

## BRIEF COMMUNICATION

# COVID-19 therapeutics and outcomes among solid organ transplant recipients during the Omicron BA.1 era

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## Abstract

Treatment outcomes associated with the use of novel COVID-19 therapeutics in solid organ transplant recipients (SOTR) are not well described in the literature. The objective of this analysis was to characterize 30-day hospitalization and other key secondary endpoints experienced by outpatient SOTR with mild-moderate COVID-19 treated with nirmatrelvir/ritonavir (NR), sotrovimab, or no SARS-CoV-2 specific treatment. This IRB-approved, retrospective study included 154 SOTR with a documented positive SARS-CoV-2 infection between December 16, 2021 and January 19, 2022 (a predominant Omicron BA.1 period in New York City). Patients who received NR ( $N = 28$ ) or sotrovimab ( $N = 51$ ) experienced a lower rate of 30-day hospitalization or death as compared to those who received no specific treatment ( $N = 75$ ) ( $p = .009$ ). A total of three deaths occurred, all among patients who initially received no specific treatment prior to hospitalization. These results suggest a role for SARS-CoV-2 specific agents in the treatment of SOTR with COVID-19, and that there does not appear to be any difference in effectiveness when comparing NR versus sotrovimab.

## 1 | INTRODUCTION

Solid organ transplant recipients (SOTR) are at high risk for morbidity due to COVID-19.<sup>1,2</sup> The risk of hospitalization or death among SOTR who develop COVID-19 has been reported to be upwards of four-times greater than that of the immunocompetent population.<sup>3</sup>

Multiple therapeutic options have been authorized by the United States Food and Drug Administration (FDA) for use in patients with mild-moderate COVID-19 who are at high risk for progression to severe disease. Sotrovimab, a monoclonal antibody that binds to and neutralizes the SARS-CoV-2 spike protein, was evaluated in a

randomized, placebo-controlled clinical trial.<sup>4</sup> Compared to placebo, sotrovimab reduced the risk of hospitalization or death from any cause through day 29 by 82%. Nirmatrelvir/ritonavir (NR), an orally available viral protease inhibitor, was also evaluated in a population of at-risk patients with mild-moderate COVID-19.<sup>5</sup> Compared to placebo, NR reduced the risk of hospitalization or death from any cause through day 28 by 89%.

However, neither of the aforementioned clinical studies enrolled SOTR. As such, it is not yet known if these agents are safe or effective in this particularly at-risk population. Case series describing outcomes of SOTR treated with either sotrovimab or NR have been

**Abbreviations:** AKI, acute kidney injury; aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; EUA, emergency use authorization; FDA, Food and Drug Administration; IQR, interquartile range; MMF, mycophenolate mofetil; NR, nirmatrelvir/ritonavir; NYPH, NewYork-Presbyterian Hospital; RRR, relative risk reduction; SCR, serum creatinine; SOTR, solid organ transplant recipient.

published, though they are limited by small sample sizes and do not include comparator populations.<sup>6-8</sup>

The objective of this analysis was to evaluate outcomes in a heterogeneous population of outpatient SOTR infected with COVID-19 during an Omicron BA.1-dominated period in New York City who received either NR or sotrovimab, compared to those who received no SARS-CoV-2 specific treatment.

## 2 | METHODS

This was an IRB-approved, retrospective study of all adult SOTR with asymptomatic, mild, or moderate COVID-19 who had a positive SARS-CoV-2 PCR test conducted within the NewYork-Presbyterian Hospital (NYPH) health system between December 16, 2021 and January 19, 2022. A report was generated from the electronic medical record to capture all adult SOTR in that time frame who either had a positive SARS-CoV-2 PCR test result in the NYPH health system or had an order placed for either NR or sotrovimab in their medication history. Patients were categorized into three groups: those who received NR within 5 days of symptom onset, those who received sotrovimab within 10 days of symptom onset, and those who received no specific treatment. Patients may have received no specific treatment either because of provider preference because they did not report to the transplant center that they were ill with COVID-like symptoms in time to receive treatment, or because treatment was not available. All patients who received NR were instructed to adhere to the previously published dosing guideline from our clinical group for managing drug interactions with immunosuppressive therapies.<sup>9</sup> The algorithm recommends holding tacrolimus or mTOR inhibitor or reducing cyclosporine dose to 20% of the baseline daily dose during the 5 days of NR treatment. Although treatment was recommended for all SOTRs with COVID-19, there was no data to guide providers on what intervention should be preferentially offered. Molnupiravir was not prioritized at our institution given that it has demonstrated relatively limited efficacy compared to other available therapeutic agents.<sup>10</sup> The choice of treatment agent (NR versus sotrovimab) was at the discretion of the treating provider and dependent on time from symptom onset, drug availability, and relative contraindications due to patient considerations such as drug-drug interactions or renal insufficiency.

