Proteinuria and Albuminuria

Moderatore: Luigi Biancone (Torino)

Presenter: Umberto Maggiore (Parma)

Systematic: Barbara Buscemi (Palermo) - Ilaria Umbro (Roma)

ERBP 2013

3.5 On which criteria should we select living kidney donors to optimize the risk–benefit ratio of their donation?

Proteinuria

- We recommend quantifying urinary protein excretion in all potential living donors. (1C)

- We recommend overt proteinuria is a contraindication for living donation [24-h total protein >300 mg or spot urinary albumin to creatinine (mg/g) ratio >300 (>30 mg/mmol)]. (1C)

- We recommend further evaluating potential living donors with persistent (more than three measurements with 3 months interval) proteinuria <300 mg/24 h by the quantification of micro-albuminuria to assess their risk of living donation. (Ungraded statement)

- We suggest considering persistent (more than three measurements with 3 months interval) micro-albuminuria (30–300 mg/24 h) a high risk for donation. (Ungraded statement)

KDIGO 2015

CHAPTER 6: EVALUATION OF PROTEINURIA IN KIDNEY DONOR CANDIDATES

Graded recommendations below were extrapolated from the 2012 KDIGO CKD Guideline

Measurement

6.1: We suggest expressing proteinuria as albuminuria and NOT as total urine protein. (2B)

6.2: We recommend reporting albuminuria in a random urine single time point collection as albumin-to-creatinine ratio (ACR) in mg/g [mg/mmol], rather than albumin concentration as mg/dL. (1B)

6.3. We suggest initial evaluation of albuminuria (screening) using urine albumin creatinine ratio (ACR) in a random (untimed) urine specimen. (2B)

6.4: Confirmation of albuminuria should be obtained using: (Not Graded)

