The impact of donor-recipient relationship on long-term outcomes in living-related donor kidney transplantation

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Abstract

Background. This study aims to evaluate the impact of the donor-recipient relationship on the long-term outcomes of living-related kidney transplantation (LRKT), which has been limitedly reported previously.

Methods. Between 2001 and 2021, a total of 598 LRKTs were categorized into five groups based on the donor-recipient relationship: 228 from mothers (M-to-C), 160 from fathers (F-to-C), 115 from siblings, 55 from spouses, and 40 from offspring. We assessed graft survival, postoperative complications within the first year, serum creatinine (Scr), and hazard ratio (HR) for all-cause graft loss.

Results. The overall 1-, 3-, 5-, 7-, and 10-year graft survival rates were 96.0%, 92.4%, 86.4%, 79.9%, and 69.9%, respectively. While the sibling group had slightly higher graft survival rates than the M-to-C and F-to-C groups, the differences were insignificant. In contrast, kidneys from spouses and offspring resulted in lower graft survival, with a higher incidence of graft loss in the offspring group within the first postoperative year. No significant differences in clinical outcomes were observed between the M-to-C and F-to-C groups, which had elevated postoperative Scr levels and a higher risk for graft loss (HR, 1.9; 95% CI: 1.2-3.4) and 1.8 (1.1-3.1) compared to the sibling group. Additionally, there was a greater risk for graft loss when the donors were spouses and offspring (HR, 3.3; 95% CI, 1.6-6.9) and 3.8 (1.7-8.4), respectively.

Conclusions. Compared to sibling donors, spouse and offspring donations significantly increased the risk of graft loss, followed by M-to-C and F-to-C pairings, which yielded higher postoperative Scr.

Keywords: Living-related kidney transplantation; donor-recipient relationship; graft survival; long-term; outcome.

Running head

Donor-recipient relationship impacts the long-term outcome of living-related kidney transplantation

List of abbreviations

AR, acute rejection; CI, confidence interval; CSRKT, Chinese Scientific Registry of Kidney Transplantation; CsA, cyclosporine; DGF, delayed graft function; ESRD, end-stage renal disease; HR, hazard ratio; HLA, human leukocyte antigen; LRKT, living-related kidney transplantation; MMF, mycophenolate mofetil; SD, standard deviation; Tac, tacrolimus.

Background

Kidney transplantation is the optimal treatment option for most patients with end-stage renal disease (ESRD). Since the Chinese government prohibited organ procurement from executed convicts in 2015 [1], organ donation after death has become the primary source for organ transplantation. However, due to the ongoing shortage of organs, living donor kidney transplantation remains an essential component of transplant programs. In recent years, the number of living donor kidney transplants has increased in mainland China, accounting for approximately 20% of all kidney transplants nationwide [2]. As China prohibits living-

unrelated organ donation, only a recipient's spouses, lineal relatives, and collateral blood relatives within three generations may legally donate a kidney. In clinical practice, the most common types of living donation are from parents to children, followed by siblings, spouses, collateral relatives, and children to parents. Many reports suggest living-related kidney transplantation (LRKT) provide better early and late outcomes than cadaveric donor transplantation in terms of rejection, postoperative complication, and graft survival [3], although there are some opposing views [4, 5]. Several studies have analyzed the impact of the relationship between donors and recipients on short- and long-term graft outcomes with contradictory results. Choi et al. [6] demonstrated that mother-to-child (M-to-C) donations have a notably lower graft survival rate than father-to-child (F-to-C) donations. On the contrary, it has been speculated that the presence of fetal-maternal microchimerism may play a role in inducing some level of immune tolerance towards transplants from M-to-C, potentially leading to enhanced graft survival rates [7, 8]. Similar contradictory conclusions have also been reported regarding kidney transplants from offspring donors. Therefore, this study aims to compare the long-term outcomes depending on donor-recipient pairings in LRKT, exploring the effect of donor-recipient relationship on kidney graft survival.

