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CLINICAL STUDY

Effect of donor age and parent-to-child transplant on living-related donor kidney transplantation: a single center's experience of 236 cases

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Abstract

To study the impact of parent-to-child transplant and older donor age on recipients' post-transplant creatinine levels, a total of 236 patients who received living donor kidney transplantation were evaluated for kidney viability based on creatinine (Cr) level. Of the 236 pairings, 113 (48%) were parent-to-child followed by sibling transplants (66, 30%). Recipient Cr levels were significantly higher at 6 months and 3 years post-transplant in the parent-to-child transplants compared to other donor–recipient relationships. In addition, donor age (average age: 44.1 ± 11.5; range: 19–66) contributed to higher recipient post-transplant Cr levels ($p < 0.01$). Pre-transplant donor and recipient Cr levels tended to result in higher post-transplant Cr levels in recipients ($p < 0.05$). Multivariate logistic regression analysis revealed that the presence of both parent-to-child transplant and older donor significantly increased the risk of elevated post-transplant Cr levels in recipients with an estimated odds ratios ranging from 3.46 (95% CI: 1.71–6.98) at 6 months to 8.04 (3.14–20.56) at 3 years post-transplant. Donor age significantly affected transplant survival as measured by higher recipient post-transplant Cr levels. In addition, parent-to-child transplant pairings, along with older donor age, significantly increased the risk of elevated post-transplant Cr levels in recipients.

Keywords

Kidney transplant, living donor, relatives, survival

History

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Introduction

Living kidney donor transplantation plays a pivotal role, globally, in managing chronic renal failure. The current trend is to increase the number of such transplantations, thereby, reducing the long waiting lists for renal transplants. In the past decade, the living kidney donation rate has remained steady in the USA, posing a particular challenge for managing terminal renal diseases.[1]

In China, relatives of patients are the sole source of living kidney transplants, with parental donors accounting for the majority of kidney donors.[2,3] The lack of cadaver kidneys and long wait times on transplant waiting lists play pivotal roles in the high number of living donor kidney transplants performed in China.

Numerous studies have shown that the long-term graft survival is markedly higher in living donor kidneys compared to cadaver donor kidneys. The high proportion of parental donors raises the question as to whether the outcome of kidney transplant from older living donors is comparable to that from younger living donors and whether living kidney donation has a long-term impact on transplant recipient survival.[4,5]

A retrospective study of 117 living donors in China found that the 5-year survival rate for transplant recipients from older living donors (≥50 years) was comparable to that of younger living donors.[6] However, the number of older donors in the study was very limited ($n = 23$) and there were no data on the impact of the parent–child transplant on the survival of the recipient.

In the current study, we retrospectively reviewed the effect of donor age on outcomes in living-related donor kidney transplantation in 236 patients with terminal renal diseases. In particular, we evaluated the impact of the parent-to-child transplant and older donor age on post-transplant creatinine levels in recipients.

Materials and methods

Subjects

The study protocol was approved by the local institutional review board at the authors' affiliated institution. Patient consent was not required because of the retrospective nature of this study. We retrospectively reviewed the clinical and surgical records of 236 patients who received living-related donor allograft transplantation between 2004 and 2012 at our hospital. All human studies have been approved by the appropriate ethics committee and have therefore been

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performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Preoperative evaluation

Potential donors underwent a comprehensive health screen prior to blood being drawn for compatibility testing. However, donors were not fully evaluated until a match was found and no donors with hypertension participated in the study. Donor evaluation included routine blood chemistries and urine tests, liver and kidney function, serum creatinine (Cr) clearance, coagulation test, liver virology, chest X-ray, ECG, ultrasonography of both kidneys and angiography including digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA).

Recipient evaluation included blood chemistries, urine tests, liver function studies, serum creatinine levels, hepatitis series, coagulation profile, blood lipid levels, HIV test, barium examination of the gastrointestinal tract or gastric endoscopy, chest X-ray, ECG, ultrasonography of both kidneys, human leukocyte antigen (HLA) typing and panel reactive antibody (PRA). Complement-dependent cytotoxicity (CDC) test was performed between the donor and recipient.