6.4.1: Albumin excretion rate (AER, mg/d) in a timed urine specimen

6.4.2: Repeat ACR if AER cannot be obtained

KDIGO 2015

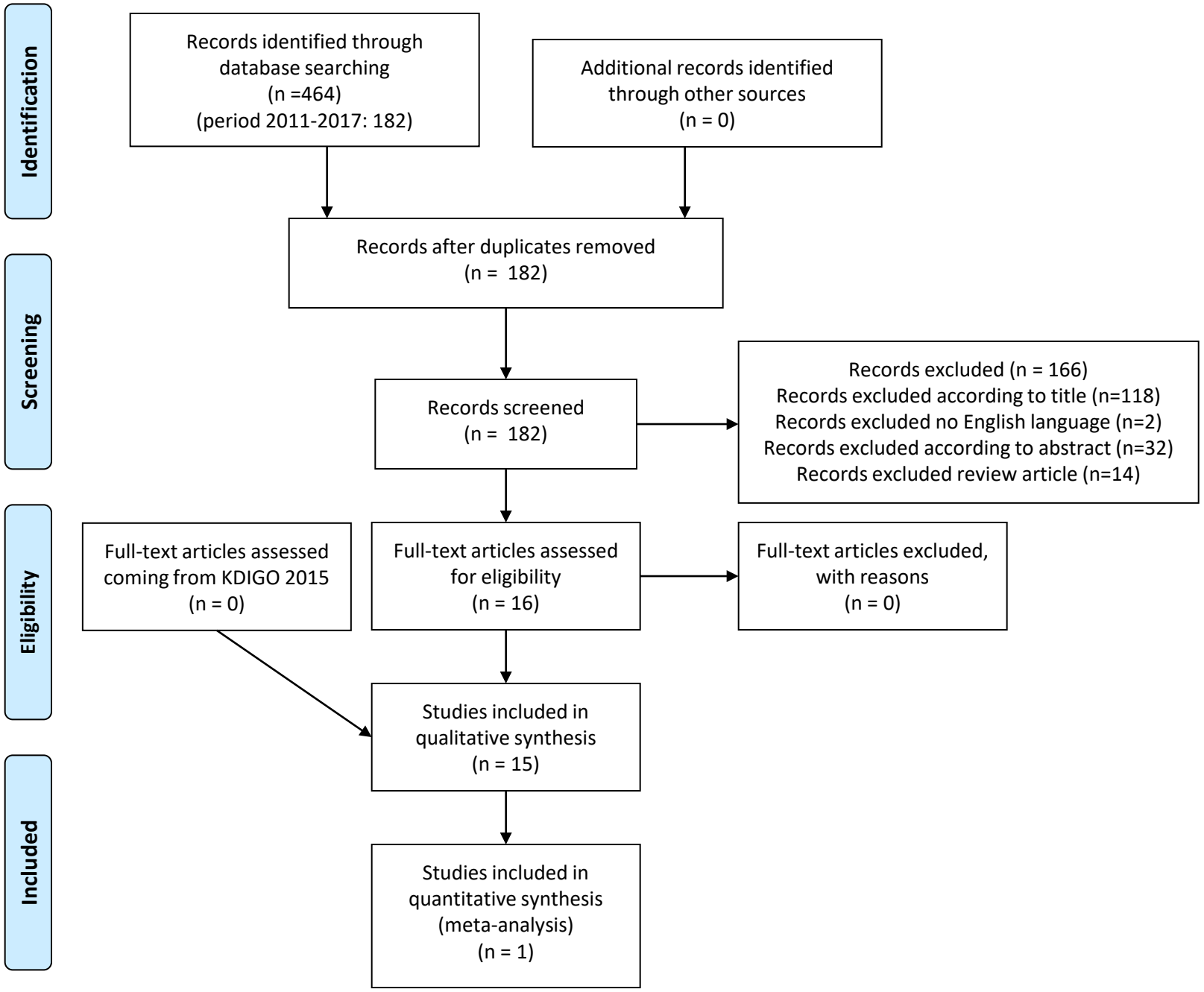
CHAPTER 6: EVALUATION OF PROTEINURIA IN KIDNEY DONOR CANDIDATES

Criteria for Acceptable Pre-Donation Albuminuria

6.5: Urine AER <30 mg/d should be considered as an acceptable level for kidney donation. (Not Graded)

6.6: The decision to approve donor candidates with AER 30-100 mg/d should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. (Not Graded)

6.7: Donor candidates with urine AER >100 mg/d should be excluded from donation (Not Graded)


Identification
Screening
Eligibility
Included
Records identified through database searching (n =464) (period 2011-2017: 182)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 182)
Records screened (n = 182)
Records excluded (n = 166)
Records excluded according to title (n=118)
Records excluded no English language (n=2)
Records excluded according to abstract (n=32)
Records excluded review article (n=14)
Full-text articles assessed coming from KDIGO 2015 (n = 0)
Full-text articles assessed for eligibility (n = 16)
Full-text articles excluded, with reasons (n = 0)
Studies included in qualitative synthesis (n = 15)
Studies included in quantitative synthesis (meta-analysis) (n = 1)

Using Implantation Biopsies as a Surrogate to Evaluate Selection Criteria for Living Kidney Donors

Ashutosh Chauhan,[1] Tayyab S. Diwan,[1] Carlos R. Franco Palacios,[1] Patrick G. Dean,[1] Julie K. Heimbach,[1] George K. Chow,[1] Mikel Prieto,[1] Fernando G. Cosio,[1] Sandra J. Taler,[1] Stephen C. Textor,[1] Yogish C. Kudva,[1] Lynn D. Cornell,[2] and Mark D. Stegall[1,3]

Transplantation 2013;96: 975–980

- In the current study, we analyzed histologic characteristics of kidney biopsies obtained at the time of living donor kidney transplantation (implantation biopsies) using the Banff criteria
- Our goal was to use the presence of moderate to severe changes (MSC) in implantation biopsies from living kidney donors as a surrogate ‘‘outcome.’’ This would allow us to determine if there were certain donor characteristics that led to a higher prevalence of MSC that might then suggest the need for changes in our donor selection criteria
- MSC was present in 4.1% (65 of 1600) of donors. The most common lesions were vascular, including cv (vascular fibrous intimal thickening, 78.4% [n=51]) and ah (arteriolar hyaline thickening, 20% [n=13]). Other lesions were very rare: ci (interstitial fibrosis, 4.61% [n=3]), ct (tubular atrophy, 4.61% [n=3]), and cg (allograft glomerulopathy [n=0])

