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Monoclonal antibody treatment for COVID-19 in solid organ transplant recipients

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Abstract

Solid organ transplant (SOT) recipients are at high risk for severe coronavirus disease 2019 (COVID-19). Studies suggest that early intervention with monoclonal antibody (MAB) treatment directed against the SARS-CoV-2 spike protein may reduce the risk of emergency department visits or hospitalization for COVID-19, especially in high-risk patients. Herein, we describe our single-center experience of 93 SOT (50 kidney, 17 liver, 11 lung, nine heart, and six dual-organ) recipients with mild to moderate COVID-19 who were treated with bamlanivimab or casirivimab-imdevimab per emergency use authorization guidelines. Median age of recipients was 55 [(Interquartile range) 44–63] years, and 41% were diabetic. Median time from transplant to MAB was 64 (IQR 24–122) months and median time from the onset of COVID-19 symptoms to the infusion was 6 (IQR 4–7) days. All patients had a minimum 30 days of study follow-up. The 30-day hospitalization rate for COVID-19-directed therapy was 8.7%. Infusion-related adverse events were rare and generally mild. Biopsy-proven organ rejection occurred in two patients, and there were no graft losses or deaths. A comparator group of 72 SOT recipients diagnosed with COVID-19 who were eligible but did not receive MAB treatment had a higher 30-day hospitalization rate for COVID-19-directed therapy (15.3%), although this difference was not statistically significant, after adjustment for age (Odds Ratio 0.49 [95% Confidence Interval 0.18–1.32], $p = 0.16$). Our experience suggests that MAB treatment, with respect to the available MAB formulations and circulating viral variants present during our study period, may provide favorable outcomes for mild to moderate COVID-19 in SOT recipients.

KEYWORDS
bamlanivimab, casirivimab-imdevimab, COVID-19, kidney transplant, monoclonal antibodies, SARS-CoV-2, solid organ transplant

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ED, emergency department; EUA, emergency use authorization; MAB, monoclonal antibody; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplant; US, United States; VUMC, Vanderbilt University Medical Center; WHO, World Health Organization

1 | INTRODUCTION

Since its emergence in late 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has reached pandemic proportions and to date is responsible for over 219 million coronavirus disease 2019 (COVID-19) cases and more than four million deaths.[1] Evidence suggests that patients with comorbidities such as older age, hypertension, coronary artery disease, diabetes, chronic kidney disease, obesity, chronic lung disease, dyslipidemia, and cancer may experience a more severe COVID-19 course.[2] In order to improve patient outcomes and to decrease the burden on the healthcare system, it is imperative to identify these high-risk patients and, if possible, to provide early interventions to decrease disease severity and progression.

Published data pertaining to the outcomes of COVID-19 in solid organ transplant (SOT) recipients include single center case series, multicenter registries, and analyses utilizing matched controls.[3–10] Some earlier reports suggested that transplant recipients may have more severe disease and worse outcomes.[3,6] However, more recent studies utilizing matched cohorts have shown conflicting results.[8–10] It is therefore unknown how, or if, chronic immunosuppression affects the disease course. Immunosuppression may prevent an effective immune response to the virus and lead to more severe disease. However, it is also hypothesized that a dampened immune response could be protective against the exaggerated and injurious inflammatory response typical of severe COVID-19.[11] Whatever the effect of immunosuppression, transplant recipients often have comorbidities known to increase the risk of severe COVID-19. In addition, SOT recipients are more likely to shed SARS-CoV-2 for a prolonged period of time[12,13] and are less likely to develop an immune response to vaccination.[14,15] Because of these features, SOT recipients are felt to be at high-risk for severe COVID-19, warranting proactive detection and treatment of COVID-19 in this patient population.

One of the treatments in the armamentarium against COVID-19 are monoclonal antibodies (MABs) which bind with high affinity to the receptor-binding domain of the spike protein of SARS-CoV-2, thus preventing the virus from binding to the angiotensin converting enzyme receptor on host cells and thereby preventing internalization. At the time of this study, three MAB formulations, bamlanivimab, bamlanivimab-etesevimab, and casirivimab-imdevimab, were available under emergency use authorization (EUA) by the United States (US) Food and Drug Administration for treatment of mild-to-moderate COVID-19 in non-hospitalized patients at high risk for progression to severe COVID-19 and/or hospitalization (of note, the EUA for bamlanivimab monotherapy was revoked on April 16, 2021 and the combination of bamlanivimab/etesevimab on June 25, 2021).[16–18] Criteria for inclusion in the initial EUA active during the study period includes patients with a body mass index (BMI) ≥35, chronic kidney disease, diabetes mellitus, immunosuppressive disease or treatment, age ≥65 years, or age ≥55 years PLUS cardiovascular disease or hypertension or chronic respiratory disease. MABs are authorized for infusion within 10 days of symptom onset and are not authorized for use in patients who are hospitalized for COVID-19 or have a new or increased oxygen requirement due to COVID-19.