Material and Methods

Data Source and Patients

This retrospective study analyzed data on kidney transplant recipients from a single center between 2001 and 2021 and the data were sourced from patient's medical records. Initially, patients over 18 years old who accepted a kidney donation from their relatives were included.

All included patients had negative donor-specific HLA antibodies (DSA) before transplantation. Patients who had undergone previous kidney transplantation, received multiple transplant organs, or ABO-incompatible transplant organs were excluded from this study. Recipients were classified into 5 groups based on the donor identity: M-to-C group (donated by a mother), F-to-C group (donated by a father), sibling group (donated by a brother or sister), spouse group (donated by a wife or husband), and offspring group (donated by a child). Follow-up information was collected at postoperative 7d, 1, 3, 6, 12 months, and every 6 months thereafter [9]. Therefore, individual opt-in patient consent was not required. This study was approved by the the ethics committee of research institutions (No. 2022080200072) and was conducted in compliance with the international human rights guidelines of the Declaration of Helsinki and the Declaration of Istanbul. Data obtained from executed prisoner donations were not included in this study.

Outcomes and Variable Definition

The primary objective of this study was to determine the survival rate of the grafts. The secondary objectives were to evaluate renal function at postoperative 1, 3, 5, 7, and 10 years, as measured by serum creatinine (Scr) levels. The outcomes also included the incidences of major postoperative complications within 1 year of transplantation, such as delayed graft function (DGF), rejection, pneumonia readmission, graft loss, and death. For the purpose of this study, all-cause graft loss was defined as patient death, nephrectomy, or graft failure (return to regular dialysis). The calculation of graft survival was based on the time from transplantation to the occurrence of all-cause graft loss or the last follow-up (May 10, 2022), whichever occurred first. The survival probabilities at 1, 3, 5, 7, and 10 years were compared

among the kidneys classified by different donor-recipient relationships. Rejection was confirmed by the administration of anti-rejection medication, with or without biopsy confirmation. DGF was defined as the need for dialysis within one week of transplantation, excluding rejection and primary non-function of the graft. The measurement of Scr was taken from a recipient who had a functioning kidney. The HLA mismatches were calculated by summing the total number of mismatches in the A, B, and DR alleles.

Statistical Analysis

Statistical analyses were performed using the SPSS 20.0 statistical software (SPSS Inc, Chicago, USA). Continuous variables were presented as mean and standard deviation for normally distributed data, and as the median and interquartile range (IQR) for non-normally distributed data. Categorical variables were described as percentages. Group comparisons were made using one-way analysis of variance and Pearson's Chi-squared test. The Kaplan-Meier method was used to analyze graft survival probabilities, which were compared among groups using the log-rank test. Cox proportional hazards regression was used to analyze risk ratios for all-cause graft survival, with hazard ratios (HRs) and their 95% confidence intervals (CIs) calculated. Since our focus was on the effect of the donor-recipient relationship, we used siblings as the reference group. After conducting univariate analysis on the baseline data in Table 1, multivariate Cox proportional hazards regression was performed by adjusting recipient and donor age (>50 years or not) [10], sex of recipient and donor, year of transplantation (before 2010 or not), histories of diabetes (yes or no). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Demographic Characteristics and postoperative complications within 1 year after transplantation

Table 1 presents the demographic data of 598 LRKTs, categorized based on the donor-recipient relationship. Of these transplants, the least number were from offspring (n=40), while the most frequently performed ones were M-to-C transplants (n=228). The M-to-C and F-to-C groups had the youngest recipient age and the eldest donor age, while the opposite was observed for the offspring donor group. The age gradient between donors and recipients in the sibling and spouse group was small, and the spousal donor group had the highest number of HLA-mismatches. Recipients from offspring kidney donation had a higher incidence of medical comorbidities, such as diabetes and cardiovascular disease, when compared to those from sibling, M-to-C, and F-to-C donations. **Table 2** demonstrates that within one year post-transplantation, the incidence of delayed graft function (DGF), rejection, pneumonia readmission, and death was similar across all groups. However, the offspring group showed a higher rate of graft loss compared to the other groups.

