# Postoperative kidney function in Japanese living kidney donors

# 日本人生体腎移植ドナーの腎提供後腎機能

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# Contents

**Abstract**

Few investigations about safety of post-donation living kidney donors have been conducted, especially in Japanese. I reviewed medical records of 1519 living kidney donors who donated in Tokyo women's medical university hospital. Using all the data or partially, I investigated their post-donation trends in glomerular filtration rate (GFR) and risk for kidney disease such as persistent proteinuria or progressive renal dysfunction, and end-stage renal disease (ESRD). Most (> 90%) donors developed GFR corresponding to chronic kidney disease (CKD) stage3, however, showed stabilized trends in GFR until 3 years after donation, distinct from those of CKD patients in the general population. Meanwhile, donors who developed ESRD had maintained GFR for long period, but which started to decline after having comorbidities known as progression factors of CKD. They had higher incidence of protenuria, acute cardiovascular events, severe infection, and hospitalization due to accelerating factors of CKD than those not developing ESRD. Furthermore, donors having persistent glomerular hematuria both pre- and post-donation had significantly higher risk for kidney disease after donation. Kidney donors might be inappropriate for labeling as CKD, however, they should be carefully evaluated and followed for long period with attention on CKD risk factors, especially those with glomerular hematuria.

## Introduction

For patients with end-stage renal disease (ESRD), living kidney transplantation (LKT) is the only therapeutic modality to effect a permanent cure, showing a steady increase in number (1) in parallel with the global rise in the prevalence of ESRD (2). The first case of LKT was performed between twins in 1954 (3).

According to development of immunosuppresive agents and methods for using them, both patient and graft survival have been notably improved, the latest rate of which in Japan have been reported as 90.7% and 90.9% at 5 years after transplantation, respectively (http://www.asas.or.jp/jst/pdf/fct2008.pdf ). Thus, organ transplantation is described as a medical miracle of the twentieth century, and LKT is currently one of the important options for renal replacement therapy.

On the other hand, since only few number of deceased kidney donation have been performed as compared with the needs for kidney transplantation all over the world, which should be essentially further advanced, the global shortage of organs for transplantation is more serious problems, including in Japan (http://www.asas.or.jp/jst/pdf/fct2008.pdf). As a result, many of unethical practices such as organ trafficking, transplant tourism, and commercialism have been recently reported. To address such urgent and growing problems, the declaration of Istanbul represented in 2008 demands to take the highest priority on the safety of donors, and to provide the proper care for living donors before, during and after donation (4) .

Before starting my investigations at 2006, few studies about the safety or prognosis of living kidney donors had been reported despite they are the main premise to perform LKT, especially in Japanese. It is warranted to investigate the detailed risk and prognosis of post-donation kidney donors themselves, to order to present that LKT is a medical practice on reasonable grounds. In particular, the proper criteria of the eligibility for living kidney donors, medical risks after donation and their predictive factors, and key point of management of kidney donors after donation still be the major problems to be elucidated.

Consequently, I have started investigations based on charts review about living kidney donors who donated in Department of surgery, Kidney center, Tokyo Women's Medical University Hospital, in which the largest number of LKT had been performed in Japan. Using all the data or partially, I conducted three clinical studies to address several unexplored issues of living kidney donors (approval number by ethical committee: 1607).

## Section 1

First, I surveyed actual condition of post-donation kidney donors in Japanese, which had been scarcely investigated, to clarify the levels of post-donation renal function and their trends after donation.

## Study No. 1: Very low but stable glomerular filtration rate after living kidney donation: Is the concept of “chronic kidney disease” applicable to kidney donors?

### Background

Living donor kidney transplantation can only be justified if otherwise healthy donors are guaranteed good health and well-being after donation (4). Many reports have suggested that their risks for perioperative complications (5, 6), short- and long-term renal death (7, 8), and mortality (9, 10) are negligibly low. Indeed, postoperative renal function of kidney donors was reported to be fairly stable as long as a few decades (10-12).

The threshold of renal function for eligibility for kidney donation is most often regarded as a glomerular filtration rate (GFR) of 80 ml/min/1.73m$^2$ (13), which has been recommended by the Amsterdam forum on the care of the live kidney donors (14, 15). This threshold, however, was determined by experience rather than solid evidence. Although a few but significant donors actually

confer a risk for developing progressive kidney dysfunction leading to end-stage kidney disease (16, 17), there are few investigations addressing exactly which level of preoperative GFR is appropriate for candidate as donors. Especially, renal prognosis of postoperative donors who developed lower GFR corresponding to advanced (stage 3 or more) chronic kidney disease (CKD) is still undetermined.

In general, GFR declines steadily with age (18-20). However, several reports have clarified that low GFR itself does not necessarily confer a bad renal prognosis unless it is accompanied by other renal risk of progression such as proteinuria, diabetes or hypertension. In this context, I assumed that kidney donors would not be necessarily at risk for progressive CKD even if with extremely low GFR, because renal progression risks had been excluded through pre-transplant donor evaluation. To prove this hypothesis, it seemed suitable to investigate Japanese kidney donors, since Japanese generally have a lower GFR (21) and Japanese donors are older (which means their renal function are potentially worse) than their Western counterparts. The aim of this study is to confirm the hypothesis that Japanese donors with a low preoperative GFR corresponding to CKD stage 3 or more does not show a functional decline with age.

## Methods

### *Study population*

I reviewed medical charts and identified 237 living kidney donors who underwent donor

nephrectomy at Tokyo Women's Medical University (TWMU) from February 2001 to December 2005. Because many donors were lost to follow-up despite of being encouraged to annual clinic visit, the number of those who had follow-up labs decreased with time, and I could identified only 162 and 77 donors who had been followed annually at least until 1 and 3 years after donation, respectively. I subsequently evaluate yearly changes in postoperative renal function of these 77 donors who was followed for at least 3 years.

***Assessment of kidney function***

An eligible renal function for living kidney donor in TWMU was equal to or more than a 2-hour creatinine clearance (Ccr) of 70 ml/min/1.73m$^2$ which was measured at outpatient clinic. In this study, I retrospectively evaluated the renal function of each donor with estimated GFR (eGFR) calculated by the abbreviated Modification of Diet in Renal Disease study equation using a coefficient of 0.881 to modify for the Japanese (22) at the time of this study, because the notion of CKD is established by the evaluation of renal function with eGFR. These measurements of serum creatinine levels were performed in the same laboratory.

In order to evaluate changes in postoperative renal function, the absolute yearly changes in eGFR was started to evaluate since 1 year after donation for avoiding the direct effect for renal function by heminephrectomy. I compared the changes in GFR of kidney donors with the reported value of those of the community-based general population in Japan (20) or of patients with CKD (23-25). Subsequently, since the clinical relevance of the absolute changes in mean eGFR is largely

affected by baseline eGFR, I additionally assessed the percent changes in mean eGFR; (mean absolute yearly change in eGFR / mean eGFR 1 year after donation). In view of undetermined effect of age to renal function in postoperative donors (26, 27), both absolute and percent changes were adjusted for age.

### *Statistical analysis*

Numbers were expressed as mean (standard deviation, SD) or median (interquartile range, IQR) values. For statistical analysis, the Student's t test or Mann-Whitney test were used to compare two independent variables when appropriate, and the z test was used when required to compare a reported value whose distribution was available. The paired t test was used to compare two matched variables in each subject. Comparison among variables divided into multi-groups was performed by analysis of variance (ANOVA). Two-sided P-values of less than 0.05 were considered as statistically significant. All statistical analyses were performed using JMP software (version 7.01, SAS Institute Inc.).

## Results

### *High prevalence of CKD stage 3 in postoperative donors*

Table 1 shows baseline characteristics of all donors (n = 237) in the preoperative evaluation. Males accounted for 43.9% (n = 104) of 237 patients and the median age was 56 years. While all

subjects fulfilled our criterion of renal function for donor eligibility (i.e. more than 70 ml/min/1.73m$^2$ of 2-hour Ccr), median value of renal function measured by *post hoc* evaluation with eGFR was significantly lower (70.6 ml/min/1.73m$^2$) than that by Ccr of 114 ml/min/1.73m$^2$ ($P < 0.001$).

In 162 donors followed at least until 1 year after donation, median age and eGFR at donation were 57 years (IQR, 49 to 64) and 70.4 ml/min/1.73m$^2$ (IQR, 63.2 to 78.1), respectively. Their baseline characteristics showed no significant difference from those in donors who dropped out of follow-up (data not shown). In *post hoc* evaluation of renal function by eGFR, 28 out of 162 (17.3%) had already been within CKD stage 3 before donation. Figure 1 showing the distribution of their eGFR 1 year after donation, with median eGFR of 46.2 ml/min/1.73m$^2$ (IQR, 41.7 to 51.0), surprisingly demonstrated that as much as 95% of postoperative donors were categorized into CKD stage 3. Even donors with eGFR less than 50 ml/min/1.73m$^2$ accounted for 66% of the population. Median absolute and percent decline in eGFR until 1 year after donation were 23.7 ml/min/1.73m$^2$ (IQR, 19.5 to 27.5) and 34.3% (IQR, 28.9 to 38.2), respectively, which were occurred at the time of heminephrectomy.

In 77 donors followed at least until 3 years after donation, median age and eGFR at donation were 57 years and 68.7 ml/min/1.73m$^2$, respectively. They also had lower median eGFR of 45.7 ml/min/1.73m$^2$ (IQR, 41.4 to 52.3) 1 year after donation, 96.1% of whom were regarded as CKD stage 3. A median eGFR 3 years after donation was 47.7 ml/min/1.73m$^2$ (IQR, 42.5 to 53.9), consequently showing high prevalence (92.2%) of CKD stage 3.

***Comparison of trends in GFR between postoperative donors and non-donor CKD patients in the general population***

Mean absolute changes in postoperative eGFR from 1 year to 3 years after donation in 77 donors had been stable showing moderate increment of 0.9 (SD, 1.7) ml/min/1.73m$^2$ per year. There was no significant difference in the increment between males and females, 0.95 (SD, 1.4) and 0.82 (SD, 1.9) ml/min/1.73m$^2$ per year, respectively (P = 0.83). As compared with CKD patients in the general population, in whom renal function declined with time as reported in the community-based studies (Table2), postoperative donors showed a significant increase in eGFR.

***Stabilized renal function in postoperative donors with extremely low GFR***

A trend in postoperative eGFR stratified by the level of preoperative eGFR is showed in Figure 2. Even donors categorized into the lowest GFR subgroup with pre-donation eGFR less than 60 ml/min/1.73m$^2$ had stable GFR until 3 years after donation. Similarly, this trend was shown in all the other categories, especially presenting significant improvement of eGFR in the second and third highest subgroup (48.9 to 50.5; P < 0.001 and 44.4 to 46.8; P = 0.02, respectively, ml/min/1.73m$^2$).

Table 3 and Table 4 show the mean absolute and percent changes in postoperative eGFR since 1 year after donation, with adjustment for age, stratified by the level of pre- and post-operative eGFR respectively. When categorized into 4 subgroups by preoperative eGFR (Table 3), 14 donors were included in the lowest subgroup of eGFR less than 60 ml/mi/1.73m$^2$ labeled as CKD stage 3,

resulting in increment of mean absolute and percent change in eGFR post-donation (0.5 ml/mi/1.73m$^2$ and 1.45 % per year, respectively). Each absolute and percent change was not inferior to those of donors of higher pre-donation eGFR categories, respectively (P = 0.66 and P = 0.50, tested by ANOVA). When categorized by postoperative eGFR (Table 4), mean eGFR 1 year after donation of 16 donors included in the lowest subgroup with eGFR less than 40 ml/mi/1.73m$^2$ showed only 36.1 (SD; 2.5) ml/mi/1.73m$^2$. Their mean absolute and percent change after donation, however, also presented increment of 0.87 ml/mi/1.73m$^2$ and 2.42 % per year, respectively. As compared with those in the other categories, each absolute and percent change had no significant difference (P = 0.25 and P = 0.14, tested by ANOVA). All the results remained same even when adjusted for age.

**Discussion**

I obtained several noteworthy results from my study. Japanese living kidney donors had high prevalence of CKD stage 3 or more after donation in the current recommended calculation of eGFR for Japanese, however, their renal function stabilized after donation, showing marked contrast with both CKD patients and the general population. It should be noted that even postoperative donors with very low eGFR less than 40 ml/min/1.73m$^2$ presented with a stable trend as well as those with higher eGFR.

The current concept of CKD is universally applied to anyone with eGFR less than 60

ml/min/1.73m$^2$, including pre- and postoperative donors. To my knowledge, my study showed the highest prevalence of advanced CKD in postoperative donors as compared with the previous reports, for example, 18% of a mean cumulative incidence of CKD stage 3 or more in a meta-analysis (28). This trend in Japanese donors has been reported by other institutes (Dr. Naganuma and Dr. Nagatani at Osaka City University in personal communication), which indicates that my result would not be produced by a center effect.

