Journal of Iranian Medical Council, Volume 5, Issue no. 1
http://dx.doi.org/10.18502/jimc.v5i1.9568

Original Article

COVID-19 Disease in Kidney Transplantation Recipients: A Single-Center Study (Experience of Dr. Shariati Hospital)

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Abstract

Background: Coronavirus disease 2019 (COVID-19 disease) is caused by SARS-CoV-2. In December 2019, several outbreaks of severe and life-threatening pneumonia with unknown organism were reported in Wuhan, China and the disease spread rapidly all over the world and caused the biggest pandemic. There was no clear information regarding incidence, morbidity, and mortality rate of COVID-19 disease in kidney transplant recipients or other solid organ transplant recipients. Therefore, we designed a study to evaluate the factors that can have any impact on kidney transplant recipients infected with SARS-Cov2.

Methods: Our research was a retrospective cross-sectional study. The study population was all adult kidney transplant recipients (> 18 years old) who were hospitalized due to COVID-19 disease according to national guidelines from 1st March, 2020 to 20th April, 2020 in Shariati Hospital, Tehran, Iran. Demographic data, common clinical complaints, vital signs, types and dose of immunosuppressive drugs, comorbidity diseases, and basic laboratory tests were extracted from the medical records using a data collection form.

Results: According to the results of our investigation, mortality rate was 69.2% in kidney transplant recipients who were admitted in our hospital. No one died under the age of 47 years, while no one survived over the age of 58 years. As a result, age can be a reliable predictor of survival rate in kidney transplant recipients with COVID-19 pneumonia. All patients in non- survivors' group were elderly and needed intubation, mechanical ventilation, and renal replacement.

Conclusion: In addition to early referral and early start of appropriate and specific treatments of COVID-19 in patients with kidney transplantation, our general advice, is discontinuation of antimetabolite drugs at admission time, dose reduction of calcineurin inhibitors, and even withdrawal of all immunosuppressive drugs except steroids in critical cases.

Keywords: Covid-19, Immunosuppressive drugs, Kidney transplantation, SARS-CoV-2, Steroids

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Received: Jun 25 2021
Accepted: Aug 14 2021

Citation to this article:

Amini M, Yaghoubi SF, Tavakoli F, Fooladgar M, Abdollahpour E, Shahilooy A, et al. COVID-19 Disease in Kidney Transplantation Recipients: A Single-Center Study (Experience of Dr. Shariati Hospital). *J Iran Med Counc.* 2022;5(1):37-47.

Introduction

Coronavirus disease 2019 (COVID-19 disease) is caused by SARS-CoV-2. First time in December 2019, several outbreaks of severe and life-threatening pneumonia with unknown organism were reported in Wuhan city in China. COVID-19 disease spread rapidly all over the world and caused the biggest pandemic in the world (1-3).

The most common manifestations of COVID-19 disease are fever, chills, dyspnea, and cough. Other manifestations are myalgia, bone pain, diarrhea, and headache. In addition to lung, SARS-CoV-2 can cause multi-organ damage including heart, kidney, and liver. At that time, there was no clear information about incidence, morbidity, and mortality rate of COVID-19 disease in kidney transplant recipients or other solid organ transplant recipients. These patients are always more prone to different kinds of infections compared with general population due to immunosuppressive drugs and dysregulation of the immune system. Thus, we decided to evaluate the prevalence of clinical symptoms, signs, comorbidity disease, and laboratory findings of COVID-19 disease in kidney transplant recipients who were admitted due to COVID-19 disease in our center. Also, we studied the prognosis and survival rate of these patients (4-8).

Materials and Methods

Study design and participants

Our research was a retrospective cross-sectional study. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences. The study population was all adult kidney transplant recipients (> 18 years old) who were hospitalized due to COVID-19 disease according to national guidelines from 1st March, 2020 to 20th April, 2020 in Shariati Hospital, Tehran, Iran. Demographic data, common clinical complaints, vital signs, types and dose of immunosuppressive drugs, comorbidity diseases, and basic laboratory tests were extracted from the medical records using a data collection form.