SOT recipients meet the inclusion criteria for MAB treatment due to immunosuppressive therapy alone and often have additional comorbidities. However, the efficacy and safety of MABs in transplant recipients have not been thoroughly described. Herein, we report our single-center experience in the utilization of MABs for treatment of COVID-19 in SOT recipients. Our objectives were (1) to describe the 30-day hospitalization rate for COVID-19-directed therapy among patients treated with MAB compared to a similar group of patients who were eligible but did not receive MAB, (2) to describe the safety of MAB treatment including infusion-related adverse events, and (3) to describe other outcomes among patients treated with MAB and compare to patients who were eligible but did not receive MAB, including 30-day all-cause hospitalization and emergency department (ED visits), biopsy-proven organ rejection, kidney function, graft loss, and death..

2 | MATERIALS AND METHODS

2.1 | Study setting and participants

We conducted a retrospective single-center cohort study of adult SOT recipients who were diagnosed with COVID-19 between November 22, 2020 and February 2, 2021 at Vanderbilt University Medical Center (VUMC), Nashville, TN.

Study inclusion criteria were: (1) age ≥18 years, (2) recipient of a kidney, pancreas, heart, liver, lung transplant including dual-organ recipients; and (3) positive SARS-CoV-2 polymerase chain reaction (PCR) nasal or nasopharyngeal swab.

The treatment cohort was composed of patients who received MAB for treatment of COVID-19. Patients were identified by either active laboratory surveillance or by passive provider referral. A daily report was generated that identified all symptomatic outpatients with a positive SARS-CoV-2 PCR test performed at VUMC. The PCR platforms utilized at VUMC were Roche 6800 COVID-19 cobas, Roche Liat cobas SARS-CoV-2, Cepheid Xpert SARS-CoV-2, and CDC LDT. Review of the electronic medical record was performed to identify risk factors for progression to severe disease as specified in the EUA. Of note, the EUA for MAB treatment is only approved for symptomatic patients. Patients were contacted to confirm the duration of symptoms, and those who qualified for MAB treatment were offered an infusion appointment. Additionally, VUMC providers were given information about the availability of MAB treatment to allow referral of patients who tested positive for SARS-CoV-2 at another laboratory. In these cases, patients with a positive PCR test regardless of platform utilized met criteria for COVID-19 infection.

The comparator cohort was composed of patients who were diagnosed with COVID-19 in an outpatient setting and were eligible but did not receive MAB therapy. Patients who were hospitalized within <2 days between COVID-19 diagnosis and admission were excluded. The rationale is that it would have been unlikely for these patients to have had sufficient time to receive MAB in the ambulatory setting as all patients in the treatment cohort received MAB ≥2 days after

initial COVID-19 diagnosis. The <2 day timeframe also likely captures patients who were more acutely ill and are therefore less comparable to the treatment cohort which excluded all seriously ill patients based on EUA criteria. In addition, if a patient attempted to get MAB treatment but was hospitalized before they could receive it, they were also excluded. Figure S1 demonstrates how the comparator group was determined.

At the time of data collection, all patients were at least 30 days from initial COVID-19 diagnosis and had the opportunity to meet the outcome of 30-day hospitalization. The Vanderbilt University Institutional Review Board (IRB#210132) approved the study.

2.2 | MAB treatment

Determination of which MAB product was infused was made by pharmacy leadership depending on allocation and supply. At the time of the study, bamlanivimab and casirivimab-imdevimab were available at VUMC. The MAB product that was highest in stock was used for a 1-week period; no provision was made to allow patients, staff, or providers to choose a specific product. Vital signs were obtained at baseline and every 15 min during and after the infusion. Initially, both MABs were infused over a 1-h period. In January 2021, the US Food and Drug Administration revised the duration of infusion time for bamlanivimab, and subsequently patients who received this antibody completed the infusion over 30 min. Patients were observed for a minimum of 1 h after the infusion to ensure there was no hypersensitivity reaction to the MAB preparation. Patients were given contact information for the infusion clinic to report delayed adverse events.

2.3 | Clinical characteristics

Clinical characteristics were collected from the electronic medical record and tabulated in a REDCap database. These included demographic and baseline characteristics (age, sex, race, co-morbidities, kidney function), transplant characteristics (time from transplant, type of transplant, induction and maintenance immunosuppression, history of acute rejection), and data pertaining to the COVID-19 clinical and treatment course (presenting symptoms, treatment, and interventions).

