Journal of the Formosan Medical Association (2013) 112, 783–788

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Gender differences in renal transplant graft survival

Po-Da Chen [a], Meng-Kun Tsai [a], Chih-Yuan Lee, Ching-Yao Yang, Rey-Heng Hu, Po-Huang Lee, Hong-Shiee Lai*

Department of Surgery, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan

Received 1 April 2013; received in revised form 17 September 2013; accepted 4 October 2013

KEYWORDS
gender difference;
graft survival;
kidney transplantation

Background/Purpose: A long-term retrospective study was conducted to assess the risk factors of renal transplant graft failure focusing on the effects of gender of both the donor and the recipient.
Methods: Medical records of primary renal transplantation performed in a single transplant hospital were reviewed. Cases of ABO incompatibility, positive cross-matches, or multiple organ transplants were excluded. A total of 766 patient records were reviewed, and variables were analyzed with Kaplan–Meier survival curves and Cox regression to determine the independent factors associated with graft survival.
Results: The overall 5-year graft and patient survival rates were 84.7% and 92.2%, respectively. Univariate analysis showed significantly poorer prognosis in male patients and in those with acute rejection, delayed function, or more mismatches in human lymphocyte antigens. Multivariate analysis with step-wise regression identified three independent prognostic factors for poor graft survival (male gender, acute rejection, and delayed function). The 5-year graft survival rates for female and male patients were 87.9% and 81.3%, respectively. The risk ratio of graft failure for male renal transplant recipients was 1.3732, when compared with that for female patients. The risk ratios for those with acute rejection and delayed function were 1.8330 and 1.5422, respectively.
Conclusion: Male gender, in addition to acute rejection and delayed function, was found to be an independent prognostic factor for poor renal transplant survival in this long-term retrospective study.

* Corresponding author. Department of Surgery, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei, Taiwan.
E-mail address: HSLai@ntu.edu.tw (H.-S. Lai).
[a] P.-D.C. and M.-K.T. contributed equally to this article.

0929-6646/$ - see front matter
http://dx.doi.org/10.1016/j.jfma.2013.10.011

Introduction

Renal transplantation has been a preferable treatment method for patients with end-stage renal disease. It is also associated with improved patient survival and quality of life when compared with dialysis. Although numerous reports on survival of kidney grafts and their recipients have been published, the factors influencing long-term survival of the renal graft is still a matter of considerable debate. More recent studies have reported that patients with a greater number of human leukocyte antigen (HLA) mismatches, the presence of acute rejection, and delayed graft function are at higher risks of graft failure. The role of other factors including age and gender of the donor and the recipient, donor type, and hepatitis profiles are currently unknown.[1–3]

In 2002, based on the data from the Collaborative Transplant Study, Zeier et al[4] reported that the donor gender–associated risk ratio for graft loss was 1.15 in female recipients and 1.22 in male recipients, and that the graft survival was worse when the donor was female and the recipient was male. However, the independent effects of recipient gender on renal transplant survival were not well documented. Therefore, we conducted a long-term retrospective study to assess the risk factors of renal transplant graft failure focusing on the effects of both donor and recipient genders. Stepwise regression procedures were performed to select a multivariate regression model of independent prognostic factors with maximal corresponding likelihood ratio statistic.

Materials and methods

Study population and design

A retrospective study was conducted to assess risk factors of renal transplant graft failure. Medical records of primary renal transplantation performed in a single hospital between April 1988 and December 2009 were reviewed. Patients with ABO incompatibility, positive cross-matches, multiple organ transplants, and second transplants were excluded.

Immunosuppressive therapy

Immunosuppressive therapy for all the patients were regimens based on a calcineurin inhibitor, either cyclosporine or tacrolimus, an antiproliferative agent, and corticosteroids. The antiproliferative agent could be mycophenolate mofetil, mycophenolate sodium, or azathioprine. Antilymphocyte antibodies were not used for induction therapy but solely for rescue of refractory acute rejection.

