KI REPORTS
KIReports.org
CLINICAL RESEARCH

Impact of Age 70 years or Older on Donors for Living-Donor Kidney Transplantation

Takahisa Hiramitsu[1], Tomoki Himeno[1], Yuki Hasegawa[1], Kenta Futamura[1], Manabu Okada[1], Yutaka Matsuoka[2], Norihiko Goto[1], Toshihiro Ichimori[1], Shunji Narumi[1], Asami Takeda[3], Takaaki Kobayashi[4], Kazuharu Uchida[2] and Yoshihiko Watarai[1]

[1]Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Department of Transplant and Endocrine Surgery, Nagoya, Aichi, Japan; [2]Department of Renal Transplant Surgery, Masuko Memorial Hospital, Nagoya, Aichi, Japan; [3]Department of Nephrology, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Aichi, Japan; and [4]Department of Renal Transplant Surgery, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan

Introduction: Kidney transplantation (KT) involving elderly living kidney donors (LKDs) is becoming more frequent because of a profound organ shortage. The efficacy of KT involving grafts obtained from LKDs aged 70 years or older has been reported. However, the safety of donor nephrectomy in LKDs aged 70 years or older, including that associated with changes in the estimated glomerular filtration rate (eGFR), has not been investigated. This study investigated the outcomes of LKDs aged 70 years or older after donor nephrectomy.

Methods: This single-center, retrospective cohort study included 1226 LKDs who underwent donor nephrectomy between January 2008 and December 2020. LKDs were stratified into the following age groups: 30 to 49 years (244 LKDs), 50 to 69 years (803 LKDs), and 70 to 89 years (179 LKDs). Surgical outcomes, postoperative eGFR changes, end-stage renal disease (ESRD) rates, and mortality rates were compared among these groups.

Results: No significant difference in surgical outcomes was identified among the groups. LKDs aged 70 to 89 years experienced the lowest eGFR changes at all time points and the lowest eGFR improvement; however, ESRD was not identified in any group during the observation period. Mortality was the highest among LKDs aged 70 to 89 years compared to the other age groups.

Conclusion: Surgical outcomes, eGFR changes, and ESRD incidences can support the safety of donor nephrectomy in LKDs aged 70 years or older. Considering the advanced age, the high mortality rates in LKDs aged 70 years or older could be considered acceptable.

Kidney Int Rep (2024) **9,** 1321–1332; https://doi.org/10.1016/j.ekir.2024.01.043
KEYWORDS: donor nephrectomy; elderly donor; estimated glomerular filtration rate; living donor kidney transplantation; mortality

See Commentary on Page 1157

Owing to a profound organ shortage, LDKT involving elderly LKDs is becoming more frequent. Although LKDs older than 60 to 70 years are classified as extended criteria donors, many reports have referred to the outcomes of LKDs aged 55 to 65 years because of the small number of living donors older than 65 years.[1-7] Only 1 study of LKDs aged 70 years or older has demonstrated their significantly better postdonor nephrectomy survival than that of healthy matched controls.[8] However, that study did not demonstrate the safety, including postoperative complications, postoperative kidney function, and ESRD rates, of donor nephrectomy of those LKDs compared to that of LKDs in other age groups.[8] During LDKT, the safety of LKDs is highly prioritized. Incidence rates of preoperative comorbidities, such as glucose intolerance, hypertension, dyslipidemia, and obesity, may increase as LKDs age.[2] These preoperative comorbidities can be risk factors for postoperative complications and inferior kidney function after donor nephrectomy.[9-12] However, no studies have reported the detailed eGFR changes after donor nephrectomy among donor age groups. During this study, we investigated the impact of donor nephrectomy on LKDs aged 70 years or older by comparing their surgical outcomes, detailed postoperative eGFR changes, ESRD

Correspondence: Takahisa Hiramitsu, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Department of Transplant and Endocrine Surgery, 2-9 Myoken-cho, Showa-ku, Nagoya, Aichi 466-8650, Japan. E-mail: thira@nagoya2.jrc.or.jp

Received 17 September 2023; revised 12 December 2023; accepted 22 January 2024; published online 1 February 2024

incidences, and mortality rates with those of LKDs in other age groups.

METHODS

Study Design

This retrospective cohort study was approved by the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital Institutional Review Board (Aichi, Japan; approval number 1416) and conducted according to the principles of the Declaration of Helsinki. LDKT was performed according to the Declaration of Istanbul. LKDs were stratified into the following age groups: 30 to 49 years, 50 to 69 years, and 70 to 89 years. Surgical outcomes, postoperative eGFRs, ESRD incidences, and mortality rates were compared among these groups. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Follow-Up Assessments

Postoperative assessments of LKDs were performed at 1, 3, 6, and 12 months after transplantation; thereafter, they were performed annually. LKDs with comorbidities were followed-up with every 1 to 3 months.

Participants

We recruited all consecutive 1230 LKDs who underwent donor nephrectomy for LDKT at our hospital between January 2008 and December 2020. Patients were followed-up with until August 2022. Four LKDs were excluded because they were younger than 30 years. Therefore, 1226 LKDs were enrolled in this study (Figure 1). All LKD data were retrospectively collected from medical records and analyzed anonymously. Therefore, the need for informed consent was waived.

Living Donors

LKDs were selected according to the LKD guidelines in Japan.[2,3] Although LKDs aged 70 years or older are classified as marginal donors according to the guidelines, the age limitation is not strict, and the surgical indication for age is determined according to general health. LKD characteristics including preoperative comorbidities such as glucose intolerance (defined as fasting glucose level $\geq$126 mg/dl, blood glucose level $\geq$200 mg/dl 2 hours after glucose administration according to the 75 g oral glucose tolerance test, blood glucose level $\geq$200 mg/dl at any time, hemoglobin A1c level $\geq$6.5%, or treatment with antidiabetic agents), hypertension (defined as blood pressure $>$140/90 mmHg or treatment with antihypertensive agents), dyslipidemia (defined as triglyceride level $>$150 mg/dl, low-density lipoprotein cholesterol level $>$140 mg/dl, high-density lipoprotein cholesterol level $<$40 mg/dl, or treatment with antihypercholesterolemic agents), and obesity (defined as body mass index $\geq$30 kg/m^2) were investigated. According to Japan's LKD guidelines, the indications for LKDs with these comorbidities are as follows: for LKDs with hypertension, blood pressure should be managed to $<$130/80 mmHg with antihypertensive agents, and urine albumin excretion should be $<$30 mg/gCr; for LKDs with glucose intolerance, the hemoglobin A1c level should be managed to $<$6.5% without administering insulin, and urine albumin excretion should be $<$30 mg/gCr; and for LKDs with obesity, the body mass index should be $<$32 kg/m^2.[2,3] The surgical results, graft quality, and adverse events of LKDs were investigated. Surgical results included warm ischemic time, operative time, and intraoperative blood loss. Graft quality included arterial length, number of preserved arteries, venous length, number of preserved veins, ureter length, and number of preserved ureters. Intraoperative adverse events included arterial injury, venous injury, open conversion, bleeding, and bowel injury. Postoperative adverse events included surgical site infection, bleeding, pneumonia, urinary tract infection, small bowel obstruction, cardiovascular events, deep venous

