluated the effectiveness of currently available mAbs against the Delta variant of SARS-CoV-2, which arose in summer 2021 in the US.

The rapidly-evolving nature of the COVID-19 pandemic, including both the emergence of new variants of the virus and use of EUAs allowing early access to novel therapeutics, makes it critical to build robust research platforms for real-world evidence generation.[13,14] In early

2021, we created a real-world evidence platform to assess the ongoing clinical impacts of mAb therapy on high-risk outpatients with early symptomatic COVID-19.

Our study objective was to evaluate the effectiveness of mAb treatment and progression to severe disease, including hospitalization, severity of hospitalization, and mortality. The goal of the overall platform was to include changes in the pandemic, including emergence of new variants, in near real-time with sufficient power to assess potential mortality benefits and effectiveness among patients with various risk factors for progression to severe disease, including vaccination status.

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 leaders, and the Colorado Department of Public Health and Environment. The study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent (#21-2935). We obtained data from the electronic health record (EHR; Epic, Verona, WI) of University of Colorado Health, the largest health system in Colorado with 13 hospitals around the state and 141,000 annual hospital admissions. EHR data were merged with statewide data on vaccination status from the Colorado Comprehensive Immunization Information System and mortality from Colorado Vital Records.

Patient Population Studied

We included patients diagnosed with SARS-CoV-2 infection between November 20, 2020 and October 7, 2021 allowing for at least 28 days of follow-up as of November 4, 2021 (n=36,077), identified using EHR-based date of SARS-CoV-2 positive testing (by polymerase chain reaction or antigen tests) or date of administration of mAb treatment (if no SARS-CoV-2 test result date available). The decision to seek mAb treatment was made by patients and clinicians, and a state-wide referral system was established by Colorado Department of Public Health and Environment to facilitate patient referrals to facilities for mAb infusion.[15] We did not exclude patients solely for lack of EUA eligibility based on EHR data, because not all eligibility criteria were consistently available in the EHR (see additional Methods in the Supplement). We excluded patients who received mAb treatment on the same day of or during hospitalization, as these patients already had the primary outcome. Logistic regression was used for propensity score estimation[16] with nearest neighbor matching[17] applied to select an approximate 2.5:1 mAb-

untreated to mAb-treated matched cohort. Matching factors included baseline demographics, clinical variables, and time (see additional Methods in the Supplement). The primary analysis cohort included patients with a documented mAb administration date (n=2,675) and propensity-matched controls who did not receive mAb treatment (n=6,677). We assessed effectiveness of matching using standardized mean differences.[18]

Outcomes

The primary outcome was all-cause hospitalization within 28 days of a positive SARS-CoV-2 test, obtained from EHR data. Secondary outcomes included all-cause hospitalization to day 90, all-cause mortality to days 28 and 90, and emergency department (ED) visits to day 28. Among those hospitalized, outcomes included disease severity based on maximum level of respiratory support, hospital and intensive care unit (ICU) length of stay (LOS), and rates of ICU admission, mechanical ventilation, and in-hospital mortality. Subgroups examined for the primary outcome included age, sex, combined race/ethnicity, insurance status, immunocompromised status, total number of other comorbidities, specific comorbidities, vaccination status, pandemic phase, and type of mAb treatment.

Variable Definitions

The treatment variable was mAb administration and the primary starting point (time zero) was the date of any SARS-CoV-2 positive test. We imputed missing test dates based on the distribution of observed mAb administration dates (see additional Methods in the Supplement). Hospitalization was defined as any inpatient or observation encounter documented in the EHR. ED visits were defined as any visit to the ED, with or without an associated inpatient or observation encounter. Presence of comorbid conditions were determined using a 90-day look back period in the EHR using established algorithms and immunosuppressed status was further validated by manual chart reviews (see additional Methods in the Supplement). COVID-19

disease severity was estimated using ordinal categories of respiratory support requirements at an encounter level, based on the highest level of support received among the following types (in increasing order): no oxygen, standard (nasal cannula/face mask) oxygen, high-flow nasal cannula or non-invasive ventilation, and invasive mechanical ventilation.[19] In-hospital mortality was the highest level of disease severity.

Pandemic phase was categorized by SARS-CoV-2 positive date based on the prevalent variant in Colorado as Pre-Alpha (November 2020 - February 2021), Alpha (March 2021 – June 2021), and Delta (July 2021 – December 2021). No virus sequencing results were available on an individual patient basis. Vaccination status at the time of SARS-CoV-2 positive date was categorized as fully vaccinated (at least 14 days after primary vaccine series) or not fully vaccinated, which included partially vaccinated (receipt of at least one vaccine dose but primary series either not completed or completed within 14 days of SARS-CoV-2 positive test date) or not known to be vaccinated. MAb treatments included bamlanivimab (Eli Lilly), casirivimab + imdevimab (Regeneron), bamlanivimab + etesevimab (Eli Lilly), and sotrovimab (GlaxoSmithKline) (see additional Methods in the Supplement for more details).

Statistical analysis

We present results descriptively and adjusted for potential confounders. All regression models for outcomes were adjusted for age, sex, race/ethnicity, insurance status, body mass index (BMI), immunocompromised status, number of comorbidities, pandemic phase, and vaccination status. For binary outcomes such as hospitalization, we used logistic regression to determine odds of the outcome. For count outcomes such as LOS, we used Poisson regression to estimate incidence rates. We analyzed disease severity using ordinal logistic regression to estimate the proportional odds. We constructed cumulative incidence curves using Kaplan-Meier estimates to visually assess temporal trends by treatment status.

We conducted subgroup analyses to estimate heterogeneity of treatment effect for the primary outcome of all-cause hospitalization to day 28. For each subgroup, we calculated unadjusted rates of hospitalization, number needed to treat (NNT) to prevent one hospitalization (based on absolute risk reduction in unadjusted hospitalization rates), and adjusted relative odds of hospitalization. Results are presented as effect sizes, with 95% confidence intervals, and were not adjusted for multiple comparisons.

Three sensitivity analyses were performed (see additional Methods in the Supplement). Briefly, the first evaluated a full imputation approach for missingness in key variables including BMI, immunocompromised status, race/ethnicity, and number of comorbid conditions. The second included only EUA-eligible subjects as verified by available EHR data. The third used a more conservative imputation method for missing SARS-CoV-2 positive test dates by assuming all missing positive test dates were ten days prior to the mAb administration date (the maximum time difference allowed by the EUA). All outcome models were repeated for these two cohorts and results compared with primary analyses. All statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).[20]

RESULTS

Characteristics of mAb-Treated and mAb-Untreated Cohorts

Of 36,077 patients with SARS-CoV-2 infection, 2,675 receiving mAbs were matched to 6,677 patients not receiving mAbs (**Appendix Figure 1** in the Supplement). The characteristics of mAb-treated and mAb-untreated patients in the primary cohort are presented in **Table 1**. The mAb-treated cohort generally reflects EUA criteria for use of mAbs, with many being older (40.7% were age ≥65 years), having higher BMI (50.1% with BMI over 25 kg/m^2) and/or having one or more comorbidities (73.6%). While there were clinically important differences between mAb-treated and mAb-untreated patents in the full cohort (**Appendix Table 1** in the Supplement), propensity matching eliminated clinically meaningful differences between groups on matching variables (**Table 1**, **Appendix Table 2** in the Supplement). The mean time from positive SARS-CoV-2 test to receipt of mAb treatment was 3.7 days (SD 2.5).

Hospitalization and Mortality

The rate of 28-day all-cause hospitalization was lower among mAb-treated compared to matched mAb-untreated controls (4.0% v 7.7%; adjusted OR 0.48, 95%CI: 0.38-0.60) (**Table 2**; full model results **Appendix Table 3** in the Supplement). All-cause 28-day mortality in the mAb-treated group was 0.1% compared to 0.9% among the mAb-untreated group (adjusted OR 0.11, 95%CI: 0.03-0.29). These differences persisted to day 90 (adjusted OR 0.53; 95%CI: 0.44-0.65 for 90-day hospitalization and 0.17; 95%CI: 0.06-0.35 for 90-day mortality). Overall ED visit rates were higher for mAb-treated compared to mAb-untreated patients (18.7% vs. 16.9%; adjusted OR 1.24; 95%CI: 1.09-1.40); however, mAb-treated patients had fewer ED visits resulting in hospitalization (16.0% vs. 37.6%; adjusted OR 0.29, 95%CI: 0.21-0.38).

Based on a time-to-event analysis, the benefits associated with reduced hospitalization are largely accrued within 10 days of the positive test date, while the mortality benefit of mAb

treatment continues to accrue over 28 days (**Figure 1**). Treatment benefits persisted to day 90 for both hospitalization and death (**Appendix Figure 2** in the Supplement).

Severity of Hospitalization

For patients requiring hospitalization, prior receipt of mAbs was associated with lower hospital LOS among survivors (5.8 vs. 8.5 days, adjusted incidence rate ratio 0.64, 95%CI: 0.51-0.82) and a lower rate of ICU admission (12.0% vs. 19.6%; adjusted OR 0.52, 95%CI 0.26-0.97), and mechanical ventilation or death (4.6% vs. 16.6%; adjusted OR 0.22, 95%CI: 0.07-0.52) (**Table 2**). For those requiring ICU care, prior receipt of mAbs was associated with shorter ICU LOS (3.5 vs. 8.6 days; adjusted incidence rate ratio 0.22; 95%CI: 0.10-0.48). Overall, severity of hospitalization was lower across the illness continuum for mAb-treated patients (**Figure 2**).

Subgroup Analyses

The relative benefit of mAb therapy on reducing 28-day hospital admissions among key demographic and clinical subgroups was broadly similar across all subgroups (**Figure 3**). Of note, the association between mAb treatment and prevention of hospitalizations was at least as high during the Delta phase (OR 0.35; 95%CI: 0.25-0.50), compared to the Alpha phase (OR 0.67; 95%CI: 0.46-0.98). In addition, there was similar relative effectiveness for fully vaccinated (OR 0.44; 95%CI: 0.25-0.77) and not fully vaccinated (OR 0.49; 95%CI: 0.39-0.62) patients. However, the absolute treatment effect was higher for subgroups with higher baseline risk of hospitalization. For example, the number needed to treat (NNT) to prevent one hospitalization was 15 for patients age 65 years or older, 17 for those with at least 2 comorbid conditions, and 24 for those not fully vaccinated against SARS-CoV-2, compared to NNT of 45 for age 18-45 years, 88 for those without comorbidities, and 81 for fully vaccinated patients. Notably, only a small proportion of patients who were fully vaccinated against SARS-CoV-2 were hospitalized

(1.8% of mAb-treated and 3.0% of mAb-untreated; **Figure 3**), and no patients died who were fully vaccinated and received mAb treatment.

