Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Original Article

Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave

Javier T. Solera #, Berta G. Árbo #, Ilona Bahinskaya, Nikki Marks, Atul Humar, Deepali Kumar *

Ajmera Transplant Centre, University Health Network, Toronto, Canada

ABSTRACT

Solid organ transplant recipients (SOTr) remain at risk of severe COVID-19. Several previous early therapies are no longer effective against new circulating variants. We performed a prospective cohort study in outpatient adult SOTr during the omicron BA.2 wave (April–May 2022), to determine the effectiveness of 3 doses of remdesivir given within 7 days of symptoms onset. Patients were followed for at least 30 days. The primary outcome was hospitalization. Of 210 SOTr that had COVID-19, we included 192. The median age was 54.5 years and 61.5% were men. The most common transplants were kidney (41.7%), lung (19.3%), liver (18.8%), and heart (6.3%). Most patients (90.1%) had previously received ≥3 COVID-19 vaccine doses. Fifteen (7.8%) were hospitalized, 5 (2.6%) required supplemental oxygen, 3 (1.6%) ICU admission, and 2 (1%) mechanical ventilation with 2 (1%) deaths. Age, the number of comorbidities, prednisone chronic treatment, and lung transplant were risk factors for hospitalization. Early remdesivir significantly decreased the hospitalization rate: adjusted hazard ratio 0.12 (95% CI: 0.03–0.57). The adjusted number needed to treat to prevent one hospitalization was 15.2 (95% CI: 13.6–31.4). No patient that received early remdesivir needed ICU admission or died. In a cohort of SOTr with COVID-19 infection, administration of 3-dose early remdesivir independently reduced the disease severity.

1. Introduction

Severe SARS-CoV-2 infection remains a threat to solid organ transplant recipients (SOTr).1–3 These severe outcomes made vaccination a priority in transplant recipients, but vaccine effectiveness of 2-doses reaches approximately 59%, with a subsequent high rate of breakthrough infections. Booster doses of the COVID-19 vaccine were implemented in the transplant population based on immunogenicity studies, and they have been shown to attenuate disease severity in transplant recipients. However, breakthrough infections continue to occur.4,5

Monoclonal antibodies have been a useful tool as early outpatient treatment for mild COVID-19 in order to prevent progression, but emerging variants continue to challenge the efficacy of these implemented treatments.6–9 For this reason, retrieving and reshaping treatment options has been necessary.

Paxlovid (Pfizer Inc.), a combination of nirmatrelvir (antiviral) and ritonavir showed a risk reduction of 89% for hospitalization and all-cause mortality in non-hospitalized adults with mild-to-moderate COVID-19 at high risk for progression to severe disease.10 However, the risk for drug interactions with calcineurin inhibitors owing to the ritonavir component of Paxlovid, makes it necessary to look for safer treatment options in transplant recipients.11

Remdesivir is a direct-acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase; with potent activity in primary human airway epithelial cells. It has been widely used since the start of the pandemic for hospitalized patients, improving clinical outcomes in those with moderate-to-severe disease.12 Recently, in a study of 562 persons with mild–moderate COVID-19, remdesivir reduced the risk of hospitalization or death by 87%, when used as a 3-day course of outpatient treatment in symptomatic patients at high risk of progression.13 Nevertheless, whether

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; NNT, number needed to treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOTr, solid organ transplant recipient.

* Corresponding author. Ajmera Transplant Centre, University Health Network 9-MaRS-9111, 585 University Avenue, Toronto, Ontario M5G 2N2, Canada.
E-mail address: deepali.kumar@uhn.ca (D. Kumar).

https://doi.org/10.1111/ajt.17199

Received 27 July 2022; Received in revised form 23 August 2022; Accepted 16 September 2022

1600-6135/© 2022 American Society of Transplantation & American Society of Transplant Surgeons. Published by Elsevier Inc. All rights reserved.
this applies to organ transplant recipients is uncertain, as only 5% of the patients included in this study were immunocompromised. We performed a prospective observational study to determine the impact of early outpatient remdesivir on hospital admission rate in SOTR.

