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COVID-19 outcomes in kidney transplant recipients receiving a combination of sofosbuvir-daclatasvir treatment; a single-center study

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ABSTRACT

Introduction: In the coronavirus disease 2019 (COVID-19) era, kidney transplantation recipients (KTRs) are at high risk due to using immunosuppressive drugs. Considering the lack of definitive cure for COVID-19, repurposing existing pharmaceuticals is a way to find an immediate medication.

Objectives: This study aimed to evaluate the COVID-19 outcomes in KTRs, receiving combination of sofosbuvir and daclatasvir (SOF-DAC) treatment.

Patients and Methods: This research was an observational study of 12 adult kidney transplant recipients with COVID-19, admitted to Shariati hospital, Tehran, Iran (October to December 2020). All the patients received a once-daily combination pill of SOF-DAC at a dose of 400/60 mg for 10 days.

Results: Around October to December 2020, 12 adult KTR patients were recruited; four patients (33.3%) died and eight patients survived (66.7%). Acute kidney injury (AKI) secondary to COVID-19 was seen in 11 patients of the study population (91.7%), including four dead cases. Two of the three patients who underwent dialysis due to kidney complications, died. The laboratory results showed that the mean level of each parameter white blood cells (WBC), international normalized ratio (INR), C-reactive protein (CRP), ferritin, D-dimer on the last day of hospital stay was significantly different between two groups of survived and dead patients at a 95% confidence level ($P<0.05$).

Conclusion: Sofosbuvir combined with DAC for treatment of KTRs with COVID-19 infection reduced the mortality rate. Further, this medication was safe. Patients tolerated it well, and no serious adverse effects were observed. Larger studies are needed to validate these results.

Implication for health policy/practice/research/medical education:
This study aimed to evaluate the COVID-19 outcomes in 12 hospitalized adult kidney transplant recipients, receiving the combination of sofosbuvir and daclatasvir (SOF-DAC) treatment. The treatment was safe and tolerated well. No serious adverse effects were observed. The mortality rate was reduced.

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Introduction

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), spread rapidly worldwide, causing a new pandemic (1). The most common complaints of patients are fever (98%), cough (76%), dyspnea (55%), and myalgia (44%). SARS-CoV-2 can cause complex multisystem disease, including acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute heart failure, secondary infection, neurological deficit, and acute kidney injury (AKI) that in severe cases, death may occur (2).

The kidneys are one of the most vital body organs whose role in COVID-19 is reciprocal. Early evidence by Lili et al showed that AKI is one of the most significant complications of severe COVID-19, increasing mortality rate (3). On the other hand, previous studies reported underlying chronic kidney disease (CKD) and organ transplantation as significant predictors of critical

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COVID-19 (4,5). Kidney transplantation recipients (KTRs) are at high risk too. These patients are more prone to various infections because of using immunosuppressive drugs. A study of more than 4000 COVID-19 patients receiving renal replacement therapy (RRT) demonstrated that COVID-19-associated mortality is high among KTRs (6). In a review by González et al, the death rate of KTRs with SARS-CoV-2 infection was reported up to 30% while, in a multi-center study evaluated 414 KTRs, the mortality rate was 50% (7,8).

Therefore, finding an efficient treatment regimen for the management of COVID-19 in kidney transplant patients is crucial owing to its poor prognosis. A part of the researchers' effort has been focused on repurposing existing pharmaceuticals to find an immediate medication. The 400 mg sofosbuvir (SOF) combined with 60 mg daclatasvir (DAC), a new-generation direct-acting antiviral (DAA), has been identified as an efficient treatment for hepatitis C virus (9,10). Further, Xue et al reported the high efficacy of SOF and DAC for treating KTRs with HCV infection (11). Regarding similar replication mechanisms between HCV and SARS-CoV-2, the combination of SOF and DAC was considered a COVID-19 pragmatic treatment option for trial. A multicenter randomized controlled trial by Abbas et al demonstrated that using SOF and DAC along with standard care significantly impacts the clinical situations of COVID-19 patients and shortens the duration of hospitalization compared with standard care alone (12).

