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Evaluating Graft Loss Risk in Living-Donor Kidney Transplants with Multiple Renal Arteries

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Background: Despite its surgical complexity, kidney transplantation (KT) with multiple renal arteries (MRA) is comparable in performance to KT with a single renal artery (SRA). This study aimed to evaluate the effect of MRA and to investigate risk factors for graft loss in living-donor KT with MRA.

Material/Methods: This study included living-donor KT recipients who underwent KT in our hospital from February 2002 to March 2023. The primary outcome was whether MRA decreased the prognosis of transplanted kidneys. The secondary outcomes were the risk factors for graft loss in KT with MRA, such as recipients' characteristic.

Results: Out of 197 recipients, 47 (23.8%) received kidneys with MRA. In inverse probability of treatment weighting, the risk of graft loss did not increase in KT with MRA, as compared to that in KT with SRA (hazard ratio [HR]: 1.46; 95% confidence interval [CI]: 0.68-3.14). MRA were associated with graft loss in ABO blood-incompatible KT (HR: 5.09, 95% CI: 1.75-14.7).

Conclusions: In ABO blood-incompatible KT, MRA can increase risk of graft loss.

Keywords: **Kidney Transplantation • Nephrons • Renal Circulation**

Abbreviations: **CIT** – cold ischemic time; **DGF** – delayed graft function; **HR** – hazard ratio; **IPTW** – inverse probability of treatment weighting; **KT** – kidney transplantation; **MRA** – multiple renal arteries; **OR** – odds ratio; **PE –** plasma exchange; **PEKT** – preemptive kidney transplantation; **PS** – propensity score; **RA** – renal artery; **SRA** – single renal artery; **SRF** – split renal function; **WIT** – warm ischemic time

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Introduction

Among all renal replacement therapies, kidney transplantation (KT) is considered the best treatment for patients with end-stage kidney disease with respect to survival rate and quality of life [1-3]. Nevertheless, the donor pool has not kept up with the demand for KT. Consequently, transplant physicians and surgeons have been forced to expand the indications for living donors, including kidneys with multiple renal arteries (MRA). The MRA population reportedly accounts for 18-30% [4], and cases of KT with MRA are sometimes encountered. Previous studies have shown that KT with MRA is more likely to compromise the clinical outcomes than KT with single renal artery (SRA) [5] and that the warm ischemic time (WIT) in KT with MRA is prolonged, resulting in an increased risk of graft loss [6,7]. Prolonged WIT can induce ischemia-reperfusion injury with innate immunogenicity, leading to chronic allograft nephropathy [6]. Additionally, KT with MRA is prone to vascular and urologic complications owing to the complexity of the procedure [4]. As mentioned above, comparisons between SRA and MRA have been studied; however, no reports exist on the indications for KT with MRA based on recipients' backgrounds. Therefore, the present study aimed to evaluate the effect of MRA and to investigate risk factors for graft loss, focused on recipients' backgrounds.

Material and Methods

Patient Selection, Data Collection, and Study Design

This study was conducted in accordance with the provisions of the 2013 Declaration of Helsinki and was approved by the Research Ethics Committee of the Nara Medical University through a centralized Institutional Review Board (project identification code: 2014).

The requirement for the acquisition of informed consent from patients was waived because of the retrospective nature of this study.

This study included a total of 197 patients who underwent KT at the Nara Medical University from February 2002 to March 2023. Data on medical history, medications, and laboratory results were retrospectively obtained from electronic medical records. KT recipients were divided into the SRA and MRA groups for subsequent analyses (**Figure 1**).

Determination of Transplant Kidneys

All donors were evaluated for renal vascular function and split renal function (SRF) using computed tomography and technetium-99m mercaptoacetyltriglycine renal scintigraphy before surgery. The transplant kidneys were determined as follows: (i) if the SRF was ≥10%, the kidney with low function was procured; (ii) if the SRF was <10%, the left kidney was procured while considering the vein length; (iii) in cases with SRF <10%, left kidney with MRA, and right kidney with SRA, the right kidney was procured.

