Estimating the Net Utility Gains Among Donors and Recipients of Adult Living Donor Kidney Transplant

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ABSTRACT

Objectives. Living donor kidney transplant relieves the disease burden of patients with end-stage renal disease but may shorten donor life expectancy; however, their quality of life (QOL) is preserved. Nevertheless, the magnitude of the net gain of this procedure is unknown. We evaluated the QOL of both donors and recipients concurrently and calculated the net utility gain.

Methods. We recruited 210 subjects who visited the kidney transplantation clinic of a university hospital. Subjects were asked to complete the 5-level EQ-5D-based questionnaire, and patient characteristics were extracted from their medical records. We performed multivariate tobit models analysis to evaluate the QOL change caused by transplant surgery and subsequently ran computational simulations to determine the net utility gains of donors and recipients. We also performed sensitivity analyses.

Results. After excluding 16 answers with missing data, we analyzed 203 answers in total. After the transplant surgery, recipients gained 0.07 in utility value while donors lost 0.04. In the net utility analysis, we found that the quality-adjusted life years gained ranged from 7.2 to 7.8 in the most favorable case observed in the combination of middle-aged recipients and elderly donors. Assuming no utility discount, the most favorable combination was that with older donors and younger recipients.

Conclusions. These findings indicated that the QOL improvement in recipients was larger than the loss among donors. When calculating the net utilities, a combination of middle-aged recipients and elderly donors yielded the largest net utility, but this was likely derived from assumption in the discount of QOL.

LIVING donor kidney transplant is a treatment option for patients with end-stage renal disease (ESRD) undergoing renal replacement therapy to survive. Particularly in Japan, where deceased donor kidney transplant is relatively rare [1], living donor kidney transplant is the major option for ESRD patients who wish to discontinue dialysis.

Dialysis therapy, including hemodialysis and peritoneal dialysis, is highly invasive, and the estimated life expectancy of patients undergoing this therapy is almost half that of a normal cohort [2]. The quality of life (QOL) of patients undergoing dialysis therapy is also much lower [3]. Kidney transplant frees these patients from dialysis and leads to evident improvements in QOL [4] and greater life

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expectancy (compared with their preoperative state) [5]. Hence, kidney transplant is thought to be valuable for recipients [6].

On the contrary, the renal function of donors is often worse after the transplant compared with their preoperative state [7,8]. While several previous studies have indicated that the overall life expectancy of kidney donors is no shorter than that of the general population [9,10], these studies have been criticized for the use of control groups of people who are less healthy than potentially eligible donors. Studies using adequately matched control groups found that the relative mortality or risk of ESRD among donors after transplant was significantly higher than that of matched controls [11,12]. Previous studies have indicated that kidney donors do not show inferior QOL parameters compared with the general population [13,14].

In summary, previous studies indicated that life expectancy and QOL of recipients may improve by kidney reception, while life expectancy of donors might be shortened. The change in QOL of donors was not significant. Considering these facts, we believe that any discussion of living donor kidney transplant as a treatment option should consider the QOL of both donors and recipients.

The desirability of living in a certain state is called utility [15] in the health economics field and is commonly used in cost-effectiveness research. The concept is suitable for our current research aim because total desirability of living among donors and recipients reflects net gains from the surgery. Some QOL measures have been developed on utility-based approach, and quality-adjusted life years (QALYs) based on such kind of measures have been used in cost-effectiveness evaluation [16,17]. The aforementioned QOL study for donors did not use utility-based QOL measure; therefore, utility of donors was still unclear.

To our knowledge, there has been no study examining the net utility outcomes of donors and recipients of kidney transplant in the same disease context using a utility-based QOL scale. Hence, in the present study, we evaluated these net utility outcomes of donors and recipients and their justification by simultaneously surveying their utilities using a utility-based scale in our kidney transplantation follow-up clinic.

MATERIALS AND METHODS

Study Design

This study was a cross-sectional observational study surveying postoperative donors and recipients as well as donor and recipient candidates whose data were then used to estimate the net utility gains of kidney transplant using computational simulation. We included 210 subjects including donors, donor candidates, recipients, and recipient candidates who visited the Kidney Transplant Clinic of Urology at Kyoto University Hospital from July 2015 to March 2017 who agreed to answer the study questionnaire after they were told the study procedure and given a paper-based consent form. Nine patients who underwent transplant during the observation period completed the survey twice: before and after their transplant. We included both sets of data in the analysis. Sixteen respondents with missing data were excluded. This study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (E2473).