Objectives

Based on the evidence of SOF-DAC treatment efficacy as well as the poor prognosis of COVID-19 in KTRs, this study aimed to evaluate the outcomes of COVID-19 in KTRs who received the SOF-DAC antiviral treatment.

Patients and Methods

Study design

This observational study was conducted on a group of hospitalized adult kidney transplant recipients, with SARS-CoV-2 infection (October 2020 and December 2020) at Shariati hospital, Tehran, Iran. To confirm COVID-19 infection, positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 and/or evidence consistent with COVID-19 on a spiral chest computed tomography (CT) scan were considered. Patients with coexisting impaired liver function test and hepatitis B virus infection were excluded. Recovery and discharge criteria of patients included; receiving complete therapy, no fever for at least three days, improvement of clinical symptoms associated with COVID-19, normal respiratory rate (12-16 breaths/min), oxygen saturation level above 93 percent (SpO_2 > 93%), normal systolic and diastolic blood pressure, and improvement or no progression of radiological evidence of COVID-19 associated pneumonia. The demographic and clinical data were extracted from medical records using a data collection form.

Therapeutic management

All the patients received a once-daily 400/60 mg SOF-DAC (Sovodak, Fanavaran Rojan Mohaghegh Daru Co, Tehran, Iran) for ten days. The hospital provided SOF-DAC free of charge to the patients. The immunosuppressive drugs routinely used by patients were modified upon hospitalization. Initially, mycophenolate and rapamycin were discontinued in all patients up to two weeks after discharge. However, cyclosporine and tacrolimus only withdrew in patients with severe symptoms. Patients with any of the following clinical conditions were considered as a severe illness: who have a respiratory rate >20 breaths/min, body temperature >38°C, septic shock that may represent virus-induced distributive shock, CT scan with evidence of more than 35-40% SARS-CoV-2 pulmonary disease, and other organ failures in addition to lung such as the kidney. Along with these managements, various medications were used to control and treat COVID-19.

Statistical analysis

Data analysis were conducted using IBM SPSS version 26.0. Quantitative variables were analyzed for the mean ± standard deviation (SD), and qualitative data were expressed as frequency and percentage. Parametric and non-parametric tests, including the chi-square test, Fischer's exact test, independent t-test, and one-way analysis of variance (ANOVA), were used to compare the differences in the effect of variables on patients' prognosis. *A P* value less than 0.05 was considered statistically significant for all tests.

Results

In this study, 12 adult KTRs with COVID-19 were recruited. All patients completed the SOF and DAC treatment. At the end of this study, four patients (33.3%) died, while eight patients survived (66.7%). The mean ± SD age of patients was 49.27 ± 10.460 years with the minimum and maximum of 36 and 63 years old, respectively. The patients who died were older than those who survived. However, it was not statistical significance (53.67 ± 3.786 versus 47.63 ± 11.868, $P=0.422$). Seven patients (58.3%) were male, and five were female (41.7%). Although most of the dead patients were female (75%), there was no significant relation between gender and mortality of KTR patients ($P=0.12$; Table 1).

The most common comorbidities were hypertension (6 patients, 50%) and diabetes mellitus (4 patients, 33.3%). Only one patient had ischemic heart disease (Table 1), and no one suffered from malignancy or underlying pulmonary disease. The body mass index (BMI) of all patients ranged between 23.01 and 28.73 kg/m^2. Although all four non-survivors were hypertensive, no significant correlation was seen between hypertension and mortality ($P=0.06$). Only 25% of dead patients were diabetic, and

Table 1. Demographic data and comorbidities of KTR patients

All patients (n=12)	Mean (SD)	Death		*P* value
		No	Yes	
Age (y), Mean (SD)	49.27 (10.460)	47.63 (11.868)	53.67 (3.786)	0.422
Height (cm), Mean (SD)	165.92 (6.067)	167.50 (5.425)	162.75 (6.801)	0.216
Weight (kg), Mean (SD)	70.58 (10.706)	72.50 (8.264)	66.75 (15.218)	0.406
Days of hospitalization, Mean (SD)	20.69 (14.710)	15.38 (21.310)	26.00 (8.120)	0.060
Gender, No. (%)				
Male	7 (58.3)	6 (75.0)	1 (25.0)	0.12
Female	5 (41.7)	2 (25.0)	3 (75.0)	
Death	4 (33.3)	-	-	-
Comorbidities, No. (%)				
Diabetes mellitus	4 (33.3)	3 (75.0)	1 (25.0)	0.667
Hypertension	6 (50.0)	2 (33.3)	4 (66.7)	0.06
Ischemic heart disease	1 (8.3)	1 (100.0)	0 (0.0)	1.00
Malignancy	0	0	0	-
Pulmonary disease	0	0	0	-
High BMI (>30) kg/m^2	0	0	0	-

