Relationship Between Tacrolimus Blood Levels and COVID-19 Pandemic in Kidney Transplant Recipients

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Background

The novel coronavirus 2019 infection (COVID-19) has been a challenge for society and health systems worldwide since the WHO declared a pandemic in March 2020. In Japan, COVID-19 prompted Tokyo to restrict on the free movement of people in March 2020.

Kidney transplant recipients are at high risk for critical COVID-19 due to chronic immunosuppression and coexisting conditions. Efforts have been invested in the development of mitigation strategies and manage the acute phase of COVID-19, however, the management of KTx recipients around COVID-19 pandemic is uncertain.

TAC is a current key drug mainly used as an immunosuppressant for KTx recipients . Lower TAC concentration or high intrapatient variability of TAC is one of the causes of acute rejection through the development of de novo donor-specific anti-human luekocyte antigen (HLA) antibodies (dnDSAs) .

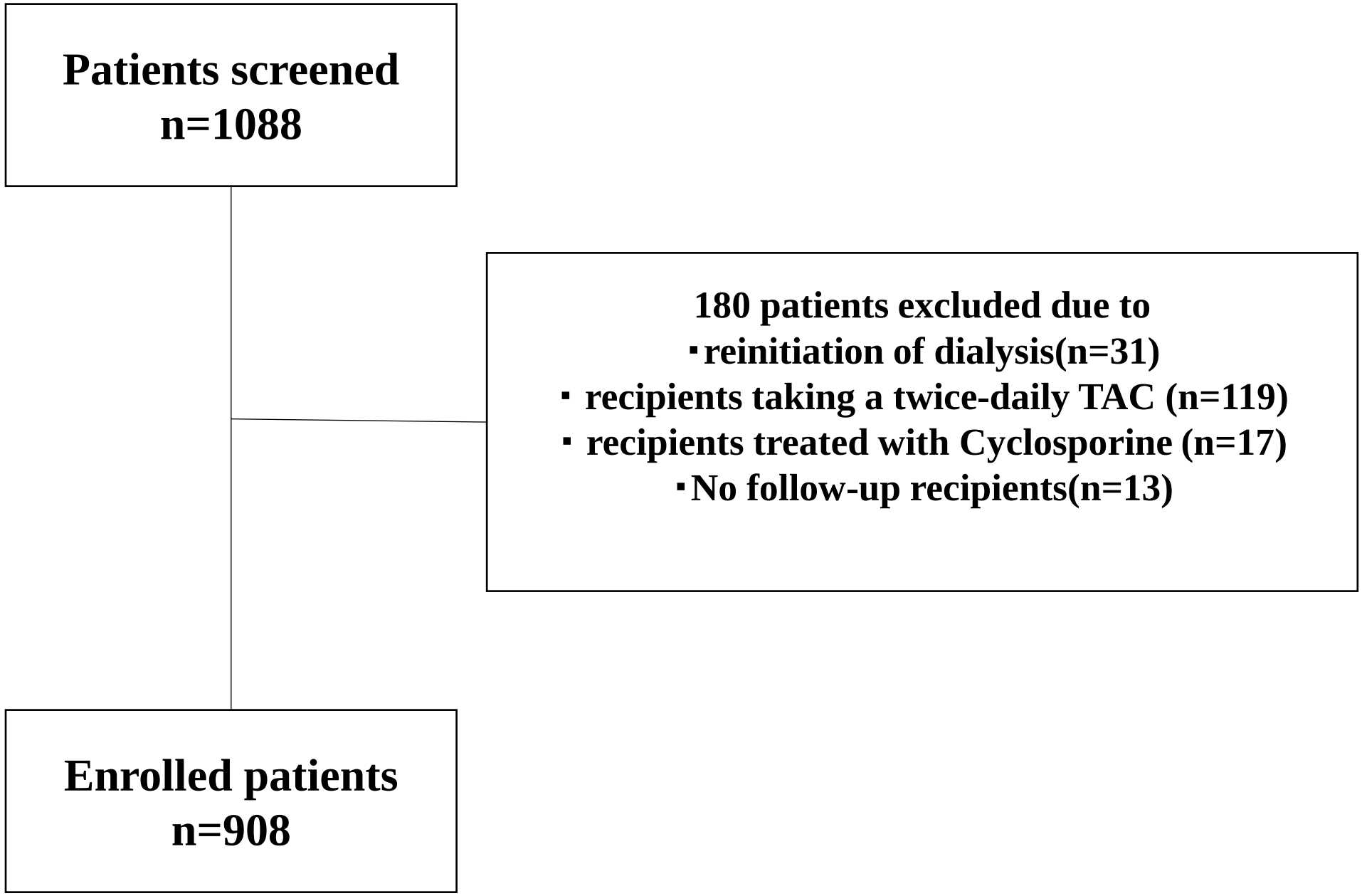
The aim of this study is to evaluate relationship between tacrolimus blood levels and COVID-19 Pandemic in kidney transplant recipients.

