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Original Article

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) monoclonal antibody (mAb) treatment: Optimal timing of mAb infusion and risk factor analysis for progressive SARS-CoV-2 infection

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ABSTRACT

Monoclonal antibody therapy was granted emergency use authorization for high-risk patients with mild-moderate coronavirus disease 2019 (COVID-19) illness. The optimal time for mAb infusion is yet to be determined. We performed a single center, retrospective, case-control risk factor analysis in adult outpatients with mild-moderate COVID-19 illness who received mAb therapy from December 2020-December 2021. Patients requiring an Emergency Department (ED) visit or inpatient admission due to COVID-19 symptoms within 28 days following mAb infusion were considered cases with progressive disease and were compared to control patients who received mAb therapy without progressive disease. Risk factors independently associated with disease progression were determined using multivariable logistic regression. A total of 1,156 (77.4%) of 1,494 patients who received mAb therapy for mild-moderate COVID-19 illness met inclusion criteria and were included in the analysis. Sixty-five (5.6%) patients had disease progression with a COVID-19-related ED encounter or inpatient admission despite mAb administration. Twenty-two (33.8%) received mAb infusion within 5 days of symptom onset. In univariate analysis, older age, Elixhauser comorbidity index, receiving bamlanivimab, and delayed mAb administration after 5 days of symptoms were associated with disease progression. In multivariate analysis, Elixhauser comorbidity index and delayed mAb administration after 5 days of symptoms were independently associated with increased risk of disease progression. Our study was able to demonstrate that both a higher Elixhauser comorbidity index and delayed mAb administration after 5 days of symptoms increases risk of COVID-19 disease progression resulting in either an ED encounter or inpatient admission.

KEYWORDS: SARS-CoV-2, COVID-19, monoclonal antibody, immunotherapy.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as the causative virus behind the Coronavirus Disease-2019 (COVID-19) pandemic in December of 2019 [1, 2]. The vicious spread of this virus resulted in widespread efforts to develop vaccines and therapeutic intervention to reduce transmission, hospital

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admissions and mortality. Among those interventions, monoclonal antibody (mAb) therapy was granted an emergency use authorization (EUA) by the United States Food and Drug Administration (FDA) for patients with mild to moderate illness and high risk of progression to severe disease [*3*] based on the results of several randomized controlled trials which showed a significant reduction in COVID-19-related hospitalizations [4-9].

From November, 2020 through December, 2022, at least one mAb product was authorized, available and recommended for use [7, 10-12] to be initiated within 7 days of symptom onset [8, 13, 14]. Real world studies have shown that mAb therapy decreases rate of emergency department (ED) visits and hospitalizations with a reduced risk in 28-day mortality [15, 16]. However, data is limited regarding optimal timing of mAb therapy to best reduce risk of disease progression.

At the time of manuscript submission, there are no mAb products authorized for use and COVID-19 treatment guidelines recommend against mAb therapy as circulating variants are not expected to be neutralized by currently available mAb products [17]. However, new variants or novel mAb therapies will likely emerge in the future making mAb treatment an attractive therapeutic option for COVID-19.

In this real world, retrospective, observational case-control study, we aim to evaluate the impact of early vs delayed mAb therapy for high-risk patients with COVID-19. We hypothesize that early mAb administration (≤5 days from symptom onset) will have the most benefit.