Renal Function Indicated by Scr

As presented in **Table 3**, the Scr levels at 1-, 3-, 5-, 7-, 10-year posttransplant were significantly higher in both the M-to-C and F-to-C groups compared to the other groups. However, patients with functioning graft kidneys in the sibling, spouse, and offspring donor groups exhibited stable and similar postoperative Scr levels during the 10-year follow-up period.

Graft Survival and Hazard Ratio for Graft Loss

The graft survival rates of the 598 kidney transplants in our cohort were as follows: 96.0% at 1 year, 92.4% at 3 years, 86.4% at 5 years, 79.9% at 7 years, and 69.9% at 10 years, respectively (**Table 4**). Although the sibling group had slightly higher graft survival rates compare to the M-to-C and F-to-C groups, the differences were not significant. Comparable graft survival rates were also observed in transplants from spouses and offspring, which were inferior to those from sibling and parent donors (**Figure 1**). Additional analysis using the Cox proportional hazard test is shown in **Table 5**, with covariate-adjusted hazard ratios (HRs) presented for all-cause graft loss depending on donor-recipient pairs, and the sibling donor group serving as the reference. The results indicate that kidney donation from spouses and offspring increases the risk of graft loss, with HRs of 3.8 (95% CI, 1.7−8.4, P=0.001) and 3.3 (95% CI, 1.6−6.9, P=0.002), respectively. It should also be noted that M-to-C and F-to-C pairing increases the risk of graft loss, with HRs of 1.9 (95% CI, 1.2－3.4，P=0.004) and 1.8 (95% CI, 1.1−3.1, P=0.024), respectively.

Discussion

Although numerous Chinese studies on LRKT have been published, most of them have only focused on short-term or mid-term follow-up periods of less than 5 years. Additionally, limited research has explained the association between donor-recipient relationships and long-term outcomes. Our study is the first to present 10-year survival data on different donor-recipient pairings, providing valuable insights into the association between donor-recipient relationships and graft survival in Chinese LRKT. We observed that parental donors were the

primary source of kidneys due to China's strict regulations on living organ donations between relatives. Furthermore, the proportion of spouse and offspring donors was comparatively lower in our study than in data reported in other research [11]. This disparity may be attributed to variances in economic, cultural, ideological, emotional, and other aspects between Eastern and Western countries.

This study found that the 1-, 5-, and 10-year graft survival rates in LRKT were equivalent to those reported by Matter *et al* [12]. We also observed that transplants from sibling donors had the highest graft survival rates, followed by M-to-C and F-to-C, although we did not find any statistical differences between them. However, kidneys from spouses and offspring donors had significantly lower survival rates compared to siblings, M-to-C pairs, and F-to-C pairs. These results contradict previous studies reporting inferior graft survival in M-to-C pairings, in comparison to transplants from other first-degree relative donors [13], as well as similar patient and graft survival rates between spousal donor kidney transplantation and other type of LRKT [14, 15]. Possible explanations for these findings include HLA mismatches, genetic susceptibilities to ESRD primary diseases, and age-related factors. Firstly, spousal recipients had higher HLA mismatches, which are believed to be linearly correlated with graft survival, particularly in LRKT [16]. Additionally, within our cohort, the spouse group had a higher proportion of male recipients receiving kidneys from female donors, which may have negatively impacted graft survival [17]. Secondly, compared to siblings, who only have a one-quarter chance of being homozygous for a susceptibility gene, parents and children have a higher genetic susceptibility to ESRD primary diseases, such as focal segmental glomerulosclerosis, polycystic kidney disease, and diabetes [18]. These diseases have been

associated with primary disease recurrence or worse graft survival, which could explain the much lower graft survival rates of the offspring group compared to the sibling group, as well as the decreasing trend of graft survival in the M-to-C and F-to-C groups in this study. Lastly, age is an important predictor of kidney transplantation outcome. Consistent with the viewpoint that older recipients have lower graft survival and higher mortality [19], we observed higher incidences of pretransplant diabetes and cardiovascular disease in the offspring group, which may account for their inferior graft survival rates.