Several reasons can be explained for this high prevalence. First and most importantly, the Japanese have indigenously lower GFR than other races (21). It is estimated that GFR of Japanese is less than that of American by 10 ml/min/1.73m$^2$ and about 10% of all Japanese have CKD stage 3 or more (29). On the other hand, this high prevalence might not be derived only from the ethnicity of Japanese, since one report has cautioned that as much as 72% of postoperative donors in one institute overseas fulfilled the diagnostic criteria of CKD stage 3 (30). In addition, the assessment of kidney function has problems. The diagnosis of CKD should be performed with eGFR, therefore I used it for post hoc evaluation of renal function in this study, since in TWMU the assessment of GFR has been made by the 2-hour Ccr method. As a result, eGFR showed a much lower value than 2-hour Ccr (70.6 vs 114.0, median, ml/min/1.73m$^2$), although all donors fulfilled a criterion of renal function, equal to or more than 70 ml/min/1.73m$^2$ by 2-hour Ccr. The large difference between values estimated by these two methods indicates each method of eGFR and even Ccr has significant error to estimate the real GFR (31, 32). The question of by what method we should estimate renal function in donor evaluation needs to be further investigated.

Another striking result in this study is that post-donation renal function was stabilized irrespective of the absolute value of pre- or post-donation GFR, even if the postoperative eGFR was less than 40 ml/min/1.73m$^2$. This finding has an important message that the absolute kidney function may not be a significant risk for kidney disease progression, it is not accompanied by progression risks such as proteinuria, hypertension, and diabetes (33, 34). In fact, several reports have recently showed that CKD would not develop if patients had only few risk factors for progression (35-38), which is in contrast with steady decline in GFR of CKD patients in the general population by aging (18, 39), which is further accelerated by reduction of baseline GFR (20). These evidences consequently suggest that kidney donors without progression risks would have fairly good renal prognosis, even if they had low GFR caused only by artificial loss of renal mass; i.e. heminephrectomy.

Increasing number of patients with CKD put much burden onto nephrologists who are short in number, as well as a potential economic burden. In Japan, as much as 10.6% are thought to have CKD defined by eGFR less than 60 (29). However, those with both low GFR and proteinuria, who are really at risk for progression (38), accounts for only less than 1% of the population. In this context, I emphasize that it might not be appropriate to apply a concept of CKD directly to those having eGFR of lower than 60 but without progression risk, including living kidney donors, as several physicians have recently mentioned (40, 41).

There are several limitations to this study. The sample size is small because of dropping out of follow-up with time, which raises concern about a selection bias and an insufficient power to

detect a significant difference. These are common problems with a number of previous studies on donors (42). In addition, co-morbidities such as hypertension and microalbuminuria, which postoperative donor has significant risk for development (28, 43, 44), might have a possibility to be potential confounders. Follow-up period of each donor was too short to discuss the longitudinal consequences of the remaining kidney function, however the stabilized trend of eGFR until 10 years after donation has been also reported in Japanese kidney donors (Dr. Naganuma and Dr. Nagatani at Osaka City University in personal communication). Finally, my result might not be applicable for the other races because subjects were consisted of only Japanese donors. Differences in renal function among races have been recently well described (45, 46), therefore similar investigations are expected to be conducted with donors from different races. Nevertheless, in light of the previous reports (35-38), I believe that my result supports that low GFR does not necessarily confer a risk for progression of CKD when without other progression risk factors.

**Conclusion**

In conclusion, most Japanese living kidney donors developed CKD stage 3 after donation, but renal function stabilized afterwards as long as 3 years after donation even if post-donation GFR was very low. This result implies the concept of CKD might not be applicable to kidney donors who had been already assured to have very few progression risks, even with low absolute value of GFR. Long-term renal or cardiovascular prognosis of donors with low GFR still remains unknown and

awaits long-term observational studies.

## Section 2

Thus, lower GFR after donation might not be a risk for kidney donors, however, it is also true that a few but significant numbers of donors had deteriorated kidney function in contrast to the safety on the majority of post-donation donors. To improve the safety of kidney donation, we should know the risks after donation and their predictive factors to avoid.

One of the worst outcomes in post-donation donors is ESRD. Therefore, I investigated clinical courses and their association with changes in renal function post-donation in donors who developed ESRD, in order to identify risk factors for ESRD after donation.

## Study No. 2: How do living kidney donors develop end-stage renal disease?

### Background

Living kidney donation has been performed with the premise of acceptable safety of kidney donors. Indeed, the long-term safety of postoperative donors has recently been documented by several reports (8, 10, 47, 48). On the other hand, there definitely are donors who developed significant kidney injuries such as proteinuria, depressed renal function corresponding to chronic kidney disease (CKD) stage 3 or more (28, 49), and even developed end-stage renal disease (ESRD) after donation. Incidence of ESRD in living kidney donors has been reported to be 0.04 to 0.7% (27,

50-52), with the median time of 20 years from donation to the event (53). It has, however, not been clearly documented how donors progressed to ESRD, and what triggers renal dysfunction.

Here, I report the clinical courses and changes in renal function of 8 donors who developed ESRD, and a case-control study of risk factors associated with developing ESRD after donation.

**Methods**

I reviewed the charts of all 1519 donors who underwent kidney donation at Tokyo Wemen's Medical University (TWMU) from June 1971 to December 2007. Although we encouraged donors annual clinic visit and lab check, at the time of this study, the rate of donors who had been regularly followed more than 5 and 10 years after donation were 21.3% (292 out of 1371) and 12.7% (148 out of 1166), respectively, and who visited us within a year was 16.7% (253 out of 1519). Many donors were lost to follow-up as above, but I could identify 8 donors who developed CKD stage 5 or ESRD after donation. In the hospital, the criteria for eligibility as a living kidney donor were equal to or more than 70 ml/min/1.73m$^2$ by a 2-hour creatinine clearance (Ccr) test, and the absence of active infection and malignancy were ascertained along with the guideline from Japanese society of transplantation. Donors were also checked full health check up including cardiovascular status and asked for specialist consultation if needed.

I obtained all the information including labs from the patient charts. In this study, I assessed glomerular filtration rate (GFR) with estimated GFR (eGFR) calculated by the abbreviated

Modification of Diet in Renal Disease study equation, using a coefficient of 0.881 to modify for the Japanese (22). I defined clinical data as follow: hypertension, more than 140 or 90 mmHg in systolic or diastolic blood pressure; proteinuria and hematuria, positive test by dipstick; diabetes mellitus, more than 200 mg/dl twice in fasting blood sugar; anemia, less than 13 or 11 g/dl if female in serum hemoglobin; dyslipidemia, more than 220 or 150 mg/dl in serum total cholesterol or triglyceride; hyperuricemia, more than 7 or 6 mg/dl if female in serum uric acid. This study was done along with the guideline for clinical research from Hearth and Labor ministry of Japan.

To identify the risk factors for developing ESRD after donation, I conducted a case-control study. For each donor who developed ESRD, I selected 3 control donors who donated at TWMU and have maintained stable renal function at least until the post-donation time when a paired case donor had developed ESRD. Control donors were matched for age (within 5 years as an acceptable error), sex, and follow-up time since donation.

Variables were expressed as mean (standard deviation; SD) values. For statistical analysis, Student's t test was used to compare two independent variables. To evaluate the relative risk for developing ESRD after donation, we used the Cox proportional-hazards model for taking the matched pair into the consideration, reported as hazard ratios (HR) with 95% confidence intervals (CI). Several patients and their matched pairs were partially excluded from analysis because of missing data or the observation period was too short to evaluate progression factors of CKD. Two-sided P-values of less than 0.05 were considered as statistically significant. All statistical analyses were performed with JMP software (version 7.01, SAS Institute Inc.).

## Results

### *Pre- and Post-donation Characteristics*

Trends in renal function of 8 donors are shown in Figure 3. Focusing on the progression factors of CKD, clinical characteristics before and after donation are shown in Table 5.

The study included 5 males and 3 females. They all donated to a family member with kidney disease needed to undergo dialysis. Mean age at donation was 47 (SD; 14.8) years. Mean BMI was 25.1 (SD; 3.1), eGFR before donation was 66.5 (SD; 10.3) ml/min/1.73m$^2$ ranging from 54.0 to 84.1, except for 2 patients whose values were not available. Mean time for the 8 donors to reach CKD stage 4 from donation was 15.2 (SD; 3.2) years, and to reach CKD stage 5 or end-stage renal disease was 16.0 (SD; 3.2) years. No one had past history of any cardiovascular (CV) events or renal diseases. As for their family histories, patient 2 and 8 had hypertension, patient 3 had diabetes mellitus, and the others had no special affairs.

Before donation, 1 patient had hypertension which was well controlled with medication, 2 patients tested positive for proteinuria by dipstick and 2 patients were smokers. In 6 donors whose right values were available, mean systolic and diastolic blood pressure at donation were 123.8 (SD; 9.2) and 73.2 (SD; 10.8) mmHg, respectively, and mean quantification value of proteinuria was 0.1 (SD; 0.09) g/day. No one had blood pressure more than 140/90 mmHg and proteinuria more than 0.2 g/day, especially proteinuria of less than 0.15 g/day and 0.17 g/day in patient 3 and 4,

respectively, who were tested positive proteinuria by dipstick. Similarly, no one had anemia, and hyperuricemia except for patient 5 having uric acid of 6.7 mg/dl. Dyslipidemia was diagnosed in patient 2, 3, and 5, with serum triglyceride of 238, 231, and 211 mg/dl, respectively.

Immediately after donation, the mean eGFR declined to 48.5 (SD; 8.7) ml/min/1.73m$^2$ ranging from 40.0 to 62.9. In long-term follow-up, however, the mean change in yearly GFR which could be evaluated in 5 donors, showed an increment of 0.46 (SD; 0.91) ml/min/1.73m$^2$ until the mean time of 13.1 (SD; 4.1) years since donation, indicating that their renal function had been stable. Hypertension was seen in 4 patients, of which 3 developed postoperatively. Persistent proteinuria was seen in as much as 5 out of 7 donors.

***Detailed description of the cases***

In Patient 1 and 2, CKD started to progress following episodes of congestive heart failure and pneumonia after a long period of stable renal function. Patient 1 had stable eGFR at least for 6 years post-donation but lost contact during follow-up. When he visited the hospital again, his eGFR was 27 ml/min/1.73m$^2$, which was a significant decline from the eGFR at his previous follow up (50.1 ml/min/1.73m$^2$), however, he had no hypertension or proteinuria. Within a year, he developed CKD stage 5 after the episodes of pneumonia and congestive heart failure (CHF), and died before initiating dialysis. Patient 2 was not followed up immediately after donation. When she visited us 20 years after donation, her renal function was not different from that taken immediately after donation. In the next two years, however, she was admitted twice for pneumonia and CHF,

subsequently developed CKD which rapidly progressed to stage 5, and died before initiating dialysis. Although the results of ultrasound cardiography (UCG) or clinical tests which were performed when they developed CHF were not available, chest x-ray showed increment of cardiothoracic ratio from 58% to 79% with pleural effusion in patient 1.

Patient 3 and 4 had stable eGFR for a long period of time despite positive test results for proteinuria at donor evaluation. Patient 3, who was lost to follow-up 6 years after donation, had a stable eGFR despite persistent proteinuria ranging from 1+ to 3+ by dipstick test and an event of cerebral infarction. According to his primary care physician, his renal function was stable after the event, until he developed CHF, although the detailed clinical data including UCG were not available. When he visited us again, he had already developed CKD stage 5. Hemodialysis (HD) was initiated the following year. Patient 4 showed stable renal function until 14 years post donation, when he developed hypertension which gradually progressed in spite of treatment with antihypertensives. His eGFR declined steadily with time, and afterwards developed to ESRD.

Patient 5 and 6 were the cases, in which de novo renal disease was suggested to be the etiology of ESRD. In patient 5, eGFR was stable at least for 7 years, when she was lost to follow-up. When she revisited us, her eGFR had declined by 38 % with uncontrolled hypertension and proteinuria. Subsequently her eGFR declined steadily until she developed ESRD. Anti-neutrophil antibodies directed against myeloperoxidase (MPO-ANCA) tested strongly positive, therefore renal vasculitis was suspected. Patient 6 was lost to follow-up immediately after donation, and when he visited us 10 years after donation his eGFR was still stable but he presented with significant

proteinuria of approximately 1 g/day. After 4 more years of stable GFR but with an increment of proteinuria up to 3 g/day, his eGFR started to decline linearly and he reached ESRD two years later. Open biopsy showed focal and segmental glomerulosclerosis (FSGS).