The dosage of calcineurin inhibitors was adjusted to the target trough levels of 200–400 ng/mL for cyclosporine and 8–16 ng/mL for tacrolimus. The target blood levels at 12 months were 100–200 ng/mL for cyclosporine and 5–8 ng/mL for tacrolimus. Mycophenolate mofetil or mycophenolate sodium was prescribed at initial doses of 1–2 g/day and 720–1440 mg/day, respectively. Azathioprine was used in some early cases at doses between 50 and 100 mg/day. The white blood cell counts were controlled to be between 4000 and 6000/mm^3 unless intolerance developed or the maximum dose was reached. Methylprednisolone (500 mg) was initially used once before reperfusion. Prednisolone, at a dose of 2.5–5 mg/day for 12 months and thereafter, was used and could be tapered down or even discontinued if significant side effects occurred.

Outcome measurement

Delayed graft function was defined as persistent oliguria (<400 mL/24 hours) or the requirement for dialysis during the 1st week after transplantation. All patients with suspicious episodes of acute rejection (persistent oliguria for more than 7 days after transplantation or elevation of creatinine level by more than 30% of baseline levels) underwent allograft renal biopsy to pursue the pathological diagnosis. An episode of acute rejection was primarily treated with methylprednisolone pulse therapy, and antilymphocyte antibodies could be used to treat those refractory to steroid therapy. Graft failure was defined as return to chronic dialysis for more than 30 days, retransplantation, graft removal, or death of the recipient with functional kidney, whichever came first. Furthermore, the status patients lost to follow-up would be considered based on their last visit.

Statistical analysis

The NCSS 8 software (NCSS, LLC, Kaysville, UT) was used for statistical analysis. Values were reported as arithmetic means $\pm$ standard deviations. Unpaired two-tailed t tests were used for normally distributed continuous variables; and the Chi-square test or Fischer exact test was used for categorical variables. A p value of 0.05 was adopted as the level of significance. Graft survival rates were estimated using the Kaplan–Meier method. Univariate analysis model with log-rank test was used to examine significance of the prognostic factors. The prognostic significance of the recipient's age, donor's age, and HLA mismatch for graft survival was determined using Cox regression model. The factors that were statistically significant in the univariate analysis were then analyzed using a multivariate regression model to determine the independent effect of each factor.

Results

Patient characteristics

We performed 852 renal transplants in a single medical center between April 1988 and December 2009. A total of 766 patients were recruited in this study, including 364 male and 402 female patients. We excluded 20 cases with ABO incompatibility, six with positive cross-matches, 27 with multiple organ transplants, and 33 with second transplants.

On average, the male patients (40.0 $\pm$ 12.5) and female patients (41.9 $\pm$ 11.7) were of similar ages when undergoing transplant. Although data could be missing in our early cases, more male recipients received renal graft from

female donors (50.2%, 114/227) than the female patients (40.5%, 122/301; $p < 0.05$, Chi-square test). The female patients had a lower body weight (50.6 ± 9.1 kg) than the males (61.7 ± 13.3 kg; $p = 0.003$), but received grafts from those with higher body weights (65.2 ± 13.7 vs. 61.9 ± 13.9, $p < 0.001$). The donor/recipient weight ratio between female and male patients was significantly different. There were no significant differences between male and female recipients in average donor age, the number of HLA mismatches, and numbers with positive hepatitis B or hepatitis C. The males had a higher incidence of delayed function (24.9%, 89/358) than females (16.8%, 66/392; $p < 0.05$), but the frequency of acute rejection was not significantly different between male (33.9%, 123/363) and female recipients (29.9%, 119/398). The average follow-up duration was 79.8 ± 58.3 months for male and 78.2 ± 49.7 months for female patients. Baseline characteristics for the male and female groups are summarized in Table 1.

