Medium-Term Outcomes of COVID-19 Infection After Kidney Transplantation for Ongoing Living and Deceased Kidney Transplantations within the COVID-19 Pandemic

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Objectives: To present the early to midterm experience of two referral kidney transplantation centers with living and deceased kidney transplantations that were performed within the COVID-19 pandemic.

Materials and Methods: All cases performed in two referral centers in Iran within the COVID-19 pandemic were investigated. Transplantations were performed from May 2020 to February 2021. The protocol for screening included nasopharyngeal RT-PCR with chest CT scan for living and deceased transplantations in center A and RT-PCR for living transplantations and chest CT scan for deceased transplantations in center B. Patients were followed for 14-26 months after transplantation regarding COVID-19 infection and its outcomes in case of infection.

Results: 103 kidney transplantations were performed during the study period including 54 (52.4%) living and 49 (47.6%) deceased kidney transplantations. Twenty-four recipients (23.3%) and a living donor (1%) were infected with COVID-19. The severity of COVID-19 infection was mild, moderate, severe, and critical in 16 (66.6%), 4 (16.6%), 2 (8.4%), and 2 patients (8.4%), respectively. Two mortalities were observed within transplantation recipients with COVID-19 infection (1.9%). 87.5% (7/8) COVID-19 infections in center B were observed in recipients of deceased transplantations who were screened only by chest CT scan.

Conclusion: The results of this study indicate a low frequency of COVID-19 mortality (1.9% for the whole cohort and 8.3% within COVID-19 infected patients) for recipients of living and deceased kidney transplantation that were performed within the COVID-19 pandemic. The above findings highlight for the first time in a large study the probability of living kidney transplantation during the COVID-19 pandemic in case strict screening of donors and recipients and close supervision of operating rooms and wards are implemented. We further hypothesize the inadequacy of chest CT scan for screening of COVID-19 in kidney transplantation surgery candidates.

Keywords: kidney transplantation; COVID-19 pandemic; living donor; deceased donor; RT-PCR COVID-19 test

INTRODUCTION

With the emergence of coronavirus disease of 2019 (COVID-19) in early 2020, the continuation of kidney transplantation activities was called into serious reconsideration. The adverse consequences of COVID-19 in patients with immune suppression and early reports of high COVID-19 fatality in patients who were previously transplanted[1,2] resulted in the closure of kidney transplantation programs from living donors in most centers. The statistics for deceased kidney transplantations also showed a decrease of 25-90 percent in many centers[3].

As a result, the waiting list for kidney transplantation substantially increased in many countries. For example, the waiting list for kidney transplantation in New York has increased by 100%[1]. Later reports, confirmed the increased propensity for infection with COVID-19 in end-stage renal disease (ESRD) patients waitlisted for transplantation[1]. Frequent visits to dialysis centers which were mainly located in hospitals rendered ESRD patients at a higher risk of infection with COVID-19[1]. High mortality of COVID-19 has been reported in kidney transplantation waitlisted patients. Craig-Shapiro and colleagues reported a 34% mortality rate of COVID-19 in waitlisted patients[1].

Also, it is noteworthy that most published literature on the outcomes of COVID-19 infection in transplantations from living and deceased donors relate to the transplantations performed before the entrance of the COVID-19 pandemic in any country and after that, transplantation activities have been suspended in most centers and up to our best knowledge, there is no large report of ongoing kidney transplantations from living donors within the COVID-19 pandemic.

In this report, we have included the ten-month experience of kidney transplantation from living and deceased donors within the COVID-19 pandemic in two referral centers from Iran. We followed kidney transplant recipients and investigated the frequency of early and mid-term COVID-19 infection in these patients and the outcomes of such an infection in them.

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Table 1. Demographic and operative characteristics of transplantations performed during the COVID-19 pandemic in two referral centers.

