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.

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COVID-19 and kidney transplantation: the impact of remdesivir on renal function and outcome - a retrospective cohort study

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ABSTRACT

Objectives: The aim of the study was to evaluate the impact of remdesivir on overall mortality, ICU mortality, and renal functional outcome in hospitalized patients with COVID-19 who received kidney transplant.

Methods: We reviewed 165 patients with KTx hospitalized owing to COVID-19 between March 1, 2020, and May 31, 2021. A total of 38 patients with KTx received a 5-day RDV treatment, whereas 127 received standard of care (SOC). Overall and ICU mortality along with functional outcome were assessed.

Results: The 2 groups had similar baseline characteristics. RDV treatment was completed in all patients without any adverse effects attributable to RDV. In terms of overall mortality, there was no difference between the RDV and SOC groups (18% vs 23%, $p > 0.05$), but the ICU mortality was significantly reduced in the RDV group (39% vs 83%, $p < 0.05$). RDV seems to have no nephrotoxic effect on patients with KTx because there was no difference in the incidence of AKI between RDV and SOC groups (50% vs 43%, $p > 0.05$), and the discharge eGFR values significantly improved in the RDV group compared with the admission values (57 ± 23 vs 44 ± 22, $p < 0.05$).

Conclusion: Five-day RDV treatment appears safe in KTx recipients, and without obvious nephrotoxic effects. Also, RDV may decrease ICU mortality attributed to COVID-19.

Introduction

Lifelong immunosuppression and the burden of comorbidities put organ transplant recipients at risk for unfavorable outcome after SARS-CoV-2 infection (Qin et al., 2021, Jager et al., 2020). The initial lack of knowledge concerning this new and puzzling disease as well as the absence of targeted and effective antiviral interventions during the early phases of the pandemic resulted in a mortality of kidney transplant (KTx) recipients exceeding 25% (Oltean et al., 2020). However, rapidly accumulating information, evolving guidelines, and several experimental treatments seem to have improved the outcomes following COVID-19 both in transplanted patients and the general population (Heldman et al., 2021, Elec et al., 2021, Villanego et al., 2021). Remdesivir (RDV), a broad-

Abbreviations: AKI, acute kidney injury; AR, acute rejection; CCI, Charlson comorbidity index; CKD, chronic kidney disease; CNI, Calcineurin inhibitors; COVID-19, Coronavirus disease 2019; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; ICU, intensive care unit; IL, interleukine; KDIGO, Kidney Disease Improving Global Outcomes; KTx, kidney transplant; LMWH, low molecular weight heparin; MMF, mycophenolate mofetil; NIH, National Institutes of Health; RDV, remdesivir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBECD, sulfobutylether-β-cyclodextrin; SOC, standard of care; STROBE, strengthening the reporting of observational studies in epidemiology; WHO, World Health Organization.

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spectrum antiviral agent that was initially developed to treat hepatitis C and Ebola virus disease (Lo et al., 2017), remains to be one of the few evidence-based targeted antiviral interventions available to date.

The urgency required in the development and review of several new anti-COVID-19 compounds, including RDV, has led to the exclusion of several risk groups from the trials conducted during 2020, such as patients with poor liver and kidney function (creatinine clearance less than 30 or 50 mL/min) (Beigel et al., 2020, Goldman et al., 2020, Spinner et al., 2020). This caution was largely justified by concerns related to previously known side effects such as potential nephrotoxicity of RDV or its inactive ingredient, the solubility enhancer sulfobutylether-β-cyclodextrin (SBECD), which can accumulate in patients with impaired renal function (Luke et al., 2010). Unfortunately, this has also resulted in a knowledge gap about the safety, optimal dosing, and efficacy of RDV in patients with reduced renal function. Hence, the impact of RDV on COVID-19 outcome in KTx recipients, who frequently have impaired renal function, is poorly known.

There are very few reports on the use of RDV in KTx recipients with COVID-19 (Elec et al., 2021, Buxeda et al., 2021, Meshram et al., 2021). This limited body of evidence generated from widely different geographic areas during various pandemic phases could not discern significant side effects and suggests that RDV was well tolerated and safe in KTx recipients with COVID-19. However, its impact on the overall outcomes and comparison with patients receiving the standard of care (SOC) is essentially missing, and only one small study attempted to balance its findings (outcome, biochemistry) against a control group of KTx with COVID-19 not receiving RDV (Elec et al., 2021). Here, we comparatively analyzed a cohort of KTx recipients with COVID-19 and receiving RDV or not during the same time period at a transplant center in Eastern Europe. The main readouts of this study were overall mortality, ICU mortality, and functional outcome.

