Increasing Use of the Expanded Criteria for Living Kidney Donation and Good Outcomes of Living Kidney Donors in Korea

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ABSTRACT

Background. Donor shortage for kidney transplantation may increase the number of expanded-criteria living donors (ECLDs). We investigated recent trends for ECLD use and the long-term outcomes of living kidney donors.

Methods. We retrospectively analyzed medical records of 1,144 living kidney donors who donated at the Seoul National University Hospital from 1993 to 2015. The expanded criteria for living donation allow the following: age $\geq$60 years, body mass index $>$30 kg/m^2, history of hypertension, estimated glomerular filtration rate $<$80 mL/min, proteinuria or microscopic hematuria, and fasting glucose $>$100 mg/dL.

Results. The mean age of donors was 40.7 $\pm$ 10.8 years, and there were 600 women (52.4%). A total of 466 donors (40.7%) met the ECLD criteria, and the proportion of ECLDs increased over time. Only 5 donors died after donation over a median follow-up of 7 years. No donor developed end-stage renal disease (ESRD). A urine protein-creatinine ratio $\geq$0.3 g/gCr was found in 14 patients and was more common in the ECLDs than in the standard-criteria living donors. The follow-up loss rate of donors was 59.3% at 5 years.

Conclusions. Both mortality and ESRD were very rare in carefully selected living kidney donors. However, living donors should be followed more carefully, because the follow-up loss rate was very high and ECLDs are increasingly used.

LIVING donor kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). Living-donor kidney transplant recipients have better long-term graft survival and quality of life than deceased-donor kidney transplant recipients [1]. More than 27,000 living kidney donations are performed worldwide every year [2]. Although long-term studies have not demonstrated an additional mortality risk for living kidney donors [3], they have demonstrated an increased risk for ESRD, with the highest rate observed among older donors [4].

Severe organ shortage led to kidney donation by donors with some medical abnormalities as a result of so-called expanded-criteria living donors (ECLDs). Old age, obesity, hypertension, decreased renal function, proteinuria, and microscopic hematuria are carefully evaluated to assess the possibility of such individuals serving as ECLDs. Donor safety is a very important issue for ECLDs [5]. Donors with specific medical abnormalities need careful postoperative management, including assessment of long-term outcomes [6]. However, the safety and efficacy of being an ECLD remains unclear despite the growth of ECLDs among older donors. Furthermore, outcomes of living kidney donors, especially ECLDs, have not been well studied in Asian populations. We therefore aimed to investigate the recent trends in ECLD use and the long-term outcomes of living kidney donors in Korea.

The first two authors contributed equally to this study.

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METHODS

Study Design and Definitions

We retrospectively studied 1,144 patients who underwent kidney donation from 1993 through 2015 at Seoul National University Hospital in Korea. Review and analysis of patient clinical records was undertaken with the approval of the Institutional Review Board. The observation period started at the time of kidney transplantation and ended at the time of the most recent follow-up visit, the date of initiation of dialysis, or the date of patient death. We linked donor information to death certificate data from Korea's National Statistical Office. Furthermore, we obtained ESRD data from the Health Industry Representatives Association of Korea. Therefore, there were no missing data for either mortality or follow-up after donation. The primary outcome was all-cause mortality of living kidney donors. The secondary outcomes were development of ESRD, proteinuria, and hypertension. The prevalence of ECLD use during the study period was also assessed.

The estimated glomerular filtration rate (eGFR) was calculated based on the Modification of Diet in Renal Disease formula and normalized with the use of mean GFR by age group [7]. Chronic kidney disease (CKD) stage was classified based on the Kidney Disease: Improving Global Outcomes 2012 guidelines [8]. Follow-up loss was defined for individuals with no medical records for the previous 2 years. ECLDs were defined as having any of the following before donation: (1) age: >60 years; (2) obesity: body mass index >30 kg/m^2; (3) hypertension: blood pressure ≥140/90 mm Hg or the use of antihypertensive medication; (4) low eGFR: <80 mL/min/1.73 m^2; (5) proteinuria: spot urine protein-creatinine ratio (UPCR) ≥150 mg/gCr; (6) microscopic hematuria: >10/high-power field; and (7) impaired fasting glucose tolerance: fasting glucose >100 mg/dL.