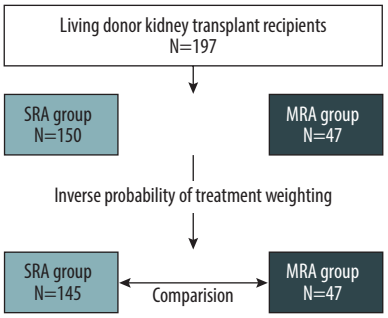

Figure 1. Flow chart for the creation of recipient cohort dataset. Out of 197 living-donor kidney transplant recipients, 150 were assigned to the single renal artery (SRA) group, whereas 47 were classified as the multiple renal arteries (MRA) group. After inverse probability of treatment weighting for the primary outcome, the MRA group was compared with the single renal artery group to investigate risk factors for MRA. As for the secondary outcome, the number of RAs and anastomotic sites was classified, and the recommended vascular processing methods were discussed. SRA – single renal artery; MRA – multiple renal arteries

Definition of Ischemic Time

WIT1 was defined as the time from renal artery (RA) clamping to nephrectomy. Cold ischemic time (CIT) was defined as the time from extracorporeal perfusion to vascular processing on the back table. WIT2 was defined as the time of renal vascular anastomosis with the iliac vasculature to the revascularization of the kidney.

Immunosuppression Therapy

In our institution, steroids, mycophenolate mofetil, basiliximab, and calcineurin inhibitors are used for induction immunosuppression therapy, whereas steroids, mycophenolate mofetil, and calcineurin inhibitors are used for maintenance immunosuppression therapy. In case of ABO blood-incompatible KT, rituximab was administered or splenectomy was performed. Double-filtration plasmapheresis and plasmapheresis were performed to remove antibodies from recipients prior to KT. The steroid dose was adjusted according to the history of rejection, and the type of calcineurin inhibitor or mycophenolate

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mofetil was changed according to the adverse effects. A mammalian target of rapamycin inhibitor was added at the discretion of the attending physician.

Anticoagulation Protocol

Intraoperatively, 2000 units of heparin were administered for thromboprophylaxis during clamping of the iliac artery and vein. No other routine antithrombotic therapy was administered.

Definition of Various Events

Vascular complications included percutaneous transluminal angioplasty, vascular thrombosis, and postoperative bleeding. Urinary complications included leakage into the surrounding tissues, anastomotic stenosis, and hydronephrosis. Delayed graft function (DGF) was defined as the need for hemodialysis at least once after KT. Rejection was not limited to those proven by histological examination but also included cases of clinically suspected rejection that required an increase in maintenance steroid dosage.

Outcomes

In this study, the primary outcome was the effect of MRA on KT, including vascular and urologic complications, DGF, rejection, graft loss, and death. The secondary outcome was the risk factors for graft loss in KT with MRA.

Statistical Analysis

Continuous and categorical variables are presented as medians (interquartile ranges) and as numbers (percentages), respectively. Comparisons between the groups were conducted using the Mann-Whitney U test and Fisher's exact test, as appropriate. Statistical analyses, including survival curve analysis, were performed using EZR (Easy R) software version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [8]. Forest plots were generated using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA). Graft survival was evaluated using death-censored graft survival. Two-sided tests were used in all cases, and statistical significance was set at $P<0.05$. Because a difference was detected between the 2 groups in the unadjusted population, the baseline characteristics were matched by calculating the propensity score (PS) for each recipient using a multivariate logistic regression model based on covariables such as sex, age, body mass index, presence or absence of preemptive kidney transplantation (PEKT), ABO blood group compatibility, left or right donor kidney, presence or absence of multiple renal veins, donor nephrectomy, and ureteral stent placement, with a caliper of 0.2. Inverse probability of treatment weighting (IPTW), which is a form of PS analysis, was applied to maximally reduce the differences between the SRA and MRA groups. IPTW was calculated as 1/PS for the MRA group and 1/(1-PS) for the SRA group and was subsequently multiplied by the percentage of patients in each group. In the IPTW population, the standardized mean difference was <0.1, indicating that the variates were well balanced (**Table 1**). For the primary outcome, a multivariate Cox regression analysis was conducted to estimate the IPTW-adjusted odds ratio (OR) and hazard ratio (HR).

Results

Demographics of Recipients

Out of 197 recipients, 47 (23.8%) were assigned to the MRA group. Among these 47 recipients, 41 had 2 RAs, 5 had 3 RAs, and 1 had 4 RAs (**Figure 1**).

Table 2 summarizes the clinical data of patients included in this study. Overall, 63 (31.9%) patients were PEKT recipients, and 139 (70.5%) received a left kidney. In this study group, no patient experienced nephrosis in the perioperative period. No genetic risk factors for thrombosis were found; however, 1 recipient with systemic lupus erythematosus was diagnosed with antiphospholipid antibody syndrome in the MRA group.

