Kidney Transplantation during the SARS-CoV-2 Pandemic in Israel: Experience from a Large-Volume Center

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Abstract: Coronavirus disease 2019 (COVID-19) has affected tens of millions of people globally since it was declared a pandemic by the World Health Organization on 11 March 2020. Since its outbreak in December 2019, the ongoing coronavirus COVID-19 pandemic has led to global social, economic and healthcare crises affecting millions of people and causing the death of hundreds of thousands of people worldwide. As with other fields of healthcare, the pandemic with its heavy workload imposed on hospital services and personnel significantly affected solid organ transplantation. Concerns for potential exposure to the virus and its related severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) have profoundly altered the process of organ donation and recovery, acceptance of organ offers, management of potential recipients and living donors, and above all transplanted and immunosuppressed patients. All those issues required prompt implementation of new practice measures and guidelines as well as continuous adaptations to the fluid and rapidly changing situation. Herein we describe a single transplant center experience with kidney transplantation during the COVID-19 pandemic; we review the national and institutional measures and restrictions undertaken in different phases of the ongoing event as well as the outcomes.

Keywords: COVID-19 infections; kidney transplantation; immunosuppression; anti-thymocyte globulin (ATG); Basiliximab

1. COVID-19 Epidemiology in Israel

The first case of COVID-19 was confirmed in Israel on 21 February 2020. During the following 12 months, more than 750,000 coronavirus cases were confirmed in Israel, and 5577 people died [1]. As in many other parts of the world, the outbreak pattern in Israel was characterized by three waves of contagion. Despite early social distancing and travel measures issued by the Israeli government and Ministry of Health on March 11, the total number of confirmed cases has reached up to 1000 within the first month, reaching a peak of 765 new cases daily in early April and bringing a restrictive national lockdown measure. Following the relaxation of these measures, the number of new patients has substantially increased, and on 10 September 2020, Israel became the country with the highest rate of COVID-19 infections per capita worldwide. The third wave of COVID-19 in Israel has reached its peak in January 2021 with 1433 fatalities (30% of overall Israeli COVID-19 deaths) after a third nationwide lockdown was declared on 24 December 2020 [2,3]. As of 18 May 2020, there were 839,119 confirmed COVID-19 cases and 6382 deaths for a case-fatality ratio of 0.8%.

The morbidity and mortality from COVID-19 are particularly high among patients with underlying chronic diseases and obesity [4–6]. Solid organ transplant patients, including kidney transplant recipients, are at increased risk of serious complications from COVID-19 because of chronic immunosuppressive and comorbidities such as diabetes,
hypothesis, and cardiovascular diseases [7–9]. A systematic review and meta-analysis of COVID-19 in kidney transplant recipients were recently published by Kremer et al. The study included 5599 kidney transplant recipients with COVID-19 and found a risk of mortality of 23%, regardless of sex, age, and comorbidities [10]. Several studies analyzed the risk of severe COVID-19 and related mortality between kidney transplant recipients and non-transplant patients; those studies showed results with opposite tendencies [11,12]. Finally, Panish et al. compared the outcomes of kidney transplant patients with COVID-19 to that of dialysis and waitlisted patients, showing a significantly lower proportion of transplanted patients who contracted COVID-19 compared with waitlisted and dialysis patients and comparable fatality ratio [13].

Official data regarding the kidney transplant recipient population in Israel is lacking, but within the patients registered and followed at our kidney transplant clinic at the Beilinson Medical Center, the mortality rate among infected kidney transplant recipients is 14%.

On 11 December 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19. A two-dose regimen of BNT162b2 mRNA COVID-19 vaccine (Pfizer BioNTech) was shown to confer 95% protection against COVID-19 in persons 16 years of age or older [14]. Israel was the first country to establish an unprecedented national vaccination campaign. The effectiveness of the BNT162b2 vaccine was validated in the general population in Israel [15], bringing in a relatively short period of time the COVID-19 morbidity to low volume, allowing society and economy reopening and normalization. As of March 2021, Israel’s outbreak has eased after hitting its peak in January this year.

2. COVID-19 and Organ Transplantation in Israel

With the outbreak of the disease in Israel, as in other parts of the world, the organ transplant activity was initially suspended, this was due to overall uncertainty and lack of knowledge and data regarding all aspects of management of the disease: clinical (risk of transmission from donor to recipient, risk related to immunosuppression, etc.) and operational (hospital resources and personnel shortage) [16,17]. The impact on organ transplantation varied with respect to organ type with preferential deferral of kidney transplant candidates who were stable on renal replacement therapy [15,18–20].

The Israeli National Transplantation Steering Committee recommended the suspension of the living donor kidney transplant programs commencing 1 March 2020 and allowing only lifesaving procedures such as liver and heart transplants. The kidney transplant activity, both from deceased and living donors, was resumed 2 months later in May 2020.