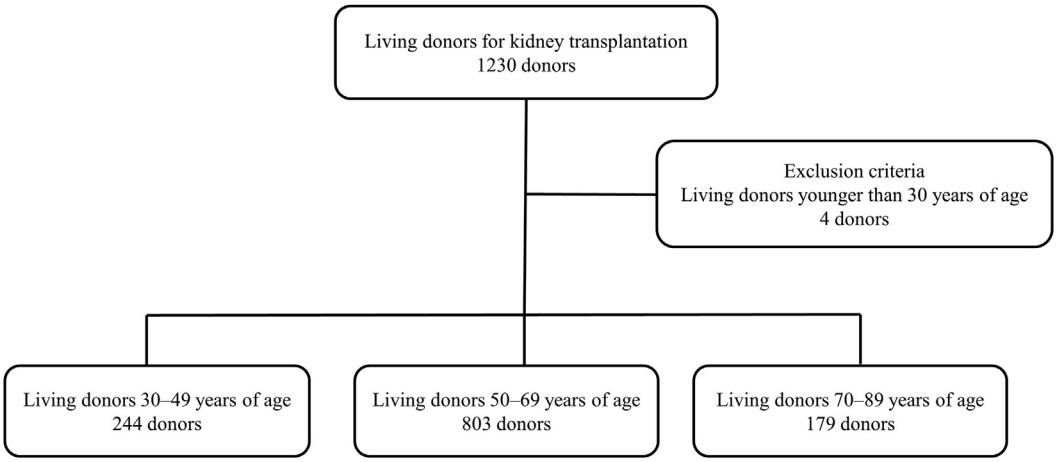

Figure 1. Patient flow chart.

Table 1. Donor characteristics

Characteristics	30–49 yr $n = 244$	50–69 yr $n = 803$	70–89 yr $n = 179$	*P*- value
Age (yr), mean (SD)	43.1 (4.7)	60.0 (5.3)	72.8 (2.5)	<0.001[a]
Sex (male), *n* (%)	83 (34.0)	285 (35.5)	80 (44.7)	0.045[a]
Height (cm), mean (SD)	162.1 (8.4)	159.3 (8.6)	157.4 (7.5)	<0.001[a]
Body weight (kg), mean (SD)	61.0 (11.7)	58.0 (10.0)	56.7 (8.7)	0.001[a]
Body mass index (kg/m^2), mean (SD)	23.0 (3.3)	22.7 (2.8)	22.7 (2.6)	0.967
Donation to first-degree relative, *n* (%)	95 (38.9)	366 (45.6)	116 (64.8)	<0.001[a]
Smoking history, *n* (%)	120 (49.2)	345 (43.0)	79 (44.1)	0.231
Brinkman index, mean (SD)	170.5 (247.7)	234.4 (385.0)	282.1 (433.7)	0.692
One or more preoperative comorbidities, *n* (%)	112 (45.9)	620 (77.2)	155 (86.6)	<0.001[a]
Hypertension, n (%)	14 (5.7)	252 (31.4)	95 (53.1)	<0.001[a]
Dyslipidemia, n (%)	90 (36.9)	499 (62.1)	121 (67.6)	<0.001[a]
Glucose intolerance, n (%)	37 (15.2)	226 (28.1)	71 (39.7)	<0.001[a]
Obesity (body mass index ≧ 30 kg/m^2), n (%)	8 (3.3)	1 (0.1)	0	<0.001[a]
Preoperative systolic blood pressure (mm Hg), mean (SD)	117.6 (12.1)	123.7 (14.4)	128.2 (14.7)	<0.001[a]
Preoperative diastolic blood pressure (mm Hg), mean (SD)	71.6 (10.5)	74.5 (10.9)	73.7 (10.7)	0.001[a]
Preoperative total cholesterol level (mg/dl), mean (SD)	195.0 (32.6)	216.7 (36.6)	206.5 (36.0)	<0.001[a]
Preoperative triglyceride level (mg/dl), mean (SD)	125.3 (91.6)	143.1 (86.1)	139.3 (77.8)	<0.001[a]
Preoperative low-density lipoprotein cholesterol level (mg/dl), mean (SD)	112.0 (29.8)	126.9 (30.1)	120.7 (30.1)	<0.001[a]
Preoperative high-density lipoprotein cholesterol level (mg/dl), mean (SD)	61.1 (13.7)	64.7 (17.2)	59.7 (14.2)	0.119
Preoperative fasting glucose level (mg/dl), mean (SD)	95.2 (10.0)	99.4 (11.4)	103.6 (16.9)	<0.001[a]
Preoperative 75 g oral glucose tolerance test results (blood glucose level 2 h after glucose administration, mg/dl), mean (SD)	116.9 (25.8)	133.1 (38.3)	145.7 (38.0)	<0.001[a]
Preoperative HbA1c level (%, SD)	5.5 (0.3)	5.8 (0.3)	5.9 (0.4)	<0.001[a]
Preoperative antihypertensive agent administration, *n* (%)	6 (2.5)	191 (23.9)	78 (43.6)	<0.001[a]
Preoperative antihypercholesterolemic agent administration, *n* (%)	3 (1.2)	134 (16.7)	57 (32.0)	<0.001[a]
Preoperative antidiabetic agent administration, *n* (%)	0	17 (2.1)	9 (5.0)	0.002[a]
Preoperative eGFR (ml/min per 1.73 m^2), mean (SD)	80.7 (13.7)	72.6 (11.8)	67.4 (11.0)	<0.001[a]
Preoperative urine albumin-to-Cr ratio (mg/gCr), mean (SD)	8.6 (15.7)	10.0 (12.3)	10.5 (9.5)	<0.001[a]

eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.
[a]Statistically significant results.

thrombosis, pulmonary embolism, and surgery-related death. Pathological findings of the baseline biopsy performed 1 hour after reperfusion that was evaluated based on the Banff criteria 2018 by transplant pathologists included glomerular sclerosis, interstitial fibrosis, tubular atrophy, and arteriolar hyalinosis.[13] The LKD prognoses, including eGFR changes, ESRD incidences, and mortality rates, were investigated. Finally, all LKDs underwent echocardiography, stress electrocardiography, respiratory function testing, and chest radiography to evaluate cardiorespiratory function. In addition, all LKDs were screened for cancer via enhanced computed tomography imaging, abdominal ultrasonography, gastrointestinal endoscopy, immunochemical fecal occult blood testing, prostate-specific antigen testing in male LKDs older than 50 years, and gynecological and breast cancer screening in female LKDs.

