Impact of Age Difference, Sex Matching, and Body Mass Index Matching Between Donor and Recipient in Renal Transplant

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ABSTRACT

Background. Various factors influence kidney transplant (KT) outcome. The impact of age difference between donor and recipient on long- and short-term graft and patient survival in living donor KT remains unclear.

Objective. We aim to determine whether age difference, sex matching, and body mass index (BMI) matching between donor and recipient affect the 12-month patient and graft survival in KT.

Method. We studied a retrospective cohort of 804 patients 18 years or older with primary KT from January 2010 to December 2014. Patient renal function and patient survival were followed up for 12 months post KT. Repeated analysis of variance measurement determined if there was a significant difference in the mean creatinine levels when the sample was grouped according to the matching groups for sex, age difference, and BMI classification. Odds ratios were computed to ascertain graft loss and graft rejection. Results were considered statistically significant if $P < .05$.

Results. Male donor–female recipient had the lowest creatinine levels over time compared with male donor–male recipient ($P < .001$) and female donor–male recipient ($P < .001$). Older donor–younger recipient with age difference of ≥ 15 years had the highest overall creatinine ($P < .001$). For BMI matching, a normal donor and an underweight recipient combination resulted in the lowest mean creatinine levels over the course of 12 months ($P < .001$). In terms of graft rejection, odds ratio was highest for a female donor and a male recipient ($P < .00a$) compared with a male donor and a female recipient. For graft loss, older donors (≥ 15 years) had the highest risk ($P < .001$) vs those older by 11 to 15 years.

Conclusion. There was significant difference in the 12-month graft function of patients when grouped according to their matching for age difference, sex, and BMI. The risk for graft rejection increases when the combination for donor-recipient is female donor–male recipient. For graft loss, this is most significant for donors who are older by ≥ 15 years than their recipients.

THE BENEFITS of kidney transplant (KT) are undeniable as this provides high-quality life years to patients with end-stage renal disease [1]. Various factors influence the outcome of KT, which can be related to factors concerning recipients, donors, and preoperative, perioperative, and postoperative matters. Some of these might be interdependent, such as the effect of pretransplant transfusion and ethnicity, sex and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) mismatches, or donor age and ischemia.

The impact of age difference between donor and recipient on long- and short-term graft and patient survival in living donor KT remains unclear [2]. Some studies show that age difference between recipient and donor may lower graft

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and patient survival rate [3–6]. Older kidney donor age and recipients with extremes of age such as younger than 18 years or older than 65 years were associated with reduced KT survival [7]. The effect of donor age was evident in both deceased and living donor KT [7]. Hence, age matching of donors and recipients can help improve total graft years [8]. Furthermore, another study showed that graft survival among elderly donors was 92.8% and 85.6% at 1 and 3 years, respectively, compared with 93.4% and 90.2% among younger donors, respectively ($P = .02$); thus, these may help in designing transplantation strategies for kidney procurement from elderly donors and for allocation to elderly recipients [9].

In contrast, several studies showed that age difference has no effect on the graft and patient survival [2,10–12]. Donor–young recipient age difference of $\geq$ 20 years had a greater risk of acute rejection early post KT but no effect on graft or patient survival [8]. Likewise, donors 60 years and older were not associated with worse outcome, and age of a donor had little impact on the graft survival [2].

Moreover, various studies showed that sex mismatching between recipient and donor has a negative impact on KT [13–16]. Female recipients had lower serum creatinine, while male recipients had higher creatinine if they received from female kidney donors [14]. Male recipients with male kidney donors had a higher estimated glomerular filtration rate than all other groups for 3 years [14]. Likewise, female recipients with male kidney donors may have greater risk for early graft loss [16]. Inversely, one study showed that sex mismatching has no effect on graft and patient survival [17]. Kidney allografts adapt to the recipient's body size and demands, independent of sex, without detrimental effects on the renal function and outcome up to mid- to long-term.