Patients and methods

We performed a retrospective cohort single center study of all KTx recipients who underwent transplantation at the Clinical Institute of Urology and Renal Transplantation (CIURT) in Cluj-Napoca, Romania, and who diagnosed with COVID-19 between March 1st, 2020 and May 31st, 2021. We comparatively analyzed hospitalized kidney transplant recipients with COVID-19 receiving RDV versus hospitalized KTx recipients with COVID-19, receiving standard of care (SOC) during the same time period. For the purpose of this study, 2 patient groups were defined: all KTx recipients receiving RDV (RDV group) and all the other hospitalized KTx irrespective of COVID-19 treatment (standard of care group [SOC]). SARS-CoV-2 infection was defined as a positive result for SARS-CoV-2 RNA on a real-time polymerase chain reaction assay of a nasopharyngeal swab. Both asymptomatic KTx recipients and patients presenting with typical symptoms such as fever (>38°C), respiratory, gastrointestinal, neurological, or general symptoms were included. Patients managed entirely on an outpatient basis and patients receiving antiviral therapy other than RDV were excluded from the analysis. The study was performed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007) and was approved by the Institutional Review Board of the Clinical Institute of Urology and Renal Transplantation (01/2021).

Patient Management

The COVID-19 treatment protocol recommended in Romania in the early phase of the pandemic (March–July 2020) was based on hydroxychloroquine (HCQ) and antiretrovirals. HCQ 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. Antiretrovirals (Lopinavir/Ritonavir, darunavir/ritonavir, or darunavir/cobicistat) were added in patients with mild and moderate forms and adequate renal function (estimated glomerular filtration rate [eGFR] >30 mL/min/1.73 m^2). From mid-July 2020, RDV was added to the treatment protocol in more severe cases, whereas HCQ and antiretrovirals were no longer recommended. When available, RDV (Veklury, Gilead Pharma) was administered in moderate and severe cases applying the five-day European Medicines Agency protocol (European Medicines Agency, 2020). Low eGFR and AKI were not considered as contraindications. RDV was started 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. Anticoagulation using low-molecular-weight heparin (LMWH) was recommended in all hospitalized patients from mid-April 2020 onward.

Antibiotics were given at the discretion of the attending medical teams. Immunosuppression was managed through contacts with the transplant nephrologists from CIURT. Immunosuppression was frequently reduced by pausing the antimetabolite (mycophenolate mofetil or mycophenolic acid) with or without adjusting calcineurin inhibitors. Tacrolimus was withdrawn in all 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 IV for stress dosing. Other therapies like tocilizumab were given as per the local availability and severity of COVID-19.

Data collection

The following data were recorded as baseline characteristics of the 3 groups: sex, age, weight, body mass index (BMI), comorbidities (hypertension, cardiovascular disease, diabetes, and malignancy), baseline and hospital admission renal function (estimated glomerular filtration rate (eGFR) using the CKD-EPI formula; baseline eGFR was collected during the last 12 months before COVID-19), Charlson comorbidity index (CCI) as previously described (Oltean et al., 2012), time from transplant, baseline immunosuppression, and treatment administered for COVID-19 management. The following data were recorded as outcomes: overall mortality, ICU mortality, COVID-19 severity (classified from mild to critical using the NIH criteria [NIH. Coronavirus Disease 2019 COVID-19 treatment guidelines, 2020]), ICU admission, oxygen therapy, mechanical ventilation, acute kidney injury (AKI) incidence during hospitalization (defined as an increase in serum creatinine by 0.3 mg/dl or more within 48 hours or as an increase of 1.5 times or more from baseline), and discharge eGFR.

Data analysis

Demographic, baseline characteristics and outcomes were assessed as counts and percentages for categorical values and as a mean (± standard deviation) or median (± range) for continuous variables. Fisher exact test was used to assess the proportions of categorical variables. Continuous variables were assessed using the Mann-Whitney U test. Kaplan-Meier and the log-rank test were used to calculate and compare survival.

Age, sex, comorbidities, chronic kidney disease grade 4–5 (baseline eGFR <30 ml/min/1.73m^2), time from transplantation, and BMI were chosen as potential risk factors based on hypotheses and/or previous studies showing a relationship with COVID-19 mortality. Analyses were performed using GraphPad Prism v.9.3. (GraphPad Software, San Diego, CA)

Table 1
Baseline characteristics of Remdesivir (RDV) and standard of care (SOC) groups.

