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TITLE:

Short-course Early Outpatient Remdesivir Prevents Severe Disease due to COVID-19 in Organ Transplant Recipients During the Omicron BA.2 Wave

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Summary:

In an organ transplant population with vaccine breakthrough COVID-19, this prospective study shows that outpatient treatment with remdesivir within seven days of symptom onset is protective of hospitalization.

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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

SD standard deviation

SOTr solid organ transplant recipient

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 and multiple comorbidities were risk factors for hospitalization. Early remdesivir significantly decreased the hospitalization rate: adjusted hazard ratio 0.12 (95%CI: 0.03 to 0.057). The adjusted number needed to treat to prevent one hospitalization was 15.2 (95%CI: 13.6 to 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.

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 (4). Booster doses of COVID-19 vaccine were implemented in the transplant population based on immunogenicity studies, and they have shown to attenuate disease severity in transplant recipients. However, breakthrough infections continue to occur (5, 6).

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 (7-9). 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 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.

Methods

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 (14). 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 diagnosis referred to our center from that date. The last patient included had a symptom onset on May 5, 2022 in order to have a minimum of 30-day follow-up on all patients.

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 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 (15). 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 200mg IV on the first day followed by 100mg 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/1.73m^2), 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.

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, 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 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 the 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.

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, and the Student's t-test and the Mann-Whitney U-test (Wilcoxon rank-sum test) to compare

continuous variables. P values <0.05 were considered significant. We estimated the risk of each outcome based on the having received remdesivir treatment as outpatient. We calculated adjusted hazard ratios (HR) and 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 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 ($p<0.05$), and those that showed an unequal distribution between remdesivir treatment groups. We also determined interaction between different covariates using 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. Between the different possible models, we chose the most accurate one, ie the one with narrowest confidence interval. Statistical analyses were performed with Stata statistical software, version 15.1 (StataCorp, LLC, College Station, TX, USA).

Results

Between April 1 and May 5, 2022, a total of 210 organ transplant recipients were assessed to eligibility due to confirmed COVID-19 diagnosis. Eighteen (8.6%) were excluded because COVID-19 was diagnosed at or during the

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 by remdesivir treatment group are shown in Table 1. The mean age of the population was 54.5 years (IQR:43.9-63.6). 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 (46.9%). 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.

Outcomes

During the follow-up period, a total of 15 patients (17.8%) 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 hospitalization (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 a 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 bebtelovimab was not admitted or required supplemental oxygen.

Impact of early outpatient remdesivir

A total of 86 patients (81.1%) received remdesivir as 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=0.013. 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 with a hazard ratio (HR) 0.12 (95% CI, 0.03 to 0.057) and adjusted number needed to treat (NNT) to prevent one admission 15.2 (95% CI, 13.6 to 31.4) (Table 2). Figure 2 displays the survival analysis of hospitalization rate by remdesivir group.

Interestingly, although lung transplant was not associated 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 to 11.94) (Table 3). Also, the protective effect of remdesivir was greater in lung transplant recipients (NNT 9.2, 95%CI, 8.2 to 19.3) than in the rest of the population (NNT 26.8, 95%CI, 24.2 to 55.1).

There were a non-significant (p=0.38) reduction in oxygen requirement for patients treated with outpatient remdesivir: only 1/86 (1.2%) patient treated required supplemental oxygen in comparison with 4/106 (3.8%) that were not treated, HR 0.21 (95% CI, 0.02 to 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 the admission. Apart from that, 5/15 (33.3%) received tocilizumab. One of the two

admitted patients that received remdesivir as 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.

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 of 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 towards better outcomes continued during the Omicron BA.2 wave (3, 16). However, our population was also highly vaccinated with either three or four doses of COVID-19 vaccine which is the most likely contributor to overall better outcomes. Another possibility includes a decrease in virulence of BA.2 compared to previous variants and immunity due to prior COVID-19 infection. Among allograft types, 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 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 numbers 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 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 antibodies therapies (8, 9).