Variable	Center A	Center B	Total
Number	53	50	103
Gender; Female, N(%)	21 (39.6)	13 (26.0)	35 (34.0)
Age (years), mean±SD (range)	37.4 ± 13.7 (9-65)	41.4 ± 13.1 (18-69)	40.5 (12-69)
Living donor, N(%)	39 (74)	14 (28)	54 (52)
First transplantation, N(%)	50 (94)	47 (94)	98 (95)
Preemptive transplantation, N(%)	10 (19)	5 (10)	16 (15)
Dialysis duration (months), median (IQR)	12 (5-24)	20 (8-30)	18 (6-30)
Preoperative creatinine; mg/dL, mean ± SD	8.4 ± 3.2	9.9 ± 3.2	8.7 (6.6-10.9)
7th postop day creatinine; mg/dL, median (IQR)	1.5 (1.2-1.9)	1.5 (1.3-2.1)	1.5 (1.3-2.0)
Preoperative hemoglobin; mg/dL, mean ± SD	11.2 ± 1.6	11.1 ± 2.5	11.1 ± 2.1
7th postop day hemoglobin; mg/dL, mean ± SD	10.0 ± 1.5	9.8 ± 1.5	9.9 ± 1.5
Follow up duration (months); median (IQR)	22 (20-24)	22 (20.7-23.7)	22 (20-24)

MATERIALS AND METHODS

After the start of the COVID-19 pandemic in Iran on the 20th of February 2020, the Ministry of Health ordered to suspend all kidney transplantations from living donors. Then in May 2020, permissions for transplantations from living donors were granted on limited indications for donor or recipient. These indications included vascular access for dialysis in recipients and the unavailability of donors in the future due to a change of residential place or workplace for donors. Then based on the review of kidney transplantations from living donors based on the above indications, the restriction on this kind of transplantation was lifted after November 2020.

All cases of kidney transplantations from living and deceased donors performed in two referral transplantation centers in Iran which were done within the COVID-19 pandemic from May 2020 until February 2021 were included in this study. We have previously published our protocol of kidney transplantation(4) and the added details based on the COVID-19 pandemic which was different in the 2 studied centers as explained below:

In center A: All personnel of the transplantation ward and operation rooms were screened for COVID-19 by nasopharyngeal specimens after the start of elective operations in May 2020. The urology ward protocol permitted elective operations for patients after a negative nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) which was performed within 1-3 days before surgery. All cases of emergent or urgent operations for patients who did not have a COVID-19 test result were done in a dedicated operating room which was not used for elective operations. Hospitalization of patients in urology and transplantation wards was permitted once a negative nasopharyngeal PCR was obtained. Patients without a negative COVID-19 test stayed in the Emergency ward or in a transition ward until when the result of the COVID-19 test was prepared. COVID-19 patients with any disease were managed in the COVID-19 ward.

Donors and recipients were first screened before hospitalization regarding clinical signs and symptoms and high-risk behaviors. In case of negative findings on the above screening, donors and recipients were referred for COVID-19 RT-PCR and assessment of COVID-19 serum immunoglobulin M (IgM) and immunoglobulin G (IgG). If the result of the above-mentioned tests were negative, the donor and recipients were referred for chest computed tomography CT scan and consultation by the infectious disease specialist who reviewed the results of PCR, serum IgM and IgG, and chest CT scan and gave permission for transplantation. Recipients of deceased transplantations were also screened for COVID-19 by nasopharyngeal RT-PCR and chest CT scan. Donors and recipients were hospitalized in the transplantation ward 1-2 days before the scheduled operation. The transplantation ward only admitted recipients and donors just before and after transplantation or in the case of need for hospitalization shortly after the discharge. Donor nephrectomy in center A was performed through a mini laparoscopic transperitoneal approach as previously explained[4]. After completion of transplantation, donors and recipients were transferred to the transplantation ward. Immunosuppressive agents included tacrolimus 0.1 mg/kg from 24 hours before transplantation, and the following medications after transplantation: mycophenolate mofetil every 8 hours; valganciclovir once daily. Prednisolone was administered 200mg IV one hour before transplantation and then 50 mg on the 1st postoperative day, 40 mg on the 2nd day, 30 mg on the 3rd day, 20 mg on the 4th day, and 15 mg until discharge. Patients were discharged on 10 mg of prednisolone and referred to a nephrologist one week after discharge for any required change in medications.

In center B: The screening protocol included screening regarding clinical signs and symptoms and high-risk behaviors for the two weeks before admission. In case of negative findings on the above screening, nasopharyngeal RT-PCR was performed for living transplantation donors and recipients. If the result of RT-PCR was negative with negative clinical and history findings no further investigation was performed. Recipients of deceased donors were screened by chest CT scan and clinical signs and symptoms. In case of suspicious findings on the aforementioned investigations, RT-PCR was requested. If no suspicious findings were observed in chest CT scan or clinical evaluation of a deceased transplant recipient in center B, no further investigation was performed. Screening of ward personnel and operating theatres personnel as explained for center A was not performed in center B. Donor nephrectomy in center B was performed through open nephrectomy in flank position.