Some researchers propose that the presence of HLA antibodies obtained during pregnancy may have a more significant influence on sensitization compared to microchimerism, increasing the risk of rejection in the graft kidneys of M-to-C, in theory [13]. Previously, it was believed that kidney donation between parent and child was a risk factor for T-cell-mediated rejection [20]. However, our results showed that most complications within one year postoperatively, such as DGF, rejection, pneumonia readmission, and death, were comparable in all groups, except for the incidence of graft loss, which was higher in the offspring group than in the sibling group. A study from China reported that parent-to-child transplant and older donor age (≥50 year) significantly increased the risk of elevated Scr levels at 6 months, 1 and 3 years post-transplant compared to situations where neither factor being present [21]. Consistent with these findings, our results showed that Scr levels in the M-t-C and F-t-C groups were significantly higher than those in other groups at 1, 3, 5, 7, 10 years after kidney transplantation, indicating that parent-to-child donation, along with older donor age, was associated with impaired graft function. Therefore, it is reasonable to assume that older donor age could lead to lower survival rates for parental donor grafts in the long-

term [18]. Our results confirm this idea, as both the M-to-C and F-to-C groups showed a trend towards inferior graft survival rates compared to the sibling group, and also increased the risk of graft loss with hazard ratios of 1.9 and 1.8, respectively. However, we did not find significant differences in clinical outcomes between M-to-C and F-to-C donor-recipient pairings.

This study also revealed another important finding. Holscher et al. found that, after adjusting for recipient and transplant-related characteristics, kidneys from offspring donors showed lower graft failure and comparable mortality compared to those from non-offspring donors, due to the younger donor age and excellent HLA matching [22]. However, Cohen et al.[23] demonstrated that transplant kidneys from offspring donors resulted in significantly increased mortality, which align with our own findings. These results could be partially explained by genetic susceptibility to certain diseases, older recipient age, and greater medical comorbidity. Therefore, due to the risk of graft loss and ethical considerations for elderly recipients and young donors, the clinical application of child-to-parent transplantation has been limited in recent years. Our findings also suggest that, whenever feasible, offspring living donors should be avoided for recipients who have multiple donor options.

The novelty of this study lies in its observation of the long-term outcomes of kidney transplantation based on different donor-recipient relationships. However, there are certain limitations. First, kidney transplants from offspring and spouses have become less common in most Chinese organ transplant centers in recent years, resulting in a small sample size for spouses and offspring donors in this retrospective, single-center analysis. This limitation affects the precision of our estimates. Secondly, similar to most long-term observational

studies, we did not thoroughly analyze the details of immunosuppressive regimen adjustments and other medications, which may cause some evaluation biases in graft survival or complication incidence. However, our long-term observation suggests that selecting the appropriate donor-recipient relationship can have a certain impact on transplantation outcomes. One hand, although there is an insignificant difference, kidneys from siblings tend to exhibit better graft survival than those from mothers, fathers. This observation may be confirmed by a larger sample size study. On the other hand, we observed significantly inferior graft survival in kidneys from spouses and offspring donors compared to those from siblings and parents. In other words, parent, spouse, and offspring donors increased the risk of graft loss compared to sibling donors.

Conclusions

Our study highlights that compared to sibling donors, donations from spouse and offspring significantly increased the risk of graft loss. This was followed by M-to-C and F-to-C pairings, which yielded higher postoperative Scr. Although short- and long-term graft survival after kidney transplantation depends on various elements that interact in a complex manner, our research highlights the importance of exercising caution when examining the donor-recipient relationships during preoperative assessments and postoperative management, particularly when the donors are children or spouses.