Diagnosis of COVID-19 disease was based on positive PCR for COVID-19 RNA in specimen of throat swab or existence of radiological evidence consistent with COVID-19 pneumonia on spiral chest CT scan in these patients. Blood tests were CBC diff, serum BUN and Creatinine, ESR, CRP, venous blood gas, Serum albumin, serum sodium, potassium, urine analysis, urine culture, and blood culture. Our management strategy for immunosuppressive drugs in kidney transplant recipients with COVID-19 pneumonia was discontinuation of antimetabolite drugs at admission time, dose reduction of calcineurin inhibitor or mTOR drugs, and even withdrawal of all immunosuppressive drugs except steroids in critical cases. Specific treatments for COVID-19 pneumonia were Hydroxychloroquine, Lopinavir/Ritonavir, Atazanavir, Oseltamivir, Azithromycin, Levofloxacin, and IVIG at that point in time.

The criteria for discharge included absence of fever for at least 3 days, substantial improvement in both clinical symptoms and signs, and also radiological signs and two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 hr apart.

All data were checked by three physicians, and a researcher adjudicated any difference in interpretation between the three primary reviewers.

Ethical Issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Tehran University of Medical Sciences approved this study. The institutional ethical committee at Tehran University of Medical Sciences approved all study protocols (IR.TUMS.VCR. REC.1399.212). Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis

Collected data were analyzed using the SPSS software (statistical package for the social sciences version 23.0 SPSS Inc., Chicago Ill, USA). Quantitative variables were expressed as mean, standard deviation or median, and qualitative variables were expressed as count and percentage. The independent sample t test or the Mann Whitney U test was used to χ^2 test, or Fisher's exact test was utilized to compare differences between survivor and non-survivor groups. The Pearson's correlation coefficient test was used to evaluate the significant correlations between the quantitative parameters within each group. Additionally, p-values less than 0.05 were considered significant.

Results

Based on the inclusion criteria, 13 kidney transplant recipients with COVID-19 pneumonia were hospitalized from 1st March, 2020 to 20th April, 2020 in Shariati Hospital, Tehran, Iran. Mean age of patients was 54 ± 12 SD years. The youngest and the oldest patients were 35 and 66 years old, respectively. Most of our patients were male (Total: 76.9% male, 23.1% female, non- survivors' group: 77.8% male, survivors' group: 75% male). The sexual distribution of male and female patients was almost similar in both groups.

The time interval between kidney transplantation and achievement of COVID-19 pneumonia was from 2 months to 28 years. Mean time interval between kidney transplantation and achievement of COVID-19 pneumonia was 12.12 years in total population, 11.75 years in survivors' group, and 12.37 years in non-survivors' group. Mean SaO2 of our patients was 90% that in non-survivors' group was less compared to the survivors' group (87 *vs.* 95%).

Most common comorbidity diseases were hypertension (76.9%) and diabetes mellitus (23.1%). Other comorbidity diseases were breast cancer, asthma, Ischemic heart disease, peptic ulcer disease, ADPKD, and acquired cystic disease of kidney. Three patients who died in the hospital had other underlying diseases, one had breast cancer and asthma, and one patient had IHD and a history of CABG.

Patients' demographics and clinical characteristics are reported in table 1.

On the admission day, non- survivors' group had a lower Systolic Blood Pressure (SBP) than survivors' group (SBP = 122 ± 8 SD and 138 ± 5 SD, respectively, p-value = 0.006). No correlation was found between other vital signs [Respiratory Rate (RR), Diastolic Blood Pressure (DBP), Heart Rate (HR), Temp] and mortality rate in our patients (Table 2).

Throat-swab specimens and/or chest CT scan were obtained for SARS-CoV-2 PCR examination after clinical remission of symptoms, including fever, cough, dyspnea, *etc*. Different tools for diagnosis are mentioned in table 3.

The most frequent of clinical symptoms were fever, dyspnea, and cough (53.8%). Nausea and vomiting (23.1%), oliguria (23.1%), weakness (15.4%), myalgia (7.7%), and diarrhea (7.7%) were other clinical symptoms (Table 4).