Internal data from our center demonstrated that the majority (>75%) of sequenced SARS-CoV-2 infections were the Omicron BA.1 variant by December 15, 2021. The Omicron BA.2 variant was not detected in New York until early February 2022 and thus would not likely be represented in this cohort.

The severity of illness was determined on the basis of definitions adapted from the National Institutes of Health. Mild COVID-19 was defined as having signs/symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste, and smell), but without evidence of lower respiratory disease (shortness of breath or dyspnea) or abnormal chest imaging. Moderate COVID-19 included individuals with evidence of

lower respiratory disease on clinical assessment or imaging but have an oxygen saturation  $\geq 94\%$  on room air. Patients with severe or critical COVID-19, defined as having an oxygen saturation  $< 94\%$  on room air, an arterial oxygen partial pressure to fractional inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $< 300$  mm Hg, respiratory rate  $> 30$  breaths per minute, lung infiltrates  $> 50\%$ , or individuals with respiratory failure, septic shock, or multiple organ dysfunction were excluded.<sup>11</sup> Patients were also excluded if they were hospitalized within 72 h of symptom onset or if they became infected with COVID-19 while already hospitalized.

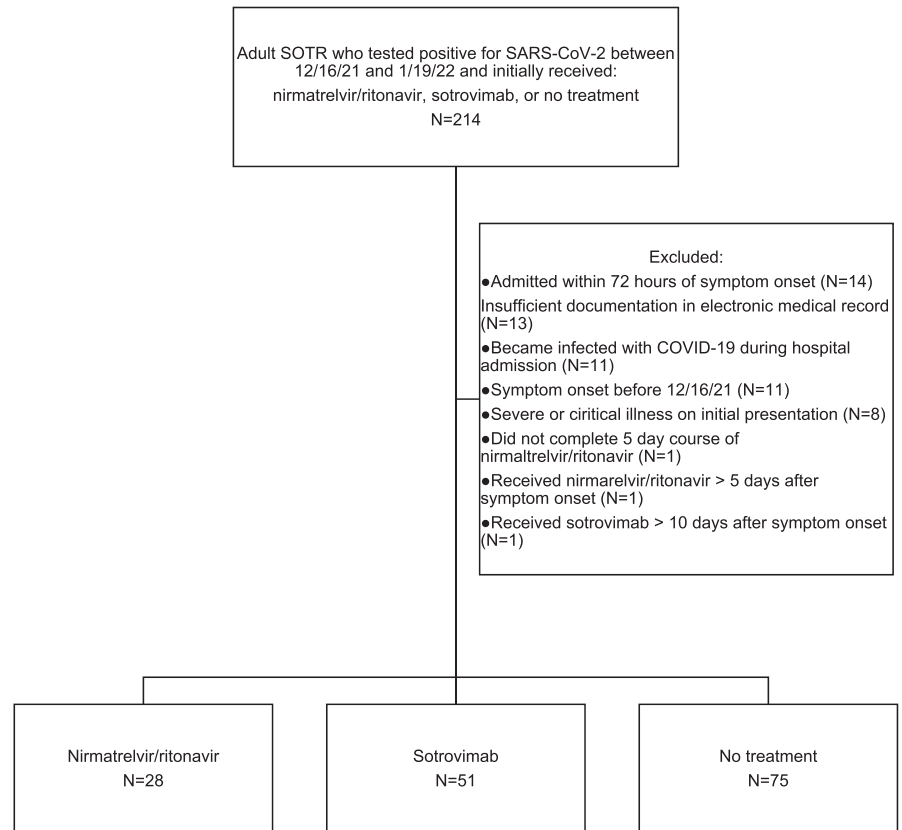
The primary outcome of interest was hospitalization or death from any cause through day 30 (defined as 30 days after symptom onset or positive SARS-CoV-2 PCR test in those who were asymptomatic). Other outcomes of interest included COVID-19-related hospitalization or death at 30 days, the incidence of acute kidney injury (AKI) defined using the acute kidney injury network (AKIN) classification, use of supplemental oxygen, receipt of other COVID-19 treatment (remdesivir, dexamethasone, and/or tocilizumab/baricitinib), and acute allograft rejection episodes through day 30. COVID-19-related hospitalization was defined as worsening of COVID-19 symptoms, including hypoxia. All endpoints were collected via manual chart review.