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Table 1. Demographic characteristics of transplants according to donor-recipient relationship (n=598)

	Sibling (n=115)	M-t-C (n=228)	F-t-C (n=160)	Spouse (n=55)	Offspring (n=40)
Recipient					
Transplantation years before 2010, n (%)	41 (35.7) [b]	31 (13.6) [a b]	20 (12.5) [a b]	19 (34.5) [b]	38 (95.0) [a]
follow-up period (year) ±SD	8.6 ± 3.9	8.8 ± 3.2	8.8 ± 3.2	8.5 ± 4.0	9.0 ± 4.8
Age (year) ± SD	40.0 ± 8.5 [b]	29.0 ± 6.0 [a b c]	30.0 ± 6.1 [a b c]	41.4 ± 7.0 [b]	50.4 ± 6.0 [a]
age>50 year, n(%)	12(10.4) [b]	0 [a b c]	0 [a b c]	10(18.2) [b]	18(45.0)
BMI (kg/m^2) ± SD	22.6 ± 3.5	21.3 ± 3.8	21.2 ± 3.9	22.8 ±1.9	23.6 ±3.5
Male, n (%)	86 (74.8)	183 (80.1)	133 (83.1)	41 (74.5)	22 (55.0)
Cause of ESRD					
Unkown, n (%)	43(37.4)	78(34.2）	55(34.3)	22(40.0)	15(37.5)
glomerular disease, n (%)	53(46.1)	111 (48.6)	76(47.8)	21(38.2)	13(32.5)
Interstitial nephropathy, n (%)	8(2.6)	20(8.7)	15 (9.4)	5(9.1)	3(7.5)
Hypertensive nephropathy, n (%)	1(0.9)	0	0	1(3.6)	1(2.5)
Diabetes nephropathy, n (%)	3(2.6) [b]	4(1.8) [b]	2(1.3) [b]	3(9.1)	6(15.0) [a]
Other, n(%)	7(6.1)	15(6.6)	12(7.5)	3(5.0)	2(5.0)
Dialysis duration (day), median [IQR]	436 [141, 552]	454 [190, 551]	533 [220, 647]	554 [99, 632]	415 [83, 687]
Pretransplant comorbidity					
Hyperuricemia, n(%)	61(53.0)	114(50.0)	84(52.5)	30(54.5)	24(60.0)
Dyslipidemia, n(%)	59(51.3)	106(46.5)	68(42.9)	25(45.5)	23(57.5)
Diabetes, n(%)	7(6.1) [b]	7(3.1) [b]	4(2.5) [b]	4(7.3)	8(20.0) [a]
Cardiovascular disease n(%)	25(21.7) [b]	34(14.9) [b]	25(15.6) [b]	13(23.6)	16(40) [a]
Donor					
Age (year) ± SD	38.2 ± 9.5 [b]	52.2± 6.5 [a b c]	55.8 ± 6.8 [a b c]	42.1 ± 8.4 [b]	25.5 ± 3.1 [a]
age>50 year, n(%)	22(19.1)	129(56.6) [a b c]	121(75.6) [a b c]	11(20.0)	0
Age gradient (year) ± SD	5.9± 4.9 [b]	24.2±4.2 [a c]	25.1± 4.4 [a c]	2.6±2.0 [b]	24.9± 4.1 [a]

Female, n(%)	60 (52.2)	228(100)	160(100)	41(74.5)	0
BMI (kg/m^2) ± SD	22.8± 3.0	23.4± 3.6	23.1± 3.2	22.3± 2.7	22.5± 2.8
Cold ischemia time (hour) ± SD	1.2 ± 0.2	1.3 ± 0.1	1.4 ± 0.3	1.2 ± 0.3	1.3 ± 0.2
Warm ischemia time (minute) ±SD	2.1± 0.5	2.2± 0.4	2.5± 0.3	2.3± 0.2	2.2± 0.3
HLA mismatches (number)±SD	1.9± 0.2	2.2± 0.2	2.1± 0.2	3.6± 0.4 [a]	2.2± 0.3
Transplant					
Antibody Induction, n(%)	84(73.0)	170 (74.6)	120(75.0)	45(81.8) [b]	24(60.0)
ATG	5(4.3)	10(4.4)	9(5.6)	8(14.5）	0
IL-2 RA	75(65.2)	154(67.5)	106(66.2)	35(63.6)	16(40.0)
ALG	4(3.5)	6(2.6)	5(3.1)	2(3.6）	8(2.0)
None induction, n(%)	31(27.0)	58(25.4)	40(25.0)	10(18.2)	16(40.0)
CsA+MPA+steroids, n(%)	16(13.9)	28(12.3)	25(15.6)	6(10.9)	3(7.5)
Tac+MPA+steroids, n(%)	92(80.0)	190(83.3)	130(81.3)	45(81.8)	34(85.0)
Other, n(%)	7 (6.1)	10(4.4)	5 (3.1)	4(7.3)	3(7.5)