The mean SpO2 of our patients was 90 (SD = 10) on

Table 1. Patients' demographics and clinical characteristics

		Survivors	Non-survivors	Total	p-value
Sex	Female	25.0%	22.2%	23.1%	-
	Male	75.0%	77.8%	76.9%	
Age (mean ± SD)		41 ± 6	60 ± 9	54 ± 12	0.003
Transplant duration (years) (mean ± SD)		11.75 ± 7.27	12.37 ± 11.83	12.12 ± 9.77	-
Diabetes mellitus (DM) (%)	No	100.0%	66.7%	76.9%	-
	Yes	0.0%	33.3%	23.1%	-
Hypertension (HTN) (%)	No	0.0%	33.3%	23.1%	-
	Yes	100.0%	66.7%	76.9%	-
Other Past Medical History (PMH) (%)	None	50.0%	66.7%	61.5%	-
	ADPKD	25.0%	0.0%	7.7%	-
	Breast Cancer & Asthma	0.0%	11.1%	7.7%	-
	IHD & CABG	0.0%	11.1%	7.7%	-
	Polycystic Kidney	0.0%	11.1%	7.7%	-
	PUD	25.0%	0.0%	7.7%	-

Table 2. Vital signs on the first day of admission

Vital signs	Non- survivors	Survivors	Total	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	-
DBP	73 ± 11	83 ± 10	76 ± 11	-
SBP	122 ± 8	138 ± 5	127 ± 11	0.006
PR	92 ± 16	89 ± 4	91 ± 14	-
RR	20 ± 2	22 ± 3	20 ± 2	-
Temp	37.4 ± 0.8	37.7 ± 0.4	37.5 ± 0.7	-
SpO_2 %	87 ± 11	95 ± 3	90 ± 10	-

DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; Respiratory Rate: RR; Pulse Rate: PR

Table 3. COVID-19 diagnosis resource

Covid-19 Diagnostic tool	Frequency	Percentage
CT	5	38.5
CT + PCR (Negative)	3	23.1
CT + PCR (Positive)	5	38.5
Total	13	100.0

admission. However, the mean SpO2 of the patients who recovered from Covid-19 was 95% (SD = 3) on the day of admission, which was relatively higher than that of the dead patients (87%, SD = 11) (p-value = 0.195).

Our results showed that patients who failed to survive the infection, had a lower systolic blood pressure than those who recovered on admission (SBP = 122 ± 8 SD and 138 ± 5 SD, respectively, p-value = 0.006). No significant correlation was observed between the other vital signs (respiratory rate, diastolic blood pressure, heart rate, and temperature) and mortality rate in the patients.

The mean temperature of the patients on the admission was 37.7 *°C* in the survivors' group, and 37.4 *°C* in the non-survivors'; this value was 37.5 *°C* in the total study population. Blood examinations were complete blood count, serum BUN and Creatinine, ESR and CRP, Venous blood gas, Serum albumin, serum Sodium, and potassium. Other laboratory examinations were urinalysis, urine culture, and blood culture. CT scan was also performed for all the patients. Frequency of examinations was determined by the treating physician.

Rate of the need to renal replacement therapy, ICU admission, intubation, and mechanical ventilation were higher in non- survivors' than survivors' group. There was a relation between ICU admission and mortality rate. (Total: 69.2% p-value = 0.052). Treatment with IVIG was used for 2 patients with Acute Respiratory Distress Syndrome (ARDS) and acute myocarditis.

Mean neutrophil count, lymphocyte count, serum creatinine, BUN, albumin, CRP, ESR, Na, and K are summarized in table 5. Also, blood culture was positive in two cases of non-survivors' group (*Acinetobacter* and *Escherichia coli*).