Materials and Methods

This single-center retrospective observational study included 1088 patients who had undergone kidney transplantation at the Department of Urology of Tokyo Women's Medical University before August 2018. All patients were followed up at Yochomachi Clinic in Tokyo.

Of these patients, 180 were excluded: reinitiation of dialysis, recipients taking a twice-daily TAC, recipients treated with Cyclosporine, recipients who did not undergo regular follow-up(regular renal biopsies and/or regular monitoring). Thus 908 patients were included in this study.

We evaluated the effects of coronavirus pandemic on clinical outcomes such as tacrolimus blood level, renal function, and rejection in kidney transplant recipients, comparing pandemic data with non-pandemic data obtained between September 2019 and August 2020 in our institute. An unpaired t test was used, and $p < 0.05$ was regarded as statistically significant.

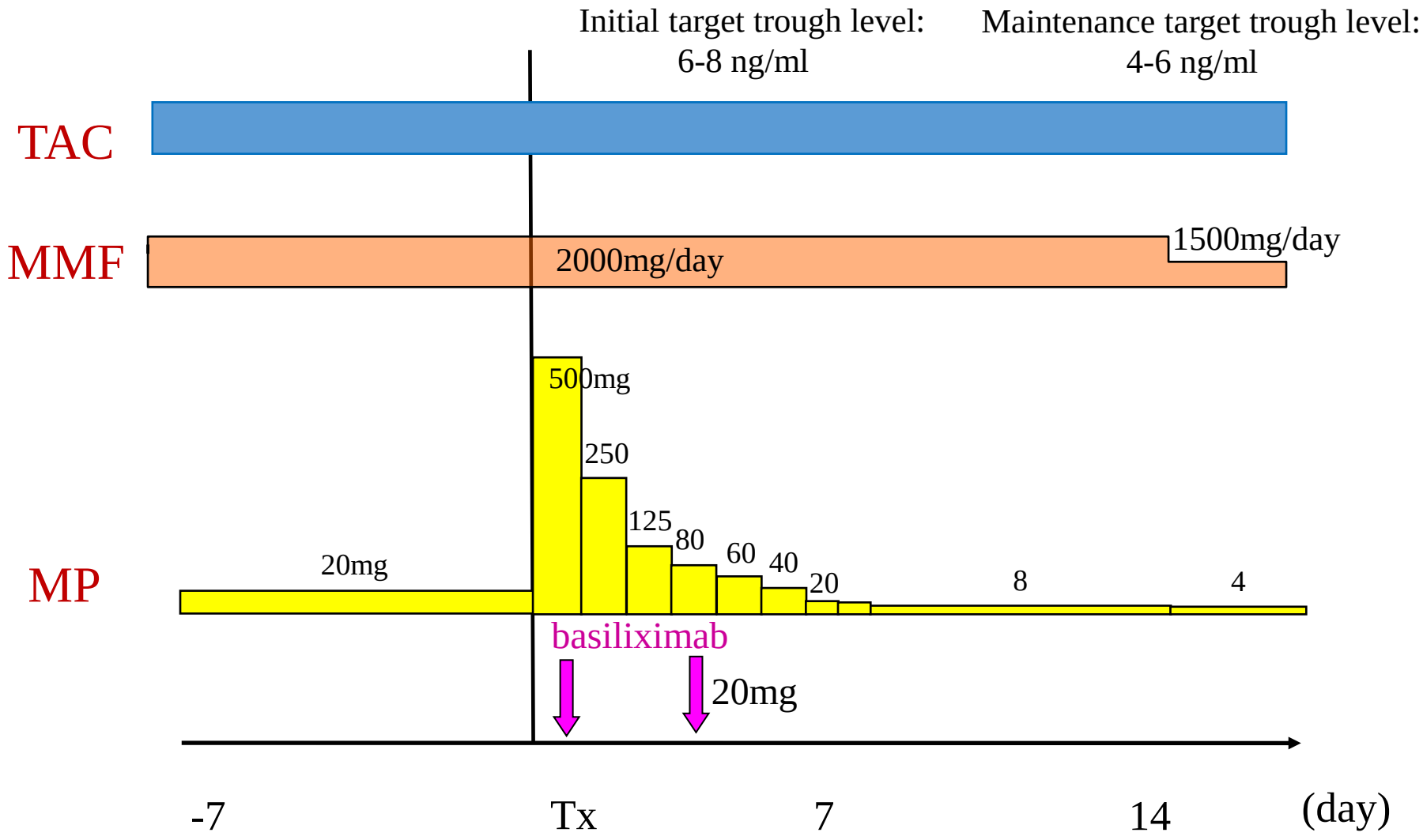

Patients screened
n=1088
180 patients excluded due to
▪reinitiation of dialysis(n=31)
▪ recipients taking a twice-daily TAC (n=119)
▪ recipients treated with Cyclosporine (n=17)
▪No follow-up recipients(n=13)
Enrolled patients
n=908

Immunosuppressive Regimen