2. Methods

2.1. Study design

We conducted a single-center prospective cohort study at the University Health Network Organ Transplant Program in Toronto, Canada. Since the start of the pandemic, all transplant recipients diagnosed with SARS-CoV-2 infection have been entered into a COVID-19 registry. As of April 3, 2022, BA.2 was the most prevalent sub-lineage (84.2%) in Ontario, followed by BA.1.1 (15.8%). From there, the weekly growth rate of BA.2 was 1.67 times that of BA.1.1, reaching a prevalence of 97.6% on May 8, 2022. Sotrovimab, the treatment of choice in Ontario for preventing disease progression in high-risk patients, was no longer effective against this sub-lineage. Therefore, on April 1st, infusion centers that were previously providing high-risk patients sotrovimab switched to providing outpatient remdesivir. As we aimed to assess the effect of remdesivir for BA.2, we restricted this analysis to patients that had symptom onset starting on April 1, 2022. We included all consecutive SOTR with COVID-19 diagnoses referred to our center from that date. The last patient included had symptom onset on May 5, 2022 in order to have a minimum of 30-day follow-up on all patients.

2.2. Study population

All adult organ transplant recipients with a confirmed diagnosis of symptomatic COVID-19 during the omicron BA.2 wave period were eligible. The diagnosis was required to be confirmed by a rapid antigen test or polymerase chain reaction (PCR). Patients were assessed in the hospital’s COVID care virtual clinic by a physician or nurse specializing in transplant care. They were treated as per current provincial guidelines. All transplant patients were considered high risk and were eligible for 3 doses of intravenous remdesivir if they presented to the clinic within 7 days of symptom onset and were not hypoxic. All decisions regarding treatment were made by the care team that included a transplant infectious diseases physician. For patients presenting within 7 days of symptom onset, the decision to administer any therapy was dependent on how unwell the patient was at the time of assessment, as well as other risk factors including comorbidities and overall immunosuppression. For those that received remdesivir, the recommended dose was 200 mg IV on the first day followed by 100 mg IV on days 2 and 3. Since the course of remdesivir was short, poor kidney function was not considered a contraindication. Patients within 7 days of symptom onset that did not receive remdesivir were given either supportive care only (no active antiviral or anti-inflammatory), nirmatrelvir/ritonavir (Paxlovid), or monoclonal antibody for early treatment. Any patient that presented at >7 days post-symptom onset was offered supportive care only.

Baseline characteristics for the cohort were recorded and included demographics, transplant characteristics, and immunosuppression as well as details of previous COVID-19 infection and vaccination. Comorbidities included: hypertension, diabetes, body mass index ≥30, coronary artery disease, congestive cardiac failure, chronic lung disease, chronic kidney disease (defined as glomerular filtration rate <60 ml/min/1.73 m²), active systemic malignancy (including those on active chemotherapy or radiotherapy, or patients with an advanced disease that could affect the short-term prognosis), and other immunodeficiencies. All patients were followed for a minimum period of 30 days or until the end of the disease course (complete clinical recovery or death). The study was approved by the University Health Network Research Ethics Board and a consent waiver was obtained for data collection.

2.3. Outcomes

The primary outcome evaluated was COVID-19-related hospitalization >24 hours within 30 days of symptom onset. Secondary outcomes included the need for supplemental oxygen (including both patients that needed to start oxygen therapy and those with oxygen at baseline that presented an increase in their requirements), admission to the ICU,
Table 1
Demographic and clinical characteristics of the patients by early remdesivir use

