Effectiveness of Casirivimab-Imdevimab Monoclonal Antibody Treatment Among High-Risk Patients With Severe Acute Respiratory Syndrome Coronavirus 2 B.1.617.2 (Delta Variant) Infection

Mohanad M. Al-Obaidi,[1] Ahmet B. Gungor,[2] Saman Nematollahi,[1] Tirdad T. Zangeneh,[1] Edward J. Bedrick,[3] Katherine M. Johnson,[4] Nicole E. Low-Adegbija,[5] Ruhaniyah Alam,[4] Pooja Rangan,[6] C. William Heise,[7] Venkatesh K. Ariyamuthu,[8] Aneesha Shetty,[8] Abd Assalam Qannus,[8] Sangeetha Murugapandian,[8] Mehmet M. S. Ayvaci,[9] Prince Mohan Anand,[10] and Bekir Tanriover[8]

[1]Division of Infectious Disease, College of Medicine, University of Arizona, Tucson, Arizona, USA, [2]Division of Nephrology, Banner University Medical Center, Tucson, Arizona, USA, [3]Department of Epidemiology and Biostatistics, College of Public Health, University of Arizona, Tucson, Arizona, USA, [4]Division of Clinical Pharmacy, Banner University Medical Center, Tucson, Arizona, USA, [5]Department of Surgery, Banner University Medical Center, Tucson, Arizona, USA, [6]Department of Medicine, Banner University Medical Center Phoenix, Phoenix, Arizona, USA, [7]Division of Clinical Data Analytics and Decision Support, Department of Medicine, College of Medicine–Phoenix, University of Arizona, Phoenix, Arizona, USA, [8]Division of Nephrology, College of Medicine, University of Arizona, Tucson, Arizona, USA, [9]Information Systems, Naveen Jindal School of Management, University of Texas at Dallas, Dallas, Texas, USA, and [10]Medical University of South Carolina, Lancaster, South Carolina, USA

Background. Real-world data on the effectiveness of neutralizing casirivimab-imdevimab monoclonal antibody (Cas-Imd mAb) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among high-risk patients may inform the response to future SARS-CoV-2 variants.

Methods. This study covers an observational retrospective data analysis in Banner Health Care System sites, mainly in Arizona. During the study period, the prevalence of SARS-CoV-2 Delta variant was between 95% and 100%. Of 29 635 patients who tested positive for coronavirus disease 2019 (COVID-19) between 1 August 2021 and 30 October 2021, in the Banner Health Care System, the study cohort was split into 4213 adult patients who received Cas-Imd mAb (1200 mg) treatment compared to a PS-matched 4213 untreated patients. The primary outcomes were the incidence of all-cause hospitalization, intensive care unit (ICU) admission, and mortality within 30 days of Cas-Imd mAb administration or Delta variant infection.

Results. Compared to the PS-matched untreated cohort, the Cas-Imd mAb cohort had significantly lower all-cause hospitalization (4.2% vs 17.6%; difference in percentages, −13.4 [95% confidence interval {CI}, −14.7 to −12.0]; $P < .001$), ICU admission (0.3% vs 2.8%; difference, −2.4 [95% CI, −3.0 to −1.9]; $P < .001$), and mortality (0.2% vs 2.0%; difference, −1.8 [95% CI, −2.3 to −1.3]; $P < .001$) within 30 days. The Cas-Imd mAb treatment was associated with lower rate of hospitalization (hazard ratio [HR], 0.22 [95% CI, .19–.26]; $P < .001$) and mortality (HR, 0.11 [95% CI, .06–.21]; $P < .001$).

Conclusions. Cas-Imd mAb treatment was associated with a lower hospitalization rate, ICU admission, and mortality within 30 days among patients infected with the SARS-CoV-2 Delta variant.

Keywords. all-cause hospitalization; casirivimab-imdevimab monoclonal antibody; Delta variant; mortality; propensity matching; SARS-CoV-2.

The coronavirus disease 2019 (COVID-19) pandemic has caused a significant number of deaths in the United States (US) and globally [1]. With ongoing infections worldwide, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations are occurring, and new variants continue to emerge. The SARS-CoV-2 variants of concern, notably the B.1.617.2 (Delta) and most recently B.1.1.529 (Omicron) variants, have reduced antibody neutralization [2].

The COVID-19 vaccines have been instrumental in preventing hospitalizations and deaths [3]. However, there is a risk of breakthrough infections secondary to waning immunity [4–6]