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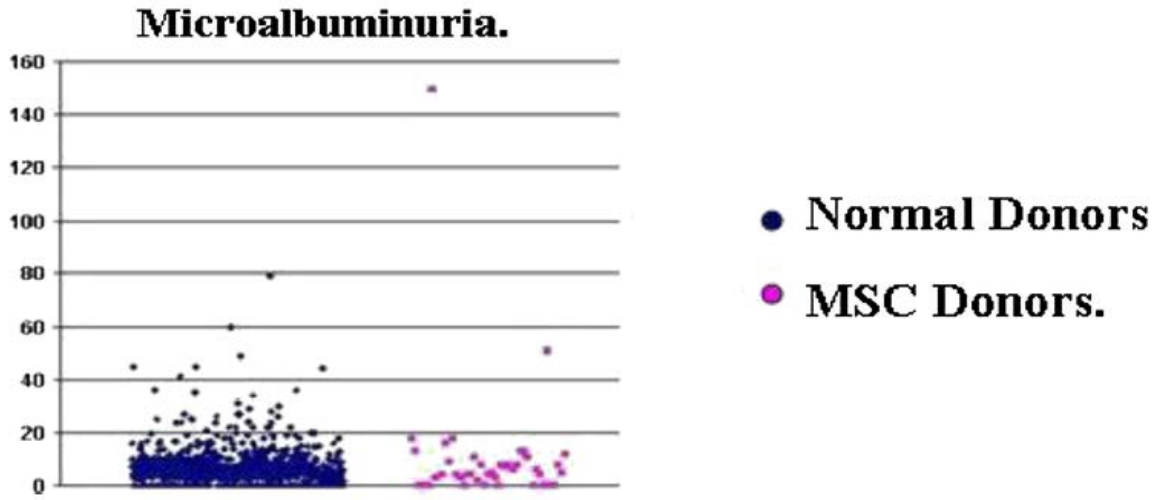

No differences in the distribution of microalbumin excretion among normal and MSC donors

- We do not recommend a change in current selection criteria and would continue to accept donors with characteristics that might be perceived as risk factors (i.e., mild hypertension and obesity) for postdonation complications such as renal failure
- We do recommend that donors with abnormal implantation biopsies be followed more closely and evaluated on a serial basis for the possible development of renal disease

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TABLE 4. Donor selection criteria

Criteria	Evaluation	Acceptability
Urinary albumin excretion	24-hr urine microalbumin excretion	Excretion less than 30 mg per day
Measured GFR	Iothalamate clearance, or	- Iothalamate clearance more than or equal to lower 5th percentile for age and GFR >70 mL/min/SA/min
	24-hr creatinine clearance	Similar criteria for creatinine clearance
	Instructed to discontinue use of nonsteroidal anti-inflammatory drugs and/or cyclooxygenase-2 inhibitors before testing	
Blood pressure	Automated oscillometric blood pressure,	Normal blood pressure
	18 hr-ambulatory blood pressure monitor, and	Hypertension; acceptable
	Hypertensive therapy RN using standardized AHA criteria	(a) Age >40 years
		(b) Caucasian
		(c) Normal blood pressure with simple treatment regimen
		(d) Donor agrees to follow-up with Mayo expanded living-donor program
Blood glucose	FPG <126 mg/dL	Acceptable levels by age
	For borderline levels, 2-hr oral glucose tolerance testing and hemoglobin A1c	Age/FPG: <30 years/<102 mg/dL, 31–49 years/<106 mg/dL, and >50 years/<110 mg/dL
		Unacceptable candidates
		(a) FPG >126 mg/dL on two occasions
		(b) Female <30 years with history of gestational diabetes
BMI	BMI calculation based on height and weight	(a) Donor age <30 years: BMI<30 kg/m^2
		(b) Donor age 30–49 years: BMI<35 kg/m^2
		(c) Donor age 50 years or older: BMI<40 kg/m^2

Short-Term Prognosis of Living-Donor Kidney Transplantation From Hypertensive Donors With High-Normal Albuminuria

Tadashi Sofue,[1,6] Masashi Inui,[2] Taiga Hara,[1] Kumiko Moriwaki,[1] Yoshio Kushida,[3] Yoshiyuki Kakehi,[4] Akira Nishiyama,[5] and Masakazu Kohno[1]