Lastly, donor-recipient BMI disparity is another factor that may have impact on KT survival. Lower graft function was observed among low donor/recipient body weight ratio group ($\leq$ 0.9) compared with medium (0.91–1.2) and high ($\geq$ 1.2) [18]. Another study concluded that low donor/recipient body surface area ratio ($\leq$ 0.9) may have increased risk for graft loss [19]. However, graft survival was similar among the groups ($<$ 1; 1–1.2; $>$ 1.2) [20,21].

With limited data in the Philippines, this study aims to elucidate the impact of donor-recipient age difference, sex matching, and BMI matching in KT.

OBJECTIVE

General Objective

We aim to determine if age difference, sex matching, and BMI matching between donor and recipient affect the 12-month patient and graft survival in KT.

Specific Objectives

1. To describe the demographic and clinical profile of donors and recipients
2. To determine if the following recipient-donor factors affect the 6- and 12-month patient and graft survival:
   a. Age difference
   b. Sex matching
   c. BMI

METHODOLOGY

We studied a retrospective cohort of all Filipino standard immunologic risk KT candidates aged 18 years or older who underwent primary KT in the National Kidney and Transplant Institute from January 1, 2010, to December 31, 2014. The following were excluded: high immunologic risk, deceased donor KT, second KT, multiple organ transplant, and incomplete data up to 12-months post KT.

Data were collected from Medical Records Section, Philippine Renal Disease Registry and Collaborative Transplant Study. The following data were collected: recipients' variables (demographic characteristics, primary renal disease, comorbidities, type and duration of dialysis); donor variables (donor type, age, sex, BMI, cold ischemia time); transplant-related variables (number of HLA matches, % panel-reactive antibody [PRA]); and the post-transplant variables (immunosuppression, renal function). The estimated glomerular filtration rate was computed using the Chronic Kidney Disease Epidemiology Collaboration equation.

Patient renal function (serum creatinine, acute rejection episodes) and patient survival were followed up for 12 months post KT ($\pm$ 4 weeks, 6 months, and 12 months after KT follow-up).

Definition of Terms

Immunologic risk classification-

1. *Standard immunologic* risks are those for first KT, PRA $<$ 20% without donor-specific antibodies (DSA), with 0 to 1 DR mismatch.
2. High *immunologic risks* are those with (+) DSA and/or PRA $>$ 20% (even without DSA).
   - *Living nonrelated donors* are donors beyond fourth degree of consanguinity.
   - *Acute rejection (biopsy-proven or clinical)* is acute deterioration in renal function associated with the specific pathologic changes in the graft and/or a rapid increase of serum creatinine of $>$ 25% from baseline.
   - *Primary nonfunction* is a condition where the graft never functioned.

Renal function classification:

1. *Excellent graft function:* serum creatinine of $<$ 130 μmol/L ($<$ 1.46 mg/dL).
2. *Good graft function:* serum creatinine of 130 to 259 μmol/L (1.47–2.92 mg/dL).
3. *Mediocre graft function:* serum creatinine of 260 to 400 μmol/L (2.93–4.5 mg/dL).
4. *Poor graft function:* serum creatinine of $>$ 400 μmol/L ($>$ 4.5 mg/dL) but without the need for dialysis.
   - *Graft loss* is the need for permanent dialysis, another KT, or death.
   - *Graft survival* is the state where the graft is functioning well and the patient does not need permanent dialysis.
   - *Patient survival* is determined as a patient being alive from the date of transplant until the date of death.