| Characteristics                      | Patients without remdesivir (N = 106) | Patients with remdesivir (N = 86) | p-valuea |
|--------------------------------------|--------------------------------------|-----------------------------------|-----------|
| Age—years (mean ± SD)                | 54.7 ± 14                            | 52.3 ± 13                         | .22       |
| Female sex—no. (%)                   | 36 (34%)                             | 38 (44.2%)                        | .18       |
| Type of transplant—no. (%)           |                                      |                                   |           |
| Kidney                               | 56 (52.8%)                           | 24 (27.9%)                        | <.001     |
| Lung                                 | 12 (11.3%)                           | 25 (29.1%)                        | .003      |
| Liver                                | 20 (18.9%)                           | 16 (18.6%)                        | 1.00      |
| Heart                                | 6 (5.7%)                             | 6 (7%)                            | .77       |
| Other combined transplantsb          | 12 (11.3%)                           | 15 (17.4%)                        | .3        |
| Years since transplant (mean ± SD)   | 7.7 ± 6.5                            | 7.1 ± 6.5                         | .48       |
| Coexisting conditions—no. (%)        |                                      |                                   |           |
| Hypertension                         | 74 (69.8%)                           | 47 (54.7%)                        | .036      |
| Diabetes mellitus                    | 38 (35.8%)                           | 26 (30.2%)                        | .44       |
| BMI > 30                             | 31 (29.2%)                           | 12 (14%)                          | .014      |
| Coronary artery disease              | 17 (16%)                             | 11 (12.8%)                        | .55       |
| Chronic cardiac failure              | 2 (1.9%)                             | 2 (2.9%)                          | 1.00      |
| Chronic lung disease                 | 16 (15.1%)                           | 21 (24.7%)                        | .1        |
| Chronic kidney diseasen              | 51 (48.1%)                           | 39 (45.3%)                        | .77       |
| Active systemic malignancy           | 3 (2.8%)                             | 2 (2.3%)                          | 1.00      |
| Other immunodeficiency               | 1 (0.9%)                             | 1 (1.2%)                          | 1.00      |
| No. of comorbidities (mean ± SD)     | 2.2 ± 1.4                            | 1.9 ± 1.2                         | .089      |
| Immunosuppressive—no. (%)            |                                      |                                   |           |
| Prednisone                           | 83 (73.8%)                           | 70 (81.4%)                        | .72       |
| Daily dose (median, IQR)             | 5 (5 to 5)                           | 5 (5 to 5)                        | .81       |
| Tacrolimus                           | 87 (81.6%)                           | 59 (68.6%)                        | .041      |
| Last level (mean ± SD)               | 7.2 ± 3                              | 8.5 ± 3.6                         | .038      |
| Cyclosporine                         | 17 (16%)                             | 25 (29.1%)                        | .036      |
| Mycophenolate                        | 67 (63.2%)                           | 61 (70.9%)                        | .28       |
| Daily dose (median, IQR)b            | 1000 (1000 to 2000)                  | 1000 (1000 to 2000)               | .37       |
| Azathioprine                         | 15 (14.2%)                           | 9 (10.5%)                         | .51       |
| Daily dose (median, IQR)             | 50 (50 to 75)                        | 75 (50 to 125)                    | 1.00      |
| Sirolimus                            | 4 (3.8%)                             | 4 (4.7%)                          | 1.00      |
| Last sirolimus level (mean ± SD)     | 8.0 ± 1.1                            | 7.5 ± 2.3                         | .74       |
| Rejection last 3 months—no. (%)      | 0 (0%)                               | 1 (1.2%)                          | .45       |
| ATG last 3 months—no. (%)            | 1 (0.9%)                             | 2 (2.3%)                          | .59       |
| Basiliximab last 3 months—no. (%)    | 0 (0%)                               | 1 (1.2%)                          | .45       |
| No. of vaccines                      |                                      |                                   | 1.00      |
| Less than 3 vaccines                 | 11 (10.4%)                           | 8 (9.3%)                          |           |
| 3 or more vaccines                   | 95 (89.6%)                           | 78 (90.7%)                        |           |
| Time since last COVID-19 vaccine-days (median, IQR) | 93 (77 to 144) | 114 (82 to 171) | .18 |
| SARS-CoV-2 reinfection—no. (%)       | 3 (2.8%)                             | 3 (3.5%)                          | 1.00      |

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

a Other combined transplants include: 18 kidney-pancreas, 3 kidney-liver transplant, 3 kidney-heart, 2 lung-kidney, and 1 heart-lung transplant. Chronic kidney disease denotes GFR < 60 ml/min/m2. Other immunodeficiency includes hypogammaglobulinemia. Active systemic malignancy includes: metastatic sigmoid adenocarcinoma, undifferentiated large cell poorly differentiated carcinoma, appendiceal goblet cell adenocarcinoma, breast cancer, and renal cancer.

b Continuous variables p-value estimated using Mann Whitney U-test (Wilcoxon rank-sum). Categorical variables p-value estimated using Fisher’s exact test.

c Mycophenolate sodium doses expressed as mycophenolate mofetil (MMF) equivalent.

Mechanical ventilation, and all-cause mortality. All the secondary outcomes were evaluated within 30 days of COVID-19 symptom onset. Other clinical outcomes registered were the length of hospitalization, and the administration of remdesivir during the hospitalization, dexamethasone, tocilizumab, and baricitinib. We compared the outcomes rate between the groups that received remdesivir before admission. Although three doses of remdesivir were prescribed, patients that received one or two doses were also considered treated. In order to analyze the effect of outpatient remdesivir on the primary outcome of hospital admission, we excluded from the analysis patients that were diagnosed with COVID at the time of admission or during hospitalization.