Urine sample was evaluated in 10 patients. Except one recovered patient, all of the patients had proteinuria on the admission day. Hematuria was not found in urine sample of the survivor's patients, but it was detected in 77% of non-survivors' patients. On the admission day, 75% of survivors' patients had no WBC, but leukocyturia was detected in 55.5% of non-survivors' patients in their urinalysis. Bacteriuria was shown in 47% of the total population, although

Table 4. Patients' chief complaints on admission

Chief complaint Survivors (%)		survivors (%)	Non-survivors (%)	Total (%)	p-value
Cough	Dry	50.0%	33.3%	38.5%	-
	No	50.0%	44.4%	46.2%	
	Wet	0.0%	22.2%	15.4%	
Weakness	No	100.0%	77.8%	84.6%	-
	Yes	0.0%	22.2%	15.4%	
Fever	No	0.0%	66.7%	46.2%	**0.026**
	Yes	100.0%	33.3%	53.8%	
Dyspnea	No	75.0%	33.3%	46.2%	-
	Yes	25.0%	66.7%	53.8%	
Nausea and vomit	No	100.0%	66.7%	76.9%	-
	Yes	0.0%	33.3%	23.1%	
Diarrhea	No	100.0%	88.9%	92.3%	-
	Yes	0.0%	11.1%	7.7%	
Oliguria	No	100.0%	66.7%	76.9%	-
	Yes	0.0%	33.3%	23.1%	
Other chief complaints	Anorexia	0.0%	11.1%	7.7%	-
	Chest Pain	0.0%	11.1%	7.7%	
	Low O_2 Sat	0.0%	11.1%	7.7%	
	Low O_2 Sat & Bloating	0.0%	11.1%	7.7%	
	Myalgia	0.0%	11.1%	7.7%	
	Number	100.0%	44.4%	61.5%	

it was more prevalent in non-survivors' (55.5%) than survivors' patients (45%). Urine culture was positive in one patient (Table 5). A more detailed lab data obtained during admission is reported in table 5.

During the hospitalization, two patients received IVIG treatment due to ARDS in one patient and myocarditis in the other.

There was a relation between the need for ICU admission and mortality, and 69.2% of the patients were admitted to ICU during hospitalization, comprising 25% of the recovered patients and 88.9% of the patients who failed to survive (p-value = 0.052). 69.2% of our patients got intubated in hospital. Intubation rate was higher in non-survivors, and 88.9% of non-survivors eventually needed Intubation, while only 25% of the recovered patients needed intubation during admission (p-value = 0.052). 53.8% of the patients underwent dialysis in the hospital. One of the recovered patients (25%) needed two sessions of dialysis during the hospitalization, and 75% of recovered patients failed to undergo dialysis during admission, although 66.7% of non-survivors had to undergo dialysis. More detailed information is mentioned in table 6.

In some patients who were admitted with severe condition, Calcineurin Inhibitors (CNIs) were discontinued. Steroid was continued with intravenous forms (Hydrocortisone 50 to 100 *mg* three times per day) or oral steroids (one patient, prednisolone 30 *mg*). Some patients received hydroxychloroquine and some of them received Kaletra.

