



The strategy of diminishing age gap effect on different donor-recipient combinations in living donor kidney transplantation

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Abstract

Background: The disparity between kidney donation and the number of uremic patients on the waiting list has increased the demand for older live-donor kidneys (OLK). However, the donor-recipient age gap may have an impact on the recipient's outcome.

Methods: Patients who underwent living donor kidney transplantation at our institute between 2005 and 2019 were enrolled and categorized into four donor-recipient groups according to age (≥ 50 years and < 50 years). The Estimated Post-Transplant Survival (EPTS) score was used to quantify the recipient's condition. Adjusted models analyzed recipient outcomes and related risks among the four groups.

Results: Of the 154 pairs of live donors and recipients, OLK did not influence overall or death-censored graft survival. The four donor-recipient combinations had similar recipient outcomes, except it slightly worsened in the "old donor to young recipient" group. The EPTS score (adjusted HR, 1.02; 95% CI, 1.01-1.04; $p = 0.014$) and rejection (adjusted HR, 4.26; 95% CI, 1.36-13.37; $p = 0.013$) were significant risk factors for overall and death-censored graft survival, respectively. Recipients with pretransplant diabetes or prior solid organ transplantation could have amplified risk effects. The main causes of graft loss were death in older recipients and chronic rejection in younger recipients.

Conclusion: OLK is safe for young recipients. Nevertheless, adequate immunosuppression should be maintained to prevent rejection and subsequent graft loss, especially for those receiving second kidney transplantation. In contrast, older recipients should avoid overt immunosuppression and control their comorbidities, such as diabetes-related complications to improve their long-term outcomes.

Keywords: Age distribution; Graft rejection; Kidney transplantation; Living donor; Survival analysis

1. INTRODUCTION

Compared to that of other developed countries, Taiwan has the highest prevalence and incidence rate of end-stage renal disease (ESRD).¹ Although kidney transplantation could relieve the dialysis burden, the disparity between the available donor kidneys and the number of ESRD patients on the transplant waiting list has been growing.² As there is a paucity of deceased donor kidneys in eastern countries,³ exploring potential live kidney donors might improve the low transplant rate in Taiwan. Currently, most kidney transplant centers in the US have no

upper age limit for live kidney donors.⁴ Moreover, additional research has revealed that the renal function of older living donors does not progressively decline after donation, suggesting that living kidney donation by the elderly is safe.⁵⁻⁷ Hence, using older live-donor kidneys (OLK) seems to be a way to increase the number of living donor kidney transplants (LDKT).

However, using OLK is a concern because older deceased-donor kidneys (ODK) have been associated with poorer graft survival.⁸ For this reason, the US transplant community has emphasized longevity matching for deceased kidney allocation according to the Estimated Post-Transplant Survival (EPTS) score and Kidney Donor Profile Index (KDPI). They prioritize the top 20% of kidneys (KDPI $\leq 20\%$) to the top 20% of waitlisted recipients with the most extended predicted survival (EPTS score $\leq 20\%$).⁹ The question remains whether OLK has better tissue quality and a shorter cold ischemic time than ODK. The OLK can still be donated to young recipients. The donor-recipient age gap, against longevity matching, might be the gray zone affecting the outcome in young recipients.

To understand the impact of the donor-recipient age gap in LDKT, this study aimed to examine long-term graft outcomes and potential risk factors for graft survival in different live donor-recipient age combinations, primarily focusing on OLK in young recipients.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 65-71.

Received February 20, 2022; accepted August 18, 2022.

doi: 10.1097/JCMA.0000000000000822.

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2. METHODS

2.1. Study population

We conducted a retrospective cohort study of patients who underwent LDKT at our institution between February 1, 2005, and December 31, 2019. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (No. 2021-05-003CCF). We enrolled 156 pairs of live kidney donors and recipients and excluded two pairs (one unexpectedly died by suicide and another had a subdural hemorrhage on the 1st postoperative day). According to the 2020 annual report on kidney disease in Taiwan, the median age of the deceased donor or living donor kidney recipients from 2014 to 2018 was between 45 and 54 years.^{10,11} In addition, the median age of live kidney donors in our study was also around 50 years. Therefore, we defined the groups as old (age ≥ 50) and young (< 50 years), and categorized the participants into four groups: group 1, old donor–old recipient; group 2, old donor–young recipient; group 3, young donor–old recipient; and group 4, young donor–young recipient. Fig. 1 shows a flowchart of patient selection.

2.2. Donor presenting factors

Age was our primary interest, and all live kidney donors had indicated an estimated glomerular filtration rate (eGFR) adjusted by age.¹² Donor nephrectomy was performed using open, intraperitoneal, or retroperitoneal approach in different program time

periods. No significant complications occurred during kidney procurement. The Remuzzi score (RS) was measured to confirm kidney quality using a time-zero biopsy.¹³

2.3. Recipient presenting factors

To precisely quantify the recipient's clinical condition, we used the EPTS score (adopted in the US kidney allocation system and published in 2013) to predict the deceased donor kidney recipients' survival times after transplantation.⁹ The score was calculated using four recipient factors: age, current diabetes status, duration of dialysis, and prior solid organ transplantation (SOT) (the EPTS calculator is available at <https://optn.transplant.hrsa.gov/resources/allocation-calculators/epts-calculator/>). Other potential confounders, including sex, cold ischemia time, preformed human leukocyte antigen (HLA) antibody, and first rejection event, were also recorded. In addition, we proved allograft rejection by kidney biopsy to distinguish between T-cell mediated rejection (TCMR), antibody-mediated rejection (ABMR), or mixed types. All recipients received a standard immunosuppression regimen with steroids, an initial dose of 1000 mg of methylprednisolone during the operation, tapering to prednisolone 20 mg over 1 week, and mycophenolate mofetil 750 mg twice daily. Tacrolimus was maintained at a level of 6–8 ng/ml. mTOR inhibitors, such as sirolimus or everolimus, were used with tacrolimus minimization or BK polyomavirus infection.