MATERIALS AND METHODS

Study setting

This observational retrospective study evaluated patients who received mAb therapy at the University of Arkansas for Medical Sciences Medical Center (UAMS-MC), a tertiary care academic institution with 535 beds in Little Rock, Arkansas, USA with statewide reach. An outpatient COVID-19 mAb infusion center began administering therapy on December 4, 2020, utilizing a centralized referral process. Early in the pandemic, patients who tested positive for COVID-19 at UAMS-MC were contacted for eligibility for mAb therapy and to offer treatment, while later in the pandemic, referrals (self and provider based) from around the state were screened for appropriateness and treatment was offered accordingly. The following information was collected at time of initial screening: date of onset of symptoms, date of COVID-19 testing, age, presence of immunocompromising conditions, cardiovascular disease, hypertension, chronic obstructive pulmonary disease (COPD), body mass index (BMI) equal to or higher than 35 kg/m^2, chronic kidney disease, diabetes, and presence of any of the following symptoms: fever, sore throat, cough, malaise, headaches, muscle pain, gastrointestinal symptoms and shortness of breath. Patients with any of the aforementioned risk factors were considered at elevated risk of disease progression and were offered mAb therapy. Patients with exposure to COVID-19 positive individuals who were at increased risk of severe disease were also offered outpatient mAb infusion for post-exposure prophylaxis. After shared decision making, patients who elected to receive mAb were then scheduled to receive the infusion at the outpatient infusion center; however, some presented to the ED to receive mAb therapy.

The outpatient infusion center initially operated from 7:30 AM to 5:00 PM Monday through Friday, with enough staffing for 4 chairs with 120-minute time slots; those were gradually increased until the center was able to accommodate 16 appointments per day by December 20, 2020. Additional staffing and chairs were added by January 19, 2021, for a total of 21 available slots per day. In July 2021 the outpatient infusion center began offering infusions Monday through Sunday with increased efficiency and capacity to accommodate 18 slots per day Monday through Friday, and 15 slots per day on Saturdays and Sundays. As demand for mAb therapy increased August-September 2021 opening hours were extended to 6:00 PM on Tuesdays, Wednesdays, and Thursdays to accommodate up to 35 patient slots per day, and 28 slots per day Friday through Monday. The mAb infusion center adjusted its

hours and staffing in response to patient demand, local infection rate and testing capacity; so it was not until October 2021 that the center was able to reduce its capacity to four chairs (Supplemental Table 1).

The choice of mAb therapy was determined based on available literature at the time, the FDA EUA criteria for outpatient treatment, COVID-19 variants' resistance patterns, available products in hand, and later the COVID-19 Treatment Guidelines Panel recommendations.

Study population

De-identified data was collected through review of electronic medical records and included symptoms at time of infusion, comorbidities, and demographics. Data collection was from December 2020 through December 2021. All adult patients over the age of 18 who received COVID-19 mAb treatment in the ED or at the UAMS-MC COVID-19 mAb infusion clinic were eligible for inclusion in the study. Patients were excluded if they received mAb in an inpatient or regional clinic setting, if indication was for post-exposure prophylaxis or if administration was beyond 10 full days from symptom onsets. Patients admitted for non-COVID 19-related diagnosis were also excluded.

Patients who were admitted or had ED visits due to COVID-19-related symptoms to UAMS-MC within 28 days of mAb administration were considered cases. Patients without ED visits or admissions to UAMS-MC were considered controls.

Study definitions

We defined a COVID-19-related encounter or admission as any presentation for symptoms consistent with progressive COVID-19 disease such as fever, worsening dyspnea, chest pain, and hypoxic respiratory failure. Examples of presenting complaints not considered COVID-19-related are listed in Supplemental Table 2.

We classified days of symptoms at time of administration as early if given on days 1-5 of symptoms and late if given on days 6-10 of symptoms.

Statistical analysis

Categorical data was analyzed using chi-squared and Fisher's exact tests where appropriate. Univariate analyses were performed and risk factors with a P-value <0.1 were considered significant and were included in multivariate analysis models. In multivariate analyses, P-values of ≤0.05 were considered statistically significant. All analyses were performed using STATA 15.0 statistical software (StatCorp, College Station, TX).

RESULTS

During the study period, 1,156 (77.4%) of 1,494 patients who received mAb therapy met inclusion criteria and were included in the analysis; Sixty-five (5.62%) of these patients were considered cases with 23 (35.4%) requiring ED visit without admission and 42 (64.6%) requiring inpatient admission (Figure 1).