-11 patients received 2.5-20 *mg* of oral steroids prior to admission

-10 patients used 720-1500 *mg* of mycophenolic acid

Table 5. Lab data obtained during admission

		Non- survivors		Survivors		Total	
Neutrophil count(%): mean ± SD		84 ± 10		75 ± 5		82 ± 10	
Lymphocyte count(%): mean ± SD		9 ± 7		16 ± 6		10 ± 7	
Na (mean ± SD)		139 ± 3		139 ± 4		138 ± 4	
K (mean ± SD)		4.49 ± 0.66		4.23 ± 0.38		4.41 ± 0.58	
Alb (mean ± SD)		3.26 ± 0.71		3.32 ± 0.59		3.27 ± 0.65	
CRP (mean ± SD)		60.4 ± 22.4		50.4 ± 46.2		56.8 ± 31.1	
ESR (mean ± SD)		51 ± 31		66 ± 41		61 ± 35	
U/A_SG (mean ± SD)		1015 ± 5		1011 ± 3		1013 ± 4	
U/A_pr , N(%)	Missing	3	33.3%	0	0.0%	3	23.1%
	1+	1	11.1%	0	0.0%	1	7.7%
	2+	0	0.0%	1	25.0%	1	7.7%
	3+	2	22.2%	1	25.0%	3	23.1%
	Neg	1	11.1	0	0.0%	1	7.7%
	Trace	2	22.2%	2	50.0%	4	30.8%
U/A_Blood, (%)N	Missing	3	33.3%	0	0.0%	3	23.1%
	2+	1	11.1%	0	0.0%	1	7.7%
	3+	2	22.2%	0	0.0%	2	15.4%
	Neg	3	33.3%	4	100.0%	7	53.8%
U/A_WBC, (%) N	Missing	3	33.3%	0	0.0%	3	23.1%
	0	1	11.1%	3	75.0%	4	30.8%
	1-2	2	22.2%	0	0.0%	2	15.4%
	1-3	0	0.0%	1	25.0%	1	7.7%
	10-12	1	11.1%	0	0.0%	1	7.7%
	3-5	1	11.1%	0	0.0%	1	7.7%
	6-8	1	11.1%	0	0.0%	1	7.7%
U/A_Bact, (%) N	Missing	3	33.3%	0	0.0%	3	23.1%
	0	1	11.1%	2	50.0%	3	23.1%
	Few	3	33.3%	1	25.0%	4	30.8%
	Mod	1	11.1%	0	0.0%	1	7.7%
	Neg	0	0.0%	1	25.0%	1	7.7%
	Rare	1	11.1%	0	20.0%	1	7.7%
(%) B/C, N	Missing	2	22.2%	0	0.0%	2	15.4%
	48 hr : Acintobacter_baumannii	1	11.1%	0	0.0%	1	7.7%
	48 hr : Ecoli_enterococus_spp VRE	1	11.1%	0	0.0%	1	7.7%
	Neg	5	55.6%	4	100.0%	9	69.2%
(%) U/C, N	Missing	4	44.4%	1	25.0%	5	38.5%
	Citrobacter spp	1	11.1%	0	0.0%	1	7.7%
	Neg	3	33.3%	3	75.0%	6	46.2%
	Skin contagious	1	11.1%	0	0.0%	1	7.7%
U/A_RBC, (%) N	Missing	3	33.3%	0	0.0%	3	23.1%
	0	1	11.1%	3	75.0%	4	30.8%
	1-2	2	22.2%	0	0.0%	2	15.4%
	15-20	1	11.1%	0	0.0%	1	7.7%
	18-20	1	11.1%	0	0.0%	1	7.7%
	2-4	0	0.0%	1	25.0%	0	7.7%
	Many	1	11.1%	0	0.0%	1	7.7%

daily prior to admission

-5 patients received 50-100 *mg* of cyclosporine, and 3 patients received 1-3 *mg* of tacrolimus daily prior to admission

-2 patients utilized 2 *mg* of sirolimus each day prior to admission

-2 patients used 50-100 *mg* of azathioprine prior to admission

The following section contains more detailed information regarding our patients and their course of hospitalization.

Our 1st patient received 5 *mg* of prednisone and 100 *mg* of cyclosporine and azathioprine daily before admission. CNIs were discontinued for the 1st patient during the first few days of hospitalization. Following the discontinuation, the patient's condition improved. After getting discharged, a low dose of CNI (cyclosporine) and azathioprine was once again started which led to the aggravation of the patient's symptoms after a few days and she discontinued all her drugs herself. Not taking the drugs for 3 days, the patient felt that her condition was getting better, and she started low dose medications. Several weeks after the discharge, she was symptom-free, and her transplanted kidney's function was acceptable.

Our 2nd patient had been receiving 1440 *mg* of mycophenolic acid and 2 mgs of tacrolimus daily before admission. He was discharged after a short period of hospitalization with low dosages of immunosuppressive drugs. The day after his discharge, his condition deteriorated, and he was admitted to another medical center. CNIs and antimetabolite drugs were discontinued there. He was in a good condition after a few weeks of getting discharged.

