ORIGINAL ARTICLE

Kidney Transplantation with Modification of Induction Protocol with Infection Control Strategy during COVID-19 Era: Graft and Patients' Outcomes

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ABSTRACT

Background: *With modifications to the induction techniques, policies against COVID-19 are strongly justified in kidney transplants.* ***Objective:*** *This study evaluated the efficacy of induction protocol modification with infection control strategy at the time of transplantation on renal graft and patient's outcome in the first 3-9 months post-renal transplant.* ***Methodology:*** *Retrospective pilot cohort research involved 24 patients who had liver-kidney or live-related kidney transplantation following the use of COVID-19 hospital transplantation management strategy. Total ATG dosage ranged from 3 mg/kg to 6 mg/kg depending on the patient's risk.* ***Results:*** *Post-transplant COVID-19 infection was detected in 16.6% (4 patients). 12.5% (3 individuals) had mild to moderate symptoms. Serum creatinine (2–2.5 mg/dl) was present in 8.3% of the individuals. 12.5% (3 patients) and 4.16% (1 patient) of COVID-19 infections occurred in the eighth or ninth week following kidney transplantation, with negative seroconversion occurring 10–14 days and 4–6 weeks, respectively, after the diagnosis. The COVID-19 result was a full improvement with increased steroids and decreased mycophenolate mofetil (MMF). The mortality was 0%. 95.8% (23 patients) had satisfactory graft function {Serum creatinine was (1.06–0.23 mg/dl)}. 4.16% (1 patient) had a residual blood creatinine level of 2.1 mg/dl after COVID-19 but didn't require dialysis. 4 patients (16.6%) had delayed graft function, and 2 patients (8.3%) with suspected rejection improved in less than a week without graft failure or the need for further treatment.* ***Conclusion:*** *Induction modification combined with effective infection control measures against COVID-19 is linked to positive renal graft and patient outcomes.*

INTRODUCTION

The new corona virus disease 2019 (COVID-19) infection emerged in Wuhan City, China, in December 2019.[1] Kidney transplant recipients have a great risk of infection due to long-term immune suppression and associated co-morbidities.[2] When transplant patients get organs from deceased donors, COVID-19 infections are more common, and they also seem to develop more frequently closer to the date of transplantation, which suggests a possible role for the induction-depleting medications used at the time of the graft. Similar to this, individuals on steroid-based regimens had a higher probability of developing COVID-19 illness.[3] Therefore, COVID-19 regulations and safeguards are strongly recommended both before and after kidney transplantation. Additionally, during the COVID-19 era, change in induction techniques became a must. This study evaluated the efficacy of induction protocol modification with infection control strategy at the time of transplantation on renal graft and patient's outcome in the first 3-9 months post-renal transplant.

METHODOLOGY

A retrospective pilot cohort study examined 24 patients who underwent live-related kidney transplantation and 1 patient who underwent liver-kidney transplant from June 2020 to April 2021 after the application of the hospital protocol for the management of transplantation during the COVID-19 pandemic illustrated in Figure 1. The strategy includes putting the donor and recipient in home isolation for 14 days before the transplant, doing COVID-19 PCR twice at 48-hour intervals before the transplant, and admitting the recipient and donors three days and one day before operation. Guaranteed social seclusion throughout follow-up for 3–9 months Telemedicine and a longer supply of drugs are being used after a kidney transplant to cut down on visits. Face masks, protective gloves, and schedule spacing are all safeguards used during clinic visits to prevent overcrowding in the waiting area. Following transplantation suspected covid-19 cases will be transported to the hospital designated by the Ministry of Health for confirmation, isolation, treatment, and seroconversion confirmation.