Immunosuppressive regimens

Induction regimen: 74 patients received rabbit anti-human anti-thymocyte immunoglobulin (ATG) and methylprednisolone (Pfizer, Dalian, Liaoning, China), 90 patients were given anti-interleukin-2 receptor (IL-2R) antibody and methylprednisolone, and 72 patients were administered with methylprednisolone only. Methylprednisolone was given intraoperatively and on postoperative days 1 and 2 at a dose of 500 mg/d.

Basic immune maintenance regimen: 111 patients received cyclosporine A (CsA), mycophenolate mofetil (MMF, Shanghai Roche, Shanghai, China) and prednisone. One hundred and twenty-five patients received tacrolimus (FK506) (Fujisawa, Osaka, Japan), MMF and prednisone. CsA was started at 4–5 $mg\,kg^{-1}\,d^{-1}$ and was titrated according to its plasma concentration to maintain a trough concentration of 150–220 μg/L. FK506 was started at a loading dose of 0.15 $mg\,kg^{-1}\,d^{-1}$ and was adjusted by its blood concentration to maintain a trough of 5–10 μg/L. MMF was administered at 1–1.5 g/d. Prednisone was started on postoperative day 3 at a loading dose of 30 mg/d and tapered over 2 months to 5–10 mg/d.

Follow-up

Donors and recipients were followed-up regularly by telephone or outpatient visit over a 5-year period. Donors were observed for postoperative complications. Recipients were evaluated for postoperative serum creatinine levels and kidney viability. In particular, the impact of the parent-to-child transplant and older donor age on post-transplant creatinine levels in recipients was evaluated.

Statistical analysis

Demographic and baseline clinical characteristics for donors and recipients were summarized as frequency (categorical variable) or mean ± SD (continuous variable). In addition, frequencies of donor–recipient relationships and gender combinations were analyzed. The summary analysis was further stratified by parent-to-child transplants versus others, and by younger (<50 years) versus older (≥50 years) donors.

Generalized estimating equation (GEE) estimates of linear regression were calculated to determine the mean differences in Cr levels in recipients at 1, 6 months, and 1, 3, 5 years post-transplant between parent-to-child transplants and the others, adjusting covariates including donor and recipient age, gender, pre-transplant Cr levels and female-to-male transplant. Similarly, GEE estimates of the mean differences of post-transplant levels in recipients between older and younger donor groups were also obtained, adjusting covariates including recipient age, donor and recipient gender, pre-transplant Cr levels and female-to-male transplant. Significance of differences between groups and effects were determined by the Z or Wald test p value from the GEE analysis.

Multivariate logistic regression analysis was performed to assess the effects of parent-to-child transplant and older donor age on a higher Cr level, which was defined as a Cr level >115 μmol/L, at 1, 6 months, and 1, 3, 5 years post-transplant in recipients, adjusting for covariates including recipient age, donor and recipient gender, pre-transplant Cr level and female-to-male transplant.

All analyses were performed using statistical software SAS 9.2 (SAS Institute Inc., Chicago, IL), and a p value less than 0.05 was considered statistically significant.

Results

Donor–recipient demographics and baseline clinical characteristics

Table 1 shows demographics and baseline clinical characteristics for donors and recipients. There were more male recipients (79%) than male donors (48%). There were, respectively, 90 (38%), 22 (9%), 96 (41%) and 28 (12%) male–male, male–female, female–male and female–female gender combinations for all 236 donor–recipient pairs. On the other hand, there were 113 (48%) parent-to-child kidney transplants, the most common type of donor–recipient relationship in this study, followed by sibling transplants (66, 30%). This resulted in a higher average age in donors (average age: 44.1 ± 11.5; range: 19–66) compared with that in recipients (32.1 ± 9.4; range: 6–65) (Table 1).