Baseline characteristics	All patients (n=165)	RDV (n=38)	SOC (n=127)	p value
Males, n (%)	68 (41.2)	21 (55)	89 (70)	**0.04**
Age, mean±SD	50± 12	53± 9	49 ± 12	0.09
18-50, n (%)	75 (45.5)	13 (34.2)	62 (48.8)	0.14
51-65, n (%)	69 (41.8)	20 (52.6)	49 (38.5)	0.14
>65, n (%)	21 (12.7)	5 (13.2)	16 (12.6)	0.99
BMI (kg/m^2), mean±SD	26±4	27±4	26±4	0.17
Obesity, n (%)	25 (15.5)	6 (15.7)	19 (15)	>0.99
Comorbidities, n (%),				
Hypertension	132 (80)	29 (76)	103 (81)	0.48
Cardiovascular disease	60 (36.3)	15 (39)	45 (35)	0.70
Diabetes	49 (29.6)	**18 (47)**	**31 (24)**	**0.01**
Malignancy	4 (2.4)	**3 (7.9)**	**1 (0.8)**	**0.04**
Baseline eGFR, mean±SD		52±20	53±27	0.94
G1-2 (>60 ml/min/1.73m^2), n (%)	60 (36,3)	10 (26)	50 (39)	0.18
G3a (45-60 ml/min/1.73m^2), n (%)	35 (21.2)	14 (37)	21 (17)	**0.01**
G3b (30-44 ml/min/1.73m^2), n (%)	32 (19.3)	8 (21)	24 (19)	0.82
G4-5 (<30 ml/min/1.73m$^{2)}$, n (%)	38 (23.2)	6 (16)	32 (25)	0.28
Admission eGFR		44±22	49±28	0.35
Charlson comorbidity index, *median (range)*	3 (2-9)	4 (2-7)	3 (2-9)	
CCI 2, n (%)	54 (33)	9 (23)	34 (27)	0.83
CCI 3 or 4, n (%)	70 (42)	17 (45)	53 (42)	0.85
CCI 5 and over, n (%)	41 (25)	12 (32)	40 (31)	>0.99
Months from transplant, median (range)	82 (5-318)	85 (6-221)	81 (5-318)	
First year after transplant, n (%)	14	5 (13)	9 (7)	0.32
Baseline immunosuppression, n (%)				
Triple regimen	127 (77)	25 (66)	102 (80)	0.08
Steroid-free	28 (17.0)	11 (29)	17 (13)	0.05
CNI-free	12 (7.3)	2 (5)	10 (8)	0.74
Tacrolimus	143 (86.7)	34 (90)	109 (86)	0.79
Cyclosporine A	10 (6.1)	2 (5)	8 (6)	>0.99
Rapamycine	4 (2.4)	2 (11)	2 (2)	**0.03**
Antimetabolites	161 (98)	37 (97)	124 (98)	>0.99
COVID-19 management, n (%)				
MMF reduction/withdrawal	89 (54)	15 (37)	74 (58)	**0.02**
CNI reduction	42 (25)	6 (16)	36 (28)	0.11
Immunosuppression cessation	48 (29)	15 (39)	39 (31)	0.48
Immunosuppression unchanged	7 (4)	2 (5)	7 (6)	0.94
HCQ	31 (19)	5 (13)	26 (20)	0.31
Tocilizumab	6 (3.6)	4 (11)	2 (2)	**0.01**
Dexamethasone	145 (88)	32 (84)	53 (41)	**0.01**
LMWH & NOAC	145 (88)	32 (84)	109 (86)	**0.01**

Abbreviations: SD=standard deviation; BMI=body mass index; eGFR = estimated glomerular filtration rate; CCI = Charlson comorbidity index; CNI = Calcineurin inhibitors; HCQ = hydroxychloroquine; LMWH =low molecular weight heparin; NOAC=novel oral anticoagulants
Data are reported as number /total number of available observations and (percent), or median and interquartile range (Q1-Q3). CCI – Charlson comorbidity index, 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.

Results

Baseline patient characteristics

At the start of the pandemic (March 1st, 2020), 1467 KTx recipients were alive and in followed-up at the Institute of Urology and Renal Transplantation in Cluj-Napoca, Romania. Furthermore, 51 patients were transplanted during the study period, resulting in a total of 1518 KTx recipients at risk for developing COVID-19 who were included in this study. During the 15 months of the study, there were 234 KTx recipients diagnosed with COVID-19 (15, 7%). A total of 59 patients (25%) were managed entirely on an outpatient basis and were excluded from the analysis. Further, 10 patients received Favipiravir and were excluded from the analysis. The remaining 165 hospitalized patients formed the basis for the current report: 38 (23%) patients received RDV as part of their COVID-19 management, whereas 127 (77%) did not (SOC group) (Table 1).

Patients in the two groups were largely similar in terms of age, time from transplantation, frequency of obesity, and comorbidities (Table 1). However, the RDV group included fewer male subjects (55% vs 70%, p <0.05), more patients with grade G3a kidney disease (37 vs 17%, p <0.05), more patients with diabetes (47% vs 24%, p <0.05), and malignancies (7.9% vs 0.8%, p <0.05) (Table 1). In terms of baseline immunosuppression, the RDV group had more patients on rapamycin (11% vs 2%, p <0.05) (Table 1). In terms of COVID-19 management, the RDV group had less mycophenolate mofetil reduction or withdrawal (37% vs 58%, p <0.05) and administration of low-molecular-weight heparin and nonvitamin K antagonist (84% vs 86%, p<0.01), whereas more patients were administered tocilizumab and dexamethasone (11% vs 2%, p<0.05, and 84% vs 41%, p<0.05, respectively) (Table 1).