Statistical Analyses

Mean values and standard deviations were calculated for continuous variables, and categoric variables were presented as percentages. The Student *t* test and chi-squared test were used for continuous and categoric variables, respectively. Trends for ECLD utilization were analyzed by means of the Cochran-Armitage trend test. Kaplan-Meier analysis was used for calculation of survival rates, and the log rank test was used to compare survival rates among different groups. *P* values of <.05 were considered to be statistically significant. The Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Chicago, Illinois) was used throughout.

RESULTS

Characteristics of Living Donors

The mean age of the 1,144 donors was 40.7 ± 10.8 years, and there were 600 female donors (52.4%). Fig 1 shows the clinical characteristics of living kidney donors. A total of 466 (40.7%) met the ECLD criteria among the 1,144 living donors. The proportions of each medical abnormality in the ECLDs were as follows: old age (2.1%), obesity (3.1%), hypertension (3.8%), low eGFR (20.6%), proteinuria (2.3%), microscopic hematuria (1.3%), and impaired fasting glucose (23.5%). Donations from old, hypertensive, obese patients and from patients with impaired fasting glucose, proteinuria, or hematuria increased over the study period (Table 1). The overall proportion of ECLDs has increased, accounting for 22.3% in the 1990s but accounting for >40% by the 2010s (Table 1).

Outcomes of Living Kidney Donors

Among the 1,144 living kidney donors, 5 died over a median follow-up of 7 years (Fig 2A). The causes of death were as follows: cerebrovascular accident, gastrointestinal malignancy, complication of diabetes mellitus, head trauma, and myocardial infarction. There was no difference in mortality ($P = .180$) between the ECLDs and the standard-criteria living donors (SCLDs). No donor required dialysis or transplantation at a median follow-up of 7 years. Renal function decreased during the 1st year and then stabilized. A total of 95 and 2 patients developed CKD 3b and CKD 4, respectively, in the ECLD group. There was a significant increase in the development of CKD 3b in the ECLD group than in the SCLD groups ($P < .001$).

The follow-up loss rate for the living kidney donors in the Seoul National University Hospital was very high. It reached 59.3% at 5 years, and 69.4% at 10 years (Fig 2B). Fourteen (3.42%) donors in the ECLD group had a UPCR ≥0.3 g/gCr after donation, whereas there was no development of this level of proteinuria in the SCLD group ($P = .001$; log rank test). Blood pressure >140/90 mm Hg was observed after donation in 24 (6.03%) and 21 (4.48%) donors in the ECLD and SCLD groups, respectively, and there was no difference in the prevalence of hypertension ($P = .812$; log rank test). Blood pressure >160/100 mm Hg was observed in 2 (0.5%) and 1 (0.21%) donors in the ECLD and SCLD groups, respectively, and these differences were not significantly different ($P = .770$; log rank test).

DISCUSSION

This study focused on the trends for ECLDs and post-donation medical problems, such as hypertension, proteinuria, ESRD, and all-cause mortality, during long-term follow-up in Korean living kidney donors. We demonstrated that ECLDs have increased during the past 20 years in Korea and that overall mortality and ESRD risk was very low in carefully selected living kidney donors.

The availability of donors is a major limiting factor in living kidney transplantation. As the discrepancy between the supply and demand for donor organs became more aggravated, the clinical application of ECLDs was tried. The definition of an ECLD, a so-called marginal living donor, has been proposed in several studies [9–11]. With an aging population, the pools of both older kidney transplant candidates and donors are likely to increase, leading to a potential increase in the use of older living kidney donors [12]. In parallel, ECLDs have increased since 2000 in the present study.

Hypertension is thought to be one of the major concerns following living kidney donation. A meta-analysis showed that kidney donors may have a 5 mm Hg greater increase in blood pressure within 5–10 years after donation than that anticipated with normal aging [13]. The risk of proteinuria

