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ORIGINAL RESEARCH

Infectious Disease

Effectiveness of subcutaneous monoclonal antibody treatment in emergency department outpatients with COVID-19

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Abstract

Objectives: To evaluate whether subcutaneous neutralizing monoclonal antibody (mAb) treatment given in the emergency department (ED) setting was associated with reduced hospitalizations, mortality, and severity of disease when compared to non-treatment among mAb-eligible patients with coronavirus disease 2019 (COVID-19).

Methods: This retrospective observational cohort study of ED patients utilized a propensity score-matched analysis to compare patients who received subcutaneous casirivimab and imdevimab mAb to nontreated COVID-19 control patients in November–December 2021. The primary outcome was all-cause hospitalization within 28 days, and secondary outcomes were 90-day hospitalization, 28- and 90-day mortality, and ED length of stay (LOS).

Results: Of 1340 patients included in the analysis, 490 received subcutaneous casirivimab and imdevimab, and 850 did not received them. There was no difference observed for 28-day hospitalization (8.4% vs. 10.6%; adjusted odds ratio [aOR] 0.79, 95% confidence intervals [CI] 0.53–1.17) or 90-day hospitalization (11.6% vs. 12.5%; aOR 0.93, 95% CI 0.65–1.31). However, mortality at both the 28-day and 90-day timepoints was substantially lower in the treated group (28-day 0.6% vs. 3.1%; aOR 0.18, 95% CI 0.08–0.41; 90-day 0.6% vs. 3.9%; aOR 0.14, 95% CI 0.06–0.36). Among hospitalized patients, treated patients had shorter hospital LOS (5.7 vs. 11.4 days; adjusted rate ratio [aRR] 0.47, 95% CI 0.33–0.69), shorter intensive care unit LOS (3.8 vs. 10.2 days; aRR 0.22, 95% CI 0.14–0.35), and the severity of hospitalization was lower (aOR 0.45, 95% CI 0.21–0.97) compared to untreated.

Conclusions: Among ED patients who presented for symptomatic COVID-19 during the Delta variant phase, ED subcutaneous casirivimab/imdevimab treatment was not associated with a decrease in hospitalizations. However, treatment was associated with lower mortality at 28 and 90 days, hospital LOS, and overall severity of illness.

1 | INTRODUCTION

1.1 | Background

Coronavirus disease 2019 (COVID-19) has resulted in 103.4 million acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and 1.1 million deaths in the United States since March 2020.[1] Although vaccination continues to be the most effective form of prevention, neutralizing monoclonal antibody (mAb) therapy became a prominent treatment option for much of the COVID-19 pandemic.[2–5]

Initially, mAbs were only available as an intravenous (IV) infusion, and medical centers around the country rapidly implemented infusion centers to keep up with demand.[6] Some emergency departments (EDs) implemented monoclonal antibody infusion sites within the ED to provide treatment for at-risk individuals.[7–9] However, IV infusions required a multiple-hour length of stay, and many EDs did not have the space or staff to care for an influx of additional patients.

In November 2020, an Emergency Use Authorization (EUA) was issued for casirivimab and imdevimab antibody combination therapy for the SARS-CoV-2 Delta variant as it was shown to reduce the risk of COVID-19 hospitalizations and death.[10–12] A single subcutaneous injection of casirivimab and imdevimab was also to reduce incidence of symptomatic COVID-19 among recently exposed patients compared to placebo.[13] Thus, subcutaneous casirivimab and imdevimab therapy provided another option for the prevention and treatment of outpatients with COVID-19.[10]

1.2 | Importance

Although studies have shown that subcutaneous casirivimab/imdevimab was safe and effective for outpatients with COVID-19 infections, additional research was needed to determine whether subcutaneous casirivimab and imdevimab has similar effectiveness in patients presenting to the ED with COVID-19. While casirivimab and imdevimab are not currently under EUA due to resistance to new variants, patients will continue to present to the ED for COVID-19 treatment and parental treatment options may re-emerge, along with current oral antiviral treatments. Therefore, it is essential to evaluate therapeutic effectiveness in this clinical setting. Lastly, EDs across the country continue to suffer from high volume and capacity constraints[14]; thus, it is crucial to evaluate the effect of providing mAb treatment on ED operations to determine the feasibility of such implementation in the future. While the specific therapeutic agents may change in the future, a study of this implementation has important implications for building platforms to rapidly deploy medical countermeasures in a future public health emergency.

