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Kidney Transplantation in Patients With the History of SARS-CoV-2 Infection

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ABSTRACT

Background. The aim of this study is to present the experience and results of kidney transplantation in patients with the history of SARS-CoV-2 infection.

Methods. We retrospectively analyzed waitlisted patients who had a history of SARS-CoV-2 infection and offered a kidney transplant between March 2020 and December 2021.

Results. Of the 97 waitlisted potential kidney transplant recipients who were offered a kidney, 13 (13.4%) had a history of SARS-CoV-2 infection. All patients were tested negative for SARS-CoV-2 at the time of the kidney offer. Successful transplantation was performed in 9 patients (5 male; average age was 40.8 years), with the average time between SARS-CoV-2 infection and transplantation of 8 months. Four of 13 patients with a history of SARS-CoV-2 infection were finally not transplanted, with 2 patients not eligible for transplantation due to significant post-COVID findings in routine pretransplant chest CT scans, and 2 patients were not transplanted because of poor donor organ quality.

Conclusions. Kidney transplantation after SARS-CoV-2 infection is possible in a setting of full recovery from acute infection, negative PCR test, and no pneumonic infiltrates on chest CT scan. A growing number of waitlisted patients with a history of SARS-CoV-2 infection imposes the need for decision-making tools and guidelines for risk/benefit assessment in these patients.

THE ongoing COVID-19 pandemic has a dramatic global effect, which has forced health care systems worldwide to adjust to new realities. Consequently, transplant activity decreased considerably [1]. Furthermore, despite various lockdown strategies and vaccination, infections are still relatively high worldwide [2]. Dialysis patients are a vulnerable subgroup, and an increasing number of waitlisted patients have a history of SARS-CoV-2 infection. Data on dialysis waitlisted patients recovering from SARS-CoV-2 infection are currently scarce and reported only through single case reports. With our extensive expertise about kidney transplantation after SARS-CoV-2 infection, we present the most extensive series of patients to date.

MATERIALS AND METHODS

Waitlisted patients with a history of SARS-CoV-2 infection who were offered a kidney from a deceased or living donor between March 2020, and December 2021 were documented. Data were retrospectively collected and recorded from medical records. Age, sex, age at kidney transplant offer/kidney transplantation, immunosuppressive protocol, donor

type, the severity of SARS-CoV-2 infection, the time between SARS-CoV-2 infection, and kidney transplant offer/kidney transplantation were recorded. Since the outbreak of the COVID-19 pandemic, waitlisted patients with ongoing SARS-CoV-2 infection were temporarily removed from the waiting list. Patients with mild and moderate clinical disease presentation were returned on the list if they had 2 negative polymerase chain reaction (PCR) tests for SARS-CoV-2 ≥ 24 hours apart, had no pulmonary infiltrates found in their chest radiograph, and had no laboratory signs of active inflammation. Patients with the severe clinical presentation were thoroughly evaluated for the waiting list retrieval 3 months after infection with an evaluation workup, including a chest computerized tomography (CT) scan. PCR tests for SARS-CoV-2 and chest CT scans were performed on all potential kidney transplant recipients apart from the routine immediate pretransplant workup at the time of the kidney transplant offer. Patients received a triple immunosuppressive regimen, including calcineurin inhibitor, antiproliferative drug, or mammalian target of rapamycin (mTOR) inhibitor, and steroids. All

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patients received basiliximab as induction immunosuppressive therapy and highly sensitized patients were treated with immunoadsorption and received steroid pulses. The study was approved by the ethics committee of the University Hospital Center Zagreb, Croatia.

RESULTS

Since the outbreak of the COVID-19 pandemic in Croatia in March 2020 through December 2021, 97 waitlisted potential kidney transplant recipients were offered a kidney from a deceased or living donor and referred for transplantation in our center. Twenty-nine patients (29.9%) were not eligible for transplantation because of various recipient or donor reasons, while 68 patients (70.1%) received a kidney transplant. All patients were tested negative for SARS-CoV-2 at the time of the offer. Thirteen (13.4%) potential transplant candidates had a history of SARS-CoV-2 infection. Successful transplantation was performed in 9 patients, with 8 receiving a kidney from a deceased donor. A 63-year-old female patient with a history of SARS-CoV-2 pneumonia received a second kidney transplant, while it was the first kidney transplant for the remaining 8 patients. There were 4 female and 5 male patients with an average age of 40.8 years (range, 18-71 years). Two patients had a history of asymptomatic SARS-CoV-2 infection, 5 presented with a mild form, and 2 had bilateral SARS-CoV-2 pneumonia. The average time between SARS-CoV-2 infection and transplantation was 8 months (range, 3-13 months). Two patients were highly immunized, requiring intensive immunosuppressive therapy, including immunoadsorption and steroid pulses. Other patients received standard immunosuppressive therapy with basiliximab induction, tacrolimus or mTOR- inhibitor, mycophenolate mofetil, and steroids. Four of 13 patients with a history of SARS-CoV-2 infection who were offered a kidney were finally not transplanted. One asymptomatic patient and one with a mild infection were not eligible for transplantation because of significant post-COVID findings on routine pretransplant chest CT scans. Patients with a history of SARS-CoV-2 pneumonia and the other with a history of mild infection were not transplanted because of poor organ quality. The average age was 59 years (range, 37-74 years), all male (Table 1).