Beginning a week before transplantation, all patients were treated following a triple immunosuppressive protocol including TAC (0.1 mg/kg/day), mycophenolate mofetil (MMF; 1500 mg/day if body weight was <50 kg, 2000 mg/day if ≥50 kg) and methylprednisolone (MP; 20 mg/day).

Recipients received basiliximab as an induction immunosuppression therapy, administered on the day of transplantation and on postoperative Day 4 . If the transplant was ABO incompatible, a single dose of rituximab (200 mg) was administered within 3–4 days before the operation.

Plasma exchange (PE) was performed according to a protocol used for ABO-incompatible transplantation or before transplantation in patients with a history of sensitization . This protocol involves a total of two or three sessions before surgery to reduce the anti-A/B antibody titer to ≥1:32 . Some patients also received preoperative PE therapy to prevent recurrence of their original kidney disease, such as focal segmental glomerulosclerosis (FSGS). Intravenous immunoglobulin (IVIG) therapy was also performed for highly sensitized cases. Antithymocyte globulin was not used for induction in our institute.



Patients received a once-daily dose of a prolonged-release formulation (Graceptor; Astellas Fujisawa). The dose was adjusted to maintain a trough level of TAC in whole blood of 8–12 ng/mL during the first month after KTx, 7–9 ng/mL during the second and third months and 4–6 ng/mL thereafter.

