Received: 2009.09.20 **Accepted:** 2009.10.08 **Published:** 2009.12.10

Improvement of renal transplantation outcome through matching donors and recipients

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Summary

Background:

To investigate the effects of age and gender matching on patient and graft survival in living unrelated kidney transplantation.

Material/Methods:

All 2649 first-time kidney transplanted cases who had received their graft from a living unrelated donor in Baqiyatallah Hospital (Tehran, Iran) were enrolled (1992–2005). Based on the age and gender matching state of the donors (D) and recipients (R), the recipients were divided into four age-match (A) and four gender-match (G) groups. Age-match groups included A_1 (R<40, D<40, n=1483), A_2 (R>40, D<40, n=1044), A_3 (R<40, D>40, n=82) and A_4 (R>40, D>40, n=40). Gender-match groups comprised G_1 (R: female, D: female, n=209), G_2 (R: male, D: male, n=1428), G_3 (R: female, D: male, n=768) and G_4 (R: male, D: female, n=244). Using Kaplan-Meier method, 6-month, to 5-year graft/patient survival rates were determined for different patient groups. Survival curves were compared using log rank test after stratification.

Results:

Male recipients living with a female donor's kidney had a shorter survival compared to both the males having received a male kidney and the females having received a female kidney. Graft survival also showed a marginally significant difference and was shorter among the males with a female kidney graft compared to the males living with a male kidney graft. In contrast, donor's sex caused no difference in patient or graft survival among female recipients. When survival curves of age-match groups were compared, both graft and patient survival times were significantly shorter among the younger patients having a kidney graft received from an older donor. Patient survival was also shorter among old recipients having received an old kidney compared with old patients having a kidney graft from a young donor. Though graft survival among the old patients with old grafts was also shorter than in those with young grafts, the difference was not significant. When the subjects were stratified by donors' age, the results showed that old patients with young kidneys survived shorter than young patients with young kidneys.

Conclusions:

Better living unrelated renal transplantation outcome is expected with younger kidney grafts (i.e. donor <40 yr) and avoiding grafting female kidneys into male recipients.

Key words:

renal transplantation • living unrelated donor • age • gender • survival

Full-text PDF:

http://www.annalsoftransplantation.com/fulltxt.php?ICID=900239

Word count:

1478 1 1

Tables: Figures:

References:

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BACKGROUND

Current evidence shows that donor's and recipient's age [1-9] and gender [10-12] influence many aspects of kidney transplantation including graft outcome. There are theories suggesting that the outcome of the graft or patient survival among the recipients for whom the kidney donor was age and gender matched may differ from those for whom such matching was not considered [13,14]. Nevertheless, this issue is still a matter of debate in practice [15]. In addition, few studies have been performed to assess the impact of donor-recipient age and gender matching on the graft outcome in living unrelated kidney transplantation. This study aimed to investigate the effects of age and gender matching on patient and graft survival among living unrelated kidney transplant recipients.

MATERIAL AND METHODS

This was a retrospective study conducted in Baqiyatallah Hospital, a six-hundred bed teaching general hospital located in north of Tehran, Iranian capital. All 2649 first-time kidney transplanted cases between the years 1992 and 2005 who had received their graft from a living unrelated donor were enrolled. Based on the age and gender matching state of the donors (D) and recipients (R), the recipients were divided into four age-match (A) and four gender-match (G) groups. Based on the recipient's and donor's age being above or below 40 years of age, the four agematch groups were defined as A, (R\le 40, D\le 40, n=1483), A_{s} (R>40, D<40, n=1044), A_{s} (R<40, D>40, n=82) and A_4 (R>40, D>40, n=40). Similarly, based on the recipient's and donor's gender, the four gender-match groups comprised G₁ (R: female, D: female, n=209), G₉ (R: male, D: male, n=1428), G_3 (R: female, D: male, n=768) and G_4 (R: male, D: female, n=244). Kaplan and Meier method was used to calculate graft and patient survival. The 5-year patient and graft survival curves in age- and gender-match groups were separately compared using log rank test after stratification. Data analysis was conducted using SPSS for windows v.13. P-values less than 0.05 were considered as statistically significant.