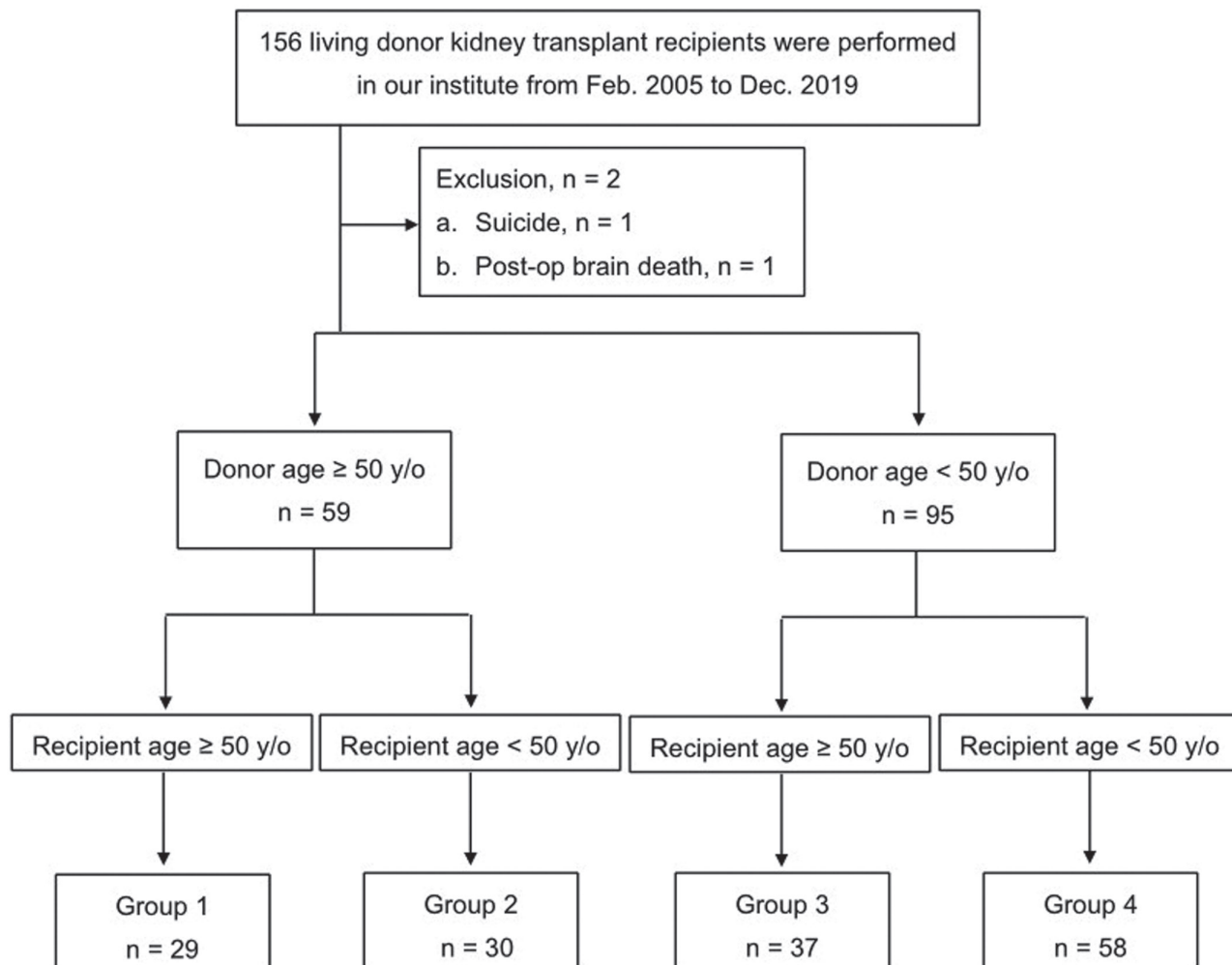


Fig. 1 Flow chart of patient selection.

2.4. Statistical analysis

The main dependent variables were death or graft failure, which were used to analyze overall graft survival and death-censored graft survival. The cohort was followed until either of the following occurred: death, graft failure, or the end of the study. Comparisons between groups were performed using the chi-square test for categorical variables and ANOVA tests for continuous variables. We used the Kaplan–Meier method to calculate the cumulative incidence of graft loss and the Cox proportional hazards model to estimate the hazard ratio (HR) and the accompanying 95% confidence interval (CI) to identify risk factors for graft failure. Covariates, such as OLK and other potential confounders, were included in the model. Those with a p -value <0.1 in the univariate model were included in the multivariate analysis. Factors of major interest, such as OLK, recipient sex, and EPTS score, were also included in the multivariate model (Model 1). Furthermore, we created another model by transforming the EPTS score into four components (Model 2). Statistical analysis was performed using the SPSS software (version 24.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. RESULTS