Table 1. Recipients' Demographic Profile

Variables	n = 804	%
Age, y		
Mean (SD)	41.7 (13.1)	-
Range	18–76	
Sex, No.		
Male	524	65.2
Female	280	34.8
BMI		
Mean (SD)	22.8 (4.0)	-
Range	13.9–40.8	
BMI classification, No.		
Underweight	102	12.7
Normal	509	63.3
Overweight/obese	193	24.0
Primary renal disease, No.		
Chronic glomerulonephritis	439	54.6
Diabetic nephropathy	162	20.1
Hypertensive nephrosclerosis	144	17.9
Autosomal polycystic kidney disease	15	1.9
Chronic pyelonephritis	4	0.5
Others	40	5.0
Renal replacement therapy, No.		
None (pre-emptive)	87	10.8
Hemodialysis	669	83.2
Peritoneal dialysis	48	6.0
HLA mismatches, No.		
0	67	8.3
1	77	9.6
2	162	20.1
3	210	26.1
4	167	20.8
5	93	11.6
6	28	3.5
Induction Therapy, No.		
None	192	23.9
Basiliximab	380	47.3
Antithymocyte globulin (ATG)	205	25.5
Alemtuzumab	25	3.1
Daclizumab	2	0.2
Maintenance immunosuppression, No.		
Cyclosporine + azathioprine + prednisone	2	0.2
Cyclosporine + mTOR + prednisone	38	4.7
Cyclosporine + mycophenolate + prednisone	273	34.0
Cyclosporine + mycophenolate	8	1.0
Tacrolimus + mTOR + prednisone	1	0.1
Tacrolimus + mycophenolate + prednisone	477	59.3
Tacrolimus + mycophenolate	2	0.2
Tacrolimus + mTOR	1	0.1
Mycophenolate only	2	0.2

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); mTOR, mammalian target of rapamycin.

Statistical Analysis

All statistical tests were run using SPSS Statistics version 21 (IBM, Armonk, NY, United States). Frequency and percentage distributions were used for nominal data, while mean, standard deviation, and range values were used for ordinal to interval-level data. Repeated analysis of variance determined if there was a significant difference in the mean creatinine levels when the sample is grouped according to the matching

Table 2. Living Donors' Demographic Profile

Variable	n = 804	%
Donor source, No.		
Living related	526	64.4
Living nonrelated	278	35.6
Sex, No.		
Male	483	60.1
Female	321	39.9
Age, y		
Mean (SD)	31.0 (8.8)	-
Range	18–57	
BMI		
Mean (SD)	23.7 (4.1)	-
Range	14.3–46.3	
BMI classification, No.		
Underweight	59	7.3
Normal	490	61.0
Overweight/Obese	255	31.7
Cold ischemia time, min		
Mean (SD)	21.8 (12.0)	-
Range	3–90	
Baseline serum creatinine, mg/dL		
Mean (SD)	0.9 (0.2)	-
Range	0.5–1.7	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 3. Donor-Recipient Relationship by Matching Group

Variables	Matching Group	n = 804	%
Sex, No.	Male-male	338	42.0
	Male-female	146	18.2
	Female-female	137	17.0
	Female-male	183	22.8
Age	≥ 15 years	275	34.2
Difference,	(recipient is older)		
No.	−15 to −11 years	95	11.8
	−10 to −6 years	148	18.4
	−5 to −1 years	95	11.8
	0 to 5 years	104	12.9
	6 to 10 years	41	5.1
	11 to 15 years	20	2.5
	< 15 years	26	3.2
	(recipient is younger)		
BMI	Underweight-underweight	12	1.5
classification,	Underweight-normal	37	4.6
No.	Underweight-overweight/obese	10	1.2
	Normal-underweight	67	8.3
	Normal-normal	316	39.3
	Normal-overweight/obese	107	13.3
	Overweight/obese-underweight	24	3.0
	Overweight/obese-normal	154	19.2
	Overweight/obese-overweight/obese	77	9.6

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

groups for sex, age difference, and BMI classification. Odds ratios (ORs) were computed to ascertain graft loss and graft rejection. Results were considered statistically significant if $P < .05$.

Ethical Consideration

The study was approved by the Institute's Research Ethics Committee. Confidentiality and anonymity were maintained by assigning a specific number to each of the subjects and allowing only investigators access to the data.

RESULTS

Of the 868 KT recipients during the study period, 804 were included in the study. The 64 recipients were excluded because of the following reasons: (1) 52 had high immunologic risk, (2) 6 had incomplete data, (3) 4 had a third KT, and (4) 2 had baseline creatinine done outside NKTI.

The recipients' mean age was 41.7 years with a 2:1 male to female ratio. The mean BMI was 22.8 with 63% having normal BMI. Around 55% had chronic glomerulonephritis as the primary renal disease, and 88% were on hemodialysis (Table 1).