Statistical Analysis

Statistical analyses of LKD characteristics were performed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. The normal distribution of eGFR data was confirmed using histograms. A linear mixed model analysis was performed to examine whether the LKD groups (30–49 years, 50–69 years, and 70–89 years) affected eGFRs over time; "case" was used as a random factor, dummy variables for "time" were used as repetitive factors, and "LKD groups" and "interaction with time" (defined as "time × donor age groups") were used as fixed factors. Sex was included as a covariate to adjust for confounding factors. The repeated-measures covariance structure comprised compound symmetry. Estimated marginal means and their standard errors and 95% confidence intervals were calculated and compared among the LKD groups at each time point. The Benjamini–Hochberg method (false discovery rate method) was used to adjust for multiple comparisons. In addition, using the same model as that used for the linear mixed analysis, the reference standard for time was set as postoperative day (POD) 6, and the estimated mean and 95% confidence interval of the difference (amount of change) relative to the eGFR on POD 6 were calculated and compared between groups according to donor age. Further analysis was performed

Table 2. Intraoperative and postoperative results

	30–49 yr	50–69 yr	70–89 yr	
	n = 244	*n* = 803	*n* = 179	*P*- value
Surgical methods for donor nephrectomy				
Hand-assisted laparoscopy, *n* (%)	226 (92.6)	756 (94.1)	171 (95.5)	0.187
Non-hand-assisted retroperitoneoscopic, *n* (%)	8 (3.3)	33 (4.1)	4 (2.2)	
Open, *n* (%)	10 (4.1)	14 (1.7)	4 (2.2)	
Operative results				
Kidney side (left), *n* (%)	221 (90.6)	742 (92.4)	162 (90.5)	0.530
Kidney weight (g), mean (SD)	169.8 (37.0)	177.2 (42.4)	186.6 (44.7)	<0.001[a]
Warm ischemic time (seconds), mean (SD)	136.7 (48.0)	142.4 (77.1)	135.3 (41.7)	0.285
Operative time (minutes), mean (SD)	207.6 (50.8)	210.0 (106.4)	200.0 (48.4)	0.328
Operative blood loss (ml), mean (SD)	30.2 (48.1)	37.6 (81.8)	32.9 (44.9)	0.066
Graft quality				
Arterial length (mm), mean (SD)	25.4 (5.3)	26.6 (5.8)	27.5 (6.0)	<0.001[a]
Number of preserved arteries				
1, *n* (%)	182 (83.9)	596 (82.2)	124 (80.0)	0.819
2, *n* (%)	31 (14.3)	119 (16.4)	29 (18.7)	
3, *n* (%)	4 (1.8)	10 (1.4)	2 (1.3)	
Venous length (mm), mean (SD)	23.4 (5.9)	22.6 (6.0)	22.6 (6.0)	0.104
Number of preserved veins				
1, *n* (%)	234 (100.0)	779 (99.2)	176 (100.0)	0.533
2, *n* (%)	0	5 (0.6)	0	
3, *n* (%)	0	1 (0.1)	0	
Ureter length (mm), mean (SD)	107.5 (16.9)	108.5 (16.7)	113.2 (51.2)	0.470
Number of preserved ureters				
1, *n* (%)	234 (100.0)	782 (99.9)	175 (100.0)	0.770
2, *n* (%)	0	1 (0.1)	0	
Intraoperative adverse events				
Arterial injury, *n* (%)	0	1 (0.1)	0	0.768
Venous injury, *n* (%)	0	2 (0.2)	0	0.590
Open conversion, *n* (%)	0	3 (0.4)	0	0.453
Bleeding, *n* (%)	0	2 (0.2)	0	0.590
Bowel injury, *n* (%)	0	1 (0.1)	0	0.768
Postoperative adverse events				
Surgical site infection, *n* (%)	20 (8.2)	54 (6.7)	18 (10.1)	0.279
Bleeding, *n* (%)	0	2 (0.2)	0	0.590
Pneumonia, *n* (%)	1 (0.4)	2 (0.2)	0	0.700
Urinary tract infection, *n* (%)	3 (1.2)	4 (0.5)	2 (1.1)	0.407
Small bowel obstruction, *n* (%)	1 (0.4)	0	0	0.133
Cardiovascular events, *n* (%)	0	0	0	NA
Deep venous thrombosis, *n* (%)	0	0	0	NA
Pulmonary embolism, *n* (%)	0	0	0	NA
Surgery-related death, *n* (%)	0	0	0	NA
Long term outcome				
Donor end-stage renal disease, *n* (%)	0	0	0	NA
Donor death, *n* (%)	0	12 (1.5)	7 (3.9)	0.005
Donor follow-up period (mos), mean (SD)	82.8 (45.3)	81.7 (46.2)	66.0 (41.7)	<0.001[a]

NA, not accessed.
[a]Statistically significant results.

using the same linear mixed model. The dependent variable was the rate of eGFR reduction, calculated as "(predonation eGFR − eGFR at each time point)/predonation eGFR."

During the mixed model analysis of the impact of LKD age on eGFR improvement after POD 6, the eGFR on POD 6 was used as the reference, and the factors associated with improved eGFRs were examined. We created a model in which the amount of change in the eGFR (using eGFR on POD 6 as the reference standard) was the dependent variable, the subject was a variable factor, and time and other parameters were fixed factors. In this model, time was treated as continuous data. In the univariate model, only time was added as a covariate when other factors were considered. For the multivariate analysis, we constructed a model with all variables (time, sex, and LKD age groups) using the forced entry method. A survival analysis was

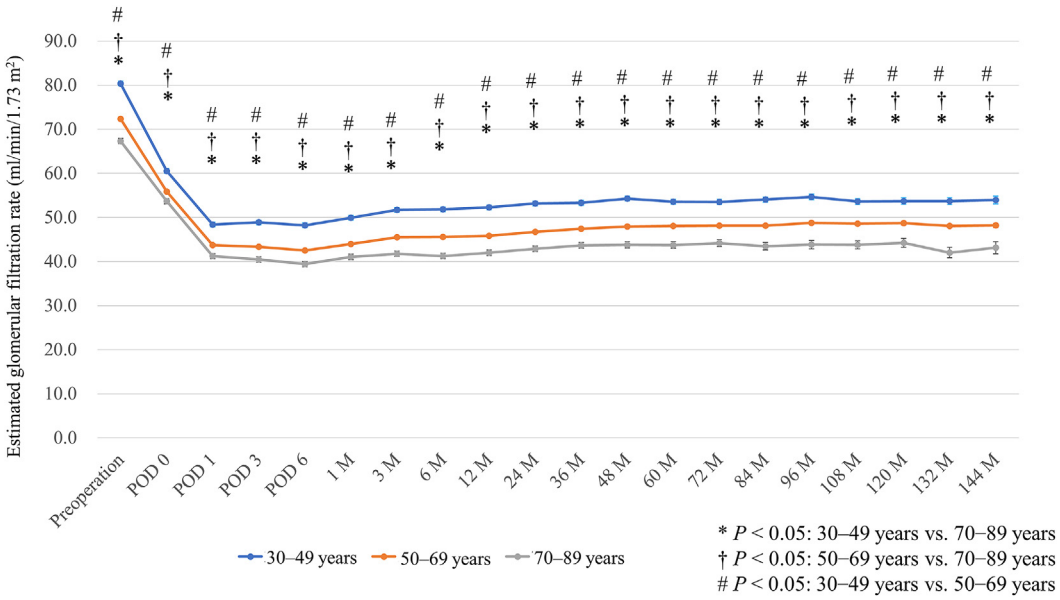

Figure 2. Estimated glomerular filtration rate changes in donors after donor nephrectomy.
Error bars indicate SDs. The estimated glomerular filtration rate was adjusted for sex. The Benjamini–Hochberg (false discovery rate [FDR]) method was used for multiplicity adjustment.
POD, postoperative day; M, postoperative month.
*$P < 0.05$ for donors aged 30–49 vs. 70–89 years.
†$P < 0.05$ for donors aged 50–69 vs. 70–89 years.
#$P < 0.05$ for donors aged 30–49 vs. 50–69 years.