All patients were followed up after discharge in nephrology and urology clinics and also by phone call.

RESULTS

The first transplantation in center A was performed in the COVID-19 pandemic on the 5th of May 2020 from a living donor and the first transplantation in center B was performed on the 8th of June 2020 from a deceased

Table 2. Details of recipients with COVID-19 infection in the post-transplantation period.

Patients number	Center	Age	Gender	Donor type	Severity*	Hospitalization	Presentation	Medication changes	Duration of infection from transplantation
1	A	22	M	L	Mild	Yes (One day)	Myalgia and mild fever	Symptomatic medication	3 weeks
2	A	53	F	C	Mild	No	Fatigue and myalgia, mild involvement in chest CT	Conservative management	4 months
3$	A	17	M	L	Mild	Yes	Nil	Conservative management	3 weeks
4$	A	22	M	L	Moderate	Yes	Presented with fever and dyspnea, patchy infiltration in chest CT	Remdesivir and plasmapheresis	5 months
5$	A	13	M	C	Mild	No	Non-symptomatic, RT-PCR was performed as screening	Transplant was rejected	1 week
6$	A	34	M	L	Moderate	Yes	Fever and dyspnea, patchy ground-glass in chest CT	Favipiravir, Remdesivir Mycophenolate withheld	10 days
7$	A	65	M	L	Moderate	Yes	Fever and dyspnea	Remdesivir and plasmapheresis	1 month
8	A	27	F	L	Mild	Yes	Fever,cough,dyspnea, mild involvement in chest CT	Conservative management	1 week
9	A	37	M	L	Mild	No	Nil	Nil	1 month
10	A	36	F	L	Mild	No	Fatigue and myalgia	Nil	7 months
11	A	22	F	L	Mild	No	Myalgia, headache	Conservative management	1 year
12	A	47	M	L	Critical	Yes	Severe respiratory symptoms,O_2 saturation drop, ICU admitted (only 1 day), Intubated, Expired	Remdesivir, Bolus steroid	2 months
13	A	29	M	L	Mild	No	Nil	Conservative management	11 months
14	A	32	M	C	Mild	No	Throat pain, fatigue	Sovodak, conservative management	10 months
15	A	36	M	C	Mild	No	Throat pain, fever	conservative management	4 months
16	A	47	F	L	Mild	No	Coryza, headache	conservative management	9 months
17	B	53	M	C	Severe	Yes	Fever and dyspnea, 80% involvement in chest CT	Remdesivir, Bolus steroid Cellcept withhold	2 months
18	B	27	F	C	Mild	No	Nil	Nil	1 week
19	B	51	F	C	Mild	No	Fever and myalgia	Levofloxacin Cellcept dose reduced	9 months
20	B	38	M	C	Critical	Yes	Severe respiratory symptoms, O_2 saturation drop, ICU admitted, Intubated, transplant rejected, Expired	Ramdesivir, plasma exchange, Levofloxacin	2 weeks
21	B	42	M	C	Moderate	Yes	Fever and dyspnea, 40% chest involvement in CT	Remdesivir, Levofloxacin Mycophenolate withhold	1 month
22	B	32	M	C	Mild	No	Fatigue, Myalgia	conservative management	6 months
23	B	68	F	C	Severe	Yes	Dyspnea, Fever	Remdesivir, Steroid	6 months
24	B	50	M	L	Mild	No	Common cold	conservative management	2 months

*Based on the WHO-China Joint Mission Classification (13)
$Patients in center A who were diagnosed with COVID-19 after screening of all patients in consequence to the detection of COVID-19 infection in one of the service personnel of transplantation ward. All these patients were transplanted within a time range of 10 day

donor. One hundred three transplantations were performed collectively in centers A and B from the start dates mentioned above till the end of the study including 53 transplantations in center A and 50 transplantations in center B. The demographics of transplantations performed in the two centers have been presented in **Table 1**.