Most of the transplanted kidneys were from living related donors (64%) with a 3:2 male to female ratio. The mean age was 31 years, and mean BMI was 23.7 with 61% within normal range (Table 2).

In terms of donor-recipient matching, 42% were male-male sex-matched, 34% were younger donor–older recipient with age difference of ≥ 15 years and 39% had normal-normal BMI matching as shown in Table 3.

Table 4 sums up the differences in the mean creatinine levels at 1 and 12 months post KT by matching group. All groups showed increasing mean creatinine levels as the observation period progressed. When donor-recipient combinations were grouped according to sex ($F = 10.7$, $P < .001$), age difference ($F = 1.3$, $P < .03$), and BMI classification ($F = 1.4$, $P < .02$), the differences were statistically significant.

When comparing the donor-recipient sex matching, male donor–female recipient had the lowest creatinine levels over time (except for the 12th month wherein female donor–female recipient matching has the lowest creatinine at 1.08 mg/dL), while the female donor–male recipient matching had the highest. This difference was statistically significant when comparing the male donor–female recipient groups with male donor–male recipient ($F = -0.23$, $P < .001$) and female donor–male recipient ($F = -0.41$, $P < .001$).

Regarding age difference, younger recipients with older donors had higher creatinine levels. In particular, older recipient–younger donor with age difference of ≥ 15 years had the highest overall creatinine levels ($F = -0.33$, $P < .001$).

Table 4. Differences in Mean Creatinine Levels by Donor-Recipient Matching Groups

Matching Group	Creatinine Level Post KT, mg/dL			F	*P* Value
	1st Month	6th Month	12th Month		
Sex					
Male-female	0.89	1.01	1.11	10.7	< .001
Male-male	1.22	1.22	1.26		
Female-male	1.35	1.46	1.56		
Female-female	0.92	1.01	1.08		
Age, y					
≥15 (older recipient)	1.06	1.11	1.14	1.3	.03
−11 to −15	1.07	1.11	1.22		
−10 to −6	1.17	1.19	1.36		
−5 to −1	1.16	1.18	1.28		
0 to 5	1.15	1.18	1.31		
6 to 10	1.14	1.18	1.33		
11 to 15	1.18	1.29	1.41		
< 15 (younger recipient)	1.40	1.53	1.73		
BMI					
Underweight-underweight	0.94	1.03	1.07	1.4	.02
Underweight-normal	1.18	1.22	1.49		
Underweight-overweight/obese	1.11	2.66	1.14		
Normal-underweight	0.89	0.99	1.06		
Normal-normal	1.15	1.17	1.23		
Normal-overweight/obese	1.26	1.24	1.24		
Overweight/obese-underweight	1.13	1.24	1.43		
Overweight/obese-normal	0.95	1.21	1.42		
Overweight/obese-overweight/obese	1.28	1.26	1.29		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); KT, kidney transplant.

For BMI matching, the best combination seems to be a normal donor and an underweight recipient, resulting in the lowest mean creatinine levels over the course of 12 months. Conversely, the overweight/obese-overweight/obese combination had the highest mean creatinine levels. When normal-underweight matching was compared with the rest, the difference was statistically significant except for underweight donor–underweight recipient and underweight donor–overweight/obese recipient combinations. This may be because the underweight-underweight combination maintained a very low level close to the normal-underweight combination while the underweight-overweight/obese pairing had dropped creatinine level on the 12th month.

The variables were also analyzed separately and jointly to understand whether these determined creatinine levels in isolation and/or in combination. Table 5 shows that individually, recipient sex is a determinant of creatinine level ($F = 25.1$, $P < .001$). Data showed that women have lower creatinine levels (mg/dL) over time (1st month = 0.90; 6th month = 1.01; 12th month = 1.09) than men (1st month = 1.26; 6th month = 1.30; 12th month = 1.37).