and reduced response to vaccination, especially among immunosuppressed patients [7]. Therefore, in addition to the vaccine, therapeutic options are essential in the fight against the COVID-19 pandemic. Researchers have been developing therapies for COVID-19 in the outpatient setting. While oral agents have been studied to treat COVID-19, including fluvoxamine [8] and, recently authorized by the US Food and Drug Administration (FDA) under Emergency Use Authorization (EUA), nirmatrelvir-ritonavir [9] and molnupiravir [10], these drugs were not approved during the period of Delta variant spread. During this time, the only available therapeutics for the outpatient management of COVID-19 were neutralizing monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein. The mAbs used to treat mild to moderate COVID-19 and/or to prevent severe disease include casirivimab-imdevimab (Cas-Imd mAb), bamlanivimab-etesevimab, and sotrovimab [11–15]. Data from clinical trials indicate a significant reduction in hospitalization rates of up to 70% with bamlanivimab, 67% with casirivimab-imdevimab, 87% with bamlanivimab-etesevimab, and 85% with sotrovimab in high-risk patients [16–20]. In addition, mAb showed a role in treating COVID-19 breakthrough infections in vaccinated individuals [21]. Also, pre–Delta variant SARS-CoV-2 real-world data showed promise for Cas-Imd mAb in reducing hospitalizations [22]. Recently, it was shown that Cas-Imd mAb decreased the rate of hospitalization among patients with COVID-19 during the early period of the Delta variant [21]. In vitro data showed that Cas-Imd mAb is possibly effective against the Delta variant [23], which presents Cas-Imd mAb as a viable option in treating the Delta variant. The Cas-Imd treatment was initially dosed at 2400 mg under the authorized FDA EUA; it was later changed to 1200 mg in June 2021 [24, 25]. In this study, we aimed to determine the effectiveness of Cas-Imd mAb (1200 mg) in reducing all-cause hospitalization, intensive care unit (ICU) admission, and all-cause mortality within 30 days of administration of Cas-Imd mAb or COVID-19 infection diagnosis.

METHODS

Patient Consent Statement
This study was approved by the Institutional Review Board of the University of Arizona with a waiver of patient consent given the retrospective nature of the study. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Overview
This study is an observational retrospective electronic health record (Cerner EHR) analysis in the Banner Health Care System (a nonprofit, large healthcare organization) which has 30 hospitals and several associated clinics across the western United States. The Banner Health Care System Monoclonal

Antibody Treatment program was established in December 2020 (see Supplementary Document A). A multidisciplinary team reviews patients for eligibility for monoclonal antibody treatment, guided by the FDA EUA.

Among 29 635 patients who tested positive for COVID-19 (positive polymerase chain reaction (PCR) or direct antigen test) between 1 August 2021, and 30 October 2021, the study cohort was split into the treatment cohort who received Cas-Imd mAb (1200 mg) and the untreated control cohort (Figure 1). During the study period, there were 22 infusion sites (for the treatment cohort) and 128 testing sites (untreated control cohort) in the Banner Health Care System. The study index date for cohorts was determined as the date of Cas-Imd mAb administration or the date of the first positive COVID-19 test. Index dates were used as an enrollment date for the study. Patients who were <18 years old, were already hospitalized, had a pulse oximetry (SpO$_2$) reading <92% [26], were on hospice care. or had "do not resuscitate" status were excluded from the cohorts. Asymptomatic high-risk patients who received Cas-Imd mAb for postexposure prophylaxis were also excluded. Clinical and demographic covariates were extracted from the Cerner EHR for the remaining patients. The clinical covariates were derived from the Charlson Comorbidity Index [27] and extracted for each patient based on *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes documented in the 5 years preceding the patient index date. Then, one-to-one propensity score (PS) matching with no replacement was used to match both cohorts (Figure 2). Postmatch cohort size was determined as 4213 pairs. For additional analysis, the matched cohort was rematched based on the COVID-19 mRNA vaccination subgroups.

The PS-matched cohort spanned the Banner Health Care System sites in multiple states, with 82.1% from Arizona, 9.4% from Colorado, 4.1% from Wyoming, 2.5% from Nevada, 1.5% from California, and 0.5% from Nebraska. During the study period, the prevalence of the Delta variant among SARS-CoV-2–infected patients was between 95% and 100% in states where the Banner Health Care System sites exist (Supplementary Figure 1*A–F*). In addition, if vaccination status of a patient residing in Arizona was missing, the vaccination status was imported from the Arizona State Immunization Information System, an online verification resource.

Outcomes
The primary outcomes were the proportion of all-cause hospitalization, ICU admission, and all-cause mortality that was observed within our electronic medical record system, within 30 days of the index date. The secondary outcomes included hospitalization length of stay (LOS) and cumulative ICU LOS, oxygen therapy, and acute kidney injury (AKI) stages during the first hospitalization. AKI is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification
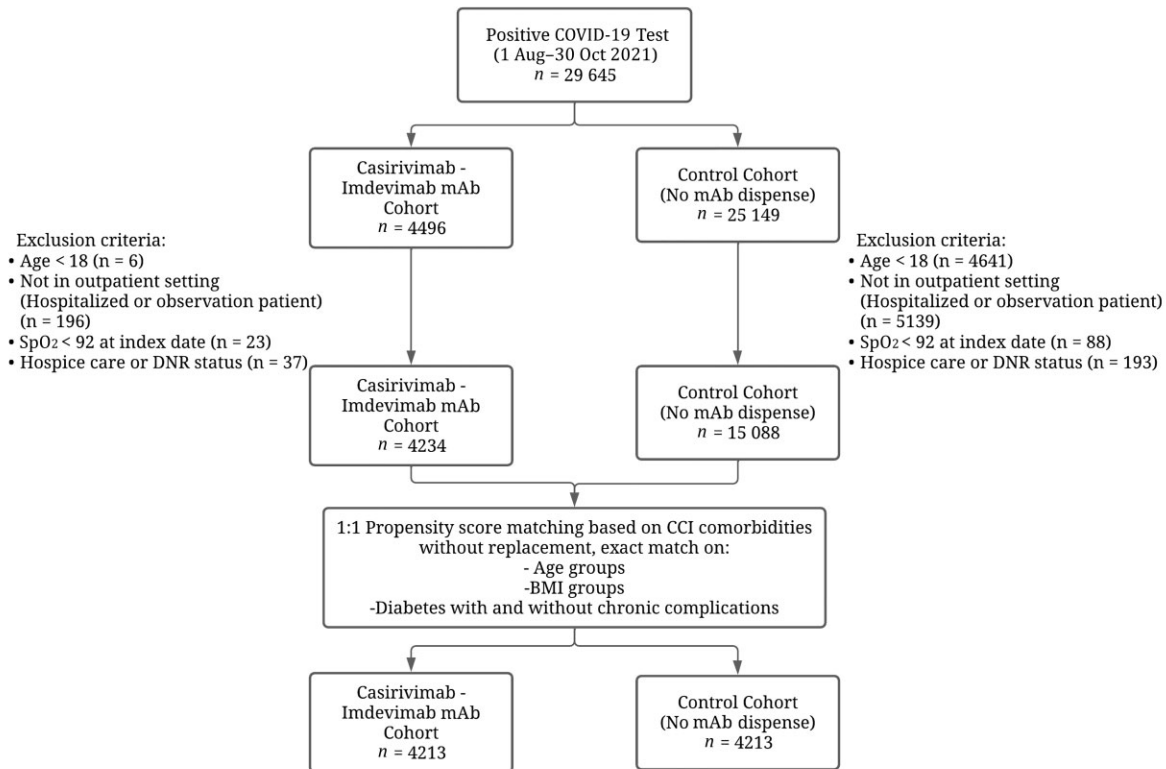
Figure 1. Flowchart for study cohort selection. Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; DNR, do not resuscitate; mAb, monoclonal antibody; SpO_2, oxygen saturation.