3.1. Characteristics of the study population

This study included 154 pairs of living donors and recipients. Recipients receiving OLK were 59 (38%) and of them, 30 (group 2) were less than 50 years. The median age of the recipients was 59 years, 33.5 years, 56 years, and 38 years, accompanied by

EPTS scores of 53.7%, 12.7%, 41.5%, and 13.3% in groups 1, 2, 3, and 4, respectively. There were no significant differences between the groups in the male-female ratio, duration of dialysis, history of prior SOT, cold ischemia time, presence of preformed HLA antibodies, rejection events, death, and death-censored graft loss, except for the pretransplant diabetes status ($p = 0.037$). Type 2 diabetes was dominant in older recipients, and type 1 diabetes was found in younger recipients. OLKs had higher RS than young live-donor kidneys, but the median was <3 . Sepsis (57%) and chronic rejection (53%) were the primary causes of death and death-censored graft loss. In addition, most deaths occurred in groups 1 and 3 (old recipient group), and more death-censored graft loss occurred in groups 2 and 4 (young recipient group). Table 1 summarizes the demographic characteristics of the study population.

3.2. Risk factors for overall and death censored graft survival

We included the donor's age and the recipient's presenting factors in the Cox proportional hazards model to determine the risk factors affecting overall and death-censored graft survival. In univariate analysis for overall survival, the recipient's EPTS score (HR, 1.02; 95% CI, 1.01-1.04; $p = 0.007$), pretransplant diabetes (HR, 3.79; 95% CI, 1.52-9.41; $p = 0.004$), prior SOT (HR, 5.31; 95% CI, 1.52-18.56; $p = 0.009$), and rejection (HR, 2.68; 95% CI, 1.07-6.73; $p = 0.035$) were independent risk factors. In Model 1 multivariate analysis, the EPTS score remained a strong risk factor (HR, 1.02; 95% CI, 1.01-1.04; $p = 0.014$) and rejection became borderline insignificant (HR, 2.56; 95%

Table 1
Baseline characteristics of recipients in four subgroups

Variables	Donor ≥ 50 years		Donor < 50 years		p
	Group 1 n = 29	Group 2 n = 30	Group 3 n = 37	Group 4 n = 58	
Donor median age, years (IQR)	57 (53-60)	56.5 (54-61)	35 (28-45)	41.5 (36.25-45)	
Recipient median age, years (IQR)	59 (55-62)	33.5 (28.25-39)	56 (52-61)	38 (31.25-43.75)	
Male, n (%)	17 (58.6)	12 (40)	23 (62.2)	24 (41.4)	0.114
Dialysis time (months), mean \pm SD	2.8 \pm 4.17	1.5 \pm 1.45	2.5 \pm 4.19	2.5 \pm 3.55	0.523
Pretransplant diabetes, n (%)	12 (41.4)	9 (30.0)	9 (24.3)	8 (13.8)	0.037
Prior solid organ transplant, n (%)	1 (3.4)	1 (3.3)	1 (2.7)	3 (5.2)	0.933
EPTS score, mean \pm SD	53.7 \pm 25.31	12.7 \pm 10.54	41.5 \pm 21.21	13.3 \pm 12.49	
CIT (minutes), mean \pm SD	93.9 \pm 88.55	60.7 \pm 49.91	94.1 \pm 67.26	112.4 \pm 100.67	0.153
Anti-HLA Ab, n (%)	4 (13.8)	6 (20.0)	5 (13.5)	12 (20.7)	0.814
Class I, n (%)	3 (10.4)	1 (3.3)	3 (8.1)	5 (8.6)	
Class II, n (%)	0 (0.0)	5 (16.7)	1 (2.7)	2 (3.4)	
Class I & II, n (%)	1 (3.4)	0 (0.0)	1 (2.7)	5 (8.6)	
Rejection ^a	11 (37.9)	13 (43.3)	14 (37.8)	22 (37.9)	0.960
ABMR, n (%)	4 (13.8)	0 (0.0)	3 (8.1)	5 (8.6)	
TCMR, n (%)	5 (17.2)	11 (36.7)	7 (18.9)	13 (22.4)	
Mixed types, n (%)	2 (6.9)	2 (6.6)	4 (10.8)	4 (6.9)	
Death, n (%)	2 (6.9)	0 (0.0)	4 (10.8)	1 (1.7)	0.923
Malignancy, n (%)	1 (3.4)	0 (0.0)	1 (2.7)	0 (0.0)	
Sepsis, n (%)	1 (3.4)	0 (0.0)	2 (5.4)	1 (1.7)	
Cardiovascular disease, n (%)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	
Death censored graft loss, n (%)	1 (3.4)	4 (13.3)	3 (8.1)	7 (12.1)	0.580
Chronic rejection, n (%)	1 (3.4)	2 (6.5)	2 (5.4)	3 (5.1)	
Glomerular nephritis, n (%)	0 (0.0)	1 (3.4)	0 (0.0)	2 (3.5)	
Infection, n (%)	0 (0.0)	1 (3.4)	1 (2.7)	2 (3.5)	
Median Remuzzi score (IQR)	1 (0-2)	2 (1-3)	1 (0-1)	0 (0-1)	
Follow-up time, month (IQR)	24 (13-54)	32 (10.5-62.5)	68 (28-117)	79 (37.75-138.75)	

ABMR=antibody-mediated rejection; CIT=cold ischemic time; EPTS=Estimated Post Transplant Survival; HLA Ab=human leukocyte antigen antibody; IQR=interquartile range; SD=standard deviation; TCMR=T cell-mediated rejection.