2.4. Statistical analysis

Demographics and baseline characteristics were analyzed by the primary endpoint of hospitalization. Risk factors were estimated by univariate analysis using Fisher’s exact test to compare categorical variables, the Student’s t-test, and the Mann–Whitney U-test (Wilcoxon rank-sum test) to compare continuous variables. p-values < .05 were considered significant. We estimated the risk of each outcome based on having received remdesivir treatment as an outpatient. We calculated adjusted hazard ratios (HR) and the number needed to treat (NNT) to prevent one admission. We used Cox (proportional hazard) regression to adjust the p value of the association between remdesivir as an outpatient and hospitalization.

For this analysis, we considered the number of comorbidities for each patient rather than individual comorbidities. To select the best Cox regression model we initially included as covariates all variables significantly associated with hospitalization on the univariate analysis (p < .05), and those that showed an unequal distribution between remdesivir treatment groups. We also determined the interaction between different covariates using the likelihood-ratio test. Due to the low number of patients hospitalized during the study (n = 15), we restricted the model to only one covariate. This was done by removing from the model all the covariates that did not produce a significant change in the remdesivir effect (considering 10% or more as the cut point) or did not improve the standard error of the estimation. Of the different possible models, we chose the most accurate one, i.e., the one with the narrowest
Table 2
Demographic and clinical characteristics of the cohort by hospitalization >24 h

| Characteristics | Non-hospitalized patients (N = 177) | Hospitalized patients (N = 15) | p-valuea |
|-----------------|-------------------------------------|--------------------------------|-----------|
| Age—years (mean ± SD) | 52.3 ± 13.2 | 68.4 ± 8.2 | <.001 |
| Female sex—no. (% ) | 70 (39.5%) | 4 (26.7%) | .41 |
| Type of transplant—no. (%) | | | |
| Kidney | 71 (40.1%) | 9 (60%) | .17 |
| Lung | 32 (18.1%) | 5 (33.3%) | .17 |
| Liver | 26 (20.3%) | 0 (0%) | .078 |
| Heart | 12 (6.8%) | 0 (0%) | .6 |
| Other combined transplantsb | 26 (5.1%) | 1 (6.7%) | .7 |
| Years since transplant (mean ± SD) | 7.5 ± 6.6 | 7.2 ± 5.4 | .86 |
| Coexisting conditions—no. (%) | | | |
| Hypertension | 109 (61.6%) | 12 (80%) | .18 |
| Diabetes mellitus | 52 (29.4%) | 12 (80%) | <.001 |
| BMI > 30 | 39 (22%) | 4 (26.7%) | .75 |
| Coronary artery disease | 23 (13%) | 5 (33.3%) | .048 |
| Chronic cardiac failure | 3 (1.7%) | 1 (6.7%) | .28 |
| Chronic lung disease | 33 (18.8%) | 4 (26.7%) | .5 |
| Chronic kidney diseasec | 76 (42.9%) | 14 (93.3%) | <.001 |
| Active systemic malignancyd | 5 (2.8%) | 0 (0%) | 1.00 |
| Other immunodeficiencye | 2 (1.1%) | 0 (0%) | 1.00 |
| No. of comorbidities (mean ± SD) | 1.9 ± 1.3 | 3.5 ± 1.2 | <.001 |
| Immunomodifiers—no. (%) | | | |
| Prednisone | 138 (78%) | 15 (100%) | .044 |
| Daily dose (median, IQR) | 5 (5 to 5) | 5 (5 to 7.5) | .42 |
| Tacrolimus | 133 (75.1%) | 13 (86.7%) | .53 |
| Last level (mean ± SD) | 7.6 ± 3.3 | 8.6 ± 3.6 | .37 |
| Ciclosporine | 40 (22.6%) | 2 (13.3%) | .53 |
| Mycophenolate | 117 (66.1%) | 11 (73.3%) | .78 |
| Daily dose (median, IQR)f | 1000 (1000 to 2000) | 1500 (1000 to 2000) | .61 |
| Azathioprine | 20 (11.3%) | 4 (26.7%) | .099 |
| Daily dose (median, IQR) | 75 (50 to 87.5) | 37.5 (25 to 62.5) | .47 |
| Sirolimus | 8 (4.5%) | 0 (0%) | 1.00 |
| Last sirolimus level (mean ± SD) | 7.7 ± 1.7 | - | |
| Rejection last 3 months—no. (%) | 1 (0.6%) | 0 (0%) | 1.00 |
| ATG last 3 months—no. (%) | 3 (1.7%) | 0 (0%) | 1.00 |
| Basiliximab last 3 months—no. (%) | 1 (0.6%) | 0 (0%) | 1.00 |
| No. of vaccines | | | |
| Less than 3 vaccines | 17 (9.6%) | 2 (13.3%) | .65 |
| 3 or more vaccines | 160 (90.4%) | 13 (86.7%) | .68 |
| Time since last COVID-19 vaccine—days (median, IQR) | 100 (78 to 164) | 125 (75 to 187) | .68 |
| SARS-CoV-2 reinfection—no. (%) | 6 (3.4%) | 0 (0%) | 1.00 |
| Outpatient early remdesivir | 84 (47.5%) | 2 (13.3%) | .013 |