BMI, body mass index.

the analysis revealed that diabetes effect on mortality was not statistically significant ($P=0.667$).

The most common symptoms were fatigue (11 patients, 83.3%) and cough (9 patients, 75%). Myalgia (50%), headache (41.7%), nausea (41.7%) and vomiting (33.3%), dyspnea (25%), and chest pain (16.7%) were other presenting symptoms associated with SARS-CoV-2 infection in KTRs. Of the four dead patients, all had fatigue (100%), three (75%) suffered from headaches, cough, and nausea, and only two (50%) had dyspnea. However, no significant correlation was seen between mortality and any clinical symptoms of COVID-19 ($P>0.05$; Table 2).

The deceased patients in comparison with surviving patients had lower SpO_2 (93.25 ± 3.500 % and 94.13 ± 4.016 %, respectively), higher respiratory rate (19.63 ± 10.690 breaths/min and 17.75 ± 1.258 breaths/min, respectively), higher body temperature (37.750 ± 0.9574°C and 37.163 ± 0.3543°C, respectively), higher pulse rate (88.00 ± 6.272 beats/min and 88.38 ± 15.874 beats/min, respectively), higher systolic (131.25 ± 21.500 mm Hg and 118.25 ± 11.720 mm Hg, respectively) and diastolic (87.00 ± 9.416 mm Hg and 77.13 ± 11.038 mm Hg, respectively) blood pressure, on the first day of hospitalization. However, statistical analysis showed no significant impact of baseline vital signs on patients' mortality ($P>0.05$; Table 3).

At baseline, spiral chest computerized tomography (CT) scan and RT-PCR were performed on all individuals to confirm COVID-19. The chest CT images of all patients showed highly suggestive findings for SARS-CoV-2 infection, while the RT-PCR test was positive at 11 patients. The ground glass opacity was seen in CT images of all KTRs, but no one had honeycomb lung. Two patients had reticular patterns of opacification in their CT images that one died (25%). In addition, lobar consolidation was seen in two surviving patients. Statistical analysis showed no significant difference between survived and non-survived KTRs based on radiological and laboratory evidence of COVID-19 ($P>0.05$).

Most KTRs used mycophenolate and prednisolone

Table 2. Clinical symptoms associated with COVID-19 in KTRs patients

Symptom		Death		*P* value
		No (%)	Yes (%)	
Fatigue	No	2 (25.0)	0 (0.0)	1.00
	Yes	6 (75.0)	4 (100.0)	
Headache	No	6 (75.0)	1 (25.0)	0.120
	Yes	2 (25.0)	3 (75.0)	
Cough	No	2 (25.0)	1 (25.0)	1.00
	Yes	6 (75.0)	3 (75.0)	
Sore throat	No	8 (100.0)	4 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	
Palpitation	No	8 (100.0)	4 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	
Nausea	No	6 (75.0)	1 (25.0)	0.120
	Yes	2 (25.0)	3 (75.0)	
Dyspnea	No	7 (87.5)	2 (50.0)	0.184
	Yes	1 (12.5)	2 (50.0)	
Vomiting	No	5 (62.5)	3 (75.0)	0.667
	Yes	3 (37.5)	1 (25.0)	
Diarrhea	No	7 (87.5)	4 (100.0)	1.00
	Yes	1 (12.5)	0 (0.0)	
Brady cardia	No	8 (100.0)	4 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	
Chest pain	No	7 (87.5)	3 (75.0)	0.590
	Yes	1 (12.5)	1 (25.0)	
Myalgia	No	3 (37.5)	3 (75.0)	0.239
	Yes	5 (62.5)	1 (25.0)	
Anosmia	No	7 (87.5)	4 (100.0)	1.00
	Yes	1 (12.5)	0 (0.0)	