[28]. The data were right censored on 30 November 2021. In this analysis, death was not used as competing risk to all-cause hospitalization or ICU admission due to small numbers.

Multivariable Propensity Score Matching

One-to-one PS matching with no replacement was performed using an optimal matching algorithm [29] that minimizes the sum of the absolute pairwise distance across the matched sample. The optimal matching algorithm was compared with nearest neighbors and complete matching algorithms and was determined the best per the covariate balance and the number of unmatched individuals. Pairs were matched exactly on age group, body mass index (BMI) group, and diabetes status (with or without complications). These variables along with the remaining demographics, clinical covariates, and time periods (composed of 2-week periods between the study start and end date) were included as predictors in a logistic regression model to estimate the PS. Distance function was determined considering its performance in minimizing the unmatched sample while keeping covariate standardized mean differences (SMDs) to a minimum. Covariate balance was assessed by looking at the SMD and empirical cumulative distribution function statistics for each covariate and by a covariate balance plot (Figure 2) that displays the SMDs before and after matching.

The MatchIt package [30] from the statistical computing software R was utilized for building and assessing the PS-matching model.

Statistical Analysis

All statistical analyses were conducted on the paired (matched) dataset. For each primary outcome, the event count and percentage of the event was reported. Ninety-five percent Clopper-Pearson confidence intervals (CIs) for percentages were computed in the R package Exactci. Exact McNemar test was used to compare the difference in percentages between the treatment and control cohorts. Differences in percentages between cohorts and related 95% CIs were reported along with the McNemar test P value. Calculations were performed using the R package exact2x2. In addition, Kaplan-Meier survival analysis was performed to evaluate the difference in time to all-cause hospitalization and mortality rates (using Stata version 17 software, StataCorp, College Station, Texas).

For secondary continuous outcomes, hospital LOS and ICU LOS, mean and standard deviation (SD) of the outcome were reported. Individuals who were not hospitalized were considered as they had zero LOS in both outcomes. A 2-part generalized linear mixed model with random effect for matched pairs was fitted to compare LOS across cohorts among patients who
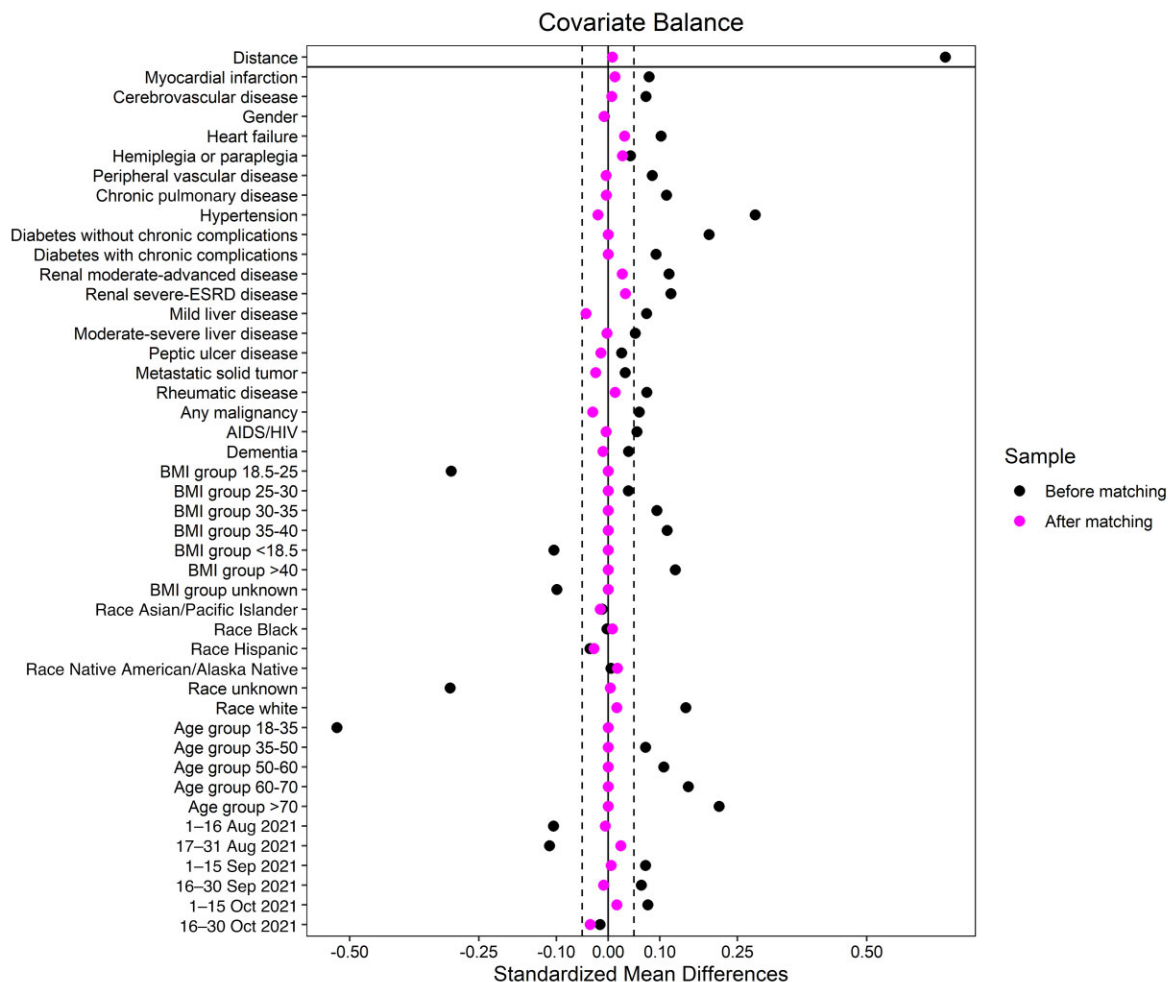
Figure 2. Covariate balance plot for before and after propensity score matching. Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