Our 3rd patient had been receiving 1000 *mg* of mycophenolic acid, 2 *mg* of sirolimus, and 7.5 *mg* of oral steroids daily prior to admission. Low dose Sirolimus (1 *mg*) was continued for him during the hospitalization. After getting discharged, the dosage of Sirolimus was changed back to its initial amount. He was in a good condition several weeks after getting discharged.

Our 4th patient had been receiving 5 *mg* of prednisone, 75 *mg* of cyclosporine, and 50 *mg* of azathioprine daily before the admission. He was treated with azathioprine 50 *mg/day* (dosage equal to that of his prior usage), and cyclosporine was discontinued in the first day of hospitalization. He failed to survive the disease. It is likely that the discontinuation of azathioprine by the treating physician could have led to a better outcome.

Our 5th patient had been receiving 1000 *mg* of mycophenolic acid and 7.5 *mg* of prednisone every day before admission. Sirolimus was prescribed for this patient. He had not received sirolimus prior to admission. He failed to survive the disease.

Our 6th patient had been receiving 1500 *mg* of mycophenolic acid and 2.5 *mg* of prednisone daily prior to admission. This patient received three doses of methyl prednisolone pulses (125 *mg*) and intravenous immune globulin due to acute respiratory

Table 6. Dialysis, ICU care, and IVIG injection during patients' admission.

		Non-survivors %	Survivors %	Total %	p-value
Dialysis	No	33.3%	75%	46.2%	0.266
	Yes	66.7%	25%	53.8%	
ICU	No	11.1%	75.0%	30.8%	0.052
	Yes	88.9%	25.0%	69.2%	
Intubated	No	11.1%	75.0%	30.8%	0.052
	Yes	88.9%	25.0%	69.2%	
IVIG Indication	ARDS	11.1%	0.0%	7.7%	-
	Myocarditis	11.1%	0.0%	7.7%	
	No	77.8%	100.0%	84.6%	

distress syndrome in three consequent days. He also died in the hospital.

Our 7th patient had been receiving 720 *mg* of mycophenolic acid, 5 *mg* of prednisone and 3 *mg* of tacrolimus every day before admission. This patient received 100 *mg* of intravenous hydrocortisone 3 times a day and intravenous immune globulin due to myocarditis. He died during the admission.

Our 8th patient had been receiving 1000 *mg* of mycophenolic acid and 3 *mg* of sirolimus daily prior to admission. CNIs were discontinued in our 4th patient due to his deteriorating condition. After getting stable, the medication was restarted, but it was once again discontinued after only 2 days due to high blood concentration. He underwent two sessions of dialysis during admission and eventually died in the hospital.

Our 9th patient had been receiving 1000 *mg* of mycophenolic acid and 20 *mg* of prednisone every day before admission. As she was admitted to the hospital, mycophenolic acid was discontinued, and prednisone dose was increased to 37.5 *mg*/day. She did not survive the infection.

Our 10th patient had been receiving 1500 *mg* of mycophenolic acid, 15 *mg* of prednisone, and 100 *mg* of cyclosporine daily before admission. Cyclosporine was discontinued on admission and mycophenolic acid was also discontinued on the second day of hospitalization. His prednisone dosage was increased to 30 *mg*/day. He died in the hospital after 14 days.

Our 11th patient had been receiving 1500 *mg* of mycophenolic acid, 5 mg of prednisone and 2 *mg* of tacrolimus prior to admission. Mycophenolic acid was discontinued on the first day of admission, and prednisone dosage was increased to 10 *mg* per day. Tacrolimus dosage was not changed and was continued for the patient in the same manner. She was discharged after 13 days of hospitalization. Overall, 9 out of 13 patients died during the admission.

Discussion

According to the results of our investigation, mortality rate was 69.2% in kidney transplant recipients who were admitted in our hospital. Survivor patients' group were younger than non-survivor patients' (mean age = 41 ± 6 SD and mean age = 60 ± 9 SD, respectively). No one died under the age of 47 years, while no one survived over the age of 58 years. As a result, age can be a reliable predictor of survival rate in kidney transplant recipients with Covid-19 pneumonia (p-value = 0.003). All patients in non-survivors' group were elderly and needed intubation, mechanical ventilation, and renal replacement.