Outcomes

In terms of overall mortality, there was no difference between the RDV and SOC groups (18% vs 23%, p >0.05) (Table 2, Figure 1A and B), but the ICU mortality was significantly reduced in the RDV group (39% vs 83%, p <0.05) (Table 2, Figure 1 C and D). The proportion of patients with severe COVID-19 was higher in the RDV group (42 % vs 14%, p <0.05), whereas the proportion of patients with mild COVID-19 disease was lower in the RDV group (8% vs 36 %, p <0.05) (Table 2, Figure 2A). In addition, the proportion of pa-

Table 2
Outcomes of Remdesivir (RDV) and standard of care (SOC) groups

Outcomes	All patients (n=165)	RDV (n=38)	SOC (n=127)	p value
Overall mortality, n (%)	36 (22)	7 (18)	29 (23)	0.66
ICU mortality, n (%)	36 (67)	7 (39)	29 (83)	**0.01**
ICU admission, n (%)	53 (32)	18 (47)	35 (27)	**0.01**
COVID-19 severity, n (%)				
Mild	49 (30)	3 (8)	46 (36)	**0.01**
Moderate	42 (26	8 (21)	34 (27)	0.53
Severe	34 (20)	16 (42)	18 (14)	**0.01**
Critical	40 (24)	11 (29)	29 (23)	0.52
Oxygen therapy, n (%)	86 (52)	32 (84)	56 (44)	0.14
Mechanical ventilation, n (%)	38 (23)	8 (21)	30 (24)	0.73
AKI, n (%)	74 (44)	19 (50)	55 (43)	0.45
Discharge eGFR, mean±SD		57±23	62±28	0.47

Abbreviations: ICU=intensive care unit; SD=standard deviation; AKI=acute renal injury; SD=standard deviation.