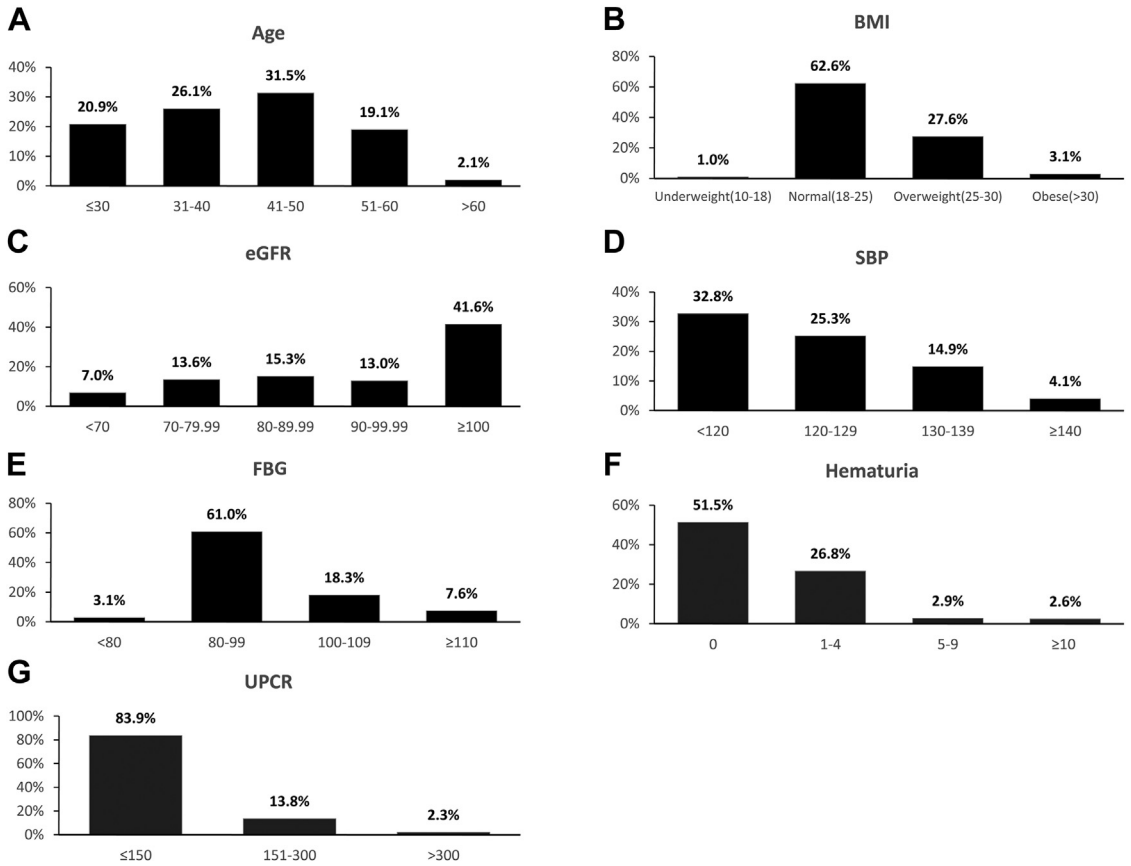

Fig 1. Clinical characteristics of living kidney donors: (**A**) age; (**B**) body mass index (BMI); (**C**) estimated glomerular fitration rate (eGFR); (**D**) systolic blood pressure (SBP); (**E**) fasting blood glucose (FBG); (**F**) degree of hematuria in living donors; (**G**) urine protein-creatinine ratio (UPCR).

or albuminuria is controversial. Some studies reported an incidence of proteinuria of ≥20%, whereas the incidence was ≤5% in others [13–17]. A meta-analysis showed a small increase of proteinuria among kidney donors [18]. In the present study, we could not assess the relative risks for hypertension or proteinuria after donation owing to a lack of control groups. However, we compared risks between the ECLD and SCLD groups and found that post-donation proteinuria was more common in the ECLD group. Therefore, donors' proteinuria should be followed more carefully, especially among ECLDs.