Assessment of QOL

We measured QOL in this study using the 5-level EQ-5D (EQ-5D-5L) developed by the EuroQoL group [18,19]. This evaluates QOL by asking respondents to report their mobility, self-care, usual activity, pain and/or discomfort, and anxiety and/or depression on 5 levels of severity. This tool is recommended by the United Kingdom's National Institute of Health and Care Excellence as an effective way of measuring the value of health and social care in adults [20] and is believed to be more effective in this regard than generic utility-based QOL measures such as the Health Utility Index or Short Form 6-Dimension. Thus, we selected it for the present study. To convert participants' responses into a utility value, we used the value set for Japanese people, which has been officially approved by the EuroQoL group [21].

Data Collection

Participants were asked to complete the paper questionnaire during their waiting time at the clinic, without the supervision of medical staff, after completing the face-to-face informed consent procedure. Besides EQ-5D-5L data, we collected patient characteristics such as age, sex, and Eastern Cooperative Oncology Group performance status from their electronic medical records for use in the statistical analysis of utility.

Statistical Analyses

Effect of transplant surgery. We performed a multivariate analysis to examine the effect of transplant surgery on patients. Specifically, we used the standard tobit model for this analysis [22] because the distribution of the dependent variable (QOL) was censored at 1 according to its definition, as shown in Fig 1. We set the upper limit of the dependent variable at 1 and the lower limit as 0 and then performed the multivariate analysis. We adjusted for age, sex, and history of ESRD. Performance status is known to be associated with low QOL [23,24]; however, because the effect of interest in this study was considered to be influenced by a change in performance status itself, we did not adjust for it. Furthermore, because of the limited number of participants, we did not include the cause of ESRD or length of dialysis before transplant in the analysis.

Simulation of total utilities of donors and recipients. To evaluate the overall outcomes of kidney transplant, we performed computational simulation. At first, we calculated the expected QALYs of donors and recipients at the time of transplant as a function of age and sex, using the rate of decline in QOL extracted from the aforementioned multivariate analysis. Specifically, the estimated QALYs (EQ) were calculated as follows:

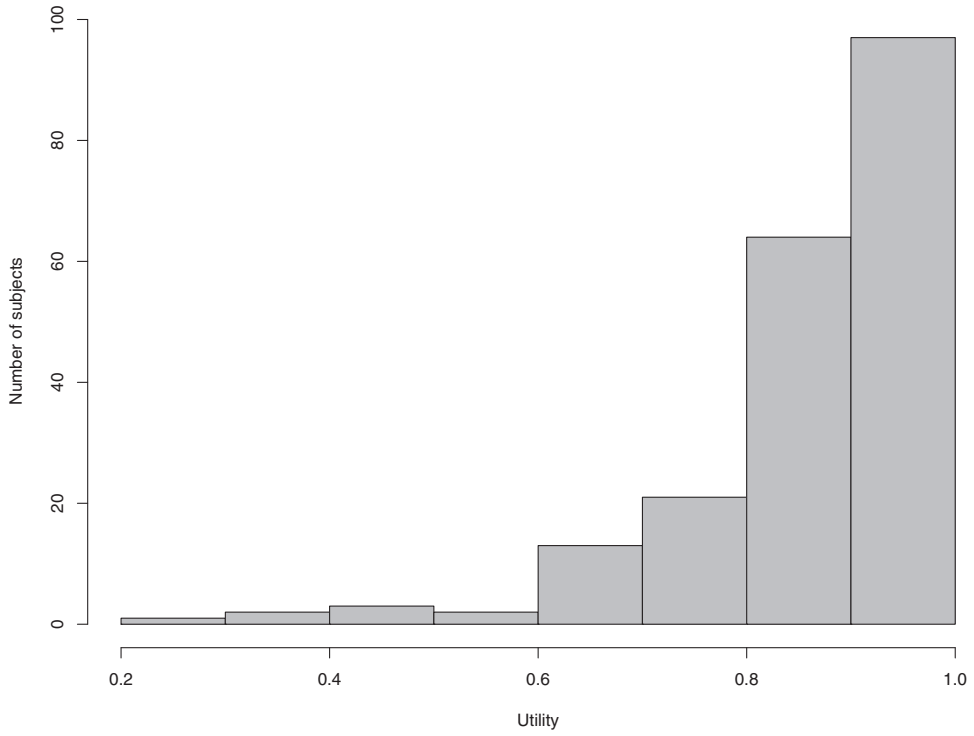

Fig 1. Distribution of health utility among the current study population. (n = 203).