^aThe first episode of rejection, proved by biopsy.

CI, 0.99-6.59; $p = 0.051$). However, in Model 2 multivariate analyses, the pretransplant diabetes (HR, 3.55; 95% CI, 1.21-10.34; $p = 0.02$), prior SOT (HR, 12.03; 95% CI, 2.87-50.48; $p = 0.001$) and rejection (HR, 3.13; 95% CI, 1.05-9.29; $p = 0.04$) were significant risk factors. A similar analysis of death-censored graft survival was performed. The recipient's pretransplant diabetes (HR, 3.34; 95% CI, 1.23-9.06; $p = 0.018$), prior SOT (HR, 4.83; 95% CI, 1.09-21.52; $p = 0.039$), and the rejection event (HR, 4.36; 95% CI, 1.41-13.55; $p = 0.011$) were the independent risk factors in the univariate analysis. In the multivariate analysis of Model 1, rejection was the only independent risk factor (HR, 4.26; 95% CI, 1.36-13.37; $p = 0.013$). In Model 2 multivariate analyses, prior SOT (HR, 11.38; 95% CI, 2.10-61.76; $p = 0.005$) and rejection (HR, 4.58; 95% CI, 1.24-16.93; $p = 0.022$) remained risk factors. Tables 2 and 3 provide detailed information.

3.3. Comparisons of overall and death censored graft survival between groups

The Kaplan–Meier method demonstrated that the cumulative overall and death-censored graft loss incidences were similar among the four groups (log-rank test; $p = 0.302$ and $p = 0.232$, respectively) (Fig. 2). Furthermore, the Cox proportional hazard models were used for posthoc comparisons of graft survival from old and young live donors (reference: young donors) and between groups (reference: group 4). The four models adjusted

by the recipient's sex, EPTS score, and rejection revealed no significant differences between all comparison groups. However, group 2 showed a trend of increasing overall risk (HR, 4.59; 95% CI, 0.95-22.16; $p = 0.058$) and death-censored graft survival (HR, 4.58; 95% CI, 0.95-22.16; $p = 0.058$) (Fig. 3).

4. DISCUSSION

During the study period, we observed that the use of OLK had increased in our institute, and the rate ranged from 0% to 61%. This was primarily attributed to parents donating to their children (16% to 30%). Therefore, in this study, we classified the study population into four groups based on the live kidney donor and recipient age rather than age gradient to assess the clinical situation precisely.¹⁴ Our results revealed that the four donor-recipient age combinations had similar overall graft and death-censored graft survivals. When compared to that of group 4, group 2 showed an increased risk of graft loss.

The leading cause of graft loss in group 2 was chronic rejection, and they had the highest rate of graft rejection (43%). TCMR was dominant (36.7%) in the first rejection episode instead of ABMR (0%). None of the patients died during the follow-up period. This result was consistent with that of our multivariate analysis of risk factors for death-censored graft survival, and graft rejection was the only significant risk factor present. We hypothesized some potential factors to explain the

Table 2

Univariate and multivariate analysis of risk factors associated with overall graft survival

Variables	Univariate		Multivariate (Model 1)		Multivariate (Model 2)	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Donor ≥50 years ^a	2.16 (0.81-5.78)	0.125	1.32 (0.47-3.69)	0.603	1.22 (0.43-3.44)	0.707
Recipient						
Male	1.26 (0.52-3.07)	0.612	0.83 (0.32-2.16)	0.704	0.92 (0.35-2.41)	0.868
EPTS score	1.02 (1.01-1.04)	0.007	1.02 (1.01-1.04)	0.014	1.01 (0.97-1.05)	0.673
Age	1.01 (0.97-1.04)	0.630				
Dialysis time	1.02 (0.91-1.14)	0.788			1.06 (0.92-1.21)	0.414
DM	3.79 (1.52-9.41)	0.004			3.55 (1.21-10.34)	0.020
Prior SOT	5.31 (1.52-18.56)	0.009			12.03 (2.87-50.48)	0.001
CIT	1.00 (0.99-1.01)	0.808				
Anti-HLA Ab	0.69 (0.16-3.06)	0.633				
Rejection	2.68 (1.07-6.73)	0.035	2.56 (0.99-6.59)	0.051	3.13 (1.05-9.29)	0.040

CIT=cold ischemic time; CI=confidence interval; EPTS=Estimated Post Transplant Survival; HLA Ab=human leukocyte antigen antibody; HR=hazard ratio; SOT=solid organ transplant.