Patient 7 and 8 developed acute kidney injury (AKI). Patient 7 had long stabilized eGFR until 11 years post donation but his renal function suddenly declined with symptoms of slight fever and nocturia. Acute pyelonephritis with acute tubular necrosis was diagnosed by open biopsy. Although he remained in CKD stage 5, his renal function stabilized with renoprotective medications. Patient 8 was in cardiogenic shock following a serious traffic accident and subsequently developed AKI requiring dialysis. Although he was once withdrawn from dialysis due to transient improvement of renal function, HD was reintroduced 4 years after donation.

***Risk factors for developing ESRD after donation***

As compared with 24 control donors, the case donors were more likely to develop persistent proteinuria (HR, 6.1; 95%CI, 1.13 to 52.8; P=0.03), acute cardiovascular events including CHF and cardiogenic shock (HR, 9.45; 95%CI, 1.83 to 58.0; P=0.01), severe infection requiring hospitalization for pneumonia and pyelonephritis (HR,12.0; 95%CI, 1.51 to 180; P=0.02), and hospitalization due to accelerating factors of CKD as above (HR, 7.8; 95%CI, 1.44 to 65.7; P=0.02) after donation (Table 6). No pre-donation factor indicated a significant risk for developing ESRD. Until renal function of case donors started to decline toward ESRD, yearly change in the mean eGFR post-donation of 5 case donors (patient 1 to 5) was 0.46 (SD; 0.91) ml/min/1.73m$^2$ per year,

which were not significantly different from those of matched control donors [0.37 (SD; 0.52) ml/min/1.73m$^2$ per year, P=0.85], nor associated with risk for ESRD.

**Discussion**

In this study, I was able to obtain several findings; (i) ESRD developed irrespective of pre-donation renal function or absence of risk factors of CKD such as proteinuria, hypertension, obesity or diabetes. (ii) In most cases, renal function stabilized for a long period (mean 13.1 years), but suddenly started to decline after being accompanied by initiating events or newly developed co-morbidities, especially risk factors of CKD such as proteinuria, hypertension, CV events or infection. Although etiologies of ESRD in kidney donors who were registered upon the United Network for Organ Sharing (UNOS) waiting list for kidney transplantation have been documented (54), there is no detailed report on the clinical course of kidney donors developing ESRD.

The important message from my study is that irrespective of the cause of the ESRD, initiating or aggravating events are risk factors for CKD (33, 34), and that most of these risks are medically controllable. Even aggravating factors such as infection could be prevented by annual work up, patient education or routine vaccination (33). Thus, this finding suggests the importance of long-term periodical follow-up, to evaluate donors for CKD related risk factors and health maintenance. In addition, because donors in my study developed ESRD after maintaining stable renal function for a long period after donation, follow-up of kidney donors should be continued

even if they seem very stable for a long time.

I identified 4 patients who probably lost kidney function due to de novo glomerulonephritis (GN) or AKI. Postoperative de novo GN in donors such as IgA nephropathy and membranous nephropathy have been documented to be the causes for developing ESRD (55). In patient 6 who showed FSGS by biopsy, it is likely that hyperfiltration imposed by nephrectomy caused glomerular scleresis (i.e. secondary FSGS) because of lower post-donation eGFR and a history of smoking. However, because many cases with the same degree of low GFR did not necessarily have nephrotic range proteinuria leading to progressive CKD, the FSGS lesion rather than hyperfiltration might be the primary condition leading to ESRD in this patient. Indeed, change in glomerular permselectivity of donors after donation was reported to be mild, despite contribution of hyperfiltration in the remaining nephron chronic kidney injury, by lacking charge selectivity of glomeruli (56).

Although as in my cases, it is difficult to predict if de novo GN or AKI will develop, it is important to have in mind that even after development of these diseases, immediate action for renoprotection still holds effective as shown in patient 7.

If postoperative complications and their management are crucial for renal prognosis of donors as our patients suggest, we should provide long-term periodical follow-up for all donors to check for and prevent occurrence of CKD and CVD, and to take renoprotective or cardioprotective actions as soon as we identify these risk factors, de novo GN, or AKI. It would also be required to educate donors about the importance of regular long-term postoperative follow-up after donation, because donors often consider themselves healthy and stop visits to the clinic by their own

judgment (54).

Much lower estimated eGFR values as compared with 2-hour Ccr values were unexpected for us, but this probably means that Ccr significantly overestimates GFR, therefore we need to abandon Ccr for evaluation of donor renal function. Still, a 2-hour Ccr of 70 ml/min/1.73m$^2$ as our donor selection criterion, which many Japanese transplant centers currently adopt, is certainly lower than 80 ml/min/1.73m$^2$ which would be the criterion in many places worldwide (13-15). On the other hand, to my knowledge, there is no solid evidence which clarified that kidney donation resulted in worse outcomes for donors with GFR less than 80 before donation. In my study, lower pre-donation eGFR in donors selected by our criteria was not associated with the risk for the worst outcome, which is developing ESRD (Table 6). This result is potentially supported by the result of a survey, also conducted in the Japanese population (52). Low GFR might not necessarily lead to CKD progression unless it is accompanied by other risk factors of CKD progression, however, until solid evidence is obtained, there is a definite need to maintain long-term follow-up with special attention to the acquisition of progression or accelerating factors of CKD.

Although my study did not detect persistent positive proteinuria test by dipstick before donation as a significant risk for ESRD, I currently consider this test as a contraindication to the selection for donors, because donors have been reported to have an additional risk for proteinuria post-donation (28, 49) and proteinuria is a strong indicator of bad renal outcome (38, 51). The presence of proteinuria in patient 3 and 4 might have been regretfully overlooked, although I could not identify the exact reason because of lack of its statement in the old chart.

I finally emphasize that all the donors should be followed continuously, at least once a year, or more often if they had any risk factors for progression of CKD, and that they should be carefully checked not only for decline of renal function, but also for development of any new risks of CKD or CVD which subsequently need to be managed.

The limitation of my study is that the number of cases is too small to have statistical power to detect the risks for ESRD that are well considered for confounding factors in analysis. Nevertheless, because this is the first report to document the course of progression of donor CKD and identified possible risks for ESRD, I believe that my results help to improve the quality of care and well-being of postoperative donors.

**Conclusion**

There are a significant number of donors who developed CKD stage 5 or ESRD. These donors tend to have stable renal function for long periods of time but suddenly start to develop progressive CKD. They do not necessarily have CKD risk factors before donation but they develop these risk factors after donation. These findings make us realize the importance of keeping long-term follow-up of donors to check for and prevent CKD risks even if their renal function remains stable for a long time, and to take immediate action if they develop these risks.

## Section 3

Another risk for post-donation donors to avoid would be kidney disease, such as persistent proteinuria or progressive decline in renal function post-donation. This is a state of health to need the regular clinic visiting and medications, which is a contradiction to the principle of LKT that donors should be ensured to be the same healthy condition between pre- and post-donation. Therefore, it is important to clarify the risk for developing kidney disease after donation and its predictive factors.

Finally, I investigated the association of developing kidney disease with clinical characteristics in donors pre- and post-donation, in order to identify predictive risk factors for kidney disease after donation, especially focusing on the findings of hematuria which had been scarcely paid attention.

## Study No. 3: Persistent glomerular hematuria in living kidney donors confers a risk for progressive kidney disease in donors after heminephrectomy.

### Background

Living donor kidney transplantation is one of the therapeutic options for end-stage kidney disease (ESKD), showing a steady increase in number (1) in parallel with the global rise of the

prevalence of ESKD (2). Because living kidney donation is only justified on the premise that it is acceptably safe (4), we should know who would be put at risk by heminephrectomy. Long-term (up to several decades) safety in kidney donors has been documented (8, 10, 11), however, it is also true that small but significant number of donors have developed overt proteinuria or progressive renal dysfunction, which could end up with ESKD after donation (51-53, 57, 58). Despite this, what factors impose post-donation risks including kidney disease upon donors has been scarcely investigated (7, 16, 17, 59), therefore the acceptable threshold of pre-donation factors such as renal function, blood pressure (BP), donor age, and body-mass index (BMI) remains unclear, with the greater diversity of eligibility for living kidney donor varying from one institute to another (13). Similarly, there is no definite threshold in the level of abnormal urinalysis. Especially, persistent hematuria has not been well investigated whether it could confer a risk for kidney disease on post-donation donors (60-63), although the possibility of its future risk has been suggested (14).

To clarify whether hematuria is a risk factor for progressive kidney disease after living kidney donation, I investigated the prevalence of hematuria in donors before and after donation, and subsequently check the association between hematuria and sign of progressive kidney disease such as development of persistent proteinuria or decline of renal function in living kidney donors.

## Methods

### *Study population*

I reviewed medical records and identified 242 donors, who donated at Department of Surgery, Kidney Center, Tokyo Women's Medical University (TWMU) from April 2001 to October 2007 and had been tested urinalyses on multiple occasions at least 3 months apart both pre- and post-donation, in order to assess the risk for developing persistent proteinuria after donation. Out of these 242 donors, I subsequently identified 163 donors who had been followed more than 2 years after donation and investigated their longitudinal trends in renal function individually in order to assess the association of yearly changes in glomerular filtration rate (GFR) with status of hematuria in donors and the risk for progressive renal dysfunction after donation.

In TWMU, the lower limit of kidney function to be eligible for living kidney donor is equal to or more than 70 ml/min/1.73m$^2$ by 2-hour creatinine clearance (Ccr). Additionally, absence of active infection and malignancy was ascertained in all donors along with the guideline for donor selection from the Japanese society of transplantation (http://www.asas.or.jp/jst/pdf/guideline_002jinishoku..pdf). Donors were also performed full workup of donor evaluation including cardiovascular tests and asked for specialist consultation if needed.

***Kidney function***

I assessed kidney function with estimated GFR (eGFR) for the Japanese (64). To exclude the effect of transient and sudden drop of kidney function by heminephrectomy, the evaluation of longitudinal changes in GFR was started at 1 year after donation. Because the absolute change of

kidney function is strongly affected by its baseline level, we used the relative change (yearly change in eGFR since 1 year after donation divided by eGFR 1 year after donation; % per year) as well as absolute change in evaluating the trends of kidney function in this study.

***Urinalysis***

I evaluated proteinuria, hematuria, and dysmorphic red blood cell (d-RBC) with voided fresh urine both before and after kidney donation. Proteinuria tested 1+ or more by dipstick (Uropaper 3; Eiken chemical co., LTD.) read by automated dipstick reader (US3100-R; Eiken chemical co., LTD.) was defined as positive, which is viewed as an acceptable surrogate for quantitative proteinuria with high specificity of protein excretion exceeding 300 mg/day or more (65). The quantitative evaluation of proteinuria by 24-hr urine collection was also performed once before donation, which defined positive proteinuria as 150 mg/day or more.

Hematuria was judged “positive” when 5 red blood cell (RBC) or more per high-power field (HPF) were detected in urinary sediment. I concurrently evaluated d-RBC, which have been reported to be useful marker of glomerular kidney disease (66, 67). Because the standardized diagnostic method for d-RBC has not been established and superiority of qualitative or quantitative evaluations in detecting d-RBC is still controversial, I use the qualitative method in this study. In detail, d-RBC was judged “positive” when 5 or more of RBC per HPF and diverse forms of RBC such as acanthocyte which suggested glomerular bleeding were observed in each of field while checking for 10 to 20 HPF in urinary sediment.

I call proteinuria or hematuria “persistent” when two or more separate urinalyses consistently showed positive proteinuria or hematuria, respectively, at interval of 3 months or more. I judged them “negative” only if these urinary abnormalities had never been detected, and judged “occasionally positive” when urinary abnormalities were neither persistent nor negative, such as in donors who showed positive dipstick proteinuria at least once. Meanwhile, d-RBC was defined “positive” even if it appeared once either pre- or post-donation.

The changes in urinalysis within 3 months after donation were excluded from the evaluation to exclude effects of heminephrectomy operation itself. Urinary tests with specific gravity more than 1.035 or less than 1.010, 8 or more of pH, and more than 10 per HPF of urinary white blood cells were also excluded in order to exclude possible measurement error, and effect of urinary tract infection.

***Blood pressure measurement***

Pre-donation BP was individually evaluated with the mean value of 3 separate measurements within a day during hospitalization for donation, measured by trained nurses while donors were seated at rest. In this study, I defined hypertension as BP more than 130/85 mmHg, because high-normal BP have already been reported to be associated with the significant risks for the progression of chronic kidney disease (CKD) and cardiovascular disease (CVD) in the general population (68-70). To evaluate the effect of antihypertensive drugs for renal outcome, donors were categorized into 3 subgroups; normotension, treated normotension, and hypertension.