Sensitivity Analyses

Three sensitivity analyses were performed, the first evaluating a full multiple imputation approach to key missing variables, the second restricting the cohort to only patients meeting EUA eligibility criteria based on available EHR data, and the third using a more conservative imputation method when the date of positive SARS-CoV-2 test was missing. None of these analyses materially changed the main results (**Appendix Tables 4-8** in the Supplement).

DISCUSSION

We report real-world evidence that demonstrates novel results on both high effectiveness of mAb treatment in reducing hospitalization during the Delta variant phase and a remarkable overall mortality benefit with an 89% lower mortality at 28 days. Neutralizing mAbs are widely seen as important tools for managing surging cases of COVID-19, yet prior studies could not evaluate effectiveness of mAbs against Delta variant infections and have been underpowered to evaluate impact of mAbs on the most clinically important outcome: patient mortality. The present study fills these key knowledge gaps.

There have also been critical gaps in understanding the effects of mAbs on important subgroups of patients, such as those with older age, comorbid conditions, and prior SARS-CoV-2 vaccination. With our large sample size, we demonstrated clinical benefits of mAb administration among virtually all subgroups examined, with similar relative benefits in terms of reduced odds of hospitalizations across all subgroups. These subgroup findings highlight the need to interpret relative benefits in light of highly variable absolute hospitalization rates, because the NNT to avert one hospitalization depends on both mAb effectiveness and baseline rates of hospitalization. For example, we found a similar relative effect size for vaccinated and unvaccinated patients, but the NNT to avert one hospitalization among unvaccinated patients is 24, while the NNT for vaccinated patients is 81. These results are of practical importance for policymakers and clinicians because there have been shortages of mAb supplies and infusion capacity.[11,12] Specifically, our findings suggest the most efficient use of limited mAb infusion capacity to alleviate strain on hospitals is to preferentially administer mAbs to patients at highest baseline risk for hospitalization, including those who are older, not fully vaccinated, or with multiple comorbid conditions. Notably, 28-day hospitalization among mAb-treated but not fully vaccinated patients was almost 3-fold higher (5.2%) than for mAb-treated patients who were

fully vaccinated (1.8%) and higher even than mAb-untreated patients who were fully vaccinated (3.0%). These data support that SARS-CoV-2 vaccination remains the first line intervention to prevent COVID-19 hospitalizations with mAb treatment best used as supplemental therapy for high-risk patients.

Limitations

This study has several limitations. The setting was a single health system; while large and representing both urban and rural settings and community and academic hospitals, it is geographically limited to one US state. Our sample had relatively low racial and ethnic minority representation, limiting our ability to detect differences across these key subgroups. While we used statewide data for mortality and vaccination status, hospitalizations were collected only within this single health system. If mAb-untreated patients were also less likely to be seen in the health system for other services (hence, 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.[21] These factors might have limited our ability to detect the impact of mAb treatment, especially between subgroups. Our EHR data does not contain information on SARS-CoV-2 variants at the patient level, so variant phases are presented chronologically. However, during Colorado's Delta phase more than 99% of sequenced SARS-CoV-2 was Delta variant.[22] Our large sample size allowed the detection of meaningful benefits of mAb therapy for most subgroups, but the study could not detect potentially relevant differences between subgroups. Our propensity scoring method achieved excellent matching between mAb-treated and mAb-untreated patient groups across multiple variables, but unmeasured confounders may remain. Finally, our study was conducted prior to the emergence of the Omicron variant and there is in vitro evidence of reduced SARS-

CoV-2 neutralization by some authorized mAbs.[23,24] Forthcoming studies will evaluate the effectiveness of each available mAb treatment during the Omicron phase of the pandemic.

Interpretation

Real-world evidence in this study demonstrated that mAb treatment was associated with lower hospitalizations and deaths among COVID-19 outpatients across multiple pandemic phases, compared to matched mAb-untreated patients. For hospitalized patients, prior mAb treatment was associated with notably lower disease severity, including reduced hospital length of stay, ICU length of stay, mechanical ventilation, and death. When access to mAbs is limited, prioritizing patients at highest risk for hospitalization has the most potential to reduce health system strain during the COVID-19 pandemic.

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Take Home Point Pullout

Study Question: Does real-world evidence demonstrate that treatment with neutralizing monoclonal antibodies (mAbs) was correlated with lower progression to severe disease and death during the Delta, Alpha, and pre-Alpha variant phases of the pandemic, adjusting for risk factors including vaccination status?

Results: We examined outcomes of 36,077 patients with COVID-19 between November 2020 and October 2021 using electronic health record data combined with state-level vaccine and mortality data, and after adjusting for multiple other factors the odds of 28-day hospitalization was reduced by more than half (OR 0.48, 95%CI 0.38-0.60) and odds of death by 89% (OR 0.11, 95%CI 0.03-0.29) among patients receiving mAbs. Results were similar across pandemic phases and multiple clinical subgroups, but the number-needed-to-treat to prevent hospitalization was much lower for subgroups with elevated baseline risk of hospitalization.

Interpretation: Real-world data revealed a strong association between receipt of mAbs and reduced hospitalization and death among COVID-19 outpatients across multiple pandemic phases and provided valuable data to inform scarce resource allocation decisions.

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

Characteristic	mAb-Treated n=2675	mAb-Untreated n=6677
Age in years*		
18-54 years	1018 (38.1%)	3025 (45.3%)
55-64 years	569 (21.3%)	1635 (24.5%)
≥65 years	1088 (40.7%)	2017 (30.2%)
Female Sex*	1453 (54.3%)	3705 (55.5%)
Race/Ethnicity*		
Non-Hispanic White	2215 (82.8%)	5323 (79.7%)
Hispanic	264 (9.9%)	775 (11.6%)
Non-Hispanic Black	64 (2.4%)	189 (2.8%)
Other	132 (4.9%)	390 (5.8%)
Insurance Status*		
Private/Commercial	1355 (50.7%)	3840 (57.5%)
Medicare	1052 (39.3%)	1989 (29.8%)
Medicaid	164 (6.1%)	543 (8.1%)
None/Uninsured	44 (1.6%)	118 (1.8%)
Other/Unknown	60 (2.2%)	187 (2.8%)
Body mass index in kg/m^2*		
<18.5	23 (0.9%)	60 (0.9%)
18.5-24.9	362 (13.5%)	875 (13.1%)
25.0-29.9	571 (21.3%)	1374 (20.6%)
≥30.0	770 (28.8%)	2013 (30.1%)
Missing	949 (35.5%)	2355 (35.3%)
Immunocompromised*	809 (30.2%)	1677 (25.1%)
Number of Other Comorbid Conditions*		
0	708 (26.5%)	1837 (27.5%)
1	681 (25.5%)	1967 (29.5%)
≥2	1286 (48.1%)	2873 (43.0%)
Diabetes	561 (21.0%)	1173 (17.6%)
Cardiovascular Disease	557 (20.8%)	1290 (19.3%)
Pulmonary Disease	891 (33.3%)	2109 (31.6%)
Renal Disease	344 (12.9%)	607 (9.1%)
Hypertension	1293 (48.3%)	2881 (43.1%)
Obesity	808 (30.2%)	2073 (31.0%)
Vaccination Status		
Not known to be vaccinated	1620 (60.6%)	4394 (65.8%)
Partially vaccinated	148 (5.5%)	485 (7.3%)
Fully vaccinated	907 (33.9%)	1798 (26.9%)
Pandemic Phase		
Pre-alpha: Nov 2020 - Feb 2021	388 (14.5%)	984 (14.7%)
Alpha: March 2021 - June 2021	615 (23.0%)	1794 (26.9%)
Delta: July 2021 - Sep 2021	1672 (62.5%)	3899 (58.4%)
Type of monoclonal antibody		
Bamlanivimab	413 (15.4%)	--
Bamlanivimab + etesevimab	87 (3.3%)	--
Casirivimab + imdevimab	2157 (80.6%)	--
Sotrovimab	18 (0.7%)	--

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

Table 2. Primary and Secondary Outcomes by Monoclonal Antibody Treatment Status

Outcome	mAb-Treated	mAb-Untreated	Adjusted OR	95% CI
Overall Sample Size	n=2675	n=6677		
All-Cause Hospitalization				
28-day (primary outcome)	108 (4.0%)	511 (7.7%)	0.48	(0.38, 0.60)
90-day	138 (5.2%)	590 (8.8%)	0.53	(0.44, 0.65)
All-Cause Mortality				
28-day	3 (0.1%)	63 (0.9%)	0.11	(0.03, 0.29)
90-day	6 (0.2%)	84 (1.3%)	0.17	(0.06, 0.35)
Any ED Visit to Day 28	501 (18.7%)	1128 (16.9%)	1.24	(1.09, 1.40)
ED Visit leading to Hospitalization	80/501 (16.0%)	424/1128 (37.6%)	0.29	(0.21, 0.38)
Hospitalized Sample Size	n=108	n=511		
Hospital LOS in days, mean (SD)*	5.8 (6.5)	8.5 (9.8)	0.64	(0.51, 0.82)
IMV or Death	5 (4.6%)	85 (16.6%)	0.22	(0.07, 0.52)
ICU Admission	13 (12.0%)	100 (19.6%)	0.52	(0.26, 0.97)
ICU LOS (days), mean (SD)*	3.5 (2.8)	8.6 (9.9)	0.22	(0.10, 0.48)

* Poisson regressions presented as adjusted incidence rate ratios with 95% confidence intervals

All regression models adjusted for age, sex, race/ethnicity, BMI, immunocompromised status, number of other comorbidities, insurance status, pandemic phase, and vaccination status

Abbreviations: mAb, monoclonal antibody; OR, odds ratio; CI, confidence interval; LOS, length of stay; ICU, intensive care unit; SD, standard deviation

FIGURE LEGENDS

Figure 1. Cumulative Incidence Plots for All-Cause Hospitalization (A) and Mortality (B) to Day 28 by Monoclonal Antibody Treatment Status

A. Hospitalization

B. Mortality

Figure 2. Maximum Respiratory Support by Monoclonal Antibody Treatment Status among Patients Hospitalized within 28 Days

Comparing severity of hospitalizations for n=108 mAb-treated and n=511 mAb-untreated patients, the maximum level of respiratory support was lower for mAb-treated patients (adjusted proportional OR 0.25; 95%CI: 0.16-0.38).