Table 2 compares baseline donor and recipient characteristics between the parent-to-child transplant group versus all others. Except for donor age (which was expected to be higher) and recipient age (which was expected to be lower in the parent-to-child group than in the others), there were no significant differences in gender proportion, mean body weight or pre-transplant Cr levels between parent-to-child transplants and others (child–parent, sibling, other relatives and spouses).

Table 3 compares baseline donor and recipient characteristics between younger (<50 years) and older (≥50 years) donor groups. Except for donor age and proportion of parent-to-child transplants, there were no significant differences in

Table 1. Baseline characteristics of kidney recipients and donors ($n = 236$) in the renal transplantation study (frequency for categorical variables, mean ± SD for continuous variables).

	Recipients	Donors
Male (%)	186 (78.8)	112 (47.5)
Age, yrs (range)	32.1 ± 9.4 (6–65)	44.1 ± 11.5 (19–66)
Weight, kg (range)	56.8 ± 10.3 (15–84)	58.1 ± 9.1 (40–90)
Pre-transplant Cr, μmol/L (range)	1046.9 ± 384.6 (45–2077)	66.9 ± 15.9 (36–132)
Donor–recipient gender combination (%)		
Male–male	90 (38.1)	
Male–female	22 (9.3)	
Female–male	96 (40.7)	
Female–female	28 (11.9)	
Donor–recipient relationship (%)		
Parent–child	113 (47.9)	
Child–parent	5 (2.1)	
Sibling	66 (30.0)	
Other collateral relatives	44 (18.6)	
Spouse	7 (3.0)	
Others	1 (0.4)	

Table 2. Baseline characteristics of recipients and donors by donor–recipient relationship groups (parent–child vs. others).

	Parent–child ($n = 113$)	Others ($n = 123$)
Recipients		
Male (%)	89 (78.8)	97 (78.9)
Age, yrs (range)	28.8 ± 7.1 (6–49)	35.3 ± 10.2 (6–65)*
Weight, kg (range)	55.7 ± 9.9 (15–75)	57.7 ± 10.5 (16–84)
Pre-transplant Cr, μmol/L (range)	1094.0 ± 384.6 (193–2059)	1003.0 ± 381.0 (45–2077)
Donors		
Male (%)	50 (44.3)	62 (50.4)
Age, yrs (range)	52.3 ± 7.3 (23–66)	36.6 ± 9.3 (19–62)*
Weight, kg (range)	58.3 ± 8.4 (40–90)	57.9 ± 9.7 (40–80)
Pre-transplant Cr, μmol/L (range)	65.8 ± 14.4 (39–110)	67.9 ± 17.1 (36–132)
Donor–recipient gender combination (%)		
Female–male	48 (42.5)	48 (39.0)
Others	65 (57.5)	75 (61.0)

Note: *$p < 0.05$ between the two groups.

Table 3. Baseline characteristics of recipients and donors by donor age groups (<50 years vs. ≥ 50 years).

	Donor age < 50 yrs ($n = 146$)	Donor age ≥ 50 yrs ($n = 90$)
Recipients		
Male (%)	115 (78.8%)	71 (78.9%)
Age, yrs (range)	33.2 ± 10.1 (6–65)	30.4 ± 7.9 (6–65)
Weight, kg (range)	56.7 ± 10.2 (16–84)	56.9 ± 10.4 (15–76)
Pre-transplant Cr, μmol/L (range)	1027.1 ± 378.3 (45–2077)	1078.0 ± 394.5 (193–1966)
Donors		
Male (%)	65 (44.5%)	47 (52.2%)
Age, yrs (range)	36.7 ± 8.0 (19–49)	55.8 ± 3.9 (50–66)*
Weight, kg (range)	57.8 ± 9.3 (40–88)	58.6 ± 8.8 (44–90)
Pre-transplant Cr, μmol/L (range)	66.8 ± 17.0 (36–132)	67.0 ± 14.0 (40–110)
Donor–recipient gender combination (%)		
Female–male	62 (42.5%)	34 (37.8%)
Others	84 (57.5%)	56 (62.2%)
Donor–recipient relationship (%)		
Parent–child	34 (23.3%)	79 (87.8%)*
Others	112 (76.7%)	11 (12.2%)*

Note: *$p < 0.05$ between the two groups.