The pandemic has caused a major disruption of the process of organ donation and recovery, resulting in declining rates of overall organ recovery. In Israel, there were a total of 97 deceased (both brain and circulatory) organ donors in 2020, a mild decrease compared to the previous year when 106 consents for organ donation were obtained. The consent rate remained stable at 60% of overall candidates for donation.

Reasons for the decline in donations were diverse and explained by changes at multiple levels in the transplant process: decline in trauma death donors, decline in hospital and ICU transfers, pressure on intensive care units beds and workforce, and potential donors with SARS-CoV-2 exposure or confirmed COVID-19 [15,19,21].

As opposed to the decline in deceased-donor kidney transplantation, there was an increase in overall living donor kidney transplantation, generally in Israel as in our transplant center. This accelerated activity was enabled due to intense effort of all caregivers at the transplant center and above all the kidney transplant coordinators, a significant increase in the paired exchange kidney transplant cases (58% increase), and most importantly, an increase in the number of living kidney donors by 10 percent in 2020 compared to 2019. This remarkable accomplishment was achieved thanks to a large number of altruistic kidney donors (188 donors in 2020, from 127 donors the year before, a 48% increase) and to the unique activity of “Matnat Chaim” (“Gift of Life”) organization. Matnat Chaim is an
Israeli non-profit organization that recruits and supports kidney donors volunteers. This outstanding enterprise was founded by Rabbi Yeshayahu Heber in 2009, at the time an end-stage renal disease patient prior to receiving a kidney donation. As of 4 April 2021, Matnat Chaim facilitated 1003 live kidney transplants. During 2020, despite the pandemic, Matnat Chaim saw a 30% increase in altruistic donations over 2019, with many young people who donated in memory of Rabbi Heber, who died of COVID-19 on April 2020 at age 55.

Overall, 381 kidney transplants were performed in Israel in 2020 (108 deceased-donor kidney transplants and 273 living-donor kidney transplants). A very mild decrease to the 391 transplants performed in 2019 (143 and 243 deceased and living donors, respectively) with the majority of the procedures performed in our transplant center.

As previously mentioned, the living donor kidney transplant program was suspended during March and April 2020, given the increased risk posed to healthy donors as well as for the recipients receiving induction immunosuppression contracting SARS-CoV-2. During the “COVID-19 year”, 1 March 2020 to 28 February 2021, we performed a total of 185 adult kidney transplants; 124 living donor (related and non-related) kidney transplants (LDKT) and 61 deceased-donor kidney transplants (DDKT). This is in comparison to the parallel period the previous year, from 1 March 2019 to 29 February 2020, where we performed a total of 193 kidney transplants, 124 LDKTs, and 69 DDKTs.

3. General Practice

Molecular COVID-19 testing and interpersonal contacts isolation were at the basis of the evaluation of kidney transplant candidates, live kidney donors, and potential deceased donors.

Kidney transplant recipients may be at a high risk of developing critical COVID-19 illness due to chronic immunosuppression and comorbidities [22]. Kidney donors were scrutinized for prevention of disease transmission to the donor and exposure of the operating room and surgical ward staff.

As a first measure, we adopted the general recommendations of the Israeli Ministry of Health and the National Transplantation Steering Committee, including:

- Donor should have no upper respiratory or other symptoms related to SARS-CoV-2 infection;
- Patients should have no history of traveling abroad in the last 14 days prior to surgery;
- Period of 14-day isolation following exposure to a suspected or proven COVID-19 patient;
- Prior to elective surgery (donor nephrectomy and living donor kidney transplant), candidates must have two nasopharyngeal swab polymerase chain reaction (PCR) COVID-19-negative tests.

The first was obtained in the community within 72 h of hospital admission and the second at the time of arrival to the hospital, within 24 h from surgery. For that reason, admission prior to elective surgery was anticipated and included an overnight stay prior to surgery.

A major team effort was directed toward minimization of inpatients contacts, both with family members and visitors as well with the transplant team personnel. Commencing 1 April 2020, a new patient’s visitor’s policy was strictly enforced. In general, unnecessary patient visits were denied allowing caregivers to enter the transplant unit only in case of debilitated patients with medical power of attorney. This restrictive policy was alleviated only after the national vaccination campaign came into effect in April 2021; from this point forward, one visitor per patient was allowed, with the visitors presenting a digital green certificate as proof of two doses of COVID-19 vaccination and no need for NPS (nasopharyngeal swab) screening.