In other reported studies, mortality rate was 28 to 47%. The number of our patients was limited and it was difficult to find a significant relationship between kidney transplantation and morbidity and mortality rate of COVID-19 disease. Therefore, these results should be considered alongside other studies from other medical centers.

One of the most important aspects to discover the relationship between kidney transplantation and morbidity and mortality rate of COVID-19 disease, can be focusing on the amount and type of immunosuppressive drugs and the difference between time of continuation and discontinuation of them.

Enver Akalin *et al* at Montefiore Medical Center in the US from March 16 to April 1, 2020 evaluated 36 adult kidney-transplant recipients with COVID-19 disease. The mortality rate was 28%. The most common initial symptoms were fever 58%, cough 53%, and dyspnea 44%, respectively. 72% of the patients were male. Median age of the patients was 60 years. The most common comorbidities were hypertension (94%) and diabetes mellitus (69%). Need for hospitalization, intubation, and renal replacement therapy were 78, 39, and 21%, respectively. They suggested to decrease the dose of immunosuppressive drugs in kidney-transplant recipients with COVID-19 disease, especially in those who have recently received anti-thymocyte globulin (8).

Nicola Bossini *et al*, from March 1 to April 16, 2020 evaluated 53 adult kidney-transplant recipients with COVID-19 disease who were admitted in 3 centers in Italy. The mortality rate was 33 %. Median age of the patients was 60 years. 79% of the patients were male. The most common comorbidities were hypertension (79%), diabetes mellitus (21%), and heart disease (19%). Need to hospitalization, incidence of ARDS, Acute Kidney Injury (AKI), ICU stay, and renal replacement therapy were 85, 60, 33, 22, and 20%, respectively. They suggested that age over 60 years and dyspnea on admission day with only a small trend toward an increased risk of death for patients on

tacrolimus, can be a predictor of mortality (9).

Sophie Caillard *et al* from March to April 2020 evaluated 279 adult kidney-transplant recipients with COVID-19 disease who were admitted in 3 centers in France. The mortality rate was 23 %. Median age of the patients was 61.6 years. 65% of the patients were male. Fever, cough, dyspnea, and diarrhea were the most common symptoms. The most common comorbidities were hypertension (90%), diabetes mellitus (41%), and heart disease (36%). Need to hospitalization, incidence of AKI, ICU stay, and renal replacement therapy were 87, 44, 36, and 11%, respectively. Graft loss occurred in 4%. They suggested that the age over 60 years, cardiovascular risk, and dyspnea on admission day, can be a predictor of mortality (10).

Marta Crespo *et al* evaluated 414 adult kidney-transplant recipients with COVID-19 disease who were admitted in a multi-center study in 2020 in Spain. The mortality rate was 50 %. Median age of the patients was 73.6 years. 75% of the patients were male. 88% of the patients were Caucasian. Fever, respiratory symptoms, and dyspnea were the most frequent COVID-19-related symptoms, and 81.4% of them had pneumonia. More than one-third of the patients showed digestive symptoms at diagnosis, combinations of nausea, vomiting, and diarrhea. The most common comorbidities were hypertension (88%), diabetes mellitus (50%), heart disease (50%), and obesity (44%). Most patients were hospitalized, but 12.1% of the patients were in intensive care units, and 17.6% needed ventilator support. Treatment for COVID-19 included frequent dosages of hydroxychloroquine, azithromycin, high-dose steroids, lopinavir/ritonavir, and tocilizumab. Need for hospitalization, incidence of AKI, and ICU stay were 94, 33, and 13%, respectively. They suggested that higher respiratory rate, anemia, lymphopenia, higher serum creatinine, D-Dimer, and C-reactive protein on admission are predictors of mortality (11).