performed to determine whether LKD age groups influenced overall donor survival. The cumulative survival rate was calculated using the Kaplan–Meier method. The Bonferroni method was used for multiplicity adjustment. All statistical analyses were performed using IBM SPSS® Statistics for Windows (version 23.0; IBM Corporation, Armonk, NY) and SAS 9.4 (SAS Institute Inc., Cary, NC). For all analyses, $P < 0.05$ was considered significant.

RESULTS

Study Population

A total of 1230 donor nephrectomy procedures were performed for LDKTs at our hospital during the study period. After excluding 4 LKDs, 1226 LKDs were enrolled in the study. They were stratified into the following age groups: 30 to 49 years (244 LKDs), 50 to 69 years (803 LKDs), and 70 to 89 years (179 LKDs) (Figure 1). The distribution of LKDs aged 70 to 89 years is presented in Supplementary Figure S1. These LKDs were followed-up with between January 2008 and August 2022 (median observation period: 73.0 months; interquartile range: 41.0–119.0 months) and included in the final analysis.

Donor Results

Descriptive Data

In Table 1, we present the donor characteristics. The following significant differences were observed among the 3 LKD groups: age ($P < 0.001$); sex ($P = 0.045$); height ($P < 0.001$); body weight ($P = 0.001$); donations to first-degree relatives ($P < 0.001$); 1 or more preoperative comorbidities ($P < 0.001$), including hypertension ($P < 0.001$), dyslipidemia ($P < 0.001$), glucose intolerance ($P < 0.001$), and obesity ($P < 0.001$); preoperative systolic blood pressure ($P < 0.001$); diastolic blood pressure ($P < 0.001$); preoperative total cholesterol level ($P < 0.001$); triglyceride level ($P < 0.001$); low-density lipoprotein cholesterol level ($P < 0.001$); preoperative fasting glucose level ($P < 0.001$); preoperative 75 g oral glucose tolerance test results (blood glucose level 2 hours after glucose administration) ($P < 0.001$); preoperative hemoglobin A1c level ($P < 0.001$); preoperative administration of antihypertensive agents ($P < 0.001$); preoperative administration of antihypercholesterolemic agents ($P < 0.001$); preoperative administration of antidiabetic agents ($P = 0.002$); preoperative eGFR ($P < 0.001$); and preoperative urine albumin-to-Cr ratio ($P < 0.001$).

Surgical Outcomes

In Table 2 and Supplementary Table S1, we present the intraoperative and postoperative outcomes of the LKD groups. No significant differences in surgical results, graft quality, and adverse events were observed; however, significant differences in kidney weight ($P < 0.001$), arterial length ($P < 0.001$), and follow-up period ($P < 0.001$) were observed.

Table 3. Estimated glomerular filtration rate changes adjusted for sex

Time	Donor age groups		Difference (ml/min per 1.73 m^2)	SD	95% CI		*P*-value[a]
					Lower limit	Upper limit	
Preoperation							
	30–49	50–69	−8.03	0.60	−9.22	−6.85	< 0.001
	30–49	70–89	−13.05	0.81	−14.64	−11.45	< 0.001
	50–69	70–89	−5.02	0.68	−6.36	−3.68	< 0.001
POD 0							
	30–49	50–69	−4.69	0.60	−5.87	−3.50	< 0.001
	30–49	70–89	−6.87	0.81	−8.47	−5.28	< 0.001
	50–69	70–89	−2.19	0.68	−3.53	−0.84	0.001
POD 1							
	30–49	50–69	−4.69	0.60	−5.87	−3.51	< 0.001
	30–49	70–89	−7.21	0.81	−8.81	−5.61	< 0.001
	50–69	70–89	−2.52	0.68	−3.86	−1.18	< 0.001
POD 3							
	30–49	50–69	−5.55	0.60	−6.74	−4.37	< 0.001
	30–49	70–89	−8.42	0.81	−10.01	−6.82	< 0.001
	50–69	70–89	−2.86	0.68	−4.20	−1.52	< 0.001
POD 6							
	30–49	50–69	−5.70	0.60	−6.88	−4.51	< 0.001
	30–49	70–89	−8.79	0.81	−10.39	−7.20	< 0.001
	50–69	70–89	−3.10	0.68	−4.44	−1.76	< 0.001
1 mo							
	30–49	50–69	−5.96	0.61	−7.15	−4.76	< 0.001
	30–49	70–89	−8.86	0.82	−10.47	−7.25	< 0.001
	50–69	70–89	−2.91	0.69	−4.26	−1.55	< 0.001
3 mo							
	30–49	50–69	−6.20	0.62	−7.41	−4.99	< 0.001
	30–49	70–89	−9.92	0.83	−11.55	−8.29	< 0.001
	50–69	70–89	−3.72	0.70	−5.09	−2.35	< 0.001
6 mo							
	30–49	50–69	−6.24	0.62	−7.46	−5.01	< 0.001
	30–49	70–89	−10.59	0.84	−12.23	−8.96	< 0.001
	50–69	70–89	−4.36	0.70	−5.72	−2.99	< 0.001
12 mo							
	30–49	50–69	−6.43	0.62	−7.65	−5.21	< 0.001
	30–49	70–89	−10.26	0.83	−11.89	−8.62	< 0.001
	50–69	70–89	−3.83	0.70	−5.20	−2.46	< 0.001
24 mo							
	30–49	50–69	−6.46	0.63	−7.69	−5.22	< 0.001
	30–49	70–89	−10.26	0.85	−11.91	−8.60	< 0.001
	50–69	70–89	−3.80	0.70	−5.18	−2.42	< 0.001
36 mo							
	30–49	50–69	−5.90	0.64	−7.15	−4.66	< 0.001
	30–49	70–89	−9.65	0.86	−11.34	−7.96	< 0.001
	50–69	70–89	−3.74	0.73	−5.17	−2.32	< 0.001
48 mo							
	30–49	50–69	−6.30	0.65	−7.58	−5.03	< 0.001
	30–49	70–89	−10.45	0.89	−12.20	−8.70	< 0.001
	50–69	70–89	−4.15	0.75	−5.62	−2.67	< 0.001
60 mo							
	30–49	50–69	−5.48	0.66	−6.78	−4.18	< 0.001
	30–49	70–89	−9.82	0.92	−11.64	−8.01	< 0.001
	50–69	70–89	−4.34	0.79	−5.89	−2.80	< 0.001
72 mo							
	30–49	50–69	−5.39	0.68	−6.72	−4.05	< 0.001
	30–49	70–89	−9.32	0.97	−11.22	−7.42	< 0.001
	50–69	70–89	−3.94	0.83	−5.56	−2.31	< 0.001
84 mo							
	30–49	50–69	−5.91	0.70	−7.29	−4.53	< 0.001