1.3 | Goals of this investigation

This investigate aims to evaluate whether subcutaneous casirivimab and imdevimab treatment given in the ED setting was associated with reduced hospitalizations, mortality, and severity of disease when compared with nontreatment among mAb-eligible COVID-19 patients. Additionally, we will evaluate the impact on ED operations by comparing ED length of stay (LOS) for those who were treated compared to those without mAb treatment.

2 | METHODS

2.1 | Study design and setting

We conducted a retrospective observational cohort study with collaboration among the University of Colorado, UCHealth, and the Colorado Department of Public Health and Environment (CDPHE). This study was approved by the Colorado Multiple Institutional Review Board (COMIRB) with a waiver of informed consent. The study sites were the EDs in UCHealth's 12-hospital system in Colorado, the largest healthcare system in the state with over 149,000 inpatient admissions and observation visits.[15] Data were obtained from the electronic health record (EHR; Epic) of the UCHealth system and merged with additional statewide data, such as vaccination status obtained from the Colorado Immunization Information System (CIIS), and mortality data obtained from Colorado Vital Records. The Colorado Vital Records utilize the Office of the State Registrar of Vital Records to obtain data on events, such as death, in Colorado and those occurring in other states among Colorado residents.[4,16]

2.2 | Selection of participants

This study included adult patients (≥18 years) who were seen at one of the 12 UCHealth hospital-based EDs with either a positive SARS-CoV-2 test (polymerase chain reaction or antigen), subcutaneous mAb administration date in the EHR, or positive screening on EHR communicable disease screening questions. The communicable disease screening was completed for all ED patients and included three questions: whether the patient had a SARS-CoV-2 viral test in the last 14 days, whether they had a close contact test positive for SARS-CoV-2, or whether they had symptoms. All patients had at least 28 days of follow-up. Patients were considered eligible for subcutaneous mAb administration while in the emergency department in accordance with the criteria outlined in the EUA for treatment and postexposure prophylaxis.[12]

Patients were excluded from the study if they received IV mAb therapy (N = 222) (Figure 1). UCHealth EDs administered subcutaneous casirivimab and imdevimab injections between November 10, 2021, and January 4, 2022, and hence the study cohort included patients whose SARS-CoV-2 positive test dates were within this time period (excluded N = 1461). However, given the lack of in vitro antiviral activity of casirivimab/imdevimab against Omicron variants,[17] patients with a positive SARS-CoV-2 test after December 9, 2021 were excluded (N = 901) as this was when Omicron infections emerged and became dominant in Colorado.[18] We did not exclude patients based on EUA

