

Kidney Transplantation during the SARS-CoV-2 Pandemic in Israel

Subjects: **Transplantation**

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

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][5][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, hypertension, and cardiovascular diseases ^{[7][8][9]}. A systemic review and meta-analysis of COVID-19 in kidney transplant recipients were recently published by Kremer et al. The study included 5559 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 [\[15\]\[18\]\[19\]\[20\]](#).

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.

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. 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).

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.

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.

4. 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 [\[22\]\[23\]](#). 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).

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