Demographics and comorbidities are shown in Table 1. Cases were older than controls with a mean age of 58.3±16.4 vs 51.8±16.5 years (P=0.001). Cases had a higher Elixhauser comorbidity index (10.5±13.0 vs 2.3±7.8; P<0.001) with higher rates of cardiovascular disease (35.4% vs 20.4%; P<0.001), diabetes (52.3% vs 24.5%; P<0.001), chronic kidney disease (27.7% vs 9.0%; P<0.001), cirrhosis (15.4% vs 6.9%; P=0.011), history of stroke and neurologic disease (38.5% vs 13.4%; P<0.001), hypertension (75.4% vs 56.6%; P=0.003), and immunosuppression (36.9% vs 21.9%; P=0.005). The rate of obesity was similar in both groups (82.5% vs 86.7%; P=0.376) (Table 1).

Both cases and controls had similar rates of fever (44.6% vs 38.8%, P=0.348), cough (89.2% vs 82.0%, P=0.139), pharyngitis (36.9% vs 34.75%, P=0.708), malaise (63.1% vs 68.7%, P=0.348), headache (49.2% vs 55.6%, P=0.313), myalgia (58.5% vs 55.6%, P=0.905) and gastrointestinal symptoms (40.0% vs 31.8%, P=0.170). However, cases had a higher rate of shortness of breath reported prior to mAb therapy infusion when compared to controls (36.48% vs 23.7%, P=0.065) (Table 1).

Selection of specific mAb product changed throughout the study period with 226 (19.6%) patients receiving bamlanivimab, 20 (1.7%) patients receiving bamlanivimab/etesevimab, and 910 (78.7%) patients receiving Casirivimab/ imdevimab. Cases received bamlanivimab at a