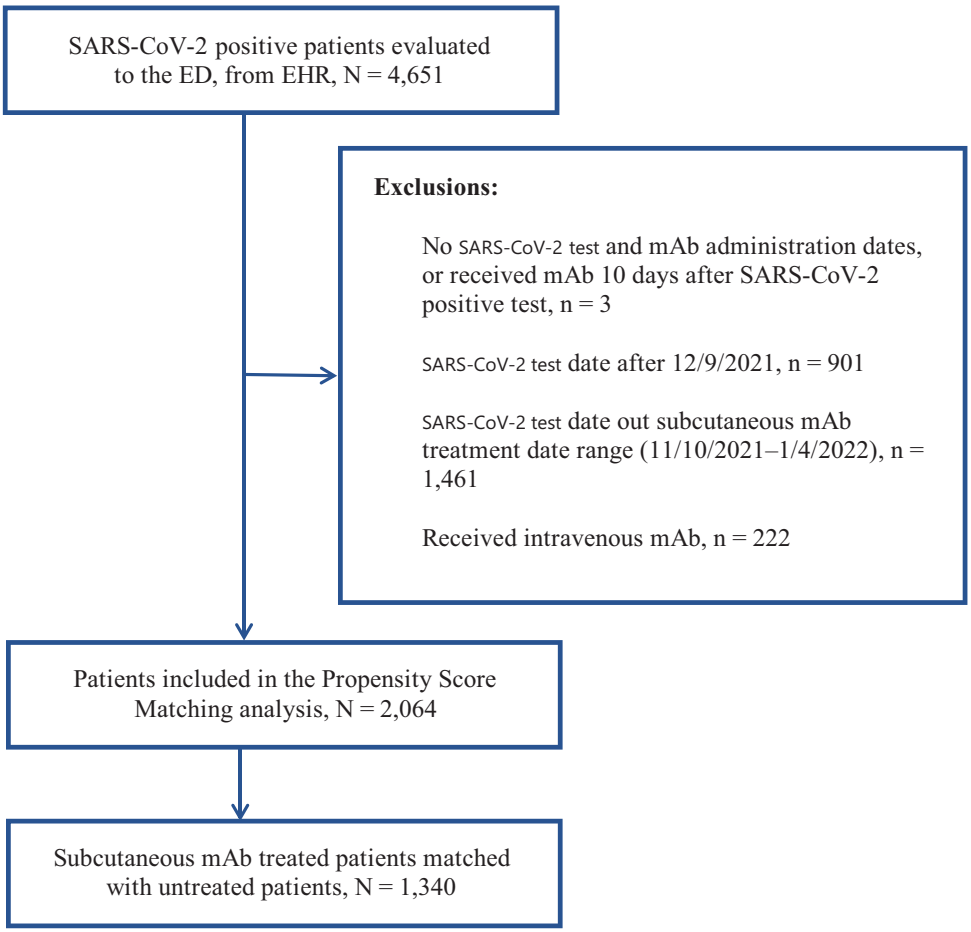

FIGURE 1 Flow diagram detailing inclusion of patients from the extraction of electronic health record (EHR) database to the analysis stage. ED, emergency department; mAb, monoclonal antibody.

eligibility due to the lack of consistently available comprehensive EHR data for all patients, although a sensitivity analysis is performed on those eligible according to the EHR based on the EUA. Finally, patients who had more than 10 days between their SARS-CoV-2 positive test and the mAb administration date were excluded in accordance with the FDA's EUA criteria (Figure 1). Additionally, we could not retrieve information from EHR regarding whether a patient was discharged home on supplemental oxygen, which was occurring at the height of the COVID-19 pandemic at UCHealth.

For patients with a missing SARS-CoV-2 test date, the positive test date was imputed based on the distribution of the differences between ED arrival dates and observed SARS-CoV-2 test dates (Supporting Information Appendix).[3,4,19]

2.3 | Interventions

The UCHealth EDs administered subcutaneous casirivimab/imdevimab for high-risk patients as treatment and postexposure prophylaxis. Patients being discharged who had COVID-19 symptoms or high-risk exposure were offered subcutaneous casirivimab and imdevimab based on EUA eligibility criteria,[12] based upon prompts to clinicians from EHR-embedded clinical decision support tools. If subcutaneous casirivimab and imdevimab was administered, the patient would receive the injection and be observed for 1 hour prior to discharge.

2.4 | Measurements

The patient-level characteristics included treatment status, age, sex, race/ethnicity, obesity status, immunosuppressed status, number of other comorbid conditions, insurance status, and COVID-19 vaccination status. Comorbid conditions (cardiovascular disease, hypertension, pulmonary disease, renal disease, and diabetes) and immunosuppressed status were determined by a 90-day lookback in the EHR database using the Charlson and Elixhauser comorbidity indices, as we have previously described.[3] Manual chart reviews were carried out to further validate the immunosuppressed status. The number of comorbidities were categorized into "none," "one," and "two or more" comorbid conditions by summing all conditions excluding immunocompromised status and obesity. Immunosuppressed status

was categorized as "not immunocompromised," "mild," or "moderate/severe" based on chronic medications or specific conditions. Additional details are available in a previously published work.[3,4,19]

2.5 | Outcomes

The primary outcome was all-cause hospitalization within 28 days of a positive SARS-CoV-2 test. Secondary outcomes were 90-day all-cause hospitalization, 28- and 90-day all-cause mortality, and ED LOS. Among the 28-day hospitalized patients, we also assessed hospital LOS, severity of hospitalization based on the maximum level of respiratory support, whether the patient was admitted to the intensive care unit (ICU), and ICU LOS.

Primary and secondary outcomes were assessed to minimize the influence of immortal time bias during outcome analyses. For instance, for mAb-treated patients, the 28-day all-cause hospitalization period commenced from the mAb treatment date, while for untreated patients, it began from the date of their initial SARS-CoV-2 positive test.