Prognostic factors for graft survival

Univariate analysis of the prognostic factors (Table 2) revealed that female recipients had a significantly longer 5-year graft survival than male recipients (87.9% vs. 81.3%; $p < 0.05$). In addition, we also identified several significant predictive factors for graft failure, including acute rejection ($p < 0.05$), delayed function ($p < 0.05$), and the number of HLA mismatches (risk ratio: 1.1374 per mismatch; $p < 0.05$). The difference in the 5-year graft survival rate in patients who received transplants from deceased donors (84.5%) and living donors (85.8%) did not reach statistical significance. The 5-year graft survival of renal transplants from male donors (85.3%) was similar to those from female donors (84.5%). Besides, grafts of higher body weight did not ensure a better graft survival; donor weight, recipient weight, and donor-to-recipient weight ratio were not significant factors for graft survival. Recipients with positive hepatitis B surface antigen (HBsAg) had a comparable 5-year graft survival (83.9%) to those with negative HBsAg (84.7%); in addition, antihepatitis C antibody positivity did not appear to influence survival (positive 85.2% vs. negative 84.4%). As for immunosuppressive therapy, 44.4% (276/622) of the patients were confirmed to have received *de novo* tacrolimus-based therapy, and 55.6% (346/622) received cyclosporine-based therapy. However, tacrolimus was not a significant factor associated with graft survival in this study.

Results of the multivariate analysis were shown in Table 3, which identified three prognostic factors for graft failure—male patients (risk ratio: 1.3732, $p < 0.05$), delayed function (risk ratio: 1.5422, $p < 0.05$), and acute rejection (risk ratio: 1.8330, $p < 0.05$).

Gender difference in donor—recipient combinations and the risk of graft loss

Kaplan—Meier estimates of graft survival, as illustrated in Fig. 1, showed that female patients had a significantly better 5-year graft survival than male patients. To evaluate whether there was an increased risk of graft loss due to an interaction between donor gender and recipient gender, a survival analysis was performed to evaluate the effect of donor gender on male and female patients.

There were 179 male donor-to-female-recipient transplants, and 113, 114, 122 male-to-male, female-to-male, and female-to-female combinations, respectively. The 5-year survival rate was relatively higher in the male-to-female group (87.9%), followed by the female-to-female group (85.5%), male-to-male group (83.9%), and female-to-male group (83.2%), which are shown in Fig. 2. The transplants from male donors tended to have better graft survival. However, the small numbers in each subgroup might compromise the statistical significance. In female recipients, transplants from male and female donors

Table 1 Demographic profiles of the male and female groups having kidney transplants between 1988 and 2009.

Characteristics[a]	Male group $N = 364$	Female group $N = 402$	p*
Age at transplantation (years)	40.0 ± 12.5	41.9 ± 11.7	NS
Donor age (years)	41.7 ± 12.7	41.6 ± 12.7	NS
Donor type (deceased)	67.6% (246/364)	70.1% (282/402)	NS
Donor gender (female)	50.2% (115/227)	40.5% (122/301)	0.027
HLA mismatch	2.93 ± 1.41	2.79 ± 1.44	NS
HBsAg (+)	16.2% (54/333)	11.8% (42/355)	NS
Anti-HCV (+)	16.5% (55/333)	16.3% (58/355)	NS
De novo tacrolimus	42.5% (128/301)	46.1% (148/321)	NS
Acute rejection	33.9% (123/363)	29.9% (119/398)	NS
Delayed function	24.9% (89/358)	16.8% (66/392)	0.008
Recipient weight (kg)	61.7 ± 13.3	50.6 ± 9.1	0.003
Donor weight (kg)	61.9 ± 13.9	65.2 ± 13.7	<0.001
Donor-to-recipient weight ratio	1.11 ± 0.66	1.32 ± 0.37	0.002
Follow-up period (mo) (range)	79.8 ± 58.3 (1—284)	78.2 ± 49.7 (1—251)	NS

Anti-HCV = antihepatitis C antibody; HbsAg = hepatitis B surface antigen; HLA = human leukocyte antigen; NS = not significant.
*The two-tailed Fisher exact test was used for categorical variables; two-tailed unpaired *t* test was used for continuous variables.
[a] Donor data would be missing in early cases.

Table 2 Univariate analysis of prognostic factors for kidney transplant survival.