^aReference: Donor <50 years

Table 3

Univariate and multivariate analysis of risk factors associated with death censored graft survival

Variables	Univariate		Multivariate (Model 1)		Multivariate (Model 2)	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Donor ≥ 50years ^a	1.79 (0.58-5.47)	0.308	1.24 (0.38-4.01)	0.723	1.08 (0.34-3.45)	0.902
Recipient						
Male	0.95 (0.35-2.58)	0.922	0.74 (0.25-2.19)	0.591	0.80 (0.28-2.33)	0.687
EPTS score	1.01 (0.99-1.03)	0.256	1.01 (0.99-1.03)	0.314	0.99 (0.96-1.03)	0.681
Age	0.99 (0.95-1.02)	0.436				
Dialysis time	0.96 (0.82-1.14)	0.644			1.00 (0.82-1.23)	0.971
DM	3.34 (1.23-9.06)	0.018			2.92 (0.96-8.91)	0.059
Prior SOT	4.83 (1.09-21.52)	0.039			11.38 (2.10-61.76)	0.005
CIT	1.00 (0.99-1.01)	0.858				
Anti-HLA Ab	0.96 (0.21-4.36)	0.960				
Rejection	4.36 (1.41-13.55)	0.011	4.26 (1.36-13.37)	0.013	4.58 (1.24-16.93)	0.022

CIT=cold ischemic time; CI=confidence interval; EPTS=Estimated Post Transplant Survival; HLA Ab=human leukocyte antigen antibody; HR=hazard ratio; SOT=solid organ transplant.

^aReference: Donor <50 years

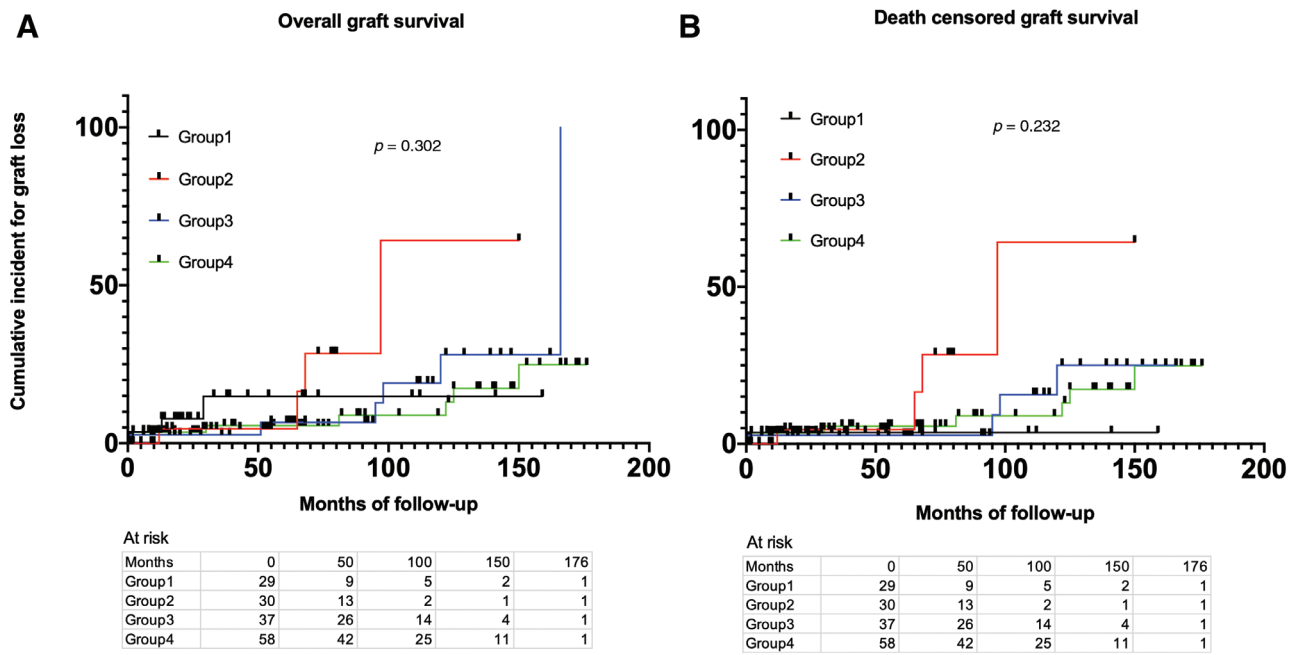


Fig. 2 Cumulative incidence of overall and death-censored graft survival between four donor-recipient combinations. A, The four combinations share similar overall graft survival (death with a functioning graft is considered graft failure) (log-rank test: $p = 0.302$). B, The four groups have similar death-censored graft survival (death with a functioning graft is censored) (log-rank test: $p = 0.232$).