2.4 | Outcomes

The primary outcome of interest was hospitalization for COVID-19-directed therapies within 30 days of COVID-19 diagnosis. Secondary outcomes of interest were all-cause hospitalization and ED visits within 30 days of COVID-19 diagnosis, biopsy-proven organ rejection, kidney function, graft loss, and death. Safety outcomes among patients who received MAB included infusion reactions (within 1 h of MAB) and delayed reactions (within 4 days of MAB).

Hospitalizations were attributed to COVID-19 if patients received COVID-19-directed therapies including steroids, immunosuppression adjustment, remdesivir, tocilizumab, or convalescent plasma. Administration of fluids or treatment of symptoms was not considered COVID-19-directed therapies. For hospitalizations that were ambiguous, three authors (BAS, KB, BPC) independently adjudicated and came to a consensus as to whether the hospitalization was for COVID-19-directed treatment. Tables S3–S6 list all hospitalizations and the brief rationale for inclusion versus exclusion in outcomes.

2.5 | Statistical analysis

Descriptive statistics were used to compare important clinical characteristics between groups. Categorical variables were presented as frequencies (percentages), and continuous variables were presented as medians (IQR). Wilcoxon rank sum test and chi-square test were utilized when appropriate to compare groups. Logistic regression was utilized to quantify the association of MAB therapy with the outcome of hospitalization for COVID-19-directed therapy and all-cause hospitalization ED visits within 30 days of COVID-19 diagnosis, adjusted for age. A p-value of <0.05 was considered statistically significant. All analyses were performed using STATA SE version 15.0 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Patient and transplant characteristics

A total of 165 SOT recipients were included in the study with 93 patients comprising the MAB treatment cohort and 72 patients comprising the comparator cohort. Patient and transplant characteristics of both cohorts are summarized in Table 1. Among the MAB treatment cohort, there were 50 (54%) kidney-alone, nine (10%) heart-alone, 17 (18%) liver-alone, 11 (12%) lung-alone, and six (6%) dual-organ recipients with a median time from transplant to MAB therapy of 64 (IQR 24–122) months. Median age was 55 (IQR 43–63) years, and majority were male (60%) and white (77%). Comorbidities included hypertension in 88 patients (95%) and diabetes in 38 (41%). The majority of patients received induction immunosuppression at the time of transplant. Alemtuzumab induction was utilized solely for kidney-alone transplant recipients. The most common agents utilized for maintenance immunosuppression were tacrolimus (87%), mycophenolate mofetil or mycophenolic acid (64%), and prednisone (58%). The comparator cohort was similar to the MAB treatment cohort except that in the MAB treatment cohort, more patients were hypertensive (88% versus 81%), there was a greater proportion of lung transplant recipients (8% versus 3%), and there was a lesser proportion of heart transplant recipients (15% versus 22%). None of the patients included in the study had a record of COVID-19 vaccination prior to COVID-19 diagnosis.