Table 4. Adjusted mean differences (SE) of post-transplant creatinine levels in recipients between parent-to-child transplants versus others, and between older (≥50 years) versus younger (<50 years) donors.

	Parent-to-child versus others	Donor age ≥ 50 years versus <50 years
Time-points post-transplant		
1 month	3.86 (5.53)	10.83 (5.76)
6 months	10.42 (5.11)*	16.96 (5.38)**
1 year	6.78 (5.53)	11.40 (5.65)*
3 years	23.69 (9.23)*	25.39 (10.40)*
5 years	2.30 (15.80)	3.22 (13.92)
Covariate		
Donor age, yrs	0.76 (0.18)**	–
Recipient age, yrs	−0.03 (0.23)	−0.05 (0.24)
Donor gender, male	11.39 (10.51)	11.07 (10.24)
Recipient gender, male	7.35 (8.06)	8.27 (7.76)
Donor pre-transplant Cr, μmol/L	0.31 (0.15)*	0.32 (0.14)*
Recipient pre-transplant Cr, μmol/L	0.01 (0.005)*	0.01 (0.005)
Female-to-male	20.27 (10.77)	20.04 (10.52)
Parent-to-child	–	11.87 (4.98)*

Notes: Results for covariate are estimated regression coefficients (SE).
*$p < 0.05$.
**$p < 0.01$.

Table 5. Adjusted rood ratio with 95% CI for parent-to-child transplant and older donor with high recipient creatinine levels (>115 μmol/L) at post-transplant time points.

1 Month post-transplant	
Parent-to-child, donor age ≥ 50 yrs	3.49 (1.72–7.06)**
Other relationship, donor age ≥ 50 yrs	2.13 (0.49–9.33)
Parent-to-child, donor age < 50 yrs	2.49 (0.97–6.39)
Other relationship, donor age < 50 yrs	1
6 Months post-transplant	
Parent-to-child, donor age ≥ 50 yrs	7.89 (3.71–16.77)**
Other relationship, donor age ≥ 50 yrs	4.78 (1.02–22.49)*
Parent-to-child, donor age < 50 yrs	2.96 (1.14–7.64)*
Other relationship, donor age <50 yrs	1
1 Year post-transplant	
Parent-to-child, donor age ≥ 50 yrs	4.48 (2.20–9.11)**
Other relationship, donor age ≥ 50 yrs	10.43 (2.01–54.20)**
Parent-to-child, donor age < 50 yrs	2.24 (0.90–5.58)
Other relationship, donor age < 50 yrs	1
3 Years post-transplant	
Parent-to-child, donor age ≥ 50 yrs	8.07 (3.15–20.63)**
Other relationship, donor age ≥ 50 yrs	9.70 (1.79–52.55)**
Parent-to-child, donor age < 50 yrs	4.70 (1.49–14.83)**
Other relationship, donor age < 50 yrs	1

Notes: Comparison with other donor–recipient relationships and donor age <50 years; adjusted for recipient age, donor and recipient gender, and pre-transplant creatinine levels.
*$p < 0.05$.
**$p < 0.01$.

gender proportion, mean body weight or pre-transplant Cr levels between younger and older donor groups.

Effects of parent-to-child transplant and older donors on post-transplant creatinine levels in recipients

GEE estimates for the differences in post-transplant recipient Cr levels between parent-to-child transplants versus all others are shown in Table 4. Compared to transplants with other donor–recipient relationships, the recipient Cr levels were significantly higher at two time-points (6 months and 3 years post-transplant) in the parent-to-child transplants. In addition, donor age (used as a continuous variable in years) was a significant covariate in this model ($p < 0.01$), with higher donor age contributing to higher recipient post-transplant Cr levels.