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

a Other combined transplants include: 18 kidney-pancreas, 3 kidney-liver transplant, 3 kidney-heart, 2 lung-kidney, and 1 heart-lung transplant. Chronic kidney disease denotes GFR < 60 ml/min/m². Other immunodeficiency includes hypogammaglobulinemia. Active systemic malignancy includes: metastatic sigmoid adenocarcinoma, undifferentiated large cell poorly differentiated carcinoma, appendiceal goblet cell adenocarcinoma, breast cancer, and renal cancer.

b Continuous variables p-value estimated using Student’s t-test and Mann Whitney U-test (Wilcoxon rank-sum). Categorical variables p-value estimated using Fisher’s exact test.

c Mycophenolate sodium doses expressed as mycophenolate mofetil MMF equivalent.

d Mycophenolate sodium doses expressed as mycophenolate mofetil MMF equivalent.

2.5. Results

Between April 1 and May 5, 2022, a total of 210 organ transplant recipients were assessed for eligibility due to a confirmed COVID-19 diagnosis. Eighteen (8.6%) were excluded because COVID-19 was diagnosed at or during hospitalization. Therefore, 192 patients were included in the analysis and followed for at least 30 days from the COVID-19 diagnosis. Eighty-six of those (44.8%) received remdesivir as an outpatient, and 106 did not. Of the patients that did not receive remdesivir, seven patients received nirmatrelvir/ritonavir (6.6%), and one received bebtelovimab in the United States (0.9%). No other COVID-19 therapies were given to the study population. Figure 1 shows the flow diagram of the study, and the outcomes stratified by early outpatient remdesivir treatment.

The demographic characteristics of patients that did and did not receive remdesivir treatment are shown in Table 1. The median age of the population was 53.6 years (SD, 13.6). Most patients were men (118/192, 61.5%) and transplant types were kidney (80, 41.7%), lung (37, 19.3%), liver (36, 18.8%), and heart (12, 6.3%). The average time from the transplant to the beginning of symptoms was 7.4 years (SD, 6.5). The majority were on triple immunosuppression with prednisone, mycophenolate, and a calcineurin inhibitor. Patients had an average number of 2.1 comorbidities (SD, 1.3), with the most common being hypertension (63%) followed by chronic kidney disease (46%). The study population was highly vaccinated: 47.9% had 4 doses, 42.2% had 3 doses, 6.8% had 2 doses, and 3.1% (6 patients) were unvaccinated. Six patients (3.1%) had a history of COVID-19 greater than 90 days prior to the current diagnosis and were considered to have reinfection.

2.6. Outcomes

During the follow-up period, a total of 15 patients (7.8%) were hospitalized, 5 (2.6%) required supplemental oxygen, 3 (1.6%) were admitted to the ICU, 2 (1%) required mechanical ventilation, and 2 (1%) died. On univariate analysis, age, diabetes mellitus, coronary artery disease, chronic kidney disease, the total number of comorbidities, and chronic prednisone treatment were significantly associated with

confidence interval. Statistical analyses were performed with Stata statistical software, version 15.1 (StataCorp, LLC).
hospitilization (Table 2). Early outpatient remdesivir was the only protective variable. There were no significant differences between allograft types with regards to hospitalization although lung transplant recipients were more likely to be treated with remdesivir whereas kidney transplant recipients were less likely to receive remdesivir. We also did not find any difference based on the number of vaccines, or the time from the last vaccine dose to the infection.