Continuous variables were compared using the Kruskal-Wallis test and categorical variables were compared using Pearson's chi-squared test. Relative risk reduction with the adjustment for organ transplant type was calculated by outcome rates in treatment groups versus the no-treatment group. Statistical analyses were performed using Stata version 14.2 (Stata Corp).

## 3 | RESULTS

Overall, 214 patients were identified and 60 patients were excluded from this analysis (Figure 1). A total of 154 adults SOTR were ultimately included: kidney = 65 (42.2%), liver = 8 (5.2%), heart = 44 (28.6%), lung = 25 (16.2%), kidney/pancreas = 2 (1.3%), dual organ transplant = 10 (6.5%). Of the 154 patients included, 28 patients (18.2%) initially received NR, 51 patients (33.1%) received sotrovimab, while 75 patients (48.7%) received no SARS-CoV-2 specific treatment. Median age at the time of COVID-19 symptom onset and time from transplant to COVID-19 were similar among the three groups (Table 1). The median time from COVID-19 symptom onset to NR and sotrovimab treatment was 2 days (IQR, 1-3) and 4 days (IQR, 3-6), respectively. In the NR, sotrovimab, and no-treatment groups, 15 (53.6%), 27 (52.9%), and 39 (52%) received at least three doses of mRNA vaccination prior to COVID-19, respectively. No patients received tixagevimab/cilgavimab prior to COVID-19. Recipients of NR who were on tacrolimus-based immunosuppression had follow up levels as per our institutional standard of care. Tacrolimus levels measured after completion of 5 days of NR were generally at-goal in the range of 4-8 ng/ml. No suprathreshold levels were detected upon first assessment after completing 5 days of NR. Key baseline demographics including COVID-19 severity and use of immunosuppressive agents prior to COVID-19 symptom onset are summarized in Table 1.

FIGURE 1 Patient cohort



A total of 4/28 patients (14.3%) in the NR group, 6/51 patients (11.8%) in the sotrovimab group, and 25/75 patients (33.3%) in the no-treatment group were hospitalized for any cause or died by day 30 ( $p = .009$ ) (Figure 2). When adjusted for organ transplant type, both NR (adjusted risk ratio [aRR] 0.21, 95% confidence interval [CI], [0.06–0.71]) and sotrovimab (aRR 0.15, CI, [0.05–0.47]) were associated with lower risk for 30-day hospitalization or death. Time from COVID-19 symptom onset (or positive SARS-CoV-2 PCR in those who were asymptomatic) to hospitalization or death did not differ between the groups (Table 2). Overall, 3/28 patients (10.7%) in the NR group, 5/51 patients (9.8%) in the sotrovimab group, and 23/75 patients (30.7%) in the no-treatment group experienced COVID-19-related hospitalization or died by day 30 ( $p = .007$ ) (Figure 2). When adjusted for organ transplant type, both NR (aRR 0.17, CI, [0.04–0.67]) and sotrovimab (aRR 0.14, CI, [0.04–0.47]) were associated with lower risk for COVID-19-related hospitalization or death by day 30. When stratifying further to compare those patients who had completed their primary COVID-19 vaccination series (a receipt of either three doses of mRNA vaccine or a single dose of Janssen adenovirus vector vaccine) versus those who did not complete their primary vaccine series, the rate of hospitalization or death at 30 days was not different among patients who received NR (0% vs 25%,  $p = .113$ ), sotrovimab (13.6% vs 10.3%,  $p = 1.000$ ), or those who received no specific treatment (37.5% vs 30.2%,  $p = .622$ ).