Transplantation 2014;97: 104–110

- The present study was conducted to test the hypothesis that hypertensive donors (HTDs) with high-normal albuminuria (HNA) have a similar prognosis to normotensive donors (NTDs)
- We investigated the effects of HNA and hypertension on transplant prognosis of the donors after living-donor kidney transplantation

Short-Term Prognosis of Living-Donor Kidney Transplantation From Hypertensive Donors With High-Normal Albuminuria

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Transplantation 2014;97: 104–110

TABLE 1. Characteristics of the donors before transplantation

	NA+NTDs	HNA+NTDs	MA+NTDs	NA+HTDs	HNA+HTDs	*P*
Donors, n	16	14	8	5	9	
UAE (mg/g Cr)	9.5 (3.6)	20.1 (4.1)[a]	37.0 (5.2)[a]	10.7 (3.3)	24.4 (7.0)[a,b]	<0.001
Age (years)	58 (8)	53 (12)	61 (9)	59 (10)	67 (7)[a]	0.02
Male, n (%)	5 (31)	4 (29)	5 (63)	1 (25)	4 (45)	0.59
SBP (mm Hg)	118 (11)	120 (11)	120 (12)	138 (8)[a]	144 (11)[a]	<0.001
Dyslipidemia, n (%)	5 (31)	8 (57)	6 (75)	3 (60)	1 (11)	0.06
BMI (kg/m^2)	23 (3)	22 (3)	22 (1)	25 (3)	24 (2)	0.08
Urinary protein (%)	0	0	0	0	0	—
Occult blood in urine (%)	0	0	0	0	0	—
Pretransplantation eGFR (mL/min)	83 (13)	85 (17)	90 (16)	100 (25)	80 (17)	0.22
Anti-hypertensive drugs, n (%)	—	—	—	0.7 (0.3)	1.1 (0.3)	0.36
Use of ARBs, n (%)	—	—	—	1 (25)	5 (56)	0.30
Use of CCBs, n (%)	—	—	—	3 (60)	4 (44)	1.00

At the time of donation, of 38 NTDs:
- 16 had normo - albuminuria (NA+NTDs)
- 14 had HNA (HNA+NTDs)
- 8 had low-grade microalbuminuria (MA+NTDs)

- Of 14 HTDs, 5 had NA (NA+HTDs) and nine had HNA (HNA+HTDs) at the time of donation
- The characteristics of donors, except for UAE at the time of donation, were similar between NA+NTDs, HNA+NTDs, and MA+NTDs. HNA+HTDs were older than NA+NTDs at the time of donation

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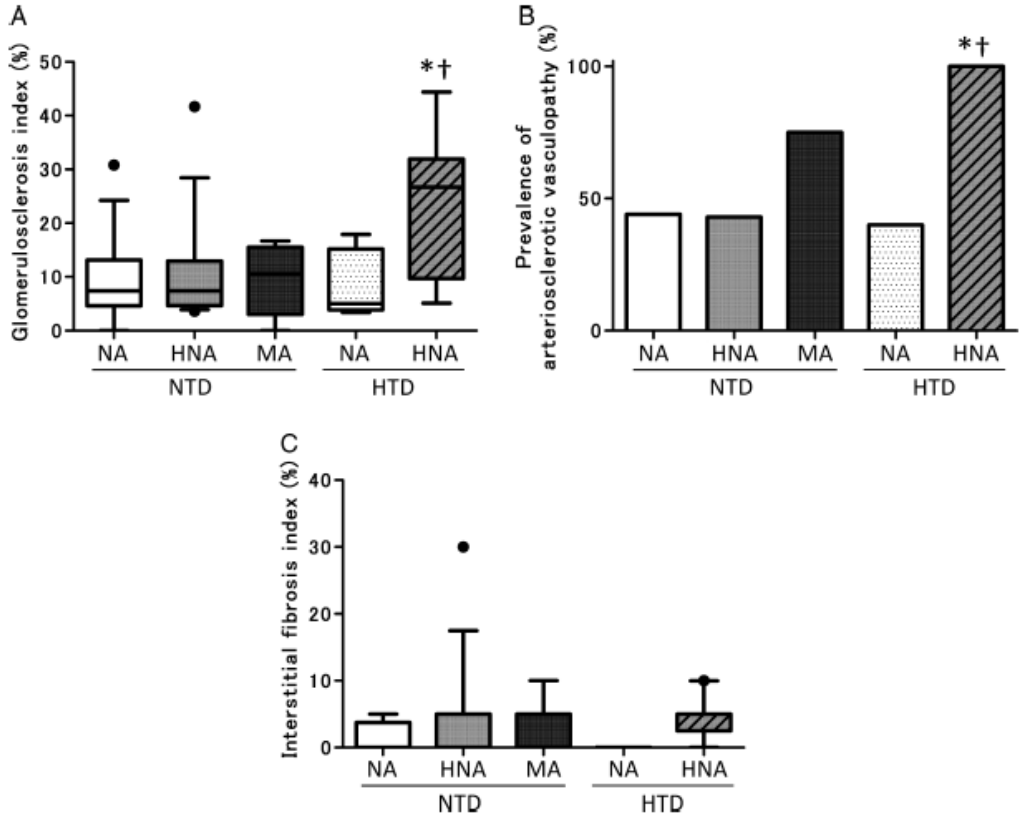