***Statistical analysis***

Categorical and continuous variables were expressed as percentage and median (interquartile range; IQR), respectively. To compare with two continuous values and the rates of two variables, I use Mann-Whitney test, and $\chi^2$ test or Fisher's exact test when appropriate. In multivariate analysis, I used the logistic-regression models to identify the risk factors for post-donation occurrence of persistent proteinuria or hematuria with d-RBC, and used the multiple linear-regression models to clarify the clinical factors affecting for the changes in kidney function after donation, especially which bring about the progressive decline in GFR. In addition to age and sex, I first included eGFR, BP, BMI, and proteinuria before donation in each model of the multivariate analysis as covariates, because they have been generally suggested to be associated with renal outcomes. Subsequently, pre-donation variables of hematuria, d-RBC, smoking status, family history of IgA nephropathy (IgAN) or Alport syndrome (AS), donation for sibling, serum albumin, hemoglobin, uric acid, total cholesterol, triglyceride, and post-donation variables of urinary abnormalities (proteinuria, hematuria, d-RBC) and time since donation were included in these models if those of P-value were less than 0.2 in each of univariate analysis. Multicollinearity and interaction between covariates were well checked in each of the model. Two-sided P-values of less than 0.05 were considered as statistically significant. All statistical analyses were performed with JMP software (version 8.01, SAS Institute Inc.).

## Results

### *Baseline clinical characteristics*

Of 242 kidney donors with median follow-up time since donation of 27 (IQR; 15 to 48) months, male accounted for 40.5% and median age at donation was 57 (IQR; 49 to 64) years, including 9.5% (n = 23) of the elderly more than 70 years. Median eGFR pre-donation was 78.6 (IQR; 70.6 to 90.6) ml/min/1.73m$^2$, and 7.9% (n = 19) had eGFR less than 60 although all donors meets our criteria of Ccr of more than 70 ml/min/1.73m$^2$. As much as 29.8% (n = 72) of all donors was hypertensive with blood pressure more than 130/85 mmHg. Forty five donors (18.6%) had taken antihypertensive medications before donation (the number of BP medication being one, two, and three accounted for 68.9%, 28.9%, and 2.2%, respectively). Sixty three donors (26%) were overweight (BMI more than 25), and 9 (3.7%) were obese (BMI more than 30) before donation.

Eleven donors (4.5%) showed pre-donation occasional dipstick proteinuria, while only 2 out of these 11 donors had more than 150 mg/day (but also less than 300 mg/day) of proteinuria by 24-hr urine collection. Pre-donation persistent hematuria was detected in 8.3% (n = 20) of donors, and hematuria was dysmorphic in 75% of these cases. This proportion of dysmorphic hematuria was significantly higher than that in donors without persistent hematuria (2.9%, $P < 0.001$). Donors with family history of IgAN or AS (n = 43) had significantly higher rate of pre-donation persistent hematuria of 18.6% than 6% in donor without family history of them ($P = 0.01$) (Table 7).

***Changes in urinary abnormalities by donation***

After donation, 8.3% (n = 20) of all donors developed persistent proteinuria within the follow-up period of this study, 40% of whom started to be tested positive only within 3 months, and 55% of the total within 12 months after donation. On the other hand, the prevalence of donors with persistent hematuria increased to 15.3% (n = 37) after donation from 8.3% (n = 20) before donation. In addition to 95% (19 out of 20) of donors with pre-donation persistent hematuria, 27.6% (8 out of 29) with pre-donation occasional hematuria and 5.2% (10 out of 193) without pre-donation hematuria developed persistent hematuria after donation (Figure 4), and 50% of whom turned to be tested positive only within 3 months, and 78% of the total within 12 months after donation. As a result, as much as 25.6% of all the donors showed occasional or persistent hematuria after donation.

***Pre- and Post-donation risk factors of persistent proteinuria after donation***

Donors who developed persistent proteinuria after donation (n = 20), as compared with the rest of donors (n = 222), had significantly higher rate of occasional proteinuria (30.0% vs. 2.3%; P < 0.001), of persistent hematuria (35.0% vs. 5.9%; P < 0.001), and of d-RBC (30.0% vs. 7.2%; P = 0.002) all before donation. They also had higher median systolic and diastolic blood pressure, and higher rate of hypertension before donation (55.0% vs. 27.5%; P = 0.02) (Table 8). The risk for persistent proteinuria could be significantly predicted by pre-donation occasional proteinuria (odds ratio, 18.6; 95% CI, 5.05 to 68.5), with sensitivity of 30.0%, specificity of 97.7%, and likelihood ratio of a positive test of 13.3, but not predicted by positive 24-hr urine protein test which was done

only once just before donation (odds ratio, 11.5; 95% CI, 0.69 to 191).

In multivariate analysis, pre-donation donors with occasional proteinuria (odds ratio, 14.0; 95%CI, 3.22 to 63.8; P < 0.001), persistent hematuria with d-RBC (odds ratio, 12.3; 95% CI, 2.65 to 59.7; P = 0.002), and hypertension (odds ratio, 3.48; 95% CI, 1.06 to 12.4; P = 0.04) had higher risk for persistent proteinuria after donation (Table 9). Age, sex, pre-donation eGFR, and BMI were not associated with this risk.

Meanwhile, donors presenting post-donation persistent hematuria had significantly higher incidence of post-donation persistent proteinuria (24.3% vs. 5.4%; P < 0.001), and post-donation d-RBC (86.5% vs. 3.0%; P < 0.001), as compared with those without post-donation persistent hematuria. In multivariate analysis, post-donation donors showing persistent dysmorphic hematuria also had higher incidence of persistent proteinuria after donation (odds ratio, 8.36; 95%CI, 2.37 to 31.5, P = 0.001).

***Risk of progressive decline in GFR after donation***

Median absolute and relative change in eGFR since 1 year after donation were an increment of 0.70 (IQR, -0.16 to 1.36) ml/min/1.73m$^2$ and 1.4 (IQR, -0.32 to 2.78) % per year, respectively, indicating that many donors had moderate improvement in kidney function after the significant drop by donation. Among men, a yearly increment of eGFR was 0.73ml/min/1.73m$^2$ and 1.43%, which were not significantly different from 0.67ml/min/1.73m$^2$ and 1.35% in women. Percent changes in eGFR post-donation were not associated with positive test of proteinuria pre-

and post-donation (P = 0.28, P = 0.86), or persistent hematuria pre-donation (-0.01% vs. 1.63% per year; P = 0.23), however, they were significantly lower in donors with post-donation persistent hematuria, (-0.01% vs. 1.76% per year; P=0.03), or post-donation d-RBC (-0.34% vs. 1.82% per year; P = 0.006). Conversely, donors with higher BMI had a greater improvement in eGFR after donation.

In multivariate analysis, GFR decreased in donors showing persistent hematuria with d-RBC post-donation (-1.69% per year; 95%CI, -3.36 to -0.01; P = 0.048) since 1 year after donation, while it improved in donors who had higher eGFR or BMI at the time of donation (Table 10). Age, sex, pre-donation BP, proteinuria and time since donation were not associated with this change.

***Risk of persistent glomeluar hematuria after donation***

Since I identified post-donation persistent hematuria as a significant risk for progression of kidney disease post-donation, we investigated pre-donation risk factors for persistent glomerular hematuria after donation. Donors showing post-donation persistent hematuria had significantly higher incidence of having family history of IgAN or AS (32.4% vs. 15.1%; P = 0.01), as compared with donors without post-donation persistent hematuria. In multivariate analysis, as a result, persistent glomerular hematuria post-donation were significantly more prevalent in donors with pre-donation persistent hematuria (odds ratio, 31.4; 95%CI, 4.3 to 263; P < 0.001), or pre-donation d-RBC (odds ratio, 15.2; 95%CI, 2.04 to 161; P = 0.007) (Table 11). There was no association of

age, sex, eGFR, BP, proteinuria before donation, and family history of IgAN or AS with this risk.

## Discussion

Although the possibility of hematuria as a risk factor for post-donation kidney disease progression has been already suggested, donor evaluation guidelines including that of the Amsterdam Forum have not identified hematuria as a definite or relative contraindication for kidney donation (14).

The most striking result in my study is that, hematuria was significantly associated with progressive kidney disease such as overt persistent proteinuria or progressive decline in renal function after donation. In fact, my results indicated pre-donation persistent dysmorphic (= glomerular) hematuria could be a strong predictor for persistent proteinuria after donation. In addition, post-donation hematuria was identified as a strong indicator of progressive decline in eGFR and post-donation persistent proteinuria. Although pre-donation hematuria was not a significant predictor of decline of kidney function post-donation, it is a high risk for post-donation persistent dysmorphic hematuria, indirectly suggesting that pre-donation hematuria is also a risk for post-donation progressive kidney disease. These results indicate the importance of checking persistence of glomerular hematuria by multiple urinalyses during donor evaluation.

As much as 25.6% of prevalence of occasional or persistent hematuria after donation means hematuria is common in living kidney donation. Because extraglomerular bleeding could be

excluded by evaluations such as computed tomography, sonography and urine cytology (63), isolated hematuria in pre- or post-donation donors is most likely to be from glomerular origin suggesting the presence of the glomerular diseases such as thin basement membrane nephropathy (TBMN), IgAN, or AS, especially if hematuria was dysmorphic. Although it is still controversial whether glomerular hematuria is acceptable for kidney donor since there are few evidence about the eligibility for candidates with isolated hematuria and their risk after donation (62, 63, 71-73), my results clearly showed that donors having persistent hematuria with d-RBC have significant risk for developing persistent proteinuria and lower GFR, which have been also known to confer worse renal outcomes in each patient with TBMN, IgAN, or AS (71, 74-77). Therefore, we should consider with greatest discretion the eligibility of potential donors with isolated but persistent dysmorphic hematuria. If they wished to be eligible anxiously, we might proceed to donor kidney biopsy, otherwise they should not be accepted.

Why persistent hematuria increases by donation is unknown. However, I could find one report suggesting that IgAN in patients with congenitally reduced nephron mass have a progressive clinical course of disease with more severe pathological findings compared with those with IgAN but intact nephron mass (78). This report implies a possibility that preexistent glomerulopathy deteriorates if the nephron mass would be reduced by donation. As much as sixteen percent (72 out of 446) of living kidney donors have been reported to have latent glomerular IgA deposition which may be early stage of IgAN (79). Thus, donation by such donors with potential glomerulopathy might result in the appearance of persistent hematuria and in turn leading to progressive kidney

disease. In addition, since TBMN has been regarded as a benign disorder among glomerulopathy accompanying hematuria, we need to evaluate whether donors with TBMN also have worse outcome before excluding these patients for donor.

In my study, the risk of family history of IgAN or AS is surely underestimated because many donors who could have it were categorized into unknown. Despite this, it was associated with hematuria pre-donation and had a tendency of having persistent glomerular hematuria post-donation, which suggests us to be careful in evaluating those prospective donors, and need to follow them up for long-period of time if they donated, until the results of further investigations would be obtained.

My results further suggest and alert that hypertension irrespective of BP medication use become an important risk for the worse renal outcome, as mentioned in the general population (80). More strict control of BP would be needed in potential kidney donors. Conversely, higher BMI was significantly associated with a greater improvement in post-donation GFR. However, we should not conclude obesity or overweight is good for donors, because in the long-term, obesity has been reported to be an independent risk factor for worse renal outcome in patients with solitary kidney including donors (10, 81). My result may reflect temporal increment of GFR in donors with overweight or obesity accelerated by hyperfiltration during the short period of time after donation.

This study has several limitations. The most important issue is that this is an observational study based on the charts review with small sample size. The lower rate of developing persistent proteinuria after donation to all subjects resulted in the lower precision of the value of estimated risk. Because timing for and period of follow-up in each donor were not uniformed, the risk for

kidney disease might be underestimated in donors with shorter period of follow-up. In the assessment of renal function, eGFR equation for Japanese was not sufficiently validated in the cohort of pre- and post-donation donors, therefore, the level of GFR and their changes after donation might be imprecise. Because this study was consisted of only Japanese, my results might not be applied to the other races and have a limit to the generalization. Finally, I could not evaluate the histological findings of kidney in donors presenting persistent hematuria because 0-hr biopsy has not been recently performed in TWMU. Nevertheless, I believe my results including the new insights into living kidney donation would help to improve the quality of selection, management and well being of living kidney donors. In future, whether donors with the risk for kidney disease would really have the worse outcome of kidney function, health status, and life-span should be ascertained in observational study with longer follow-up period of time.

In conclusion, persistent glomerular hematuria both pre- and post-donation in donors was a significant risk for both persistent proteinuria and progressive renal dysfunction. Eligibility of potential donors with isolated hematuria, especially with dysmorphic one and family history of IgA nephropathy and Alport syndrome, should be considered with greatest discretion.

**Summary**

Results of my investigations are summarized as follows:

*From study No.1*; most (> 90%) of Jananese living kindey donors had lower GFR corresponding to CKD stage 3 after donation, however the following trends of GFR until 3 years after donation had showed stabilization, distinct from CKD in the general population. This result suggests a possibility of inadequacy for post-donation kidney donors to apply the current diagnostic definition of CKD.