before hospitalization (11, 91.7%, Table 4). Of all dead patients, three (75%) received mycophenolate, and all used prednisolone. However, no significant correlation was seen between non-survival and taking these two drugs ($P=1.00$). In addition, four KTRs used tacrolimus, and six used cyclosporine as part of their immunosuppressive regimen. In both groups, only one patient died (25%, $P=0.667$, and $P=0.239$, respectively). Among all eight surviving patients, no one had received rapamycin. Furthermore, five KTRs took angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and three died (75%). Nevertheless, there was no statistically significant relation ($P=0.12$).

Besides taking SOF-DAC, other medications were prescribed depending on the patient's clinical condition (Table 5). Among four non-survived patients, all (100%) took dexamethasone and methylprednisolone, three patients (75%) used interferon, and just one got remdesivir (25%). However, no medication significantly affected the mortality of KTRs because of COVID-19 ($P>0.05$).

The mean ± SD of various hematological and biochemistry parameters of both survived and non-survived groups are reported in Table 6. Most parameters were measured on the first day of admission, seven days after, and on the last day of hospitalization (which is shown by adding 1, 7, and E subscripts to the symbol of parameters, respectively). The results of the independent samples T-test showed that the mean level of WBC_E was significantly different between two groups of survived and dead patients at a 95% confidence level ($P=0.016$). Further, the mean of each parameter international normalized ratio (INR), C-reactive protein (CRP), ferritin, D-dimer on the last day of hospital stay (INR_E, CRP_E, ferritin $_E$, D-dimer $_E$) was significantly higher in deceased patients than survived ones ($P=0.045$, 0.025, 0.049 and 0.002, respectively).

None of the patients had increased liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during taking SOF and DAC. No clinical and paraclinical complications associated with the use of SOF and DAC were seen in patients during the study period.

Discussion

Early in the novel coronavirus pandemic, the lack of approved treatment has forced medical experts to use various antiviral and anti-inflammatory drugs to control

Table 3. Vital signs of patients on hospital admission

Vital signs Mean (SD)	**Death**		**P value**
	No	**Yes**	
O_2 saturation (%)	94.13 (4.016)	93.25 (3.500)	0.720
Respiratory Rate (breaths/min)	17.75 (1.258)	19.63 (10.690)	0.740
Temperature (°C)	37.163 (.3543)	37.750 (.9574)	0.142
Pulse rate (beats/min)	83.38 (15.874)	88.00 (6.272)	0.594
Systolic blood pressure (mm Hg)	118.25 (11.720)	131.25 (21.500)	0.196
Diastolic blood pressure (mm Hg)	77.13 (11.038)	87.00 (9.416)	0.158

Table 4. Immunosuppressive drugs of KTRs

All patients (n=12)	**Frequency (%)**	**Death**		***P* value**
		No	**Yes**	
Mycophenolate				
Yes	11 (91.7)	8 (100.0)	3 (75.0)	1.00
No	1 (8.3)	0 (0.0)	1 (25.0)	
Tacrolimus				
Yes	4 (33.3)	3 (37.5)	1 (25.0)	0.667
No	8 (66.7)	5 (62.5)	3 (75.0)	
Cyclosporine				
Yes	6 (50.0)	5 (62.5)	1 (25.0)	0.239
No	6 (50.0)	3 (37.5)	3 (75.0)	
Rapamycin				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	-
No	12 (100.0)	8 (100.0)	4(100.0)	
Prednisolone				
Yes	11 (91.7)	7 (87.5)	4 (100.0)	1.00
No	1 (8.3)	1 (12.5)	0 (0.0)	
ACEI/ARB				
Yes	5 (41.7)	2 (25.0)	3 (75.0)	0.12
No	7 (58.3)	6 (75.0)	1 (25.0)	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 5. Treatments for COVID-19 patients besides SOF and DAC