Table 3 shows the comparison of outcomes between the SRA and MRA groups. No significant differences in blood loss, complications, graft loss, and recipient death were detected; however, the ischemic time was longer in the MRA group. The CIT (SRA vs MRA, $P<0.001$) and WIT1 (SRA vs MRA, $P<0.001$) were significantly prolonged in the MRA group; WIT2 did not differ significantly between the 2 groups ($P=0.143$).

Effect of MRA on KT

The relative risk of poor outcomes was examined after IPTW adjustment. No increased risks of vascular and urologic complications, DGF, and rejection were found in MRA group compared with the SRA group. Additionally, KT with MRA was not associated with increased risks of graft loss and death when compared with KT with SRA (**Table 4, Figure 2A, 2B**).

Association Between Recipients' Backgrounds and Graft Survival in KT with MRA

The subgroup analysis showed that MRA were associated with graft loss when compared with SRA in ABO blood-incompatible KT (HR: 5.09, 95% CI: 1.75-14.7, $P=0.002$). In the subgroup with MRA, 4 out of 6 recipients with graft loss exhibited biopsy-confirmed rejection, and there was no graft loss due to the acute antibody-related rejection characteristic of ABO blood-incompatible KT (**Figure 3**).

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Table 1. Demographic date after applying the IPTW for KT recipients with SRA and MRA. In the IPTW population, the standardized mean difference was <0.1.

Variables	Unadjusted population				IPTW population		
	SRA	MRA	p-value	SMD	SRA	MRA	SMD
Number	150	47			145	47	
Gender, n (%)							
Men	94 (62.7)	25 (53.2)			88 (60.6)	30 (63.8)	
Women	56 (37.3)	22 (46.6)	0.305*	0.193	57 (39.3)	17 (36.1)	0.04
Donor gender, n (%)							
Men	55 (36.7)	23 (48.9)			57 (39.3)	16 (34.0)	
Women	95 (63.3)	24 (51.1)	0.171*	0.25	88 (60.6)	31 (66.0)	0.1
Age at KT, n (%)							
<50 years	77 (51.3)	27 (57.4)			76 (52.4)	23 (48.9)	
≥50 years	73 (48.7)	20 (42.6)	0.506*	0.123	69 (47.5)	24 (51.0)	0.078
BMI (kg/m^2) at KT, n (%)							
<25	111 (74.0)	34 (72.3)			104 (72.4)	32 (68.1)	
≥25	39 (26.0)	13 (27.7)	0.851*	0.037	41 (27.6)	15 (31.9)	0.1
PEKT, n (%)	48 (32.0)	15 (31.9)	1.000*	0.002	48 (33.1)	17 (36.1)	0.041
ABO blood group compatibility, n (%)							
Compatibility	107 (71.8)	32 (68.1)			104 (71.7)	35 (74.5)	
Incompatibility	42 (28.2)	13 (31.9)	0.638*	0.439	41 (28.3)	12 (25.5)	0.071
Donor-nephrectomy, left or right, n (%)							
Left	117 (78.5)	26 (55.3)			106 (73.1)	36 (76.5)	
Right	32 (21.5)	21 (44.7)	0.509*	0.003	39 (26.9)	11 (23.4)	0.043
MRV, n (%)	14 (9.5)	6 (12.8)	0.582*	0.105	15 (10.3)	4 (8.5)	0.071
Donor-nephrectomy method, n (%)							
Open	12 (26.7)	24 (53.3)			52 (35.9)	16 (11.0)	
HALS	27 (60.0)	14 (31.1)			63 (43.4)	20 (42.6)	
Laparoscope	6 (13.3)	7 (15.6)	0.016*	0.254	30 (20.7)	11 (23.4)	0.089
Ureteral stent placed, n (%)	48 (33.1)	19 (40.4)	0.382*	0.152	51 (35.1)	16 (34.0)	0.014

* Fisher exact test. IPTW – inverse probability of treatment weights; KT – kidney transplant; SRA – single renal artery; MRA – multiple renal arteries; SMD – standardized mean difference; BMI – body mass index; PEKT – preemptive kidney transplantation; MRV – multiple renal vein.

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Table 2. Clinical information in KT recipients with SRA and MRA.