[a] p<0.05 *vs*. the sibling group. [b] p<0.05 *vs*. the offsrping group. [c] p<0.05 *vs*. the spouse group. ALG, anti-lymphocyte immunoglobulin; ATG, antithymocyte immunoglobulin; BMI, Body mass index; CsA, Cyclosporine A； ESRD, end stage of renal disease; F-to-C, father-to-child; HLA, human leukocyte antigen; IL-2 RA, interlukin-2 receptor antagonist; IQR, interquartile range; MMF, mycophenolate mofetil; M-to-C, mother-to-child; Offspring, kidney from offspring; SD, standard deviation. Scr, Serum creatinine; Tac, Tacrolimus. Sibling, kidney from sibling donor; Spouse, kidney from spousal donor

Table 2. Postoperative complications within 1-year post-transplantation according to donor-recipient relationship (n, %)

	Sibling (n=115)	M-t-C (n=228)	F-t-C (n=160)	Spouse (n=55)	Offspring (n=40)
DGF	3(2.6)	11(4.8)	6(3.8)	2(3.6)	2(5.0)
Rejection	10(8.7)	18(7.9)	10(6.3)	8(14.5)	4(10.0)
Pneumonia readmission	5(4.3)	24(10.5)	1(5.0)	1(5.0)	3(15.0)
Graft loss	1(0.9)	7(3.1)	2(1.3)	4(7.2)	4(10.0) [a]
Death	1(0.9)	3(1.3)	1(0.6)	1(1.8)	3(15.0)

[a] p<0.05 vs. the sibling group.

Table 3. Postoperative serum creatinine levels according to donor-recipient relationship (μmol/L, n)

Postoperation	Sibling (n=115)	M-t-C (n=228)	F-t-C(n=160)	Spouse (n=55)	Offspring (n=40)
1 year	103.5±22.2(101)	120.3±35.7 (217) [a]	122.7±32.1(149) [a]	114.2±36.7(50)	106.3±28.4(37)
3 year	107.3±29.5 (95)	124.5±35.4 (206) [a]	125.2±33.4(140) [a]	105.5±22.8(41)	108.9±25.7(32)
5 year	108.5±29.5 (87)	128.6±36.9 (157) [a]	130.1±34.6(110) [a]	108.1±22.8(36)	114.3±28.8(29)
7 year	116.3±35.1 (74)	137.7±38.8(179) [a]	138.1±35.9(66) [a]	114.9±22.5(24)	108.7±20.7(22)
10 year	110.8±26.7 (45)	145.3±40.8 (60) [a]	147.2±41.3(30) [a]	109.3±5.8(14)	102.6±23.2(15)

[a] p<0.05 *vs*. the sibling group. Patients with missing data or with a nonfunctioning graft are deleted for calculation.

Table 4. Graft survival probabilities by Kaplan-Meier analysis according to donor-recipient relationship (%, 95% CI)

Postoperation	Sibling (n=115)	M-t-C (n=228)	F-t-C (n=160)	Spouse (n=55)	Offspring (n=40)	Overall (n=598)
1 yr	98.2 [97.0－99.4]	96.1 [94.8－97.4]	96.8 [95.5－98.1]	87.8 [81.2－94.4] [a]	87.0 [78.1－93.3] [a]	96.0 [95.2－96.8]
3 yr	94.7 [92.6－96.8]	92.8 [91.1－94.5]	92.8 [90.7－94.9]	79.4 [71.2－87.6] [a]	82.6 [73.4－88.6] [a]	92.4 [91.3－93.5]
5 yr	90.8 [88.0－93.6]	85.0[82.4－87.6]	88.3 [85.5－91.1]	75.3 [66.5－84.1] [a]	78.3 [65.7－84.3] [a]	86.4 [84.9－87.9]
7 yr	87.4 [84.4－90.7]	79.8 [76.6－83.0]	78.4 [74.2－82.6]	70.9 [66.4－75.4] [a]	60.9 [56.3－65.5] [a]	79.9 [77.9－81.9]
10 yr	80.7 [76.3－85.1]	68.7 [63.5－73.9]	68.3 [62.8－73.8]	54.7 [50.3－59.1] [a]	56.5 [52.3－60.7] [a]	69.9 [67.1－72.7]