Combining certain variables, sex and age matching affected creatinine levels ($F = 1.69$, $P < .03$). Female donors–younger male recipients were worse off than their counterparts. Furthermore, age with BMI matching affected creatinine levels ($F = 1.80$, $P < .003$). Younger recipients with overweight or obese donors had higher creatinine levels over time. The greater the age and BMI difference, the greater the level of creatinine over the course of the study.

Although there were relatively few cases of graft rejection (n = 43, 5%), ORs were still computed to determine the relative risks when comparing the different matching groups (Table 6). Nonetheless, the findings are merely indicative given the small sample size of graft rejection.

Table 5. Determinants of Creatinine Levels

Variable	F	*P* Value
Donor sex	1.35	.25
Donor age	0.87	.71
Donor BMI	1.66	.192
Donor sex * donor age	0.54	.985
Donor sex * donor BMI	0.12	.886
Donor age * donor BMI	0.41	> .99
Donor sex * donor age * donor BMI	0.64	.92
Recipient sex	25.10	< .001*
Recipient age	1.04	.40
Recipient BMI	0.98	.38
Recipient sex * recipient age	0.74	.89
Recipient sex * recipient BMI	1.92	.15
Recipient age * recipient BMI	1.15	.21
Recipient sex * recipient age * recipient BMI	0.64	.90
Sex match * age match * BMI match	0.61	.98
Sex match * age match	1.69	.03*
Sex match * BMI match	0.32	> .99
Age match * BMI match	1.80	.003*

Abbreviation: BMI, body mass index.
*Statistically significant.

Table 6. Odds Ratio of Graft Rejection per Matching Group

Matching Group*	OR	95% CI		*P* Value
		Lower	Upper	
Sex				
Female-male vs male-female	4.35	1.39	13.64	.006†
Female-male vs male-male	3.11	1.05	9.16	.03†
Male-female vs male-male	0.71	0.35	1.46	.36
Female-female vs male-female	3.25	1.03	10.22	.03†
Female-female vs male-male	2.32	0.79	6.87	.12
Female-female vs female-male	0.75	0.18	3.04	.68
BMI‡				
Normal-normal vs normal-underweight	3.13	1.24	7.88	.02†
Normal-normal vs normal-overweight	1.62	0.63	4.16	.22
Normal-overweight vs normal-underweight	1.94	0.67	5.61	.17
Overweight-normal vs overweight-underweight	2.88	0.83	10.06	.10

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; OR, odds ratio.
*All age-matching groups did not yield statistically significant results; hence, these are not reported because of the numerous combinations that make it unwieldy for the table.
†Statistically significant.
‡The following matching groups did not experience graft rejection: all underweight combinations and obese/overweight donor-obese/overweight recipient group.

In terms of sex groupings, there were 3 significant comparisons. Of these 3, the greatest risk was observed for female donor–male recipient vs male donor–female recipient matching group. Female donor–male recipient combination was 4.35 times more likely to experience graft rejection ($P < .006$) than the male donor–female recipient group. On the other hand, none of the age matching groups have statistically significant results. For BMI matching, the risk for graft rejection is 3.13 higher for normal donor–normal recipient compared with normal donor–underweight recipient.

Similarly, there were very few patients who experienced graft loss (n = 8, 1%), at an almost negligible proportion. As such, findings are indicative rather than generalizable given this very small sample size. Nevertheless, ORs were also ascertained across the different matching groups to identify the risks (Table 7).

Results show that risk for graft loss was statistically significant only for age matching groups. Specifically, combinations where the donors are considerably older than recipients had higher risks of graft loss than those with younger donors. The greatest OR was observed for the matching group with an age gap of $\geq$ 15 years compared with those with at least an 11-year age gap. In fact, matching groups where the donor is $\geq$ 15 years older than the recipient are 30.33 times more likely to experience graft loss than their younger counterparts ($P < .001$).