- The glomerulosclerosis index in HNA+HTDs (23 [13]%) was significantly higher than that in NA+NTDs (10 [8]%; P=0.03) or NA+HTDs (9 [6]%; P=0.04)
- The prevalence of arteriosclerotic vasculopathy was significantly higher in HNA+HTDs (100%) than in NA+NTDs (44%; P=0.008) or NA+HTDs (40%; P=0.03)
- The interstitial fibrosis index in HNA+HTDs was similar to that in the other donor groups

Pathologic analysis of pretransplantation biopsies. A, glomerulosclerosis index. B, prevalence of arteriosclerotic vasculopathy. C, Interstitial fibrosis index. AS, arteriosclerosis; *PG0.05 vs. NA+NTDs; †PG0.05 vs. NA+HTDs.

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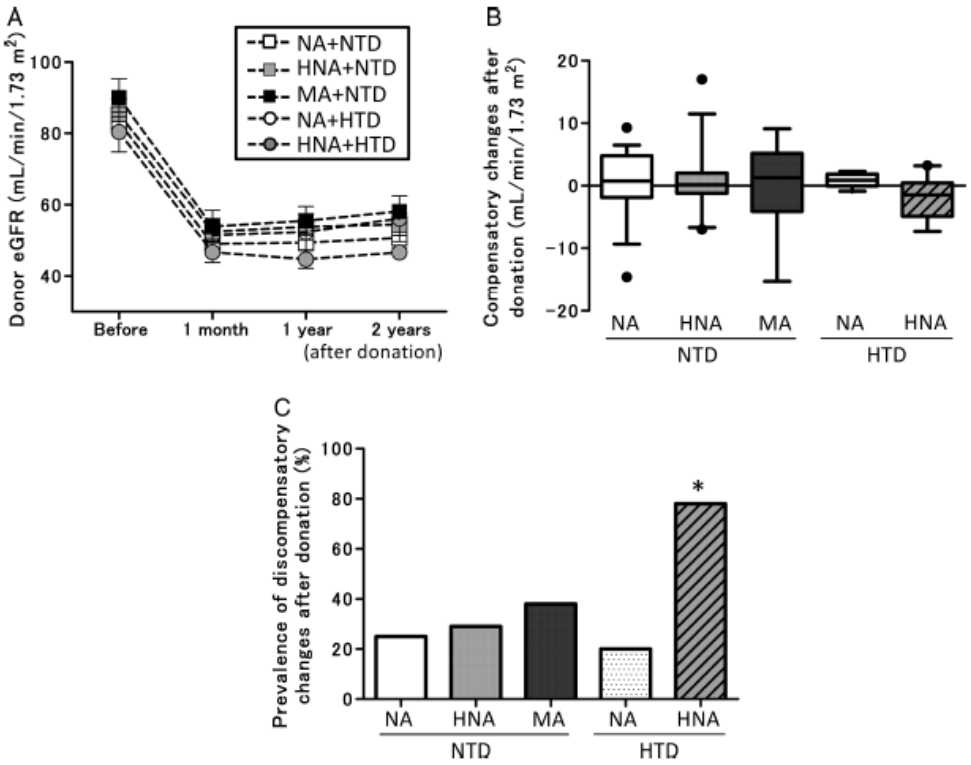