There were three deaths, all of which occurred in patients who originally presented with mild COVID-19 symptoms and received no treatment. One patient was admitted for shortness of breath 12 days following symptom onset. This patient's course was complicated by

acute hypoxic respiratory failure/pneumonia secondary to COVID-19 infection, and the patient died 36 days after symptom onset. Another patient was admitted 9 days following symptom onset with 1 week of altered mental status and fevers. The patient died from hypoxic respiratory failure/pneumonia and shock (cardiogenic versus septic) secondary to COVID-19 infection 29 days after symptom onset. The last patient presented with shortness of breath and several days of fevers and chills 7 days following symptom onset. This patient died as a result of hypoxic respiratory failure/pneumonia and septic shock secondary to COVID-19 infection 38 days after symptom onset.

The majority of patients were free from AKI by day 30 (96.4% in NR, 89.8% in sotrovimab, and 72% in no-treatment group;  $p = .017$ ). A total of 2/28 patients (7.1%) in the NR group, 2/51 patients (3.9%), and 9/75 patients (12%) in the no-treatment group required supplemental oxygen by day 30. No patients required mechanical ventilation in the NR or sotrovimab groups, while 4/75 (5.3%) patients in the no-treatment group required mechanical ventilation by day 30 (Table 2).

No patients received both NR and sotrovimab. More patients received inpatient remdesivir and dexamethasone in the no-treatment group (7.1% in NR, 3.9% in sotrovimab, 21.6% in no treatment). No patients received tocilizumab or baricitinib in the NR and sotrovimab groups, while one patient received baricitinib in the no-treatment group (Table 2).

There were no episodes of acute allograft rejection in the NR or sotrovimab groups by day 30. One lung transplant recipient who originally presented with mild COVID-19 but received no treatment had suspected acute rejection within 30 days following symptom onset. Due to severe fatigue, the patient did not go to a scheduled sotrovimab

TABLE 1 Baseline characteristics

	Nirmatrelvir/ritonavir (N = 28)	Sotrovimab (N = 51)	No treatment (N = 75)	p-value
Age at time of COVID-19 symptom onset (years)	57.6 (44.3–68.6)	53.3 (45–61.6)	53.3 (37.6–64.6)	.513
Male sex	11 (39.3)	21 (41.2)	32 (42.7)	.976
Organ transplant				
Kidney	4 (14.3)	18 (35.3)	43 (57.3)	<.001
Liver	2 (7.1)	0 (0)	6 (8)	
Heart	11 (39.3)	19 (37.3)	14 (18.7)	
Lung	11 (39.3)	4 (9.8)	9 (12)	
Kidney/pancreas	0 (0)	1 (2)	1 (1.3)	
Dual organ	0 (0)	8 (15.7)	2 (2.7)	
BMI (kg/m <sup>2</sup> )	25.3 (22.3–30)	24.6 (21.5–30.2)	27 (23.3–29.5)	.707
History of previous COVID-19 infection	4 (14.3)	5 (9.8)	7 (9.3)	.730
SCr prior to COVID-19 symptom onset (mg/dL)	1.2 (0.9–1.6)	1.4 (1.1–1.9)	1.7 (1.2–2.2)	.033
Time from transplant to COVID-19 symptom onset (years)	3.9 (1.8–10.6)	3.4 (0.8–10.7)	4 (2.3–8.1)	.52
COVID-19 symptom severity <sup>a</sup>				
Asymptomatic	2 (7.1)	3 (5.9)	8 (10.7)	.657
Mild	25 (89.3)	45 (88.2)	59 (78.7)	
Moderate	1 (3.6)	3 (5.9)	8 (10.7)	
mRNA vaccine				
1 dose	1 (3.6)	2 (3.9)	3 (4)	1.000
2 doses	8 (28.6)	14 (27.5)	22 (29.3)	
3 doses	15 (53.6)	27 (52.9)	39 (52)	
Adenovirus vector	1 (3.6)	2 (3.9)	4 (5.3)	1.000
Immunosuppressive agents administered within 6 months prior to COVID-19 symptom onset				
Lymphocyte depleting agent	2 (7.1)	5 (9.8)	3 (4)	.419
High dose steroids <sup>b</sup>	5 (17.9)	10 (19.6)	5 (6.7)	.074
Rituximab	1 (3.6)	0 (0)	1 (1.3)	.44
Bortezomib	0 (0)	0 (0)	0 (0)	–
Maintenance immunosuppressive agents prior to COVID-19 symptom onset				
Tacrolimus (ng/ml)	8.6 (6.4–13.8)	7.8 (5.6–10.7)	6.8 (5.1–8)	.01
Cyclosporine (ng/ml)	75.9 (73.1–79.3)	174.3 (107.8–254.7)	144.9 (103–152.8)	.148
Everolimus (ng/ml)	4.1 (3.6–4.5)	4 (3.1–6.4)	4.1 (3.9–4.3)	.997
MMF equivalents (mg/day)	2000 (1000–2000)	1750 (1000–2000)	1000 (1000–2000)	.003
Azathioprine (mg/day)	–	100 (100–150)	100 (100–100)	.524
Prednisone (mg/day)	5 (5–5)	5 (3–5)	5 (5–5)	.349
Belatacept	3 (10.7)	5 (9.8)	20 (27)	.027