The overall incidence of ESRD among living kidney donors during the first 10 years after donation has been reported to be low as 0.2%–0.5% [14,19,20]. Several studies about ESRD risk have the limitations of high follow-up loss and short follow-up period [21]. There was

Table 1. Trends for ECLD Utilization

Expanded Criterion	Year				Total (n = 1,144)	*P* Value*
	1993–1999 (n = 206)	2000–2004 (n = 207)	2005–2009 (n = 270)	2010–2015 (n = 461)		
Age >60 y	2.0%	0.0%	0.4%	4.1%	2.1%	.009
HTN	0.5%	0.5%	3.7%	6.9%	3.8%	<.001
BMI >30 kg/m^2	1.9%	1.9%	3.0%	4.1%	3.1%	.073
FBG >100 mg/dL	11.7%	27.5%	24.8%	26.2%	23.5%	.001
eGFR <80 mL/min/1.73 m^2	10.7%	18.4%	30.7%	14.0%	18.4%	.003
UPCR >150 mg/g Cr	1.5%	1.9%	2.6%	2.6%	2.3%	.328
Hematuria >10/HPF	0.5%	0.0%	0.7%	2.6%	1.3%	.006
ECLD	22.3%	42.0%	49.6%	43.2%	40.7%	<.001

Abbreviations: HTN, hypertension; BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; UPCR, urine protein creatinine ratio; Cr, creatinine; HPF, high-power field; ECLD, extended criteria of living donor.

**P* for trend according to the Cochran Armitage trend test.

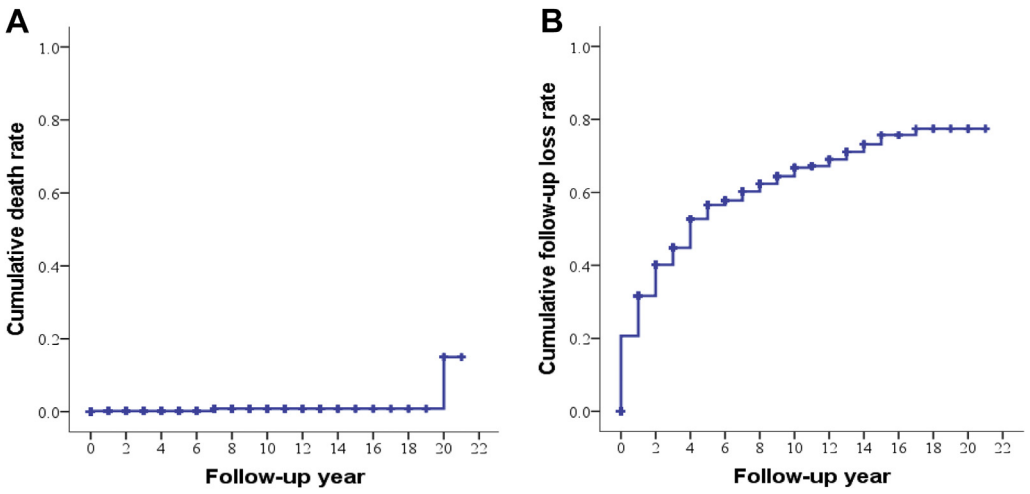

Fig 2. Outcomes of living kidney donors: (**A**) cumulative death rate; (**B**) cumulative follow-up loss rate.

no ESRD development in 1,144 donors at a median follow-up of 7 years in the present study, where ESRD incidence was analyzed without missing data with the use of a national database. Although a Norwegian study reported a much higher incidence of ESRD [22], a few confounding factors, such as difference in baseline ages, different degree of complete follow-up, and different eras, could have led to those results. The mortality rate in the present study was similar to a large-scale study in the United States [3] and less than the Norwegian study [22]. Overall, the risk for ESRD and mortality is low, and most potential living donors are willing to accept the very low risk when the recipient is a family member or a close friend. However, potential donors should be informed of increased risks, however small.

There are a few limitations in the present study. First, it was a small-scale retrospective study with a high follow-up loss rate, although we tried to overcome this limitation partially by using a national statistical database. Second, we performed a single-arm study without either a healthy control group or a control group from the general population, and therefore we could not compare risks associated with donation compared with that for control groups. Third, only a single tertiary referral center participated in this study. Therefore, further multicenter, prospective studies with control groups and lower loss to follow-up rates are needed to confirm the findings of the present study. Nevertheless, the present study was the first study to investigate the long-term outcomes of Asian living kidney donors, and it successfully demonstrated that both mortality and ESRD risk are very low in Asian populations, similar to the risk in Western countries.

In conclusion, both mortality and progression to ESRD were very rare in carefully selected kidney donors, and most donors had preserved renal function without proteinuria. However, living donors should be followed more carefully, because the follow-up loss rate was high and the use of ECLDs who have greater risks for post-donation complications is increasing.

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