# COVID-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment

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## ABSTRACT

*Objectives:* The lack of effective treatments for coronavirus disease 2019 (COVID-19) has mandated the repurposing of several drugs, including antiretrovirals and remdesivir (RDV). These compounds may induce acute kidney injury and are not recommended in patients with poor renal function, such as kidney transplant (KTx) recipients.

*Methods:* The records of 42 KTx recipients with COVID-19 were reviewed. Some of them were receiving antiretrovirals ($n = 10$) or RDV ($n = 8$) as part of COVID-19 management. Most patients were male (71%) and their median age was 52 years. The median glomerular filtration rate in these patients was 56 ml/min. Regarding disease severity, 36% had mild disease, 19% had moderate disease, 31% had severe disease, and 12% had critical disease. Subgroups, i.e., patients receiving antiretrovirals, RDV, or no antivirals, were comparable in terms of patient age, comorbidities, and immunosuppression.

*Results:* Seven patients (16.6%) died during hospitalization. Acute kidney injury was found in 24% of KTx recipients at admission. Upon discharge, estimated glomerular filtration rate (eGFR) increased in 32% and decreased in 39% of the KTx recipients compared with the admission rate. The decrease was more prevalent in the RDV group (80%) compared with KTx recipients without any antiviral treatment (29%) ($p < 0.05$). Most patients (62%) returned to baseline eGFR values within 1 month of discharge. The proportion was similar between the patients receiving antiviral treatment and those not receiving this treatment.

*Conclusions:* KTx recipients run a high risk of COVID-19-related renal impairment. Antivirals appear to be safe for use without major risks for kidney injury.

## Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic continues to ravage the world and claim the lives of thousands of individuals every day. COVID-19 patients may develop different degrees of disease severity, varying from mild forms to critical disease, evolving with acute respiratory distress syndrome, sepsis, and multiorgan failure (Cummings et al., 2020; Karagiannidis et al., 2020). Severe forms result from a combination of the ensuing cytokine storm, the procoagulant state, and the direct viral tropism for various organs. Advanced age, the presence of multiple comorbidities, and certain medications have been repeatedly confirmed as risk factors for critical disease and negative outcomes (Cummings et al., 2020; Zhou et al., 2020). Organ transplant recipients usually present concurrent comorbidities and increased frailty, and receive long-term immunosuppressive medications, placing them at much higher risk of an unfavourable outcome (Kates et al., 2020; Ravanan et al., 2020; Oltean et al., 2020).

The lack of specific antiviral medications against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the rapid repurposing of several drugs, including several antiretrovirals (darunavir and lopinavir). Antiretrovirals are generally

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prescribed along with a pharmacokinetic booster (ritonavir or cobicistat) aimed at blocking their cytochrome P450 3A (CYP3A)-mediated metabolism and prolonging their half-life (Dhampalwar et al., 2020). Antiretroviral therapies have previously been associated with acute kidney injury (AKI), particularly interstitial nephritis and proximal tubular injury (Parkhie et al., 2010). Likewise, several randomized controlled trials have reported a significantly higher frequency of renal severe adverse events in COVID-19 patients receiving the lopinavir/ritonavir combination, particularly in intensive care patients (Dhampalwar et al., 2020; Cao et al., 2020).

Initially developed as an investigational agent for Ebola, remdesivir (RDV) is a nucleotide analogue that inhibits viral RNA-dependent RNA polymerase and interferes with viral RNA replication. RDV is not recommended in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m$^2$, unless the potential benefit outweighs the potential risk (Adamsick et al., 2020). Although there are concerns about its potential toxicity in patients with kidney disease, data from randomized controlled trials in COVID-19 patients with normal kidney function have not demonstrated an increased risk of renal adverse events (Wang et al., 2020; Beigel et al., 2020), and some centres have lifted eGFR restrictions on RDV, although safety data are scarce and more information is needed (Adamsick et al., 2020).

The calcineurin inhibitors (CNI) cyclosporine A and tacrolimus form the mainstay of immunosuppression in organ transplantation. Both drugs are metabolized by CYP3A in the liver and the intestine, and are nephrotoxic at higher concentrations (Gregoire et al., 2020). As the boosters ritonavir and cobicistat can inhibit CYP3A, it has been expected that CNI would increase (Elens et al., 2020). Although one of the critical steps in managing transplanted patients has been lowering the immunosuppression (Oltean et al., 2020; Maggiore et al., 2020), there has been increasing concern about supratherapeutic CNI levels that may negatively impact renal function. Moreover, this could raise confusion with other causes of renal dysfunction, most notably acute rejection.