Following provincial 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 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 first assessment. Nevertheless, baseline characteristics of

both groups were very similar, and any characteristics with an unequal distribution between groups were included in the multivariate analysis. Other limitations included the use of rapid antigen test as the diagnostic tool used in most of our patients, though all patients that were eventually hospitalized had a SARS-CoV-2 PCR performed. Only a few patients had sequencing to confirm the COVID-19 variant, but >90% of isolates submitted to public health laboratory during the study period were Omicron BA.2 (14). Also, patients diagnosed at the time of the admission were excluded, since hospitalization was our primary outcome. This may underestimate the severity of Omicron BA.2 variant in organ transplant recipients.

In summary, this study provides evidence of 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:

No funding was received for this study.

Conflict of Interest:

D.K. has received research grants from Roche, GSK and advisory fees from Roche, GSK, Merck, Astellas, Sanofi, Exevir. A.H. has received clinical trials grant from Merck and advisory fees from Merck. All other authors have no relevant disclosures.

Data Availability Statement:

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

Figure Legends:

Figure 1: Flow diagram of the study population and outcomes stratified by remdesivir treatment

Figure 2: Kaplan-Meier curve of time to hospitalization through 30 days of follow-up by remdesivir treatment group. P value estimated with log-rank test.

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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 value †
Age – years (mean±SD)	54.7±14	52.3±13	0.22
Female sex – no. (%)	36 (34 %)	38 (44.2%)	0.18
Type of transplant – no. (%)			
Kidney	56 (52.8%)	24 (27.9%)	<0.001
Lung	12 (11.3%)	25 (29.1%)	0.003
Liver	20 (18.9%)	16 (18.6%)	1.00
Heart	6 (5.7%)	6 (7%)	0.77
Other combined transplants*	12 (11.3%)	15 (17.4%)	0.3
Years since transplant (mean±SD)	7.7±6.5	7.1±6.5	0.48
Coexisting conditions – no. (%)			
Hypertension	74 (69.8%)	47 (54.7%)	0.036
Diabetes mellitus	38 (35.8%)	26 (30.2%)	0.44
BMI >30	31 (29.2%)	12 (14%)	0.014
Coronary artery disease	17 (16%)	11 (12.8%)	0.55
Chronic cardiac failure	2 (1.9%)	2 (2.3%)	1.00
Chronic lung disease	16 (15.1%)	21 (24.7%)	0.1
Chronic kidney disease*	51 (48.1%)	39 (45.3%)	0.77
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	0.089
Immunosuppressant – no. (%)			
Prednisone	83 (78.3%)	70 (81.4%)	0.72
Daily dose (median, IQR)	5 (5 to 5)	5 (5 to 5)	0.81
Tacrolimus	87 (82.1%)	59 (68.6%)	0.041
Last level (mean±SD)	7.2±3	8.5±3.6	0.038
Cyclosporine	17 (16%)	25 (29.1%)	0.036
Mycophenolate	67 (63.2%)	61 (70.9%)	0.28
Daily dose (median, IQR)¶	1000 (1000 to 2000)	1000 (1000 to 2000)	0.37
Azathioprine	15 (14.2%)	9 (10.5%)	0.51
Daily dose (median, IQR)	50 (50 to 75)	75 (50 to 125)	0.18
Sirolimus	4 (3.8%)	4 (4.7%)	1.00
Last sirolimus level (mean±SD)	8.0±1.1	7.5±2.3	0.74
Rejection last 3 months – no. (%)	0 (0%)	1 (1.2%)	0.45
ATG last 3 months – no. (%)	1 (0.9%)	2 (2.3%)	0.59
Basiliximab last 3 months – no. (%)	0 (0%)	1 (1.2%)	0.45
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)	0.18
SARS-CoV-2 reinfection – no. (%)	3 (2.8 %)	3 (3.5%)	1.00

* Other combined transplants include: 18 kidney-pancreas, 3 kidney-liver transplant, 3 kidney-heart, 2 lung-kidney and 1 heart-lung transplant. BMI: body mass index, IQR: Interquartile range, SD: Standard deviation. Chronic kidney disease denotes GFR<60ml/min/m^2. 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.