TABLE 1 Patient and transplant characteristics

	MAB[c] patients (*N* = 93)	Comparator patients (*N* = 72)	All patients (*N* = 165)	*p*-value
Age, years	55.1 (42.8–63.5)	52.0 (41.7–66.3)	53.3 (42.0–63.8)	0.443
Sex				
Male	56 (60.2)	39 (54.2)	95 (57.6)	0.436
Female	37 (39.8)	33 (45.8)	70 (42.4)	
Race				0.532
White	72 (77.4)	57 (79.2)	129 (78.2)	
Black	15 (16.1)	14 (19.4)	29 (17.6)	
Hispanic	3 (3.2)	1 (1.4)	4 (2.4)	
Others	3 (3.2)	0 (0)	3 (1.8)	
Body mass index, kg/m^2	29.9 (25.4–34.2)	30.6 (27.1–34.2)	30.1 (26.3–34.2)	0.462
Comorbidities[*]				
Hypertension	88 (94.6)	58 (80.6)	146 (88.5)	0.005
Diabetes mellitus	38 (40.9)	24 (33.3)	62 (37.6)	0.322
COPD[a]	3 (3.2)	3 (4.2)	6 (3.6)	0.749
Asthma	8 (8.6)	2 (2.8)	10 (6.0)	0.120
CAD[b]	17 (18.3)	5 (6.9)	22 (13.3)	0.034
Time from transplant, months	64.0 (24.0–121.8)	57.6 (23.4–123.3)	58.9 (23.9–121.9)	0.833
Type of organ transplant				
Kidney	50 (53.8)	40 (55.6)	90 (54.5)	0.819
Heart	9 (9.7)	16 (22.2)	25 (15.1)	0.026
Liver	17 (18.3)	14 (19.4)	31 (18.8)	0.849
Lung	11 (11.8)	2 (2.8)	13 (7.9)	0.032
SPK[d]	3 (3.2)	2 (2.8)	5 (3.0)	0.868
SLK[e]	1 (1.1)	0 (0)	1 (0.6)	0.377
SHK[f]	2 (2.2)	0 (0)	2 (1.2)	0.211
Type of donor				0.378
Deceased	70 (75.3)	58 (80.6)	126 (77.3)	
Living	23 (24.7)	14 (19.4)	37 (22.7)	
Induction agent at time of transplant				0.481
Alemtuzumab	35 (37.6)	27 (37.5)	62 (37.6)	
Basiliximab	18 (19.4)	8 (11.1)	26 (15.8)	
Anti-thymocyte globulin	6 (6.5)	7 (9.7)	13 (7.9)	
Steroids only	34 (36.5)	30 (41.7)	64 (38.8)	
History of acute rejection	24 (27.3)	24 (34.8)	48 (30.6)	0.311
Time from acute rejection, months	41.0 (25.5–59.0)	35.2 (18.6–65.8)	40.0 (20.5–63.0)	0.901
History of acute rejection <6 months	3 (3.2)	2 (2.8)	5 (3.0)	0.868
Maintenance immunosuppression*				
Tacrolimus	81 (87.1)	63 (87.5)	144 (87.3)	0.939
Cyclosporine	8 (8.6)	6 (8.3)	14 (8.5)	0.951
MMF[g]/MPA[h]	60 (64.5)	46 (63.9)	106 (64.2)	0.934
Azathioprine	6 (6.5)	5 (6.9)	11 (6.7)	0.900
Sirolimus/everolimus	9 (9.7)	10 (13.9)	19 (11.5)	0.401

(Continues)

TABLE 1 (Continued)

	MAB[c] patients (*N* = 93)	Comparator patients (*N* = 72)	All patients (*N* = 165)	*p*-value
Prednisone	54 (58.1)	36 (50.0)	90 (54.6)	0.302
Baseline serum creatinine, mg/dl	1.24 (1.05–1.58)	1.24 (1.04–1.57)	1.24 (1.05–1.58)	0.916

Note: Values are expressed as frequencies (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.
*Not mutually exclusive.
[a]Chronic obstructive pulmonary disease.
[b]Coronary artery disease.
[c]Monoclonal antibody.
[d]Simultaneous pancreas-kidney.
[e]Simultaneous liver-kidney.
[f]Simultaneous heart-kidney.
[g]Mycophenolate mofetil.
[h]Mycophenolic acid.
[i]Emergency department.

3.2 | Clinical presentation and management of the MAB treatment cohort

Among the MAB treatment cohort, patients' symptoms attributed to COVID-19 prior to the infusion are listed in Table 2. The most common symptoms were cough (82%), congestion (76%), fatigue (75%), headache (68%), and myalgias (61%).

3.3 | MAB therapy

Seventy-one of 93 patients (76.3%) received bamlanivimab, and 22 patients (23.7%) received casirivimab-imdevimab. The median time from the onset of COVID-19 symptoms to the infusion was 6 (IQR 4–7) days while the median time from the diagnosis of COVID-19 (positive PCR test) to the infusion was 3 (IQR 2–5) days.

3.4 | Outcomes

3.4.1 | Hospitalization

Among the MAB treatment cohort, most patients (91.3%) were treated in the outpatient setting for COVID-19. There were 14 patients (15%) who were hospitalized within 30 days of COVID-19 diagnosis, of which eight patients (8.7%) received COVID-19-directed treatment. Baseline characteristics were similar between patients hospitalized for COVID-19 ($n = 8$) and those not hospitalized for COVID-19 ($n = 85$) (Table S1). Shortness of breath as a pre-infusion symptom was more common in the hospitalized for COVID-19 group (87.5% versus 47%, $p = 0.03$). All eight patients hospitalized for COVID-19 received bamlanivimab (Table 2). The median time from COVID-19 diagnosis to hospitalization was 5 (IQR 4–12) days. The median time from MAB to hospitalization was 2.5 (IQR 0–5.5) days. The average length of hospital stay was 7.2 days (range 1–19 days). The World Health Organization (WHO) disease severity criteria[19] of these patients are summarized in Table3. Two patients required admission to the intensive care unit, and one required mechanical ventilation. Both patients were discharged from the hospital on oxygen at the time of study follow-up (Table 3). Seven patients received steroids, five received remdesivir, and 10 patients had their antimetabolite reduced or held. None of the patients were treated with tocilizumab, baricitinib, or convalescent plasma. Six additional patients who received MAB were admitted for reasons that did not warrant COVID-19-directed therapy within 30 days of COVID-19 diagnosis (Table S6). One of these admissions was a lung transplant recipient who experienced an asymptomatic drop in home spirometry and was found to have acute rejection. The other admissions were for biliary colic, urosepsis, chest pain, acute kidney injury/metabolic acidosis, and diarrhea/anemia. In addition to the hospitalizations noted, there was one patient in the treatment cohort who presented to the ED without being admitted. The patient presented with a fever and a mild acute kidney injury. He had received MAB earlier that day. He was given intravenous fluids and was sent home (Table S7).