Note: Continuous variables reported as median (IQR), categorical variables reported as n (%).

Abbreviations: BMI, body mass index; MMF, mycophenolate mofetil; SCr, serum creatinine.

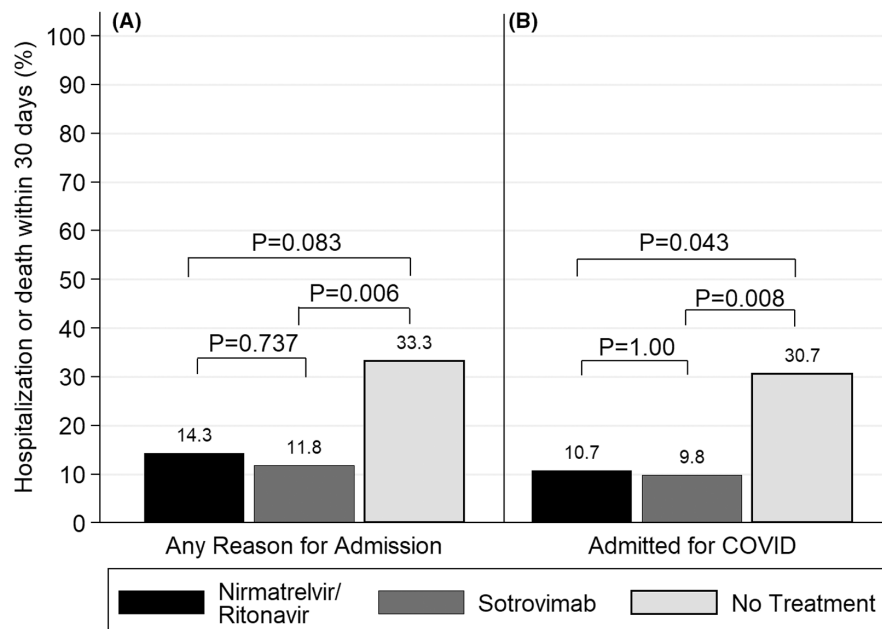
<sup>a</sup>COVID-19 symptom severity defined by the National Institutes of Health.

<sup>b</sup>Defined as at least 1 mg/kg prednisone equivalents (associated with treatment of allograft rejection).

infusion appointment and thus received no treatment. Intermittent non-adherence with transplant medications, due to illness-related fatigue, was reported. This patient was hospitalized for hypoxia 15 days following the initial symptom onset. The differential diagnosis upon

admission to the hospital included pneumonia due to COVID-19/bacterial superinfection versus acute cellular rejection. After a 39-day hospitalization during which the patient received IV remdesivir and dexamethasone, broad-spectrum antibacterial therapy, and pulsed

**FIGURE 2** Bar graph showing (A) primary outcome of hospitalization or death within 30 days from symptom onset and (B) secondary outcome of hospitalization or death related to COVID-19 within 30 days from symptom onset.