An analysis of the renal function in transplant recipients with COVID-19 receiving different antivirals has not been performed so far. As this patient group usually has impaired kidney function and prolonged use of nephrotoxic drugs, we set out to analyse the short-term effects of two different types of antiviral drugs in a cohort of renal transplant (KTx) recipients.

## Patients and methods

A retrospective review was performed of all patients who underwent kidney transplantation at the Clinical Institute of Urology and Renal Transplantation in Cluj-Napoca, Romania, who were alive on April 1, 2020 and became ill with COVID-19 between April 1 and October 10, 2020. COVID-19 positivity was defined as a positive result for SARS-CoV-2 RNA on real-time PCR assay of a nasopharyngeal swab, as well as typical symptoms such as a temperature >38 °C and respiratory, gastrointestinal, neurological, or general symptoms.

In the first part of the study (April–July 2020), the COVID-19 treatment protocol recommended in Romania was based on hydroxychloroquine (Plaquenil, Sanofi). Hydroxychloroquine was started with a loading dose of 400 mg orally twice daily for 1 day, and then continued at 200 mg orally twice daily for 7–10 days. Caution was taken in individuals with pre-existing QT prolongation or those at risk of QT prolongation. Lopinavir/ritonavir (LPV/r) (Kaletra, AbbVie, Ludwigshafen, Germany), darunavir/ritonavir (DRV/r) (Prezista, Janssen-Cilag SpA, Latina, Italy), or darunavir/cobicistat (DRV/c) (Rezolsta, Janssen-Cilag) were generally added in those with mild and moderate forms with adequate renal function (GFR > 30 ml/min). LPV/r was given at a dose of 400/100 mg twice daily for 7–10 days. From mid-July 2020, RDV was added to the treatment protocol in more severe cases, while antiretrovirals were phased out. When available, RDV was administered at a dose of 200 mg/day on the first day, followed by 100 mg/day over the next 4 days, given as an intravenous infusion. Dexamethasone and antibiotics were also given at the discretion of the medical teams attending the patients. The use of anticoagulation using low molecular weight heparin (LMWH) was recommended in hospitalized patients.

Immunosuppression was reduced by holding the antimetabolite (mycophenolate mofetil (MMF) or mycophenolic acid (MPA)), with or without adjustment of CNI. Tacrolimus was withdrawn in patients receiving antiretrovirals and adjusted to maintain a trough level of 4–6 ng/ml in the other patients. Steroids were either kept at the maintenance dose or converted to intravenous for stress dosing.

Three subgroups were defined within the patient cohort: patients receiving antiretrovirals, patients receiving RDV, and patients receiving neither. All available medical records of the patients were reviewed, and data on demographics, medical history, comorbidities, therapeutic interventions (antivirals, antibiotics, changes in immunosuppression, corticosteroid therapies,

**Table 1**
Patient demographics and baseline immunosuppression.

|  | All patients (n = 42) | Antiretrovirals (n = 10) | Remdesivir (n = 8) | No antivirals (n = 24) |
|---|---|---|---|---|
| **Male** (n %) | 30 (71) | 9 (90) | 6 (75) | 15 (63) |
| **Age** (median/range) | 52 (20–72) | 56 (20–62) | 51.5 (40–58) | 52 (26–72) |
| **Months from transplant** (median, range) | 58 (5–214) | 83 (5–152) | 102 (9–180) | 48 (8–214) |
| **Comorbidities** |  |  |  |  |
| **Hypertension**, n (%) | 27 (64) | 6 (67) | 6 (75) | 15 (60) |
| **Diabetes**, n (%) | 11 (26) | 2 (22) | 1 (14) | 8 (32) |
| **CCI** (median range) | 3 (2–8) | 3 (2–5) | 3 (2–4) | 3 (2–8) |
| **Baseline eGFR** (median range) | 56 (20–120) | 72 (33–120) | 42 (20–71) | 59 (27–104) |
| **Baseline immunosuppression**, n (%) |  |  |  |  |
| **Tacrolimus** | 41 (98) | 9 (90) | 8 (100) | 24 (100) |
| **Cyclosporine A** | 1 (2) | 1 (10) | - | - |
| **Antimetabolites** | 42 (100) | 10 (100) | 8 (100) | 24 (100) |
| **Low-dose steroids** | 37 (88) | 9 (100) | 6 (86) | 22 (85) |

CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate (ml/min/1.73 m$^2$).

respiratory support), and outcomes were collected and analysed. Disease severity was classified from mild to critical (COVID-19 Treatment Guidelines Panel, 2020). The comorbidity assessment was performed using the age-adjusted Charlson comorbidity index (CCI) (Oltean et al., 2012). CCI includes 19 different medical conditions, and each comorbid disorder is graded from 1 to 6 points to sum an index score. Additional points were added for age, and each decade over the age of 40 years was assigned a comorbidity score of 1. Renal function was assessed on data collected 1–2 months before COVID-19, at admission, at discharge, and 1 month after hospital discharge (or the resolution of symptoms) using the CKD-EPI formula. AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in baseline serum creatinine by $\geq 0.3$ mg/dl within 48 hours, or a 1.5–1.9 times increase in serum creatinine from baseline within 7 days (Thomas et al., 2015). The study was approved by the Institutional Review Board of the Clinical Institute of Urology and Renal Transplantation (4/2020).

### Statistical analyses

Discrete data are described as the frequency expressed as a percentage. Continuous data are expressed as the median and range unless stated otherwise. Given the small group size and data distribution, the Kruskal–Wallis test and Mann–Whitney $U$-test were used for the data analysis. Fisher's exact test was employed for analyses of contingency tables. A $p$-value <0.05 was considered significant.

## Results

### Patients

A total 1467 KTx recipients were in follow-up with a functioning graft at the study centre and 42 of these contracted COVID-19 during the study period, corresponding to a prevalence of 2.86%. The characteristics of all 42 SARS-CoV-2-positive KTx recipients are presented in Table 1, both as a single patient cohort and separately for the three subgroups according to the treatment

received (antiretrovirals, RDV, and no antivirals). Overall, the median patient age was 52 years (range 20–72 years), and 71% of the entire cohort were male. Median baseline eGFR for the entire cohort was 50 ml/min/1.73 m$^2$ (range 20–120 ml/min/1.73 m$^2$), whereas median CCI was 3 (range 2–8). Four patients (9.5%) received their transplants in the year preceding the COVID-19 infection. Disease severity was mild in 16 cases (38%), moderate in eight (19%), severe in 13 (31%), and critical in five (12%).

The three subgroups, i.e., patients receiving antiretrovirals, RDV, or no antivirals, did not differ in terms of patient age, comorbidities (as reflected by CCI), or baseline immunosuppression. Patients receiving antiretrovirals had significantly higher baseline eGFR than those receiving RDV (70 ± 26 vs 42 ± 14 ml/min/1.73 m$^2$, $p < 0.05$). KTx recipients not receiving antivirals had significantly more mild and moderate disease forms ($p < 0.001$).

### Patient management and outcomes

Details on patient management are presented in Table 2. Eighteen patients (43%) required supplemental oxygen and eight patients (19%) were admitted to the intensive care unit. All but two patients had their immunosuppression lowered: the antimetabolite was discontinued in 36 (86%) and reduced in the remaining six (14%). Tacrolimus was withdrawn in 11 cases (26%) and reduced in 14 (33%). Thirty-six patients (86%) received anticoagulation with LMWH or non-vitamin K antagonist oral anticoagulants (NOAC).

In the antiretrovirals group, all patients had the antimetabolite (mycophenolate mofetil) discontinued. Also, tacrolimus was temporarily withheld in six patients (60%) and reduced in the remaining four due to the risk of supratherapeutic concentrations secondary to pharmacological interactions. In the RDV group, the antimetabolite was suspended in all patients, whereas tacrolimus was discontinued in half of the patients and reduced in a further two (25%). Twenty-one of the patients (88%) receiving no antivirals had their antimetabolite withdrawn, while the other two received lower doses. Three patients (12.5%) had tacrolimus suspended, while a further 10 (42%) received a lower dose. Further information is given in **Supplementary Material** Table S1.