have LOS >0, by evaluating the model's fixed effects for Cas-Imd mAb use. The estimated coefficient, 95% CI of the coefficient, and the statistical significance of the fixed antibody effect were reported. The R package GLMMadaptive was used to fit the mixed model.

For our categorical secondary outcomes, intensity of oxygen therapy and AKI stages during hospitalization, counts, and percentages were reported. The subcategories for both variables were grouped into 2 clinically meaningful categories due to the small sample size. Wald test of no differences was conducted to compare the distributions for treatment and control cohort cases, given a hospitalized patient.

An additional analysis was conducted to assess how the primary outcomes differ based on COVID-19 messenger RNA (mRNA) vaccination status. An individual was considered fully vaccinated if 14 days had passed after their final dose of the vaccine before the index date. First, the Stuart-Maxwell test for marginal homogeneity was used to compare vaccination status between the treatment and control cohorts. Then, the postmatch treatment and control cohorts were combined and then split into vaccinated and unvaccinated cohorts, excluding the individuals with missing vaccination status. The optimal matching method was used to rematch both vaccinated and unvaccinated cohorts separately for the PS calculation, using the same model in the previous analysis [31]. Following the optimal rematching, 949 pairs (n = 1898) were matched in the vaccinated cohort, and 2732 (n = 5464) were matched in the unvaccinated cohort. Primary outcome counts and percentages with Clopper-Pearson CIs were reported. Finally, the hazard ratio (HR) for the effect of Cas-Imd mAb treatment on time to primary outcomes was calculated using a Cox proportional hazards model adjusted for COVID-19 mRNA vaccination status.

Missing Data

Data were missing in 22 (2.4% of hospitalized) patients for intensity of oxygen therapy, 26 (2.8% hospitalized) patients for

serum creatinine and AKI categories, and 461 (5.5% of the study cohort) patients for vaccination status. Observations with missing data on secondary outcomes were considered free of the outcome for their respective statistical tests.

RESULTS

Patient Characteristics

Table 1 shows the characteristics of the Cas-Imd mAb and untreated control cohorts before and after PS matching. All post-PS-matching covariate SMDs were below a 0.05 threshold, indicating an optimal matching (Figure 2). In the post-PS-matched cohort, the median age of patients in the Cas-Imd mAb treatment arm was 50 (interquartile range [IQR], 34–64) years; 55.9% were female, and 67.8% were White race. Some of the high-risk characteristics were age $\geq$65 years (30.6%), BMI $\geq$35 kg/m^2 (35.3%), diabetes mellitus (17.6%), chronic lung disease (18.2%), kidney disease–any stage (8.5%), and human immunodeficiency virus (HIV)/AIDS (5.6%). The median time from COVID-19 PCR positivity to infusion was 1 day (IQR, 0–2 days) in the Cas-Imd mAb treatment cohort, shown in Supplementary Figure 2. In a subgroup analysis based on number of days from COVID-19 PCR positivity to Cas-Imd mAb infusion, we categorized time to mAb infusion variable as <2 vs $\geq$2 days and as <3 vs $\geq$3 days and calculated the proportion of patients who are hospitalized and died in the mAb-treated cohort (Supplementary Table 1). The results show no significant difference regarding the hospitalization and mortality in both categories.