Among the comparator cohort, there were 14 patients (19.4%) who were hospitalized ≥2 days after being diagnosed with COVID-19, of whom 11 (15%) required a hospital admission for COVID-19-directed treatment. Among the 11 patients hospitalized for COVID-19, the median time from COVID-19 diagnosis to hospitalization was 9 (IQR 4–11) days. The average hospital length of stay was 6.7 days (range 2–19 days). The WHO disease severity criteria[19] of these patients are summarized in Table 3. One kidney transplant recipient was admitted to the intensive care unit and died 12 days after admission after electing not to be intubated and transitioning to comfort care measures. Another heart transplant recipient with stage IV lung cancer died 7 days after hospital admission after presenting with worsening pleural effusions and superimposed pneumonia. The patient transitioned to comfort care measures. Among the three patients who were hospitalized and did not receive COVID-19-directed treatment, one was admitted for acute kidney injury, one was admitted for nausea and vomiting, and one was asymptomatic and diagnosed with COVID-19 during preoperative screening for a surgical resection of an aggressive parotid tumor. In addition to the hospitalizations noted, one patient

TABLE 2 Clinical presentation and management of MAB patients

	All MAB[d] patients (*N* = 93)	No hospitalization for COVID-19[a] (*N* = 85)	Hospitalization for COVID-19[a] (*N* = 8)	*p*-value
Symptoms prior to infusion*				
Fever	41 (44.1)	36 (42.3)	5 (62.5)	0.273
Cough	76 (81.7)	68 (80.0)	8 (100.0)	0.162
Shortness of breath	47 (50.5)	40 (47.1)	7 (87.5)	0.029
Diarrhea	43 (46.2)	39 (45.9)	4 (50.0)	0.823
Congestion	71 (76.3)	65 (76.5)	6 (75.0)	0.925
Sore throat	29 (31.2)	26 (30.6)	3 (37.5)	0.687
Loss of taste	9 (9.7)	9 (10.6)	0 (0)	0.333
Loss of smell	24 (25.8)	24 (28.2)	0 (0)	0.081
Fatigue	71 (76.3)	64 (75.3)	7 (87.5)	0.437
Myalgias	57 (61.3)	52 (61.2)	5 (62.5)	0.941
Headache	63 (67.8)	58 (68.2)	5 (62.5)	0.740
Nausea	35 (37.6)	31 (36.5)	4 (50.0)	0.450
Vomiting	12 (12.9)	11 (12.9)	1 (12.5)	0.972
Monoclonal antibody				
Bamlanivimab	71 (76.3)	63 (74.1)	8 (100.0)	0.100
Casirivimab-Imdevimab	22 (23.7)	22 (25.9)	0 (0)	
Time from COVID-19[a] diagnosis to MAB[d] therapy, days	3 (2–5)	3 (2–5)	4 (2.5–5)	0.588

Note: Values are expressed as frequencies (percentages).
*Not mutually exclusive.
**Therapy started after presenting to emergency department or hospital.
[a]Coronavirus disease 2019.
[b]Immunosuppression.
[c]Mycophenolate mofetil.
[d]Monoclonal antibody.
[e]Emergency department.

in the comparator cohort was seen in the ED without being admitted. He presented with fever and sore throat 17 days after being diagnosed with COVID-19 and was found to have streptococcal pharyngitis for which he was prescribed antibiotics and subsequently discharged home (Table S7).

After adjusting for age, there was no statistically significant difference in the odds of hospitalization for COVID-19 in patients who received MAB versus those who did not (OR 0.49 [95% CI 0.18–1.32], $p = 0.161$). In addition, there was no significant statistical difference in the odds of all-cause hospitalization and ED visits in patients who received MAB versus those who did not (OR 0.71 [95% CI 0.32–1.57], $p = 0.40$), adjusted for age (Table S2).