$$\mathrm{EQ}\,(status, age, sex) = \sum_{Y=0}^{100-age} \left(\frac{\begin{array}{c} 1 - a \times (if\ sex\ is\ female) - b \times Y \\ -c_1 \times (if\ status\ is\ Recipient\ or\ Recipient\ Candidate) \\ +c_2 \times (if\ status\ is\ Recipient) - c_3 \times (if\ status\ is\ Donor) \end{array}}{(1+r)^Y} \times \prod_{i=age}^{age+Y} survival(status, i, sex) \right)$$

$$status \in \{Donor, DonorCandidate, Recipient, RecipientCandidate\}$$

Here, a is the decline in QOL relating to female sex, b is the rate of QOL decline, c_1 is the effect of history of ESRD on utility, c_2 is the effect of kidney reception, and c_3 is the effect of kidney donation. These coefficients were derived from the aforementioned multivariate analysis. Furthermore, r is the annual discount rate of QOL. We used a 2% discount rate in our base case analysis, adhering to the Japanese guideline for economic evaluations of drugs and medical devices [25]. The term *survival* (*status*, *age*, *sex*) was defined as the annual survival rate based on their status (donor, donor candidate, recipient, or recipient candidate), their age, and their sex.

Next, the effect of transplant operation on donors and recipients was calculated as follows:

$$\begin{aligned} Effect_{Donor}(age, sex) &= EQ(DonorCandidate, age, sex) \\ &\quad - EQ(Donor, age, sex) \end{aligned}$$

$$\begin{aligned} Effect_{Recipient}(age, sex) &= EQ(RecipientCandidate, age, sex) \\ &\quad - EQ(Recipient, age, sex) \end{aligned}$$

Subsequently, the net effect of transplant surgery was calculated as follows:

$$\begin{aligned} Net\ Effect &= Effect_{Donor}(age\ on\ donation, sex) \\ &\quad + Effect_{Recipient}(age\ on\ reception, sex) \end{aligned}$$

The survival rate as function of subjects' status, age, and sex was determined as follows. First, for donors and donor candidates, we referred to the complete life table of Japanese citizens and the extracted mortality rate of each sex and age between 15 and 100 years old. Subsequently, the survival rates of donors and donor candidates were calculated by subtracting the mortality rate from 1.0. Referring to former studies showing that mortality rate of kidney donors was almost equal to that of the general population [9] but was 1.3 times the rate of potential donation candidates [11], we assumed that the mortality rate of donors was equal to the general population and that of donor candidates was 1/1.3 × the mortality rate of the general population.

Table 1. Patient Characteristics (n = 207)

	Donor (n = 55)	Donor Candidate (N = 16)	Recipient (N = 67)	Recipient Candidate (N = 65)
Patient characteristics				
Age, mean (SD), y	65.0 (11.2)	56.8 (13.5)	49.8 (13.1)	49.4 (11.6)
Female sex, No. (%)	33 (60.0)	12 (75.0)	25 (37.3)	30 (46.2)
Utility, mean (SD)	0.92 (0.12)	0.95 (0.07)	0.89 (0.15)	0.85 (0.16)
ECOG performance status ≥1, mean (SD)	2 (3.6)	0 (0)	3 (4.5)	9 (13.8)
Causes of ESRD, No. of patients (%)				
Diabetic kidney disease			5 (7.5)	10 (15.4)
IgA nephropathy			20 (29.9)	18 (27.7)
ADPKD			6 (9.0)	6 (9.2)
Others including unknown			36 (53.7)	31 (47.7)
Length of dialysis (before transplant in recipients)				
≤1 y or pre-emptive			25 (37.3)	3 (4.6)
1–5 y			26 (38.8)	26 (40.0)
>5 y			12 (17.9)	36 (55.4)
Unknown			4 (6.0)	0 (0.0)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease.