Primary and Secondary Outcomes

Table 2 and Supplementary Table 2 show the results of the primary and/or secondary outcomes within 30 days in the post-PS-matched cohorts. Compared to the untreated control cohort, the percentage of patients with all-cause hospitalizations in the Cas-Imd mAb cohort was 4.2% (95% CI, 3.6%–4.8%) vs 17.6% (95% CI, 16.4%–18.7%) (P < .001); the percentage of patients with ICU admission in the Cas-Imd mAb cohort was 0.3% (95% CI, 0.25%–0.5%) vs 2.8% (95% CI, 2.3%–3.3%; P < .001); and the proportion of patients with all-cause mortality was 0.2% (95% CI, .1%–.4%) vs 2.0% (95% CI, 1.6%–2.4%; P < .001). Death rarely occurred (8 of 4213 patients in the Cas-Imd cohort and 83 of 4213 patients in the untreated control cohort) and mostly happened in the ICU (75 of 91). Sixteen patients died without hospitalization to the Banner Healthcare Centers (assumed to have died either at home or other healthcare facilities). Kaplan-Meier survival analysis showed significant differences in time to all-cause hospitalization and mortality between the Cas-Imd mAb treatment and PS-matched untreated cohort (Supplementary Figures 3 and 4). Supplementary Figures 5A, 5B, 6A, and 6B illustrate the substratification of Kaplan-Meier survival analysis according to

baseline SpO$_2$ (substratifying the cohort SpO$_2$ 92%–95% and $\geq$96%), demonstrating comparable results. In terms of the secondary outcomes, compared to the untreated control cohort, the mean for hospital LOS was 5.3 (SD, 5.3) days in the Cas-Imd mAb cohort vs 6.9 (SD, 7.9) days (P = .06), and the mean for ICU LOS was 3.6 (SD, 4.8) days in the Cas-Imd mAb cohort vs 3.8 (SD, 5.3) days (P = .85). The generalized linear mixed model that estimates the mean ratio of cohorts showed that upper 95% CIs of both hospital LOS and ICU LOS outcomes include 1. The percentage of the highest-intensity oxygen requirements (including mechanical ventilation/continuous positive airway pressure–bilevel positive airway pressure/high-flow oxygen) were lower in the Cas-Imd mAb cohort (25.8% vs 42.5%; P < .001) compared with the untreated control cohort. The percentage of the KDIGO AKI stage 2–3 in the Cas-Imd mAb cohort (1.4%) was lower than in the untreated cohort (6.1%; P < .001).

Subgroup Analysis Stratified Based on COVID-19 Vaccination Status

Table 3 shows the primary outcomes for the PS-rematched Cas-Imd mAb–treated and untreated cohorts, stratified by vaccination status. The study cohort received COVID-19 mRNA vaccines from Pfizer-BioNTech (67.9%) and Moderna (32.1%). The prevalence of COVID-19 mRNA vaccination was lower among study participants (28.3% in the Cas-Imd mAb cohort vs 23.8% in the control untreated cohort; P < .001) as compared to the state and national reported vaccination rates. In terms of the primary outcomes, the lowest all-cause hospitalization (1.7%)/ICU admission (0.0%)/mortality (0.0%) rates were observed in the vaccinated Cas-Imd mAb treatment cohort while the highest all-cause hospitalization (23.3%)/ICU admission (3.7%)/mortality (2.3%) rates were encountered in the unvaccinated untreated cohort. The primary outcomes were similar between the Cas-Imd mAb–treated unvaccinated cohort and the untreated vaccinated cohort. In multivariable Cox proportional hazards models, Cas-Imd mAb treatment and COVID-19 mRNA vaccination were independently associated with lower rate of all-cause hospitalization (HR, 0.22 [95% CI, .19–.26]; P < .001 vs HR, 0.23 [95% CI, .18–.30]; P < .001) and mortality (HR, 0.11 [95% CI, .06–.21]; P < .001 vs HR, 0.37 [95% CI, .20–.70]; P = .02), respectively.

DISCUSSION

This study is one of the largest real-world studies reporting the use of Cas-Imd mAb in reducing mortality and hospitalization among high-risk populations during the pandemic period when infections were caused predominantly by the SARS-CoV-2 Delta variant [32]. Our study includes a diverse population of adults (approximately 20% Hispanic, 5% Black, and 1.5% American Indian). The untreated cohort was also more predisposed to higher oxygen requirement and