3.4.2 | Infusion reactions

Adverse events related to MAB infusion were uncommon. Immediate infusion reactions, defined as occurring within 1 h of the infusion, were rare and mild except in one patient who experienced an anaphylactic-type reaction which required termination of the infusion after 7 min and responded to antihistamines and intravenous steroids without further escalation of care. Three patients experienced intravenous infiltration, one patient was asymptomatic but demonstrated heart rate variability between 40–130 beats/min during the infusion, and one patient felt flushed and experienced palpitations a few minutes after starting the infusion – symptoms resolved quickly after the infusion was paused and did not recur after the infusion was resumed. Some patients developed transient hypotension or hypertension documented during their infusion encounter; all were assessed by a clinician, and none required intervention. Some possible delayed infusion reactions, defined as occurring within 4 days of the infusion, included headache (two patients), diarrhea (one patient), nausea (one patient), stomach pain (one patient), back and neck pain (one patient), and lower extremity edema (one patient).

3.4.3 | Acute rejection, kidney function, graft loss, death

Among the MAB treatment cohort, there were two episodes of biopsy-proven organ rejection within 30 days of COVID-19 infection and MAB treatment. One rejection episode was in a heart transplant recipient;

TABLE 3 Disease severity of patients hospitalized for COVID-19[a]

	MAB[b] patients (*N* = 8)	Comparator patients (*N* = 11)
WHO[c] criteria		
Non-severe disease	3 (37.5)	2 (18.2)
Severe disease	4 (50)	8 (72.7)
Critical disease	1 (12.5)	1 (9.1)
Intensive care unit stay	2 (25)	1 (9.1)
Intubation	1 (12.5)	0 (0)
Acute kidney injury	6 (75)	4 (36.4)
Renal replacement therapy	0 (0)	1 (9.1)
Initial laboratory results		
Lymphocyte count, x10^3/mcl	0.64 (0.37–0.70)	0.67 (0.28–0.78)
C-Reactive Protein, mg/L	109 (56–182)	72 (33–118)
Ferritin, ng/ml	770 (250–2121)	453 (308–1657)
Procalcitonin, ng/ml	0.25 (0.15–0.34)	0.16 (0.10–0.29)
Serum creatinine, mg/dl	1.79 (1.54–2.27)	1.97 (1.17–2.21)
Length of hospital stay, days	4 (2.5–9.5)	8 (3-8)
Discharged on oxygen	3 (37.5)	5 (45.5)
Death	0	2 (18.2)

Note: Values are expressed as frequencies (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.
[a]Coronavirus disease 2019.
[b]Monoclonal antibody.
[c]World Health Organization.

biopsy showed mild acute cellular rejection, and the patient did not require treatment. This patient's maintenance immunosuppression regimen consisted of sirolimus and mycophenolate mofetil and was not adjusted during the course of the patient's COVID-19. The patient had a history of mild acute cellular rejection about 3.5 years prior as well. The second rejection episode occurred in a lung transplant recipient; biopsy showed minimal acute cellular rejection, and the patient was treated with steroids with improvement in clinical symptoms and spirometry. This patient's maintenance immunosuppression regimen was tacrolimus, mycophenolate mofetil, and prednisone, and mycophenolate mofetil was held during the patient's course of COVID-19. This patient had no history of rejection. Serum creatinine values for the MAB treatment cohort at baseline and at 30 ± 7 days post-MAB were similar; baseline median serum creatinine was 1.24 (IQR 1.05–1.58) mg/dl (99% of patients had a baseline serum creatinine), and follow-up median serum creatinine was 1.20 (IQR 1.02–1.47) mg/dl (76% of patients had a follow-up serum creatinine). There were no graft losses or deaths in the 30-day study follow-up period.

Among the comparator cohort, as noted above, two patients died within 30 days of COVID-19 diagnosis. There were no acute rejection episodes nor death-censored graft losses. Serum creatinine values for the comparator cohort at baseline and at 30 ± 7 after COVID-19 diagnosis were similar; baseline median serum creatinine was 1.24 (IQR 1.04–1.57) mg/dl (100% of patients had a baseline serum creatinine), and follow-up median serum creatinine was 1.20 (IQR 1.02–1.53) mg/dl (97% of patients had a follow-up serum creatinine).

4 | DISCUSSION

To our knowledge, this study describes the largest cohort of SOT recipients treated with MAB therapy for COVID-19 and demonstrates that among high-risk, immunosuppressed outpatients infected with COVID-19, MAB therapy is associated with low risk of hospitalizations for COVID-19, and a favorable safety profile. Our cohort of patients was diverse in terms of organs transplanted and exhibited multiple risk factors for severe COVID-19 including older age, overweight/obesity, hypertension, diabetes mellitus, and coronary artery disease.