Results

Table1. Clinical features in kidney transplant recipients	
Variable	Value
Total number	908
Age, years(SD)	54.7(12.5)
Male, n, %	603(61.5)
Elapsed time after transplantation, years(SD)	9.1(6.3)
Diabetic mellitus, n, %	130(13.2)
Living kidney transplantation, n, %	935(95.4)
ABO incompatible, n, %	120(12.2)
Serum creatinine, mg/dl(SD)	1.56(1.02)

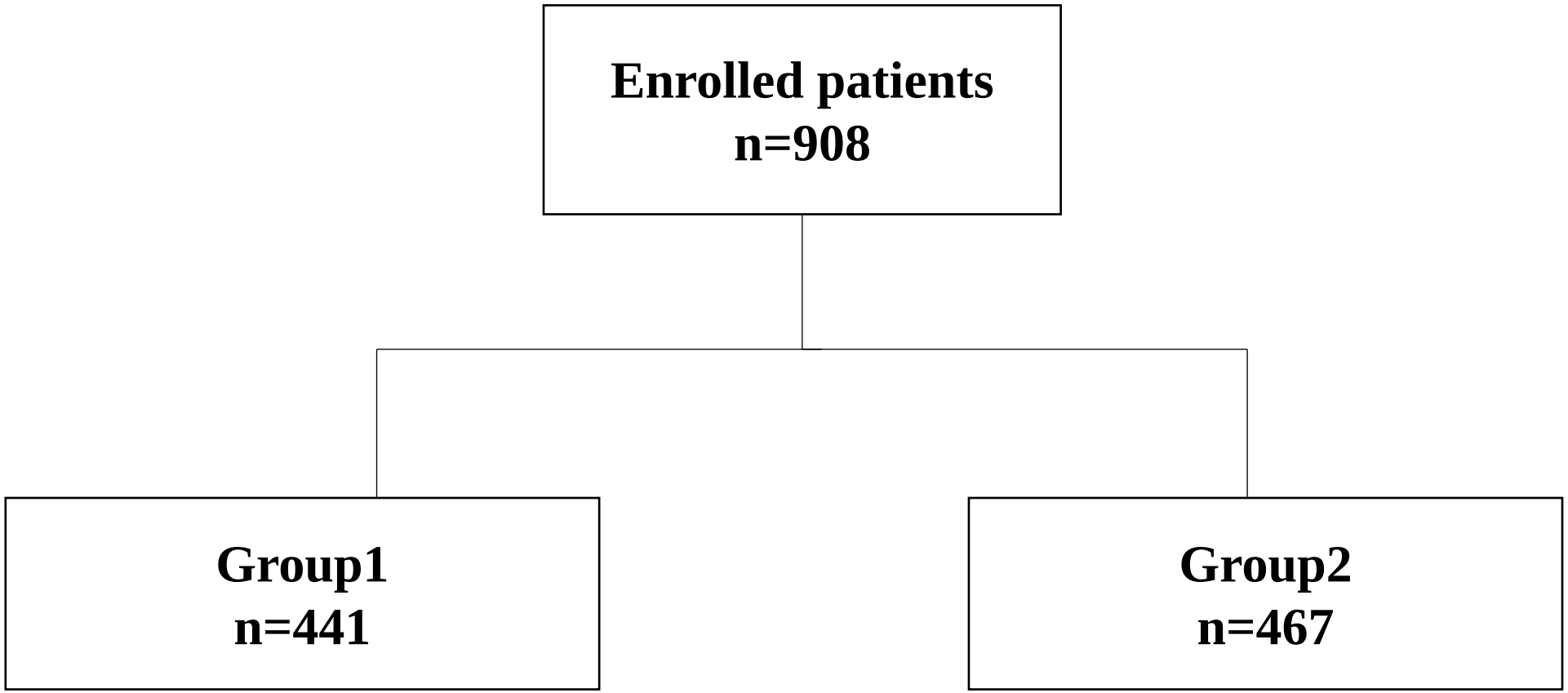
Table2. Clinical outcome between pandemic and non-pandemic

	non-pandemic	pandemic	P value
interval between hospital visit ,week(SD)	5.5±2.6	7.3±4.5	2.68×10^{-14}
rate of changes in oral medication, %(SD)	7.7(3.4)	6.0 (6.7)	0.450
rate of deviation from the target trough level, %(SD)	35.4(28.5)	38.3(27.3)	0.134
coefficient of variation, %(SD)	15.4(7.2)	14.8(7.6)	0.162
Serum creatinine, mg/dl(SD)	1.56±1.0	1.60±1.1	0.481
Biopsy-proven rejection	0	3	0.084

・Rate of changes in oral medication was defined as the number of tacrolimus dose changes divided by the number of hospital visits during the observation period.