The reasons for chronic kidney failure were: hypertension (37 patients, 35.9%), idiopathic (14 patients, 13.6%), Alport syndrome (4 patients, 3.9%), diabetes mellitus (4 patients, 3.9%), polycystic kidney disease (7 patients, 6.8%), nephritis syndrome (5 patients, 4.9%), nephrotic syndrome (14 patients, 13.6%), reflux nephropathy (4 patients, 3.9%), and other miscellaneous causes (14 patients, 13.6%).

Patients' follow-up duration ranged from 14 months to 26 months in center A and from 19.5 to 25 months in center B.

Twenty-four patients (23.3%) were diagnosed with COVID-19 infection in the hospitalization period or posttransplantation period investigation including sixteen patients in center A and eight patients in center B. In center A out of sixteen COVID-19 infections, 12 were from living donors, and 4 were from deceased donors. Five of the cases were identified when one of the service personnel of the transplantation ward in center A was identified to be infected with COVID-19. He had mild symptoms for some days before being diagnosed with COVID-19 infection. After this observation, all personnel of the transplantation ward of center A were reinvestigated for COVID-19 infection by nasopharyngeal RT-PCT and also all hospitalized patients in this ward. Furthermore, transplantation was suspended for 2 weeks in this center. During this investigation, 5 transplantation recipients (4 from living donors and one from a deceased donor) and one donor were diagnosed

with COVID-19 infection. Patients without symptoms or with mild symptoms were managed as outpatient and patients with moderate to severe symptoms were kept hospitalized. The donor with COVID-19 infection was a mother who gave her kidney to her child. Both mother and child were hospitalized when screening was performed. The child who was the transplant recipient was not infected and was kept hospitalized and her mother who has COVID-19 infection without any symptoms was managed as an outpatient without any complications or need for readmission. Eleven other COVID-19 infections were detected in the whole transplantations that were performed in center A out of this short period mentioned above. In center A, one patient died due to the severity of pulmonary involvement. Another patient from the center A cohort also died in the follow up period due to cardiac arrest at home.

In center B, 7 posttransplantation COVID-19 infections were observed in recipients of deceased donors (7/35, 20.0%) and only one COVID-19 infection was observed in recipients of living donors (1/14, 7.1%). Four patients were hospitalized due to the severity of their COVID-19 infection of whom one patient died.

Another four patients in the center B cohort experienced mild flu-like symptoms and were assumed to be suffering from common cold according to their nephrologist and did not perform COVID-19 PCR. All these four patients experienced a subtle course of disease and recovered with symptomatic medications.

Details on cases of posttransplantation COVID-19 infection and their management are given in Table 2.

DISCUSSION

The results of this study reveal a recipient COVID-19 mortality rate of 1.9% (2/103) and no mortality for donors for the kidney transplantation activities that were performed under regulatory protocols in the COVID-19 pandemic. To our best knowledge, this is the first report of experience with ongoing living kidney transplantations within the COVID-19 pandemic including short and medium term frequency and outcomes of COVID-19 infection in these recipients. The infection rate with COVID-19 for donors and recipients was 23.3% (24/103) and the mortality rate for transplant patients who were infected with COVID-19 was 8.3% (2/24) during 14-26 months of follow up after transplantation. The reported frequencies show that performing living and deceased kidney transplantations in the COVID-19 pandemic can be permissible in case strict regulatory disciplines are followed to ensure safety in the operation room and hospitalization wards. The mortality percent of recipients with COVID-19 is 3.86 times the average mortality rate of COVID-19 in Iran but is considerably lower than earlier high mortality rates for old-time transplanted patients infected with COVID-19 from our center(2) or other centers around the world which were reported in a range of 6-46%(5). The mortality rate of transplanted patients with COVID-19 in the current report is one of the lowest figures presented in the literature. Also in donors, only one case of COVID-19 infection was observed in a mother who gave her kidney to her child who experienced a mild COVID-19 infection and recovered by outpatient management and did not require hospitalization. One of the interesting findings of this study is that most cases (7/8, 87.5%) of COVID-19 infection in center B were observed in recipients of deceased donors. The protocol for screening of recipients in center B was different for recipients of living versus deceased donors. Recipients of deceased donors were screened only by chest CT scan while recipients of living donors were screened by nasopharyngeal RT-PCR. This observation can challenge the adequacy of chest CT scan in the screening of transplantation recipients.