**Table 2**
Disease severity, management, and outcome

| | All patients (n = 42) | Antiretrovirals (n = 10) | Remdesivir (n = 8) | No antivirals (n = 24) |
|---|---|---|---|---|
| **Disease severity** | | | | |
| Mild | 16 (38) | - | 2 (25) | 14 (58) |
| Moderate | 8 (19) | 4 (40) | - | 4 (17) |
| Severe | 13 (31) | 4 (40) | 4 (50) | 5 (21) |
| Critical | 5 (12) | 2 (20) | 2 (25) | 1 (4) |
| **Chest radiology** | | | | |
| Bilateral findings | 18/25 | 7/7 | 4/5 | 7/13 |
| **Treatment** | | | | |
| MMF reduction/ withdrawal | 38 (90) | 10 (100) | 8 (100) | 20 (83) |
| CNI reduction/withdrawal | 25 (60) | 10 (100) | 6 (75) | 9 (38) |
| HCQ | 16 (38) | 8 (80) | 2 (25) | 6 (25) |
| Tocilizumab | 2 (5) | - | 1 (13) | 1 (4) |
| LMWH and NOAC | 37 (81) | 10 (100) | 8 (100) | 19 (79) |
| Dexamethasone | 19 (45) | 6 (60) | 4 (50) | 9 (38) |
| Oxygen therapy | 18 (43) | 6 (60) | 6 (75) | 6 (25) |
| Intensive care admission | 7 (17) | 3 (30) | 3 (38) | 1 (4) |
| **Outcome** | | | | |
| Discharged | 35 (83) | 8 (80) | 5 (63) | 22 (92) |
| Dead | 7 (17) | 2 (20) | 3 (37) | 2 (8) |

CNI, calcineurin inhibitors; CRRT, continuous renal replacement therapy; HCQ, hydroxychloroquine; LMWH, low molecular weight heparin; MMF, mycophenolate mofetil; NOAC, non-vitamin K antagonist oral anticoagulants. Data are presented as number/total number of available observations or number (percent).
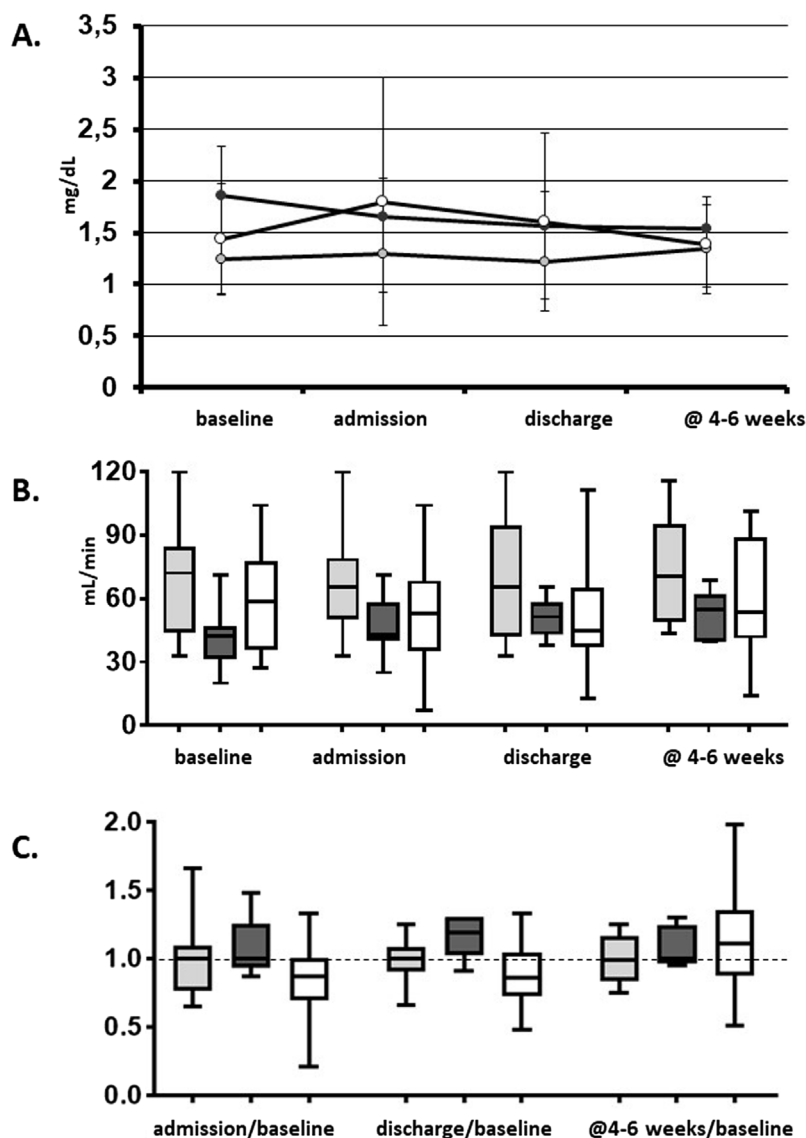
**Figure 1.** Renal function during COVID-19 and in the early post-infection period shown as serum creatinine (A), estimated glomerular filtration rate (eGFR) (B), and the ratios between eGFR at admission, discharge, and follow-up and baseline eGFR (C) in patients receiving antiretrovirals (light grey), remdesivir (dark grey), and standard of care only (white). Error bars show the lowest/highest values.