(Continued on following page)

Table 3. (Continued) Estimated glomerular filtration rate changes adjusted for sex

Time	Donor age groups		Difference (ml/min per 1.73 m^2)	SD	95% CI		P-value[a]
					Lower limit	Upper limit	
	30–49	70–89	−10.59	1.03	−12.60	−8.58	< 0.001
	50–69	70–89	−4.68	0.89	−6.42	−2.94	< 0.001
96 mo							
	30–49	50–69	−5.89	0.73	−7.32	−4.46	< 0.001
	30–49	70–89	−10.84	1.11	−13.01	−8.67	< 0.001
	50–69	70–89	−4.95	0.97	−6.84	−3.05	< 0.001
108 mo							
	30–49	50–69	−5.00	0.77	−6.51	−3.48	< 0.001
	30–49	70–89	−9.82	1.15	−12.07	−7.58	< 0.001
	50–69	70–89	−4.83	0.99	−6.76	−2.89	< 0.001
120 mo							
	30–49	50–69	−5.03	0.82	−6.64	−3.41	< 0.001
	30–49	70–89	−9.48	1.26	−11.94	−7.02	< 0.001
	50–69	70–89	−4.46	1.09	−6.60	−2.31	< 0.001
132 mo							
	30–49	50–69	−5.60	0.89	−7.34	−3.86	< 0.001
	30–49	70–89	−11.68	1.42	−14.46	−8.89	< 0.001
	50–69	70–89	−6.08	1.26	−8.54	−3.61	< 0.001
144 mo							
	30–49	50–69	−5.76	1.01	−7.75	−3.78	< 0.001
	30–49	70–89	−10.81	1.63	−14.01	−7.62	< 0.001
	50–69	70–89	−5.05	1.45	−7.90	−2.20	0.001

95% CI, 95% confidence interval; POD, postoperative day.
[a]Statistically significant results.

eGFR Changes

In Figure 2, we present the eGFR changes adjusted for sex among the 3 LKD groups. The eGFRs of LKDs aged 30 to 49 and 70 to 89 years were the highest and lowest, respectively, among the 3 LKD groups. Differences in eGFR among the 3 LKD groups that were unadjusted (Supplementary Table S2) and adjusted for sex (Table 3) showed significant differences at all time points. However, the eGFR improved slightly in all LKD groups after POD 6 (Figure 2).

Although the eGFR reduction between the preoperative period and POD 6 was the highest and lowest among LKDs aged 30 to 49 and 70 to 89 years, respectively, according to the unadjusted and adjusted analyses (Figure 3a, Supplementary Tables S3 and S4), the reduction rate of eGFR between the preoperative period and POD 6 was similar among the 3 LKD groups according to the adjusted analysis (Figure 3b and Supplementary Tables S5 and S6). The results of mixed model analyses of the impact

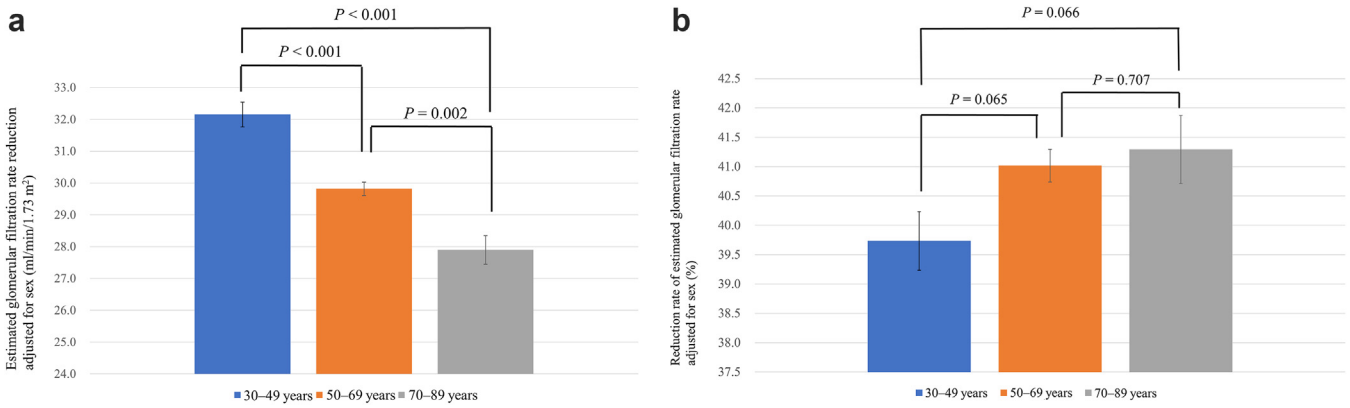

Figure 3. (a)Estimated glomerular filtration rate reduction between the preoperative period and postoperative day (POD) 6 adjusted for sex. $P <$ 0.001 for donors aged 30–49 vs. 70–89 years, $P = 0.002$ for donors aged 50–69 vs. 70–89 years, and $P < 0.001$ for donors aged 30–49 vs. 50–69 years. (b) Reduction rate of estimated glomerular filtration rate between the preoperative period and postoperative day (POD) 6 adjusted for sex. $P = 0.066$ for donors aged 30–49 vs. 70–89 years, $P = 0.707$ for donors aged 50–69 vs. 70–89 years, $P = 0.065$ for donors aged 30–49 vs. 50–69 years.

Table 4. Mixed model analysis of the impact of donor age on estimated glomerular filtration rate improvement after postoperative day 6

	Unadjusted					Adjusted for sex				
			95% CI					95% CI		
	Estimate	SD	Lower limit	Upper limit	*P*-value	Estimate	SD	Lower limit	Upper limit	*P*-value
Donor age group					0.027[a]					0.007[a]
30–49 yr	ref					ref				
50–69 yr	−0.248	0.263	−0.764	0.268	0.345	−0.275	0.259	−0.784	0.233	0.289
70–89 yr	−0.928	0.355	−1.624	−0.231	0.009[a]	−1.074	0.351	−1.763	−0.385	0.002[a]

95% CI, 95% confidence interval; ref, reference.
[a]Statistically significant results.

of LKD groups on eGFR improvement after POD 6 are shown in Table 4. Significantly low eGFR improvement among LKDs aged 70 to 89 years was indicated by the unadjusted ($P = 0.009$; estimate: −0.928; 95% confidence interval: −1.624 to −0.231) and adjusted ($P = 0.002$; estimate: −1.074; 95% confidence interval: −1.763 to −0.385) analyses.