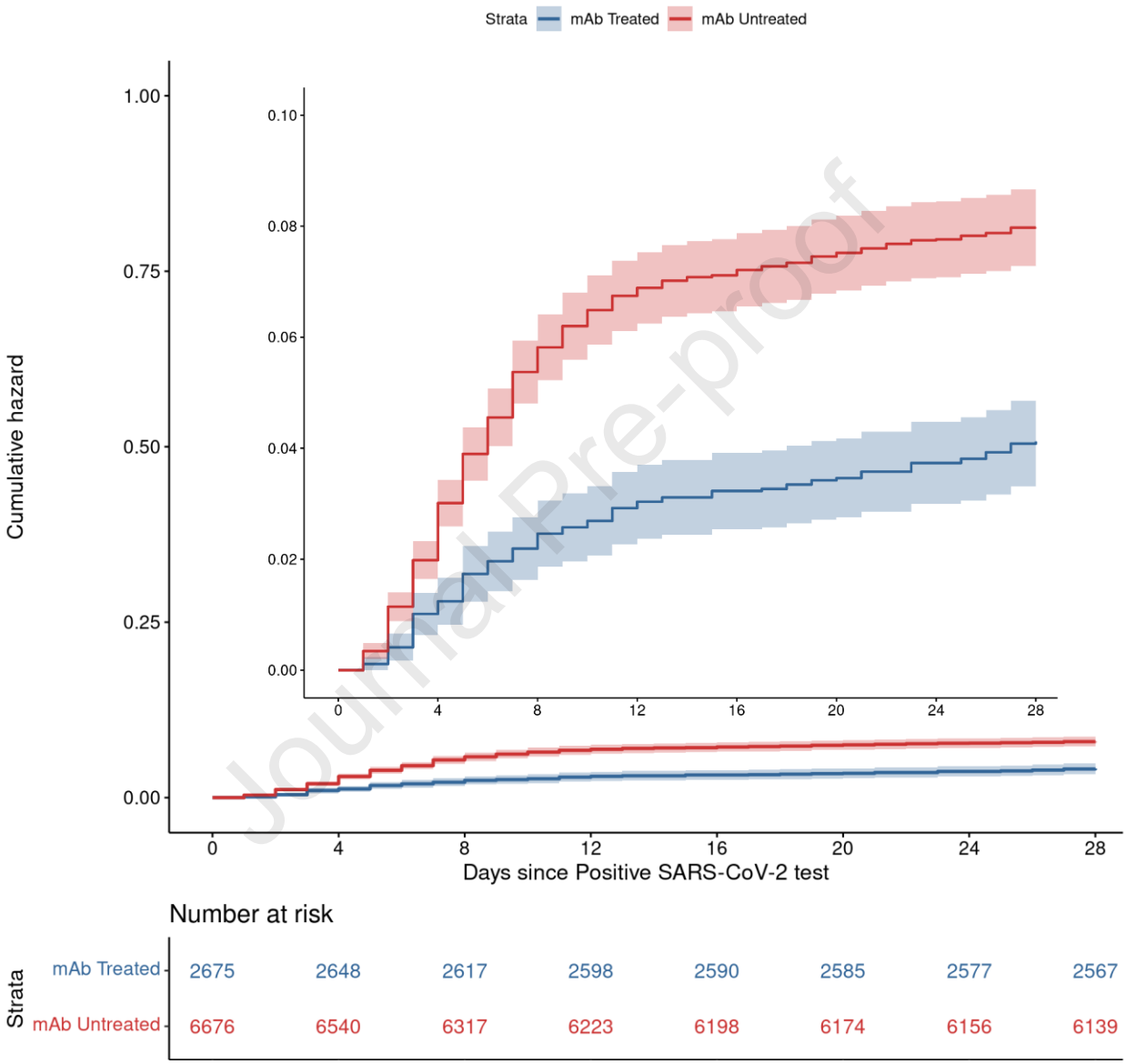
Figure 3. Subgroup Analysis of Monoclonal Antibody Effect on 28-day Hospitalization

For each subgroup, we calculated unadjusted rates of hospitalization, number needed to treat (NNT) to prevent one hospitalization (based on absolute risk reduction in unadjusted hospitalization rates), and adjusted relative odds of hospitalization. Each adjusted odd ratio represents a separate model. All regression models adjusted for age, sex, race/ethnicity, BMI, immunocompromised status, number of comorbidities, insurance status, pandemic phase, and vaccination status. Results were not adjusted for multiple comparisons.

Abbreviations: mAb, monoclonal antibody; NNT, number needed to treat; OR, odds ratio; CI, confidence interval

Figure 1. Cumulative Incidence Plots for All-Cause Hospitalization (A) and Mortality (B) to Day 28 by Monoclonal Antibody Treatment Status

A. Hospitalization



B. Mortality

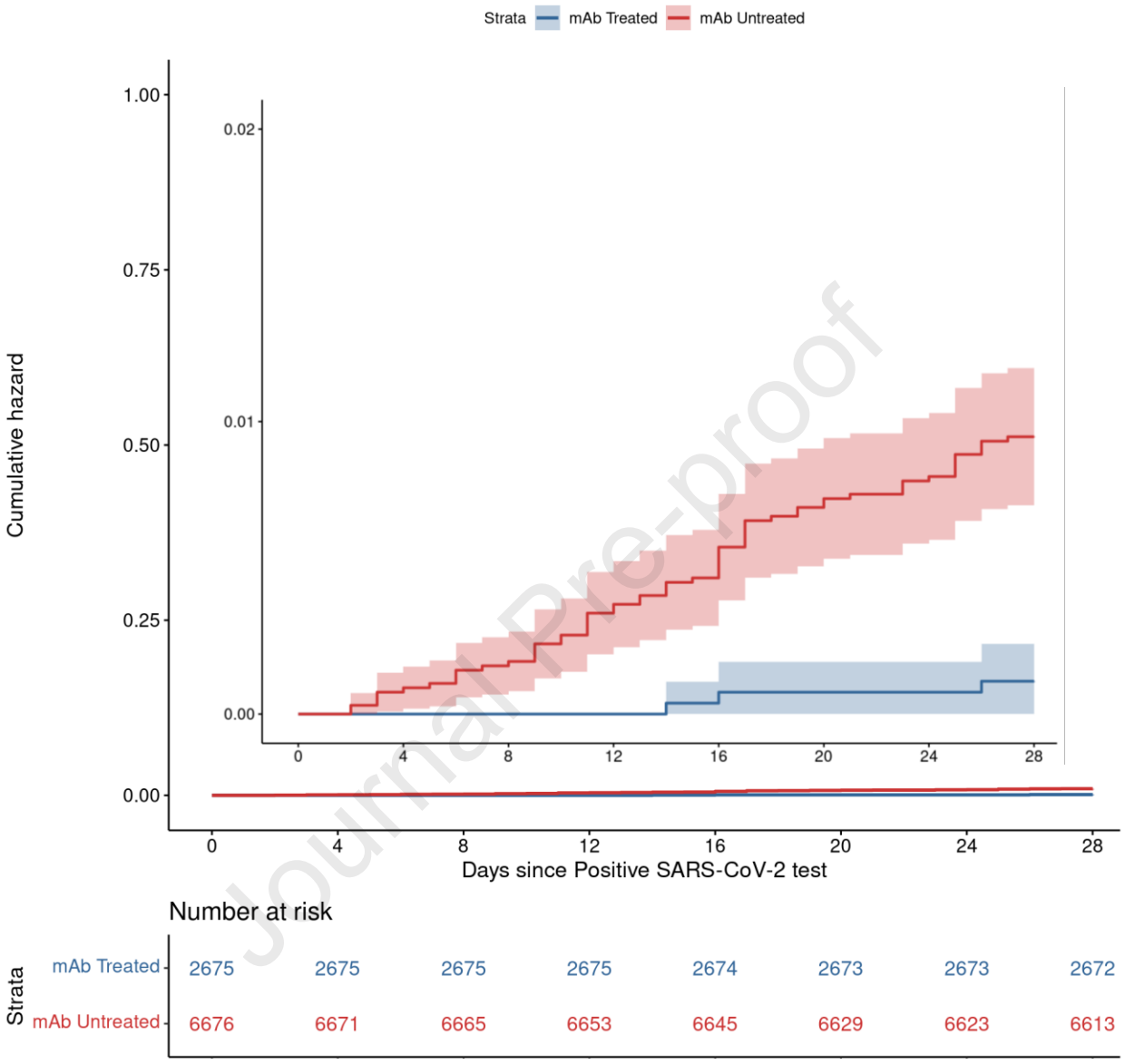


Figure 2. Maximum Respiratory Support by Monoclonal Antibody Treatment Status among Patients Hospitalized within 28 Days