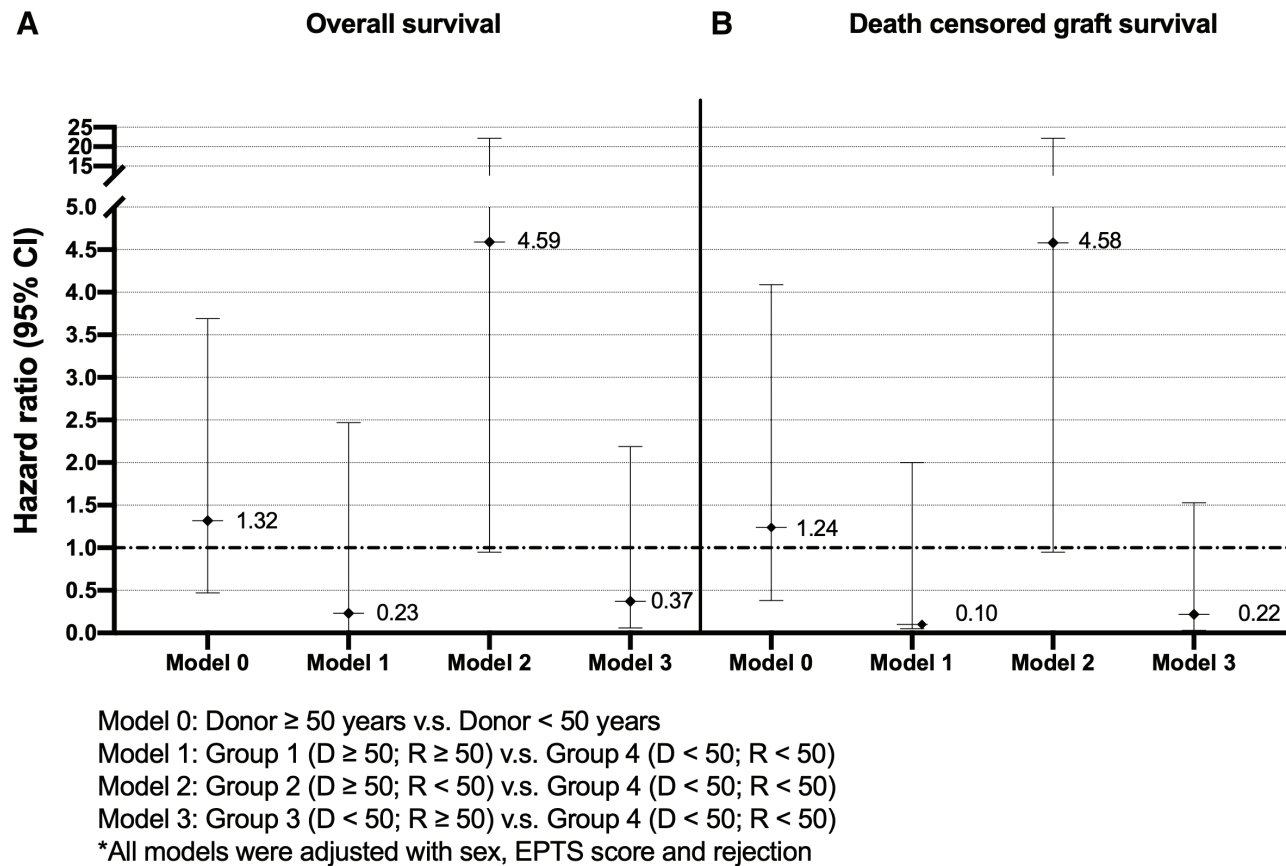


Fig. 3 Recipient outcomes comparing different models. Model 0: a comparison between donor age ≥ 50 and < 50 years. Models 1, 2, and 3: comparisons between groups 1, 2, 3, and group 4 separately. All models adjusted with sex, EPTS score, and rejection. A, The overall graft survival is not different in all models. The group 2 with worse outcome, but not significant (group 2: HR, 4.59; 95% CI, 0.95-22.16; $p = 0.058$). B, Similar outcomes in death-censored graft survival (group 2: HR, 4.58; 95% CI, 0.95-22.16; $p = 0.058$). CI=confidence interval; D=donor; R=recipient.

rejection effect in group 2. First, OLKs have more immunogenic expression than that of the kidneys from live-young donors;¹⁵ young recipients usually have more active immunity;¹⁶ and finally, younger people might have poorer drug compliance.¹⁷ This induces a vicious cycle of proinflammation, rejection, and new immune activation. Group 4, which included young recipients, showed similar graft loss results.

Rather than that of young recipients, the leading cause of graft failure in older recipients (groups 1 and 3) was death ($n = 7$) related to malignancy ($n = 2$), infection ($n = 4$), and cardiovascular disease ($n = 1$), which commonly reflected the recipient's condition. This study used the EPTS score to represent the recipient's clinical status and found that it was the most representative factor affecting overall graft survival. The United Network for Organ Sharing (UNOS) established this score by analyzing the causality between the characteristics of deceased donor kidney recipients and their post-transplant outcomes.⁹ A higher EPTS score indicated lower patient survival after transplantation. Hence, we applied this score to off-label use to quantify the recipient's condition. Our reasons are that the formula components for calculating EPTS scores, such as age and diabetes status, are well-recognized risk factors for predicting the recipient's mortality.¹⁸ The other factors, dialysis time, and prior SOT are uniquely fit for kidney recipients.¹⁹ In addition, the EPTS score ranges from 0% to 100%, and it is easy to interpret the recipient's overall risks. After reviewing the seven deaths in groups 1 and 3, we found that they had a median EPTS score of 74%, and six recipients had higher EPTS scores (73% to 96%).

We further analyzed the impact of the four components of the EPTS score on overall and death-censored graft survival. We found that diabetes status was negative for overall graft survival, and previous SOT also reduced overall and death-censored graft survival. The 2020 Taiwan annual report on kidney disease revealed that transplant recipients with diabetes had a shorter mean survival time than those without diabetes (4 vs. 5.5 years).¹⁰ In this context, we considered that diabetes contributed to mortality risk in overall graft survival and did not affect the death-censored graft survival. In our study, four SOT patients received a second kidney transplant, one received a heart, and another, a pancreas transplant. To our knowledge, patients who underwent prior SOT might have a high risk of immunological issues, such as rejection, leading to lower graft survival. Two large cohort studies have also investigated whether the recipients who had a second kidney transplant or previous nonrenal SOT had worse overall and death-censored graft survival.^{20,21} In addition, rejection remained critical in influencing the overall graft survival in patients with a second kidney transplant²⁰ instead of death in patients with prior nonrenal SOT.²¹ These results confirmed our findings.