None of the 6 patients with SARS-CoV-2 reinfection were hospitalized, required supplemental oxygen, admission to the ICU, mechanical ventilation, or died. Of the 7 patients that received Paxlovid as outpatients, 2 were hospitalized (24%), but none required oxygen, ICU admission, or died. One patient was admitted for 72 hours due to diarrhea and the other patient was admitted for 25 days due to tacrolimus toxicity in the context of Paxlovid administration. The sole patient that received bgeteblovimab was not admitted or required supplemental oxygen.

2.7. Impact of early outpatient remdesivir

A total of 86 patients (44.8%) received remdesivir as an outpatient within 7 days of symptom onset. Most received 3 doses of the intravenous antiviral, with only 2 patients that received 1 dose. Hospitalization occurred in 2/86 (2.3%) patients that received outpatient remdesivir and 13/106 (12.3%) of those that did not, p = .001. Due to the low rate of events for hospitalization, we did not perform a multivariate analysis to adjust the effect of each variable. Instead, lung transplant and early outpatient remdesivir were the only variables included in the Cox regression model. Using this adjustment, remdesivir use was protective of hospitalization rate, especially in lung transplant recipients. We did not find any association with hospitalization in the univariate analysis, there was a high rate of remdesivir use in lung recipients. Therefore, after adjusting by remdesivir use, there was an increased risk of hospitalization in lung transplant recipients: HR 3.94 (95% CI, 1.31–11.94) (Table 3). Also, the protective effect of remdesivir was greater in lung transplant recipients (NNT 9.2, 95% CI, 8.2–19.3) than in the rest of the population (NNT 26.8, 95% CI, 24.2–55.1).

There was a non-significant (p = .38) reduction in oxygen requirement for patients treated with outpatient remdesivir: only 1/86 (1.2%) patients treated required supplemental oxygen in comparison with 4/106 (3.8%) that were not treated, HR 0.21 (95% CI, 0.02–2.03). No patient in the early remdesivir group was admitted to the ICU, required mechanical ventilation, or died by day 30 of follow-up. There were no differences in the duration of hospitalization in the remdesivir (median 11 days [IQR 8–14]) and no remdesivir (median 6 days [IQR 4–15]) groups.

Six of the 13 hospitalized patients that did not receive remdesivir previously (46.2%), were treated with remdesivir and dexamethasone during admission. Apart from that, 5/15 (33.3%) received tocilizumab. One of the two admitted patients that received remdesivir as an outpatient (50%) received another course of remdesivir and dexamethasone during the hospitalization. None of the patients included in the study received baricitinib. This information is summarized in Figure 1.

3. Discussion

We report a real-world prospective observational study of COVID-19-positive organ transplant recipients during the omicron BA.2 wave. In our population, the administration of early intravenous remdesivir was the only variable associated with a reduction in disease severity. Consistent with previous literature, advanced age and multiple comorbidities remain significant risk factors for severe disease during BA.2.

Similar to omicron BA.1 studies, that showed a reduction in the COVID-19 severity when compared with non-omicron variants, the trend toward better outcomes continued during the omicron BA.2 wave.3,7,16 However, our population was also highly vaccinated with either three or four doses of the COVID-19 vaccine which is the most likely contributor to overall better outcomes. Another possibility includes a decrease in the virulence of BA.2 compared to previous variants and immunity due to prior COVID-19 infection. Among allograft types, the lung was the only one associated with a higher risk of hospitalization, which is consistent with the higher risk of severe respiratory infections in this group. Contrary to previous studies, in our cohort prednisone treatment as maintenance immunosuppression was associated with a higher hospitalization rate.16

In our study, remdesivir, when given within the first 7 days of symptom onset, was effective in reducing the hospitalization rate, especially in lung transplant recipients. We did not find that remdesivir administration reduced the need for supplemental oxygen. This is likely
explained because of the small number of patients that needed oxygen. It is remarkable that no patient that received remdesivir needed ICU care or died due to COVID-19. This is despite a greater proportion of lung transplant recipients in this group, which has historically had poor COVID-19 outcomes. Remdesivir has demonstrated efficacy in the prevention of severe COVID-19 outcomes in the general population, but previous studies did not include a significant number of transplant recipients, and none has been performed during the omicron BA.2 wave.\(^{12,13}\) This is particularly relevant because, contrary to what happened during the BA.1 wave when sotrovimab was a highly effective treatment, this subvariant is not susceptible to most of the currently available monoclonal antibody therapies.\(^{14}\)