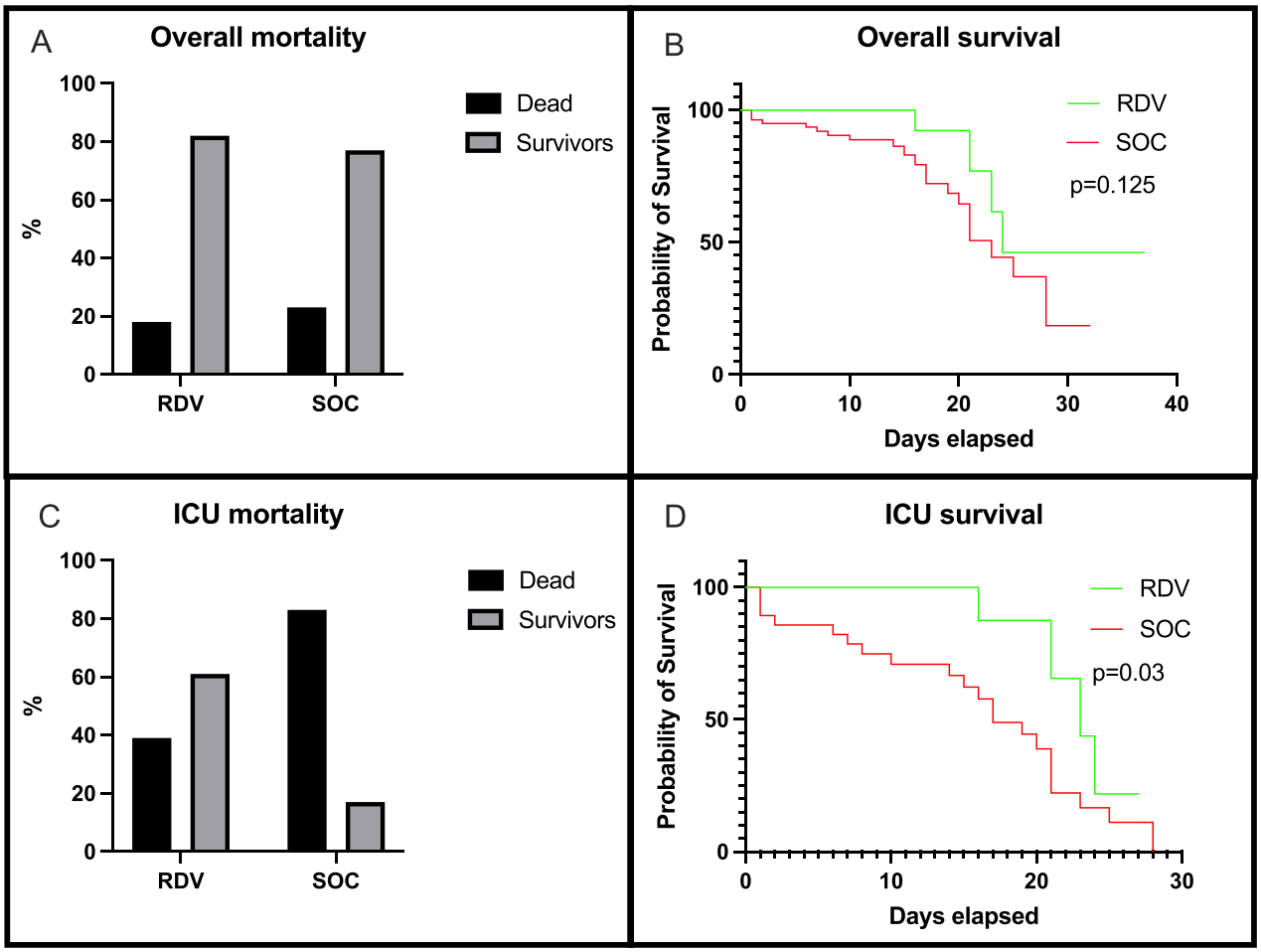

Figure 1. A) Overall mortality of Remdesivir (RDV) and standard of care (SOC) groups. B) Kaplan–Meier overall survival analysis for RDV and SOC groups. C) Intensive care unit (ICU) mortality for RDV and SOC groups. D) Kaplan–Meier ICU survival for RDV and SOC groups.

tients requiring ICU admission was significantly higher in the RDV group than patients receiving SOC (47% vs 27%, p <0.05).

Univariate analysis for mortality showed significant differences between survivors and nonsurvivors for the following confounding factors: the number of patients aged over 65 (HR: 2.51 [1.11–5.14], p <0.05), CCI (HR 1.81 [1.06–1.6], p <0.05), recent transplant (<12 months) (HR 2.4 [0.96–5.21], p <0.05), and stage 4–5 chronic kidney disease at baseline (HR 3.81 [1.96–7.35], p <0.05). In multivariate Cox regression, the following confounding factors reached statistical significance for association with shorter survival: recent transplant (<12 months) [HR 3.14 [1.07–8.77], p <0.05), stage 4–5 chronic kidney disease at baseline (HR 7.49 [3.25–17.9], p <0.05) and COVID-19 severity (HR 8.12 [4.32–18.2], p <0.05).

Supplemental oxygen was required significantly more often in patients receiving RDV than patients receiving SOC (84% vs 44%, p <0.05), and there was no difference in the proportion of patients requiring mechanical ventilation (21% vs 24%, p >0.05) (Table 2).

Toxicity and renal function

No serious adverse effects attributable to RDV were noted, and the 5-day RDV treatment was completed in all patients.

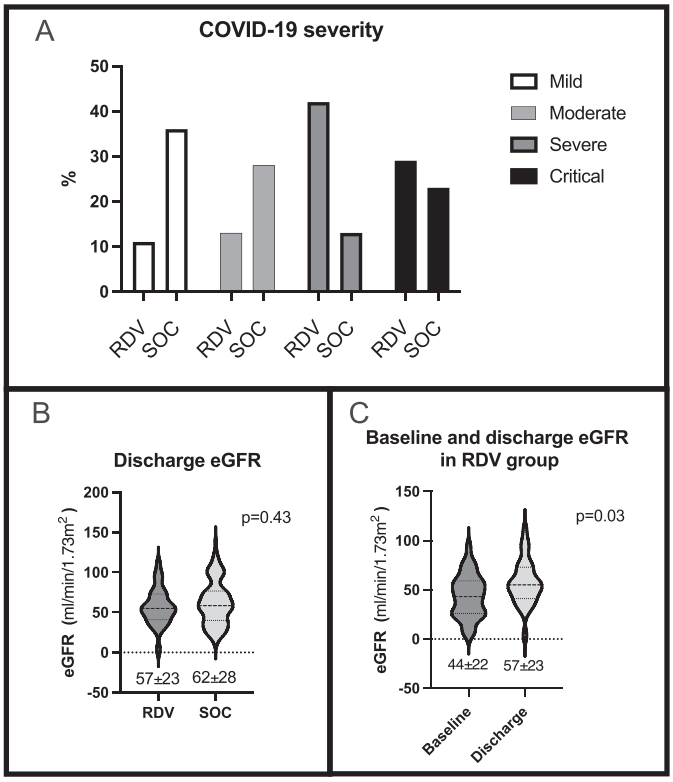

Figure 2. A) COVID 19 severity for Remdesivir (RDV) and standard of care (SOC) groups. B) Violin plot with mean and standard deviation representation of discharge estimated glomerular filtration rate (eGFR) for RDV and SOC groups. C) Violin plot with mean and standard deviation representation of baseline and discharge eGFR for RDV group.