Log-rank test	Category	Number of patients	5-year graft survival	*p*
Recipient gender	Male	364	81.3%	0.008
	Female	402	87.9%	
Donor gender	Male	292	85.3%	NS
	Female	236	84.5%	
Donor type	Deceased	528	84.5%	NS
	Living	238	85.8%	
HbsAg	Positive	96	83.9%	NS
	Negative	592	84.7%	
Anti-HCV (+)	Positive	113	85.2%	NS
	Negative	575	84.4%	
De novo tacrolimus	Yes	276	85.4%	NS
	No	346	82.9%	
Acute rejection	Yes	242	76.1%	<0.001
	No	519	88.9%	
Delayed function	Yes	155	79.2%	<0.001
	No	595	86.4%	

Cox's regression	Regression coefficient	Standard error	Risk ratio	*p*
Age at transplantation	−0.0039	0.0058	0.9961	NS
Recipient weight	0.0077	0.0077	1.0078	NS
Donor weight	0.0008	0.0128	1.0008	NS
Donor-to-recipient weight ratio	−0.4653	0.5207	0.6279	NS
Donor age	0.0147	0.0084	1.0148	NS
HLA mismatch	0.1287	−0.0521	1.1374	0.0150

Anti-HCV = antihepatitis C antibody; HbsAg = hepatitis B surface antigen; HLA = human leukocyte antigen; NS = not significant.

showed no significant difference with regard to graft survival. The log-rank test showed that transplants from male and female donors had similar survival rates in male patients. The influence of the donor gender on graft survival might be diminished by the strong effect of the recipient gender.

Discussion

The role of gender in solid organ transplantations such as lung, heart, and liver has been extensively studied, and the data from some investigations suggested that female donors to male recipients could be a risk factor for graft loss.[5–7] As for renal transplantation, limited reports also implied inferior long-term graft survival when female kidneys are transplanted into male patients,[4,8] yet the independent effect of recipient gender on renal transplant survival needs to be documented.

Previous studies examining donor–recipient size mismatch debated a graft survival advantage for kidney recipients who receive larger organs in relation to their own body size.[9,10] In this study, the body weights of donors for female patients were heavier than recipients, yet a higher body weight ratio between the donor and the recipient did not reflect a better graft survival. In addition, the donor gender did not have a significant influence on the graft survival in our data, although a higher rate of kidney graft loss from female donor had been documented with possible lower donor body weight and fewer nephrons from female kidneys.[11]

Table 3 Multivariate Cox regression analysis of the factors with statistical significance in the univariate analysis.

Cox's regression	Regression coefficient	Standard error	Risk ratio	*p*
Male gender	0.3171	0.1427	1.3732	0.026
Acute rejection	0.6059	0.1406	1.8330	<0.001
Delayed function	0.4332	0.1503	1.5422	0.004

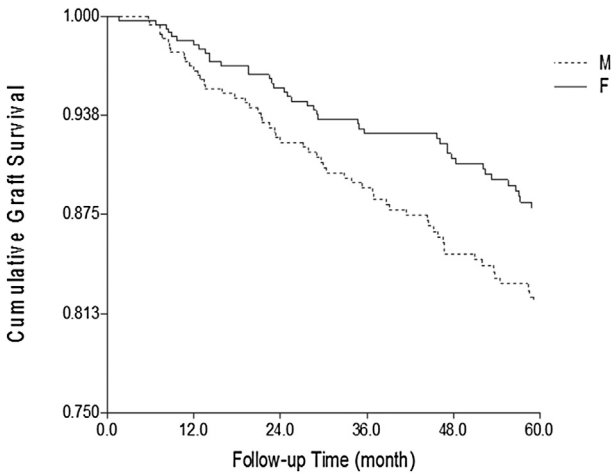

Figure 1 Kaplan–Meier survival curves showing the difference between male and female recipients ($p < 0.05$).