Following proportional recommendations, three doses of remdesivir were only given to patients who were within 7 days of symptoms onset. Despite this, some patients within 7 days of symptoms did not receive remdesivir. This was primarily due to: patients being considered a low risk at first assessment, lack of an infusion center in their area, not being able to access the infusion center, or refusal to have therapy. The level of immunization (including vaccination status or antibody titers) was not taken into consideration when prescribing remdesivir.

Our study has some limitations. Since this was not a randomized trial, there may be differences in the groups that received remdesivir vs. no remdesivir. For example, those that did not receive remdesivir may have had a longer time from symptom onset to the first assessment. Nevertheless, the baseline characteristics of both groups were very similar, and any characteristics with an unequal distribution between groups were considered in the multivariate analysis. Other limitations included the use of a rapid antigen test as the diagnostic tool used in most of our health laboratory during the study period were omicron BA.2.\(^{15}\) Also, patients diagnosed at the time of admission were excluded, since hospitalization was our primary outcome. This may underestimate the severity of the omicron BA.2 variant in organ transplant recipients.

In summary, this study provides evidence of the real-world utility of early remdesivir therapy in transplant patients infected with SARS-CoV-2 during the omicron BA.2 wave. In our population, remdesivir treatment was independently associated with a significant reduction in the hospitalization rate even after adjusting for age, comorbidities, and type of transplant, thus highlighting the importance of rapid diagnosis of COVID-19 and the beneficial effect of early therapies in organ transplant recipients.

**Funding information**

No funding was received for this study.

**Disclosure**

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. D.K. has received research grants from Roche and GSK and advisory fees from Roche, GSK, Merck, Astellas, Sanofi, and Exevir. A.H. has received clinical trials grant from Merck and advisory fees from Merck. All other authors have no relevant disclosures.

**ORCID**

Javier T. Solera \(\text{https://orcid.org/0000-0001-6833-6625}\)
Berta G. Arboi \(\text{https://orcid.org/0000-0003-2880-3780}\)
Deepali Kumar \(\text{https://orcid.org/0000-0003-1961-0477}\)

**References**

1. Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. *Clin Infect Dis*. 2021;73(11):e4090–e4099. https://doi.org/10.1093/cid/cia1097.
2. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800–1808.
3. Marinelli T, Ferreira VH, Ieroullo M, et al. Prospective clinical, virologic, and immunologic assessment of COVID-19 in transplant recipients. *Transplantation*. 2021; 105(10):2175–2183.
4. Embi PJ, Levy MR, Naleway AL, et al. Effectiveness of 2-dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizations among immunocompromised adults - nine states, January-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(44):1553–1559.
5. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med*. 2021;385(13):1244–1246.
6. Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals. U.S. Food and Drug Administration; 2021. Updated August 12, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-scattermoreimmunocompromised.
7. Solera JT, Arboi BG, Alahzarni A, et al. Impact of vaccination and early monoclonal antibody therapy on COVID-19 outcomes in organ transplant recipients during the omicron wave. *Clin Infect Dis*. 2022; ciac324. https://doi.org/10.1093/cid/ciac324.
8. Berani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *Nature*. 2022;604(7906):553–556.
9. Plans D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 omicron to antibody neutralization. *Nature*. 2022;602(7908):671–675.
10. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;385(15):1397–1408.
11. Fishbane S, Hirsch JS, Nair V. Special considerations for Paxlovid treatment among SARS-CoV-2 infected transplant recipients. *Am J Kidney Dis*. 2022;75(10):e524–e528.
12. Garibaldi BT, Wang K, Robinson ML, et al. Real-world effectiveness of Remdesivir in transplant recipients in this group, which has historically had poor COVID-19 outcomes. Remdesivir has demonstrated efficacy in the prevention of severe COVID-19 outcomes in the general population, but previous studies did not include a significant number of transplant recipients, and none has been performed during the omicron BA.2 wave.\(^{12,13}\) This is particularly relevant because, contrary to what happened during the BA.1 wave when sotrovimab was a highly effective treatment, this subvariant is not susceptible to most of the currently available monoclonal antibody therapies.\(^{14}\)