Renal Replacement Therapy

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Comparison of outcomes in kidney transplantations involving blood- related and non-blood-related living donors: a multicenter retrospective study by the Michinoku renal transplant network

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Abstract

Background This study aimed to compare the outcomes of living-donor kidney transplantation with blood- and non-blood-related donors, across multiple facilities. Previous reports comparing these outcomes have been single-center studies. As the donors were the recipients' spouses in all cases with non-blood-related donors, we independently compared the outcomes of wife-to-husband (WTH) and husband-to-wife (HTW) transplantations. No previous multicenter studies have compared transplant outcomes between spouses in this manner.

Methods This retrospective study used a shared database including 643 cases from 6 facilities that primarily used tacrolimus as a calcineurin inhibitor. We used propensity score matching to compare the outcomes of transplantations with blood- and non-blood-related donors and those of WTH and HTW transplantations.

Results Of the 643 cases examined, 381 and 262 had blood- and non-blood-related donors, respectively. All non-blood-related donor cases had spouses as donors. After propensity score matching, 84 cases each were selected from the blood- and non-blood-related donor groups for comparison, with no significant intergroup difference in the time to graft loss. Among the 262 interspousal transplantations, 91 were HTW transplantations and 171 were WTH transplantations. Following propensity score matching, 58 cases each were selected from the WTH and HTW groups for comparison, with no significant intergroup difference in the time to graft loss.

Conclusions In this large multicenter retrospective study, no significant differences were observed in the outcomes of transplantations with blood- and non-blood-related donors. Furthermore, no significant differences were observed in the outcomes of WTH and HTW cases. Many centers that use tacrolimus-based four-drug immunosuppressive therapy may have similar trends as those observed in this study, making our findings significant for planning transplantation involving kidneys donated from patients' spouses.

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Keywords Graft loss, Husband-to-wife transplantation, Kidney transplantation, Living–donor kidney transplant, Wife-to-husband transplantation

Background

Japan is facing a shortage of deceased kidney donors for transplantation, with only 141 cases recorded in 2020—representing < 10% of all kidney transplants [1]. Therefore, living-donor kidney transplantations (hereinafter referred to as "transplantations") account for most cases, with an increasing number of transplantations involving spouses as non-blood-related donors. In 2020, spousal transplantations accounted for 42.8% of all kidney transplantations in Japan, significantly surpassing the percentage of transplants from parents (30.5%) [1]. Previously, transplantations involving non-blood-related donors were considered to pose high immunological risks, owing to the increased rate of human leukocyte antigen (HLA) mismatching compared with those involving blood-related donors. However, previous studies [2–13] have reported no significant differences in the outcomes of transplantations involving blood- and non-blood-related donors. Notably, cyclosporin and azathioprine have been administered in previous studies as the primary immunosuppressant, which deviates from the current tacrolimus (TAC)-based regimens [4, 7].

Furthermore, prior studies on these transplantations have all been single-center studies, and none have compared the differences in outcomes of wife-to-husband (WTH) and husband-to-wife (HTW) transplantations. As the immunosuppressive regimens vary based on the facility, multicenter investigations on this topic would benefit the field. Therefore, we conducted a multicenter study using a shared database created by six hospitals that use TAC as the primary immunosuppressive agent and compared the outcomes of transplantations with both blood- and non-blood-related donors.

Methods

Participants

This study analyzed 643 cases of living-donor kidney transplantations performed between January 1, 1997, and December 31, 2021, at participating facilities, including Iwate Medical University Hospital. Using a shared database, the outcomes of kidney transplantations with blood- and non-blood-related donors were retrospectively examined. Furthermore, in spousal kidney transplantations, the outcomes of WTH and HTW transplantations were analyzed independently. As the six participating facilities were not affiliated, their immunosuppressive drug regimens and doses were not identical. However, all facilities primarily used TAC as the primary calcineurin inhibitor (CNI) and introduced a regimen of four drugs (TAC, methylprednisolone, basiliximab, and mycophenolate mofetil) during the perioperative period. Additionally, various recipient-related factors were included in the analysis, including age, sex, body mass index (BMI), presence of comorbidities including diabetes and hypertension, history of renal replacement therapy, blood relation to the donor, presence of ABO incompatibility, number of HLA mismatches, type of CNI used, results of flow cytometric panel reactive antibody assay (PRA), presence of donor-specific antibody (DSA), plasmapheresis status, use of rituximab (RIT), use of everolimus (EV), occurrence of transplant rejection, and occurrence and time to graft loss. Rejection was defined based on the clinical diagnosis of rejection, which is based on each facility's criteria and does not necessarily require histopathology, and required therapeutic intervention. Donor-related factors such as age, sex, BMI, preoperative renal function, height, weight, estimated glomerular filtration rate (eGFR), serum creatinine level, donor kidney side (left or right kidney), method of donor nephrectomy, kidney weight, and the presence and types of marginal donor factors were also included in the analysis. The marginal donor-related factors refer to those that may affect the suitability of a donated kidney for transplantation. These factors included age ≥ 70 years, presence of hypertension, presence of diabetes, BMI ≥ 30 kg/m^2, and creatinine clearance rate ≤ 80 mL/min or an eGFR ≤ 70 mL/min.

