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Pediatric kidney transplantation during the COVID-19 pandemic

Hiroshi Tamura

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Abstract

A waiting list for non-emergency transplant medical care was recommended in the first half of 2020 due to the coronavirus disease 2019 (COVID-19) pandemic. Hence, the number of kidney transplants temporarily declined. However, the waiting list for transplant medical care was lifted in the latter half of 2020 with the establishment of a polymerase chain reaction test system and the spread of infection prevention. The basic stance is to recommend vaccination to post-transplant recipients, recipients, and donors who are scheduled to undergo transplantation, and their families, with the start of vaccine therapy in 2021. The mortality rate of patients undergoing kidney transplants who had COVID-19 is slightly higher than healthy persons, and acute kidney injury was reported to lead to graft loss. However, pediatric cases of severe disease are rare and without deaths. Kidney transplantation medical care will be continuously provided by implementing infection prevention and treatments based on the latest evidence, promoting donated kidney transplantation, and hoping that pediatric patients with renal failure will grow up healthy, both physically and mentally, and become independent members of society, just like healthy children.

Key Words: Kidney transplantation; COVID-19 pandemic; Children

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Core Tip: Nearly 60 years have passed since dialysis was first introduced in Japan in 1965 for children with end-stage renal disease. During this period, dialysis therapy, renal transplantation, and renal failure-related treatments (especially clinical applications of erythropoietin and growth hormone) have made remarkable progress, and the era of focusing on prolonging the life of children with end-stage renal disease has completely passed. Patients receiving kidney transplants are at a higher risk of death than the general population during the coronavirus disease 2019 pandemic. However, pediatric cases of severe disease are rare and without deaths. We will continue to provide kidney transplantation medical care by implementing infection prevention measures and treatment based on the latest evidence, and by promoting donated kidney transplantation. We also hope that pediatric patients with renal failure will grow up to be healthy, both physically and mentally, and become independent members of society, just like healthy children.

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INTRODUCTION

In recent years, end-stage renal disease treatment by renal transplantation has become a completely established medical treatment even in the pediatric field with the development of new immunosuppressants and advances in intraoperative and postoperative management[1].

The novel coronavirus infection that spread in 2020 has had a major impact on transplant medicine.

The morbidity and mortality of novel coronavirus disease 2019 (COVID-19) in immunosuppressed patients undergoing kidney transplants were apprehended to be high. Little evidence was presented on corona infection in patients on renal transplant, and many questions were initially unresolved.

This study aimed to explore the treatment of patients undergoing renal transplants in Japan and outline the issues of pediatric end-stage disease treatment during the COVID-19 pandemic.

PEDIATRIC KIDNEY TRANSPLANTATION DURING THE COVID-19 PANDEMIC

COVID-19 infection status

The Japan Society for Transplantation reported 838 people infected with COVID-19 from March 3, 2020, to August 15, 2022. Of these patients, 625 (75%) had kidney transplants, followed by 190 (23%) with liver transplants. Additionally, those in their 50 s and 60 s accounted for 317 (38%) cases (Table 1).

Of the 838 patients who had organ transplants with known progress (1 patient with an unknown prognosis), 26 (3%) died, wherein 12 died over the age of 70 years. The general mortality rate of COVID-19 is approximately 0.2%, and the mortality rate of patients with organ transplants is high although age control is necessary. Conversely, only a few children had severe cases without death (Table 2).

The United States reported that 1925 (10.6%) of 18121 organ transplant recipients were COVID-19 positive. Of these, 35.3% had acute kidney injury and 1.5% had graft loss.

Concomitant cases were 86.7% and 62.2% among COVID-19-positives and 67.2% and 48.5% among non-positives for hypertension and diabetes, respectively ($P < 0.01$). Fewer than 20 (< 1%) deaths occurred among COVID-19-positive organ transplant patients[2]. Interestingly, the mortality rate is the same or slightly lower than that of the general population although the morbidity rate is high.

Moreover, the United States reported that 11% of deaths among waiting patients in 2020 were attributed to COVID-19. These patients were more likely to be male, obese, and belonging to racial/ethnic minorities.

Nearly 1 in 6 (16%) active transplant recipients in the United States died in 2020 due to COVID-19 and were younger, more likely to be obese, less educated, and belong to racial/ethnic minority groups than those who died of other causes. The mortality rate among those waiting (24%) was higher than those who received a kidney transplant (20%) in 2020 than in 2019. This analysis showed a high COVID-19-related mortality rate among waiting list candidates and kidney transplant recipients in the United States in 2020[3].