Pathological Findings of the Baseline Biopsy Performed 1 Hour After Reperfusion

In Table 5, we present the pathological findings of the baseline biopsy performed 1 hour after LDKT. The scores of interstitial fibrosis, tubular atrophy, and arteriolar hyalinosis were significantly higher among LKDs aged 70 to 89 years compared to those of the other LKD groups. Among the 3 LKD groups, glomerular sclerosis was most frequently identified among LKDs aged 70 to 89 years. The biopsy results showed that the glomerular sclerosis incidence was significantly higher among LKDs aged 70 to 89 years.

Table 5. Results of the baseline biopsy performed 1 h after kidney transplantation

	30–49 yr	50–69 yr	70–89 yr	
	n = 244	*n* = 803	*n* = 179	*P*-value
ci score, *n* (%)				
0	234 (97.1)	691 (87.0)	141 (79.7)	<0.001[a]
1	7 (2.9)	98 (12.3)	35 (19.8)	
2	0	5 (0.6)	1 (0.6)	
ct score, *n* (%)				
0	197 (81.7)	453 (57.1)	73 (41.2)	<0.001[a]
1	44 (18.3)	336 (42.3)	104 (58.8)	
2	0	5 (0.6)	0	
ah score, *n* (%)				
0	175 (72.6)	407 (51.3)	84 (47.5)	<0.001[a]
1	43 (17.8)	215 (27.1)	45 (25.4)	
2	21 (8.7)	128 (16.1)	43 (24.3)	
3	2 (0.8)	44 (5.5)	5 (2.8)	
Glomerulosclerosis, *n* (%)	105 (43.6)	576 (72.5)	146 (82.5)	<0.001[a]
Rate of glomerulosclerosis according to the biopsy specimen results (%), mean (SD)	3.8 (5.7)	10.3 (11.1)	14.2 (12.4)	<0.001[a]

ah, arteriolar hyalinosis; ci, interstitial fibrosis; ct, tubular atrophy.
[a]Statistically significant results.

ESRD

During the observation period, ESRD was not identified among the 3 LKD groups.

Donor Mortality Rate

Significant differences in mortality rates were identified among the 3 LKD groups during the observational period. The mortality rate was the highest among LKDs aged 70 to 89 years (Figure 4). A total of 19 donors died as a result of different causes. In LKDs aged 50 to 69 years, deaths attributable to lung cancer ($n = 1$), pancreatic cancer ($n = 1$), multiple organ failure ($n = 1$), cerebral infarction ($n = 1$), abdominal aortic aneurysm rupture ($n = 1$), amyotrophic lateral sclerosis ($n = 1$), brain cancer ($n = 1$), heart failure ($n = 1$), suspected suicide ($n = 1$), and unknown causes ($n = 3$) were observed. Deaths attributable to colon cancer ($n = 2$), prostate cancer ($n = 1$), pancreatic cancer ($n = 1$), aspiration pneumonia ($n = 1$), renal pelvic cancer ($n = 1$), and an unknown cause ($n = 1$) were observed among LKDs aged 70 to 89 years.

DISCUSSION

This study demonstrated similar surgical outcomes, including graft quality and adverse events, among the 3 LKD groups. Although eGFR changes and improvement in LKDs aged 70 to 89 years were the lowest among the 3 LKD groups, eGFR improved slightly after POD 6, and ESRD was not observed in any group during the observation period. Among the 3 LKD groups, the mortality rate of LKDs aged 70 to 89 years was the highest.

This is the first study to meticulously demonstrate preoperative comorbidities, including hypertension, dyslipidemia, glucose intolerance, and obesity, among LKDs of different age groups. These comorbidities may have increased the incidences of perioperative adverse events and caused inferior kidney function, ESRD, and high mortality rates in other studies.[9-12,14-19] Elderly individuals are at a high risk for perioperative adverse events because these comorbidities increase as patients age.[20,21] During this study, the incidences of hypertension, dyslipidemia, and glucose intolerance increased

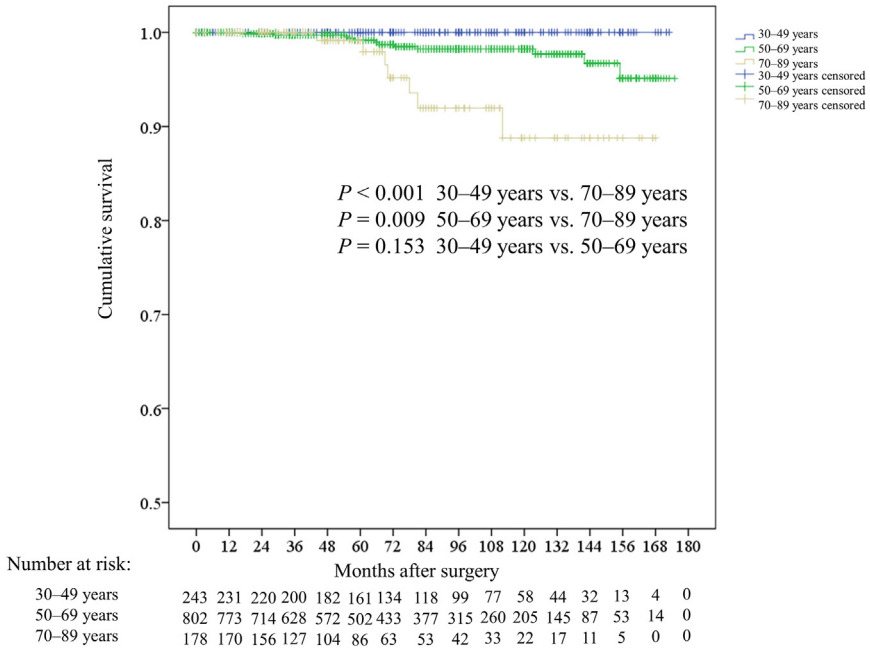

Figure 4. Postoperative mortality rate of donors. The Bonferroni method was used for multiplicity adjustment. $P < 0.001$ for donors aged 30–49 vs. 70–89 years, $P = 0.009$ for donors aged 50–69 vs. 70–89 years, and $P = 0.153$ for donors aged 30–49 vs. 50–69.

with the donor's age, consistent with the results of previous studies.[22,23] However, obesity was observed more often among young LKDs than among elderly LKDs. The preoperative blood pressure, serum lipid metabolism markers, and serum glycometabolism markers were significantly inferior among LKDs aged 70 to 89 years. However, preoperatively, these comorbidities were well-managed with medication within the ranges indicated by the Japanese LKD guidelines, and these administration rates also increased with donor age.[2,3] Under these well-managed conditions, donor nephrectomy was performed for all LKD groups.