2.6 | Analysis

We implemented propensity score matching (PSM) to reduce confounding due to unbalanced covariates in investigating the treatment effect on the outcomes. Propensity scores were calculated using multivariable logistic regression to estimate the probability of receiving subcutaneous mAb therapy. The covariates included in the propensity score model were age, sex, body mass index, race/ethnicity, number of comorbid conditions, immunocompromised status, insurance status, and COVID-19 vaccination status. No interaction terms between the covariates were included in the model. The estimates of propensity score were then used to match subcutaneous mAb-treated patients to untreated patients in a maximum 1:2 ratio, without replacement, using a greedy nearest neighbor matching method with calipers width of 0.2.[20,21] We used the standardized mean differences (SMDs) to assess whether the balance of covariates between the two treatment groups was attained based on a threshold of 0.1.[22,23]

To evaluate the effect of subcutaneous mAb treatment, multivariable logistic regression models were fitted for binary outcomes, such as all-cause hospitalizations, all-cause mortalities, and ED visits to estimate the odds of the outcome, whereas multivariable negative binomial regression models were used for count outcomes including length of stay to estimate rate ratios between treated and untreated. When outcomes were rare events (i.e., the outcome under consideration had a small incident probability), for example, in the case of all-cause mortality outcomes, Firth's bias-reduced multivariable logistic regression model was fitted.[24] Multivariable ordered logistic regression was used to model the proportional odds of severity of hospitalization, which was an ordinal outcome. While treatment status was the main predictor, all regression models were adjusted for all covariates of interest, which were included in the PSM analysis. These variables were adjusted in the outcome model because they are both confounders of treatment and have a direct association with the outcomes regardless of treatment status. Further, using Kaplan–Meier estimates, cumulative incidence curves were plotted to summarize the cumulative rates of hospitalization and mortality over 28-day time by treatment status.

Considering the limitations of the PSM approach, we implemented inverse probability of treatment weighting (IPTW) with trimming threshold as an alternative to the PSM analysis.[25,26] Additionally, a methodological sensitivity analysis without matching was conducted to examine the primary and secondary outcomes within the entire cohort. We then compared the results obtained by these two analyses.

The restrictions we implemented, specifically the calipers for PSM and trimming thresholds for IPTW analyses, led to a few treated patients being discarded in both approaches. As a result, we focused our analysis on the matched population.[27,28] Further, the estimations of the marginal effects were computed using g-methods, enabling us to interpret the results of the outcomes analyses as effect measures rather than odds ratios.[29–33]

Two additional sensitivity analyses were carried out. First, a cohort of patients who met the EUA-qualifying condition, confirmed from the EHR database, were analyzed using the same approach as described above. Second, a more conservative imputation method was implemented for missing SARS-CoV-2 positive test dates, which assumed that all missing SARS-CoV-2 positive test dates were 10 days prior to the mAb administration date (the maximum days of symptom onset). On each of these sensitivity analysis cohorts, similar propensity score matching as the primary analysis was used to target a maximum 1:2 ratio of treated to untreated cohort of patients. All outcome models fitted, and cumulative curves plotted in the primary analysis were repeated for these two cohorts, and the results were compared with those from the primary analysis.

All statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing).[21,34–37]

3 | RESULTS

3.1 | Characteristics of study subjects

Between November 10 and December 9, 2021, 2064 patients presented to the UCHealth EDs who met the study inclusion criteria (Figure 1). The full cohort prior to propensity score matching can be found in Supporting Information Appendix, Table A1. We matched 490 patients who received subcutaneous casirivimab and imdevimab injections with 850 patients who did not receive any kind of mAb therapy. We reported the baseline characteristics and SMDs of treated and untreated patients in the matched cohort in Table 1. About 15% of mAb treated patients in the original cohort did not have matches from the untreated group and were excluded from the PSM analysis. Baseline characteristics for the three patient groups (untreated/matched, treated/matched, and treated/unmatched) are presented in Supporting Information Appendices, Table A2.

TABLE 1 Baseline characteristics of coronavirus disease 2019 (COVID-19) patients by subcutaneous monoclonal antibodies treatment group in the matched cohort.