Seven patients (16.6%) died, all within 28 days of the COVID-19 diagnosis: three had the severe COVID-19 form, while four had critical disease. Patients who ultimately did not survive had higher CCI compared with survivors: median 3 (range 2–8) vs 4 (range 3–8) ($p$ = 0.01). Two patients (20%) in the antiretrovirals group, three in the RDV group (37.5%), and two in the group receiving no antivirals (8%) died during the initial hospitalization. The remaining patients were discharged at home and had at least 1 month of follow-up. No rejection episodes have been recorded so far.

*Renal function*

Baseline eGFR values for the entire patient cohort, as well as for the three subgroups, are shown in Table 1. Patients receiving antiretrovirals had a higher mean baseline eGFR than those receiving RDV. Nineteen patients (33%) had signs of impaired kidney function upon admission, as reflected by increased

creatinine or a lower eGFR compared to pre-COVID-19 values (Figure 1). Patients who ultimately did not survive had lower mean baseline eGFR compared with survivors (41 ± 19 vs 60 ± 24, $p$ = 0.03). The proportion of patients presenting with worsening of kidney function was similar across the three groups (40%, 37.5%, and 54% in the antiretrovirals, RDV, and no antivirals groups, respectively).

Upon admission, AKI (as defined by KDIGO) was present in 10 patients (24%), showing mild (two patients), moderate (four patients), severe (three patients), and critical (one case) COVID-19 severity. Two patients, one in the antiretrovirals group and one in RDV group, received continuous renal replacement therapy during hospitalization, both of whom ultimately died.

Upon discharge, eGFR was higher (>2 ml/min) than the value at admission in 32% of the patients and lower in 39% of the patients. The latter proportion appeared significantly higher in the group receiving RDV (80%) compared with the patients without antiviral

treatment (29%) ($p < 0.05$). The proportion of patients showing a decrease in eGFR in the groups receiving antiretrovirals did not differ when compared to the patients without antiviral treatment (33% and 29%, respectively). The changes in eGFR in each group are shown in Figure 1B. Most patients (62%) returned to baseline eGFR values within 1 month after discharge (Figure 1C). The proportion was similar between the patients receiving antiviral treatment and those not receiving this treatment.

## Discussion

This analysis confirmed the unfavourable outcomes and high mortality of KTx recipients following SARS-CoV-2 infection. In addition, the current results suggest that KTx recipients with COVID-19 do not have significantly poorer early renal outcomes after receiving two different antiviral regimens compared with KTx recipients not receiving antiviral treatment.

Kidney injury has been reported during COVID-19 infection, likely due to a synergistic effect of the virus-induced direct cytotropic effect, dehydration secondary to fever and diarrhoea, cytokine-mediated inflammatory injury, and haemodynamic instability in severe cases (Argenziano et al., 2020). The known nephrotoxic effects of several drugs and drug–drug interactions may be added to these factors. The current findings indicate that renal dysfunction is more frequent in the KTx population than in the non-transplanted population (Yang and Yang, 2020), likely due to the reduced nephron mass of the transplanted kidneys. However, in the present study cohort, the dysfunction was mild in most of the cases and did not require renal replacement therapy. A certain recovery was already noted at discharge, yet a worse kidney function than the baseline persisted in the early post-infection period in almost half of the patients.

Apart from COVID-19 itself, several drugs used during the course of the disease may have negatively influenced kidney graft function. The potential nephrotoxicity of LPV/r and its interactions with a number of other nephrotoxic drugs, particularly tacrolimus, are likely contributors. A small series of non-transplanted COVID-19 patients found almost four times higher lopinavir concentrations compared with HIV-infected patients receiving a similar dosage, and suggested that the down-regulation of cytochrome P450 by active infection and inflammation is responsible for the decreased metabolism of the antiretrovirals (Gregoire et al., 2020). This phenomenon will likely impact the pharmacokinetics of several drugs with nephrotoxic potential, particularly antibiotics, despite tacrolimus being reduced or withdrawn early in the treatment.