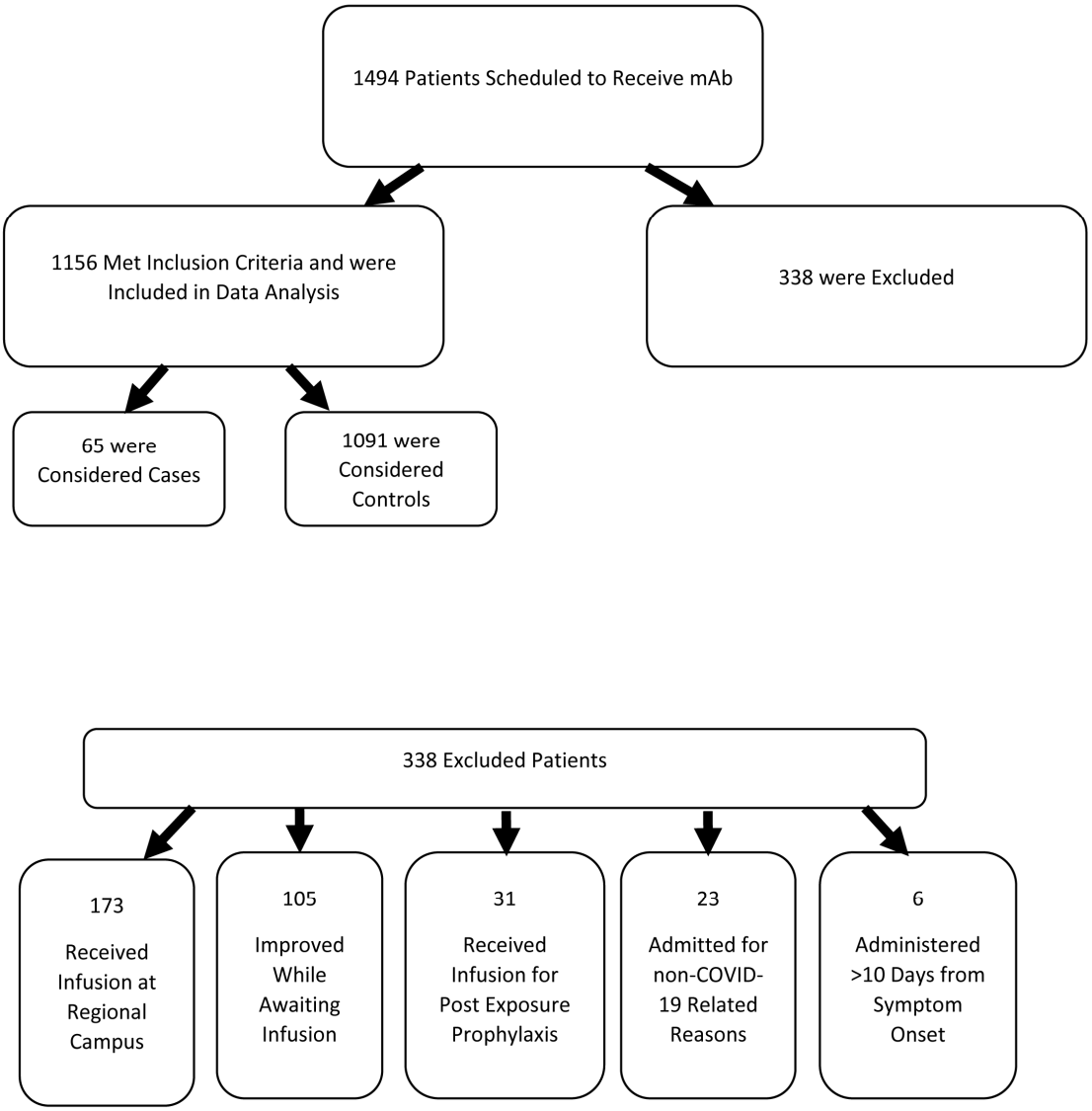

Figure 1. Breakdown of screened patients and reasons for exclusion.

higher rate than controls (36.9% vs 18.5%; P<0.001). Alternatively, cases received casirivimab/ imdevimab less frequently compared to controls (61.5% vs 79.7%; P<0.001). Twenty-four (10.6%) of the 226 patients who received bamlanivimab had disease progression while only 40 (4.4%) of the 910 patients who received casirivimab/ imdevimab had disease progression (P<0.001). Of note, patients who received bamlanivimab had delayed mAb administration compared to the rest of the cohort with a higher mean day of symptoms at time of administration (6.2±1.8 vs 5.1±2.3d; P=0.038).

Cases received mAb infusion later in their course of illness than controls (6.5±2.2 vs 5.8±2.2 days; P=0.005). Forty-three (66.2%) of the 65 cases received delayed mAb infusion after 5 days of symptoms and were more likely to have disease progression (66.2% vs 47.9%; P=0.004).

In multivariate analysis, Elixhauser comorbidity index (OR 1.07; 95%CI 1.04-1.09; P<0.001) and delayed mAb administration after 5 days of symptoms (OR 1.75 95% CI 1.00-3.04; P=0.049) were independently associated with increased risk of disease progression.

Table 1. Risk factors, symptoms and mAb therapy selection and its association with ED or hospital admissions for COVID-19 infection.

	ED visit or admission for COVID-19				
	Case (N=65)	**Control (N=1091)**	**Univariate P-value**	**Multivariate OR; 95% CI**	**Multivariate P-value**
Demographics					
Age, mean (SD)	58.3 (16.4)	51.8 (16.5)	**0.001**	1.01; 0.99-1.03	0.275
Female	37	646	0.715		
Race/ethnicity			0.399		
Black	23	291			
White	40	717			
Asian	0	15			
Other/unknown	2	68			
Ethnicity			0.440		
Hispanic	3	40			
Non-hispanic	62	1051			
Comorbidities					
Cardiovascular disease	32	223	**<0.001**		
Diabetes mellitus	34	267	**<0.001**		
Chronic lung disease	19	228	0.111		
Chronic kidney disease	18	98	**<0.001**		
Liver	10	75	**0.011**		
Neurologic	25	146	**<0.001**		
BMI, mean (SD)	32.8 (9.4)	33.1 (8.2)	0.615		
BMI>25 (n=724)	47 (82.5)	578 (86.7)	0.376		
Hypertension	49	617	**0.003**		
Immunosuppressed	24	239	**0.005**		
Pregnant	3	25	0.205		
Elixhauser comorbidity index, mean (SD)	10.5 (13.0)	2.3 (7.8)	**<0.001**	**1.07; 1.04-1.09**	**<0.001**
Symptoms					
Fevers	29	423	0.348		
Cough	58	895	0.139		
Pharyngitis	24	378	0.708		
Shortness of breath	23 (35.4)	258 (23.7)	**0.065**	1.61; 0.92-2.80	0.096
Malaise	41	749	0.348		
Headache	32	607	0.313		