Second, for recipients and recipient candidates, we used mortality data from the Japanese Society of Dialysis Therapy [26]. Based on an exponential regression of these data, the mortality rate of dialysis patients was $1.32 \times 10^{-3} \times e^{0.06 \times age}$. In the recipient groups, we did not consider sex differences because of the limited amount of data. We used that value as the mortality rate for recipient candidates, assuming that all recipient candidates were undergoing dialysis therapy for simplicity. As for recipients, data from the United States Renal Data System showed that the mortality rate of kidney recipients is about one-fifth that of dialysis patients [27]. Therefore, we used the mortality rate of recipient candidates multiplied by 0.2 as recipients' mortality rate. The survival rates of both groups were calculated by subtracting the mortality rates from 1.0, just as for the donors and donor candidates.

To visualize the results, we drew a heat map showing the total utilities, with the vertical axis showing donors' age at transplant and the horizontal axis showing recipients' age at transplant.

Sensitivity Analysis

To examine the effect of 2 assumptions from the above analysis—QOL discount rate and QOL decline rate with age—we conducted a sensitivity analysis. Specifically, we established 2 conditions for each of the assumptions: for discount rate, we set it as 0.00 (no discount) and 0.04 (based on the aforementioned Japanese guideline) [25]; for decline rate, we set the age-related QOL decline as 0 and twice that of the originally estimated value. We also drew a heat map to display these results.

All analyses and the heat map drawings were conducted using R 3.4.3 software [28] and the VGAM package [29].

Table 2. Estimated Coefficients of Parameters for Health Utility

	Estimate	SE	*P* Value
Main Analysis			
Kidney donation	−0.04	0.08	.59
Kidney reception	0.07	0.04	.10
Effect of covariates			
Age	−0.003	0.001	.05
Female sex	−0.05	0.04	.15
History of ESRD	−0.22	0.08	<.01

Abbreviation: ESRD, end-stage renal disease.

RESULTS

We initially included 219 answers, although 16 of them were excluded because of missing data. We ultimately analyzed 203 answers from 194 patients. Table 1 shows the characteristics of respondents. Recipients and recipient candidates were generally younger than donors and donor candidates. With regard to sex, donors and donor candidates had a larger proportion of women. Donors' and donor candidates' utilities and Eastern Cooperative Oncology Group performance status were generally higher. The causes of ESRD did not differ between recipients and recipient candidates, but recipient candidates had received dialysis therapy for longer than recipients.

Table 2 shows the results of the multivariate analysis examining the change in utility derived from kidney transplant, adjusted for age, sex, and history of ESRD. We found that the kidney donation led to a 0.04 decrease in utility value, while kidney reception led to a 0.07 increase. Older age and female sex had negative effects on utility value, while the history of ESRD had much stronger effects on utility value compared with other factors. The *P* values of the estimates of kidney donation and reception were higher than .05, as were those for the effects of age and sex.

Figure 2 shows the heat map of the net utility gains derived from kidney transplant, with results classified by color. Lighter colors indicate favorable net utility gains while darker colors indicate the opposite. For transplants from male donors to male recipients (shown in upper left of the figure), the most favorable combination of ages were 80-year-old donors and 45-year-old recipients, with a net gain of 7.74 QALYs. In contrast, the most unfavorable combination was for 20-year-old donors and 80-year-old recipients, which led to a net gain of 3.93 QALYs. For other combinations of sexes of donors and recipients, almost similar results were extracted. Generally, middle-aged recipients had more favorable QALYs than younger or older recipients.