Even though the EPTS score and its four components showed varying significance in our analysis, the results could be explained as each had a different weightage and was individually proportionate to the EPTS score. Therefore, we suggest using the EPTS score as the initial screening tool and checking for the presence of diabetes or prior SOT to further stratify the recipient's risk of graft rejection or mortality. For example, if the patient has an EPTS score $>50\%$ and has diabetes or has undergone nonrenal SOT before kidney transplantation, we should be more cautious about the patient's risk of mortality. However, post-transplant rejection should be prevented in patients with an EPTS score $<50\%$, especially in those receiving second kidney transplantation.

Lim et al²² and Englum et al²³ using the database from Australia and New Zealand Dialysis and Transplant Registry and UNOS, demonstrated that the outcomes for OLKs were inferior to the kidneys from young living donors but better than those from expanded criteria donors. However, their study

showed that the distribution of recipients who received OLKs increased with age, similar to the concept of longevity matching. The longevity matching, such as young kidneys to young recipients, or old kidneys to old recipients, has been applied in western countries to increase the graft utility for allocating deceased donor kidneys.²⁴ We consider that this concept might affect the selection of living kidney donors in these studies. In contrast, our data showed that the number of recipients receiving OLKs was slightly higher in group 2 (young recipients, $n = 30$) than in group 1 (old recipients, $n = 29$). We noted that almost all parents donated in group 2, which might show that the parents had high enthusiasm for kidney donation to their children in Taiwanese society. Unlike previous results, we revealed that the overall or death-censored graft survival of OLKs was similar to that of young live-donor kidneys, and OLKs did not need to follow the rule of longevity matching. In addition, the diminishing concern around OLKs was probably attributed to the rigorous donor selection criteria in our institution, such as having an estimated glomerular filtration rate of >80 mL/min/1.73 m² without microscopic hematuria, normal urine protein, a body mass index <30 kg/m², normal blood sugar, controlled blood pressure, and donors need to be nonsmokers or discontinued smoking before donation.²⁵ The time-zero biopsy proved the quality of OLKs by RS which were all less than three.²⁶

Our study designed four common combinations of donor and recipient in LDKT because we considered the interaction between donor quality and recipient condition to display the actual post-transplant outcomes. However, our results showed that the outcome effects did not differ between the old and young live-donor kidneys, but the recipient's clinical status dominated graft survival. Bae et al²⁷ recently analyzed the Scientific Registry of Transplant Recipients data to predict survival after deceased donor kidney transplantation using donor-recipient combinations. They showed that if the candidates had a lower EPTS score, the donor quality offered fewer survival benefits, whereas it significantly impacted the survival outcome for those with a higher EPTS score. Based on this, we found that young recipients (groups 2 and 4 with low EPTS scores) showed similar graft survival after receiving old or young live-donor kidneys. Although the risk for graft loss slightly increased in group 2, we predicted good results if they could prevent rejection. In addition, we proved that the kidney quality of young and older live donors was nearly comparable for senior recipients because they (groups 1 and 3 with high EPTS scores) shared matching outcomes. However, we have to control their underlying diseases and avoid overt immunosuppression, which increases the risk of malignancy²⁸ and infection,²⁹ leading to mortality.

Our study had several limitations. First, it was a single-center study. Although we identified that OLK was safe in young recipients, we were unsure if our results could be generalized to other kidney transplant centers in Taiwan. Hence, a nationwide population-based study is needed to confirm these findings. Second, we used the EPTS score to represent the recipient's general condition, but the external validation in Taiwan remains unknown.³⁰ However, from our experience, we consider that the recipient with an EPTS score above 70% should be cautious about post-transplant mortality by sepsis. Third, the use of OLKs increased over the last 5 years. Therefore, groups 1 and 2 had shorter median follow-up times than groups 3 and 4 (24 and 32 months vs. 68 and 79 months), which made the outcome in group 2 somewhat uncertain. Finally, we used "50 years" to separate the young and old kidneys according to the median donor age. We know it is difficult to convince everyone that our definition of OLK is "old." However, the donor-recipient relationship in Group 2 was all parent-child who answered our primary interest in this study.

In conclusion, OLK is a safe option for young recipients. However, adequate immunosuppression should be maintained to prevent rejection events and subsequent graft loss, especially for those receiving a second kidney transplant. Furthermore, older recipients should control their comorbidities to improve their long-term survival.