Characteristic	Untreated frequency (%)	Treated frequency (%)	SMD[a]
	N = 850	N = 490	
Sex: female	466 (54.8)	273 (55.7)	0.018
Age (years)			0.071
18–44	345 (40.6)	184 (37.6)	
45–64	316 (37.2)	185 (37.8)	
≥65	189 (22.2)	121 (24.7)	
Race ethnicity			0.028
Non-Hispanic White	579 (68.1)	336 (68.6)	
Non-Hispanic Black	65 (7.6)	36 (7.3)	
Hispanic	180 (21.2)	105 (21.4)	
Other	26 (3.1)	13 (2.7)	
Obesity	226 (26.6)	128 (26.1)	0.011
Diabetes	144 (16.9)	80 (16.3)	0.017
Cardiovascular	143 (16.8)	84 (17.1)	0.009
Pulmonary	240 (28.2)	130 (26.5)	0.038
Renal	74 (8.7)	47 (9.6)	0.031
Hypertension	301 (35.4)	194 (39.6)	0.086
Comorbidity[b]			0.039
None	364 (42.8)	213 (43.5)	
One	217 (25.5)	117 (23.9)	
Two or more	269 (31.6)	160 (32.7)	
Immunocompromised			0.050
None	735 (86.5)	416 (84.9)	
Mild	62 (7.3)	42 (8.6)	
Moderate/severe	53 (6.2)	32 (6.5)	
Insurance			0.045
Private/commercial/medicare	567 (66.7)	335 (68.4)	
Medicaid	214 (25.2)	114 (23.3)	
None/unknown/uninsured	69 (8.1)	41 (8.4)	
COVID vaccine: ≥1 vaccination	219 (25.8)	147 (30.0)	0.095
ED LOS, min (mean (SD))	193.9 (166.5)	206.5 (191.1)	0.070

Abbreviations: SMD, standardized mean difference; ED LOS, length of stay in the emergency department; SD, standard deviations.
[a]SMD ≤ 0.1 implies that adequate balance of the covariate has been achieved between the two treatment groups.
[b]The number of comorbidities excluding immunocompromised status and obesity.

For the variables included in the PSM analysis, the SMDs were not greater than 10%, confirming the required balance was attained between the mAb treated and untreated groups of patients. The match cohort was 55% female, 68% non-Hispanic white, and 30% had two or more comorbid conditions. Fewer than 15% of patients had either mild or moderate to severe immunocompromised status and interestingly, only about one-quarter of the patients had received at least one COVID-19 vaccination. Treated patients received their subcutaneous mAb a mean of 1.4 days (SD 2.2) days since SARS-CoV-2 positive test date.

3.2 | Main results

The odds of all-cause hospitalizations were similar among the subcutaneous mAb-treated group compared to the matched untreated group: 28-day hospitalization (8.6% vs. 10.6%; adjusted odds ratio [aOR] 0.79, 95% confidence interval [CI] 0.53–1.17) and 90-day hospitalization (11.6% vs. 12.5%; aOR 0.93, 95% CI 0.65–1.31) (Table 2). This pattern was confirmed in a basic time-to-event analysis (Kaplan–Meier estimates) where the overlap between the cumulative incidence curves for the treated and untreated groups was inconsequential (Figure 2A).

TABLE 2 Primary and secondary outcomes results from unadjusted and adjusted models.

	Frequency (%)			
Outcome	**Untreated**	**Treated**	**Unadjusted**	**Adjusted**
Overall sample size	***n* = 850**	***n* = 490**	**OR (95% CI)**	**OR (95% CI)**
Hospitalization				
28 days	90 (10.6)	42 (8.6)	0.79 (0.54, 1.16)	0.79 (0.53, 1.17)
90 days	106 (12.5)	57 (11.6)	0.92 (0.66, 1.30)	0.93 (0.65, 1.31)
All-cause mortality				
28 days	26 (3.1)	3 (0.6)	0.19 (0.06, 0.65)	0.18 (0.08, 0.41)
90 days	33 (3.9)	3 (0.6)	0.15 (0.05, 0.50)	0.14 (0.06, 0.36)
ED LOS in hours, mean (SD)[a]	3.23 (2.8)	3.44 (3.2)	1.06 (0.96, 1.18)	1.06 (0.96, 1.17)
Hospitalized sample size	***n* = 90**	***n* = 42**		
Hospital LOS in days, mean (SD)[a]	11.42 (13.5)	5.74 (5.8)	0.49 (0.32, 0.73)	0.47 (0.33, 0.69)
IMV or death	24 (26.7)	6 (14.3)	0.46 (0.17, 1.27)	0.44 (0.17, 1.19)
ICU admission	18 (20.0)	6 (14.3)	0.67 (0.24, 1.86)	0.65 (0.25, 1.67)
ICU LOS in days, mean (SD)[a]	10.22 (12.4)	3.83 (3.8)	0.29 (0.08, 1.05)	0.22 (0.14, 0.35)