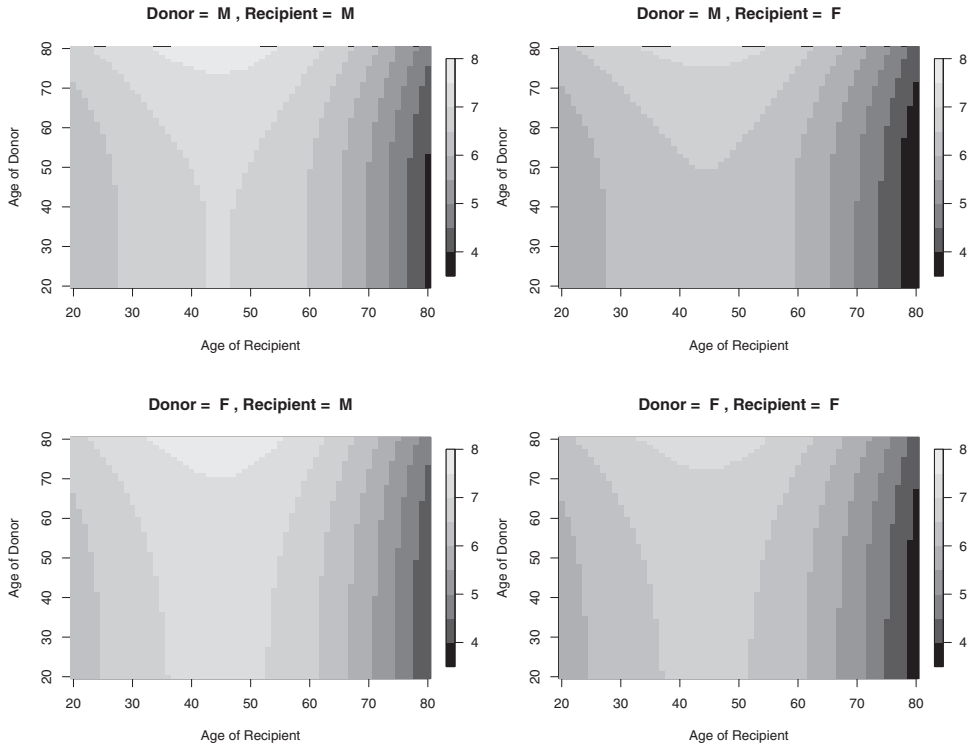

Fig 2. Heat map of total additional health utility among donors and recipients. Lighter colors mean favorable utility while darker colors mean unfavorable utility. (Upper left) Donor: Male, Recipient: Male, maximum additional QALYs = 7.74, minimum = 3.93; (Upper right) Donor: Male, Recipient: Female, max = 7.19, min = 3.57; (Lower left) Donor: Female, Recipient: Male, max = 7.77, min = 4.07; (Lower right) Donor: Female, Recipient: Female, max = 7.22, min = 3.70. Abbreviation: QALY, quality-adjusted life year.

Figure 3 shows the heat maps under the assumptions of discount rates of 0.00 (no discount) and 0.04 in male donors and male recipients. With regard to the discount rate of 0.00, the total outcome became favorable when recipient age was younger and donor age was older, with the maximum net QALY gain being 17.01 (donor = 80 years old, recipient = 20 years old) and the minimum QALY gain being 2.63 (donor = 20 years old, recipient = 80 years old). When the discount rate was set to 0.04, the most favorable combination was for relatively older recipients and younger donors, with a maximum net QALY gain of 5.00 (donor = 80 years old, recipient = 59 years old) and a minimum gain of 2.82 (donor = 60 years old, recipient = 20 years old).

The heat map of the sensitivity analysis for the age-related QOL decline rate is shown in Fig 4. Regardless of whether the age-related QOL decline was 0 or twice that estimated in the base case analysis, the results were similar to those obtained in the base case analysis.

DISCUSSION

We conducted a QOL survey and calculated the utility values concurrently for donors, recipients, and their candidates, followed by a computational simulation to identify the net health utility gains among donors and recipients.

The change in utility from before to after kidney transplant among recipients [4,30] and donors [31,32] has been studied before, but these studies examined either recipients or donors. Furthermore, patients' QOL might vary depending on their context, including motivational, societal, and cultural differences [33,34]. For instance, the utilities of patients with chronic kidney disease grade 3 in Japan whose disease is due to kidney donation might differ from those in the United States whose disease is due to chronic glomerulonephritis. Hence, the net effect among donors and recipients has not been evaluated thus far.