**TABLE 2** Secondary outcomes through day 30

	Nirmatrelvir/ritonavir (N = 28)	Sotrovimab (N = 51)	No treatment (N = 75)	p-value
Time from symptom onset to hospitalization (days)	17.5 (6-28)	13.5 (12-21)	10 (7-12)	.217
<b>AKI<sup>a</sup></b>				
No AKI	27 (96.4)	44 (89.8)	54 (72)	.017
Stage 1	1 (3.6)	1 (2)	14 (18.7)	
Stage 2	0 (0)	2 (4.1)	2 (2.7)	
Stage 3	0 (0)	2 (4.1)	5 (6.7)	
<b>Oxygen requirement</b>				
No oxygen requirement	26 (92.9)	49 (96.1)	62 (82.7)	.172
Supplemental oxygen	2 (7.1)	2 (3.9)	9 (12)	
Mechanical ventilation	0 (0)	0 (0)	4 (5.3)	
<b>Other COVID-19 agents used</b>				
Remdesivir	2 (7.1)	2 (3.9)	16 (21.6)	.011
Dexamethasone	2 (7.1)	2 (3.9)	16 (21.6)	.011
Tocilizumab/baricitinib	0 (0)	0 (0)	1 (1.3)	1.000
Acute rejection episode <sup>b</sup>	0 (0)	0 (0)	1 (1.3)	1.000

Note: All variables as reported as n (%).

Abbreviation: AKI, acute kidney injury.

<sup>a</sup>Acute kidney injury defined according to the Acute Kidney Injury Network classification.

<sup>b</sup>Suspected rejection episode, not biopsy-confirmed.

steroids for presumed acute rejection, the patient was discharged to an acute rehabilitation facility on room air.

Additionally, we performed a post hoc subgroup analysis to specifically evaluate endpoints among only heart or lung transplant recipients (N = 79) to account for differences in this population with regard to previously reported COVID-19-related outcomes, baseline maintenance immunosuppression, and the tolerability of immunosuppressive therapy minimization during acute COVID-19 (Tables S1 and S2 and Figure S1).

## 4 | DISCUSSION

In this single-center, case series comprised of a heterogeneous population of outpatient SOTR with asymptomatic, mild, or moderate COVID-19, we demonstrate that treatment with either NR or sotrovimab is associated with a lower risk of 30-day hospitalization or death. We also report no differences in rates of hospitalization, death, or other key secondary endpoints between NR and

sotrovimab among a population of comparably immunosuppressed and at-risk cardiothoracic transplant recipients.

Previous epidemiologic studies evaluating outcomes among SOTR with COVID-19 have concluded that the incidence of hospitalization may be as high as 40%–60%.<sup>12,13</sup> However, even in the post-vaccine era, SOTR continue to experience significant morbidity and mortality. Cochran et al. report a 26% hospitalization rate during the Omicron BA.1 era among a large cohort of SOTR.<sup>14</sup> Further, Radcliffe et al. similarly report a high overall rate of hospitalization among SOTR in the BA.1 era, however, morbidity appears to have been attenuated by treatment with either molnupiravir or sotrovimab.<sup>15</sup> Herein, we report an overall 30-day hospitalization rate of 22.7%. However, this rate is likely overestimated due to our inability to capture patients who may have either tested positive with commonly available home testing kits without ever testing positive within our healthcare system or those SOTR whose course was asymptomatic and were never known to be infected with SARS-CoV-2.