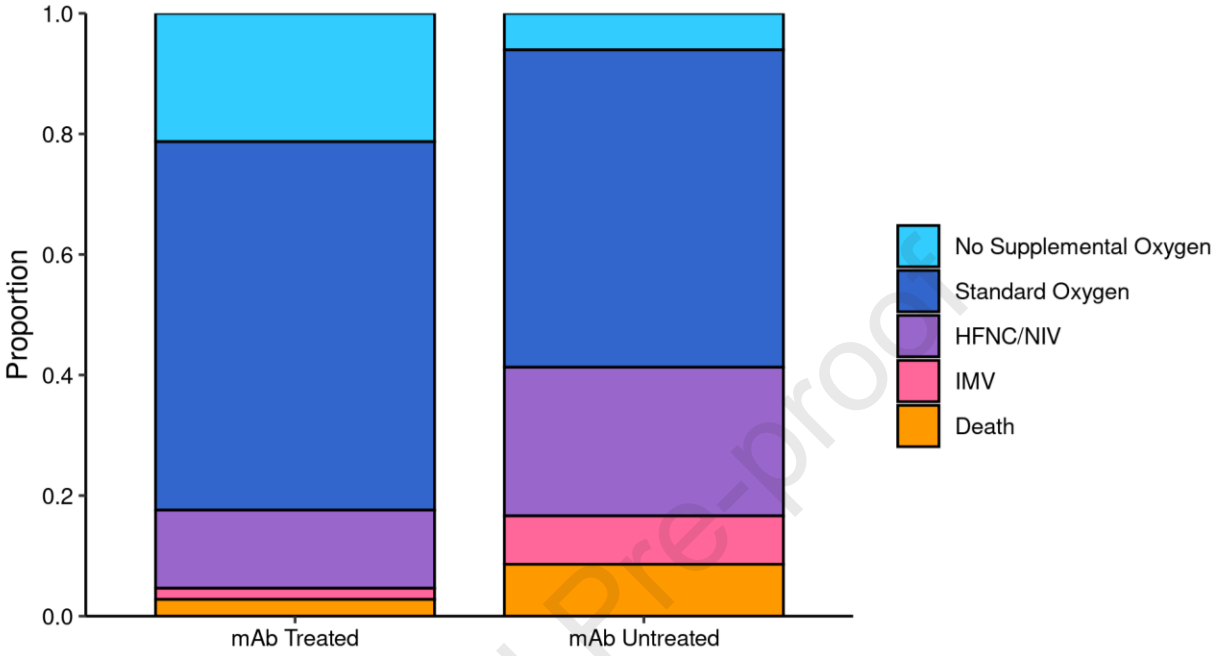
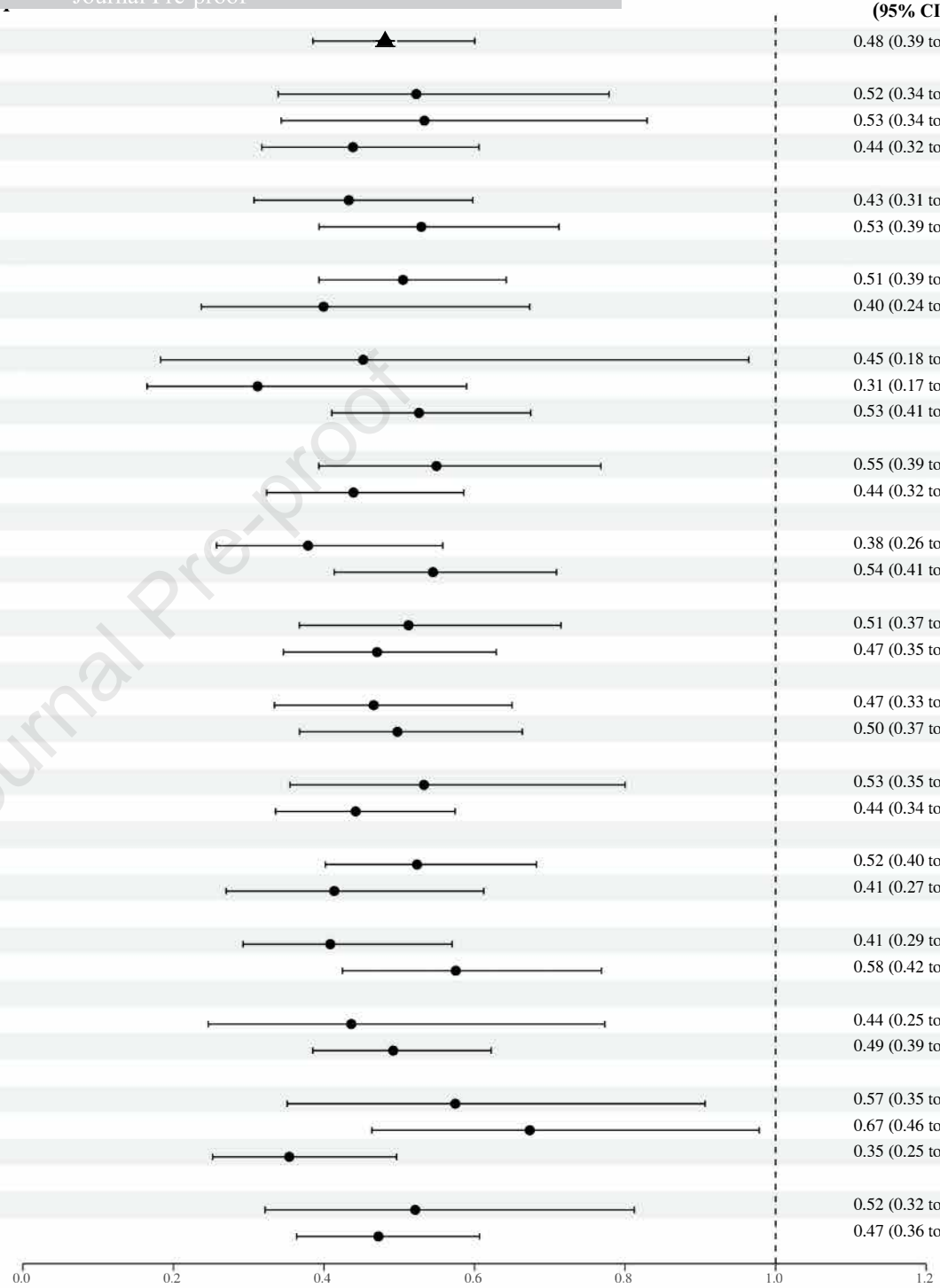


Figure 3.

Subgroup	n per group	mAb Untreated n hospitalized(%)	mAb Treated n hospitalized(%)	NNT	Adjusted OR (95% CI)
Overall	9352	511 (7.7%)	108 (4.0%)	28	0.48 (0.39 to 0.60)
Age in years					
18-54	4043	154 (5.1%)	29 (2.8%)	45	0.52 (0.34 to 0.78)
55-64	2204	128 (7.8%)	27 (4.7%)	32	0.53 (0.34 to 0.83)
≥ 65	3105	229 (11.4%)	52 (4.8%)	15	0.44 (0.32 to 0.61)
Sex					
Female	5158	250 (6.7%)	45 (3.1%)	27	0.43 (0.31 to 0.60)
Male	4194	261 (8.8%)	63 (5.2%)	28	0.53 (0.39 to 0.71)
Race/Ethnicity					
Non-Hispanic White	7538	385 (7.2%)	90 (4.1%)	32	0.51 (0.39 to 0.64)
Other	1814	126 (9.3%)	18 (3.9%)	19	0.40 (0.24 to 0.67)
Number of Other Comorbid Conditions					
0	2545	39 (2.1%)	7 (1.0%)	88	0.45 (0.18 to 0.96)
1	2648	99 (5.0%)	11 (1.6%)	29	0.31 (0.17 to 0.59)
≥ 2	4159	373 (13.0%)	90 (7.0%)	17	0.53 (0.41 to 0.67)
Immunocompromised Status					
Immunocompromised	2486	185 (11.0%)	51 (6.3%)	21	0.55 (0.39 to 0.77)
Not Immunocompromised	6866	326 (6.5%)	57 (3.1%)	29	0.44 (0.32 to 0.59)
Diabetes Status					
Diabetes	1734	187 (15.9%)	35 (6.2%)	10	0.38 (0.26 to 0.56)
No Diabetes	7618	324 (5.9%)	73 (3.5%)	41	0.54 (0.41 to 0.71)
Cardiovascular Disease Status					
Cardiovascular Disease	1847	218 (16.9%)	52 (9.3%)	13	0.51 (0.37 to 0.71)
No Cardiovascular Disease	7505	293 (5.4%)	56 (2.6%)	36	0.47 (0.35 to 0.63)
Pulmonary Disease Status					
Pulmonary Disease	3000	221 (10.5%)	48 (5.4%)	20	0.47 (0.33 to 0.65)
No Pulmonary Disease	6352	290 (6.3%)	60 (3.4%)	33	0.50 (0.37 to 0.66)
Renal Disease Status					
Renal Disease	951	115 (18.9%)	39 (11.3%)	13	0.53 (0.35 to 0.80)
No Renal Disease	8401	396 (6.5%)	69 (3.0%)	28	0.44 (0.34 to 0.57)
Hypertension Status					
Hypertension	4174	321 (11.1%)	79 (6.1%)	20	0.52 (0.40 to 0.68)
No Hypertension	5178	190 (5.0%)	29 (2.1%)	34	0.41 (0.27 to 0.61)
Obesity Status					
Obese	2881	275 (13.3%)	46 (5.7%)	13	0.41 (0.29 to 0.57)
Non-Obese	6471	236 (5.1%)	62 (3.3%)	55	0.58 (0.42 to 0.77)
Vaccination Status					
Fully vaccinated	2705	54 (3.0%)	16 (1.8%)	81	0.44 (0.25 to 0.77)
Not fully vaccinated	6647	457 (9.4%)	92 (5.2%)	24	0.49 (0.39 to 0.62)
Pandemic Phase					
Pre-Alpha	1372	107 (10.9%)	24 (6.2%)	21	0.57 (0.35 to 0.91)
Alpha	2409	159 (8.9%)	40 (6.5%)	42	0.67 (0.46 to 0.98)
Delta	5571	245 (6.3%)	44 (2.6%)	27	0.35 (0.25 to 0.50)
mAb Medication Type					
Bamlanivimab	413	511 (7.7%)	24 (5.8%)		0.52 (0.32 to 0.81)
Casirivimab + Imdevimab	2157	511 (7.7%)	80 (3.7%)		0.47 (0.36 to 0.61)



Supplementary Appendix

Supplement to: Wynia MK *et al.*
Real-World Evidence of Neutralizing Monoclonal Antibodies for Preventing Hospitalization and Mortality in COVID-19 Outpatients

This Appendix has been provided by the authors to give readers additional information about the work.

Table of Contents

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We also wish to thank patients and families for their participation in research to accelerate discovery and rapidly advance clinical care in the pandemic; numerous colleagues who provided support for this project; frontline health care workers for their tireless efforts and life-saving contributions; and researchers around the world working together in the quest to inform healthcare practice and improve patient outcomes of COVID-19.

Supplementary Methods

Description of Demographic Variables

Age was determined at the time of positive SARS-CoV-2 test or mAb administration if SARS-CoV-2 test date was not available in the electronic health record (EHR). We categorized age into 18-54, 55-64, and ≥65 years, based on thresholds that were defined in the original monoclonal antibody (mAb) Emergency Use Authorization (EUA) criteria (Table S8). Sex was defined as legal sex in the EHR and was binarized into female and male (non-binary status was not explicitly defined), and this field was missing for two subjects. To preserve sample size, the variables race and ethnicity were combined and categorized into non-Hispanic white, non-Hispanic black, Hispanic, and other. In the subgroup analysis race/ethnicity is binarized into non-Hispanic white and other to allow for a large enough sample size for subgroup analyses. Continuous body mass index (BMI in kg/m^2) was categorized into 4 categories: underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obese (≥30.0). The number of comorbid medical conditions was calculated using obesity, hypertension, cardiovascular disease, diabetes, pulmonary disease, and renal disease, and was categorized into none, one, or two or more. Immunocompromised status was categorized separately. All individual comorbid conditions were considered as binary variables with either evidence of the comorbid condition or no evidence of the comorbid condition in the EHR.