Statistical analyses

Propensity score matching based on various recipient- and donor-related factors were used to compare the engraftment periods of transplantations with blood- and non-blood-related donors. These factors included recipient age, BMI, presence of diabetes, history of renal replacement therapy, presence of ABO incompatibility, number of HLA mismatches, type of CNI used, use of RIT, use of EV, donor age, eGFR, BMI, and kidney side, and presence of marginal donor-related factors. Based on these factors, 84 cases were selected from blood- and non-blood-related transplantation groups. Similarly, 58 cases each were selected from the WTH and HTW groups, and the engraftment periods were compared. Engraftment period was analyzed using the Kaplan–Meier method, and intergroup clinical factors were analyzed using the log-rank test. The analyses were

conducted using JMP version 14.0.0 (JMP Statistical Discovery, Cary, NC, USA), and statistical significance was set at $p < 0.05$.

Results

Table 1 presents the characteristics of the kidney transplant recipients ($n = 643$) and donors ($n = 643$). The median age of the recipients was 47 years, with men comprising 64.3% ($n = 414$). Of these, 157 recipients (24.4%) had undergone preemptive kidney transplantations, and 160 recipients (24.8%) exhibited ABO incompatibility. The median number of HLA mismatches was 3. Transplantations involving blood- and non-blood-related donors accounted for 381 (59.3%) and 262 (40.7%) cases, respectively; all non-blood-related donors were spouses. Of the 262 spousal transplantation cases, 91 (34.7%) were HTW transplantations, whereas 171 (65.3%) were WTH transplantations. Among the CNIs used, TAC was the most used, accounting for 634 cases (98.6%). RIT and EV were administered in 213 (33.1%) and 204 (31.7%) cases. Transplant rejection occurred in 243 cases (37.7%). Graft loss occurred in 110 cases (17.1%), with median time to graft loss of 77 months (range 0–273 months). The median age of donors was 58 years, with a higher proportion of women ($n = 384$; 59.7%) among them. The median eGFR and BMI were 81.7 mL/min and 23.5 kg/m^2, respectively. Left kidney nephrectomy was performed in 595 cases (92.5%), with laparoscopic surgery being the predominant approach employed in 598 cases (93%). Marginal donor factors were present in approximately half of the donors ($n = 355$; 55.2%).

Table 2 presents the characteristics of transplant recipients in blood- ($n = 381$) and non-blood-related ($n = 262$) donor cases. Of the analyzed characteristics, significant differences between the two groups were observed in age, presence of diabetes ($p < 0.0001$), ABO incompatibility ($p < 0.0001$), number of HLA mismatches ($p < 0.0001$), presence of DSA ($p = 0.003$), plasmapheresis status ($p < 0.0001$), use of RIT ($p < 0.0001$), use of EV ($p < 0.0001$), and donor age ($p < 0.0001$). However, only the difference in the number of HLA mismatches after propensity score matching remained significant ($p < 0.0001$).

Figure 1 depicts the time to graft loss in cases involving transplants from blood- ($n = 84$) and non-blood-related ($n = 84$) donors following propensity score matching. The median follow-up period was 80 months; the median time to graft loss was 73 months for the blood-related group and 74 months for the non-blood-related group. No significant difference in time to graft loss was observed between the two groups ($p = 0.3170$).