Eight patients (8.7%) treated with MAB therapy required a hospital admission and received COVID-19-directed treatment within 30 days after COVID-19 diagnosis, compared to 11 patients (15%) who did not receive MAB therapy. This difference however did not reach statistical significance. There was also no significant statistical difference when all-cause hospital admissions and ED visits were evaluated as the outcome. It is interesting to note that none of the 22 patients who received casirivimab-imdevimab were hospitalized, and that all eight patients hospitalized in the MAB treatment group received bamlanivimab monotherapy, which is no longer available for EUA use due to concerns for reduced efficacy with the emergence of SARS-CoV-2 viral variants. We do not have data on the specific variants that infected our patients, but speculate whether these hospitalized patients could have been infected with variants resistant to bamlanivimab. Based on a consolidated Centers for Disease Control report on viral variants in the state of Tennessee prior to April 24th, 2021, during which our cohort

was diagnosed with COVID-19, Tennessee had 812 cases of variant B.1.1.7, five cases of variant P.1, and one case of variant B.1.351. This report is not broken down by month, so the exact number of variant cases during our data collection range is uncertain. Importantly, our cohort was infected with SARS-CoV-2 prior to the wide circulation of the delta variant and before widespread availability of COVID-19 vaccines.

Prior studies of COVID-19 in SOT recipients have reported much higher hospitalization rates of 84% and 75%.[5,6] However, these studies were conducted earlier in the global course of COVID-19 when outpatient testing was not as readily available, so are likely skewed toward sicker patients and may have missed the mild-to-moderate outpatient cases like those reported here. However, even among 41 kidney transplant recipients with confirmed or suspected COVID-19 initially managed as outpatients in New York City, Husain and colleagues[7] reported a 32% hospitalization rate. The 8.7%–15% hospitalization rate observed in our patient population is notably higher than the 0.9%–1.6% rate reported in the BLAZE-1 (blocking viral attachment and cell entry with SARS-CoV-2 neutralizing antibodies) study.[20] The BLAZE-1 study evaluated the efficacy and adverse effects of bamlanivimab monotherapy, bamlanivimab-etesevimab, or placebo in outpatients diagnosed with mild to moderate COVID-19. In this study, 387 of 577 (67%) patients had at least one risk factor for severe COVID-19, although there is no documentation of inclusion/exclusion of SOT recipients. One of the study's secondary endpoints was the proportion of patients with COVID-19-related hospitalization, ED visit, or death at day 29. The rates of COVID-19-related hospitalizations or ED visits were lower in the monotherapy (1.6%) and combination therapy (0.9%) groups compared to placebo (5.8%). One possible reason for lower rates of hospitalization/ED visits in BLAZE-1 compared to our experience is the inclusion of lower risk patients in BLAZE-1; all of our patients were considered high risk, while BLAZE-1 was composed of only 67% high risk patients with no data available to determine what proportion of these were SOT recipients.

More recent studies describing the use of MAB treatment include a retrospective case-control study by Kumar et al. which showed that the use of bamlanivimab for 218 ambulatory patients with mild-to-moderate COVID-19 led to a lower 30-day hospitalization rate compared to a control group of 185 patients who did not receive MAB treatment (7.3% vs. 20%); 27% of the patients in this study were immunosuppressed (HIV, malignancy, autoimmune disease, or transplant).[21] A letter by Dhand et al. described the use of casirivimab-imdevimab for treatment of COVID-19 in 25 SOT recipients, none of whom experienced progression of symptoms or required hospitalization.[22] A retrospective review by Yetmar et al. described the use of MAB (75.3% bamlanivimab) for treatment of COVID-19 in 73 SOT recipients; of these patients, 12.3% were hospitalized, and none experienced intubation, rejection, or death.[23] Earlier administration of MAB also appeared to be more efficacious in this study. The 30-day hospitalization rate in our cohort of SOT patients treated with MAB is similar to these more recent studies, with the benefit of having an SOT comparator group that shows similar hospitalization rate to the study by Kumar et al.[21]

Overall, our study suggests that MAB treatment, with respect to the available formulations and circulating viral variants present during our study period, may have favorable outcomes and minimal adverse events. Similar to the BLAZE-1 study, adverse events related to MAB infusion in our study were uncommon.[12] Immediate infusion reactions were rare and mild other than one patient who experienced an anaphylactic-type reaction which responded to therapy but required termination of the infusion. Admittedly, the delayed reactions may have been unreliable since there was no active follow-up of patients following infusion. These delayed reactions could have also been related to the COVID-19 infection rather than the therapy.