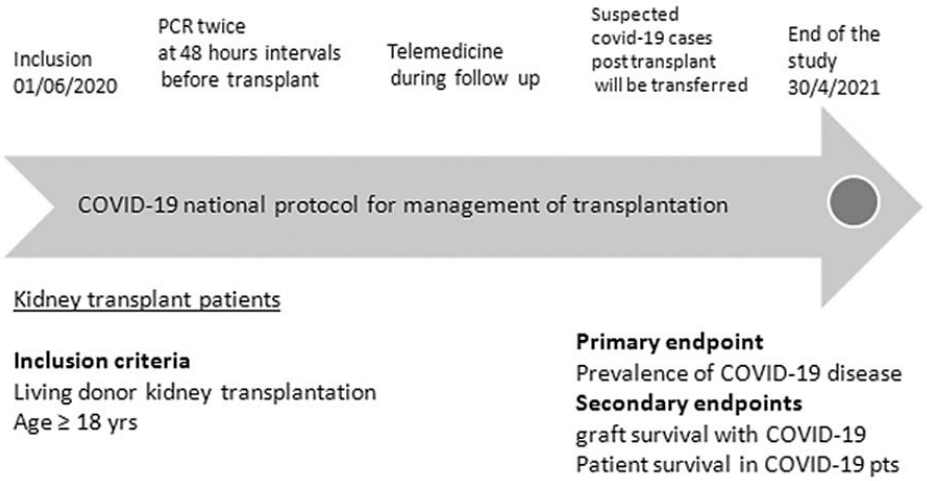

Fig. 1: The image depicts the layout of this observational prospective cohort research, which was carried out on 24 kidney transplant patients, including one who underwent a combined liver and kidney transplant and is currently being actively followed up in our transplant clinic.

The immune-suppressive protocol was by anti-thymocyte globulin (ATG) for induction and maintenance immunosuppression was a steroid, mycophenolate mofetil (MMF), and Tacrolimus. ATG induction dose was 3 mg/kg to 6mg/kg total dose according to the patient's risk. Low to standard-risk transplant recipients received ATG 3 mg/kg total dose over 4 days and high-risk recipients received 4.5 to 6mg/kg total dose over 4 days. For COVID-19-positive transplant patients, immunosuppressive adjustments included a 30% dosage reduction of mycophenolate mofetil and a 30%–50% dose reduction of CNIs in clinically mild to moderate instances, with cessation in patients with severe symptoms or those on ventilators. We attain the policy of vaccination 3 months before transplantation.

All patients' data included history taking, clinical examinations, routine complete blood counts (CBC), and chemistry tests for AST, ALT, total bilirubin, direct bilirubin, and serum creatinine (both before and after transplantation), recorded timing of covid-19 infection after transplantation and its course {recovery, complication or mortality} and graft function {recovery, dysfunction, loss} immediately after transplantation with this modified induction protocol and after any episode of covid-19 infection. A valid informed consent form has been signed by each patient. The protocol was authorized by our institution's ethical committee number (FWA 000017585 FMASU 136 /2021) before the study got underway, and it complies with the Helsinki and Istanbul Declarations.

Statistic evaluation: the statistical software for the social sciences, version 20 (SPSS Inc., Chicago, Illinois, USA) was used to collect, edit, code, and enter the data. Quantitative information was presented as mean with standard deviation (SD) for parametric data or median with interquartile ranges (IQR) for nonparametric data, while qualitative information was given as numbers and percentages.

RESULTS

The demographic data for recipients was shown in Table 1. The mean age was 26.16±10.98 years, the mean serum creatinine before transplant was 7.2±2.12 mg/dl, and the PCR for COVID-19 before kidney transplantation was negative. The patient's immunological background was human leucocytic antigen (HLA) mismatched in 83.3 % (20 patients) ranging from 1 to 3 mismatched alleles. Ten patients (41.6%) tested positive for the panel reactive antibody (PRA). Four patients (16.6%) had donor-specific antibodies (DSA) found, with mean-SD (2956.121361.5) mean fluoresce intensity (MFI). All patients tested negative for complement-dependent cytotoxicity (CDC) crossmatch.

Table 1: Demographic data and immunological background of the kidney transplant recipients.