Risk factors for mortality were analyzed in a meta-analysis of 4440 patients who received renal transplants. Age, diabetes, heart disease, malignancy, and donated kidney transplantation were significant independent risk factors[4].

Japan reported a relatively low number of 6 (0.46%) cases of COVID-19 among 1279 outpatient renal transplant recipients in September 2020. Additionally, there were no fatalities and one person had a graft loss.

Table 1 Number of coronavirus disease 2019-infected transplant patients by organ in Japan as of August 15, 2022

Organ	Kidney	Liver	Lung	Hart	Pancreas	Small intestine
Number	625	190	13	9	1	0

Table 2 Number of coronavirus disease 2019-infected transplant patients by age in Japan as of August 15, 2022

Age (yr)	Under 10	10-29	30-49	50-69	Over 70
Number	55	125	261	317	79
Fatalities	0	0	0	14	12

Graft loss was found in 1 of 6 (16.6%) cases of COVID-19[5]. This is higher than the 1.5% graft loss rate reported in the United States. There is no doubt that a case of kidney transplant has undergone graft loss due to COVID-19 although comparisons are difficult because the numbers of mothers greatly differ.

According to reports overseas, the mortality rate is generally 20%–30%, which is higher than that of the general population[6–10]. The mortality rate in Japan is lower than in overseas reports, which may be due to differences in domestic infection status and reporting timing, although the mortality rate in Japan is higher than in the general population.

Comparison with patients undergoing dialysis

The risk of infection is reported to be twice as high in patients undergoing dialysis than those receiving transplants, but the risk of death varies depending on the country and facility[11,12]. The Japan Society for Transplantation reported that patients undergoing dialysis are 2.5 times higher than patients receiving transplants, as shown in Table 3.

Therefore, the benefits of kidney transplantation are greater than continuing to wait for patients with renal failure in Japan. In particular, pediatric patients on dialysis often develop heart failure due to infection, and no deaths were reported due to post-transplant infection; thus, we believe transplantation is a great advantage. Proceeding with transplants similar to before COVID-19 is necessary while continuing careful infection control and vaccination promotion.

Current status of kidney transplantation during the COVID-19 pandemic

The Japan Society for Transplantation conducted an “Emergency Questionnaire on Transplant Medicine in Japan Due to the Spread of COVID-19” in April and June 2020. The aggregate data suggested an increased number of facilities performing living-donor kidney transplantation, from 38% in April to 48.6% in June.

Donated kidney transplants also steadily increased, from 35.5% in April to 50.0% in June.

However, nearly half of the facilities remained cautious at this point.

The number of kidney transplants has gradually increased since July 2020 due to the infection situation in Japan, infection prevention, infection control measures, and polymerase chain reaction testing system at each transplant facility, which has been recovering to the same level as usual since July 2020.

An international research team, including the University of Paris, has compiled an analysis of the number of organ transplants performed worldwide and revealed a decrease of approximately 16% from 2019 to 2020 due to the influence of the COVID-19 pandemic.

The team collected organ transplant data from 22 countries in Europe, North America, South America, and Asia, and analyzed the impact of the COVID-19 pandemic. Many countries have well-developed medical systems, and 22 countries account for > 60% of the world’s total number of transplants. The team hypothesizes that the full-scale epidemic began on the day in 2020 when each country reported its 100th case. The number of transplants performed until the end of December of the same year was compared with the same period in 2019.

Four organs were analyzed, including the heart, lungs, liver, and kidneys. Multiple organs transplanted into the same patient, such as heart–lung simultaneous transplantation, were counted separately.

The results revealed > 70000 transplants for the four organs combined in 2019, which decreased by > 10000 in 2020 with < 60000 transplants. The overall decrease rate is 15.92%, including 19.14% in kidney, 10.57% in liver, 15.51% in lung, and 5.44% in heart transplants (Table 4)[13]. During the same period, transplants performed in Japan for all four organs accounted for > 2100 in 2019 to > 700 in 2020. The decrease rate is remarkable at 66.71%. The rate of decline in the United Kingdom and France, which were hit by large waves of the pandemic, was approximately 30%, but that in the United States, which also experienced large epidemics, was just > 4%, and Germany remained at > 10%[13].