The results of the multivariate analysis using tobit models indicated that older age and female sex had negative effects on QOL, both of which were found in previous studies using the EQ-5D-5L [35–37]. This result indicates that the target population was not so deviated from the general population and that our result has external generalizability. Regarding the utility change from kidney transplant, relatively larger utility changes were observed in recipients compared with donors, but the statistical difference was not significant because of the limited number of data. Although the positive effect on the recipient was larger than the negative effect on donors, the difference in absolute values was rather small. Especially regarding the difference between recipients and recipient candidates, it was smaller than the crude difference between previously reported QOLs of

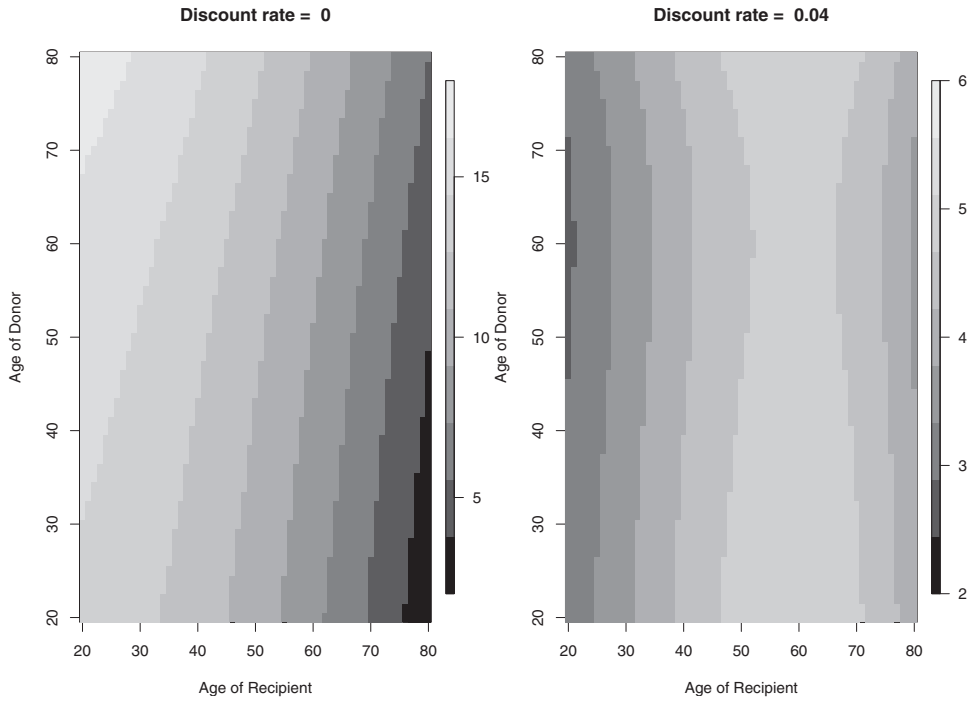

Fig 3. Heat maps of sensitivity analysis for discount rate. Discount rate was set as 0 (left figure, maximum additional QALY = 17.01, minimum = 2.63) and 0.04 (right figure, max = 5.00, min = 2.82). Lighter colors indicate more favorable utility while darker colors indicate more unfavorable. Both figures show results of male-to-male transplant. Abbreviation: QALY, quality-adjusted life year.