Table 7. Odds Ratio of Graft Loss per Matching Group

Matching Groups	OR	95% CI		*P* Value
		Lower	Upper	
Sex				
Female-male vs male-female	0.83	0.13	5.04	.60
Female-male vs male-male	0.36	0.06	2.17	.25
Male-female vs male-male	0.43	0.06	3.11	.39
Female-female vs male-female	1.88	0.17	20.93	.60
Female-female vs male-male	0.81	0.07	9.04	.87
Female-female vs female-male	2.26	0.23	21.95	.47
Age, y[†]				
≥ 15 vs 11 to 15	30.33	2.62	350.61	< .001[*]
≥ 15 vs < 15	10.92	0.66	179.92	.04[*]
0 to 5 vs 11 to 15	9.78	0.83	113.70	.03[*]
BMI[‡]				
Normal-normal vs normal-underweight	9.63	0.86	107.80	.08
Overweight-normal vs overweight-overweight	1.00	0.09	11.20	.74
Overweight-normal vs overweight-underweight	3.30	0.29	37.92	.35
Higher vs same BMI	3.30	0.20	54.93	.42

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; OR, odds ratio.

[*]Statistically significant.

[†]Donor and recipients who have the same age did not experience graft loss. As there are several combinations for this variable, only those with statistically significant results are shown.

[‡]The following matching groups did not experience graft loss: all underweight combinations; and normal donor-obese/overweight recipient group.

DISCUSSION

This study showed that donor-recipient disparity regarding sex, age, and BMI affects 12-month allograft renal function, such as creatinine levels, graft rejection, and graft loss.

Based on sex matching, the male donor–female recipient group had the lowest mean creatinine levels compared with all groups. It is noteworthy that the highest mean creatinine levels were observed among the female donor–male recipient group. This supports the previous literature where serum creatinine levels were higher in renal allografts from female donors to male recipients [22]. The higher creatinine levels may be attributed to nephron underdosing wherein female kidneys tend to have lower number of nephrons compared with men, thereby increasing the workload of the individual nephrons for the recipient [23].

This study was also able to demonstrate that female donor–male recipient combination results in a greater risk for graft rejection. The findings corroborate other studies wherein recipients receiving larger kidneys relative to their body size (eg, female recipients of male kidneys) had higher graft survival [24,25]. Moreover, male recipients generally had poorer graft survival than female recipients because of the general observation that women have better compliance on health, such as undergoing follow-up visits and habit change [26]. This was demonstrated in this study wherein regardless of donor sex, men have higher creatinine levels over time. Hence, donor-recipient sex disparity is a determinant of graft survival [27].

In terms of donor-recipient age difference, increasing recipient age resulted in improved transplant survival and lower rejection rates [28]. Conversely, older kidney donors may also affect the younger recipients' creatinine levels, resulting in worse graft and patient survival as well as a significantly higher risk of graft loss and patient death [29]. These findings were similar to this study in which a larger age gap between older donors with younger recipients showed higher mean creatinine levels over time and greater risk for graft loss—the highest among other variables. This may be because of the young age of the kidney being transplanted to the patients, resulting in lower creatinine levels.

Body mass index may also influence graft outcome. Extreme donor-recipient BMI mismatch wherein the living donor was heavier may confer an independent risk for allograft loss [30]. This was not supported by this study as it found that the normal donor–normal recipient matching group had a greater risk of graft loss when compared with other combinations. Nonetheless, further analysis of this BMI matching shows that the normal donor–normal recipient group had a female donor who was 13 years older than the recipient. Therefore, the multivariate analyses are still congruent with results of previous research. Moreover, this study was able to show that recipients receiving from normal BMI donors had significantly lower mean creatinine levels.

The variables were also analyzed individually and jointly to determine creatinine levels. Individual analyses reveal that female recipients had lower creatinine levels regardless of donor sex. When combining certain variables, sex with age matching and age with BMI matching affected graft function. Therefore, female donors–younger male recipients had higher creatinine levels along with younger recipients with overweight or obese donors. These findings are congruent with the aforementioned discussions from past research.

CONCLUSION

There was a significant difference in the 12-month graft function of patients when grouped according to their matching for age difference, sex, and BMI. The risk for graft rejection increases when the combination for donor-recipient is female donor–male recipient and normal donor–normal recipient. For graft loss, this is most significant for donors who are ≥ 15 years older than their recipients.

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