Characteristics	SRA	MRA
Number	150	47
Gender, n (%)		
Men	94 (62.7)	25 (53.2)
Women	56 (37.3)	22 (46.6)
Donor gender, n (%)		
Men	55 (36.7)	23 (48.9)
Women	95 (63.3)	24 (51.1)
Age at KT, median (IQR)	49.0 (39.2-59.7)	43 (34.5-54.0)
Primary kidney disease, n (%)		
Diabetes mellitus	31 (20.6)	14 (29.7)
IgA nephropathy	42 (28.0)	7 (14.9)
Nephrosclerosis	12 (8.0)	3 (6.3)
Others	65 (43.3)	24 (51.0)
BMI (kg/m^2) at KT, median (IQR)	22.1 (19.4-25.1)	22.3 (20.0-25.3)
PEKT, n (%)	48 (32.0)	15 (31.9)
ABO blood group compatibility, n (%)		
Match	68 (45.6)	20 (42.6)
Mismatch	39 (26.2)	12 (25.5)
Incompatibility	42 (28.2)	15 (31.9)
Donor-nephrectomy method, n (%)		
Open	12 (26.7)	24 (53.3)
HALS	27 (60.0)	14 (31.1)
Laparoscope	6 (13.3)	7 (15.6)
Donor-nephrectomy, left or right, n (%)		
Left	117 (78.5)	26 (55.3)
Right	32 (21.5)	21 (44.7)
Number of RA, n (%)		
SRA	150 (100)	
MRA		
2 RA		41 (87.2)
3 RA		5 (10.6)
4 RA		1 (0.02)
MRV, n (%)	14 (9.5)	6 (12.8)
Anastomosed to illiac artery, internal or external, n (%)		
Internal	98 (68.1)	31 (66.0)
External	42 (29.2)	16 (34.0)
Common	4 (2.8)	0
Ureteral stent placed, n (%)	48 (33.1)	19 (40.4)

KT – kidney transplant; IQR – interquartile range; BMI – body mass index; PEKT – preemptive kidney transplantation; HALS – hand assistant laparoscopic surgery; MRV – multiple renal veins; MRA – multiple renal arteries.

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Table 3. Comparison of outcome between KT recipients with SRA and MRA. The ischemic time was longer in the MRA group, but no significant differences in blood loss, complications, graft loss, and recipient death were detected.

Parameter	SRA	MRA	p-value
Total operation time (minutes), median (IQR)	376.5 (332.0-451.0)	465.0 (354.0-563.0)	<0.0001*
Warm ischemic time 1 (minutes), median (IQR)	6.0 (5.0-7.0)	8.0 (6.5.0-11.0)	<0.0001*
Cold ischemic time (minutes), median (IQR)	27.0 (21.0-41.0)	59.0 (47.0-69.5)	<0.0001*
Warm ischemic time 2 (minutes), median (IQR)	62.0 (53.0-72.0)	67.0 (52.5-98.0)	0.143*
Total ischemic time (minutes), median (IQR)	97.0 (86.0-122.0)	131.0 (115.0-175.5)	<0.0001*
Blood loss (mL), median (IQR)	230.5 (124.5-451.5)	290.0 (127.5-439.0)	0.678†
Complications, n (%)			
Vascular	20 (13.3)	6 (12.7)	1.000*
Urologic	13 (8.7)	5 (10.6)	0.685*
Delayed graft function, n (%)	10 (6.7)	4 (9.3)	0.518*
Rejection, n (%)	71 (51.8)	23 (50.0)	0.832*
Graft loss, n (%)	25 (16.7)	12 (25.5)	0.176*
Death, n (%)	26 (17.4)	11 (23.4)	0.365*

* Fisher exact test. KT – kidney transplant; SRA – single renal artery; MRA – multiple renal arteries; IQR – interquartile range.

Table 4. Relative risk of poor outcome loss in KT recipients. KT with MRA was not associated with increased risks of vascular and urologic complications, delayed graft function, rejection, graft loss, and death when compared with KT with SRA.