Table 3 Number of coronavirus disease 2019 cases in Japan and overseas, infection rate and number of deaths, mortality rate as of October 26, 2021

	Total number	Number of infected	Infection rate (%)	Fatalities	Mortality (%)
World	770000000	241000000	3.12	4900000	2.03
United States	328000000	45000000	13.72	720000	1.60
Japan	127000000	1700000	1.34	18000	1.11
Dialysis patient	340000	2600	0.77	412	15.85
Transplant recipient	35000	266	0.75	17	6.39

Table 4 Reduction rate (%) of organ transplants in 2020 due to coronavirus disease 2019

	Total number	Kidney	Liver	Lung	Heart
World	15.92	19.14	10.57	15.51	5.44
Japan	66.71	69.63	67.45	26.47	36.11
United States	4.13	5.44	1.23	10.18	2.25
United Kingdom	31.31	35.54	17.95	47.92	3.87
Germany	10.53	13.15	6.50	11.32	3.40
France	28.96	34.28	19.04	31.27	13.65

Japan's influence is particularly large among other developed countries. Kidney transplantation, which has a large number of organ transplants in Japan, was avoided. Japan reported a low number of organ donations from brain death and a high percentage of living-donor kidney transplantation; thus, poses a risk that the organ donor will become infected with living-donor transplantation. Therefore, not only patients but also medical providers have become more cautious about transplants in Japan.

Vaccine efficacy in patients receiving a renal transplant

The BNT162b2 (Pfizer-BioNTech) vaccine was reported in 39 healthy controls, 19 pre-transplant recipients, and 109 post-transplant recipients. Positive antibody titers were reported in 100% of healthy controls, 90% of pre-transplant recipients, and 45% of post-transplant recipients. The risk factors for non-elevation of antibody titer include advanced age and long history of dialysis before transplantation [14].

Another study on the BNT162b2 (Pfizer-BioNTech) vaccine revealed positive spike protein antibodies in 52.4% of 82 post-transplant recipients 43 d after vaccination and ≥ 60 years as the risk factor for not increasing antibody titers. Age and use of antimetabolites have been reported. A high percentage of post-transplant patients are unable to obtain sufficient antibody titers although the vaccination efficacy cannot be judged based on these results alone due to the small number of studied cases [15].

An evaluation of the booster effect of 3 doses of vaccine was also reported.

The BNT162b2 (Pfizer-BioNTech) vaccine administration in 71 patients receiving kidney transplants at 3-week intervals caused positive antibodies in 34% of cases.

Third vaccination was given to 48 negative-antibody cases after 8 wk, which revealed positive antibodies in 55% of cases. The antibody-positive rate was lower than that of generally healthy people although the number of antibody-positive cases increased after 3 vaccination doses [16].

These results suggest the necessity to consider completing two vaccination doses before transplantation, as much as possible, and ≥ 3 vaccination doses after transplantation.

Issues in Japan (donated kidney transplant)

The proportion of donated kidney transplants in all kidney transplants is approximately 50% and 60% in the United States and the United Kingdom, respectively, whereas only approximately 10% in Japan.

This slump in the number of donated kidney transplants is a major social issue facing all of Japan's transplant medicine, and continued efforts are needed to promote donated kidney transplantation.

Since 2011, when the Revised Organ Transplantation Law came into effect, 10–15 pediatric donor kidney transplants were performed annually in Japan. The average waiting period for all patients is 14.5 years, which is extremely long, but consideration is given to prioritizing children under the age of 16 years for donated kidney transplants, and the average waiting period is 2.8 years. Therefore, kidney donations from pediatric donors were prioritized in children (2018). The number of kidney donations from children has rapidly increased, and nearly 30 pediatric donor kidney transplants have been

performed annually.

The Japan Organ Transplant Network reported that organ donations were made from 60 brain-dead people, in 2020, which decreased by 34 people from the previous year, and taking a closer look at the background is necessary. The number of brain deaths is conceivable to decrease because of the nationwide refraining from going out, which resulted in fewer traffic accidents. Additionally, the number of organ donations, including donations after cardiac arrest, and the number of performed transplants have significantly decreased. The number of organs that can be donated remained small compared to the number of people who wish to receive a transplant. Therefore, further efforts are hoped to be made to spread awareness of transplant medicine, including organ transplant donation cards, as well as the development of artificial organs and regenerative medicine.

CONCLUSION

Nearly 60 years have passed since dialysis was first introduced in Japan in 1965 for children with end-stage renal disease. During this period, dialysis therapy, renal transplantation, and renal failure-related treatments (especially clinical applications of erythropoietin and growth hormone) have made remarkable progress, and the era of focusing on prolonging the life of children with end-stage renal disease has completely passed. Patients receiving kidney transplants are at a higher risk of death than the general population during the COVID-19 pandemic. However, pediatric cases of severe disease are rare and without deaths.

We will continue to provide kidney transplantation medical care by implementing infection prevention measures and treatment based on the latest evidence, and by promoting donated kidney transplantation.

We also hope that pediatric patients with renal failure will grow up to be healthy, both physically and mentally, and become independent members of society, just like healthy children.

FOOTNOTES

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