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

¶ mycophenolate sodium doses expressed as mycophenolate mofetil (MMF) equivalent.

Table 2. Demographic and Clinical Characteristics of the Cohort by Hospitalization >24h

Characteristics	Non-hospitalized patients (N=177)	Hospitalized patients (N=15)	P value †
Age – years (mean±SD)	52.3±13.2	68.4±8.2	<0.001
Female sex – no. (%)	70 (39.5 %)	4 (26.7%)	0.41
Type of transplant – no. (%)			
Kidney	71 (40.1%)	9 (60%)	0.17
Lung	32 (18.1%)	5 (33.3%)	0.17
Liver	36 (20.3%)	0 (0%)	0.078
Heart	12 (6.8%)	0 (7%)	0.6
Other combined transplants*	26 (5.1%)	1 (6.7%)	0.7
Years since transplant (mean±SD)	7.5±6.6	7.2±5.4	0.86
Coexisting conditions – no. (%)			
Hypertension	109 (61.6%)	12 (80%)	0.18
Diabetes mellitus	52 (29.4%)	12 (80%)	<0.001
BMI >30	39 (22%)	4 (26.7%)	0.75
Coronary artery disease	23 (13%)	5 (33.3%)	0.048
Chronic cardiac failure	3 (1.7%)	1 (6.7%)	0.28
Chronic lung disease	33 (18.8%)	4 (26.7%)	0.5
Chronic kidney disease*	76 (42.9%)	14 (93.3%)	<0.001
Active systemic malignancy*	5 (2.8%)	0 (0%)	1.00
Other immunodeficiency*	2 (1.1%)	0 (0%)	1.00
No. of comorbidities (mean±SD)	1.9±1.3	3.5±1.2	<0.001
Immunosuppressant – no. (%)			
Prednisone	138 (78%)	15 (100%)	0.044
Daily dose (median, IQR)	5 (5 to 5)	5 (5 to 7.5)	0.42
Tacrolimus	133 (75.1%)	13 (86.7%)	0.53
Last level (mean±SD)	7.6±3.3	8.6±3.6	0.37
Cyclosporine	40 (22.6%)	2 (13.3%)	0.53
Mycophenolate	117 (66.1%)	11 (73.3%)	0.78
Daily dose (median, IQR) ¶	1000 (1000 to 2000)	1500 (1000 to 2000)	0.61
Azathioprine	20 (11.3%)	4 (26.7%)	0.099
Daily dose (median, IQR)	75 (50 to 87.5)	37.5 (25 to 62.5)	0.47
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			0.65
Less than 3 vaccines	17 (9.6%)	2 (13.3%)	
3 or more vaccines	160 (90.4%)	13 (86.7%)	
Time since last COVID-19 vaccine – days (median, IQR)	100 (78 to 164)	125 (75 to 187)	0.68
SARS-CoV-2 reinfection – no. (%)	6 (3.4 %)	0 (0%)	1.00
Outpatient early remdesivir	84 (47.5%)	2 (13.2%)	0.013

* Other combined transplants include: 18 kidney-pancreas, 3 kidney-liver transplant, 3 kidney-heart, 2 lung-kidney and 1 heart-lung transplant. BMI: body mass index, IQR: Interquartile range, SD: Standard deviation. Chronic kidney disease denotes GFR<60ml/min/m^2. 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.

† 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.