There are certain logistical and practical considerations that make the use of sotrovimab and NR challenging in SOTR. During the era we report on, both sotrovimab and NR were limited in availability both regionally and nationally. Sotrovimab, as with other monoclonal antibody therapies authorized for use in patients with COVID-19, requires intravenous administration, and thus coordinating timely care can be difficult, particularly in areas with limited resources and drug supply.<sup>16</sup> NR use in SOTR poses the specific challenge of managing drug–drug interactions with commonly used immunosuppressive medications.<sup>9</sup> Although the previously published NYPH protocol can effectively help manage the ritonavir-related drug interactions, this protocol requires intensive therapeutic drug monitoring and should not be followed if drug levels cannot be adequately measured over time.<sup>6,17</sup> Additionally, NR is not recommended for patients with an eGFR <30ml/min, and as such renal transplant recipients or other SOTR with chronic kidney disease may be excluded from this treatment option. Treatment with both sotrovimab and NR should be initiated as soon as possible after confirmation of COVID-19; the FDA emergency use authorization (EUA) criteria for NR specifies that treatment should begin within 5 days of symptom onset, whereas the sotrovimab EUA (prior to its authorization being revoked in the United States) specified first that treatment should occur within 10 days of symptom onset before it was later revised to 7 days.<sup>18,19</sup> Meeting either of these time points to treat outpatient SOTR requires effective communication with the transplant care team and subsequent access to drug therapy.

The SARS-CoV-2 Omicron variant rapidly gained a foothold across the United States beginning in December 2021. Initially, the BA.1 sub-lineage was the dominant strain. However, the BA.2 sub-lineage was detected in New York first in early February, 2022 which almost immediately presented challenges for treating COVID-19. Compared to its neutralizing activity against BA.1, sotrovimab demonstrates significantly reduced activity against BA.2.<sup>20</sup> As such, the FDA revoked authorization for use of sotrovimab in certain United States regions on March 25, 2022 and subsequently in all US regions by April 5, 2022.<sup>21</sup> Nirmatrelvir (as well as molnupiravir and remdesivir) demonstrate activity against the BA.2 variant that is comparable to the ancestral strain

and other variants of concern.<sup>20</sup> Bebtelovimab, the most recently authorized monoclonal antibody for COVID-19, also retains neutralizing activity against BA.2.<sup>22</sup> However, bebtelovimab poses similar logistical challenges to those previously attributed to sotrovimab: It requires intravenous administration, is not universally available across the United States in sufficient supply to treat all high-risk patients, and should be administered within 7 days of symptom onset.<sup>23</sup> It is unclear how the relative effectiveness of NR or other antiviral treatments would compare to bebtelovimab in a population of SOTR with mild–moderate COVID-19; this should be actively explored in future studies.

Our analysis has a number of important strengths worth emphasizing. First, we report a large cohort of heterogeneous SOTR infected with SARS-CoV-2 during a defined time period known to be dominated by a single variant of concern. This avoids confounding when multiple variants with varying levels of disease severity are represented within a population. Second, we include populations of patients treated with different agents that make comparison possible. Among the sub-population of heart and lung transplant recipients (who were comparably immunosuppressed at baseline and approximately evenly distributed across the three defined groups), there was a markedly reduced incidence of hospitalization through day 30 among recipients of either NR or sotrovimab relative to those similar patients who received no treatment. Despite the change in Omicron sub-lineage dominance across the United States that has led to the withdrawal of sotrovimab authorization, our finding that NR demonstrated comparable efficacy to an effective (at the time) monoclonal antibody treatment is an important finding. Third, all SOTR within the NR group received identical management in regards to the drug interactions with immunosuppressive agents. This makes the assessment of secondary endpoints such as AKI more interpretable.

Our analysis should be viewed in light of a number of limitations. As previously stated, the morbidity experienced by the group of patients who received no specific treatment may be overestimated due to our inability to assess our entire SOTR population during this time period. Further, it is not clear that the higher incidence of morbidity in the group of patients who received no treatment was a direct result of initially withholding antiviral treatment. It is possible that hospitalization was, in fact, deemed part of the treatment pathway to permit closer inpatient monitoring and administration of remdesivir.<sup>24</sup> Considering the limited sample size, there may also be unquantifiable differences in COVID-19 severity or patient characteristics at baseline that influenced outcomes between the groups that were not accounted for. As a retrospective analysis, data extraction from the medical record may be susceptible to inaccuracies.

Our results suggest a role for SARS-CoV-2 specific agents in the treatment of SOTR with COVID-19. NR and sotrovimab were associated with a similar incidence of hospitalization or death at 30 days. Future studies should assess the relative effectiveness of bebtelovimab use in SOTR with mild–moderate COVID-19 in the BA.2 era.

## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.



## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

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

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