- There were no significant differences in post-transplantation eGFR between the groups of donors, but eGFR tended to be lower in HNA+HTDs than in NA+HTDs at 1 year after donation
- The compensatory changes in kidney function after donation tended to be lower in HNA+HTDs than in the other donor groups, although the differences were not statistically significant
- The risk of discompensatory changes in kidney function after donation was significantly higher in HNA+HTDs than in NA+NTDs (Fig. 2C; OR [95% CI], 10.5 [1.51Y72.9]; P=0.02)

Donor kidney function after donation. A, serial eGFR profiles. B, compensatory changes in kidney function after donation. C, prevalence of discompensatory changes in kidney function after donation. *PG0.05 vs. NA+NTDs.

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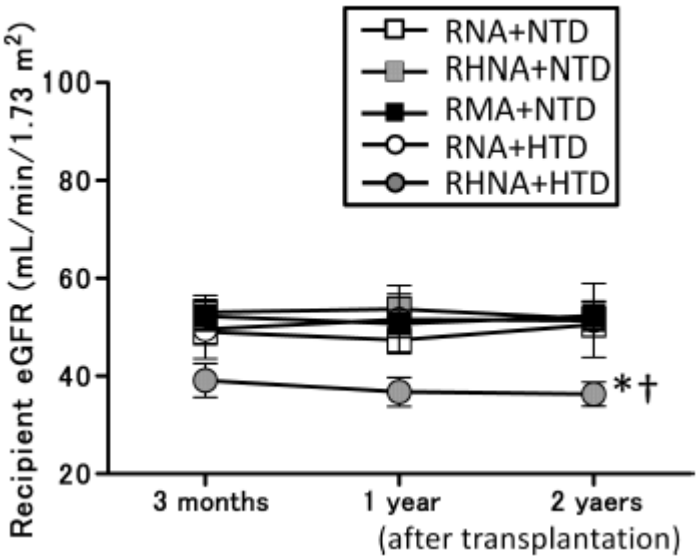

- The coexistence of hypertension and UAE 915 mg/g Cr was associated with discompensatory changes after donation in univariate analysis but not in multivariate analysis (adjusted OR [95% CI], 6.04 [0.19Y192]; P=0.31)
- Donor hypertension or UAE 915 mg/g Cr alone were not significantly associated with discompensatory changes after donation in univariate or multivariate analyses

- The pathologic characteristics of preimplantation biopsies were not significantly associated with discompensatory changes after donation in univariate analysis (glomerulosclerosis index 910%, OR [95% CI], 2.64 [0.82Y8.46]; P=0.15; arterioscleroticvasculopathy, OR [95% CI], 1.43 [0.45Y10.2]; P=0.58; interstitial fibrosis index 910%, OR [95% CI], 0.86 [0.07Y 10.2]; P=1.00)

Prospective Measurement of Urinary Microalbumin in Living Kidney Donor Nephrectomy: Toward Understanding the Renal Functional Recovery Period

http://dx.doi.org/10.1016/j.juro.2014.03.106
Vol. 192, 1172-1177, October 2014
0022-5347/14/1924-1172/0
THE JOURNAL OF UROLOGY®

Young Eun Yoon, Kwang Suk Lee, Kyung Hwa Choi, Kwang Hyun Kim, Seung Choul Yang and Woong Kyu Han*

- This study was conducted to assess the relationship between microalbuminuria (MA) and kidney donor renal function
- Our hypotheses were:
  - 1) donors with MA before nephrectomy may have worse remnant renal function
  - 2) MA is associated with delayed recovery of renal function
  - 3) MA can reflect histological abnormalities in implantation biopsies (IB)
- UACR was used as a measure of MA. The normal range of UACR is defined as less than 30 mg/gm. Differences between donors with MA before the operation and normal donors were investigated
- Histological examinations were performed only in donors who agreed to IB before donor nephrectomy