At hospital discharge, there was no sign of RDV nephrotoxicity, with no difference in the incidence of AKI between RDV and SOC groups (50% vs 43%, $p>0.05$); whereas, the admission eGFR values significantly improved in the RDV group compared to the discharge values (44±22 vs 57±23, $p<0.05$) (Table 2, Figure 2C). There was no difference in the discharge eGFR between RDV and SOC groups (57 ± 23 vs 62 ± 28 ml/min/1.73 m^2, $p>0.05$) (Table 2, Figure 2B).

Discussion

This study reports the outcomes of hospitalized kidney transplant recipients with COVID-19 treated with RDV compared with patients receiving SOC alone. The results suggest that RDV has a positive impact on COVID-19 patients in terms of ICU mortality and that the drug is not associated with significant nephrotoxicity. Consequently, these results suggest that recommendations on RDV use in the normal populations could be extended to KTx recipients.

The landmark paper of Beigel et al has provided essential knowledge about optimal dosing and timing, adverse effects, and outcomes of RDV (Beigel et al., 2020). Currently, RDV is recommended in hospitalized patients requiring supplementary oxygen (i.e., severe disease forms) but not mechanical ventilation, with or without dexamethasone, as a 5- or 10-day treatment protocol, administered as soon as possible after the onset of symptoms and preferably, within the first week. However, because severe COVID-19 typically begins to manifest 8–12 days after symptom onset, it is possible that in some patients, including patients in this study, RDV administration was initiated late in the course of the disease. Hence, the window of opportunity in the first days after infection, when intense viral replication occurs, can easily be missed. The median time from onset of symptoms and diagnosis and treatment start was within this time frame, and although several patients received RDV after more than 10 days from the first symptoms, they all survived.

This study suggests that RDV significantly decreased ICU mortality, possibly limiting disease progression. This finding is in line with several much larger studies in nontransplanted patients, where RDV reduced the odds of death during the study and shortened the time to clinical recovery, particularly in hospitalized patients requiring oxygen supplementation but who were not in very critical condition (intubated or on extracorporeal membrane oxygenation) (Beigel et al., 2020, Olender et al., 2021).

Impaired renal function following RDV treatment has been the main concern because of the potential accumulation, and renal tubule toxicity of RDV's active metabolite or its inactive ingredient, SBECD, used to improve its aqueous solubility (Luke et al., 2010). Consequently, all initial studies on RDV have excluded patients with kidney impairment (eGFR <30–50 ml/min/1.73 m^2), an exclusion criterion that has led to a gap of knowledge in terms of efficacy and safety of RDV in this vulnerable patient group, especially KTx patients

In this study, there was no difference in terms of AKI incidence for RDV and SOC groups (50% vs 43%, $p>0.05$). Similar to previous reports, the short RDV course applied in this study did not add to the other causes of renal impairment, such as dehydration, viral tropism, endothelial dysfunction, coagulopathy, or systemic inflammation (Buxeda et al., 2021, Meshram et al., 2021). Moreover, there was an improvement in renal function during the hospitalization, the discharge eGFR being significantly increased compared to baseline (Figure 2C). This apparent improvement, likely owing to several factors such as the decrease or discontinuation of calcineurin inhibitors, rehydration, and resolution of the disease, did not seem to be negatively affected by RDV.

RDV is metabolized by the cytochrome P450 3A4, similar with tacrolimus. Although no apparent drug-drug interactions (DDI) are expected between RDV and Tacrolimus (Deb et al., 2021), some cytokines such as IL-1, IL-6, or interferon-gamma may downregulate cytochrome P450 (CYP) enzyme activity Harvey and Morgan, 2014) , which may theoretically result in supratherapeutic levels of both RDV and tacrolimus. In contrast with Lopinavir/Ritonavir (Kaletra), which has been frequently used during the first months of the pandemic and where DDI between it and numerous drugs, including Tacrolimus, are well known, this concern has been largely theoretical during the use of RDV (Elens et al., 2020). In addition, in patients with severe and critical disease, in whom the "cytokine storm" could have developed, tacrolimus administration was frequently reduced or even discontinued (Maggiore et al., 2020).

This study has several significant limitations. Until October 2020, the length of hospitalization for individuals infected with SARS-CoV-2 in Romania was regulated through a governmental ordinance to at least 10 days of hospitalization or 14 days from the start of symptoms, even if the patients have recovered completely. Unfortunately, this ambitious measure that aimed at ensuring optimal isolation during and after COVID-19 also turned the length of hospital stay into an irrelevant outcome measure for over half of the study period.