*From study No.2*; post-donation donors who developed ESRD had stabilized kidney function for long period, however, the acquirement of risk factors known as progression or accelerating factors of CKD triggered to start sudden decline in renal function leading to ESRD. After donation, they had higher incidence of persistent protenuria, acute cardiovascular events, severe infection, and hospitalization due to accelerating factors of CKD than those not developing ESRD. This result implies that development for ESRD may be potentially controllable by medications, and therefore indicates the importance of long-term follow-up with special attention to risk factors of CKD such above, in order to check for and prevent CKD risks, and to take immediate action if they develop these risks.

*From study No.3*; living kidney donors having persistent glomerular hematuria both pre- and post-donation had significantly higher risk for kidney disease (persistent proteinuria or progressive

decline in GFR) after donation. This result suggests the need for great discretion in defining of potential donors with isolated glomerular hematuria, with paying attention to possible risk of having family history of IgA nephropathy and Alport syndrome.

## Conclusion

Living kidney donors have lower GFR regarded as kidney disease by the current definition of CKD after donation, but may not have to be simply applied it only with the level of post-donation GFR because of the following stabilized renal function after donation. Meanwhile, to prevent post-donation development for kidney disease or ESRD, we should evaluate them carefully and follow them up for long period with special attention on risk factors known as progression or accelerating factors of CKD, especially those with hematuria. In accordance with my results, potential donors with persistent glomerular hematuria should be excluded for donor and their BP needs to be controlled less than 130/85 mmHg before donation.

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**References**


1. Horvat LD, Shariff SZ and Garg AX. Global trends in the rates of living kidney donation. Kidney Int 75: 1088-1098, 2009

2. Schena FP. Epidemiology of end-stage renal disease: International comparisons of renal replacement therapy. Kidney Int 57: S39-S45, 2000

3. Murray JE and Harrison JH. Surgical management of fifty patients with kidney transplants including eighteen pairs of twins. Am J Surg 105: 205-218, 1963

4. Steering Committee of the Istanbul Summit. Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. Lancet 372: 5-6, 2008

5. Johnson EM, Remucal MJ, Gillingham KJ, Dahms RA, Najarian JS and Matas AJ. Complications and risks of living donor nephrectomy. Transplantation 64: 1124-1128, 1997

6. Siebels M, Theodorakis J, Schmeller N, Corvin S, Mistry-Burchardi N, Hillebrand G, Frimberger D, Reich O, Land W and Hofstetter A. Risks and complications in 160 living kidney donors who underwent nephroureterectomy. Nephrol Dial Transplant 18: 2648-2654, 2003

7. Velosa JA, Offord KP and Schroeder DR. Effect of age, sex, and glomerular filtration rate on renal function outcome of living kidney donors. Transplantation 60: 1618-1621, 1995

8. Najarian JS, Chavers BM, McHugh LE and Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 340: 807-810, 1992

9. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tyden G and Groth CG. Kidney donors live longer. Transplantation 64: 976-978, 1997

10. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR and Matas AJ. Long-term consequences of kidney donation. N Engl J Med 360: 459-469, 2009

11. Ramcharan T and Matas AJ. Long-term (20-37 years) follow-up of living kidney donors. Am J Transplant 2: 959-964, 2002

12. Goldfarb DA, Matin SF, Braun WE, Schreiber MJ, Mastroianni B, Papajcik D, Rolin HA, Flechner S, Goormastic M and Novick AC. Renal outcome 25 years after donor nephrectomy. J Urol 166: 2043-2047, 2001

13. Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, Hanto DW and Rodrigue JR. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant 7: 2333-2343, 2007

14. Delmonico F. A Report of the Amsterdam Forum On the Care of the Live Kidney Donor: Data and Medical Guidelines. Transplantation 79: S53-S66, 2005

15. Norden G, Lennerling A, Nyberg G. Low absolute glomerular filtration rate in the living kidney donor: a risk factor for graft loss. Transplantation 70: 1360-1362, 2000

16. Rook M, Hofker HS, van Son WJ, Homan van der Heide JJ, Ploeg RJ and Navis GJ. Predictive capacity of pre-donation GFR and renal reserve capacity for donor renal function after living kidney donation. Am J Transplant 6: 1653-1659, 2006

17. Lee JH, Kim SC, Han DJ, Chang JW, Yang WS, Park SK, Lee SK, Park JS and Kim SB.

Risk factors for MDRD-GFR of less than 60 mL/min per 1.73 m2 in former kidney donors. Nephrology (Carlton) 12: 600-606, 2007

18. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. Nephrol Dial Transplant 21: 2577-2582, 2006

19. Kronborg J, Solbu M, Njolstad I, Toft I, Eriksen BO and Jenssen T. Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromso study. Nephrol Dial Transplant 23: 2818-2826, 2008

20. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Makino H, Hishida A and Matsuo S. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res 31: 433-441, 2008

21. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, Ura N, Kiyohara Y, Hirakata H, Moriyama T, Ando Y, Nitta K, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A and Matsuo S. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 11: 156-163, 2007

22. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A and Matsuo S. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic

kidney disease. Clin Exp Nephrol 11: 41-50, 2007

23. Eriksen BO and Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int 69: 375-382, 2006

24. Jones C, Roderick P, Harris S and Rogerson M. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. Nephrol Dial Transplant 21: 2133-2143, 2006

25. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, Rogers NL and Teschan PE. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int 51: 1908-1919, 1997

26. Gracida C, Espinoza R, Cedillo U and Cancino J. Kidney transplantation with living donors: nine years of follow-up of 628 living donors. Transplant Proc 35: 946-947, 2003

27. Fehrman-Ekholm I, Duner F, Brink B, Tyden G and Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation 72: 444-449, 2001

28. Garg AX, Muirhead N, Knoll G, Yang RC, Prasad GV, Thiessen-Philbrook H, Rosas-Arellano MP, Housawi A and Boudville N. Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression. Kidney Int 70: 1801-1810, 2006

29. Imai E. Equation for estimating GFR from creatinine in Japan. Nippon Rinsho. 66: 1725-1729, 2008

30. Wan RK, Spalding E, Winch D, Brown K and Geddes CC. Reduced kidney function in living kidney donors. Kidney Int 71: 1077; author reply 1077, 2007

31. Bertolatus JA and Goddard L. Evaluation of renal function in potential living kidney donors. Transplantation 71: 256-260, 2001

32. Issa N, Meyer KH, Arrigain S, Choure G, Fatica RA, Nurko S, Stephany BR and Poggio ED. Evaluation of creatinine-based estimates of glomerular filtration rate in a large cohort of living kidney donors. Transplantation 86: 223-230, 2008

33. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39: S1-S266, 2002

34. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M and Koyama A. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int 71: 159-166, 2007

35. Lindeman RD, Tobin J and Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 33: 278-285, 1985

36. Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, Larsen E, Ghali WA, Southern DA, McLaughlin K, Mortis G and Culleton BF. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int 69: 2155-2161, 2006

37. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, De Jong PE and Gansevoort RT. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc

Nephrol 17: 2582-2590, 2006

38. Iseki K, Kinjo K, Iseki C and Takishita S. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. Am J Kidney Dis 44: 806-814, 2004

39. Keough-Ryan TM, Kiberd BA, Cox JL, Thompson KJ and Clase CM. Development of end stage renal disease following an acute cardiac event. Kidney Int 74: 356-363, 2008

40. Poggio ED and Rule AD. A critical evaluation of chronic kidney disease--should isolated reduced estimated glomerular filtration rate be considered a 'disease'? Nephrol Dial Transplant 24: 698-700, 2009

41. Barri Y, Parker T, 3rd, Kaplan B and Glassock R. Primum non Nocere: is chronic kidney disease staging appropriate in living kidney transplant donors? Am J Transplant 9: 657-660, 2009

42. Ommen ES, Winston JA and Murphy B. Medical risks in living kidney donors: absence of proof is not proof of absence. Clin J Am Soc Nephrol 1: 885-895, 2006

43. Garg AX, Prasad GV, Thiessen-Philbrook HR, Ping L, Melo M, Gibney EM, Knoll G, Karpinski M, Parikh CR, Gill J, Storsley L, Vlasschaert M and Mamdani M. Cardiovascular disease and hypertension risk in living kidney donors: an analysis of health administrative data in Ontario, Canada. Transplantation 86: 399-406, 2008

44. Boudville N, Prasad GV, Knoll G, Muirhead N, Thiessen-Philbrook H, Yang RC, Rosas-Arellano MP, Housawi A and Garg AX. Meta-analysis: risk for hypertension in

living kidney donors. Ann Intern Med 145: 185-196, 2006

45. McClellan W, Warnock DG, McClure L, Campbell RC, Newsome BB, Howard V, Cushman M and Howard G. Racial differences in the prevalence of chronic kidney disease among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. J Am Soc Nephrol 17: 1710-1715, 2006

46. Norris KC and Agodoa LY. Unraveling the racial disparities associated with kidney disease. Kidney Int 68: 914-924, 2005

47. Lezaic V, Jaksic E, Simic S, Blagojevic R, Radivojevic D and Djukanovic L. Remnant kidney function in kidney donors. Transplant Proc 31: 367, 1999

48. Haberal M, Karakayali H, Moray G, Demirag A, Yildirim S and Bilgin N. Long-term follow-up of 102 living kidney donors. Clin Nephrol 50: 232-235, 1998

49. Gossmann J, Wilhelm A, Kachel HG, Jordan J, Sann U, Geiger H, Kramer W and Scheuermann EH.. Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. Am J Transplant 5: 2417-2424, 2005

50. Hartmann A, Fauchald P, Westlie L, Brekke IB and Holdaas H. The risk of living kidney donation. Nephrol Dial Transplant 18: 871-873, 2003

51. Sommerer C, Morath C, Andrassy J and Zeier M. The long-term consequences of living-related or unrelated kidney donation. Nephrol Dial Transplant 19 Suppl 4: iv45-iv47, 2004

52. Okamoto M, Akioka K, Nobori S, Ushigome H, Kozaki K, Kaihara S and Yoshimura N.

Short- and long-term donor outcomes after kidney donation: analysis of 601 cases over a 35-year period at Japanese single center. Transplantation 87: 419-423, 2009

53. Fehrman-Ekholm I, Norden G, Lennerling A, Rizell M, Mjörnstedt L, Wramner L and Olausson M. Incidence of end-stage renal disease among live kidney donors. Transplantation 82: 1646-1648, 2006

54. Ellison MD, McBride MA, Taranto SE, Delmonico FL and Kauffman HM. Living kidney donors in need of kidney transplants: a report from the organ procurement and transplantation network. Transplantation 74: 1349-1351, 2002

55. Bia MJ, Ramos EL, Danovitch GM, Gaston RS, Harmon WE, Leichtman AB, Lundin PA, Neylan J and Kasiske BL. Evaluation of living renal donors. The current practice of US transplant centers. Transplantation 60: 322-327, 1995

56. Borchhardt KA, Yilmaz N, Haas M and Mayer G. Renal function and glomerular permselectivity late after living related donor transplantation. Transplantation 62: 47-51, 1996

57. Kido R, Shibagaki Y, Iwadoh K, Nakajima I, Fuchinoue S, Fujita T and Teraoka S. How Do Living Kidney Donors Develop End-Stage Renal Disease? Am J Transplant 9: 2514-2519, 2009

58. Pereira RB, Scheeren J, Castro D, Machado G, Jost G, Mello RJ, Capeletti T, Zanette T, Fonseca VF, Keitel E, Santos AF, Bianchini JJ, Garcia CD and Garcia VD. Follow-up of kidney donors who developed uremia and went on the waiting list for a transplant: should

they have allocation priority? Transplant Proc 40: 1012-1013, 2008

59. Kasiske BL, Ma JZ, Louis TA and Swan SK. Long-term effects of reduced renal mass in humans. Kidney Int 48: 814-819, 1995

60. Sobh MA, Moustafa FE, el-Din Saleh MA, Tawfik A and Ghoneim MA. Study of asymptomatic microscopic hematuria in potential living related kidney donors. Nephron 65: 190-195, 1993

61. Koselj M, Rott T, Kandus A, Vizjak A and Malovrh M. Donor-transmitted IgA nephropathy: long-term follow-up of kidney donors and recipients. Transplant Proc 29: 3406-3407, 1997

62. Koushik R, Garvey C, Manivel JC, Matas AJ and Kasiske BL. Persistent, asymptomatic, microscopic hematuria in prospective kidney donors. Transplantation 80: 1425-1429, 2005

63. Vadivel N, Stankovic A, Rennke HG and Singh AK. Accepting prospective kidney donors with asymptomatic urinary abnormalities: are we shooting in the dark? Kidney Int 71: 173-177, 2007

64. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H and Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009