COVID-19 infection in transplant patients has mostly been reported in patients who received a transplant before the COVID-19 pandemic or from patients who had received a transplant before the entrance of the pandemic to a country or region and then have been infected with COVID-19. One of the main issues investigated in the outcome of COVID-19 infection in transplant patients is the interval between transplantation and infection with COVID-19. Most studies have reported transplants with a long interval between transplantation and infection with COVID-19. In these series, the mortality rate has been reported widely from 6% by Montguad-Marrahi and colleagues (6) to 46 % by Clarke et al.[5]. The relationship of the time since transplantation with the outcome of COVID-19 infection was investigated in two studies(7). These studies failed to disclose any relationship between the time since transplantation and outcomes of COVID-19 in transplant patients. Besides, two studies that investigated the mortality of COVID-19 in transplant patients who were infected within 60 days after transplantation reported a high mortality rate of up to 46% which is one of the highest mortality rates of COVID-19 in transplant patients(8, 9). Nevertheless, there is limited experience on the outcome of COVID-19 in the early time after kidney transplantation and up to our best knowledge, we could not find studies that report the outcomes of ongoing transplantations in living donor transplantations that were performed within the established COVID-19 pandemic. The importance of such investigation lies in the different behavior of people, medical personnel, and hospitals regarding the adoption of COVID-19 safe practices(10, 11). Any delay in the adoption of safety protocols in the advent of COVID-19 in any region can result in higher infection and mortality rates in the primary surge of COVID-19 and relative improvement after the primary surge in many countries due to better adoption and regulation of safety protocols and better access to personal protective equipment. Furthermore, the highest dose of immunosuppressive regimens is in the first month after transplantation and the RECOVERY study reported a favorable outcome of high dose of corticosteroids in some severe cases of COVID-19[12].

In Iran, as indicated above, all living transplantation activities were prohibited after the entrance of COVID-19 by the Ministry of Health. After two months, living kidney transplantations were possible for limited indications of donor and recipient. The deceased kidney transplantations also faced a dramatic drop down in the first two months after the COVID-19 pandemic in Iran. The investigation of the results of living kidney transplantations by limited indications lately by the ministry of health resulted in a lifting of the constrictions for living kidney transplantation during the COVID-19 pandemic by the Ministry of Health.

One of the reasons which cause to think of a different outcome of COVID-19 infection during the early days after kidney transplantation is the high dose of immu-

nosuppressive regimen during the early days after transplantation. This high dose can theoretically predispose patients to a higher propensity for COVID-19 infection. But on the other hand, another theory describes a smoother complication of COVID-19 in early transplantation as the mechanism of tissue injury in COVID-19 is immune-mediated tissue injury which will be smoother under high doses of immunosuppressive regimens[12].

The mortality rate of transplanted patients infected with COVID-19 in the current report is one of the lowest reports. The investigation of the reasons behind this observation is out of the scope of this report. One of the considerations in this report is the performance of donor nephrectomy by mini laparoscopy in one of the reported centers. The favorable outcomes of this report considering the low COVID-19 infection rate in the first month after donation and transplantation is a clue to the relative safety of the described protocol for screening of donors and recipients despite performance of a laparoscopic donor nephrectomy. Previous reports from our center during the early days of the COVID-19 pandemic in Iran revealed a very high mortality (8/12; 75%) of previously transplanted patients with COVID-19 infection in the early advent of COVID-19 in Iran[2]. However, despite sustaining a relatively high mortality among old transplantations with COVID-19 infection, the results of COVID-19 infection in the early days after transplantation in our experience have been more favorable. Further studies are needed to replicate our findings.

In consideration of the results of the current report, the following limitations should be taken into account: This report investigated the COVID-19 infection and mortality of kidney transplantations during the early-midterm period after transplantation, the possibility of infection with COVID-19 and its consequences in the longterm cannot be ruled out however if even such infections occur, it will not influence the early-midterm infection and mortality rate of COVID-19 after transplantation which is the main focus of this study; the protocol for donor and recipient screening and also protocols for screening and personnel and restrictions in the wards and operating rooms were not the same for centers of the study however data regarding outcomes of each center and the details of safety protocols for each center has been explained in this report.

CONCLUSIONS

The findings of our study disclose that provided strict criteria are implemented to screen donors and recipients for kidney transplantation including radiologic, and PCR investigation of COVID-19 infection associated with isolation of transplantation wards and careful monitoring of patients flow in the operating rooms, the performance of ongoing living and also deceased kidney transplantation during the COVID-19 pandemic can be associated with a low mortality profile.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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