REFERENCES

- Chen CF, Chen FA, Lee TL, Liao LF, Chen CY, Tan AC, et al. Current status of dialysis and vascular access in Taiwan. *J Vasc Access* 2019;20:368–73.
- Lu YW, Yang CC. The current status of kidney transplantation in Taiwan. *Ann Transplant Res* 2017;1:1006.
- Wu MY, Wu MS. Taiwan renal care system: a learning health-care system. *Nephrology* 2018;23:112–5.
- Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, et al. The medical evaluation of living kidney donors: a survey of US transplant centers. *Am J Transplant* 2007;7:2333–43.
- Dols LC, Kok NF, Roodnat JL, Tran TC, Terkivatan T, Zuidema WC, et al. Living kidney donors: impact of age on long-term safety. *Am J Transplant* 2011;11:737–42.
- Tekin S, Yavuz HA, Yuksel Y, Yucetin L, Ates I, Tuncer M, et al. Kidney transplantation from elderly donor. *Transplant Proc* 2015;47:1309–11.
- Keys DO, Jackson S, Berglund D, Matas AJ. Kidney donor outcomes ≥ 50 years after donation. *Clin Transplant* 2019;33:e13657.
- Querard AH, Foucher Y, Combesure C, Dantan E, Larmet D, Lorent M, et al. Comparison of survival outcomes between expanded criteria donor and standard criteria donor kidney transplant recipients: a systematic review and meta-analysis. *Transpl Int* 2016;29:403–15.
- Organ Procurement and Transplantation Network 2020. A guide to calculating and interpreting the estimated post-transplant survival (EPTS) score used in the kidney allocation system (KAS). Available at https://optn.transplant.hrsa.gov/media/1511/guide_to_calculating_interpreting_epts.pdf. Accessed September 15, 2021.
- National Health Research Institutes, Taiwan. 2020 annual report on kidney disease in Taiwan. Available at <https://lib.nhri.edu.tw/NewWeb/nhri/ebook/39000000465141.pdf>. Accessed July 3, 2022.
- Tsai SF, Lin MH, Hsu CC, Wu MJ, Wang IK, Chen CH. Trends of kidney transplantation from the 2020 annual report on kidney disease in Taiwan. *J Formos Med Assoc* 2022;121:S20–9.
- Andrews PA, Burnapp L, Manas D, Bradley JA, Dudley C; British Transplantation Society; Renal Association. Summary of the British transplantation society/renal association UK guidelines for living donor kidney transplantation. *Transplantation* 2012;93:666–73.
- Naesens M. Zero-time renal transplant biopsies: a comprehensive review. *Transplantation* 2016;100:1425–39.
- Ferrari P, Lim W, Dent H, McDonald SP. Effect of donor–recipient age difference on graft function and survival in live-donor kidney transplantation. *Nephrol Dial Transplant* 2011;26:702–8.
- Fijter JW, Mallat MJK, Doxiadis IIN, Ringers J, Rosendaal FR, Claas FHJ, et al. Increased immunogenicity and cause of graft loss of old donor kidneys. *J Am Soc Nephrol* 2001;12:1538–46.
- Lim WH, Chang SH, Coates PT, McDonald SP. Parental donors in live-donor kidney transplantation associated with increased rejection rates and reduced glomerular filtration rates. *Transplantation* 2007;84:972–80.
- Takemoto SK, Pinsky BW, Schnitzler MA, Lentine KL, Willoughby LM, Burroughs TE, et al. A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. *Am J Transplant* 2007;7:2704–11.
- Zhang H, Wei Y, Liu L, Li J, Deng R, Xiong Y, et al. Different risk factors for graft survival between living-related and deceased donor kidney transplantation. *Transplant Proc* 2018;50:2416–20.
- Rose C, Gill J, Gill JS. Association of kidney transplantation with survival in patients with long dialysis exposure. *Clin J Am Soc Nephrol* 2017;12:2024–31.
- Trébern-Launay K, Foucher Y, Giral M, Legendre C, Kreis H, Kessler M, et al. Poor long-term outcome in second kidney transplantation: a delayed event. *PLoS One* 2012;7:e47915.
- El-Husseini A, Aghil A, Ramirez J, Sawaya B, Rajagopalan N, Baz M, et al. Outcome of kidney transplant in primary, repeat, and kidney-after-renal solid-organ transplantation: 15-year analysis of recent UNOS database. *Clin Transplant* 2017;31:e13108.
- Lim WH, Clayton P, Wong G, Campbell SB, Cohnen S, Russ GR, et al. Outcomes of kidney transplantation from older living donors. *Transplantation* 2013;95:106–13.
- Englum BR, Schechter MA, Irish WD, Ravindra KV, Vikraman DS, Sanoff SL, et al. Outcomes in kidney transplant recipients from older living donors. *Transplantation* 2015;99:309–15.
- Lee D, Kanellis J, Mulley WR. Allocation of deceased donor kidneys: a review of international practices. *Nephrology (Carlton)* 2019;24:591–8.
- Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, et al. Summary of kidney disease: improving global outcomes (KDIGO) clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation* 2017;101:1783–92.
- Remuzzi G, Grinyò J, Ruggenti P, Beatini M, Cole EH, Milford EL, et al. Early experience with dual kidney transplantation in adults using expanded donor criteria. Double kidney transplant group (DKG). *J Am Soc Nephrol* 1999;10:2591–8.
- Bae S, Massie AB, Thomas AG, Bahn G, Luo X, Jackson KR, et al. Who can tolerate a marginal kidney? Predicting survival after deceased donor kidney transplant by donor-recipient combination. *Am J Transplant* 2019;19:425–33.
- Sprangers B, Nair V, Launay-Vacher V, Riella IV, Jhaveri KD. Risk factors associated with post-kidney transplant malignancies: an article from the cancer-kidney international network. *Clin Kidney J* 2018;11:315–29.
- Agrawal A, Ison MG, Danziger-Isakov L. Long-term infectious complications of kidney transplantation. *Clin J Am Soc Nephrol* 2022;17:286–95.
- Clayton PA, McDonald SP, Snyder JJ, Salkowski N, Chadban SJ. External validation of the estimated posttransplant survival score for allocation of deceased donor kidneys in the United States. *Am J Transplant* 2014;14:1922–6.