Table 1. Clinical Covariate Balance Before and After Propensity Score Matching

Clinical Covariates	After PS Matching			Before PS Matching		
	Cas-Imd mAb Treatment Cohort	Untreated Control Cohort	SMD	Cas-Imd mAb Treatment Cohort	Untreated Control Cohort	SMD
No.	4213	4213		4234	15 088	
Age, y, median (IQR)	50.0 (38.0–64.0)	50.0 (38.0–63.0)		50.0 (38.0–64.0)	40.0 (29.0–55.0)	
Age group, y						
18–35	822 (19.5)	822 (19.5)	0.00	827 (19.5)	6085 (40.3)	−0.52
36–50	1330 (31.6)	1330 (31.6)	0.00	1343 (31.7)	4278 (28.4)	0.07
51–60	769 (18.3)	769 (18.3)	0.00	771 (18.2)	2121 (14.1)	0.11
61–70	655 (15.5)	655 (15.5)	0.00	655 (15.5)	1489 (9.9)	0.15
>70	637 (15.1)	637 (15.1)	0.00	638 (15.1)	1115 (7.4)	0.21
Sex, male	1860 (44.1)	1877 (44.6)	−0.01	1872 (44.2)	6729 (44.6)	−0.01
Race/Ethnicity						
White	2855 (67.8)	2822 (67.0)	0.02	2869 (67.8)	9165 (60.7)	0.15
Black	233 (5.5)	225 (5.3)	0.01	234 (5.5)	842 (5.6)	0.00
Hispanic	885 (21.0)	932 (22.1)	−0.03	891 (21.0)	3392 (22.5)	−0.04
Asian/Pacific Islander	37 (0.9)	43 (1.0)	−0.02	37 (0.9)	148 (1.0)	−0.01
Native American/Alaska Native	62 (1.5)	53 (1.3)	0.02	62 (1.5)	211 (1.4)	0.01
Unknown	141 (3.3)	138 (3.3)	0.00	141 (3.3)	1330 (8.8)	−0.31
BMI, group, kg/m^2						
<18.5	31 (0.7)	31 (0.7)	0.00	33 (0.8)	257 (1.7)	−0.11
18.5–25	569 (13.5)	569 (13.5)	0.00	572 (13.5)	3605 (23.9)	−0.30
26–30	1210 (28.7)	1210 (28.7)	0.00	1214 (28.7)	4061 (26.9)	0.04
31–35	1036 (24.6)	1036 (24.6)	0.00	1045 (24.7)	3111 (20.6)	0.09
36–40	600 (14.2)	600 (14.2)	0.00	600 (14.2)	1538 (10.2)	0.11
>40	466 (11.1)	466 (11.1)	0.00	467 (11.0)	1050 (7.0)	0.13
Unknown	301 (7.1)	301 (7.1)	0.00	303 (7.2)	1466 (9.7)	−0.1
Myocardial infarction	118 (2.8)	109 (2.6)	0.00	118 (2.8)	224 (1.5)	0.08
Heart failure	154 (3.7)	129 (3.1)	0.03	155 (3.7)	263 (1.7)	0.10
Cerebrovascular disease	126 (3.0)	121 (2.9)	0.01	127 (3.0)	264 (1.7)	0.07
Hemiplegia or paraplegia	31 (0.7)	21 (0.5)	0.03	31 (0.7)	55 (0.4)	0.04
Peripheral vascular disease	134 (3.2)	137 (3.3)	0.00	136 (3.2)	258 (1.7)	0.09
Chronic pulmonary disease	767 (18.2)	773 (18.3)	0.00	774 (18.3)	2101 (13.9)	0.11
Hypertension	1234 (29.3)	1272 (30.2)	−0.02	1247 (29.5)	2487 (16.5)	0.28
Diabetes without chronic complications	590 (14.0)	590 (14.0)	0.00	604 (14.3)	1122 (7.4)	0.20
Diabetes with chronic complications	150 (3.6)	150 (3.6)	0.00	168 (4.0)	326 (2.2)	0.09
Renal disease, mild-moderate-advanced (CKD stage 1–4)	189 (4.5)	165 (3.9)	0.03	195 (4.6)	323 (2.1)	0.12
Renal disease, severe (CKD stage 5 and ESRD)	168 (4.0)	140 (3.3)	0.03	174 (4.1)	257 (1.7)	0.12
Mild liver disease	226 (5.4)	267 (6.3)	−0.04	229 (5.4)	562 (3.7)	0.07
Moderate to severe liver disease	44 (1.0)	45 (1.1)	0.00	45 (1.1)	79 (0.5)	0.05
Peptic ulcer disease	44 (1.0)	50 (1.2)	−0.01	44 (1.0)	117 (0.8)	0.03
Rheumatic disease	110 (2.6)	101 (2.4)	0.01	111 (2.6)	215 (1.4)	0.07
Malignancy including skin cancers and lymphoproliferative disorders	109 (2.6)	129 (3.1)	−0.03	109 (2.6)	245 (1.6)	0.06
Metastatic solid tumor	26 (0.6)	34 (0.8)	−0.02	26 (0.6)	54 (0.4)	0.03
HIV/AIDS	235 (5.6)	239 (5.7)	0.00	238 (5.6)	654 (4.3)	0.06
Dementia	39 (0.9)	43 (1.0)	−0.01	39 (0.9)	82 (0.5)	0.04
Time period						
1–16 Aug 2021	538 (12.8)	546 (13.0)	−0.01	540 (12.8)	2457 (16.3)	−0.11
17–31 Aug 2021	682 (16.2)	644 (15.3)	0.02	685 (16.2)	3071 (20.4)	−0.11
1–15 Sep 2021	848 (20.1)	838 (19.9)	0.01	850 (20.1)	2591 (17.2)	0.07
16–30 Sep 2021	757 (18.0)	771 (18.3)	−0.01	761 (18.0)	2341 (15.5)	−0.06
1–15 Oct 2021	730 (17.3)	703 (16.7)	0.02	735 (17.4)	2180 (14.4)	0.08
16–30 Oct 2021	658 (15.6)	711 (16.9)	−0.03	663 (15.7)	2448 (16.2)	−0.02

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; PS, propensity score; SMD, standardized mean difference.