EHR Curation of Comorbidities

We defined comorbidities based on the updated Charlson and Elixhauser Comorbidity Indices[1,2] as implemented in the 'icd' R package[3] and reported previously from the same health system.[4] From the eligibility criteria above, we categorized a patient as having

diabetes, renal disease, pulmonary disease, cardiovascular disease, or immunocompromised status if those conditions were present for that patient in either the Charlson or Elixhauser system. For obesity and hypertension, we used only the Elixhauser system. Because of the importance of immunocompromised status as a risk factor for hospitalization and mortality from COVID-19, we additionally defined patients as immunocompromised if any of the below medications were present in the EHR medication administration record during the 90-day lookback period. The list of medications was developed jointly by an expert team of UCHealth pharmacists and Infectious Disease physicians. We evaluated the accuracy of the EHR medication curation by manually reviewing the charts of 2,555 patients. EHR curation accurately classified 85% of patients. Potentially discordant patients most often had received immune-suppressing medications prior to our IRB-approved 90-day lookback period or had received prednisone or methylprednisolone at doses under the expert-defined dose threshold.

List of immune-suppressing medications

- Alemtuzumab
- Belatacept in past 2 months
- Calcineurin inhibitors (tacrolimus and cyclosporine – excludes topical/ophthalmic administration routes)
- Eculizumab
- mTOR-inhibitors (everolimus, sirolimus – excludes topical routes)
- Mycophenolate, azathioprine, cyclophosphamide in the last 1 month
- Prednisone or methylprednisolone, oral or IV only (≥10 mg prednisone equivalent)
- Rituximab

- Thymoglobulin
- TNF-α inhibitor (e.g., infliximab, etanercept, golimumab, adalimumab, certolizumab)

Missing Data Techniques

Of the 3,164 patients who received mAb treatment, 1,593 (50.3%) were missing an initial positive SARS-CoV-2 test date in the UCHealth EHR, suggesting many initial tests were performed outside the UCHealth system. For the primary analysis, a distribution of the time difference between positive SARS-CoV-2 test date and mAb administration date was created for subjects who had both. Then, time differences were randomly sampled with replacement from this distribution and were used to impute positive test dates for the patients who only had a mAb administration date. We evaluated a sensitivity analysis to this approach by imputing the maximum allowed time difference between SARS-CoV-2 positive date and mAb administration date (10 days) for all patients missing the first date.

In the full cohort (prior to propensity matching), 20,010 (55.5%) of patients were missing BMI. This is typical of EHR studies. A missing category for BMI was introduced and BMI with 5 levels (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2, and missing) was used during propensity matching and analysis. A combination of reported BMI and reported obesity status was used in determining eligibility. A patient was considered eligible if they had a reported BMI higher than the threshold (either 25 or 35 depending on the date) or if they were indicated as "obese" in the EHR.

A complete case analysis was performed for propensity matching. All comorbid conditions were missing from the EHR for 2,077 (5.7%) patients. Race/ethnicity was

missing for 1,996 (5.5%) of patients. A total of 3,407 (9.4%) of patients were removed for the propensity matching.

We performed sensitivity analysis we evaluated a full multiple imputation approach. We started with the full dataset prior to propensity matching. Variables imputed included continuous BMI, which was then categorized, immunocompromised status, race/ethnicity, and number of comorbid conditions (none, one, two or more). We used the MICE package in R to create 20 imputed datasets. For multi-level categorical missing data we used random forest (race/ethnicity and number of comorbid conditions). For immunocompromised we specified logistic regression and for BMI we used linear regression (PMM). Variables included in the imputation model included: 28-day hospitalization, treatment status, age, gender, race/ethnicity, insurance status, comorbid conditions, BMI, and vaccine status. For each of the 20 imputed datasets we used the propensity matching approach described below. We then fitted the outcome model on each of the 20 imputed matched datasets. We combined coefficients from outcome model for treatment by Rubin's B-W calculation to calculate the SE's and 95% CI based on these SE's and then back transformed to the OR scale.

Propensity Matching

The propensity matched dataset was created through a logistic regression propensity score matching process. Nearest neighbor matching was used, with a maximum ratio of 3:1 mAb-untreated and mAb-treated groups. In the matching process, we lost both mAb-treated and mAb-untreated subjects and ended up with a ratio of approximately 2.5:1. A common support was used for both the cases and controls, and a caliper width of < 0.2*SD of the propensity distribution was applied[4]. The standardized mean differences of each level of all

covariates included in the model were calculated to compare the means and prevalence in the propensity matched dataset. A standardized mean difference of <0.1 was considered to have a non-meaningful imbalance in the data[3].

The baseline characteristics included in the propensity matching process were age in years, sex, race/ethnicity, BMI, insurance status, immunocompromised status, number of other comorbid conditions, and days from initial cohort date, November 20, 2020 (as a quadratic effect).

Model Fitting

Each of the models presented in Table 2 were fitted using the same group of adjustment variables. The variables that were included were age, sex, race/ethnicity, BMI, insurance status, vaccination status, pandemic phase, number of comorbid conditions, and immunocompromised status. A significance level of 0.05 was used to determine statistical significance; 95% confidence intervals (CIs) were also used to evaluate clinical significance.

Subgroup Analysis

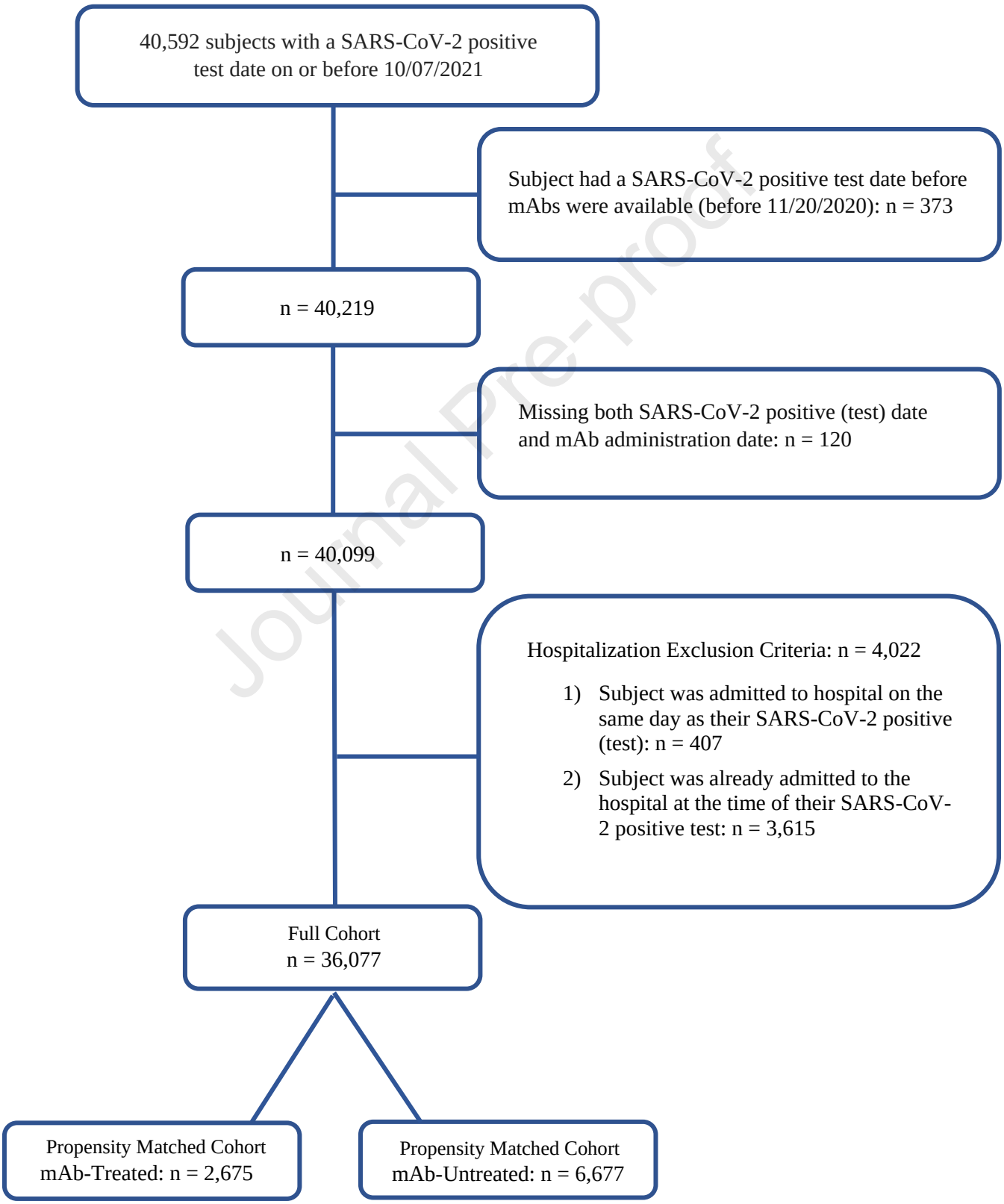
To evaluate the potential heterogeneity of the treatment effect across key subgroups of interest the above model for the primary outcome (28-day hospitalization) was fitted separately for each of the 14 subgroups of interest. More specifically, for each subgroup an interaction was included between the subgroup variable and the treatment variable, and the main effects of the other variables included for adjustment. The subgroups investigated included age in years, sex, race/ethnicity, number of comorbid conditions, immunocompromised status, diabetes status, cardiovascular disease status, pulmonary disease status, renal disease status, hypertension status, obesity status, vaccination status, pandemic phase, and mAb medication type.

A total of 29 treatment effects were estimated and all subgroup analyses that were performed were reported in Figure 3. Heterogeneity was assessed visually through a forest plot, and subgroup odds ratio estimates were compared. Statistical tests of significance for each interaction term were not reported in the paper, as this analysis was likely underpowered and the potential for Type I error due to multiple comparisons was not accounted for[4]. Subgroup analyses were post hoc specified. Within-level results are presented for each estimated treatment effect by subgroup.

In addition, raw counts and rates are reported for each subgroup. The number needed to treat (NNT) was calculated based on the raw rates as the inverse of the absolute risk reduction. NNT was not calculated for mAb medication type.