The relatively small size, unequal distribution between groups, and the retrospective design preclude solid conclusions, and the results need to be interpreted cautiously. Some relevant clinical or laboratory data (notably daily creatinine or liver function tests) could not be reliably assessed and compared because its availability was inconsistent between the 2 study groups. Kidney function and injury were assessed based only on serum creatinine, a widely available yet coarse parameter. In addition, although the groups were largely similar in terms of demographics, comorbidities, and immunosuppression, we found several significant differences in terms of kidney graft function, diabetes, and malignancies, which

may have reflected a certain selection bias. However, this selection bias did not favor the RDV group, which had worse baseline eGFR and more patients with diabetes and malignancies (Table 1). Despite these circumstances, these patients had better ICU survival, which may suggest a certain benefit of RDV.

Despite these limitations, this analysis also has several strengths—notably, the presence of a contemporary control group and the use of the same RDV treatment protocol throughout the study. The study population matched well with other larger studies or meta-analyses in terms of patient age, comorbidity burden, and overall results (ICU admission rate, mortality) (Oltean et al., 2020, Chen et al., 2021, Jayant et al., 2021). Although the study period stretched over 3 pandemic waves and presents an evolutionary experience where COVID-treatment protocols have changed over time (Elec et al., 2021, Villanego et al., 2021), patients in the 2 study groups received simultaneously, albeit not randomized, either RDV or SOC, according to the recommendation at that point in time.

In conclusion, this study indicates that RDV was safe and well tolerated in KTx recipients with COVID-19. Its administration did not appear to negatively impact the renal outcome of KTx. Although the ability of RDV to improve the overall mortality remains unclear, there may be a certain patient subgroup with noncritical disease that may benefit from RDV treatment.

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Conflict of interest

The authors have no conflicts of interests to declare.

Ethical considerations

The study was reviewed and approved by the Ethical Review Committee of the Clinical Institute for Urology and Renal Transplantation (01/2021).

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References

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC. ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813–26.

Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, Cacho J, Cabello Pelegrin S, Melilli E, Aladrén MJ, Galeano C, Lorenzo I, Mazuecos A, Saura IM, Franco A, Ruiz–Fuentes MDC, Sánchez-Cámara LA, Siverio O, Martin ML, González-García E, López V, Martin-Moreno PL, Moina I, Moral Berrio E, Moreso F, Portolés JM, Santana-Estupiñán R, Zárraga S, Canal C, Sánchez-Álvarez E, Pascual J, Crespo M. Use and Safety of Remdesivir in Kidney Transplant Recipients With COVID-19. Kidney Int Rep 2021;6(9):2305–15 Sep.

Chen JJ, Kuo G, Lee TH, Yang HY, Wu HH, Tu KH, Tian YC. Incidence of Mortality, Acute Kidney Injury and Graft Loss in Adult Kidney Transplant Recipients with Coronavirus Disease 2019: Systematic Review and Meta-Analysis. J Clin Med 2021;10(21):5162 Nov 4.

Deb S, Reeves AA, Hopefl R, Bejusca R. ADME and Pharmacokinetic Properties of Remdesivir: Its Drug Interaction Potential. Pharmaceuticals (Basel) 2021;14(7):655.

Elec AD, Oltean M, Goldis P, Cismaru C, Lupse M, Muntean A, Elec FI. COVID-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment. Int J Infect Dis 2021;104:426–32.

Elec FI, Bolboacă SD, Muntean A, Elec AD, Cismaru C, Lupşe M, Oltean M. Comparing the First and Second Wave of COVID-19 in Kidney Transplant Recipients: An East-European Perspective. Eur Surg Res 2021:298–305 Jul 29. doi:10.1159/000517559.

Elens L, Langman LJ, Hesselink DA, Bergan S, Moes DJAR, Molinaro M, Venkataramanan R, Lemaitre F. Pharmacologic Treatment of Transplant Recipients Infected With SARS-CoV-2: Considerations Regarding Therapeutic Drug Monitoring and Drug-Drug Interactions. Ther Drug Monit 2020;42(3):360–8.

European Medicines Agency. Summary on compassionate use. Amsterdam, The Netherlands: Remdesivir. Gilead. European Medicines Agency; 2020 Available from https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf .

Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A. GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020;383(19):1827–37.

Harvey RD, Morgan ET. Cancer, inflammation, and therapy: effects on cytochrome p450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clin Pharmacol Ther 2014;96(4):449–57.