Table 1. Patient and graft survival rates/times among the different age-match and gender-match groups. See text for definitions of patient groups G_1-G_4 , and A_1-A_4 .

| Patient group | | Survival rates | | | | | Survival time mean±SD | 050/61 |
|------------------------------|----|----------------|------|------|------|------|-----------------------|---------------|
| | | 6-mo | 1-yr | 2-yr | 3-yr | 5-yr | (months) | 95% CI |
| Gender-match | | | | | | | | |
| | G1 | 90% | 88% | 84% | 77% | 73% | 84.27±4.23 | 75.98–92.56 |
| | G2 | 90% | 87% | 83% | 79% | 70% | 79.08±1.65 | 75.84-82.32 |
| | G3 | 88% | 86% | 83% | 80% | 73% | 81.55±2.15 | 77.34–85.76 |
| | G4 | 90% | 86% | 79% | 73% | 51% | 68.40±3.65 | 61.25-75.56 |
| - Patient Survival - - | G1 | 96% | 95% | 94% | 93% | 89% | 105.53±1.26 | 103.06-108.00 |
| | G2 | 94% | 93% | 92% | 90% | 84% | 98.46±2.13 | 94.28-102.64 |
| | G3 | 94% | 93% | 92% | 90% | 55% | 73.98±6.29 | 61.65-86.31 |
| | G4 | 95% | 94% | 89% | 85% | 55% | 52.74±7.38 | 38.28±67.20 |
| Age-match | | | | | | | | |
| - Graft survival - - | A1 | 90% | 88% | 83% | 79% | 70% | 80.24±1.50 | 77.29-83.19 |
| | A2 | 89% | 87% | 83% | 81% | 73% | 82.37±2.26 | 77.95-86.80 |
| | A3 | 83% | 77% | 72% | 61% | 37% | 52.59±5.19 | 42.42-62.77 |
| | A4 | 70% | 70% | 66% | 66% | 43% | 45.19±6.85 | 31.77-58.61 |
| - Patient Survival - - | A1 | 96% | 95% | 94% | 93% | 90% | 107.66±3.14 | 101.50-113.81 |
| | A2 | 94% | 93% | 90% | 90% | 87% | 102.37±1.47 | 99.50-105.24 |
| | А3 | 94% | 93% | 85% | 90% | 88% | 102.56±1.91 | 98.82-106.30 |
| | A4 | 95% | 94% | 71% | 85% | 68% | 87.74±3.90 | 80.09-95.38 |

CI – confidence interval.

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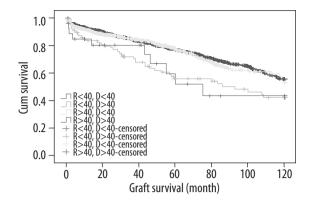


Figure 1A. Graft survival in age-match groups.

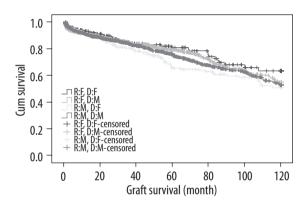


Figure 1B. patient survival in age-match groups.

RESULTS

The donors comprised 2196 (82.9%) males, and 453 (17.1%) females with 2530 (95.5%) being 40 years old or younger, and 119 (4.5%), older than 40. The recipients consisted of 1682 (63.4%) males and 967 (36.6%) females, of whom 1566 (59.2%) were 40 years old or younger and 1083 (40.8%), older.

Table 1 shows 6-month to 5-year survival rates for both age- and sex-match groups of the recipients. Figure 1 shows the graft and patient survival curves among different recipient groups. According to survival rates in Table 1 and the survival curves in Figure 1, it seems that the survival of the grafts and patients were lower among the recipients who had received their kidney from an over-40 year-old living unrelated donor regardless of recipients' age (i.e. groups A_3 and A_4). A similar result was observed among the male recipients who had received a graft from a female donor (i.e. group G_4). However, statistically comparing all of the four survival curves in age and gender groups was not possible without stratification

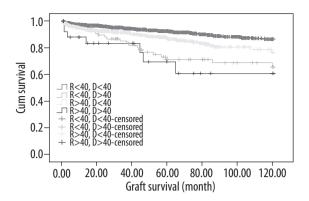


Figure 1C. graft survival in gender-match groups.

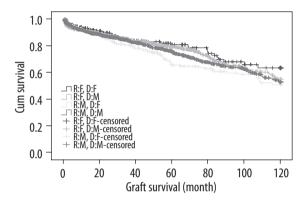


Figure 1D. patient survival in gender-match groups.

since the Kaplan-Meier survival curves crossed in Figure 1 (i.e. the proportional hazard assumption did not hold true). In order to use a log rank test to compare survival curves, we used stratification method to divide the subjects into gender and age subgroups, and then compared the survival curves in these subgroups. Separate stratifications were performed by donors' and recipients' gender to assess the statistical difference between gender-match groups. A similar strategy was used for age-match groups after stratifying the subjects by donors' and recipients' age (i.e. ≤40 and >40 years).