Table 3 presents the characteristics of the 262 recipients of transplants from spousal donors, including 91 and 171 cases of HTW and WTH transplantation,

Table 1 Characteristics of all recipients and donors

	n	Median	Range
Recipients	643		
Age (years)		47	8–75
Sex, male/female	414/229		
BMI (kg/m^2)		22.4	13.3–43.3
DM, yes/no	122/521		
HT, yes/no	434/143		
RRT, yes/no	486/157		
HD	382		
PD (and HD)	99		
Transplantation	5		
PEKT	157		
Blood-related, yes/no	381/262		
Non-blood-related, HTW/WTH	91/171		
ABO-i, yes/no	160/483		
Mismatch HLA		3	0–6
CNI TAC/CYA	634/9		
Flow PRA class I, +/–	48/502		
Flow PRA class II, +/–	118/432		
DSA, yes/no	19/193		
Pre-PE/DFPP, yes/no	166/476		
RIT, yes/no	213/430		
EV, yes/no	204/438		
Rejection event, yes/no	243/399		
Graft loss, yes/no	110/533		
Period (months)		77	0–273
Donors	643		
Age (years)		58	24–80
Sex, male/female	259/384		
BMI (kg/m^2)		23.5	14.2–38.4
eGFR (mL/min)		81.7	49.6–140.3
GFR (mL/min)		97.0	36.4–284
Creatinine (mg/dL)		0.78	0.52–1.09
Kidney, left/right	48/595		
Operation method, open/laparoscopic	45/595		
Kidney weight (g)		200	86–390
Marginal donor, yes/no	355/288		
Age > 70 years, yes/no	62/581		
HT, yes/no	154/489		
DM, yes/no	34/609		
BMI > 30 kg/m^2, yes/no	32/611		
CCR < 80 mL/min or eGFR < 70 mL/min	257/386		

BMI body mass index, *DM* diabetes mellitus, *HT* hypertension, *RRT* renal replacement therapy, *HD* hemodialysis, *PD* peritoneal dialysis, *PEKT* preemptive kidney transplantation, *HTW* husband to wife, *WTH* wife to husband, *ABO-i* ABO incompatible, *CNI* calcineurin inhibitor, *TAC* tacrolimus, *CYA* cyclosporine, *PRA* panel reactive assay, *PE/DFPP* plasma exchange/double-filtration plasmapheresis, *RIT* rituximab, *EV* everolimus, *eGFR* estimated glomerular filtration rate, *CCR* creatinine clearance

Table 2 Characteristics of blood- and non-blood-related recipients and donors

	Entire cohort			Propensity score–matched cohort		
	Related (*n* = 381)	**Unrelated (*n* = 262)**	***p* value**	**Related (*n* = 84)**	**Unrelated (*n* = 84)**	***p* value**
Age (years)	38 (8–75)	57 (26–72)	< 0.0001	53 (34–75)	53 (26–72)	0.2519
Sex						
Male	243	171	0.6987	49	51	0.8752
Female	138	91		35	33	
BMI (kg/m^2)	21.8 (13.3–43.3)	22.0 (15.0–40.1)	0.5744	23 (16–36)	23 (15–40)	0.7381
DM						
Yes	51	71	< 0.0001	20	22	0.8588
No	330	191		64	62	
HT						
Yes	240	194	0.0804	56	59	0.6933
No	91	52		18	15	
RRT						
Yes	297	189	0.0917	59	57	0.8676
No	84	73		25	27	
ABO						
Yes	62	98	< 0.0001	18	24	0.3731
No	319	164		66	60	
Mismatch HLA	2 (0–6)	4 (0–6)	< 0.0001	3 (0–6)	5 (0–6)	< 0.0001
Flow PRA class I						
+	21	27	0.0612	3	9	0.1289
–	290	212		68	63	
Flow PRA class II						
+	57	61	0.0416	9	19	0.0568
–	254	178		62	53	
DSA						
Yes	5	14	0.0033	1	5	0.1959
No	118	75		24	23	
Pre-PE/DFPP						
Yes	73	93	< 0.0001	16	22	0.2728
No	308	168		68	61	
RIT						
Yes	94	119	< 0.0001	28	27	0.8676
No	287	143		56	57	
EV						
Yes	94	98	< 0.0001	28	27	1
No	287	163		56	57	
CNI						
TAC	376	258	0.0093	84	83	1
CYA	5	4		0	1	
Donor age (years)	60 (25–80)	56.5 (24–76)	< 0.0001	54 (27–80)	53 (24–73)	0.7382
Donor sex						
Male	164	95	0.0841	37	35	0.8762
Female	217	167		47	49	
Donor eGFR (mL/min)	81 (49.8–137.8)	82.5 (51.6–140.3)	0.4324	86 (54–137)	82 (53–131)	0.5276
Donor CCR (mL/min)	93 (36.4–284)	99.1 (43.2–229.7)	0.0647	100 (45–200)	97 (43–186)	0.2452
Donor BMI (kg/m^2)	23.8 (14.2–38.4)	23.1 (16.1–37.6)	0.0500	24 (17–32)	23 (16–38)	0.6717
Kidney						
Left	29	6	0.8644	7	7	1