Other important outcomes in our patient population treated with MAB included acute rejection, kidney function, graft loss, and death. We observed only two episodes of biopsy-proven acute rejection within 30 days of MAB therapy. Whether these episodes of acute rejection were related to COVID-19, MAB therapy, immunosuppression adjustments, or none of these factors is unknown. Kidney function was stable and excellent at approximately 1-month post-COVID-19 or MAB therapy which is relevant to all of our patients since acute kidney injury is a common complication of COVID-19. There were no events of graft loss or death. No deaths were reported in the MAB trials, although mortality has been reported to be up to 20%–30% in other studies describing outcomes of COVID-19 in SOT recipients.[5,20,22,23] This comparison in mortality outcomes between our patient cohort and those previously reported in SOT recipients infected with COVID-19 must however be taken in the context that our cohort had only mild to moderate symptoms prior to MAB therapy, and our patients were well enough to present for outpatient testing rather than to the ED or hospital.

The strengths of our study include the largest cohort of SOT recipients reported to date to have received MAB therapy, along with granular efficacy and safety data provided and the presence of a comparator group. Although we did not detect a significant difference in our primary outcome between the MAB treatment group and the comparator group, our experience demonstrates the feasibility of MAB administration for the management of COVID-19 in high-risk SOT recipients in an outpatient setting, and an overall acceptable adverse profile.

The study has the inherent limitations of a retrospective observational study including, but not limited to, the possibility of missing data related to patient characteristics and outcomes if not reported in the electronic medical record, patients that are not included in the study because we were unaware of their SARS-CoV-2 infection, and the need to retrospectively identify a comparator group potentially leading to selection bias. The comparator arm was not matched due to the small sample size of potential comparators, although we did note that important baseline characteristics between both groups were similar. The study follow-up was relatively short, and hospitalizations at outside facilities may have been missed. Importantly, bamlanivimab, either as monotherapy or in combination with etesevimab, is no longer authorized for use given concerns for reduced efficacy with the emergence of SARS-CoV-2 viral variants. Despite this, we believe that our experience utilizing MAB therapy is still clinically relevant. Our study suggests that MAB therapy appears to be a safe and possibly effective

treatment during our study period and could still be beneficial in the future.However, the effectiveness of different MAB formulations against circulating SARS-CoV-2 variants should be monitored and the treatment adjusted accordingly. Importantly, our study includes patients who received casirivimab-imdevimab which is still in use currently. A prospective study utilizing currently approved MAB therapy is needed to confirm the findings of our study. We do not have data about the specific viral variants which infected our patients, but note that this cohort was infected prior to the wide circulation of the delta variant.

In conclusion, our experience supports the hypothesis that MAB therapy appears to be a safe option for the management of COVID-19 in high-risk SOT recipients in an outpatient setting. Our MAB treatment group had an overall lower 30-day hospitalization rate than a comparator group of patients who were eligible but did not receive MAB treatment which is encouraging, although this was not statistically significant, and the retrospective nature of the data collection makes it difficult to draw any firm conclusions about outcome differences. We believe our findings are timely and informative to the transplant community as we continue to explore the best approach in preventing severe COVID-19 disease in this vulnerable SOT patient population, especially in the context of reduced effectiveness of vaccination and the current surge of COVID-19.[14]

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CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interest to disclose as described by Transplant Infectious Disease.

AUTHOR CONTRIBUTIONS

Bonnie Ann Sarrell, Karen Bloch, Beatrice P. Concepcion, Alissar El Chediak, Kayla Kumm, Kaitlyn Tracy, Rachel C. Forbes, Anthony Langone, Lora Thomas, Kelly Schlendorf, Anil J. Trindade, Roman Perri, and Patty Wright contributed through conception and design of the work. Bonnie Ann Sarrell, Karen Bloch, Beatrice P. Concepcion, Alissar El Chediak, Kayla Kumm, Kaitlyn Tracy, Rachel C. Forbes, Anthony Langone, Lora Thomas, Kelly Schlendorf, Anil J. Trindade, Roman Perri, and Patty Wright contributed through acquisition of data and revising the manuscript. Bonnie Ann Sarrell, Karen Bloch, and Beatrice P. Concepcion contributed through analysis. Bonnie Ann Sarrell, Karen Bloch, Beatrice P. Concepcion, Rachel C. Forbes, Anthony Langone, Lora Thomas, Kelly Schlendorf, Anil J. Trindade, Roman Perri, and Patty Wright contributed in the interpretation of data for the work and drafting . All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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