Amulti-centric cohort study including 104 hospitalized kidney transplant patients with COVID-19 disease between March 4 and April 17, 2020 was conducted by Alexandra Fava *et al* in Spain. The mortality rate was 50 %. Median age of the patients was 59.7 years. 56% of the patients were male. The most common comorbidities were hypertension (87%), diabetes mellitus (31%), heart disease (30%), and obesity (27%). Need for hospitalization, incidence of AKI, and ICU stay were 100%, 47%, and 23%, respectively. They suggested that older age, ARDS on admission, and elevated LDH on admission are predictors of mortality (12).

A multi-center study was performed by Susan Hartzell *et al* at which included 18 kidney transplant recipients admitted at Mount Sinai Hospital in USA due to active COVID-19 from March 24 to May 10, 2020. They found that the mortality rate was 39 %. Median age of the patients was 55.2 years. Over 50% of the patients were male. The most common comorbidities were hypertension (90%), obesity (33%), and heart disease (17%). Need to hospitalization, incidence of AKI, and ICU stay were 100, 89, and 61%, respectively. They found out that the humoral immune system is activated in COVID-19 infected kidney transplant recipients (13).

As reported by previous studies (9,12,13), diabetes mellitus and hypertension were the most common comorbidities in the patients, but contrary to our expectations, they were not proven as risk factors for a higher mortality rate in our study group (p-value > 0.05).

Low SBP on the admission day was shown to be an independent risk factor for mortality in our study group (p-value = 0.006). We suggest that future studies assess SBP levels as potential risk factors.

In a previous study, the mortality rate in ICU-admitted COVID-19 patients with a history of kidney transplant was reported as 68% (14). In our study, the mortality rate of the ICU-admitted patients was 88.9%. A possible explanation for this difference may be the continuation of the immunosuppressive drugs during admission.

77% of our non-survivors presented with hematuria on admission day, whereas none of the survivors were shown to have hematuria during the hospitalization. Although no significant association was demonstrated between the presence of hematuria and higher mortality rate in the study (p-value > 0.05), further studies should assess hematuria as a risk factor for the severity of the disease and higher mortality rates in kidney transplant patients hospitalized due to Covid-19. Patients that failed to survive the infection, had needed dialysis during admission more than the

survivors (66.7 *vs*. 25%), but this difference was not statistically significant.

Antimetabolites drugs (mycophenolate mofetil and azathioprine) were discontinued in all the patients, except for one patient whose azathioprine treatment was continued during the hospitalization. CNIs were discontinued in some the severely ill patients on admission. Steroids were continued via intravenous forms (Hydrocortisone or Dexamethasone).

This study had some important limitations. One of the more significant limitations is that given the retrospective nature of this study, we failed to determine some of the inflammatory markers like ferritin and LDH, and some factors such as patients' Body Mass Index (BMI) due to lack of the required data in their medical records, making it impossible to assess any potential association between such factors and the severity of the disease or patient mortality. Limitations such as small sample size could make such evaluations even more difficult and necessitate more caution when taking our results into consideration. We were also unable to determine the factors that influenced the clinicians' decision making regarding the drug prescriptions and the timing of intubation with this study design; therefore, it is difficult to draw conclusions on whether a limitation of resources or other factors caused this high rate of ICU admission and death. Nevertheless, our results seem promising and further studies with larger sample sizes from other centers could help interpret them more appropriately. Our findings suggest that lower amounts of immunosuppression during hospitalization and higher SBPs on admission day could lead to a higher chance of survival. Our study also shows higher chances of survival in patients not requiring ICU care. The results also point out the likelihood of hematuria and dialysis requirement during hospitalization as predictors of a poor outcome in COVID-19 patients with a history of kidney transplant.

We propose that one of the most important things to study can be focusing on the factors that seem to influence the disease course such as hematuria, SBP on admission, need for dialysis in the hospital, the amount of immunosuppression, and the difference between continuation and discontinuation of these drugs. Assessing any correlation between such factors and disease course and prognosis in kidney transplant patients should be the aim of future researches.

Conclusion

In addition to early referral and early start of appropriate and specific treatments of COVID-19 in patients with kidney transplantation, our general advice is to discontinue antimetabolite drugs at admission time, dose reduction of CNIs, and even withdrawal of all immunosuppressive drugs except steroids in critical cases.

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