Table 2 (continued)

	Entire cohort			Propensity score–matched cohort		
	Related ($n=381$)	Unrelated ($n=262$)	*p* value	Related ($n=84$)	Unrelated ($n=84$)	*p* value
Right	352	243		77	77	
Kidney weight (g)	200 (100–390)	200 (86–335)	0.3892	195 (104–380)	200 (102–310)	0.7278
Marginal donor						
Yes	237	118	0.1131	44	41	0.7577
No	144	144		40	43	

Values are presented as median (range) or *n*

BMI body mass index, *DM* diabetes mellitus, *HT* hypertension, *RRT* renal replacement therapy, *ABO-i* ABO incompatible, *HLA* human leukocyte antigen, *PRA* panel reactive assay, *DSA* donor-specific antibody, *PE/DFPP* plasma exchange/double-filtration plasmapheresis, *RIT* rituximab, *EV* everolimus, *CNI* calcineurin inhibitor, *TAC* tacrolimus, *CYA* cyclosporine, *eGFR* estimated glomerular filtration rate, *CCR* creatinine clearance

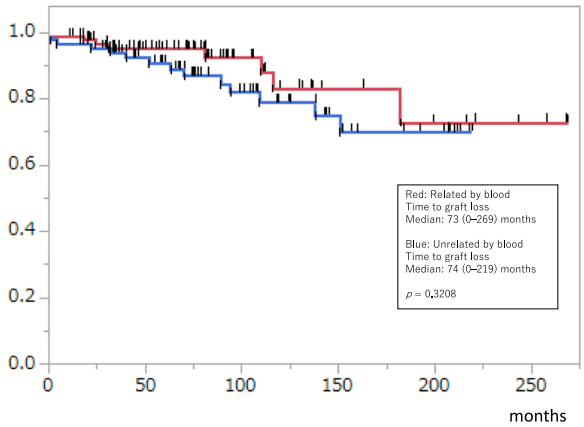

Fig. 1 Time to graft loss in cases of transplantation with blood- and non-blood-related donors after propensity score matching

respectively. Significant differences were observed between the two groups in recipient age ($p<0.0001$), BMI ($p=0.0080$), presence of diabetes ($p=0.0115$), presence of class 1 as determined by PRA ($p=0.0016$), presence of class 2 as determined by PRA ($p=0.0236$), presence of DSA ($p=0.0135$), donor creatinine clearance (CCR) ($p=0.0225$), donor BMI ($p=0.0163$), and transplanted kidney weight ($p<0.0001$). However, following propensity score matching, only differences in the transplanted kidney weight remained significant between the two groups ($p=0.0020$).

Figure 2 presents the time to graft loss for the HTW and WTH groups after propensity score matching. The median time to graft loss was 68.5 months in the HTW transplantation group and 74 months in the WTH transplantation group. No significant difference was observed between the two groups ($p=0.7626$).

Discussion

In this multicenter study, no significant differences were observed in the outcomes of transplantations involving living-donor kidneys from blood- and non-blood-related donors. Moreover, no significant differences were observed among cases involving transplants from non-blood-related donors in the outcomes of HTW and WTH transplantations.