The results of the analyses after stratification confirmed that male recipients living with a female donor's kidney had a shorter survival compared to both the males having received a male kidney (p=0.022, recipients' gender stratification) and the females having received a female kidney (p=0.018, donors' gender stratification). Graft survival also showed a marginally significant difference (p=0.051, donors' gender stratification) and was shorter among the males with a female kidney graft compared to the males living

with a male kidney graft. In contrast, donor's sex caused no difference in patient (p=0.342) or graft (p=0.323) survival among female recipients.

When survival curves of age-match groups were compared (after stratification for recipients' age), both graft (p=0.001) and patient (p<0.001) survival times were significantly shorter among the younger patients (≤40 years) having a kidney graft received from an older (>40 years) donor. Patient survival was also shorter among old recipients having received an old kidney compared with old patients having a kidney graft from a young donor (p=0.021, stratified by recipients' age). Though graft survival among the old patients with old grafts was also shorter than in those with young grafts, the difference was not significant (p=0.081). However, this seemed to be due to the low sample size of old patients living with an old graft. When the subjects were stratified by donors' age, the results showed that old patients with young kidneys survived shorter than young patients with young kidneys (p<0.001).

DISCUSSION

Having compared the effect of age- and gendermatching on the outcome of renal transplants from living unrelated donors, this study showed that regardless of the recipients' age, the outcome of a kidney graft from a living unrelated donor older than 40 years of age is worse than that received from a younger donor. A worse graft outcome was also observed in the male recipients who received a graft from a female donor. These results show that the donor's (but not recipient's) age has a higher impact on the graft survival than an absolute age-match of donors and recipients. In contrast, gender-matching was important among male but not female recipients.

The results of this study are consistent with the many other previous reports in cadaveric renal transplantation (). What seems essential in terms of our results are the facts that HLA mismatches are not considered in patient selection. Some hypotheses have tried to explain why a female kidney graft functions poorly in a male recipient. One is the possible effect of hyperfiltration because women tend to have smaller kidneys with namely 17% fewer nephrons than men [13,14]. This phenomenon, known as nephron underdosing, increases the workload of the individual nephrons [16,17]. Experimental [18,17] and clinical studies [19–21] have underlined the adverse effect of nephron underdosing. Evidence

shows that long-term graft function is better when two kidney grafts are transplanted in one recipient compared to the conventional single kidney graft [20-22]. Furthermore, in allogeneic or syngeneic transplantation, a reduction of nephron mass had an adverse effect on graft function and morphology [23]. Nevertheless, there has been a contradicting report by Vianello indicating that an imbalance of kidney/body-weight ratio between the donor and recipient had no major effect on kidney graft function and survival after 4 years [24]. A second hypothesis relates the difference in transplantation outcomes not to the different number of nephrons, but to the glomerular volume [25,26]. A third hypothesis indicates that the female kidney expresses higher levels of HLA antigens and is therefore more antigenic [27,28]. This hypothesis is supported by the finding that the survival of the kidney grafts from female compared with male donors is particularly poorer in highly sensitized recipients [29]. However, it has been reported that HLA matching does not completely abrogate the donor gender effect in the first cadaver or living related donor renal transplants [30,31]. A fourth hypothesis has described this shorter survival of female kidneys in male recipients by an influence of chromosomal sex or sex hormones on vascular endothelial cells, a potential interface relevant for allograft recognition [32]. Indeed, according to this hypothesis, sex hormones may influence some endothelial cell features. For instance, androgen exposure increases mononuclear cell adhesion to vascular endothelial cells [33], and both androgens and estrogens influence endothelial cell proliferation [34].

Regarding the poorer outcome of the kidney grafts from an older donors regardless of recipient's age, there have been reports indicating that sclerotic changes occur in the kidney by aging [13,14,26].

In our results, we also found a poorer 5-year patient survival, but we did not have the causes for graft loss or causes of death. This needs further investigations.

Finally, a retrospective overview of the transplantation records in our center gave interesting results. In our transplantation center, more than 95% of the donors were under 40 years of age, and transplantation from female donors to male recipients happened in only 9% of all transplantations. These figures, based on our findings should be considered as a positive point, and

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might partially explain the decent survival rates of renal allografts in our transplantation center [34,35].

Unfortunately, we did not register the causes for graft loss, which could provide a comparison between age and gender study groups.

CONCLUSIONS

We conclude that better graft outcome may be expected by encouraging kidney transplantation from younger living unrelated donors (<40 years), and avoiding grafting female kidneys into male recipients.

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