Abbreviations: CI, confidence interval; ED LOS, length of stay in the emergency department; IMV, intermittent mandatory ventilation; ICU, intensive care unit.

[a]Negative binomial regression models were fitted.

In contrast, all-cause mortality in the subcutaneous mAb-treated group was substantially lower compared to the untreated group for 28-day mortality (0.6% vs. 3.1%; aOR 0.19, 95% CI 0.08–0.41) and for 90-day all-cause mortality (0.6% vs. 3.9%; aOR 0.14, 95% CI 0.06–0.36). This finding was also confirmed using Kaplan–Meier estimates (Figure 2B).

The mean ED LOS for patients in the subcutaneous mAb-treated group and the untreated group were, respectively, 3.4 (SD 3.2) h and 3.2 (SD 2.8) h (adjusted rate ratio [aRR] 1.06, 95% CI 0.96–1.17).

In hospitalized patients, we found that subcutaneous mAb-treated patients had a shorter hospital LOS (mean 5.7 [SD 5.8] days vs. 11.4 [SD 13.5] days; aRR 0.47, 95% CI 0.33–0.69) and shorter LOS in the ICU compared to untreated patients (mean 3.8 [SD 3.8] days vs. 10.2 [SD 12.4] days; aRR 0.22, 95% CI 0.14–0.35). Point estimates for ICU admission and mechanical ventilation or death favored subcutaneous mAb treatment, though power/sample size was limited, and we could not exclude a null association (Table 2). Furthermore, the overall severity of hospitalization was lower across the illness levels for subcutaneous mAb-treated patients, as shown in Figure 3 (aOR 0.45, 95% CI 0.21–0.97).

The full cohort primary and secondary outcomes can be found in Supporting Information Appendix, Table A3. The IPTW approach we employed as a methodological sensitivity analysis yielded results closely comparable to those of the primary analyses (Supporting Information Appendix, Tables A4 and A5). Furthermore, two sensitivity analyses as described were carried out to assess the robustness of the primary analyses. Neither of these analyses markedly changed the results obtained in the primary analyses (Supporting Information Appendix, Tables A6, A7, and A8; Figures A1 and A2).

4 | LIMITATIONS

There were several limitations to this study. Although this study included multiple EDs in variable settings, including academic, community, rural, and urban, all patients included in this study were from a single health system in the state of Colorado. Data for mortality and vaccination status were collected using a statewide database, but hospitalizations were only available within the UCHealth system. Not all patients who received subcutaneous mAb in the ED had an observed positive SARS-CoV-2 test. Patients who met the EUA criteria for treatment and screened positive on the EHR communicable disease screening questions were offered treatment. Additionally, we could not retrieve information from EHR regarding whether a patient was discharged home on supplemental oxygen, which was occurring at the height of the COVID-19 pandemic at UCHealth. This could have impacted the patient cohort as these patients, with likely a high disease severity, were ineligible for mAb treatment. Further, only patients infected during the predominantly Delta variant phase of the pandemic, prior to the emergence of Omicron, were included. This was due to the known loss of antiviral activity to the Omicron variant.[38]

There were notable methodologic limitations. First, about 15% of mAb-treated patients who met the study's eligibility were excluded from the outcome analysis as they did not have a match in the propensity score matching analysis. Additionally, for the analysis of missing SAR-CoV-2 test dates, we utilized a practical single imputation method rather than a multiple imputation in our primary and sensitivity analyses. Lastly, although the matching methods utilized (PSM and IPTW) considerably reduced baseline differences between the mAb-treated and untreated populations, we were unable to account for all