Treatments		Death		*P* value
		No (%)	Yes (%)	
Remdesivir	No	6 (75.0)	3 (75.0)	1.00
	Yes	2 (25.0)	1 (25.0)	
Interferon	No	5 (62.5)	1 (25.0)	0.239
	Yes	3 (37.5)	3 (75.0)	
IVIg	No	8 (100.0)	4 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	
Dexamethasone	No	0 (0.0)	0 (0.0)	-
	Yes	8 (100.0)	4 (100.0)	
Methylprednisolone	No	4 (50.0)	0 (0.0)	1.00
	Yes	4 (50.0)	4 (100.0)	
Hydroxychloroquine	No	7 (87.5)	4 (100.0)	1.00
	Yes	1 (12.5)	0 (0.0)	
Hemoperfusion	No	8 (100.0)	4 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	
Mechanical ventilation	No	8 (100.0)	0 (0.0)	-
	Yes	0 (0.0)	4 (100.0)	

IVIg, Intravenous immune globulin.

clinical symptoms of COVID-19 disease. A multicenter randomized controlled trial showed that the combination of SOF and DAC accompanied with standard care significantly reduced the counted symptoms with no deterioration, improved oxygen saturation, and decreased the incidence of mortality in moderate or severe COVID-19 patients compared to standard care alone (12).

Importantly, among COVID-19 patients, solid organ transplant recipients like KTRs are at high risk for severe COVID-19 owing to suppression of the immune system. Thus, the present study investigated the outcomes of COVID-19 in 12 KTR adults, receiving SOF-DAC treatment in addition to other antiviral and anti-inflammatory medications. To our knowledge, this was the first study to evaluate the SOF-DAC treatment on KTRs with SARS-CoV-2 infection.

Previous studies more considered the outcome of hospitalized KTRs with COVID-19. In these papers, treatment protocols were mainly based on the use of prior recommended drugs, including hydroxychloroquine, azithromycin, high-dose steroids, lopinavir/ritonavir, interferon, and tocilizumab along with changes in immunosuppressive regimens. In a review of six retrospective studies by Jawdeh, which evaluated less than 100 KTRs, the mortality rate was up to 30% (13). Two multi-center cohort studies in Spain demonstrated the fatality rate of 50% associated with COVID-19 among KTRs (8,14).

In our previous single-centered study of 13 adult KTRs with COVID-19, conducted in the early days of the pandemic in Iran, the mortality rate was 69%. By adding SOF and DAC to previously proposed medications, this study found a 33.3% mortality rate of KTRs with SARS-CoV-2 infection. However, because of the small sample size in this research based on our limitations, the mortality rate may suffer from inaccuracy and could not be cited.

Table 6. Laboratory data of KTRs with COVID-19

Laboratory data, Mean (SD)	Death		*P* value
	No	Yes	
WBC_1 (/mm^3)	7645.00 (5900.775)	4742.50 (1506.704)	0.366
WBC_E (/mm^3)	7325.71 (2509.634)	19000.00 (10377.296)	**0.016**
Hemoglobin (g/dL)	10.30 (2.68)	9.32 (1.85)	0.533
Lymph (/mm^3)	5.22 (3.25)	6.66 (7.23)	0.674
BUN_1 (mg/dL)	53.15 (28.8663)	43.25 (15.5858)	0.542
BUN_7 (mg/dL)	51.75 (20.906)	45.75 (16.860)	0.631
BUN_E (mg/dL)	52.38 (24.237)	90.25 (52.734)	0.110
Cr_1 (mg/dL)	2.69 (1.14640)	3.76 (3.14202)	0.552
Cr_7 (mg/dL)	2.61 (1.57889)	2.50 (1.97484)	0.918
Cr_E (mg/dL)	2.46 (1.26096)	4.82 (3.27961)	0.247
AST_1 (U/L)	23.63 (9.665)	29.50 (18.120)	0.471
AST_E (U/L)	30.86 (13.247)	17.00 (0.0)	0.366
ALT_1 (U/L)	20.50 (11.058)	22.50 (8.386)	0.758
ALT_E (U/L)	41.43 (41.323)	20.00 (0.0)	0.654
ALP_1 (U/L)	172.50 (90.626)	153.75 (43.285)	0.708
ALP_E (U/L)	137.29 (73.851)	115.00 (0.0)	0.787
Bill T_1 (mg/dL)	1.09 (.66785)	0.60 (.29439)	0.106
Bill T_E (mg/dL)	0.96 (0.4099)	0.0 (0.0)	-
Bill D_1 (mg/dL)	0.35 (0.2726)	0.25 (.1915)	0.530
Bill D_E (mg/dL)	0.56 (.4336)	0.0 (0.0)	-
PT_1 (s)	13.20 (2.8904)	13.72 (1.2447)	0.740