65. Eknoyan G, Hostetter T, Bakris GL, Hebert L, Levey AS, Parving HH, Steffes MW and Toto R. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive

and kidney diseases (NIDDK). Am J Kidney Dis 42: 617-622, 2003

66. Schramek P, Schuster FX, Georgopoulos M, Porpaczy P and Maier M. Value of urinary erythrocyte morphology in assessment of symptomless microhaematuria. Lancet 2: 1316-1319, 1989

67. Kohler H, Wandel E and Brunck B. Acanthocyturia--a characteristic marker for glomerular bleeding. Kidney Int 40: 115-120, 1991

68. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R and Levey AS. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 139: 244-252, 2003

69. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB and Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 345: 1291-1297, 2001

70. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y and Takishita S. Blood pressure predicts risk of developing end-stage renal disease in men and women. Hypertension 41: 1341-1345, 2003

71. Savige J, Rana K, Tonna S, Buzza M, Dagher H and Wang YY. Thin basement membrane nephropathy. Kidney Int 64: 1169-1178, 2003

72. Kashtan CE. Women with Alport syndrome: risks and rewards of kidney donation. Nephrol Dial Transplant 24: 1369-1370, 2009

73. Gross O, Weber M, Fries JW and Muller GA. Living donor kidney transplantation from relatives with mild urinary abnormalities in Alport syndrome: long-term risk, benefit and outcome. Nephrol Dial Transplant 24: 1626-1630, 2009

74. Szeto CC, Lai FM, To KF, Wong TY, Chow KM, Choi PC, Lui SF and Li PK. The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. Am J Med 110: 434-437, 2001

75. Kashtan CE. The wages of thin. J Am Soc Nephrol 18: 2800-2802, 2007

76. Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Dahan K, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schröder C, Sanak M, Carvalho MF, Saus J, Antignac C, Smeets H and Gubler MC. X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. J Am Soc Nephrol 14: 2603-2610, 2003

77. Kashtan CE. Alport syndrome and the X chromosome: implications of a diagnosis of Alport syndrome in females. Nephrol Dial Transplant 22: 1499-1505, 2007

78. Hotta O, Chiba S, Furuta T, Sudou K, Horigome I and Taguma Y. Clinicopathological study of IgA nephropathy in patients with congenitally reduced nephron mass. Clin Nephrol 44: 362-366, 1995

79. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H and Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. Kidney Int 63: 2286-2294,

2003

80. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT Jr, Whelton PK, Barzilay J, Batuman V, Eckfeldt JH, Farber MA, Franklin S, Henriquez M, Kopyt N, Louis GT, Saklayen M, Stanford C, Walworth C, Ward H and Wiegmann T. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. Ann Intern Med 144: 172-180, 2006

81. Gonzalez E, Gutierrez E, Morales E, Hernández E, Andres A, Bello I, Díaz-González R, Leiva O and Praga M. Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. Kidney Int 68: 263-270, 2005

**Table 1.** Clinical characteristics of all 237 donors and 77 donors including in study population.

| Variable | Over all | | Study population | |
|---|---|---|---|---|
| | N=237 | Range | N=77 | P Value* |
| *Physical and biochemical examinations* | | | | |
| Male, *n* (%) | 104 (43.9) | | 32 (41.6) | 0.62 |
| Age, *median* (years) | 56 (49 to 63) | 21 to 76 | 57 (49 to 64) | 0.43 |
| Body mass index, *mean* (kg/m$^2$) | 23.2 (3.3) | 14.4 to 33.7 | 23.5 (3.2) | 0.32 |
| Systolic blood pressure, *mean* (mmHg) | 124.3 (15.3) | 88 to 172 | 124.8 (14.8) | 0.70 |
| Diastolic blood pressure, *mean* (mmHg) | 75.9 (11.6) | 46 to 104 | 77.4 (10.6) | 0.18 |
| Albumin, *median* (g/dl) | 4.3 (4.1 to 4.5) | 3.5 to 4.9 | 4.3 (4.1 to 4.5) | 0.74 |
| Hemoglobin, *median* (g/dl) | 13.7 (1.5) | 8.2 to 17.1 | 13.7 (1.4) | 0.88 |
| Uric acid, *median* (mg/dl) | 5.0 (1.4) | 1.7 to 9.3 | 5.1 (1.3) | 0.75 |
| Total cholesterol, *mean* (mg/dl) | 201.6 (36.4) | 102 to 291 | 197.1 (37.0) | 0.16 |
| Triglyceride, *median* (mg/dl) | 120 (82 to 185) | 35 to 538 | 128 (83 to 191) | 0.62 |
| *Renal function tests* | | | | |
| Estimated GFR, *median* (ml/min/1.73m$^2$)§ | 70.6 (64.1 to 77.7) | 44.1 to 125.4 | 68.7 (62.0 to 78.4) | 0.14 |
| Creatinine clearance, *median* (ml/min/1.73m$^2$)† | 114.0 (96.6 to 130.6) | 72.0 to 218.8 | 111.9 (96.9 to 33.3) | 0.94 |
| CKD stage 3 or more at evaluation, *n* (%) | 36 (15.2) | | 14 (18.2) | 0.37 |

Values were expressed as number (%), mean (SD), and median (IQR) when appropriate. *; Comparison with the other 160 donors who had not been followed until 3 years after donation. §; Post-hoc evaluation at the time of this study. †; Creatinine clearance in 2-hours was measured in outpatient clinic.

**Table 2.** Comparison the mean absolute changes in eGFR of postoperative donors with those of CKD patients and the general populations.

| | This study | Imai *et al.* (19) | Erikson *et al.* (22) | Jones *et al.* (23) | MDRD study group (24) | |
|---|---|---|---|---|---|---|
| | | | | | Study A | Study B |
| N | 77 | 120727 | 3047 | 726 | 553 | 219 |
| Characteristics of studied subjects | Postoperative kidney donors | Community-based study in the Japanese | Patients with CKD stage3 in the general population | CKD patients before nephrology referral | CKD patients with diverse renal diseases included in MDRD study | |
| Age, *years* | 57 (49 to 64) | ≥40 | 75 (67 to 81) | 72±14 | 52.2±12 | 50.8±12 |
| eGFR at baseline, *ml/min/1.73m$^2$* | 45.7 (41.4 to 52.3) | N/A§ | 55.1 (50.8 to 57.9) | 29 (18 to 38) | 25-55 | 13-24 |
| Follow-up, *years* | 2.0 | 10 | 3.7 | 2.9 | 2.3 | 2.2 |
| Yearly change in eGFR, *ml/min/1.73m$^2$* | 0.90±1.7 | -0.36* | -1.03* | -5.4 (-13 to -2)** | -3.8±4.2** | -4.0±3.1** |
| Rate of subjects with yearly change in eGFR <0, *%* | 27.3 | N/A | 73* | 84** | 81** | 89** |

Variables were expressed as Mean±SD, Median (IQR). Only values or range of variables were expressed if their detailed distributions were not available. §; Subjects were widely included patients with CKD stage1 to 5. *; $P<0.01$ and **; $P<0.001$ versus this study.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
N/A, not available.

**Table 3.** Yearly changes in renal function since 1 year after donation stratified by the quartiles of preoperative eGFR, with adjustment for age (N=77).

| | Preoperative eGFR, ml/min/1.73m$^2$ | | | |
|---|---|---|---|---|
| | eGFR ≥ 80 | eGFR 70 to 79 | eGFR 60 to 69 | eGFR < 60 |
| | N=12 | N=23 | N=28 | N=14 |
| *Change in mean eGFR ml/min/1.73m$^2$ (95% confidence interval)* | | | | |
| Absolute change, ml/min/1.73m$^2$ | 0.61 (-0.30 to 1.52) | 1.25 (0.25 to 2.25) | 0.95 (0.43 to 1.46) | 0.50 (-0.42 to 1.42) |
| Percent change, % | 1.10 (-0.50 to 2.70) | 2.85 (0.71 to 4.98) | 2.17 (1.07 to 3.27) | 1.45 (-1.28 to 4.19) |
| *Age-adjusted change in mean eGFR ml/min/1.73m$^2$ (95% confidence interval)* | | | | |
| Absolute change, ml/min/1.73m$^2$ | 0.79 (-0.15 to 1.74) | 1.23 (0.23 to 2.24) | 0.95 (0.50 to 1.41) | 0.36 (-0.61 to 1.32) |
| Percent change, % | 1.43 (-0.22 to 3.07) | 2.80 (0.65 to 4.95) | 2.15 (1.18 to 3.12) | 1.01 (-1.83 to 3.85) |

eGFR, estimated glomerular filtration rate

**Table 4.** Yearly changes in renal function since 1 year after donation stratified by the quartiles of eGFR 1 year after donation, with adjustment for age (N=77).

| | Postoperative eGFR 1 year after donation, ml/min/1.73m$^2$ | | | |
|---|---|---|---|---|
| | eGFR ≥ 60 | eGFR 50 to 59 | eGFR 40 to 49 | eGFR < 40 |
| | N=3 | N=22 | N=36 | N=16 |
| *Change in mean eGFR ml/min/1.73m$^2$ (95% confidence interval)* | | | | |
| Absolute change, ml/min/1.73m$^2$ | -0.38 (-2.52 to 1.76) | 0.49 (-0.28 to 1.26) | 1.28 (0.67 to 1.88) | 0.87 (0.04 to 1.70) |
| Percent change, % | -0.62 (-4.11 to 2.88) | 0.95 (-0.48 to 2.38) | 2.83 (1.50 to 4.16) | 2.42 (-0.01 to 4.83) |
| *Age-adjusted change in mean eGFR ml/min/1.73m$^2$ (95% confidence interval)* | | | | |
| Absolute change, ml/min/1.73m$^2$ | -0.38 (-2.59 to 1.83) | 0.55 (-0.23 to 1.32) | 1.27 (0.68 to 1.87) | 0.80 (-0.04 to 1.64) |
| Percent change, % | -0.61 (-4.22 to 3.00) | 1.06 (-0.38 to 2.49) | 2.82 (1.50 to 4.14) | 2.22 (-0.22 to 4.66) |

eGFR, estimated glomerular filtration rate

**Table 5.** Clinical characteristics before and after donation in 8 donors who developed ESRD.

| Variables | Number of patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| *Before donation* | | | | | | | | |
| Sex | M | F | M | M | F | M | F | M |
| Age, years | 72 | 55 | 49 | 40 | 56 | 20 | 45 | 41 |
| eGFR, (ml/min per 1.73m$^2$) | 68.9 | 54.0 | 84.1 | 69.4 | 60.7 | N/A | N/A | 62.5 |
| BMI, kg/m$^2$ | 25.2 | 25.5 | 30.5 | 24.7 | 23.5 | N/A | N/A | 21.1 |
| Hypertension | | | | | ○ | | | |
| Proteinuria | | | ◎ | ◎ | | | | |
| Hematuria | | | | | | | | |
| Smoke | | | | | | ○ | | ○ |
| *After donation until developing CKD stage 4* | | | | | | | | |
| eGFR immediately after donation, (ml/min per 1.73m$^2$) | 40.0 | 43.7 | 50.5 | 62.9 | 43.9 | 41.7‡ | 60.7‡ | 44.9 |
| Time for Development, years | 14.0 | 20.9 | 16.5 | 16.3 | 10.9 | 13.6 | 13.9 | 0.3 |
| Hypertension | | ○ | ○ | ◎ | ◎ | | | |
| Proteinuria | | ◎ | ◎ | ◎ | ◎ | ◎ | | |
| Hematuria | ◎ | | ◎ | | ◎ | | | |
| Diabetes mellitus | | | ◎ | | | | | |
| Anemia | | ◎ | | | | ◎ | | |
| Dyslipidemia | ○ | | ◎ | ○ | ○ | | | |
| Hyperuricemia | ◎ | ◎ | | | | | | |
| *Time for developing ESRD, years* | 14.8 | 22.0 | 16.5 | 18.0 | 12.0 | 14.9 | 13.9 | 0.8 |

○; positive finding or newly development, but well controlled with medications. ◎; persistent positive finding with or without medications. Blank; negative findings. ‡; eGFR evaluated in the next visiting after donation. N/A, not available.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Definitions: Hypertension, more than 140 or 90 mmHg in systolic or diastolic blood pressure; Anemia, less than 13 or 11 g/dl if female in serum hemoglobin; Dyslipidemia, more than 220 or 150 mg/dl in serum total cholesterol or triglyceride; Hyperuricemia, more than 7 or 6 mg/dl if female in serum uric acid.