Table 1 continued..

	ED Visit or Admission for COVID-19				
	Case (N=65)	**Control (N=1091)**	**Univariate P-value**	**Multivariate OR; 95% CI**	**Multivariate P-value**
Myalgia	38	646	0.905		
GI symptoms	26	347	0.170		
mAb therapy					
Bamlanivimab	24 (36.9)	202 (18.5)	**<0.001**	1.57; 0.89-2.80	0.120
Bamlanivimab with etesevimab	1	19	0.689		
Casirivimab with imdevimab	40	870	**<0.001**		
Subcutaneous* (n=15)	2 (5.0)	13 (1.5)	0.138		
Intravenous (n=895)	38 (95.0)	857 (98.5)	0.138		
Day of symptoms, mean (SD)	6.5 (2.2)	5.8 (2.2)	**0.005**		
Early (1-4 days)	22	568	**0.004**		
Late (5-10 days)	43 (66.2)	523 (47.9)	**0.004**	**1.75; 1.00-3.04**	**0.049**

SD: Standard deviation, BMI: Body mass index, mAb: Monoclonal antibody.

Forty-two (3.6%) patients in this study required hospitalization with a mean length of stay of 4.9±3.6 days. Six (14.3%) of these patients required ICU level of care and none required vasopressor support or mechanical ventilation. One admitted patient was transitioned to hospice care and died due to COVID-19 disease. Twenty-four (57.1%) required supplemental oxygen (Tables 2, 3).

DISCUSSION

Our study reports the experience of a tertiary healthcare center in the state of Arkansas providing outpatient mAb therapy to patients with mild-moderate COVID-19 infection during December 2020 through December 2021 when various mAb therapies were authorized for emergency use by the FDA. We specifically looked at patients who required an ED visit or hospitalization following mAb therapy to retrospectively identify risk factors associated with their disease progression. Our study demonstrates that patients with advanced age, BMI higher than 25, cardiovascular disease, hypertension, diabetes, chronic kidney disease, neurological disease and immunosuppression still had an increased risk of disease progression requiring an ED visit or admission for more than 24 hours due to their COVID-19 infection following mAb therapy. Our study was able to demonstrate a statistically significant correlation between early mAb administration and reduced risk of hospitalization, specifically if given during the first 5 days of symptoms. This is the first retrospective study, to our knowledge, that demonstrates that timing mAb infusions in the first five days of symptoms improves clinical outcomes. Although mAb therapy is no longer a recommended treatment option for current circulating variants of COVID-19, the general trend of improved outcomes with early infusion can remain clinically relevant in planning future responses to a coronavirus outbreak or should new mAb therapies be developed to tackle arising SARS-CoV-2 variants. Our finding of reduced hospitalizations with mAb infusions within 5 days of symptom onset highlight the importance of

Table 2. Outcomes in patients admitted for COVID-19 and association with length of stay, oxygen requirements and inflammatory lab values.