Pre-transplant donor and recipient Cr levels were also significant covariates in this model ($p = 0.03$ and 0.04, respectively); higher pre-transplant donor and recipient Cr levels tended to result in higher post-transplant Cr levels in recipients. Female-to-male transplants had higher post-transplant recipient Cr levels compared to transplants with other gender combinations, but the effect was not significant ($p = 0.06$). This analysis revealed that the differences in post-transplant recipient Cr levels were significant between parent-to-child transplants compared with other donor–recipient relationships, even if the donor age had been adjusted.

On the other hand, Cr levels of recipients whose donor's age was ≥50 years were significantly higher than those with donor age <50 years at 6 months, 1 and 3 years post-transplant, after adjusting for parent-to-child transplant and other covariates in GEE analysis of linear regression (Table 4). The parent-to-child transplant remained a significant covariate in this model ($p = 0.02$), in addition to the donor pre-transplant Cr levels ($p = 0.02$). The effect of female-to-male transplant was not significant ($p = 0.06$). This analysis, together with the previous one, shows that donor age and parent-to-child transplant were factors jointly affecting Cr levels over several post-transplant time points in recipients.

Risks of parent-to-child transplant and older donor for high recipient post-transplant creatinine

Multivariate logistic regression analysis, performed at each time point post-transplant, is shown in Table 5. The presence of both parent-to-child transplant and older donor age significantly increased the risk of elevated post-transplant Cr levels in recipients when compared to the absence of both factors; the estimated odds ratio ranged from 3.46 (95% CI: 1.71–6.98) at 6 months to 8.04 (3.14–20.56) at 3 years post-transplant. The analysis at 5 years post-transplant was not convergent and hence was omitted.

As shown in Table 5, the presence of only older donor age or parent-to-child transplant could also lead to significantly elevated risk of high post-transplant recipient creatinine levels at certain time points post-transplant, but the effect of the older donor age appeared to be larger than parent-to-child transplant. In fact, when the donor was older (>50 years), parent-to-child transplant tended to reduce the risk of high post-transplant creatinine in recipients at later time points (1 and 3 years post-transplant) compared to transplants with other donor–recipient relationships, although the effect from such an interaction was only marginally significant ($p = 0.08$ at 1 and 3 years post-transplant). The estimated effects for covariates in the models over post-transplant time points showed that high pre-transplant donor Cr levels ($p = 0.02$), high recipient Cr levels ($p = 0.01$) and female-to-male transplant ($p = 0.05$) were significant risk factors for high

creatinine levels in recipients immediately (1 month) after transplant, but became insignificant at subsequent time points post-transplant.

Discussion

Our results showed that recipient Cr levels were significantly higher at 6 months and 3 years post-transplant in the parent-to-child transplants compared to transplants with other donor–recipient relationships. In addition, donor age contributed to higher recipient post-transplant Cr levels ($p < 0.01$; Table 4). Higher pre-transplant donor and recipient Cr levels tended to result in higher post-transplant Cr levels in recipients ($p < 0.05$; Table 4). Multivariate logistic regression analysis revealed that the presence of both parent-to-child transplant and older donor age significantly increased the risk of high post-transplant Cr levels in recipients when compared to the absence of both factors, with an estimated odds ratio ranging from 3.46 (95% CI: 1.71–6.98) at 6 months to 8.04 (3.14–20.56) at 3 years post-transplant (Table 5).

There is no definite age requirement for living kidney donors based on clinical grounds, however, 50 years of age is often used as the demarcation between younger versus older donors due to the marked differences in the function of the kidney transplant after this time point.[7] Lim et al.[8] revealed that the renal function of recipients of kidneys from younger donors at 1 and 5 years post-transplant was better than that of recipients of kidneys from older donors. Jain et al.[7] also found that the GFR of kidney transplant recipients was markedly lower when the donors were $\geq$50 years of age compared to donors <50 years of age during a 5-year follow-up. We also showed that higher donor age contributed to higher recipient post-transplant Cr levels ($p < 0.01$; Table 4). This finding may be due to lower GFR in donors $\geq$50 years of age as higher pre-transplant donor and recipient Cr levels tended to result in higher post-transplant Cr levels in recipients ($p < 0.05$; Table 4). Similar results were reported in other studies where donor eGFR and donor age were found to be independent risk factors for clinical outcomes of living kidney transplants.[9]