**Table 6.** Risk factors for developing ESRD after donation.

| Variable | Case N=8 | Control N=24 | Crude risk Hazard ratio (95%CI) | Crude risk P Value | Adjusted risk* Hazard ratio (95%CI) | Adjusted risk* P Value |
|---|---|---|---|---|---|---|
| Male sex, n (%) | 5 (62.5) | 15 (62.5) | | | | |
| Age ,years | 47.4 (14.8) | 48.5 (11.3) | | | | |
| Pre-donation eGFR †¶ | 66.6 (10.3) | 71.4 (12.3) | 0.95 (0.87 to 1.02) | 0.14 | 0.93 (0.83 to 1.01) | 0.07 |
| Pre-donation BMI †¶ | 25.1 (3.1) | 23.6 (2.2) | 1.18 (0.80 to 1.66) | 0.40 | 1.16 (0.80 to 1.63) | 0.41 |
| Past history of hypertension, n (%) | 1 (12.5) | 4 (16.7) | 0.90 (0.05 to 5.21) | 0.92 | 1.00 (0.05 to 7.02) | 0.99 |
| Proteinuria before donation, n (%) | 2 (25.0) | 1 (4.2) | 2.56 (0.36 to 12.0) | 0.30 | 2.52 (0.33 to 16.2) | 0.34 |
| Smoking, n (%) | 2 (25.0) | 6 (25.0) | 1.45 (0.20 to 7.00) | 0.67 | 1.31 (0.12 to 10.5) | 0.81 |
| eGFR immediately after donation ¶ | 48.5 (8.7) | 48.4 (8.6) | 1.00 (0.03 to 15.4) | 0.92 | 0.98 (0.88 to 1.08) | 0.74 |
| Yearly change in post-donation eGFR ‡¶ | 0.46 (0.91) | 0.37 (0.52) | 1.09 (0.35 to 12.2) | 0.45 | 1.59 (0.27 to 11.2) | 0.61 |
| CKD progression factor acquired after donation § | | | | | | |
| Persistent proteinuria, n (%) | 5 (71.4) | 3 (14.3) | 4.92 (1.04 to 34.8) | 0.04 | 6.10 (1.13 to 52.8) | 0.03 |
| Uncontrolled hypertension, n (%) | 2 (28.6) | 2 (9.5) | 2.86 (0.40 to 14.7) | 0.26 | 3.27 (0.40 to 22.6) | 0.24 |
| CKD accelerating factor acquired after donation** | | | | | | |
| Acute cardiovascular event, n (%) | 4 (50.0) | 0 (0) | 6.03 (1.40 to 25.8) | 0.02 | 9.45 (1.83 to 58.0) | 0.01 |
| Severe infection, n (%) | 3 (37.5) | 0 (0) | 4.74 (0.95 to 19.9) | 0.06 | 12.0 (1.51 to 180) | 0.02 |
| Cardiovascular disease, n (%) | 3 (37.5) | 3 (12.5) | 1.40 (0.28 to 5.89) | 0.66 | 1.63 (0.30 to 8.77) | 0.55 |
| Hospitalization due to CKD accelerating factor, n (%) | 5 (62.5) | 2 (8.3) | 4.45 (1.07 to 22.0) | 0.04 | 7.80 (1.44 to 65.7) | 0.02 |

Variables were expressed as number (%) or mean (SD). *; Adjusted for age and sex.

Exclusion of patient with matched pairs from analysis and the reason: †; Patient 6, 7, and ‡; Patient 6, 7, 8 (missing data), §; Patient 8 (too short-term observation to evaluate CKD progression factors). ¶; Evaluation of risk by increment of 1 unit in each variable (eGFR, ml/min/1.73m$^2$; BMI, kg/m$^2$).

**; Each category of CKD accelerating factors includes several disorders as follow: Acute cardiovascular event, CHF or cardiogenic shock; Severe infection, pneumonia or pyelonephritis needed for admission; Cardiovascular disease, CHF, cerebral infarction or sick sinus syndrome.

Abbreviations: BMI, body-mass index; CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

**Table 7.** Pre-donation association of microscopic hematuria with clinical characteristics related to kidney function.

| Variable | Microscopic hematuria, n (%) | | | | P Value |
|---|---|---|---|---|---|
| | Total | No | Occasional | Persistent | |
| | 242 (100) | 193 (79.3) | 29 (12.1) | 20 (8.3) | |
| Occasional proteinuria by dipstick | | | | | |
| No | 231 | 214 (92.6) | | 17 (7.4) | 0.16 |
| Yes | 11 | 8 (72.7) | | 3 (27.3) | |
| Family history of IgA nephropathy or Alport syndrome | | | | | |
| No | 199 | 187 (94.0) | | 12 (6.0) | 0.02 |
| Yes | 43 | 35 (81.4) | | 8 (18.6) | |
| Urinary dysmorphic RBC | | | | | |
| No | 220 | 215 (97.7) | | 5 (2.3) | <0.001 |
| Yes | 22 | 7 (31.8) | | 15 (68.2) | |

**Table 8.** Association between characteristics at baseline and persistent proteinuria after donation in 242 living kidney donors.

| Variable | Proteinuria after donation | | P Value |
|---|---|---|---|
| | No or Occasional (n=222) | Persistent (n=20) | |
| Male sex, % | 40.0 | 45.0 | 0.67 |
| Age, years | 57 (49 to 64) | 61 (54 to 69) | 0.15 |
| ≥70, % | 8.6 | 20.0 | 0.11 |
| Body-mass index, kg/m$^2$ | 22.8 (20.9 to 25.0) | 24.0 (21.6 to 25.4) | 0.32 |
| ≥30, % | 4.5 | 5.0 | 1.00 |
| Systolic blood pressure, mmHg | 118 (112 to 129) | 132 (113 to 150) | 0.02 |
| Diastolic blood pressure, mmHg | 74 (66.0 to 80.3) | 77 (68.5 to 88.0) | <0.001 |
| Systolic ≥130 or Diastolic ≥85, % | 27.5 | 55.0 | 0.02 |
| Treatment with antihypertensives, % | 17.1 | 35.0 | 0.07 |
| eGFR, ml/min/1.73m$^2$ | 78.6 (70.7 to 91.0) | 80.2 (69.4 to 85.1) | 0.96 |
| CKD stage 3, % | 7.7 | 10.0 | 0.66 |
| Proteinuria | | | |
| Occasional positive test by dipstick, % | 2.3 | 30.0 | <0.001 |
| 24-hr urine protein of ≥ 150 mg/day, % | 0.5 | 5.0 | 0.16 |
| Hematuria | | | |
| Occasional, % | 12.6 | 5.0 | 0.48 |
| Persistent, % | 5.9 | 35.0 | <0.001 |
| Urinary dysmorphic RBC, % | 7.2 | 30.0 | 0.01 |
| Smoking, % | 24.8 | 25.0 | 1.00 |
| Donation for sibling, % | 66.2 | 75.0 | 0.42 |
| Family history of kidney disease | | | |
| IgA nephrolpathy or Alport syndrome, % | 15.3 | 20.0 | 0.37 |
| Other chronic glomerulopathy, % | 13.1 | 20.0 | 0.49 |
| Unknown, % | 8.6 | 0 | 0.38 |
| Albumin, g/dl | 4.3 (4.1 to 4.5) | 4.3 (4.0 to 4.4) | 0.46 |
| Hemoglobin, g/dl | 13.5 (12.8 to 14.3) | 13.6 (12.2 to 14.6) | 0.73 |
| Uric acid, mg/dl | 4.8 (4.1 to 5.9) | 4.9 (4.0 to 6.0) | 0.74 |
| Total cholesterol, mg/dl | 202 (178 to 232) | 209 (171 to 221) | 0.78 |
| Triglyceride, mg/dl | 111 (76 to 177) | 118 (85 to 155) | 0.66 |
| Time since donation, month | 27 (15 to 48) | 35 (18 to 47) | 0.37 |

Variables were expressed as median (interquartile range), or percentage.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

**Table 9.** Risk for persistent proteinuria after kidney donation in 242 living kidney donors.

| Variable | Univariate analysis | | Multivariate analysis† | |
|---|---|---|---|---|
| | Odds ratio (95%CI) | P Value | Odds ratio (95%CI) | P Value |
| Pre-donation characteristics | | | | |
| Proteinuria by dipstick (versus negative test) | | | | |
| Occasional | 18.6 (5.04 to 72.2) | <0.001 | 14.0 (3.22 to 65.8) | <0.001 |
| Hematuria (versus negative test) | | | | |
| Occasional | 0.53 (0.03 to 2.90) | 0.53 | 0.39 (0.02 to 2.74) | 0.39 |
| Persistent without d-RBC | 3.77 (0.18 to 28.1) | 0.31 | 3.80 (0.17 to 33.5) | 0.33 |
| Persistent with d-RBC | 10.0 (2.96 to 33.0) | <0.001 | 12.3 (2.65 to 59.7) | 0.002 |
| Blood pressure (versus normotension) | | | | |
| Treated normotension | 2.59 (0.37 to 11.9) | 0.30 | 0.85 (0.08 to 5.76) | 0.88 |
| Hypertension | 3.74 (1.40 to 10.6) | 0.01 | 3.48 (1.06 to 12.4) | 0.04 |
| Post-donation characteristics | | | | |
| Hematuria (versus negative test)§ | | | | |
| Occasional | 1.65 (0.24 to 6.92) | 0.56 | 3.40 (0.45 to 17.7) | 0.20 |
| Persistent without d-RBC | 4.75 (0.23 to 36.6) | 0.25 | 8.07 (0.33 to 86.8) | 0.16 |
| Persistent with d-RBC | 6.33 (2.19 to 18.2) | <0.001 | 8.36 (2.37 to 31.5) | 0.001 |

†: Adjusted for age, sex, proteinuria, hematuria, eGFR, and body-mass index before donation. Excluded variables from covariates which had P-Value more than 0.2 in univariate analysis: smoking, donation for sibling, family history of IgA nephropathy or Alport syndrome, serum albumin, hemoglobin, uric acid, total cholesterol, triglyceride, and time since donation.

§: Hematuria before donation was excluded from the multivariate model because of significant bias in the distribution of hematuria between pre- and post-donation.

Abbreviations: CI, confidence interval; d-RBC, dysmorphic red blood cell; eGFR, estimated glomerular filtration rate.

**Table 10.** Association between yearly percent changes in glomerular filtration rate since 1 year after donation and clinical characteristics in 163 living kidney donors.

| Variable | Univariate analysis | | Multivariate analysis † | |
|---|---|---|---|---|
| | β (95%CI) | P Value | β (95%CI) | P Value |
| Pre-donation characteristics | | | | |
| Body-mass index, kg/m$^2$, 1 unit | 0.26 (0.11 to 0.42) | 0.001 | 0.20 (0.02 to 0.38) | 0.03 |
| eGFR, ml/min/1.73m$^2$, 1 unit | 0.03 (-0.01 to 0.06) | 0.12 | 0.04 (0.01 to 0.07) | 0.04 |
| Proteinuria by dipstick (versus negative test) | | | | |
| Occasional | -0.01 (-2.49 to 2.48) | 1.00 | -0.27 (-2.79 to 2.24) | 0.83 |
| Post-donation characteristics | | | | |
| Hematuria (versus negative test) | | | | |
| Occasional | 0.23 (-1.56 to 2.03) | 0.80 | 0.29 (-1.50 to 2.08) | 0.75 |
| Persistent without d-RBC | -0.10 (-3.53 to 3.33) | 0.96 | -0.74 (-4.21 to 2.73) | 0.67 |
| Persistent with d-RBC | -2.07 (-3.70 to -0.44) | 0.01 | -1.69 (-3.36 to -0.01) | 0.048 |
| Time since donation, month, 1 unit | -0.02 (-0.05 to 0.01) | 0.12 | -0.03 (-0.06 to 0.01) | 0.08 |

†: Adjusted for age, sex, proteinuria, eGFR, body-mass index all before donation, hematuria after donation, and variables with P-Value less than 0.2 in univariate analysis; serum albumin, uric acid, total cholesterol at donation, and donation for sibling ($R^2$=0.15).

Excluded variables from covariates which had P-Value more than 0.2 in univariate analysis: pre-donation variables of hematuria, smoking, family history of IgA nephropathy or Alport syndrome, serum hemoglobin, and triglyceride; post-donation variables of proteinuria.

Abbreviations: CI, confidence interval; d-RBC, dysmorphic red blood cell; eGFR, estimated glomerular filtration rate.