We acknowledged the difficulty and the psychological burden inflicted on the patients, but the policy was proved to be a valuable measure as no nosocomial inpatient new COVID-19 cases were documented during the study period.
The outbreak of the pandemic was associated with uncertainty regarding the management of immunosuppressed patients and, specifically, their susceptibility to viral infections. As an intuitive protective measure, we sought to reduce the overall immunosuppression burden by avoiding, whenever immunologically appropriate, the usage of anti-thymocyte globulin (ATG) as an induction immunosuppressive agent. ATG administration, with its prolonged T-cell depletion effect [23], is associated with a higher incidence of post-transplant viral infections, most notably involving cytomegalovirus (CMV) and Epstein-Barr virus (EBV) [24]. This practice change affected the deceased-donor kidney transplant immunosuppression guidelines (see ahead).

The high efficacy of the mRNA-based BNT162b2 vaccine against SARS-CoV-2 [16] and the clever and fast coronavirus national immunization program launched by the Israeli authorities on 20 December 2020 has changed dramatically the dynamics of the epidemic in a relatively short period of time. In fact, by 24 February, 85% of individuals older than 60 years were already vaccinated with two doses. As of January 2021, following the American Society of Transplantation [25], the Israeli transplant society recommended people with advanced CKD, those on dialysis, and transplant candidates and recipients to receive the two doses of the BNT162b2 vaccine. However, in regard to kidney transplant recipients, response to vaccination was expected to be diminished [26], particularly in those patients maintained on mycophenolic acid (MPA) immunosuppression [27]. Indeed, our group recently evaluated the rates of antibody response to the mRNA vaccine among kidney transplant recipients, which was proved to be inadequate. In fact, only 112 (36.4%) out of 308 transplant recipients tested positive for anti-S antibodies 2–4 weeks after receiving the second dose of the BNT162b2 vaccine [28]. Further on, Tau et al. reported 25 kidney transplant recipients who had breakthrough COVID-19 infection and severe clinical course after receiving one or two doses of mRNA-based SARS-CoV-2 vaccine [29].

4. Living Donor Kidney Transplant Program

All potential kidney donors had to be screened for COVID-19 by history, chest imaging, and microbiologic testing prior to elective surgery by RT-PCR of an upper respiratory tract specimen (e.g., nasopharyngeal swab).

Initially, patients were instructed to obtain two consecutive negative tests within 72 h from surgery, one at the community and the other upon admission the evening prior to surgery. Commencing October 2021, pre-operative testing was changed to a single RT-PCR performed within 24 h from surgery, usually on the evening of hospital admission.

Candidates with active COVID-19 and/or signs or symptoms of other respiratory illnesses had to be deferred for transplantation. The optimal deferral period is not known. We adopted the AST suggestion [30], waiting until symptoms resolution and at least two negative RT-PCRs prior to approval.

During the study period, we performed two living non-related kidney transplants where the organ was retrieved from a previously positive SARS-CoV-2 donor; those procedures were uneventful.

Kidney recipient candidates had to fulfill the above-mentioned requirements of pre-operative screening. The management of patients who recovered from COVID-19 is not well defined, and data regarding the risk of induced immunosuppression, disease recurrence, and long-term morbidity is lacking [31]. As of February 2021, we approved kidney transplantation patients who were fully recovered clinically from COVID-19 infection. During the study period, we performed 5 of such procedures, all of which were successful, and no COVID-19 recurrence of re-infection was reported.

Our perioperative immunosuppression protocol for living donor kidney transplantation was not affected by the COVID-19 pandemic. For induction immunosuppression, low immunological risk patients (e.g., first transplant, negative panel of reactive antibodies [PRA]) received two 20 mg doses of interleukin 2 receptor antibody basiliximab (Simulect®; Novartis) intraoperatively and on postoperative day number 4. High-risk patients (re-transplantation, any positive PRA > 0%, low acceptable titer of donor-specific antibodies,
etc.) received three doses of 1 mg/Kg rabbit anti-thymocyte globulin (Thymoglobulin®, Sanofi-Genzyme): intra-operative dose and additional two doses postoperatively according to the lymphocytes count (absolute lymphocyte count is monitored daily postoperatively when the count is equal or greater than 0.2 K/µl patients are eligible for the second or third TMG dose).

Maintenance immunosuppression included steroids taper (to a low dose of prednisone 5 mg QD within few weeks), tacrolimus, and mycophenolate.

During the “COVID-19 year”, March 2020 to March 2021, we performed 124 living donor kidney transplants (103 living non-related and 21 living-related donors); of those, 17 patients underwent re-transplantation (14 patients received a second kidney transplant, 1 patient a third transplant, and 2 patients a fourth kidney transplant). Two patients underwent combined kidney and blood stem cell transplant (Stanford protocol), and two patients underwent kidney transplants after previous solid organ transplants (heart/lung and liver). The mean age of the recipients was 50.85 years (22–75 years); 70 were males (56%) and 54 were females (44%).