・Rate of deviation from the target trough level was defined as the number of the blood concentration of tacrolimus deviated from the target trough level (4-6 ng / ml) divided by the number of hospital visits.

・Coefficient of variation(CV)(%)=(δ(standard deviation; SD)/μ(mean)) × 100
This is an indicator of variations in tacrolimus blood levels[1)].



Enrolled patients were further divided into two groups according to the mean hospital visit interval after the COVID-19 pandemic.The average interval was less than 6 weeks in group 1 and more than 6 weeks in group 2.

Table3. Clinical features in kidney transplant recipients	group1	group2	P value
number	441	467	
Age, years(SD)	54.0(12.7)	54.5(12.9)	0.513
Male, n, %	284(64.4)	300(64.2)	0.960
Elapsed time after transplantation, years(SD)	7.3(5.0)	10.5(6.2)	9.41×10^{-7}
Diabetic mellitus, n, %	57(12.9)	47(10.0)	0.211
Living kidney transplantation, n, %	425(96.4)	444(95.1)	0.327
ABO incompatible, n, %	62(14.1)	55(11.8)	0.323
Serum creatinine, mg/dl(SD)	1.58(1.1)	1.65(1.2)	0.522

Table4. Clinical outcome between group1 and group2	group1	group2	P value
rate of changes in oral medication, %(SD)	7.7(3.4)	6.0 (6.7)	0.001
rate of deviation from the target trough level, %(SD)	35.4(28.5)	38.3(27.3)	0.850
coefficient of variation, %(SD)	15.4(7.2)	14.8(7.6)	0.525
Serum creatinine, mg/dl(SD)	1.56±1.0	1.60±1.1	0.156
Biopsy-proven rejection	3	0	0.114

Discussion

In this study, the interval between hospital visits for kidney transplant patients was extended after COVID-19 pandemic, however, serum creatinine levels, incidence of biopsy-proven rejection, tacrolimus blood concentration were not significant different between pandemic data and non-pandemic data.

Patients in Group 1 had a shorter period after kidney transplantation and needed to change tacrolimus doses more frequently. There were three acute rejection cases that occurred during the observation period, all of which were Group 1 patients.

As demonstrated by a population-based registry study of >4,000 patients with a diagnosis of COVID-19 who were receiving kidney replacement therapy, COVID-19-associated mortality is 19.9% in kidney transplant recipients[2]. In general terms, optimal disease management is still being debated, and the therapeutic approach still lacks significant evidence[3].

In kidney transplant recipients, mitigation strategies to reduce the risk of exposing patients to the virus remain paramount. Remote care, telemedicine and minimization of blood tests may be helpful[4].

Limitation

・The dose and blood concentration of immunosuppressants except for TAC were unknown.

・Patients less than 1 year after kidney transplantation at high risk of COVOD-19 are excluded.

・In this study, the patients were followed up for 6 months after COVID-19 pandemic, therefore the long-term clinical outcome was not evaluated.

Conclusion

In kidney transplant recipients, blood levels of tacrolimus were maintained at target trough levels during COVID-19 pandemic.

Reference

1)Emilio Rodrigo, et al. Within-Patient Variability in Tacrolimus Blood Levels Predicts Kidney Graft Loss and Donor-Specific Antibody Development. Transplantation. 2016 Nov;100(11):2479-2485.

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3)Federico Alberici, et al. Management of Patients on Dialysis and With Kidney Transplantation During the SARS-CoV-2 (COVID-19) Pandemic in Brescia, Italy. Kidney Int Rep. 2020 Apr 4;5(5):580-585.

4)Annette Bruchfeld, et al. The COVID-19 pandemic: consequences for nephrology. Nat Rev Nephrol. 2021 Feb;17(2):81-82.