¶ mycophenolate sodium doses expressed as mycophenolate mofetil MMF equivalent

Table 3. Variables associated with hospitalization. *

Variable	Not hospitalized (N=177)	Hospitalized (N=15)	Hazard ratio (95% CI) †	p value †
Age – years (mean±SD)	52.3±13.2	68.4±8.2	–	<0.001
Lung transplant †	32 (18.1%)	5 (33.3%)	3.94 (1.31 to 11.94)	0.015
Diabetes mellitus	55 (29.4%)	12 (80%)	–	<0.001
Coronary artery disease	23 (13%)	5 (33.3%)	–	0.048
Chronic kidney disease	76 (42.9%)	14 (93.3%)	–	<0.001
No. of comorbidities (mean±SD)	1.9±1.3	3.5±1.2	–	<0.001
Prednisone	138 (78%)	15 (100%)	–	0.044
Early outpatient remdesivir – no. (%) †	84 (47.5%)	2 (13.3%)	0.12 (0.03 to 0.57)	0.007

* SD: Standard deviation.

† Adjusted hazard ratios and p-values were estimated with Cox regression using as covariables early outpatient remdesivir and lung transplant. For the rest of variables, p-value was estimated using Student's t-test for continuous variables, and Fisher's exact test for categorical variables.

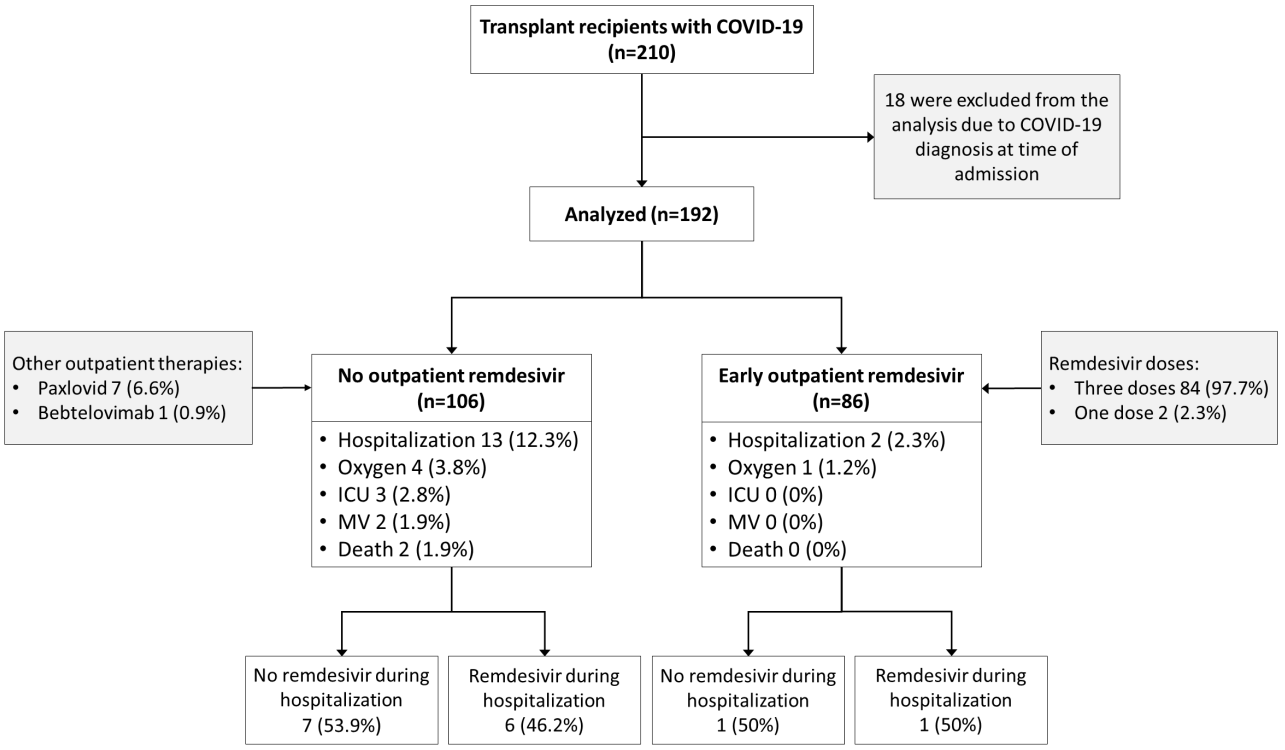

Figure 1. Flow diagram of the study population and outcomes stratified by remdesivir treatment. COVID-19 coronavirus disease 2019, ICU intensive care unit admission, MV mechanical ventilation requirement. Hospitalization indicates COVID-related hospitalization, death indicates all-cause mortality. All the outcomes were evaluated within 30 days of COVID-19 diagnosis.