In Japan, living-kidney donations are restricted to blood relatives within six degrees of kinship or in-laws within three degrees of kinship. Although kidney transplantations between parents and children were prevalent in the past, since 2015, the proportion of transplantations involving spouses as donors (37.3%) has surpassed that of transplantations with parents as recipients (34.7%) [14], and the proportion of transplantations involving spouses has been increasing ever since. Currently, spouses are considered primary donor candidates. In this study, all 262 cases of transplantations involving non-blood-related donors involved spouses as donors. In 1995, Terasaki et al. [2] reported that the clinical outcomes in living-donor kidney transplantation between spouses were equivalent to those between blood relatives. Since then, similar findings have been reported. Thus, the perception that transplantations between spouses are less successful than those between blood relations is no longer accurate [5, 7–9, 11, 13]. In this study, the engraftment rates in transplantations involving spouses as donors were favorable; no significant difference was observed before performing propensity score matching. Although a difference in the number of HLA mismatches was still observed after propensity score matching ($p<0.0001$), the favorable outcomes in transplantations between spouses can be partly attributed to the advancement of immunosuppressive agents. Since the facilities in the database are not affiliated hospitals, their immunosuppressive regimens are not uniform. However, all transplant recipients in these facilities underwent TAC-based

Table 3 Characteristics of recipients and donors in cases of transplantation involving spouses

	Entire cohort			Propensity score–matched cohort		
	HTW (*n* = 91)	**WTH (*n* = 171)**	***p* value**	**HTW (*n* = 58)**	**WTH (*n* = 58)**	***p* value**
Age (years)	56 (31–70)	58 (26–72)	0.0036	56 (32–71)	56 (26–69)	0.9475
BMI (kg/m^2)	20.9 (15–40.1)	22.6 (16.4–37)	0.0008	21 (16.6–40.1)	21.5 (16.9–27.1)	0.3818
DM						
Yes	16	55	0.0115	12	9	0.4694
No	75	116		46	49	
HT						
Yes	68	126	0.9533	44	41	0.4949
No	18	34		11	14	
RRT						
Yes	64	125	0.6340	40	45	0.2941
No	27	46		18	13	
ABO-i						
Yes	31	67	0.4152	22	23	0.8489
No	60	104		36	35	
Mismatch HLA	4 (0–6)	4 (0–6)	0.9772	4 (1–6)	5 (2–6)	0.9426
Flow PRA class I						
+	17	10	0.0016	8	4	0.2473
–	68	144		47	49	
Flow PRA class II						
+	29	32	0.0236	19	10	0.0661
–	56	122		36	43	
DSA						
Yes	10	4	0.0135	5	2	0.2685
No	27	48		18	19	
Pre-PE/DFPP						
Yes	37	56	0.2147	22	22	1
No	54	114		36	36	
RIT						
Yes	46	73	0.2238	26	29	0.5770
No	45	98		32	29	
EV						
Yes	35	63	0.8235	28	19	0.3726
No	56	107		56	38	
CNI						
TAC	91	167	0.1415	58	58	–
CYA	0	4		0	0	
Donor age (years)	58 (25–76)	55 (24–73)	0.5774	54 (25–76)	55 (24–70)	0.3661
Donor eGFR (mL/min)	81.2 (52.9–131.1)	83.1 (51.6–140.3)	0.2405	81.6 (52.9–131.1)	79.4 (55.6–119.5)	0.9074
Donor CCR (mL/min)	103.7 (42.2–186.4)	97.6 (45.3–229.7)	0.0225	101.4 (43.9–185.6)	97.4 (55.5–186)	0.1614
Donor BMI (kg/m^2)	23.7 (17–33.1)	22.6 (16.1–37.6)	0.0163	23.4 (17–29.6)	23.2 (16.5–37.6)	0.3596
Kidney						
Left	86	157	0.4236	54	53	0.7285
Right	5	14		4	5	
Kidney weight (g)	225 (149–335)	180 (86–330)	< 0.0001	220 (149–335)	192.5 (102–290)	0.0002
Marginal donor						
Yes	40	78	0.7973	36	21	0.3443
No	51	93		32	37	

Values are presented as median (range) or *n*

BMI body mass index, *DM* diabetes mellitus, *HT* hypertension, *RRT* renal replacement therapy, *ABO-i* ABO incompatible, *HLA* human leukocyte antigen, *PRA* panel

Table 3 (continued)

reactive assay, *DSA* donor-specific antibody, *PE/DFPP* plasma exchange/double-filtration plasmapheresis, *RIT* rituximab, *EV* everolimus, *CNI* calcineurin inhibitor, *TAC* tacrolimus, *CYA* cyclosporine, *eGFR* estimated glomerular filtration rate, *CCR* creatinine clearance