	Hospitalization outcomes (N=42)
Length of stay, mean (SD)	4.9 (3.6)
ICU admission	6 (14.3)
Vasopressor requirement	0 (0)
Death	1 (2.4)
Oxygen requirement	24 (57.1)
Low flow (Nasal cannula)	19 (45.2)
High flow (Venturi mask, high flow nasal cannula, BiPAP)	5 (11.9)
Mechanical ventilation	0 (0)
Labs	
Absolute lymphocyte count nadir	0.87 (0.5)
Peak C-reactive protein in mg/L	101.1 (78.8)
Peak ferritin in ng/mL	627.3 (599.3)

SD: Standard deviation, ICU: Intensive care unit, BiPAP: Bilevel positive airway pressure.

extended infusion hours at mAb infusion centers, prioritizing early referrals and same day scheduling and making mAb therapy available all days of the week to facilitate scheduling patients for infusions within 5 days of developing symptoms, particularly those with the aforementioned risk factors who area at most risk for disease progression.

Those who received bamlanivimab alone were more likely to require a COVID-19-related admissions or ED visit (P-value <0.001); this perhaps reflects the response of circulating variants to mAb therapy at the time bamlanivimab was available [13, 18-20]. Gottlieb *et al.* demonstrated that treatment with bamlanivimab/ etesevimab, resulted in a reduction of SARS-CoV-2 viral load at day 11 but a similar effect was not observed with bamlanivimab monotherapy [21, 22]. Moreover, the reduction in COVID-19-related admissions and emergency department visits was statistically significant only in the group receiving combination mAb; it is unclear if this is directly related to the reduction in viral load seen with the combination of bamlanivimab/etesevimab. It is also worth noting that the primary measured end point was viral load at day 11 which, given the course of SARS-CoV-2 infection, might be associated with more immune and inflammatory activation and less viral shedding [2]. However, given our own center's experience with mAb infusion, it is worth pointing out that bamlanivimab was the only available product early in the pandemic at a time when herd immunity was low, vaccines were not yet widespread, and mortality rates were highest during the pandemic. Additionally, potential confounders for why bamlanivimab increased risk of disease progression compared to other products include delayed diagnosis during this period of the pandemic due to slow turn-around-time of test results and infancy stage of infusion clinics resulting in inefficient delivery of care. In our study, patients received bamlanivimab later in their disease course compared to patients who received other products (6.2d vs 5.1d; P=0.038). Thus, bamlanivimab efficacy or its effect on viral response and shedding might not be the only reason for increased risk of disease progression

Table 3. Hospitalization outcomes in patients admitted for COVID-19, organized by date of mAb administration.

	Hospitalization outcomes (N=42)		
	0-5d (N=14)	6-10d (N=28)	P-value
Length of stay, mean (SD)	4.9 (3.4)	4.9 (3.7)	0.500
ICU admission	3	3	0.311
Vasopressor requirement	0	0	
Death	1	0	0.333
Oxygen requirement	11 (78.6)	13 (46.4)	0.047
Low flow (Nasal cannula)	9 (64.3)	10 (35.7)	0.436
High flow (all 3)	2	3	0.547
Venturi mask	0	2	0.439
High flow nasal cannula	2	2	0.407
BiPAP	0	1	0.667
Mechanical ventilation	0	0	
Labs			
Absolute lymphocyte count nadir	0.94 (0.5)	0.83 (0.6)	0.7208
Peak C-reactive protein in mg/L	84.0 (72.6)	111.4 (82.4)	0.1753
Peak ferritin in ng/mL	634.3 (629.8)	623.4 (598.5)	0.5188

SD: Standard deviation, ICU: Intensive care unit, BiPAP: Bilevel positive airway pressure.

and in multivariate analysis, this finding was not significant.

It may appear that infusion of casirivimab/imdevimab had a protective effect leading to fewer hospitalizations and ED visits in the cases group (40 vs 870, P=<0.001), but this was likely related to less virulent SARS-CoV-2 variants circulating at that point in the pandemic, higher utilization of mAb infusion centers and efficiency, increased vaccine uptake and due to higher herd immunity. Casirivimab/imdevimab were used in equal doses during clinical trials to avoid selecting for treatment-resistant mutants. Weinreich *et al.* hypothesized that their antibody cocktail would show the most benefit in patients with higher viral loads, and less immune activation as would happen early on in their disease course. They demonstrated that casirivimab/imdevimab cocktail resulted in enhanced viral clearance, particularly in seronegative patients [5, 23]. Phase three of this clinical trial showed that symptomatic outpatients treated with casirivimab/imdevimab experienced a significant reduction in COVID-19-related hospitalizations, death from any cause, and viral load [5, 23].