This study demonstrated intraoperative and postoperative results, such as graft quality and adverse events. Surgery was safely performed for the 3 LKD groups without any significant differences in graft quality and adverse events; however, significantly longer arterial lengths and heavier kidney weights were observed among LKDs aged 70 to 89 years. Surgery-related death was not observed in any group. Although previous reports defined elderly donors as those older than 55 to 65 years, perioperative complications after donor nephrectomy did not increase.[4–6] During this study, surgery results of the donors were similar among all groups. This indicated that age 70 years or older did not impair safe donor nephrectomy, although preoperative comorbidities were significantly more common among those aged 70 to 89 years. The cardiovascular system, pulmonary function, kidney function, and general health of LKDs were fully evaluated before surgery.[24] Donor nephrectomy was indicated for LKDs with either no preoperative comorbidities or preoperative comorbidities that were managed per the guidelines before surgery.[2,3,24] These preoperative evaluations and the management of LKDs might have led to the safety of donor nephrectomy, even among LKDs aged 70 years or older. However, the impact of kidney grafts from LKDs aged 70 to 89 years on the outcomes of recipients is also essential. This issue has been investigated previously,[25] and it was observed that LDKTs involving LKDs aged 70 to 89 years and recipients with a donor-recipient age difference of 10 to 15 years (i.e., elderly recipients) exhibited the lowest graft survival and highest mortality rates compared to those involving LKDs aged 30 to 49, 50 to 69, and 70 to 89 years and recipients with donor-recipient age differences of 10 to 15 or 15 to 40 years.[25]

A comparison of the eGFR changes among the 3 LKD groups showed that they had similarly declined by POD 6 and improved gradually after POD 6. These trends of eGFRs are similar to those previously reported.[2,26] However, no studies have investigated the detailed eGFR changes after donor nephrectomy among LKDs stratified by age. This study meticulously investigated the differences in eGFRs among LKD age groups and eGFR improvements after donor nephrectomy. Among the LKD groups, the eGFRs of those aged 70 to 89 years were the lowest at all time points, including the preoperative period. However, the eGFR after POD 6 improved slightly in all groups.

The similar reduction rate of eGFR among the 3 LKD groups can explain the highest and lowest eGFR reduction among LKDs aged 30 to 49 years and LKDs aged 70 to 89 years, respectively, between the

preoperative period and POD 6, because LKDs aged 30 to 49 and 70 to 89 years had the highest and lowest preoperative eGFRs, respectively. However, whereas LKDs aged 30 to 49 years experienced the highest improvement in postoperative eGFRs, those aged 70 to 89 years experienced the lowest improvement in postoperative eGFRs. The postoperative eGFR reduction based on the preoperative eGFR and the lowest postoperative eGFR improvement could contribute to the lowest eGFR changes at all time points in LKDs aged 70 to 89 years. The results of the baseline biopsy could explain these findings. The interstitial fibrosis scores, tubular atrophy scores, arteriolar hyalinosis scores, and glomerular sclerosis were the lowest among LKDs aged 30 to 49 years and highest among those aged 70 to 89 years, which might have resulted in the highest and lowest preoperative eGFRs, eGFR changes, and eGFR improvements among LKDs aged 30 to 49 and 70 to 89 years, respectively. These baseline biopsy findings might be attributable to age and preoperative comorbidities, as indicated by a previous study that observed an amplified effect of comorbid conditions.[10] However, the improvement in postoperative eGFR among LKDs aged 30 to 49 years was only approximately 5.7 ml/min per 1.73 m^2 during 12 years after donor nephrectomy.

ESRD was not identified in any group during the observation period. A previous study found that the ESRD rate of LKDs was higher than that of healthy controls at 15 years after surgery.[27,28] However, ESRD in LKDs aged 70 years or older has not been previously investigated, possibly because of the differences in life expectancy among races and countries. The association between the remaining duration of life and time to ESRD should be investigated. In Japan, the average life expectancy was 81.5 years for men and 86.9 years for women in 2019.[29] Considering the life expectancy, the observation period should be at least 10 to 15 years to enable a sufficient evaluation of ESRD in LKDs aged 70 years or older. Although the short-term results of this study were excellent, studies with longer follow-up periods are needed.

Mortality rates were significantly higher for LKDs aged 70 to 89 years than for other LKD groups, although the mortality rates compared with healthy age-matched controls were not investigated in this study. Previously, the 10-year mortality rates of LKDs aged 70 years or older were superior to those of healthy matched controls.[8] However, the mortality rates of LKDs aged 70 years or older were not compared to those of younger LKDs in the previous study.[8] Despite the short observation period, we demonstrated that LKDs aged 70 to 89 years had inferior mortality than those of other LKD groups. This result is rational, considering the life expectancy of the Japanese population. However, the causes of death are important. During this study, deaths of LKDs were not caused by ESRD, but some unknown causes of death were identified. Among the 1226 LKDs included in this study, 19 (1.5%) died. This incidence is acceptable; however, it is too low to investigate for causative factors other than age. Large-scale prospective studies with longer observation periods are expected.

Considering the eGFR changes, ESRD risk, and mortality rates, the indications for preoperative eGFRs for LKDs should be optimized. LKDs aged 30 to 49 years have a life expectancy of approximately 30 to 60 years; furthermore, their eGFR reduction between the preoperative period and POD 6 was the highest, and their eGFR improvement was sluggish thereafter. The preoperative eGFRs of LKDs aged 30 to 49 years should be strictly followed according to the indications for preoperative eGFR (>80 ml/min per 1.73 m^2) provided by the LKD guidelines in Japan.[2,3] However, for LKDs aged 70 to 89 years, the life expectancy is approximately 10 to 15 years, and their eGFR reduction between the preoperative period and POD 6 was the lowest, although their eGFR improvement was the most sluggish among the 3 LKD groups. These results support the previous guidelines provided by the British Transplant Society, Canadian Transplant Society, and European Renal Best Practice, which indicated that the preoperative eGFRs of LKDs should not be the same and should be adapted according to the age of the LKDs to increase the indications for LKD. However, according to the previous guidelines provided by Kidney Disease Improving Global Outcomes 2017 and Japan, the indications for preoperative eGFRs are the same for all ages.[2,3,24,30–32]

This study was limited by its retrospective nature, the lack of comparison with a healthy population, and low incidence of events, including ESRD and death. Prospective investigations of the impact of donor nephrectomy on a large population of elderly LKDs aged 70 years or older with long observation periods, including comparison with a healthy population, are warranted.

In conclusion, donor nephrectomy can be performed safely for LKDs aged 70 years or older. Despite the low eGFR changes and improvement after donor nephrectomy, LKDs aged 70 years or older can maintain their kidney function without ESRD. Regarding life expectancy, LDKTs involving LKDs aged 70 years or older are associated with favorable outcomes. The results of this study may aid in the discovery of optimal indications for preoperative eGFRs of LKDs and increase the number of eligible LKDs.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

AUTHOR CONTRIBUTIONS

TH designed the study, acquired data, interpreted the results, and drafted the manuscript; TH, OM, and YH acquired data; KF, NG, TI, SN, AT, and TK interpreted the results; KU and YW approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Age distribution of living kidney donors aged 70 to 89 years.

Table S1. Clavien–Dindo grade for postoperative adverse events.

Table S2. Unadjusted estimated glomerular filtration rate changes.

Table S3. Unadjusted differences in estimated glomerular filtration rates from postoperative day 6.