Despite efforts to obtain alternative sources of organ transplants,[10] there is still a critical worldwide shortage of living organs. Several countries have decided to accept expanded criteria for living donors, including elderly, marginal, unrelated and ABO-incompatible individuals.[6,11,12] In China, the primary source of kidney transplants is parental donors,[2] however, there is little information in the current literature concerning the effect of the parent–child transplant on living-related donor kidney transplantation survival.[13] Deng et al.[14] analyzed the clinical characteristics of 175 living-related kidney transplants, including 63 cases (36%) of parent–child transplants and found that one-year survival rates of the patients and grafts were 99.3% and 98.2%, respectively. Xue et al.[15] investigated the effect of living-related donor kidney transplantation in 158 patients of which seven transplants were donated by spouses and 151 were from donors with blood relationships with the recipients. They found a favorable one year patient/graft survival rate of 95.5%. However, Miles et al.[16] investigated death-censored graft survival among living-related donor–recipient pairings including child-to-mother, child-to-father, mother-to-child, father-to-child, 1-haplotype matched siblings and HLA-identical siblings. They found that HLA-identical sibling recipients had the best survival, however, mother-to-child transplants had the poorest graft survival (hazard ratio = 2.61, $p < 0.0001$) possibly related to immune sensitization of kidneys transplanted between mothers and their offspring.[16] Similar results were noted in another study of 374 patients who underwent living-related renal transplantation.[17] Choi et al.[17] assessed long-term graft survival according to donor–recipient pairing which included 21 cases (5.6%) of child-to-father pairing, 28 (7.5%) child-to-mother pairings, 179 (47.9%) one-haplotype-matched siblings pairings, 46 (12.3%) father-to-child pairings and 100 (26.7%) mother-to-child pairings.[17] Mother-to-child showed the poorest graft survival (HR 17.188, $p = 0.005$) possibly related to presensitization to HLA during the pregnancy, as fetal blood exposed to the maternal circulation can induce maternal immunization to paternal HLA inherited by the fetus.[5,17–19] Herein may lie one possible explanation for the significantly higher recipient Cr levels seen at 6 months and 3 years post-transplant in the parent-to-child transplants compared to transplants from other donor–recipient relationships in our study. This presensitization to HLA during pregnancy would also provide an explanation for our finding that female-to-male transplants ($p = 0.05$) were significant risk factors for high creatinine levels in recipients 1 month after transplant. In addition, Choi et al.[17] found that father-to-child pairing experienced poorer outcomes than child-to-father pairs (HR = 11.579, $p = 0.017$), however, the underlying mechanism for the results from these pairings was less clear. Future studies examining the relationship between immune sensitization and parent-to-child transplants would be useful to confirm our findings, and may contribute to a better understanding of immune sensitization mechanism in living-related donor transplantation.

Our study had several limitations including its retrospective/single center nature and its limited sample size. We also did not break-out the parent–child pairing into father-to-child versus mother-to-child parings. In addition, there are a number of articles in literature that focus on the psychological aspects affecting graft survival and compliance that could also apply to living kidney donation.[20,21] We also noticed that trend but did not analyze it in our manuscript. Therefore, our findings require further validation by longer prospective studies involving a larger sample size across multiple clinical centers involving more donor–recipient pairings including father-to-child and mother-to-child parings, as well as pre- and postoperative psychological aspects of recipients.

In conclusion, donor age significantly affected transplant survival as measured by higher recipient post-transplant Cr levels. In addition, parent-to-child transplant pairings, along with older donor age, significantly increased the risk of elevated post-transplant Cr levels in recipients. Immune sensitization may contribute to poorer graft survival in parent-to-child transplants compared to other living-related donor–recipient relationships.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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