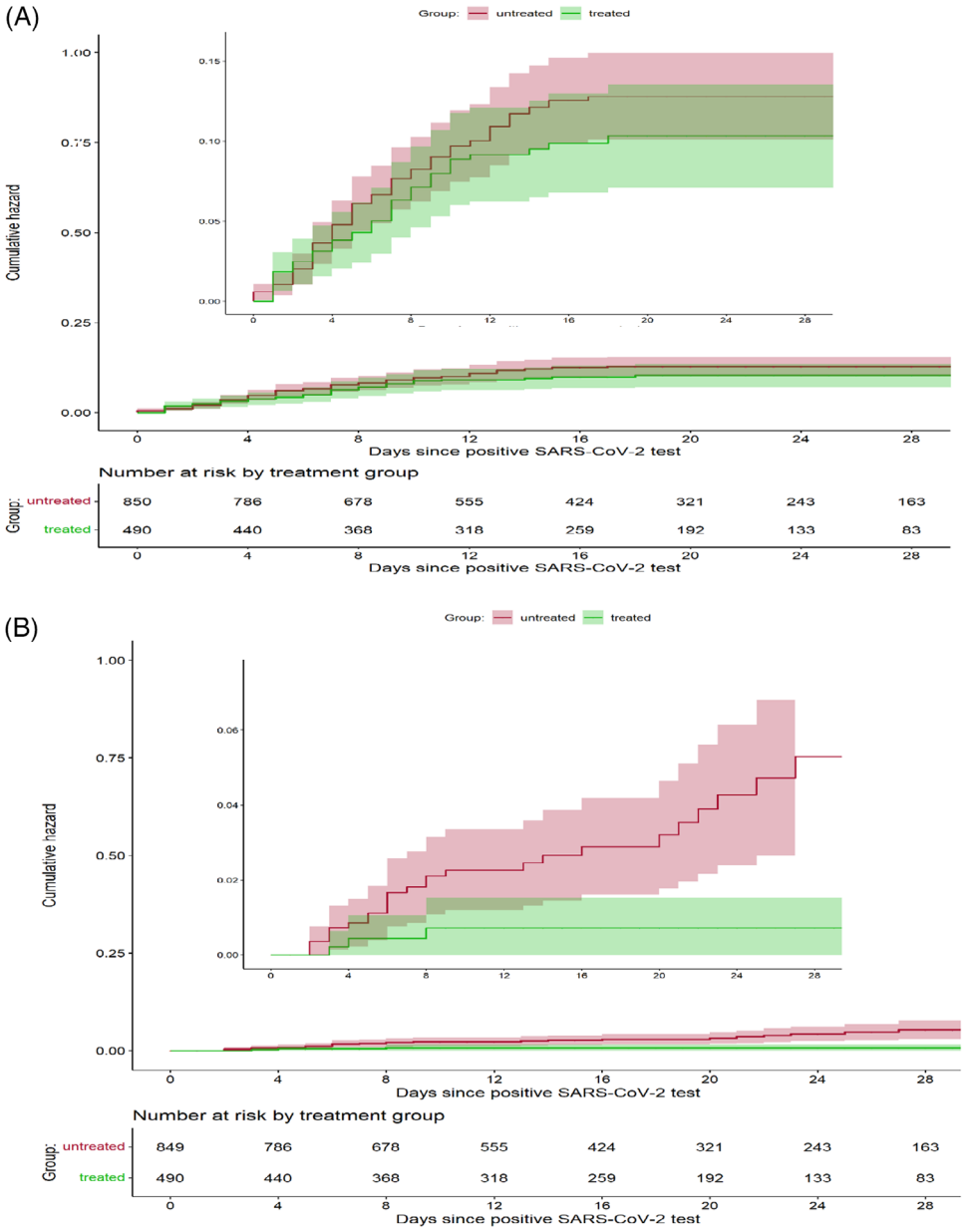

FIGURE 2 (A) Cumulative incidence plots for all-cause hospitalization to day 28 by subcutaneous monoclonal antibodies treatment group. (B) Cumulative incidence plots for all-cause mortality to day 28 by subcutaneous monoclonal antibodies treatment group.

unmeasured confounders. Therefore, it is possible that conclusions between treatment and outcomes were due to unmeasured variables.

5 | DISCUSSION

Among patients who presented to the ED for mild-moderate COVID-19, there was no association between subcutaneous casirivimab and imdevimab treatment and 28- or 90-day all-cause hospitalizations. However, treatment was associated with markedly lower all-cause mortality at 28 and 90 days. We also found that among patients who required hospitalization, subcutaneous mAb treatment was associated with a shorter hospital and ICU LOS, and the overall severity of hospitalization was lower. This study demonstrates that although there was no observed benefit in all-cause hospitalizations among mAb-treated ED patients, there appear to be benefits in critical outcomes.