Outcome	N Events		Unadjusted population			IPTW population		
	SRA (reference)	MRA	OR	95% CI	p-value	OR	95% CI	p-value
Complications, n (%)								
Vascular	20 (13.3)	6 (12.7)	1.25	0.423-3.720	0.683	1.4	0.490-3.970	0.532
Urologic	13 (8.7)	5 (10.6)	0.951	0.358-2.530	0.92	1.36	0.537-3.430	0.519
Delayed graft function, n (%)	10 (6.7)	4 (9.3)	1.44	0.427-4.830	0.559	1.19	0.291-4.860	0.809
Rejection, n (%)	71 (51.8)	23 (50.0)	0.93	0.477-1.810	0.83	1.19	0.606-2.330	0.617
			HR	95% CI	p-value	HR	95% CI	p-value
Graft loss, n (%)	25 (16.7)	12 (25.5)	1.525	0.765-3.038	0.229	1.469	0.687-3.141	0.32
Death, n (%)	26 (17.4)	11 (23.4)	1.321	0.645-2.702	0.446	1.81	0.836-3.919	0.132

KT – kidney transplant; IPTW – inverse probability of treatment weights; OR – odds ratio; CI – confidence interval; SRA – single renal artery; MRA – multiple renal arteries; HR – hazard ratio.

Discussion

While KT with MRA reportedly has a longer ischemic time owing to vascular complexity, the graft survival rate of KT with MRA does not differ from that of KT with SRA [9-13]. Among ischemic times, WIT2 is particularly associated with poor outcomes such as rejection, DGF, and graft loss [7,14,15]. In our institution, despite the long ischemic time, MRA were not risk factors for DGF, graft rejection, or graft loss compared with SRA. The CIT was significantly prolonged in the MRA group compared with the SRA group; however, the WIT2 was almost equal between the 2 groups. The good prognosis of the graft with MRA may be attributed to adequate vascular processing on the back table, which reduces the time required for anastomosis of the renal and iliac vasculature [16].

In the subgroup analysis, we examined the backgrounds of recipients in whom MRA were risk factors for graft loss and found

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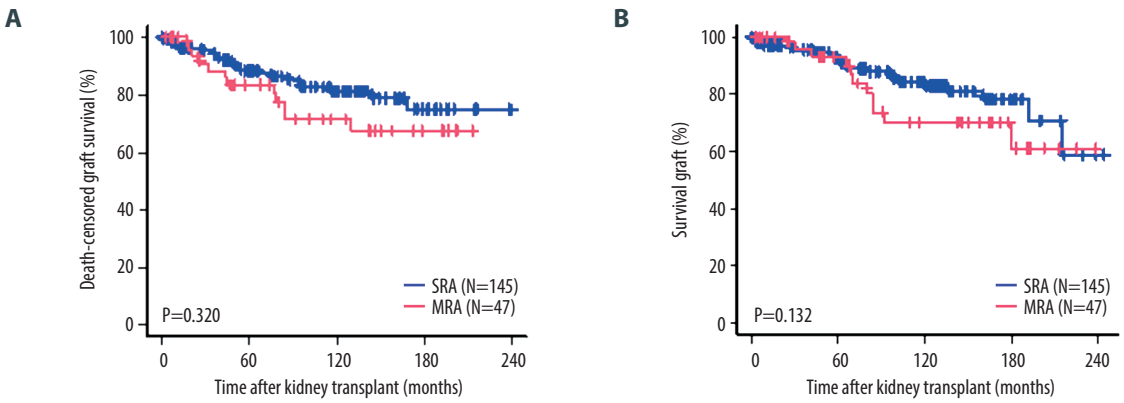

Figure 2. Kaplan-Meier curves for graft survival and recipient survival. The risks of graft loss and recipient mortality were investigated using Cox regression analysis. Graft survival curves were plotted for the single renal artery (SRA) group and multiple renal arteries (MRA) group. The risk of graft loss did not increase in the MRA group compared with that in the SRA group (**A**). MRA were not associated with a risk of recipient mortality (**B**). SRA – single renal artery; MRA – multiple renal arteries. *This figure was created by using EZR (Easy R) software version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).*