	Patients N=24
Age in years (mean±SD)	26.16±10.98
duration of transplantation in months	9.93±3.71
S. creatinine before transplantation (mg/dl)	7.2±2.12
	N (%) =24(100%)
sex males	9(37.5%)
females	**15(62.5%)**
Related donor Mothers	**8(33.3%)**
Fathers	6 (25.0%)
Brothers	5(20.8%)
Sisters	3(12.5%)
Sons	1(4.16%)
wife	1(4.16%)
WBCS 10^6/cmm	7.5+3.14
HGB gm/dl	10.25+2.89
PLT 10^6/cmm	239.44+86.67
S.CR (mg/dl)	7.02±2.17
	median(IQR)
AST IU/l	16(10)
ALT IU/L	14.5(5)
ABO	
A	7(29.1%)
B	4 (16.6)
AB	3 (12.5%)
O	10 (41.6%)
CROSS MATCH	negative in all patients
PRA positive patients	10 (41.6%)
PRA CLASS I %	
Patients N (%)	7(29.1%)
median IQR	13(13)
PRA CLASS II %	
Patients N (%)	6(25%)
median IQR	11.5(19.75)
DSA (MFI)	
N (%),	4(16.6%),
MEAN±SD	2956.12±1361.5

Polymerase chain reaction (PCR) post-transplant was used to identify COVID-19 infection in 16.6% (4 patients). Moderate to subclinical symptoms were seen [figure 2]. 8.3% (2 patients) had increasing blood creatinine (2-2.5 mg/dl) and 12.5% (3 patients) had an infection with mild to severe symptoms. 4.16% (1 patient) experienced 2 bouts of infection. The first incident occurred during screening just before the ureteric stent was removed on the ninth week, and the second event occurred 24 weeks after the kidney transplant with modest symptoms (fever, minimal pulmonary ground-glass opacity, and no need for oxygen assistance).

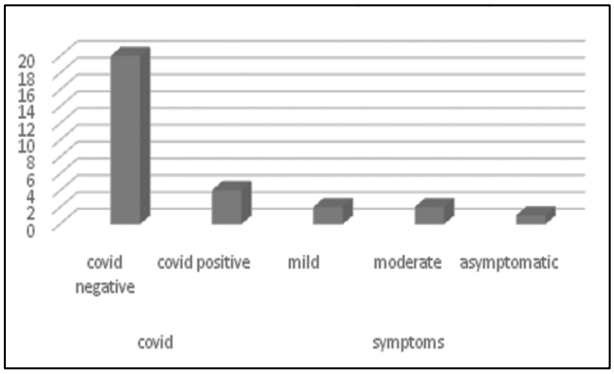

Fig. 2: COVID-19 outcome in first 3-9 months Post renal transplantation

In the post–renal transplant interval COVID-19 infection occurred between the eighth and ninth week in 12.5% (3 patients) and 24 weeks in 4.16% (1 patient), with negative seroconversion occurring 10–14 days and 4–6 weeks following the diagnosis, respectively.

Complete improvement with immune suppression modification (increasing steroid to 40 mg and decreasing mycophenolate mofetil (MMF) dosage 30%), and mortality was 0%, according to the COVID-19 result.

95.8% of patients (23 patients) showed satisfactory graft function, as measured by the mean serum creatinine (1.060.23 mg/dl), in the first 3–9 months following a kidney transplant. 4.16% (1 patient) exhibited residual blood creatinine levels of 2.1 mg/dl after COVID-19 but did not require hemodialysis. In 4 patients (16.6%), there was delayed graft function. Two patients (8.3%) with suspected rejection improved in less than a week, without graft failure or the need for further treatment. **(Table 2)**

Table 2: Renal graft outcome in first 3-9 months

	Patients N=24 mean ± SD
S. creatinine before transplantation mg/dl	7.02±2.17
Good graft function	
N (%)	23 (95.8%)
S. creatinine post-transplant (mg/dl)	1.06±0.23
Delayed graft function	4 (16.6 %)
Rejection	2(8.3%)
COVID-19 infection N (%)	4(16.67%)

DISCUSSION

Early in 2020, COVID-19 spread from China to the majority of the world's nations, putting the majority of people in direct or indirect danger of contracting the virus. Due to their compromised immune system and co-morbid conditions, patients undergoing kidney transplants were thought to be especially vulnerable to developing severe COVID-19 illness.[4] This study evaluated the efficacy of induction protocol modification with infection control strategy at the time of transplantation on renal graft and patient's outcome in the first 3-9 months post-renal transplant.