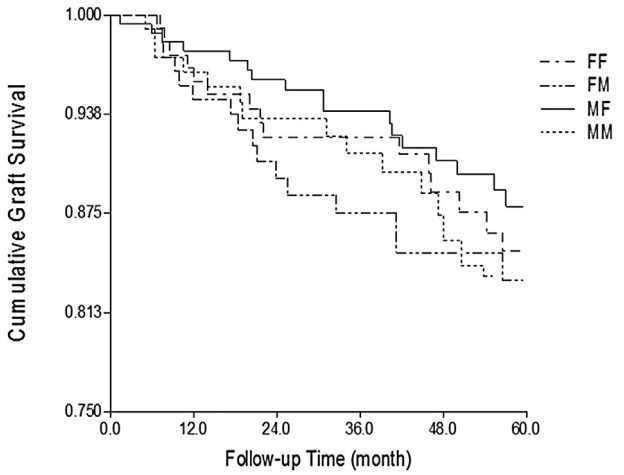

Figure 2 Kaplan—Meier plots detailing the relative difference in graft survival among four donor—recipient gender combinations. The graft survival curves for female recipients receiving transplants from either male or female donors showed no significant difference ($p > 0.05$), and so did those for male recipients ($p > 0.05$).

By contrast, male recipient gender was revealed as a prognostic factor for poor renal transplant survival in this long-term retrospective study. By analyzing data on 73,477 primary renal transplants collected in the US Renal Data System database, Meier-Kriesche et al[12] reported that females had a 10% increased odds of acute rejection, but conversely a 10% lower risk of graft loss secondary to chronic allograft failure. Protection afforded by hormones and complex immunological processes in women might explain their better long-term prognosis.[12,13] Reviews also suggested that female kidney, perhaps related to sensitization after pregnancy, is less likely to develop chronic graft rejection.[14] Our study supported the hypothesis that the grafts from female donors to male patients have a worst prognosis, although the difference between the gender combinations did not reach statistical significance with limited number in each combination.

As expected, regardless of gender, our data reported acute rejection as a negative independent risk factor for renal graft loss, and the risk of poor graft outcome with the incidence of delayed graft function and the increase in the number of HLA mismatches, which were compatible with previous studies.[15—17] Our data revealed that female patients tend to have less number of HLA mismatches and less acute rejection, but the difference was not significant. In addition, the female patients tend to encounter less delayed graft function after renal transplantation. The correlation may have partial roles, but the difference in gender continued to be an independent factor determining in graft survival. However, we had reported that changes in creatinine level after transplantation could be one of the most important prognostic factors for graft survival.[18]

The increase in the number of kidneys transplanted has led to concern about whether the organ pool expansion has affected patient and graft survival.[19,20] However, renal transplants from deceased donors, in this study, did not have a significantly worse outcome than those from living donors, and no significant difference was noted in donors of advanced age. There could be other factors, in addition to the biological effects, associated with the worse prognosis of male patients. Noncompliance is one of the most important problems in modern medicine, and it could be encountered in nearly half of the patients with acute rejection after transplantation, which may lead to late rejection, organ loss, and recipient death in kidney transplant recipients.[21,22] Using biographical questionnaires, it was documented that women had better immunosuppressant compliance than men.[23,24] In addition, women complied with more regular follow-up visits, less alcohol use (habit change), and more frequent antineoplastic prophylactic examinations.[25] In general, women appear to have better compliance than men after transplantation, and show more concern with regard to protecting graft function.

This study was limited by its retrospective nature; however, the single-center design minimized center-specific effects such as differences in immunosuppression protocols and perioperative and postoperative care. In conclusion, the results of this study showed that recipient gender, in addition to acute rejection and delayed graft function, was an independent risk factor associated with renal graft survival. Further studies on gender differences in *de novo* antibody, recurrent diseases, and compliance might help to figure out why gender played an important role in renal transplant graft survival in Taiwan.

Acknowledgments

The authors declare no potential conflicts of interest, including financial interests and relationships and affiliations relevant to the subject of this manuscript.