DISCUSSION

There are only 9 cases of successful kidney transplantation in patients with a history of SARS-CoV-2 infection reported in the literature to date, all but one from a deceased donor [3–9]. The time between SARS-CoV-2 infection and kidney transplantation varied from 4 weeks [4] to 2.5 months [9]. Our study's average time between the infection and kidney transplantation was 8 months (range, 3-13 months). In previous reports, all kidney transplant recipients received standard immunosuppressive therapy, including basiliximab induction followed by tacrolimus, mofetil (MMF), and steroids [3-6,8,9]. In contrast, the patient reported receiving simultaneous kidney and pancreas transplants received thymoglobulin induction followed by tacrolimus and steroids [7]. Here we report for the first time a

successful kidney transplantation after SARS-CoV-2 infection in 2 highly sensitized patients treated with immunoadsorption. Maintenance dialysis patients are highly vulnerable with mortality rates from acute COVID-19 exceeding 20% [10]. Kidney transplantation is renal replacement therapy of choice for patients with end-stage kidney disease [11]. However, increased susceptibility to infection due to immunosuppressive therapy is a significant concern in pandemics [12]. Therefore, renal transplant programs were suspended worldwide [1]. Early studies show high mortality rates of kidney transplant recipients infected with SARS-CoV-2 ranging from 10% to 50% [13]. In a large population-based study using data from the European Dialysis and Transplant Association (ERA-EDTA) registry, Jager et al investigated mortality after COVID-19 among patients receiving renal replacement therapy. Comparing mortality risk in kidney transplant recipients versus dialysis patients with COVID-19, we found that the mortality risk in transplant recipients was 28% higher [10]. In a large French nationwide study, Thauinat et al compared the effect of the COVID-19 pandemic on the mortality of renal transplant recipients and candidates after the first pandemic wave. In both populations, increased mortality attributed to COVID-19 was observed compared to the period before the pandemic. The authors found that increased risk of death due to COVID-19 was similar for kidney transplant recipients and candidates in high viral risk areas but significantly higher for candidates in low viral risk areas suggesting kidney transplant programs should be maintained in low-risk areas [14]. In the study by Craig-Shapiro et al, waitlisted patients required hospitalization more often (82% vs 65%) and had a higher risk of mortality than renal transplant recipients (34% vs 16%) [15]. They conclude that COVID-19 dramatically affects waitlisted patients by decreasing their opportunities for transplantation and significantly increasing mortality [15]. The decision-making on whether a patient would benefit more from remaining on dialysis or if transplanted remains a significant challenge [16]. Understanding complex immune response to SARS-CoV-2 has a crucial role in assessing the durability of protective immunity after COVID-19 [17]. End-stage renal disease (ESRD) patients have an impaired innate and adoptive immune response; therefore, it is crucial to understand humoral and cellular immune responses after SARS-CoV-2 infection and vaccination. In a recent meta-analysis, Ikizler et al presented a review on the immunogenicity of prior COVID-19 infection and the response to the COVID-19 vaccines among patients on maintenance dialysis and kidney transplant recipients. Data suggest the durability of serologic immune response after COVID-19 infection in both groups. Dialysis patients develop robust antibody titers after the second vaccine dose, while immune response among kidney transplant recipients is much weaker [18]. A robust, delayed T cell immune response was recorded among dialysis patients who became seronegative 6 months after COVID-19 [19]. Ferreira et al investigated a T cell response following SARS-CoV-2 infection and mRNA vaccination in solid organ transplant recipients. While solid organ transplant recipients (SOTRs) after natural SARS-CoV-2 infection generate a robust T cell response,

Table 1. Patient Characteristics; Severity of SARS-CoV-2 Infection; Timing of the Kidney Transplant Offer; the Outcome of the Kidney Transplant Offer; and Immunosuppressive Therapy