Heldman MR, Kates OS, Safa K, Kotton CN, Georgia SJ, Steinbrink JM, Alexander BD, Hemmersbach-Miller M, Blumberg EA, Multani A, Haydel B, La Hoz RM, Moni L, Condor Y, Flores S, Munoz CG, Guitierrez J, Diaz EI, Diaz D, Vianna R, Guerra G, Loebe M, Rakita RM, Malinis M, Azar MM, Hemmige V, McCort ME, Chaudhry ZS, Singh PP, Hughes Kramer K, Velioglu A, Yabu JM, Morillis JA, Mehta SA, Tanna SD, Ison MG, Derenge AC, van Duin D, Maximin A, Gilbert C, Goldman JD, Lease ED, Fisher CE, Limaye APUW Covid-19 SOT Study Team. Changing Trends in Mortality Among Solid Organ Transplant Recipients Hospitalized for Covid-19 During the Course of the Pandemic. Am J Transplant 2021 Sep 12Epub ahead of print. PMID: 34514710. doi:10.1111/ajt.16840.

Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, Collart F, Hemmelder MH, Ambühl P, Kerschbaum J, Legeai C, Del Pino Y Pino MD, Mircescu G, Mazzoleni L, Hoekstra T, Winzeler R, Mayer G, Stel VS, Wanner C, Zoccali C, Massy ZA. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 2020;98(6):1540–8.

Jayant K, Reccia I, Bachul PJ, Al-Salmay Y, Pyda JS, Podda M, Perez-Gutierrez A, Dor FJMF, Becker Y, di Sabato D, LaMattina J, Barth R, Fung J, Witkowski P. The Impact of COVID-19 on Kidney Transplant Recipients in Pre-Vaccination and Delta Strain Era: A Systematic Review and Meta-Analysis. J Clin Med 2021;10(19):4533 Sep 30.

Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, Flint M, McMullan LK, Siegel D, MO Clarke, Mackman RL, Hui HC, Perron M, Ray AS, Cihlar T, Nichol ST, Spiropoulou CF. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep. 2017;7:43395.

Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). J Pharm Sci 2010;99(8):3291–301 Aug. doi:10.1002/jps.22109.

Maggiore U, Abramowicz D, Crespo M, Mariat C, Mjoen G, Peruzzi L, Sever MS, Oniscu GC, Hilbrands L, Watschinger B. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. Nephrol Dial Transplant 2020;35(6):899–904.

Meshram HS, Kute VB, Patel H, Banerjee S, Navadiya V, Desai S, Rizvi SJ, Mishra V, Chauhan S. Feasibility and safety of remdesivir in SARS-CoV2 infected renal transplant recipients: A retrospective cohort from a developing nation. Transpl Infect Dis 2021;23(4):e13629 Aug.

Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, Wang S, Walunas TL, Swaminathan S, Slim J, Chin B, De Wit S, Ali SM, Soriano Viladomiu A, Robinson P, Gottlieb RL, Tsang TYO, Lee IH, Hu H, Haubrich RH, Chokkalingam AP, Lin L, Zhong L, Bekele BN, Mera-Giler R, Phulpin C, Edgar H, Gallant J, Diaz-Cuervo H, Smith LE, Osinusi AO, Brainard DM, Bernardino JIGS-US-540–5773 and GS-US-540–5807 Investigators. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. Clin Infect Dis 2021;73(11):e4166–74.

Oltean M, Søfteland JM, Bagge J, Ekelund J, Felldin M, Schult A, Magnusson J, Friman V, Karason K. Covid-19 in kidney transplant recipients: a systematic review of the case series available three months into the pandemic. Infect Dis (Lond) 2020;52(11):830–7.

Oltean S, Ţăţulescu D, Bondor C, Slavcovici A, Cismaru C, Lupşe M, Muntean M, Jianu C, Marcu C, Oltean M. Charlson's weighted index of comorbidities is useful in assessing the risk of death in septic patients. J Crit Care 2012;27(4):370–5 Aug.

Qin CX, Moore LW, Anjan S, Rahamimov R, Sifri CD, Ali NM, Morales MK, Tsapepas DS, Basic-Jukic N, Miller RA, van Duin D, Santella RN, Wadei HM, Shah PD, Gage N, Malinis M, Aslam S, Todesco E, Werbel WA, Avery RK, Segev DL. Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients. Transplantation 2021;105(11):e265–6.

Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Le Turnier P, Chang SC, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A, Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, FM; Marty. GS-US-540-5774 Investigators. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324(11):1048–57 PMID: 32821939; PMCID: PMC7442954. doi:10.1001/jama.2020.16349.

Villanego F, Mazuecos A, Pérez-Flores IM, Moreso F, Andrés A, Jiménez-Martín C, Molina M, Canal C, Sánchez-Cámara LA, Zárraga S, Ruiz-Fuentes MDC, Aladrén MJ, Melilli E, López V, Sánchez-Álvarez E, Crespo M, Pascual J. Spanish

Society of Nephrology COVID-19 Group. Predictors of severe COVID-19 in kidney transplant recipients in the different epidemic waves: Analysis of the Spanish Registry. Am J Transplant 2021;21(7):2573–82 Jul.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP-STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7 Oct 20PMID: 18064739. doi:10.1016/S0140-6736(07)61602-X.

National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum. Accessed Nov 2021.