Table 2. Primary and Secondary Outcomes in the Post–Propensity Score–Matched Cohorts

Outcome	Cas-Imd mAb Treatment Cohort (n = 4213)		Untreated Control Cohort (n = 4213)		Difference, % (95% CI)[b]	P Value
	No. (%)	(95% CI)[a]	No. (%)	(95% CI)[a]		
Primary outcomes in post-PS-matched cohorts						
All-cause hospitalization within 30 d	176 (4.2)	(3.6–4.8)	740 (17.6)	(16.4–18.7)	−13.4 (−14.7 to −12.0)	<.001
ICU admission within 30 d	13 (0.3)	(.2–5)	116 (2.8)	(2.3–3.3)	−2.4 (−3.0 to −1.9)	<.001
Mortality in 30 d	8 (0.2)	(.1–4)	83 (2.0)	(1.6–2.4)	−1.8 (−2.3 to −1.3)	<.001

Outcome	Cas-Imd mAb Treatment Cohort (n = 176)	Untreated Control Cohort (n = 740)	Ratio of Means for Cohorts[c]	95% CI for Mean Ratio of Cohorts[c]	P Value
Secondary outcomes in post-PS-matched cohorts					
Hospital LOS, d, mean (SD)	5.3 (5.3)	6.9 (7.9)	0.86	(.74–1.01)	.06
ICU LOS, d, mean (SD)	3.6 (4.8)	3.8 (5.3)	0.95	(.54–1.67)	.85

Outcome	Cas-Imd mAb Treatment Cohort (n = 176)	Untreated Control Cohort (n = 740)	Difference Between Cohorts (Proportions)	95% CI for Difference (Proportions)	Wald Test of No Differences (P Value)
Highest intensity oxygen requirement					
MV, CPAP-BiPAP, high-flow oxygen	42 (25.8)	311 (42.5)	16.8 (3.9)	(9.1–24.4)	18.6 (<.001)
Nasal cannula–room air	121 (74.2)	420 (57.5)	−16.8 (3.9)	(−24.4 to −9.2)	
AKI in the hospitalization					
No AKI, KDIGO stage 1	138 (98.6)	601 (93.9)	−4.7 (1.4)	(−7.4 to −2.0)	11.5 (<.001)
KDIGO stage 2/3	2 (1.4)	39 (6.1)	4.7 (1.4)	(2.0–7.4)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AKI, acute kidney injury; BiPAP, bilevel positive airway pressure; Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CI, confidence interval; CPAP, continuous positive airway pressure; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; LOS, length of stay; MV, mechanical ventilation; PS, propensity score; SD, standard deviation.

[a]The Clopper-Pearson method was used to calculate 95% CIs for the outcome percentages using the R package (Exactci).

[b]Exact McNemar test was used to compare the percentage difference between the treatment and control cohorts.

[c]Comparison between 2 continuous variables in paired data was calculated using R package GLMMadaptive for a fixed treatment effect from a 2-part mixed model.

Table 3. Distribution of Coronavirus Disease 2019 Vaccination Status Among Post–Propensity Score (PS)–Matched Cohort, the Primary Outcomes Stratified by Vaccination Status Among Post-PS-Matched Cohort, Multivariable Cox Proportional Hazard Models for All-Cause Hospitalization, and Mortality Adjusted for Vaccination Status Among Post-PS-Matched Cohort

Distribution of COVID-19 mRNA Vaccination Status Among Post-PS-Matched Cohort					
	Cas-Imd mAb Treatment Cohort (n = 4213)	Untreated Control Cohort (n = 4213)	χ^2 Test[a]	P Value	
Fully vaccinated against COVID-19					
Yes	1192 (28.3)	1003 (23.8)	217.52	<.001	
No	2943 (69.9)	2827 (67.1)			
Missing	78 (1.9)	383 (9.1)			
Primary Outcomes Among COVID-19 mRNA Vaccinated Subgroup After PS Matching					
	Cas-Imd mAb (n = 949)		Control Cohort (n = 949)		
	No. (%)	(95% CI)	No. (%)	(95% CI)[b]	Difference, % (95% CI)[c]	P Value
All-cause hospitalization within 30 d	16 (1.7)	(1.0–2.7)	60 (6.3)	(4.9–8.1)	−4.6 (−6.5 to −2.8)	<.001
ICU admission within 30 d	0 (0.0)	(0–.4)	9 (0.9)	(.4–1.8)	−0.9 (−1.8 to −.2)	.004
Mortality in 30 d	0 (0.0)	(0–.4)	8 (0.8)	(.4–1.7)	−0.8 (−1.7 to −.2)	.01
Primary Outcomes Among COVID 19 Unvaccinated Subgroup of Patients After PS Matching					
	Cas-Imd mAb (n = 2732)		Control Cohort (n = 2732)		
	No. (%)	(95% CI)	No. (%)	(95% CI)[b]	Difference, % (95% CI)[c]	P Value
All-cause hospitalization within 30 d	150 (5.5)	(4.7–6.4)	637 (23.3)	(21.7–24.9)	−18.3 (−20.1 to −16.4)	<.001
ICU admission within 30 d	12 (0.4)	(.2–.8)	101 (3.7)	(3.0–4.5)	−3.3 (−4.1 to −2.6)	<.001
Mortality in 30 d	8 (0.3)	(.1–.6)	62 (2.3)	(1.7–2.9)	−2.6 (−3.2 to −1.9)	<.001
Multivariable Cox Proportional Hazards Model for All-Cause Hospitalization Within 30 d of Index Date in the Post-PS-Matched Cohort					
	HR	(95% CI)	P Value		
Cas-Imd mAb (Yes)	0.22	(.19–.26)	<.001		
Fully vaccinated against COVID-19					
Yes	0.23	(.18–.30)	<.001		
Missing	0.16	(.10–.26)	<.001		
Multivariable Cox Proportional Hazards Model for Mortality Within 30 d of Index Date in the Post-PS-Matched Cohort					
	HR	(95% CI)	P Value		
Cas-Imd mAb (Yes)	0.11	(.06–.21)	<.001		
Fully vaccinated against COVID-19					
Yes	0.37	(.20–.70)	.002		
Missing	0.50	(.20–1.23)	.13		

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; mRNA, messenger RNA; PS, propensity score.