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- Before donor nephrectomy mean UACR was 7.1 ± 12.7 mg/gm. A correlation analysis showed that UACR was correlated with age (p=0.036), but not with gender, laterality, body mass index or preoperative eGFR

- Eight donors (3.1%) had preoperativeMA (UACR 30 mg/gm or greater). These donors exhibited a lower MDRD-eGFR compared with other donors (90.3 vs 96.7 ml/minute/1.73 m2). However, this difference did not reach statistical significance (p=0.286). The MA group also had a lower MDRD-eGFR at 6 months after kidney donation (60.5 vs 65.8 ml/minute/1.73 m2, p=0.245)

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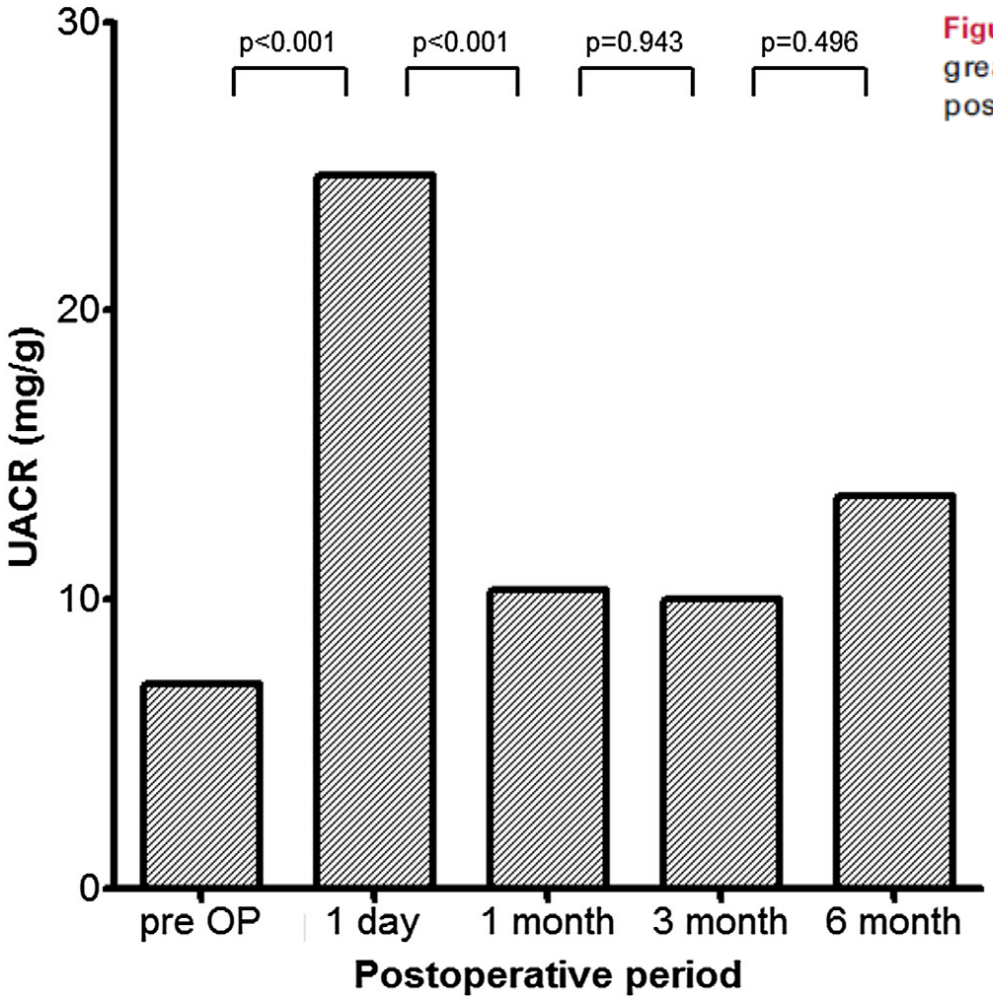

Figure 1. Overall change in UACR. UACR increases were greatest on postoperative day 1 and stabilized from 1 month postoperatively. *Pre OP*, preoperatively.