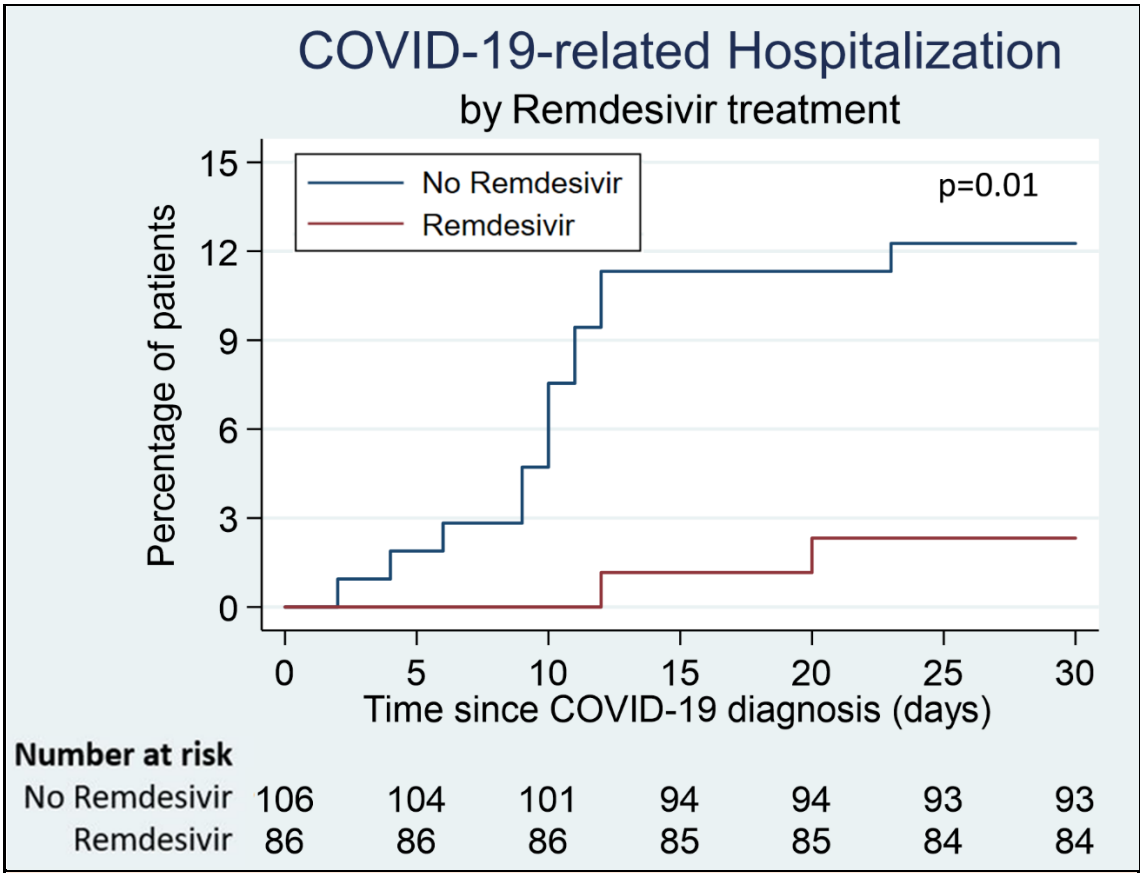

Figure 2. Kaplan-Meier curve of time to hospitalization through 30 days of follow-up by remdesivir treatment group. P value estimated with log-rank test.