PT	Sex	Age (y)	SARS-CoV-2 Infection Characteristics	Time Between SARS-CoV-2 Infection and Potential Tx (months)	Donor Type	Tx	Immunosuppressive Therapy
1	F	24	Asymptomatic	3	DCD	Yes	basiliximab, TAC, MMF, steroids
2	M	25	Mild	9	DCD	Yes	basiliximab, TAC, MMF, steroids
3	M	18	Mild	7	living	Yes	basiliximab, TAC, MMF, steroids
4	M	56	Mild	3	DCD	Yes	basiliximab, TAC, Evero, steroids
5	F	63	Pneumonia	9	DCD	Yes	IA, basiliximab, steroid pulses, basiliximab, TAC, MMF, steroids
6	M	71	Mild	5	DCD	Yes	basiliximab, TAC, MMF, steroids
7	M	44	Pneumonia	11	DCD	Yes	basiliximab, TAC, MMF, steroids
8	F	38	Asymptomatic	12	DCD	Yes	basiliximab, TAC, MMF, steroids
9	F	28	Mild	13	DCD	Yes	IA, basiliximab, steroid pulses, TAC, MMF, steroids
10	F	63	Asymptomatic	5	DCD	Yes	Basiliximab, TAC, MMF, steroids
10	M	37	Asymptomatic	6	DCD	No	N/A
11	M	74	Mild	3	DCD	No	N/A
12	M	67	Mild	10	DCD	No	N/A
13	M	58	Pneumonia	7	DCD	No	N/A

DCD, donor after cardiac death; Evero, everolimus; F, female; M, male; MMF, mycophenolate-mophetil, N/A, not applicable; PT, patient; TAC, tacrolimus; Tx, kidney transplantation.

among vaccinated transplant recipients, the T cell response was low [20]. Therefore, it is fair to hypothesize that waitlisted patients with a history of SARS-CoV-2 infection carry a shield of T cell immunity when infected with COVID-19, and are highly susceptible during the early posttransplant period. Guidelines regarding timing and indications for kidney transplantation in this pandemic lack good evidence and are currently based on experts' opinions based on the emerging evidence. According to current recommendations, all potential recipients should be screened for epidemiologic history, and the most common screening test used is the nasopharyngeal swab PCR test. If screened positive, patients should be excluded as recipients for at least 28 days [21]. Some recommendations are for 2 negative PCR tests at least one day apart to qualify for transplantation after SARS-CoV-2 infection [22]. Other than a negative PCR test, a chest CT scan should be done on all potential recipients with or without a history of SARS-CoV-2 infection [23]. All donors should have a negative PCR test to qualify for organ donation [21]. Puodziukaite et al reported on 2 patients with the history of SARS-CoV-2 infection who received a kidney from SARS-CoV-2 positive patient [9]. All patients from our study were offered a kidney at least 3 months after SARS-CoV-2 infection and were tested negative on the nasopharyngeal swab PCR test at the time of the potential transplantation. Our routine pretransplant evaluation in a pandemic setting includes a CT chest scan. Full recovery, negative nasopharyngeal swab PCR test, no pulmonary infiltrates on chest CT scan, and suitable quality donor qualify patients for kidney transplantation [21]. Apart from these criteria, some cases reported positive IgG antibody testing at transplantation [6–9]. There is even a suggestion for routine serologic IgG antibody testing for all waitlisted patients [6]. In our group, 2 of 13

patients with a history of SARS-CoV-2 infection were not eligible for transplantation because of infection sequelae in terms of pulmonary infiltrates detected on the chest CT scan. In comparison, 11 patients fully recovered and were suitable for transplantation, with 2 of them not transplanted because of the poor quality of donor. Serology testing for SARS-CoV-2 in our series of patients was not done as it was not available at that time. This study has several limitations. First, baseline anti-SARS-CoV-2 antibodies were not determined. Second, the follow-up period is relatively short. Finally, this is a single-center study conducted in a tertiary referral center. Together with a relatively small number of patients in the study, this may limit our results' generalizability. However, this is the first study focused on the problem of kidney transplantation in patients with a history of acute SARS-CoV-2 infection.

CONCLUSIONS

Kidney transplantation after SARS-CoV-2 infection is possible in a setting of full recovery from acute infection, with a negative PCR test and no pneumonic infiltrates on a chest CT scan. A growing number of waitlisted patients with a history of SARS-CoV-2 infection imposes the need for decision-making tools and guidelines for risk/benefit assessment in these patients. Lacking guidelines regarding the indications and timing for kidney transplantation decisions is challenging, and additional studies are needed.

DATA AVAILABILITY

Data will be made available on request.

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