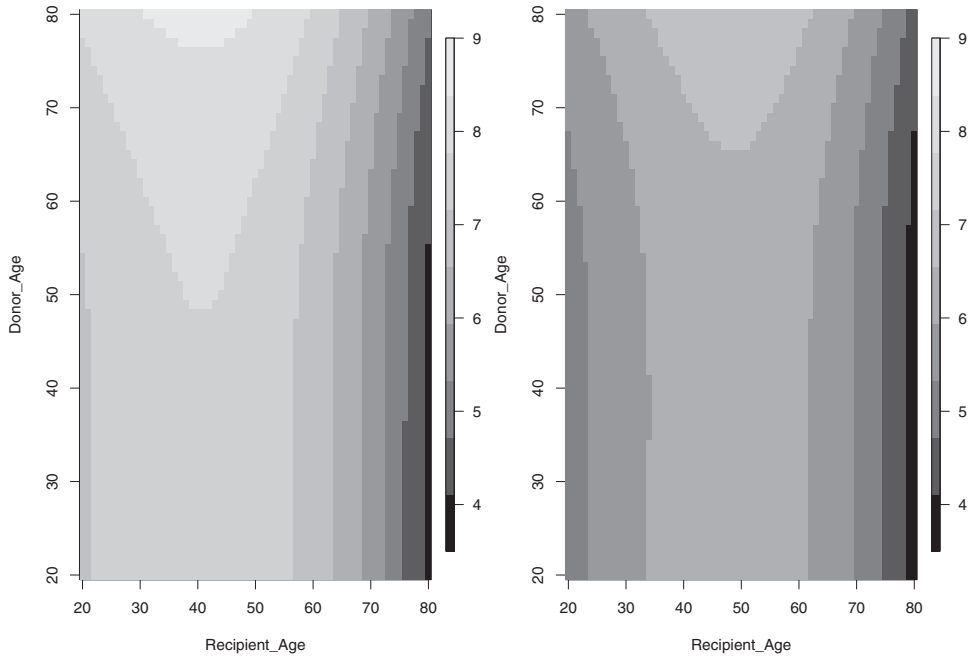

Fig 4. Heat maps of sensitivity analysis for assumption of age-related decline rates. Lighter colors indicate more favorable utility while darker colors indicate more unfavorable. Left figure shows the results for an age-related QOL decline of 0 and right figure shows that for a decline of twice that estimated in the base case. Both figures show results of male-to-male transplant. Abbreviation: QOL, quality of life.

chronic kidney disease grade 3 and dialysis patients [3]. This finding can perhaps be explained by the fact that the utility of recipient candidates was not impaired much in comparison with dialysis patients shown in previous research. That is, patients with ESRD who were evaluated as eligible for transplant surgery by specialists could be relatively healthier than those with ESRD in general, so it is possible that we overestimated the effect of transplant by using utility data from a general dialysis cohort.

As for the simulation of net utility gains, we obtained the paradoxical result that middle-aged recipients and elderly donors was the most favorable combination. Intuitively, one would think that a higher net utility gain would be found for younger recipients and elderly donors because the utility might improve when donors' life expectancy is shorter and recipients' is longer. This result can be explained by the assumption of the discount rate for utilities. As shown in Fig 3, when no utility discount was assumed, the most favorable combination was between young recipients and elderly donors. When a higher utility discount was assumed, the utility change in the far future would have little effect on subjects, so younger recipients could not receive as much benefit as middle-aged ones. Similarly, older recipients exhibited smaller utility changes because of the shorter life expectancies at the time of transplant when compared with middle-aged patients. Consideration of the time discount of utility values or QOL is recommended in the Consolidated Health Economic Evaluation Reporting Standards guideline [38], an official guideline on the methodology used for economic evaluations of health care, to adequately reflect time preferences for the consequences of a decision. However, the guideline recommends no universal discount rate, instead instructing researchers to choose one that is appropriate for their analyses. The guideline also suggests that the rate will vary according to the setting, and in some cases no discount can be justified. In summary, this assumption is a relatively rough one, so it is necessary to interpret the results carefully. Accordingly, this result does not discount the notion that transplant to younger recipients is most ideal from the viewpoint of maximizing utility gains. However, we might still consider that younger recipients might not be the most favorable target when considering patient time preferences.

The current study has several limitations. First, the number of donor candidates was relatively small because of the research setting, thereby weakening the statistical power. As a result, the standard errors of the estimated coefficients were large, making it difficult to interpret the results with certainty. In addition, our study design was cross-sectional because of limited resources. Therefore, a utility comparison was made between patients, resulting in weaker external validity when compared with an intra-subject comparison (which a longitudinal design would allow). Second, in the computational simulation, we used utility changes with estimated coefficients that did not show statistical significance, which weakens the internal validity of the analysis. Third, we did not consider the difference in costs, which is important when discussing justification of kidney transplant. Previous reports indicated that the costs of kidney transplant were generally lower for recipients than for dialysis patients [39,40]. Considering cost and utility might lead to younger recipients being favored for kidney transplant. Lastly, we could not discuss the significance of the absolute value of QALY gains resulting from transplant. There is no clear threshold for whether a certain amount of QALYs acquired from various combinations were valuable for society, making it difficult to interpret the justification.

CONCLUSIONS

From this concurrent survey of kidney transplant donors and recipients, we found relatively larger utility changes in recipients compared with donors. Computational simulation using these estimated variables indicated a positive net utility change among donors and recipients and indicated that middle-aged recipients could be benefitted by larger utility gains compared with younger recipients.

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