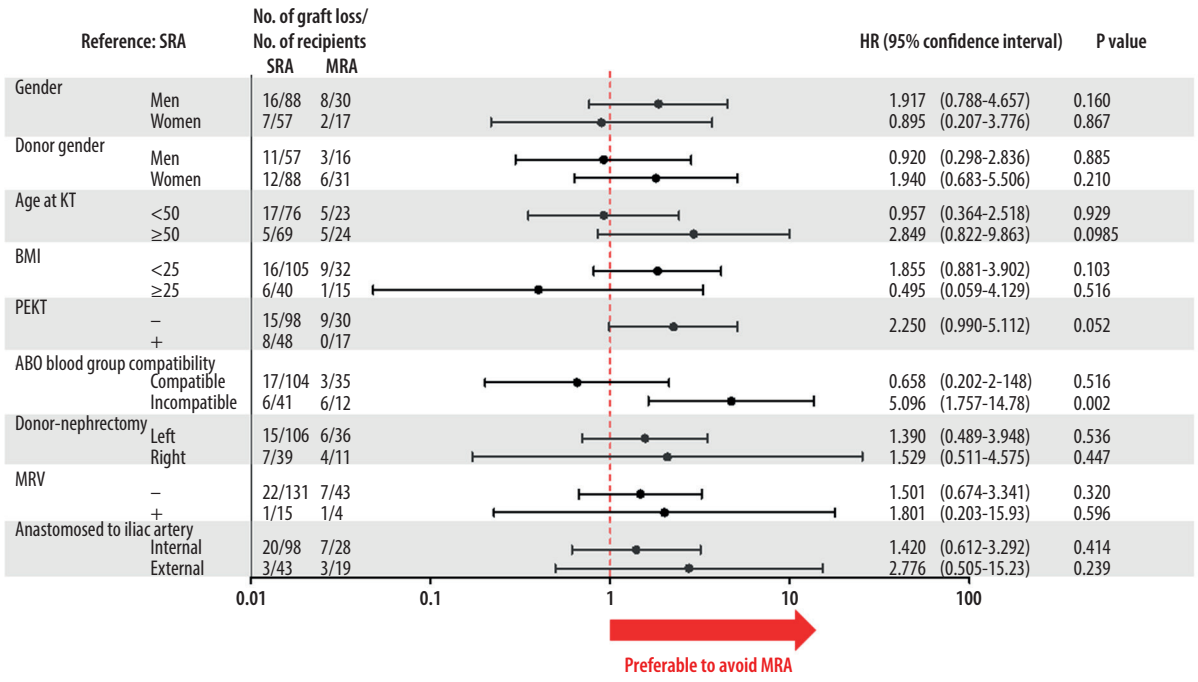

Figure 3. Forest plot of factors related to graft loss in the inverse probability of treatment weighting population. A subgroup analysis of graft loss was performed using a forest plot. Beyond the dotted line to the right, multiple renal arteries (MRA) were risk factors for graft loss in the subgroup. IPTW – inverse probability of treatment weighting; SRA – single renal artery; MRA – multiple renal arteries; HR – hazard ratio; KT – kidney transplantation; BMI – body mass index; PEKT – preemptive kidney transplantation; MRV – multiple renal veins. *This figure was created by using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA).*

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that grafts with MRA should not be used in ABO blood-incompatible KT. This may be due to the enhanced immunologic effects of MRA on vascular endothelial cells. In blood-incompatible KT, anti-ABO antibodies are controlled by immunosuppressive therapy, and graft loss is reduced during the acute phase. However, cases of graft loss still exist during the chronic phase and show progressive and extensive narrowing of the graft artery due to immunologic damage to the vascular [17]. RA stenosis after KT is strongly associated with graft loss [18,19]. It has been shown that vascular injury by anastomosis at suture lines promotes immunologic activation [20], and MRA may be strongly affected by the immunologic response because more vascular processing is necessary in MRA than in SRA. Additionally, MRA may be more prone to immunologic effects owing to the increased number of vascular endothelial cells. Vascular endothelial cells have been reported to change from victim to accomplice with the immunologic response [21]. The longer the length of the arterial tree, the greater the damage caused by the immunologic response [19]. From another perspective, in our institution, ABO blood-incompatible KT recipients undergo 1 plasma exchange (PE) the day before surgery in the protocol. Fresh frozen plasma was used as a replacement fluid in PE, and it could impact coagulation parameters. Specifically, frequent PE requires careful evaluation [22]. The effect on thrombosis was considered minimal because only 1 PE was performed; however, the possibility that it affected the recipients could not be ruled out. This study had some limitations. First, the types of immunosuppressive therapies and their modifications are not mentioned. Second, differences in recipient management and advances in medical technology cannot be excluded owing to the length of the study.

Conclusions

KT with MRA was not associated with a risk of complications, graft loss, or recipient death. However, ABO blood-incompatible KT might increase the risk of graft loss.

Patient Permission/Consent Declarations

All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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