Table 6. Continued

Laboratory data, Mean (SD)	Death		*P* value
	No	Yes	
PT_E (s)	10.83 (1.2738)	12.95 (2.9682)	0.153
INR_1	1.08 (0.18079)	1.18 (0.08808)	0.317
INR_E	0.98 (0.14639)	1.23 (0.15716)	**0.045**
HBs Ag (IU)	0.00 (0.000)	0.00 (0.000)	-
HCV Ab (IU)	0.00 (0.000)	0.00 (0.000)	-
CRP_1 (mg/dL)	29.44 (27.0057)	71.25 (39.0246)	0.063
CRP_7 (mg/dL)	19.21 (31.5408)	64.00 (34.3802)	0.056
CRP_E (mg/dL)	27.17 (43.315)	90.25 (15.019)	**0.025**
ESR_1 (mm/h)	50.50 (30.739)	77.25 (16.419)	0.140
ESR_7 (mm/h)	44.86 (33.786)	59.33 (25.736)	0.530
ESR_E (mm/h)	45.67 (26.151)	79.67 (13.796)	0.078
$Ferritin_1$ (ng/mL)	1192.38 (1259.543)	914.75 (1154.466)	0.720
$Ferritin_7$ (ng/mL)	1263.00 (744.864)	1567.33 (1976.616)	0.784
$Ferritin_E$ (ng/mL)	559.14 (509.024)	1636.33 (1022.187)	**0.049**
$D\text{-}dimer_1$ (ng/mL)	483.80 (104.414)	856.00 (704.988)	0.457
$D\text{-}dimer_7$ (ng/mL)	410.00 (0.0)	1443.50 (645.588)	0.416
$D\text{-}dimer_E$ (ng/mL)	313.25 (162.426)	2200.00 (0.0)	**0.002**

PT, prothrombin time; INR, international normalized ratio; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 1, first day of admission; 7, seven days after admission; E, last day of hospitalization.

Thus, more studies with more patients are needed to achieve a reliable mortality rate.

In our study now, the mean age of the non-survived group was more than recovered patients, and most of the dead patients were female. About comorbidities, we observed hypertension in 50% of the study population that all dead patients were hypertensive. Diabetes mellitus was the second most common comorbidity (33.3%) among KTRs with a 25% mortality rate (one of four dead patients). Although we did not find any statistically significant correlation between age, gender, and comorbidities with a mortality rate of patients, there was consensus in previous studies that older age, male sex, hypertension, and diabetes mellitus were predictors of mortality of KTRs with COVID-19 (14-16).

Acute kidney injury is a significant complication in hospitalized patients with SARS-CoV-2 infection and is independently associated with a high fatality rate. Despite preliminary studies in China and Italy reporting up to 10% AKI in COVID-19 patients, the larger population-based surveys showed the widespread presence of AKI and other kidney diseases in COVID-19 patients (3,17). In a large cohort study, Chan et al demonstrated that the AKI occurred in almost 50% of COVID-19 patients, that a quarter of them developed severe AKI and required RRT, particularly acute dialysis. It is important to note that of all COVID-19 patients with AKI, only 30% survived, and their renal function was recovered (3).

Moreover, all of the non-survived patients had AKI. Therefore, the mortality rate in AKI patients was 36.4%. However, the correlation between AKI and mortality was not statistically significant. Following, three patients (27.3%) underwent dialysis due to developing severe AKI and two of them died (66.7%). In KTRs with SARS-CoV-2 infection, the incidence of AKI is remarkably high and has been known to be a significant factor in mortality. A multi-center study by Hartzell et al reported an incidence rate of 89% for AKI among KTR patients (18). This evidence well illustrates the effect of renal involvement on the prognosis of COVID-19 patients. Therefore, accurate patient management in the early stages of COVID-19 and prevention of multi-organ damages, including the kidneys, is very important.