COVID-19 infection was detected in 4 patients (16.6%) after kidney transplantation with the form of infection ranging from moderate to asymptomatic. 3 patients (12.5%), and 1 patient (4.16 %) had 2 episodes of infection. The most prevalent types were mild in 114 (30.6%) patients and moderate in 101 (27.1%), according to Moataz et al.,[5]in A Systematic Scoping Review for COVID-19 in 823 Transplant patients. But in our study no severe or critical Form was detected despite severe or critical in Moataz et al.,[5] was 157 (42.2%). According to Michelle et al.,[2] 66 (5%) of the 1216 kidney transplant recipients who were recruited had the COVID-19 illness, which is more common than the 0.3% frequency seen in France's general population.

Handling and manipulation of immunosuppressants during COVID-19 infection is an art, and it is the key to recovery from infection with preservation of graft function. Kidney transplantation has faced many problems during the COVID-19 pandemic.[3] In our study, instances demonstrated full recovery after increasing the amount of the steroid to 40 mg and lowering the dosage of the MMF by 30%, with zero percent mortality or no requirement for oxygen support. In a research from China, Zhang et al.[6] observed no reported mortalities among 5 kidney transplants that tested positive for COVID-19 and had non-severe infections. Despite Ahmed et al.,[7] suggest stopping antiproliferative in mild cases with other comorbidities and in severe cases and low trough level (2–4 ng/dl) for infected kidney transplant recipients. According to Alberici etal.,[8] an Italian research, hospitalized transplant patients who tested positive for COVID-19 had a 25% overall death risk. The reported mortality among COVID-19 transplant recipients in another multicenter study by Carvedi and his colleagues[9] was 32%. According to Pereira et al., [10] 46 hospitalized patients did not receive oxygen treatment, and some patients with mild illnesses had positive results and did not require hospitalization. With the use of ERA-EDTA data, the European Renal Association COVID-19 Database (ERACODA) established that kidney transplant recipients in Europe who had COVID-19 had a significant death risk. In 1013 patients, COVID-19-related mortality was 19.9% (17.5-22.5%) among renal transplant recipients.[11] The better outcome was returning to our infection control and Social distancing also none of the covid-19 patients developed severe symptoms. The majority of guidelines advise continuing to use standard immunosuppressive dosages in accordance with recognized protocols.[12] However, British transplant society (BTS) recommendations for all patients support halting antiproliferative medicines and contemplating reducing calcineurin inhibitors, whereas Canadian Society of Transplantation (CST) guidelines advise evaluating a decrease in immune-suppression.[13-14] Immunosuppressive medication manipulation is a highly delicate problem.

In our study, the renal graft function was satisfactory in the first 3 to 9 months following the transplant of 23 patients (95.8%), with a mean serum creatinine of 1.06±0.23 mg/dl. one patient (4.16%) had a serum creatinine of 2.1 mg/dl did not need dialysis. Despite the fact that Torki et al.,[15] showed that only ten patients out of 104 (9.6%) had their transplants in the previous year or less, two of whom passed away with decreased graft function and eight of whom were released with functioning grafts. In kidney transplants, AKI with COVID-19 is typical. According to a review by Moataz et al.,[5] acute kidney injury (AKI) occurred in 63 (7.7%) of the cases, including 29 patients who required de novo dialysis. AKI was only detected in 0.5% of COVID-19, according to Guan et al.[16] This could be because transplant recipients experience a more severe COVID-19 course, some immune suppressants have nephrotoxicity or kidney transplant recipients experience chronic rejection. In our study one patient (4.16%) had a rising serum creatinine of 2.5 mg/dl.