CI, confidence interval

Table 5. Adjusted hazard ratios for graft survival according to donor-recipient relationship

group	Hazard ratio (95% CI)	*P* value
Sibling	1.00 (Ref)	—

M-to-C	1.9 [1.2－3.4]	0.024
F-to-C	1.8 [1.1－3.1]	0.022
Spouse	3.3 [1.6－6.9]	0.001
Offspring	3.8 [1.7－8.4]	0.002

Adjusted for age of recipient and donor (>50 year or not), gender of recipient and donor, transplant era (before 2010 or not), diabetes history (yes or no).

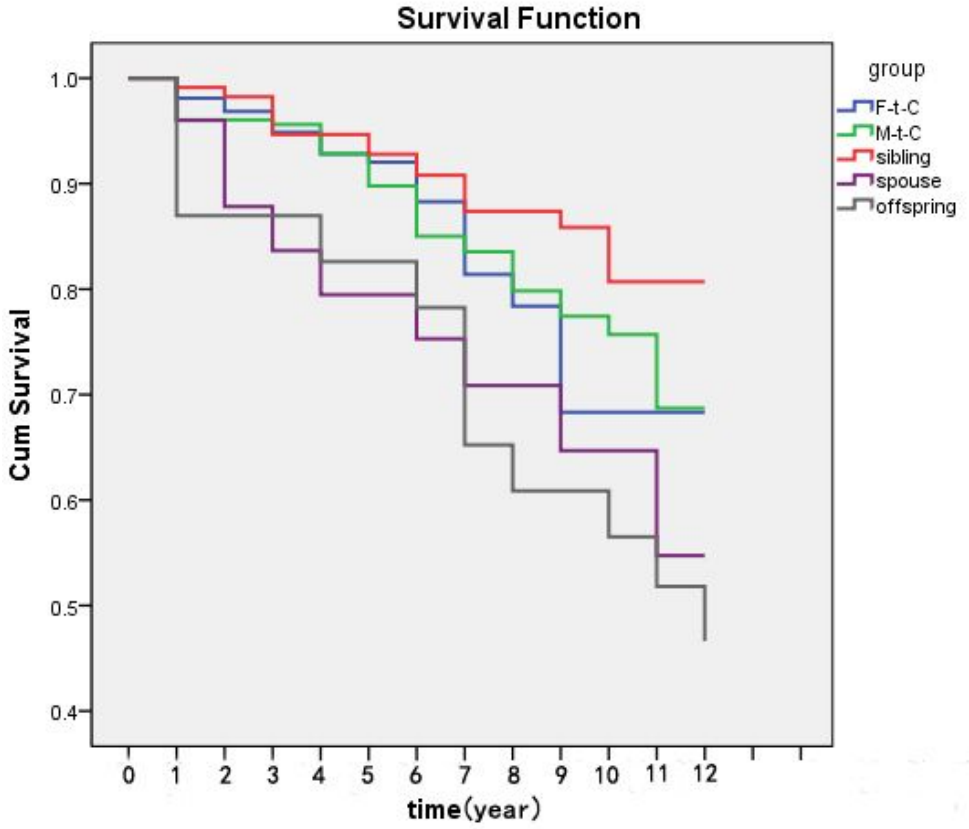

Figure 1. Graft survival probabilities according to donor-recipient relationship. Inferior outcomes were observed in patients who received kidney transplants from spouse and offspring donors.