Of the 124 kidney recipients, 4 patients (3.2%) contracted COVID-19 infection post-transplant; 1 patient had mild disease, 1 patient developed severe clinical scenario but recovered, and 2 patients died (1.6%). Both the patients with mild and severe clinical syndrome received basiliximab induction, whereas the two patients who died received thymoglobulin induction immunosuppression.

The mean time from transplant to COVID-19 infection was 141.5 days (75–228 days).

Of note, two of the donors were eligible for donation after recovery from mild COVID-19 infection.

During the different phases of the pandemic, we maintained our routine pre-transplant process, and donor and recipient selection criteria and work-up were not changed.

Potential kidney donors, who completed their pre-operative evaluation, were assigned to surgery only if they had no symptoms or known contact with SARS-CoV-2 infection, as well as two negative respiratory secretions swabs tested with reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Donor history and COVID-19 testing have become a routine part of the process of donor evaluation as recommended by the UNOS/OPTN, the American Association for the Study of Liver Disease (AASLD), and the American Society of Transplant Surgeons (ASTS). Candidates for donation who had contact with confirmed COVID-19 patients while waiting for surgery had to complete a 14 days quarantine before the surgery date was rescheduled. Later on, since January 2021, as more knowledge about the disease was gathered, we accepted for donation also candidates who had fully recovered from a COVID-19 infection.

5. Deceased-Donor Kidney Transplant and Organ Acceptance Practices

Upon the outbreak of the pandemic, The Israeli National Transplantation Steering Committee recommended against recovering organs from a donor with suspected or confirmed COVID-19, as it was universally accepted that any donor with a current COVID-19 infection would be excluded from donating any organ [32,33]. By March 2020, all potential organ donors were screened for SARS-CoV-2 infection with RT-PCR testing. Starting February 2021, deceased donors with a history of COVID-19 infection were approved for abdominal organs donation. During the study period, we performed three successful transplantations of organs (liver and two kidneys) recovered from donors with previous COVID-19 infections. No transmission of SARS-CoV-2 was reported from the donor to recipients.

As previously mentioned, as a result of the pandemic and concerns regarding excessive immunosuppression in kidney recipients, we adjusted our induction immunosuppression protocol for deceased-donor kidney recipients. Prior to this change, low immunological risk patients received a single dose of 1.5 mg/Kg rabbit anti-thymocyte globulin (Thymoglobulin®, Sanofi-Genzyme) intraoperatively, whereas high-risk recipients received the standard three doses of thymoglobulin 1 mg/kg. Since May 2021, low immunological
risk deceased-donor kidney recipients received basiliximab (2 doses of 20 mg) induction as the low-risk living donor recipients.

During the “COVID-19 year”, March 2020 to March 2021, we performed 61 deceased-
donor kidney transplants, 56 of the organs (91%) retrieved from brain-dead donors (DBD), and 5 kidneys (9%) from donors after circulatory death (DCD). Nine recipients underwent re-transplant (six patients underwent a second kidney transplant, two patients a third transplant, and one patient a fourth kidney transplant). One patient underwent a dual kidney transplant (two-in-one), and another patient underwent simultaneous liver-kidney transplantation (SLK). The mean recipients age was 56 years (range 26–79 years); 40 patients were males (65%) and 21 were females (35%).

Of those 61 patients, 7 patients (11.5%) contracted COVID-19 infection post-transplant, 2 patients who received thymoglobulin induction had mild clinical course, 1 patient who received basiliximab induction had a severe respiratory disease but recovered, and 4 patients (6.5%) died, 3 of them received thymoglobulin induction, and 1 patient received basiliximab. The mean time from transplant to COVID-19 infection was 146 days (40–256 days).

6. Summary

The COVID-19 pandemic posed significant healthcare challenges, magnified in the organ transplant field handling immunosuppressed patients in the community and nosocomial environment. Maintaining high-volume kidney transplant activity under those circumstances required ongoing adaptations under a climate of uncertainty and lack of knowledge. Following an activity suspension period, we resumed the kidney transplant activity owing to a strict social distancing, patient’s visitors, and COVID-19 RT-PCR testing policies. During the study period, the “COVID-19 year”, we managed to maintain transplant volume compared to the previous year, performing a total of 185 adult kidney transplants; 124 living donor (related and non-related) kidney transplants (LDKT), and 61 deceased-donor kidney transplants (DDKT), with suitable clinical.

The main clinical practice change consisted of the transition from thymoglobulin to basiliximab induction immunosuppression for low-risk deceased-donor kidney transplant recipients.

With a median follow-up of 11 months (6–17 months) from kidney transplant, 11 patients (5.94%) acquired post kidney transplant SARS-CoV-2 infection, and 6 patients (3.24%) died.

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Informed Consent Statement: Patient consent was waived.

Data Availability Statement: Institutional database is available upon request. The Israeli national transplant center data is available upon—https://www.adi.gov.il/.

Conflicts of Interest: The authors declare no conflict of interest.

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