The relationship between immunosuppressive drugs and COVID-19 outcomes is often known as the double-edged sword. Excessive immunosuppression could lead to increased viral load and delayed recovery, while a competent immune system could cause the most severe forms of COVID-19. Solid transplant recipients are more prone to severe SARS-CoV-2 infection by being chronically immunosuppressed. Therefore, efficient adjustment of immunosuppressive drugs plays a significant role in the prognosis of KTRs with COVID-19. However, complete immunosuppression withdrawal is not recommended. In this study, most of the KTRs had a history of receiving mycophenolate and prednisolone (11 patients, 91.7%) at baseline. Although Kato et al showed that mycophenolic acid inhibits the SARS-CoV-2 replication in vitro, expert-opinion-based COVID-19 guidelines recommended to withdraw or reducing the mycophenolate dose in COVID-19 patients (19, 20). In addition, in a prospective cohort study of liver transplant patients with COVID-19, Colmenero et al observed that while mycophenolate treatment initially acted as an independent predictor

to increase the risk of severe COVID-19 in a dose-dependent-manner, calcineurin and mammalian target of rapamycin (mTOR) inhibitors did not cause the worse outcomes (21). In our previous study of 13 KTRs in the early pandemic, because of lacking accurate knowledge of the COVID-19, all immunosuppressive drugs were discontinued or reduced, and dexamethasone was not used in their treatment. However, in the present study, the mycophenolate was discontinued at the baseline and all the patients received dexamethasone and SOF-DAC. In patients with a severe condition, methylprednisolone, remdesivir, and interferon were administered as a part of the treatment regimen. This therapeutic management caused a lower mortality rate of 33.3%.

Considering laboratory biomarkers is important in determining the prognosis of COVID-19 patients and evaluating the treatments. In a review article, Ponti et al demonstrated that hematologic, biochemical, inflammatory, and immune biomarkers show abnormalities in severe COVID-19 patients. Recent studies have shown cytokine-induced coagulation disorders as one of the leading causes of multiple organ damage in patients with severe SARS-CoV-2 infection (22). In a meta-analysis of three large studies, a significant increase of WBC count, serum ferritin, and D-dimer was seen in non-survived patients compared to survivors (23). Further, the rise of inflammatory biomarker CRP has shown an association with the severity of COVID-19 (24). In our study, the laboratory results showed that the mean level of each parameter WBC, INR, CRP, ferritin, D-dimer on the last day of hospital stay was significantly different between two groups of survived and dead patients at a 95% confidence level ($P<0.05$).

Conclusion

According to the high risk of COVID-19 in kidney transplant recipients, SOF combined with DAC may be reduce the mortality rate in KTR patients with SARS-CoV-2 infection. The SOF and DAC appear to be safe and well-tolerated. The immunosuppressive medication regimen must be adjusted in KTRs patients with COVID-19, based on the disease severity and type of immunosuppressive drug. The baseline withdrawal of antimetabolite drugs such as mycophenolate was suggested, thanks to its synergic action with SARS-CoV-2 in deleterious effect on depleting peripheral lymphocytes.

Limitations of the study

Our study results should be interpreted in light of limitations. The main limitation of our study is its small sample size. Furthermore, the retrospective nature of this study made us unable to get all the variables for more analysis. Furthermore, we do not have a control group. Thus, it is impossible to assess a definite association between variables and mortality rate. However, in the time of the COVID-19 pandemic and the urgent need for effective treatment for critically ill patients, including kidney transplant recipients, our study results offer proof of concept and feasibility data for future larger studies.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests. They do not have any financial relationship with the pharmaceutical distributor company, and this drug has been provided to hospitalized patients for free directly through the hospital.

Ethical approval

The principles of the Helsinki Declaration were followed in this research. The study protocol was approved by the Ethical Committee of the Tehran University of Medical Sciences (ethical code #IR.TUMS.DDRI.REC.1399.028). All patients expressed their informed consent through a written form. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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