References

1. Pirsch JD, Ploeg RJ, Gange S, D'Alessandro AM, Knechtle SJ, Sollinger HW, et al. Determinants of graft survival after renal transplantation. *Transplantation* 1996;**61**:1581—6.
2. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. *Lancet* 2004;**364**:1814—27.
3. Lai HW, Chang CC, Chen TH, Tsai MC, Chen TY, Lin CC. Safety and efficacy of adefovir therapy for lamivudine-resistant hepatitis B virus infection in renal transplant recipients. *J Formos Med Assoc* 2012;**111**:439—44.
4. Zeier M, Döhler B, Opelz G, Ritz E. The effect of donor gender on graft survival. *J Am Soc Nephrol* 2002;**13**:2570—6.
5. Weiss ES, Allen JG, Patel ND, Russell SD, Baumgartner WA, Shah AS, et al. The impact of donor-recipient sex matching on survival after orthotopic heart transplantation: analysis of 18 000 transplants in the modern era. *Circ Heart Fail* 2009;**2**:401—8.
6. Yoshizumi T, Shirabe K, Taketomi A, Uchiyama H, Harada N, Ijichi H, et al. Risk factors that increase mortality after living donor liver transplantation. *Transplantation* 2012;**93**:93—8.
7. Miñambres E, Llorca J, Subrviola B, Ballesteros MA, Ortiz-Melón F, González-Castro A. Influence of donor-recipient gender mismatch in early outcome after lung transplantation. *Transplant Proc* 2008;**40**:3076—8.
8. Øien CM, Reisaeter AV, Leivestad T, Dekker FW, Line PD, Os I. Living donor kidney transplantation: the effects of donor age and gender on short- and long-term outcomes. *Transplantation* 2007;**83**:600—6.

9. Goldberg RJ, Smits G, Wiseman AC. Long-term impact of donor-recipient size mismatching in deceased donor kidney transplantation and in expanded criteria donor recipients. *Transplantation* 2010;**90**:867—74.
10. McGee J, Magnus JH, Islam TM, Jaffe BM, Zhang R, Florman SS, et al. Donor-recipient gender and size mismatch affects graft success after kidney transplantation. *J Am Coll Surg* 2010;**210**. 718—725.e1, 725—6.
11. Kasiske BL, Umen AJ. The influence of age, sex, race, and body habitus on kidney weight in humans. *Arch Pathol Lab Med* 1986;**110**:55—60.
12. Meier-Kriesche HU, Ojo AO, Leavey SF, Hanson JA, Leichtman AB, Magee JC, et al. Gender differences in the risk for chronic renal allograft failure. *Transplantation* 2001;**71**: 429—32.
13. Silbiger SR, Neugarten J. The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 1995;**25**: 515—33.
14. Sanfey H. Gender-specific issues in liver and kidney failure and transplantation: a review. *J Womens Health (Larchmt)* 2005; **14**:617—26.
15. Lefaucheur C, Loupy A, Hill GS, Andrade J, Nochy D, Antoine C, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *J Am Soc Nephrol* 2010;**21**: 1398—406.
16. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant* 2011;**11**:2279—96.
17. Suthanthiran M, Strom TB. Renal transplantation. *N Engl J Med* 1994;**331**:365—76.
18. Tsai MK, Hu RH, Lee CJ, Lee PH. Prognostic significance of six-month estimated glomerular filtration rate in cadaveric renal transplantation. *J Formos Med Assoc* 2005;**104**:180—4.
19. Knoll G. Trends in kidney transplantation over the past decade. *Drugs* 2008;**68**:3—10.
20. Rizzari MD, Suszynski TM, Gillingham KJ, Matas AJ. Consideration of donor age and human leukocyte antigen matching in the setting of multiple potential living kidney donors. *Transplantation* 2011;**92**:70—5.
21. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. *Drugs* 2007;**67**: 1463—81.
22. Nankivell BJ, Kuypers DR. Diagnosis and prevention of chronic kidney allograft loss. *Lancet* 2011;**378**:1428—37.
23. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. *Transplantation* 1993;**55**: 51—6.
24. Rosenberger J, Geckova AM, van Dijk JP, Nagyova I, Roland R, van den Heuvel WJ, et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. *Transpl Int* 2005;**18**:1072—8.
25. Kobus G, Małyszko J, Małyszko JS, Puza E, Bachórzewska-Gajewska H, Myśliwiec M. Compliance with lifestyle recommendations in kidney allograft recipients. *Transplant Proc* 2011;**43**:2930—4.