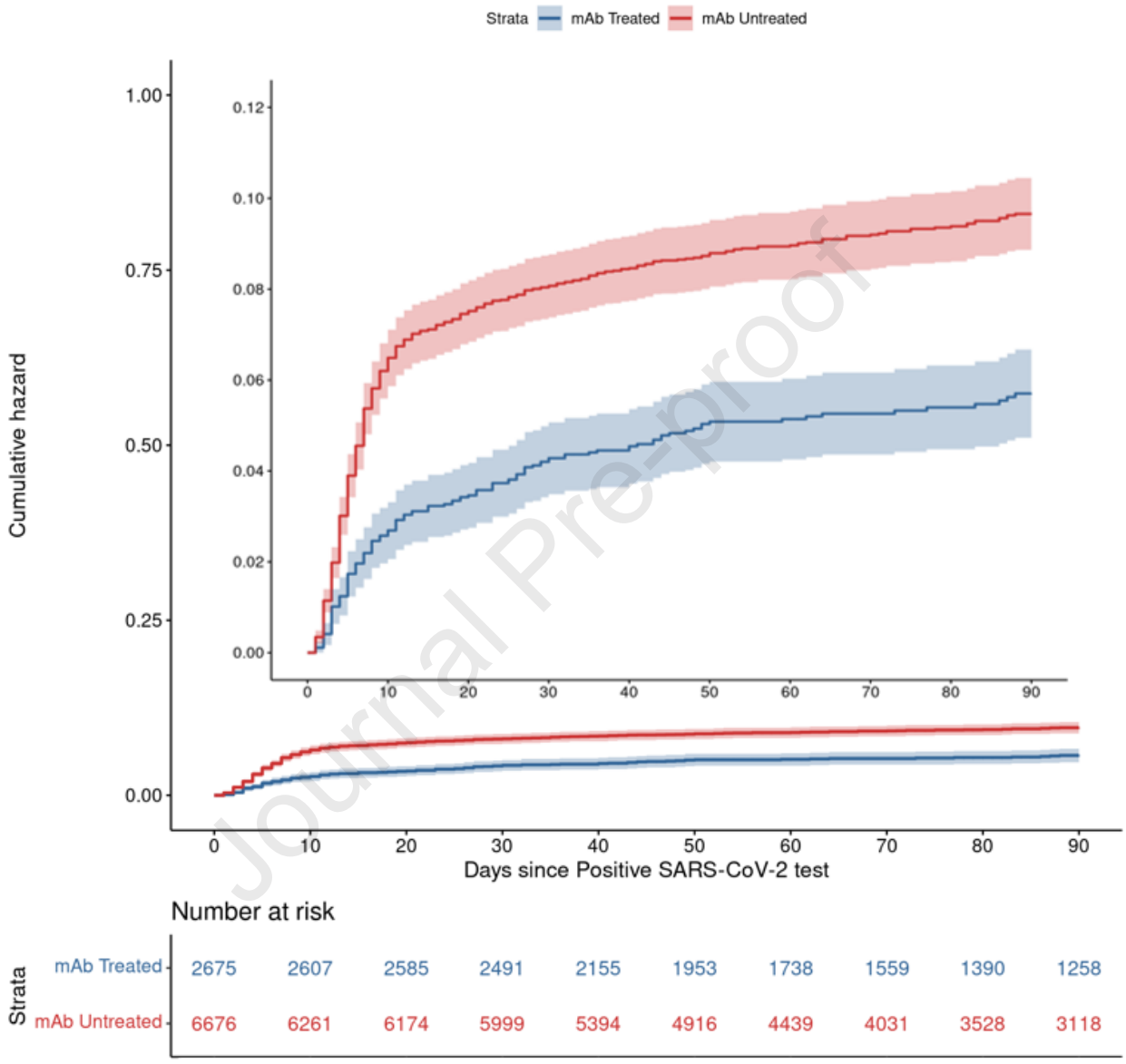
Appendix Figures

Appendix Figure 1: Flow of Patients into the Primary Study Cohort

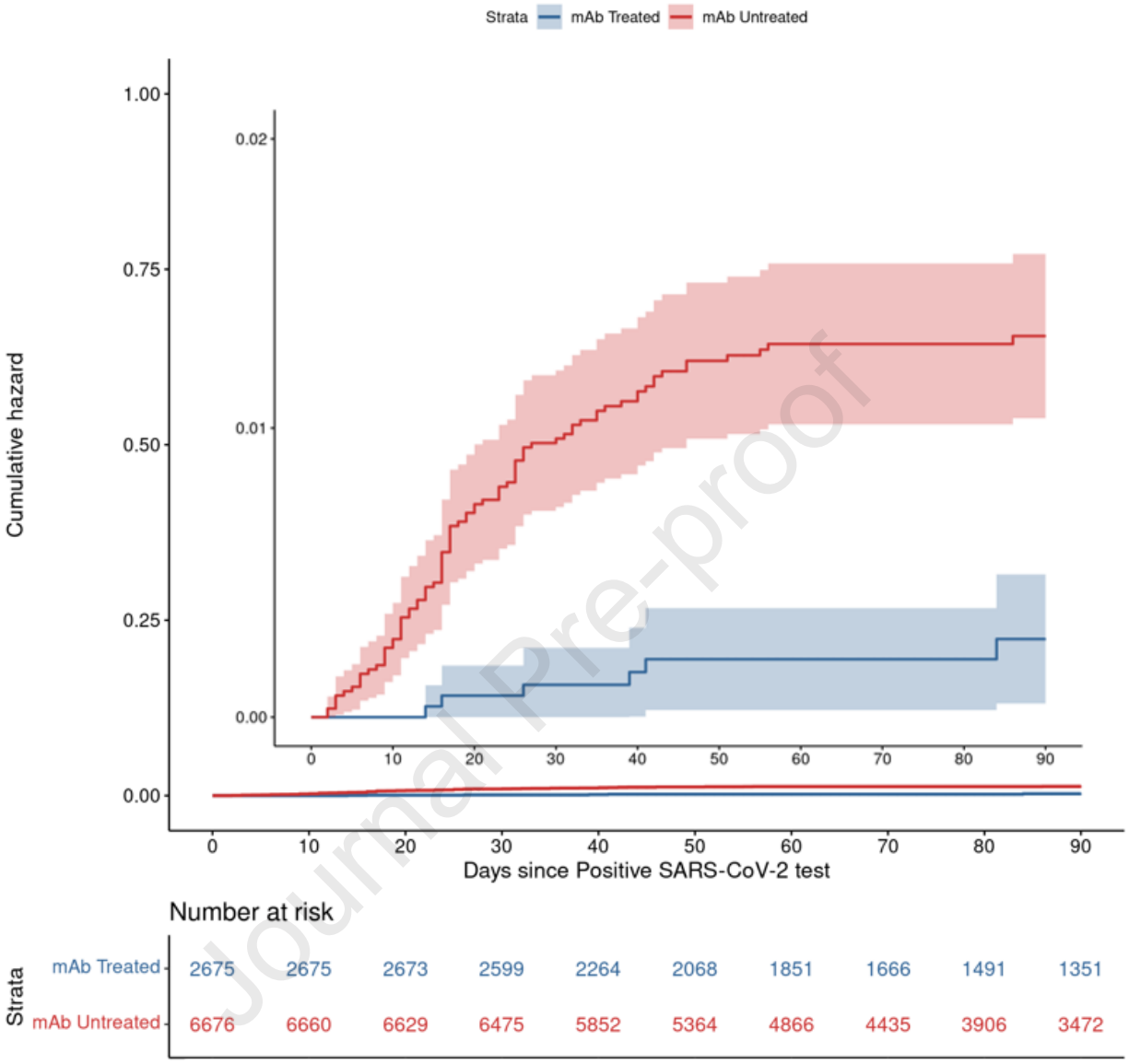


Appendix Figure 2. Cumulative Incidence Plots for All-Cause Hospitalization (A) and Mortality (B) to Day 90 by Monoclonal Antibody Treatment Status

A.



B.



Appendix Tables

Appendix Table 1. Baseline Characteristics by Monoclonal Antibody Treatment Status for Full SARS-CoV-2 Positive Cohort, Prior to Propensity Matching

Characteristic	mAb-Treated n=2758	mAb-Untreated n=33319
Age in years		
18-54 years	1052 (38.1%)	25075 (75.3%)
55-64 years	586 (21.2%)	4669 (14.0%)
≥65 years	1120 (40.6%)	3575 (10.7%)
Sex		
Female	1491 (54.1%)	17681 (53.1%)
Male	1267 (45.9%)	15636 (46.9%)
Missing	0 (0.0%)	2 (0.0%)
Race/Ethnicity		
Non-Hispanic White	2229 (80.8%)	22311 (67.0%)
Hispanic	267 (9.7%)	5263 (15.8%)
Non-Hispanic Black	64 (2.3%)	1488 (4.5%)
Other	133 (4.8%)	2326 (7.0%)
Missing	65 (2.4%)	1931 (5.8%)
Body mass index in kg/m^2		
<18.5	23 (0.8%)	204 (0.6%)
18.5-24.9	365 (13.2%)	3784 (11.4%)
25.0-29.9	577 (20.9%)	4666 (14.0%)
≥30.0	780 (28.3%)	5668 (17.0%)
Missing	1013 (36.7%)	18997 (57.0%)
Immunocompromised		
Yes	819 (29.7%)	3281 (9.8%)
No	1917 (69.5%)	27993 (84.0%)
Missing	22 (0.8%)	2045 (6.1%)
Number of Other Comorbid Conditions		
0	747 (27.1%)	18488 (55.5%)
1	689 (25.0%)	6887 (20.7%)
≥2	1299 (47.1%)	5890 (17.7%)
Missing	23 (0.8%)	2054 (6.2%)
Diabetes		
Yes	567 (20.6%)	2523 (7.6%)
No	2168 (78.6%)	28742 (86.3%)
Missing	23 (0.8%)	2054 (6.2%)
Cardiovascular Disease		
Yes	563 (20.4%)	2346 (7.0%)
No	2172 (78.8%)	28919 (86.8%)
Missing	23 (0.8%)	2054 (6.2%)
Pulmonary Disease		
Yes	896 (32.5%)	5628 (16.9%)

No	1839 (66.7%)	25637 (76.9%)
Missing	23 (0.8%)	2054 (6.2%)
Renal Disease		
Yes	349 (12.7%)	1108 (3.3%)
No	2386 (86.5%)	30157 (90.5%)
Missing	23 (0.8%)	2054 (6.2%)
Hypertension		
Yes	1310 (47.5%)	6321 (19.0%)
No	1425 (51.7%)	24944 (74.9%)
Missing	23 (0.8%)	2054 (6.2%)
Obesity		
Yes	814 (29.5%)	5089 (15.3%)
No	1921 (69.7%)	26176 (78.6%)
Missing	23 (0.8%)	2054 (6.2%)
Vaccination Status		
Not known to be vaccinated	1678 (60.8%)	28250 (84.8%)
Partially vaccinated	154 (5.6%)	1630 (4.9%)
Fully vaccinated	926 (33.6%)	3439 (10.3%)
Pandemic Phase		
Pre-Alpha: Nov 2020 - Feb 2021	399 (14.5%)	16926 (50.8%)
Alpha: March 2021 - June 2021	628 (22.8%)	7995 (24.0%)
Delta: July 2021 - Sep 2021	1731 (62.8%)	8398 (25.2%)
Type of Monoclonal Antibody		
Bamlanivimab	425 (15.4%)	-
Bamlanivimab + etesevimab	95 (3.4%)	-
Casirivimab + imdevimab	2220 (80.5%)	-
Sotrovimab	18 (0.7%)	-