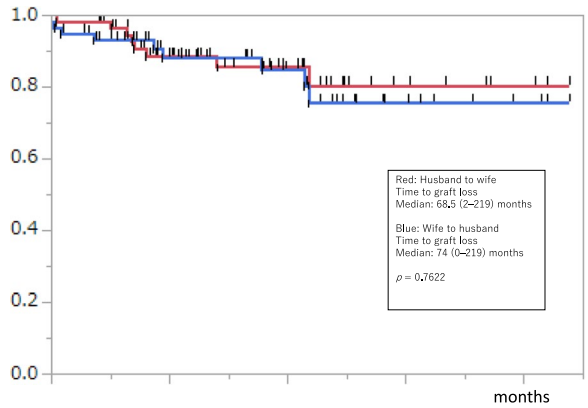

Fig. 2 Time to graft loss in cases of transplantation with spouses as donors after propensity score matching

immunosuppressive regimens. This study is the first to compare the outcomes of transplantations involving blood-related donors and spouses across multiple facilities. Our findings suggest that the outcomes of spousal kidney transplantation were not inferior to those of transplantations involving blood-related donors in participating facilities that used a standard TAC-based immunosuppressive regimen, which is currently commonly administered in Japan. Moreover, the present study examined differences in HTW and WTH transplantation outcomes among spousal kidney transplantations. The findings revealed that WTH transplantations (65.3%) were more common than HTW transplantations (34.7%). This may be attributed to the higher prevalence of chronic kidney disease among men than among women in Japan. In Japan, a larger proportion of men undergo dialysis treatment. Thus, several factors may contribute to the higher prevalence of chronic kidney disease among men, including lifestyle factors that exacerbate kidney conditions such as obesity, high salt intake, and smoking, as well as the higher prevalence of diabetes, hypertension, and hereditary diseases with poorer prognosis among men. Moreover, in women, estrogen may inhibit the progression of chronic kidney disease via mechanisms such as enhanced nitric oxide production in vascular endothelial cells [15] and suppressed angiotensin-converting enzyme activity [16]. This implies that the progression of chronic kidney disease may be slower in women. Additionally, in this study, when comparing the patient characteristics, the HTW group included younger recipients with lower BMIs who received kidneys with significantly lower weights ($p < 0.0001$) than those in the WTH group. Moreover, after performing propensity score matching for these two groups, a significant difference was observed only in the weight of the transplanted kidney ($p = 0.0020$); no significant difference was observed in the time to graft loss. This comparison also revealed no statistically significant difference in the engraftment rates of the two groups, even before propensity score matching. Thus, our findings indicate that the transplantation outcomes are not significantly impacted even in transplantations mismatched in terms of body size and kidney weight, as in cases of transplantation from women to men.

The present study had several limitations. First, we used a retrospective analysis of a multi-institutional database with constraints in terms of data verifiability. Second, variations between the facilities are likely regarding indications and criteria for patient selection for immunologically high-risk cases, such as those positive for donor-specific antibodies or exhibiting blood type incompatibilities. Finally, the immunosuppressive regimens administered during the perioperative period were not uniform across all facilities. Thus, detailed investigation of immunosuppressive regimens was difficult using the joint database method. Nonetheless, to our knowledge, this is the first to use propensity score matching to analyze the long-term outcomes in living-donor kidney transplantations involving blood- and non-blood-related donors using a large sample size across multiple facilities. It may provide insights into the factors that affect the outcome of living-donor kidney transplantation.

Conclusion

In this multicenter study, we investigated engraftment in living-donor kidney transplantations with both blood- and non-blood-related donors. Our findings revealed no significant difference in engraftment rates between these transplantation types. Moreover, no significant differences were observed in engraftment rates between cases of HTW and WTH transplantations.

Abbreviations

BMI	Body mass index
CNI	Calcineurin inhibitor
DSA	Donor-specific antibodies
eGFR	Estimated glomerular filtration rate
EV	Everolimus
HLA	Human leukocyte antigen
HTW	Husband-to-wife
PRA	Panel reactive assay
RIT	Rituximab
TAC	Tacrolimus
WTH	Wife to husband

Supplementary Information

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Supplementary Material 1.

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Author contributions
TM prepared the original draft. MT, MS, HN, SH, SM, RM, JS, TA, YT, HS, NT, CO, and TH performed the investigation and supervision. WO conceptualized and supervised the study. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Iwate Medical University Hospital (MH2021-162). Informed consent was obtained using an opt-out approach.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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