Most transplant recommendations recommend anti-thymocyte globulin induction treatment for kidney transplantation, albeit the ideal dosage and timing of administration have not yet been established.[7,17] In our trial, transplant recipients at low to moderate risk were given 3 mg/kg of ATG over the course of 4 days, whereas recipients at high immunological risk were given 4.5 to 6 mg/kg over the course of 4 days. According to the research, early post-transplant infection problems and morbidity have been linked to full-dose ATG induction treatment (7–10 mg/kg).[18, 19] Recently, it has been popular to use "reduced" dosages of ATG. [19-22] which is highly needed during the COVID-19 pandemic. Our results showed modification of induction was associated with COVID infection in 4 patients (16.67%). symptoms ranging from mild to asymptomatic form did not need hospital admission. This was consistent with Shingare, et al.'s description of two live donor kidney transplant (LDKT) patients who were found to have SARS-COV-2 infection at days 19 and 7 post-transplant in their 2020 study.[23] When diagnosed, they only had a few symptoms, and they never experienced respiratory issues or allograft malfunction. patients with high immunological risk

received a 4.5 to 6mg/kg total dose of ATG over 4 days. PRA was positive in 10 patients (41.6%) patients. DSA was detected in 4 patients (16.6%) with mean ±SD (2956.12±1361.5) MFI. patients were reassessed for DSAs after 3 months that became below 3500 MFI without desensitization protocol. According to Gurk-Turner et al.,[20] total rATG dosages less than or equal to 7.5 mg/kg are safe and effective in attaining a low rate of acute rejection (AR) and graft outcomes equivalent to greater doses in high-risk kidney transplant recipients. 1-6 mg/kg/dose administered over a period of 1 to 10 days. In high-risk patients, Zayan et al.'s[24] assessment of discrepancies in total cumulative dosages found no changes in immunosuppressive outcomes between more or less than 7.5 mg/kg. Less infection and lymphoma were linked to total doses of less than 7.5 mg/kg. In our study modification of induction in kidney transplant recipients with low to standard risk 3 mg/kg total dose and 4.5 to 6mg/kg total dose in high immunological risk was associated with good graft function in 23 patients (95.8%) with mean serum creatinine post-transplant (1.06±0.23) mg/dl. In 4 individuals (16.6%), graft function was observed to be delayed. In less than a week, 2 patients (8.3%) with suspected rejection improved without graft failure or the requirement for dialysis. Klem et al.[25] evaluated the 1-year AR rate, patient survival, and graft survival in kidney transplant recipients (KTRs) receiving a total of 4.5 mg/kg or six mg/kg of ATG; their findings were consistent with ours. They stated that the 4.5 mg/kg and six mg/kg cohorts' 1-year AR rates were 10% and 11%, respectively, and that both groups' 1-year patient and graft survival rates were 100%. Younger age, the lack of additional comorbidities, and a lower dosage of anti-thymocyte globulin (ATG) used as induction may have helped LDKT patients have a better result than deceased donor kidney transplant recipients with COVID-19, according to Shingare et al.[23]

In this study, in the post–renal transplant interval covid-19 infection occurred between the eighth and ninth week in 12.5% (3 patients) and 24 weeks in 4.16% (1 patient), with negative seroconversion occurring 10–14 days and 4–6 weeks following the diagnosis, respectively. the earlier period of post-renal transplant is associated with more risk due to the effect of induction therapy.

CONCLUSION

Induction modification combined with effective infection control measures against COVID-19 is linked to positive renal graft and patient outcomes. The limitation of this study is the small number of patients.

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Statement and declaration

Funding and Competing interests: no funds, grants or other support was received.

Compliance with Ethical standard and consent:

All patients participated in this study have given written informed consent. The ethical approval was obtained from the ethics committee of our institution before the study began, and the procedures used in this study adhere to tenets of Helsinki and Istanbul Declarations.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Author Contributions:

M.E. idea of the research, study design, formulation, reading, and manuscript writing.

Ah.E. and Ab.E. clinical follow-up of patients, writing, reading, and final revision of the manuscript.

S.A. Data collection, sampling, clinical follow-up of patients, reading and interpretation, formulation, and manuscript writing. All authors read and approved the final manuscript.

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