The main limitation to this study is that it was a retrospective observational study thus limiting complete ascertainment of all data. The nature of symptoms that were reported by patients, date of symptom onset, and risk factors were required to be entered into the electronic medical record before mAb therapy could be ordered, thus is subject to human error and not all symptoms or risk factors might have been reported at the time of initial screening for mAb therapy eligibility. Another noteworthy limitation is that our study only tracked ED visits or hospitalizations at UAMS-MC as we could not reliably track visits

or extract hospitalization details from other hospitals, but patients who received mAb at UAMS-MC could have presented to other hospitals with disease progression and that would not be accounted for in our data.

The results of this retrospective study should be interpreted knowing that mAb therapy is no longer recommended for the treatment of COVID-19 and that there are no mAb's currently authorized for use by the FDA given that circulating dominant variants are unlikely to be susceptible. However, this study could still serve as a guide for future treatment recommendations or designs of studies that aim to look at the utilization of mAb therapy.

CONCLUSION

In summary, our study demonstrates that mAb infusion within 5 days of symptom onset is associated with a significant reduction in disease progression to either ED encounters or inpatient admissions due to COVID-19. Patients with cardiovascular disease, hypertension, diabetes, chronic kidney disease, neurological disease, liver disease, and immunosuppression are more likely to require admission for COVID-19 despite mAb therapy. Although mAb therapy is not currently available for use, if future use of mAb therapy is indicated, we recommend initiating treatment as soon as possible prioritizing administration within 5 days of symptom onset.

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L.A. was involved in data cleaning, literature review, manuscript writing, review, table design and final text writing and submission.

C.W. was involved in data cleaning.

B. B., M.D. and S.P. were involved in data acquisition.

JR.C. and R.D. were involved in study design, conception.

R.D. was involved in data analysis, manuscript writing, editing, table design & manuscript review L.A., C.W., B.B., M.D., M. K., JR.C. and R.D. were involved at various stages of manuscript review.

All authors, except for Stacy Petty who unfortunately passed away before submission, were involved in the review of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIALS

Supplemental Table 1. Working pattern of SARS-Cov-2 monoclonal infusion clinic during study period.

	Clinic open days of week	Clinic open hours per day	Clinic chairs available	Maximum daily patients infused
12/04/20-01/18/21	5	Mon-Fri (730a-5p)	4	12
01/19/21-07/16/21	5	Mon-Fri (730a-5p)	8	21
07/17/21-08/03/21	7	Mon-Fri (8a-5p) Sat-Sun (8a-3p)	8 8	18 15
08/04/21-08/09/21	7	Mon, Fri (8a-5p) Sat-Sun (8a-3p)	8 8	21 15
08/10/21-08/24/21	7	Mon, Fri (8a-5p) Tues-Thurs (730a-6p) Sat-Sun (8a-3p)	8 8 8	28 35 28

Supplemental Table 1 continued..

	Clinic open days of week	Clinic open hours per day	Clinic chairs available	Maximum daily patients infused
08/25/21-10/03/21	7	Mon-Sun (8a-3p)	6	28
10/04/21-12/02/21	6	Mon, Fri (8a-3p) Sat (8a-11a)	4 4	12 6

Supplemental Table 2. Examples of chief complaints during ED visits or admissions unrelated to COVID-19 illness.

Septic arthritis
Suicidal ideation
Pregnancy (labor)
Orthopedic fracture
Vaginal bleeding
Cellulitis
Angina
Urinary tract infections
Abdominal pain
Medication refill
Chemotherapy/stem cell transplant
Abnormal labs
Scheduled endoscopy
Surgical procedures

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