Prior mAb studies have found that treatment with mAb is associated with decreased hospitalizations and death among outpatients with COVID-19 in the community.[10,11] Furthermore, a recent study has shown that individuals with early asymptomatic SARS-CoV-2 infection experienced a decrease in SARS-CoV-2 viral load and a lower likelihood of COVID-19 hospitalization or emergency department visits when treated with subcutaneous casirivimab and imdevimab.[39] Our findings align with these findings, suggesting that the reduction in viral load among patients who received subcutaneous casirivimab and imdevimab may contribute to a decrease in the severity of illness.

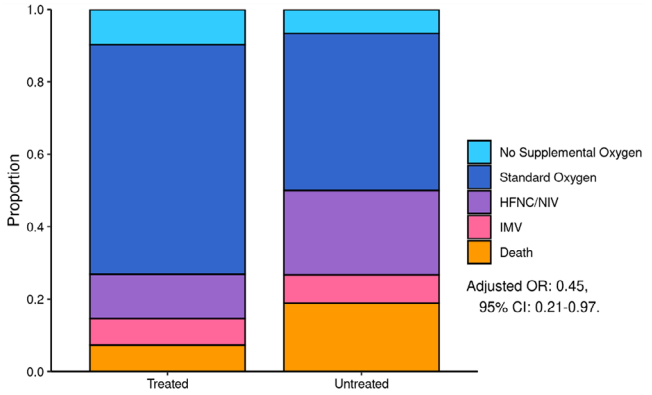

FIGURE 3 Maximum respiratory support by subcutaneous monoclonal antibodies treatment group among patients hospitalized within 28 days. CI, confidence interval; OR, odds ratio.

Few studies have directly examined treatment in the ED population while in the ED care setting. The differences between our findings and those of previous studies might be explained by the fact that patients who present to the ED are seeking medical care and possible hospitalization and this may be different than other outpatients. Indeed, the overall rate of hospitalization and mortality is substantially higher than those seen in prior studies in our health system during the Delta variant phase.[3,4] Therefore, an ED visit for COVID-19 symptoms could be a marker of increased disease severity.

The consideration of adding additional treatments in the ED setting can have unintended operational impacts. EDs across the country have worsening capacity constraints from rising arrivals and increased inpatient boarding.[14] Our study found that the ED LOS for treated patients was similar to untreated patients across multiple EDs in our health system. This finding indicates that offering subcutaneous mAb treatment in the ED is unlikely to negatively impact ED operations, which was the main reason for offering subcutaneous versus intravenous treatment.

Although subcutaneous casirivimab and imdevimab are no longer available for COVID-19 treatment, these data support the potential effectiveness and feasibility of implementing parenteral antiviral treatment for COVID-19 and other pandemic infectious diseases in the future for high-risk patients in the ED setting.

AUTHOR CONTRIBUTIONS

Sarah K. Wendel and Adane F. Wogu contributed equally to this study. Sarah K. Wendel, Adane F. Wogu, and Adit A. Ginde conceived and designed the study. Adit A. Ginde obtained research funding. Adane F. Wogu, Nichole E. Carlson, Laurel Beaty, and David A. Mayer supervised the conduct of data collection, managed the data, including quality control and analysis, and wrote sections of the analysis and revised the manuscript. Tellen D. Bennett, David A. Mayer, and Seth Russell performed the data collection. Sarah K. Wendel, Kelly Bookman, Sean M. Michael, and Richard D. Zane undertook clinical/operational design. Sarah K. Wendel, Adane F. Wogu, Nichole E. Carlson, Laurel Beaty, and Adit A. Ginde drafted the manuscript, and all authors contributed substantially to its revision. Sarah K. Wendel and Adane F. Wogu take responsibility for the paper as a whole.

CONFLICT OF INTEREST STATEMENT

All authors attest to meeting the four ICMJE.org authorship criteria.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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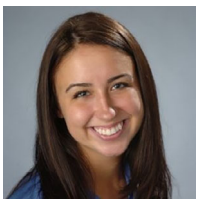

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