Table S4. Differences in estimated glomerular filtration rates from postoperative day 6 adjusted for sex.

Table S5. Unadjusted differences in the reduction rate of estimated glomerular filtration rate from preoperation.

Table S6. Differences in the reduction rate of estimated glomerular filtration rates from preoperation, adjusted for sex.

The Strengthening the Reporting of Observational Studies in Epidemiology statement.

REFERENCES

1. Hourmant M, Lerat L, Karam G. Donation from old living donors: how safe is it? *Nephrol Dial Transplant*. 2013;28:2010–2014. https://doi.org/10.1093/ndt/gft069
2. Hiramitsu T, Tomosugi T, Futamura K, et al. Preoperative comorbidities and outcomes of medically complex living kidney donors. *Kidney Int Rep*. 2019;5:13–27. https://doi.org/10.1016/j.ekir.2019.10.002
3. Morozumi K, Ichimaru N, Katayama A, et al. Living kidney donor guideline. Accessed March 1, 2023. https://cdn.jsn.or.jp/guideline/pdf/Donor-guidelines.pdf
4. Minnee RC, Bemelman WA, Polle SW, et al. Older living kidney donors: surgical outcome and quality of life. *Transplantation*. 2008;86:251–256. https://doi.org/10.1097/TP.0b013e31817789dd
5. O'Brien B, Mastoridis S, Sabharwal A, Hakim N, Taube D, Papalois V. Expanding the donor pool: living donor nephrectomy in the elderly and the overweight. *Transplantation*. 2012;93:1158–1165. https://doi.org/10.1097/TP.0b013e31824ef1ae
6. Jacobs SC, Ramey JR, Sklar GN, Bartlett ST. Laparoscopic kidney donation from patients older than 60 years. *J Am Coll Surg*. 2004;198:892–897. https://doi.org/10.1016/j.jamcollsurg.2004.02.018
7. Gero D, Dib F, Matter M, et al. Outcomes of kidney donors over 60 years old: a single-center cohort study. *World J Surg*. 2017;41:2940–2948. https://doi.org/10.1007/s00268-017-4071-y
8. Berger JC, Muzaale AD, James N, et al. Living kidney donors ages 70 and older: recipient and donor outcomes. *Clin J Am Soc Nephrol*. 2011;6:2887–2893. https://doi.org/10.2215/CJN.04160511
9. Epstein M. Aging and the kidney. *J Am Soc Nephrol*. 1996;7:1106–1122. https://doi.org/10.1681/ASN.V781106
10. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) hospital infection control practices advisory committee. *Am J Infect Control*. 1999;27:97-96. https://doi.org/10.1016/S0196-6553(99)70088-X
11. Yoon YE, Choi KH, Lee KS, Kim KH, Yang SC, Han WK. Impact of metabolic syndrome on postdonation renal function in living kidney donors. *Transplant Proc*. 2015;47:290–294. https://doi.org/10.1016/j.transproceed.2014.10.051
12. Ohashi Y, Thomas G, Nurko S, et al. Association of metabolic syndrome with kidney function and histology in living kidney donors. *Am J Transplant*. 2013;13:2342–2351. https://doi.org/10.1111/ajt.12369
13. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. 2018 Reference guide to the Banff Classification of renal allograft pathology. *Transplantation*. 2018:1795–1814. https://doi.org/10.1097/TP.0000000000002366
14. Nogueira JM, Weir MR, Jacobs S, et al. A study of renal outcomes in obese living kidney donors. *Transplantation*. 2010;90:993–999. https://doi.org/10.1097/TP.0b013e3181f6a058
15. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009;360:459–469. https://doi.org/10.1056/NEJMoa0804883
16. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2011;6:2364–2373. https://doi.org/10.2215/CJN.02180311
17. Beddhu S, Kimmel PL, Ramkumar N, Cheung AK. Associations of metabolic syndrome with inflammation in CKD: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis*. 2005;46:577–586. https://doi.org/10.1053/j.ajkd.2005.06.014
18. Pammer LM, Lamina C, Schultheiss UT, et al. Association of the metabolic syndrome with mortality and major adverse cardiac events: a large chronic kidney disease cohort. *J Intern Med*. 2021;290:1219–1232. https://doi.org/10.1111/joim.13355
19. Matas AJ, Berglund DM, Vock DM, Ibrahim HN. Causes and timing of end-stage renal disease after living kidney donation. *Am J Transplant*. 2018;18:1140–1150. https://doi.org/10.1111/ajt.14671

20. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20:12. https://doi.org/10.1007/s11906-018-0812-z

21. Tzimas P, Petrou A, Laou E, et al. Impact of metabolic syndrome in surgical patients: should we bother? *Br J Anaesth*. 2015;115:194–202. https://doi.org/10.1093/bja/aev199

22. Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016. *JAMA*. 2020;323:2526–2528. https://doi.org/10.1001/jama.2020.4501

23. Kuzuya M, Ando F, Iguchi A, Shimokata H. Age-specific change of prevalence of metabolic syndrome: longitudinal observation of large Japanese cohort. *Atherosclerosis*. 2007;191:305–312. https://doi.org/10.1016/j.atherosclerosis.2006.05.043

24. Lentine KL, Kasiske BL, Levey AS, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation*. 2017;101(8S suppl 1):S1–S109. https://doi.org/10.1097/TP.0000000000001769

25. Hiramitsu T, Tomosugi T, Futamura K, et al. Adult living-donor kidney transplantation, donor age, and donor-recipient age. *Kidney Int Rep*. 2021;6:3026–3034. https://doi.org/10.1016/j.ekir.2021.10.002

26. Lam NN, Lloyd A, Lentine KL, et al. Changes in kidney function follow living donor nephrectomy. *Kidney Int*. 2020;98:176–186. https://doi.org/10.1016/j.kint.2020.03.034

27. Mjøen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. *Kidney Int*. 2014;86:162–167. https://doi.org/10.1038/ki.2013.460

28. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. *JAMA*. 2014;311:579–586. https://doi.org/10.1001/jama.2013.285141

29. World Health Organization (WHO). Life expectancy and Healthy life expectancy data by country. Accessed July 9, 2023. http://apps.who.int/gho/data/node.main.SDG2016LEX?lang=en

30. British Transplantation Society. BTS/RA living donor kidney transplantation guidelines 2018. Accessed June 2, 2023. https://bts.org.uk/wp-content/uploads/2018/07/FINAL_LDKT-guidelines_June-2018.pdf

31. Richardson R, Connelly M, Dipchand C, et al. Kidney paired donation protocol for participating donors 2014. *Transplantation*. 2015;99(10 suppl 1):S1–S88. https://doi.org/10.1097/TP.0000000000000918

32. European Renal Best Practice Transplantation Guideline Development Group. European Renal Best Practice Transplantation Guideline Development Group. European renal best practice transplantation guideline development group. ERBP guideline on the management and evaluation of the kidney donor and recipient. *Nephrol Dial Transplant*. 2013;28(suppl 2):ii1–ii71. https://doi.org/10.1093/ndt/gft218