[a]Stuart-Maxwell Test for marginal homogeneity χ^2 test.

[b]The Clopper-Pearson method was used to calculate 95% CIs for the outcome percentages using the R package (Exactci).

[c]The exact McNemar test was used to compare the percentage difference between the treatment and control cohorts.

mechanical ventilation and developed higher AKI stages than the Cas-Imd mAb group.

Cas-Imd efficacy against SARS-CoV-2 was shown previously in a clinical trial with COVID-19 patients who received Cas-Imd mAb having lower SARS-CoV-2 viral loads and hospitalization [14]. Another recent study from the Mayo Clinic showed that administration of Cas-Imd mAb was associated with a lower risk of hospitalization in high-risk populations [22]; however, that study included a smaller number of patients (N = 1392) during the period predating the Delta variant spread compared to our investigation. In addition, we demonstrate that the rates of 30-day ICU admission and all-cause mortality are significantly lower in the Cas-Imd mAb–treated group compared to previous studies.

In our subgroup analysis based on vaccination status, we found that Cas-Imd mAb retained its efficacy in lowering the rates of hospitalizations, ICU admissions, and all-cause mortality and endured its effect even when the individual was fully vaccinated, but the effect size was smaller compared to the unvaccinated cohort. Our study shows that approximately 25% of the PS-matched population, mainly from Arizona, were fully vaccinated, which is a number lower than that reported by the Arizona Department of Health Services (AZDHS) [33]. Such a difference in the number of vaccinated populations could be either secondary to the underlying characteristics of the population that visited our hospital system or secondary to lacking data of reported vaccinations. Moreover, our cohort had a higher percentage of hospitalizations and deaths than the

same period reported by AZDHS [33]. This could be related to the high-risk population included in the study as we matched our controls with the Cas-Imd mAb cohort on our institutional mAb eligibility criteria, or to a lesser extent because of the included population from the states of Montana and Colorado [19, 34]. Similar to previous reports [35], our study shows that fully vaccinated adults (not boosted) had significantly reduced hospitalization, ICU admission, and death compared to the unvaccinated cohort.

For the study's secondary outcomes, patients receiving Cas-Imd mAb had significantly reduced oxygen requirements and AKI, including the need for renal replacement therapy. The findings of our study corroborate with other randomized placebo-controlled trials which reported that the use of other mAb products reduced the risk of hospitalization and death in high-risk patients with mild to moderate COVID-19 infections [13].

This study has significant implications for treating COVID-19 and preventing its complications, as we show that delivering monoclonal antibodies directed toward a SARS-CoV-2 Delta variant can significantly lower hospitalization rates, ICU stay, and all-cause mortality. The Omicron variant has spread very quickly since December 2021; hence, there exists a pandemic with mainly the Omicron variant coinciding with declining incidence of Delta variant infections among newly infected patients [36]. It is crucial to know predominantly which variants are causing most infections in order to administer appropriate mAbs for patients infected with SARS-CoV-2 (ie, Cas-Imd mAb for the Delta variant and sotrovimab for the Omicron variant). This study highlights the role of mAbs in reducing COVID-19–associated complications; a similar approach can be used to assess the effectiveness of other mAbs or for other SARS-CoV-2 variants. Furthermore, our results show that irrespective of COVID-19 vaccination status, receiving mAbs led to significantly reduced hospitalization rates, ICU stays, and all-cause mortality, which is essential in treating breakthrough infections. Such findings have implications for unvaccinated individuals and immunocompromised individuals who will have attenuated immune responses to vaccines and may benefit from passive immunity for the treatment of COVID-19.

Our study has several strengths, including a large sample size from an extensive hospital network system that evaluated >8400 patients (the largest reported real-world experience) with analysis capturing the Delta variant period exclusively. This includes patients in both rural and urban settings with excellent representation of minority groups. Moreover, the study matched patients according to different risk factors that minimized bias by utilizing optimal PS matching. We also imported the vaccination data from the Arizona State Immunization Information System.

The limitations of our study include the retrospective design, which may be associated with reporting and selection biases, and the lack of information regarding possible hospitalizations and deaths that occurred outside of Banner Health. Lack of information about previous infections and possible missing immunization information limits further interpretation of the benefits of mAb based on previous immune status. In addition, a diverse subgroup of patients with hematopoietic stem-cell or solid organ transplants were not included as a separate category in the propensity analysis due to small sample size; such patients are known to have poorer outcomes and more likely to be referred to mAb treatment. Last, missing information regarding patients' earliest symptom date may have introduced a selection bias.

In conclusion, Cas-Imd mAb treatment was associated with a lower hospitalization rate, ICU admission, and all-cause mortality within 30 days among those with COVID-19 infections. Both Cas-Imd mAb treatment and COVID-19 mRNA vaccination were independently associated with a lower hospitalization and mortality rate.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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