**Table 11.** Pre-donation risk factors for persistent glomerular hematuria after kidney donation in 242 living kidney donors.

| Variable | Univariate analysis | | Multivariate analysis† | |
|---|---|---|---|---|
| | Odds ratio (95%CI) | P Value | Odds ratio (95%CI) | P Value |
| Proteinuria by dipstick (versus negative test) | | | | |
| Occasional | 2.61 (0.55 to 9.62) | 0.17 | 0.58 (0.02 to 7.99) | 0.72 |
| Hematuria (versus negative test ) | | | | |
| Occasional | 10.1 (3.32 to 31.7) | <0.001 | 3.88 (0.80 to 16.7) | 0.09 |
| Persistent | 150.6 (40.4 to 769) | <0.001 | 31.4 (4.30 to 263) | <0.001 |
| Urinary dysmorphic RBC (versus negative test) | | | | |
| Positive | 100.8 (29.9 to 471) | <0.001 | 15.2 (2.04 to 161) | 0.007 |
| Family history of IgA nephropathy or Alport syndrome (versus negative test) | | | | |
| Positive | 3.46 (1.51 to 7.74) | 0.01 | 3.45 (0.84 to 13.8) | 0.09 |

†: Adjusted for age, sex, proteinuria, hematuria, dysmorphic RBC, eGFR, and body-mass index all before donation, in addition to serum albumin, hemoglobin, smoking status, and family history of IgA nephropathy or Alport syndrome.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

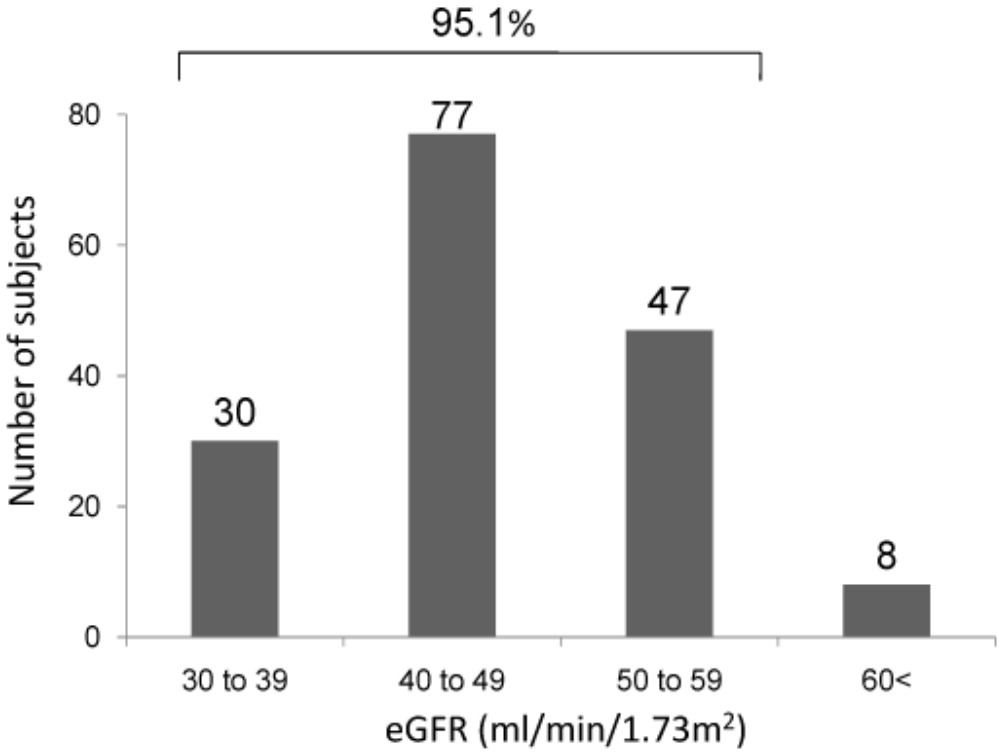


**Figure 1.** Distribution of eGFR 1 year after donation (N=162).

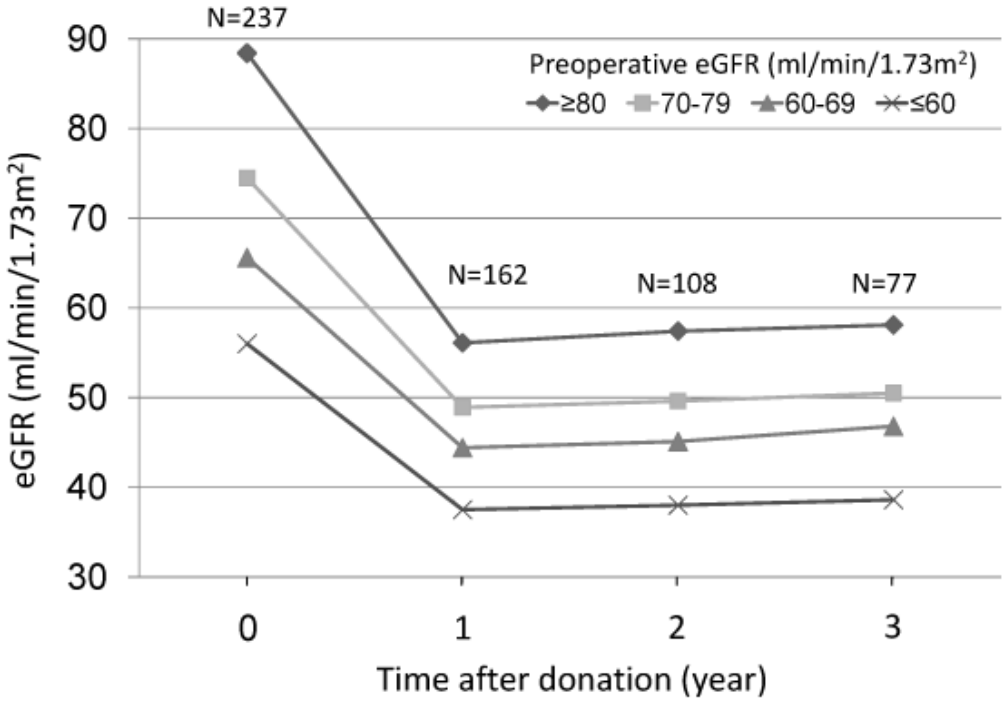


**Figure 2.** Trend of mean renal function in postoperative donors until 3 years after donation.

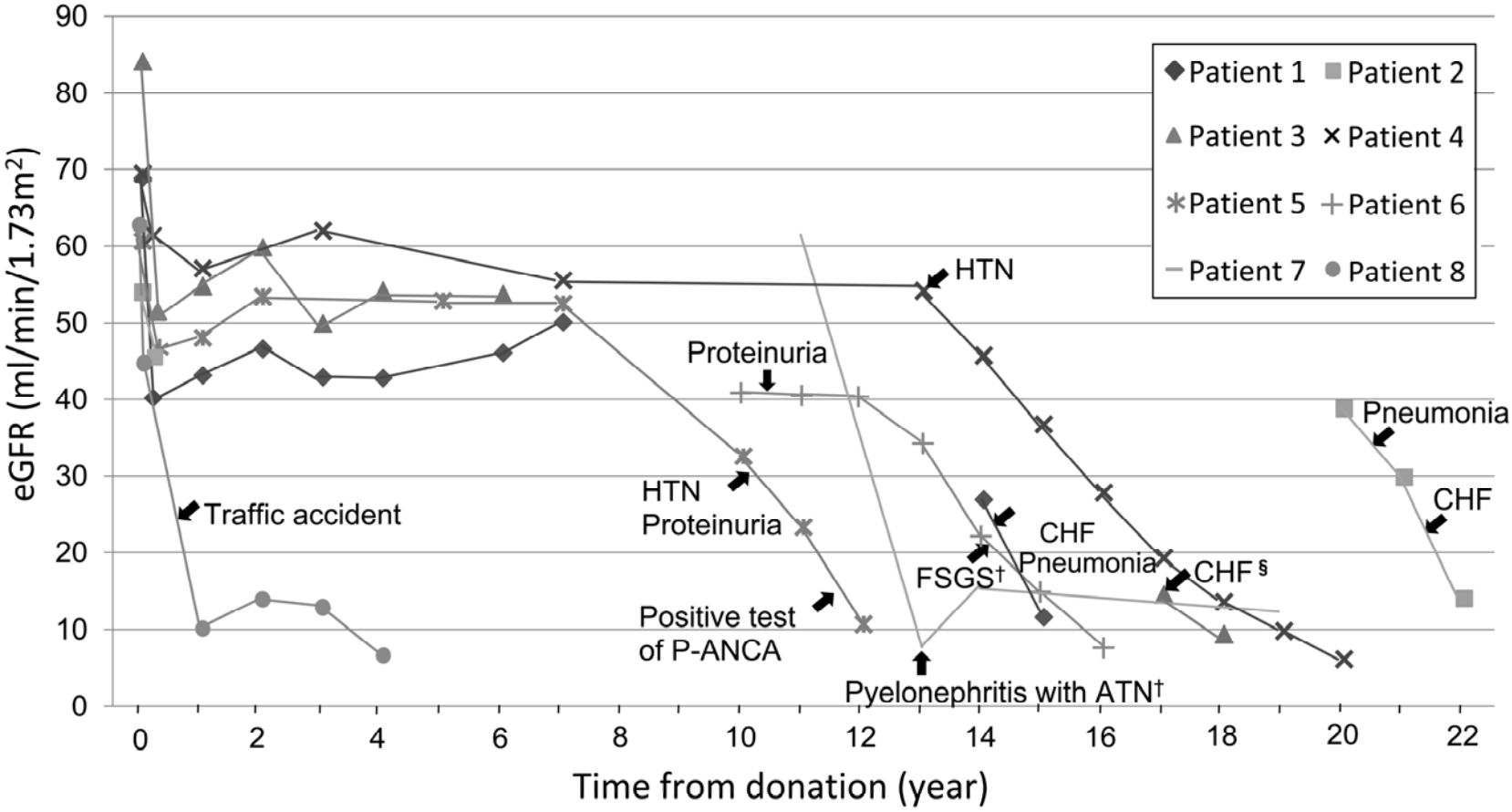


**Figure3.** Clinical courses in living kidney donors who developed end-stage renal disease. Because some patients were temporarily lost to follow-up, lines in patient 1 to 3 were discontinuous. Preoperative renal function in patient 6 and 7 were not available.

†; Biopsy proven diagnosis.

§; Congestive heart failure developed before transplant clinic visit at 17 years after donation. A primary care physician informed us of the stable renal function in patient 3 until the previous year.

Abbreviations: ATN; acute tubular necrosis, CHF; congestive heart failure, eGFR; estimated glomerular filtration rate, FSGS; focal segmental glomerular sclerosis.

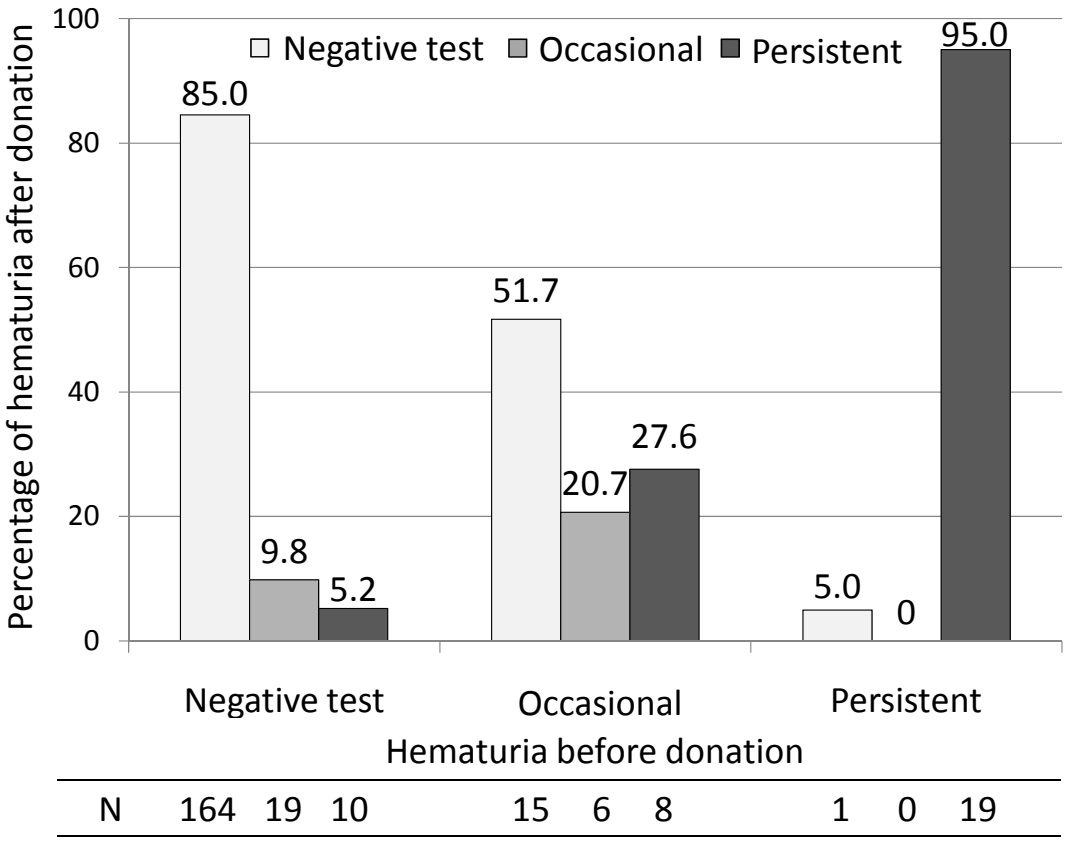


**Figure 4.** Distribution of changes in hematuria by donation in 242 living kidney donors.