The exclusion of patients with an eGFR $<30$ ml/min/1.73 m$^2$ (i.e., stage 4 chronic kidney disease (CKD)) from clinical trials using RDV has generated a significant knowledge gap in safety data for RDV, as up to 15% of KTx recipients have stage 4 or 5 CKD at 5 years after transplantation (Marcén et al., 2010). Moreover, AKI, CKD, and end-stage renal disease (ESRD) are frequently found in patients with COVID-19 (Bowe et al., 2020), further underscoring the need for additional safety data. Although the data need to be interpreted with caution, we have to stress that two out of the four patients (9.5%) with CKD stage 4 in this cohort, both receiving RDV, did not survive.

The patient group detailed herein presents a dynamic, evolutionary experience following the changing treatment guidelines during 2020 (Maggiore et al., 2020; Dagens et al., 2020). Although the median age of the patients appears slightly lower than in other reports, the overall patient profile in terms of comorbidities and sex distribution appears to be similar to other reports (Felldin et al., 2021; Lubetzky et al., 2020). The overall outcomes of this first Eastern European cohort of transplant patients are comparable to those of patients in other single-centre reports or registry analyses, and this further suggests the existence of yet unidentified risk factors particular to this patient group (Caillard et al., 2020; Felldin et al., 2021; Hoek et al., 2020; Hillbrands et al., 2020; Kute et al., 2020; Nair et al., 2020).

The use of antiretrovirals in KTx recipients with COVID-19 was widespread in the first months of the pandemic (Alberici et al., 2020; Oltean et al., 2020), as LPV/r was recommended as a first-line or second-line agent in many countries (Dagens et al., 2020). Recent data from the Solidarity Trial found that neither RDV, hydroxychloroquine, LPV/r, nor interferon affected overall mortality and hospital stay in hospitalized patients (World Health Organization Solidarity Trial, 2020). The earlier results from the RECOVERY Trial showing that LPV/r monotherapy was not an effective treatment for hospitalized COVID-19 patients had already led to a change of practice and lower use of antiretrovirals.

An increase in creatinine is a hallmark of kidney allograft rejection, albeit rather unspecific. Considering the universal immunosuppression lowering in KTx recipients with COVID-19 and the resulting increased rejection risk, it is imperative to identify and understand other potential causes of kidney injury, including any antiviral treatments that may lead to a creatinine increase. We speculate that the prompt creatinine lowering and function recovery observed after the COVID-19 episode was partly due to the reduction or suspension of CNI. In line with other reports, no suspicion of allograft rejection was recorded in this study, in spite of the significant immunosuppression lowering, and we believe that the COVID-19-associated lymphocytopenia may safely allow for a temporary 'drug holiday' of up to 2 weeks.

Although it would be tempting to speculate on the efficiency of both treatments, the small size of the patient cohort and its heterogeneity in terms of disease severity and individual medications precludes any solid conclusions on the impact of the antiviral drugs on the outcomes of COVID-19. Whereas the current results suggest that RDV use may result in worse kidney function when compared to no antivirals in KTx recipients, the proportion of mild and moderate disease was significantly higher in the group not receiving antivirals. However, it is possible that this finding may have been dependent on the disease severity, not disease treatment. Nonetheless, the present study provides further data and allows a glimpse into the potential renal side effects and safety profile of antivirals in this particularly vulnerable patient population, as well as the time course of renal dysfunction in this risk group.

Another limitation is the assessment of kidney injury based on serum creatinine alone, which is a rather coarse parameter. No specific assessments of glomerular or tubular injury were consistently available. However, considering the particularities of the kidney in the KTx population (immune and non-immune graft injury, recurrence of the initial renal disease on the grafted kidney), it would have been difficult to interpret such data correctly in the actual context of superimposing COVID-19 and antivirals. Moreover, the data add to the limited literature on antivirals in transplanted patients and will hopefully contribute to comparisons and benchmarking of renal effects of other emerging treatment strategies, such as favipiravir, nitazoxanide, and nelfinavir (Zhao et al., 2020; Gavriatopoulou et al., 2020).

In conclusion, this analysis showed that the two different types of antiviral did not lead to significant and protracted kidney impairment in KTx recipients with COVID-19. More extensive studies or meta-analyses are required to further explore this hypothesis in this vulnerable patient population.

## Funding

There is no funding source to be reported.

## Ethical considerations

The study was reviewed and approved by the Ethics Review Committee of the Clinical Institute for Urology and Renal Transplantation (04/2020).

## Conflict of interest

The authors do not report any conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.01.023.

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