Abbreviations: mAb, monoclonal antibody; SD, standard deviation

Appendix Table 2. Standard Mean Differences for Propensity Matched Cohort

Characteristic	mAb-Treated Mean	mAb-Untreated Mean	Standardized Mean Difference
Distance	0.234	0.231	0.014
Age in years			
18-54 years	0.381	0.385	-0.009
55-64 years	0.213	0.246	-0.081
≥65 years	0.407	0.369	0.076
Sex			
Female	0.543	0.552	-0.018
Male	0.457	0.448	0.018
Race/Ethnicity			
Non-Hispanic White	0.099	0.107	-0.029
Hispanic	0.024	0.025	-0.008
Non-Hispanic Black	0.828	0.813	0.039
Other	0.049	0.054	-0.023
Body mass index, kg/m^2 *			
<18.5	0.009	0.009	-0.004
18.5-24.9	0.135	0.136	-0.003
25.0-29.9	0.213	0.216	-0.007
≥30.0	0.288	0.302	-0.032
Missing	0.355	0.336	0.040
Immunocompromised			
Immunocompromised	0.698	0.710	-0.028
Not immunocompromised	0.302	0.290	0.028
Number of Other Comorbid Conditions			
0	0.265	0.243	0.050
1	0.255	0.278	-0.053
≥2	0.481	0.480	0.002
Insurance			
Private/Commercial	0.061	0.071	-0.039
Medicare	0.393	0.361	0.066
Medicaid	0.016	0.015	0.010
None/Uninsured	0.022	0.025	-0.016
Other/Unknown	0.507	0.528	-0.044
Time between Cohort Inception (11/20/2020) and SARS-CoV-2 test			
Days	223.219	223.48	-0.003
$Days^2$	57946.6	57682.9	0.008

Abbreviations: mAb, monoclonal antibody; SAR-CoV-2, severe acute respiratory syndrome coronavirus-2

Appendix Table 3. Full Model Results for 28-Day Hospitalization Primary Outcome

Characteristic	Adjusted OR	95% CI
Treatment Status		
mAb-Untreated	Reference	
mAb-Treated	0.48	(0.38, 0.60)
Age in years		
18-54	Reference	
55-65	1.42	(1.12, 1.80)
≥65	1.37	(1.00, 1.89)
Sex		
Female	Reference	
Male	1.51	(1.27, 1.80)
Race/Ethnicity		
Non-Hispanic White	Reference	
Hispanic	1.30	(1.00, 1.67)
Non-Hispanic Black	0.72	(0.40, 1.21)
Other	1.57	(1.08, 2.25)
Insurance Status		
Private/Commercial	Reference	
Medicare	1.57	(1.17, 2.10)
Medicaid	1.22	(0.87, 1.69)
None/Uninsured	1.28	(0.51, 2.72)
Other/Unknown	1.17	(0.63, 2.03)
Body Mass Index in kg/m^2		
<18.5	Reference	
18.5-24.9	1.13	(0.50, 2.28)
25.0-29.9	0.89	(0.69, 1.15)
≥30.0	0.91	(0.71, 1.17)
Missing	0.03	(0.01, 0.06)
Immunocompromised Status		
No	Reference	
Yes	1.22	(1.01, 1.46)
Number of Other Comorbid Conditions		
0	Reference	
1	1.66	(1.17, 2.40)
≥2	3.78	(2.73, 5.34)
Pandemic Phase		
Pre-Alpha	Reference	
Alpha	1.39	(1.08, 1.79)
Delta	1.51	(1.18, 1.95)
Vaccination Status		
Fully vaccinated	Reference	
Not known to be vaccinated	3.65	(2.77, 4.87)

Abbreviations: mAb, monoclonal antibody; OR, odds ratio; CI, confidential interval

Appendix Table 4. Primary and Secondary Outcomes by Monoclonal Antibody Treatment Status for Missing Data Sensitivity Analysis.

Outcome	Adjusted OR	95% CI
All-Cause Hospitalization		
28-day (primary outcome)	0.47	(0.37, 0.58)
90-day	0.58	(0.48, 0.70)
All-Cause Mortality		
28-day	0.11	(0.04, 0.34)
90-day	0.16	(0.08, 0.36)
Any ED Visit to Day 28	1.21	(1.07, 1.36)
ED Visit leading to Hospitalization	0.29	(0.22, 0.39)

Appendix Table 5. Baseline Characteristics by Monoclonal Antibody Treatment Status for Sensitivity Analysis Cohort 1

Characteristic	Full Cohort		Matched Cohort	
	mAb-Treated (n=2497)	mAb-Untreated (n=14549)	mAb-Treated (n = 2445)	mAb-Untreated (n = 5943)
Age in years*				
18-54	870 (34.8%)	8172 (56.2%)	857 (35.1%)	2566 (43.2%)
55-64	507 (20.3%)	2802 (19.3%)	501 (20.5%)	1346 (22.6%)
≥65	1120 (44.9%)	3575 (24.6%)	1087 (44.5%)	2031 (34.2%)
Sex*				
Female	1367 (54.7%)	8195 (56.3%)	1343 (54.9%)	3266 (55.0%)
Male	1130 (45.3%)	6354 (43.7%)	1102 (45.1%)	2677 (45.0%)
Race/Ethnicity*				
Non-Hispanic White	2004 (80.3%)	9447 (64.9%)	1996 (81.6%)	4694 (79.0%)
Hispanic	258 (10.3%)	2867 (19.7%)	256 (10.5%)	742 (12.5%)
Non-Hispanic Black	63 (2.5%)	914 (6.3%)	63 (2.6%)	172 (2.9%)
Other	131 (5.2%)	1053 (7.2%)	130 (5.3%)	335 (5.6%)
Missing	41 (1.6%)	268 (1.8%)	-	-
Insurance Status*				
Medicaid	144 (5.8%)	1830 (12.6%)	1176 (48.1%)	3302 (55.6%)
Medicare	1073 (43.0%)	3408 (23.4%)	1047 (42.8%)	1982 (33.4%)
None/Uninsured	42 (1.7%)	484 (3.3%)	142 (5.8%)	430 (7.2%)
Other/Unknown	45 (1.8%)	532 (3.7%)	35 (1.4%)	93 (1.6%)
Private/Commercial	1193 (47.8%)	8295 (57.0%)	45 (1.8%)	136 (2.3%)
Body Mass Index, kg/m^2*				
<18.5	21 (0.8%)	93 (0.6%)	20 (0.8%)	48 (0.8%)
18.5-24.9	321 (12.9%)	1590 (10.9%)	318 (13.0%)	729 (12.3%)
25.0-29.9	569 (22.8%)	2855 (19.6%)	563 (23.0%)	1292 (21.7%)
≥30.0	772 (30.9%)	4799 (33.0%)	762 (31.2%)	1893 (31.9%)
Missing	814 (32.6%)	5212 (35.8%)	782 (32.0%)	1981 (33.3%)
Immunocompromised*				
Yes	819 (32.8%)	3281 (22.6%)	808 (33.0%)	1676 (28.2%)
No	1666 (66.7%)	10996 (75.6%)	1637 (67.0%)	4267 (71.8%)
Missing	12 (0.5%)	272 (1.9%)	-	-
Number of Other Comorbid Conditions*				
0	509 (20.4%)	3557 (24.4%)	492 (20.1%)	1358 (22.9%)
1	678 (27.2%)	4993 (34.3%)	670 (27.4%)	1801 (30.3%)
≥2	1297 (51.9%)	5718 (39.3%)	1283 (52.5%)	2784 (46.8%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Diabetes				
Yes	567 (22.7%)	2523 (17.3%)	561 (22.9%)	1126 (18.9%)
No	1917 (76.8%)	11745 (80.7%)	1884 (77.1%)	4817 (81.1%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Cardiovascular Disease				

Yes	562 (22.5%)	2264 (15.6%)	556 (22.7%)	1216 (20.5%)
No	1922 (77.0%)	12004 (82.5%)	1889 (77.3%)	4727 (79.5%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Pulmonary Disease				
Yes	887 (35.5%)	4148 (28.5%)	882 (36.1%)	1941 (32.7%)
No	1597 (64.0%)	10120 (69.6%)	1563 (63.9%)	4002 (67.3%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Renal Disease				
Yes	349 (14.0%)	1108 (7.6%)	343 (14.0%)	563 (9.5%)
No	2135 (85.5%)	13160 (90.5%)	2102 (86.0%)	5380 (90.5%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Hypertension				
Yes	1305 (52.3%)	5635 (38.7%)	1287 (52.6%)	2720 (45.8%)
No	1179 (47.2%)	8633 (59.3%)	1158 (47.4%)	3223 (54.2%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Obesity				
Yes	814 (32.6%)	5089 (35.0%)	808 (33.0%)	2015 (33.9%)
No	1670 (66.9%)	9179 (63.1%)	1637 (67.0%)	3928 (66.1%)
Missing	13 (0.5%)	281 (1.9%)	-	-
Vaccination Status				
Not known to be vaccinated	1494 (59.8%)	11524 (79.2%)	1461 (59.8%)	3926 (66.1%)
Partially vaccinated	144 (5.8%)	740 (5.1%)	140 (5.7%)	405 (6.8%)
Fully vaccinated	859 (34.4%)	2285 (15.7%)	844 (34.5%)	1612 (27.1%)
Pandemic Phase				
Pre-Alpha: Nov 2020 - Feb 2021	376 (15.1%)	5991 (41.2%)	369 (15.1%)	954 (16.1%)
Alpha: March 2021 - June 2021	570 (22.8%)	2764 (19.0%)	565 (23.1%)	1494 (25.1%)
Delta: July 2021 - Sep 2021	1551 (62.1%)	5794 (39.8%)	1511 (61.8%)	3495 (58.8%)
Type of Monoclonal Antibody				
Bamlanivimab	401 (16.1%)	-	394 (16.1%)	-
Bamlanivimab + etesevimab	91 (3.6%)	-	85 (3.5%)	-
Casirivimab + imdevimab	1987 (79.6%)	-	1948 (79.7%)	-
Sotrovimab	18 (0.7%)	-	18 (0.7%)	-

Abbreviations: mAb, monoclonal antibody; SD, standard deviation

Appendix Table 6. Primary and Secondary Outcomes by Monoclonal Antibody Treatment Status for Sensitivity Analysis Cohort 1

Outcome	mAb-Treated	mAb-Untreated	Adjusted OR	95% CI
Overall Sample Size	**n=2445**	**n=5943**		
All-Cause Hospitalization				
28-day	106 (4.3)	482 (8.1)	0.47	(0.38, 0.59)
90-day	136 (5.6)	544 (9.2)	0.54	(0.44, 0.66)
All-Cause Mortality				
28-day	3 (0.1)	57 (1)	0.12	(0.03, 0.32)
90-day	6 (0.2)	74 (1.2)	0.18	(0.07, 0.39)
All ED Visits				
28-day	482 (19.7)	1055 (17.8)	1.19	(1.05, 1.36)
Hospitalized sample size	**n=106**	**n=482**		
Hospital LOS in days, mean (SD)*	5.7 (6.5)	8.5 (10.1)	0.67	(0.53, 0.85)
IMV or Death	5 (4.7)	87 (18)	0.2	(0.07, 0.47)
ICU Admission	13 (12.3)	98 (20.3)	0.55	(0.27, 1.02)
ICU LOS in days, mean (SD)*	3.5 (2.8)	8.6 (9.9)	0.24	(0.11, 0.52)

* Poisson regressions presented as adjusted incidence rate ratios with 95% confidence intervals

All regressions adjusted for age, sex, race/ethnicity, BMI, immunocompromised status, number of other comorbidities, insurance status, pandemic phase, and vaccination status

Abbreviations: mAb, monoclonal antibody; OR, odds ratio; CI, confidence interval; LOS, length of stay; ICU, intensive care unit; SD, standard deviation

Appendix Table 7. Baseline Characteristics by Monoclonal Antibody Treatment Status for Sensitivity Analysis Cohort 2

	Full Cohort		Matched Cohort	
	mAb-Treated (n=2896)	mAb-Untreated (n=33319)	mAb-Treated (n=2797)	mAb-Untreated (n=6864)
Age in years*				
18-54	1107 (38.2%)	25075 (75.3%)	1068 (38.2%)	3194 (46.5%)
55-64	611 (21.1%)	4669 (14.0%)	592 (21.2%)	1647 (24.0%)
≥65	1178 (40.7%)	3575 (10.7%)	1137 (40.7%)	2023 (29.5%)
Sex*				
Female	1571 (54.2%)	17681 (53.1%)	1525 (54.5%)	3762 (54.8%)
Male	1325 (45.8%)	15636 (46.9%)	1272 (45.5%)	3102 (45.2%)
Missing	0 (0.0%)	2 (0.0%)	-	-
Race/Ethnicity*				
Non-Hispanic White	2341 (80.8%)	22311 (67.0%)	2322 (83.0%)	5481 (79.9%)
Hispanic	275 (9.5%)	5263 (15.8%)	272 (9.7%)	811 (11.8%)
Non-Hispanic Black	65 (2.2%)	1488 (4.5%)	65 (2.3%)	192 (2.8%)
Other	139 (4.8%)	2326 (7.0%)	138 (4.9%)	380 (5.5%)
Missing	76 (2.6%)	1931 (5.8%)	-	-
Insurance Status*				
Medicaid	173 (6.0%)	3601 (10.8%)	1421 (50.8%)	3997 (58.2%)
Medicare	1129 (39.0%)	3540 (10.6%)	1096 (39.2%)	1992 (29.0%)
None/Uninsured	64 (2.2%)	1728 (5.2%)	170 (6.1%)	537 (7.8%)
Other/Unknown	64 (2.2%)	2142 (6.4%)	46 (1.6%)	140 (2.0%)
Private/Commercial	1466 (50.6%)	22308 (67.0%)	64 (2.3%)	198 (2.9%)
Body Mass Index, kg/m^2 *				
<18.5	23 (0.8%)	204 (0.6%)	23 (0.8%)	58 (0.8%)
18.5-24.9	374 (12.9%)	3784 (11.4%)	371 (13.3%)	856 (12.5%)
25.0-29.9	600 (20.7%)	4666 (14.0%)	593 (21.2%)	1398 (20.4%)
≥30.0	808 (27.9%)	5668 (17.0%)	794 (28.4%)	2028 (29.5%)
Missing	1091 (37.7%)	18997 (57.0%)	1016 (36.3%)	2524 (36.8%)
Immunocompromised*				
Yes	847 (29.2%)	3281 (9.8%)	832 (29.7%)	1669 (24.3%)
No	2026 (70.0%)	27993 (84.0%)	1965 (70.3%)	5195 (75.7%)
Missing	23 (0.8%)	2045 (6.1%)	-	-
Number of Other Comorbid Conditions*				
0	807 (27.9%)	18488 (55.5%)	759 (27.1%)	1980 (28.8%)
1	733 (25.3%)	6887 (20.7%)	723 (25.8%)	1997 (29.1%)
≥2	1332 (46.0%)	5890 (17.7%)	1315 (47.0%)	2887 (42.1%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Diabetes				
Yes	588 (20.3%)	2523 (7.6%)	578 (20.7%)	1154 (16.8%)
No	2284 (78.9%)	28742 (86.3%)	2219 (79.3%)	5710 (83.2%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Cardiovascular Disease				

Yes	583 (20.1%)	2346 (7.0%)	574 (20.5%)	1286 (18.7%)
No	2289 (79.0%)	28919 (86.8%)	2223 (79.5%)	5578 (81.3%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Pulmonary Disease				
Yes	924 (31.9%)	5628 (16.9%)	915 (32.7%)	2137 (31.1%)
No	1948 (67.3%)	25637 (76.9%)	1882 (67.3%)	4727 (68.9%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Renal Disease				
Yes	356 (12.3%)	1108 (3.3%)	350 (12.5%)	604 (8.8%)
No	2516 (86.9%)	30157 (90.5%)	2447 (87.5%)	6260 (91.2%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Hypertension				
Yes	1357 (46.9%)	6321 (19.0%)	1336 (47.8%)	2904 (42.3%)
No	1515 (52.3%)	24944 (74.9%)	1461 (52.2%)	3960 (57.7%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Obesity				
Yes	837 (28.9%)	5089 (15.3%)	829 (29.6%)	2060 (30.0%)
No	2035 (70.3%)	26176 (78.6%)	1968 (70.4%)	4804 (70.0%)
Missing	24 (0.8%)	2054 (6.2%)	-	-
Vaccination Status				
Not known to be vaccinated	1777 (61.4%)	28250 (84.8%)	1707 (61.0%)	4477 (65.2%)
Partially vaccinated	147 (5.1%)	1630 (4.9%)	141 (5.0%)	460 (6.7%)
Fully vaccinated	972 (33.6%)	3439 (10.3%)	949 (33.9%)	1927 (28.1%)
Pandemic Phase				
Pre-Alpha: Nov 2020 - Feb 2021	402 (13.9%)	16926 (50.8%)	390 (13.9%)	997 (14.5%)
Alpha: March 2021 - June 2021	642 (22.2%)	7995 (24.0%)	630 (22.5%)	1733 (25.2%)
Delta: July 2021 - Sep 2021	1852 (64.0%)	8398 (25.2%)	1777 (63.5%)	4134 (60.2%)
Type of Monoclonal Antibody				
Bamlanivimab	425 (14.7%)	-	413 (14.8%)	-
Bamlanivimab + etesevimab	98 (3.4%)	-	90 (3.2%)	-
Casirivimab + imdevimab	2344 (80.9%)	-	2265 (81.0%)	-
Sotrovimab	29 (1.0%)	-	29 (1.0%)	-

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

Appendix Table 8. Primary and Secondary Outcomes by Monoclonal Antibody Treatment Status for Sensitivity Analysis Cohort 2

Outcome	mAb-Treated	mAb-Untreated	Adjusted OR	95% CI
Overall Sample Size	**n=2797**	**n=6864**		
All-Cause Hospitalization				
28-day	103 (3.7)	508 (7.4)	0.45	(0.36, 0.56)
90-day	138 (4.9)	578 (8.4)	0.53	(0.43, 0.64)
All-Cause Mortality				
28-day	2 (0.1)	61 (0.9)	0.07	(0.01, 0.24)
90-day	6 (0.2)	83 (1.2)	0.17	(0.07, 0.36)
All ED Visits				
28-day	527 (18.8)	1121 (16.3)	1.28	(1.13, 1.45)
Hospitalized sample size	**103**	**508**		
Hospital LOS in days, mean (SD)*	5.9 (6.6)	8.4 (10)	0.68	(0.54, 0.87)
IMV or Death	5 (4.9)	89 (17.5)	0.21	(0.07, 0.50)
ICU Admission	13 (12.6)	104 (20.5)	0.52	(0.26, 0.96)
ICU LOS in days, mean (SD)*	3.5 (2.8)	8.6 (9.8)	0.23	(0.11, 0.48)

* Poisson regressions presented as adjusted incidence rate ratios with 95% confidence intervals

All regressions adjusted for age, sex, race/ethnicity, BMI, immunocompromised status, number of other comorbidities, insurance status, pandemic phase, and vaccination status

Abbreviations: mAb, monoclonal antibody; OR, odds ratio; CI, confidence interval; LOS, length of stay; ICU, intensive care unit; SD, standard deviation

Appendix Table 9. Monoclonal Antibody Emergency Use Authorization Eligibility Criteria

Prior to June 1, 2021	After June 1, 2021
Body mass index of 35 kg/m^2 or more	Body mass index of 25 kg/m^2 or more
Chronic kidney disease	Chronic kidney disease
Diabetes	Diabetes
Immunosuppressive disease or currently receiving immunosuppressive treatment	Immunosuppressive disease or are currently receiving immunosuppressive treatment
65 years of age or older	65 years of age or older
55 years of age or older AND have either cardiovascular disease OR hypertension OR chronic obstructive pulmonary disease/other chronic respiratory disease	Chronic respiratory diseases, cardiovascular disease, or hypertension
	Pregnancy
	Sickle cell disease
	Neurodevelopmental disorders
	Medical related technology dependence
	Other medical conditions or factors (eg, race or ethnicity) that places individual patients at risk for progression to severe COVID-19

Supplementary References

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