- At postoperative day 1 UACR was increased to 24.7 ± 18.9 mg/gm
- One month after donation UACR decreased to 10.3 ± 10.7 mg/gm ($p < 0.001$), and remained stable at 3 months (10.0 ± 10.2 mg/gm, $p=0.943$) and 6 months (13.6 ± 20.1 mg/gm, $p=0.496$) after the operation

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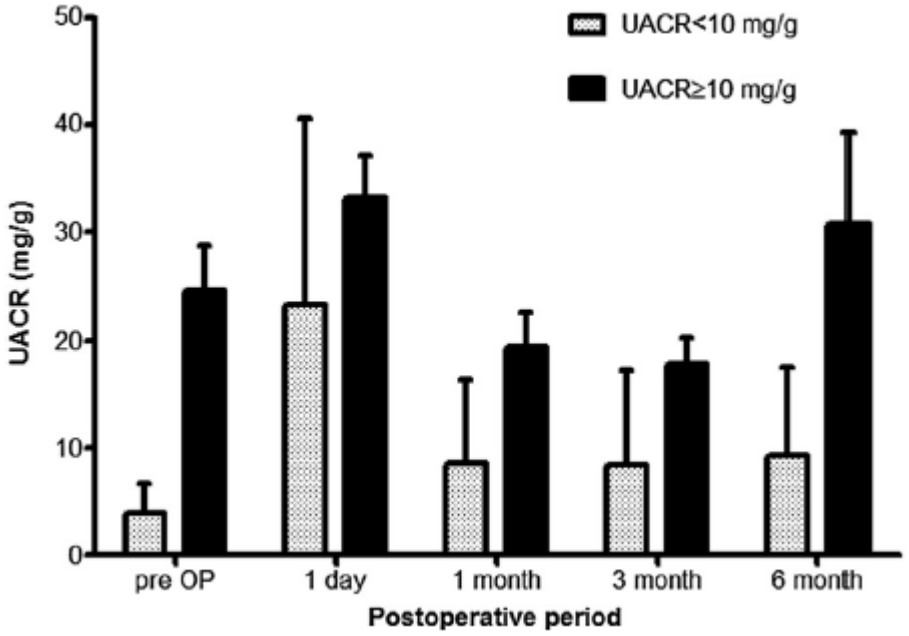

Figure 2. Postoperative UACR. Donors with preoperative UACR 10 mg/gm or greater had higher postoperative UACR throughout observation period than those with preoperative UACR less than 10 mg/gm. All differences between 2 groups were statistically significant ($p < 0.001$). *Pre OP*, preoperatively.

- In correlation analyses preoperative UACR was correlated with UACR at 1 day (r2¼0.039, p <0.001), and 1 month (r2¼0.033, p¼0.009), 3 months (r2¼0.027, p¼0.045) and 6 months (r2¼0.210, p<0.001) postoperatively.
- Overall 40 donors (15.4%) with preoperativeUACR10 mg/gm or greater consistently had higher postoperative UACR values than the other donors
- However, renal function changes were not different between the 2 groups throughout the observation period

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- Of the 259 donors 127 (49%) agreed to a time-zero IB and of these donors 70 (55.1%) had histological abnormalities on IB
- Among the 8 MA donors 6 provided IB. All biopsies of the MA group were histologically abnormal (p=0.024):
  - 1 had IgA nephropathy
  - 1 had arteriosclerosis
  - 1 had focal global glomerulosclerosis
  - 1 had tubular atrophy
  - 2 had hyaline arteriosclerosis
- Even among normal UACR donors those with a UACR 10 mg/gm or greater exhibited abnormal histology. Among donors with UACR 10 mg/gm or greater 84.2% (16 of19) had an abnormal histology whereas 50% of donors with a UACR less than 10 mg/gm had an abnormal histology (p=0.006). Moreover increased UACR was associated with IgA nephropathy (15.8% vs 2.8%, p=0.043).

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- We sought to determine the significance not only of definitive MA (UACR 30 mg/gm or greater) but also that of the subclinical value of 10 mg/gm UACR
- In the current study UACR increased immediately after the operation, which may have occurred because of the compensatory hyperfiltration of the contralateral remnant kidney
- Accordingly we might conclude that donors with a higher preoperative UACR should be followed regularly for years and closely monitored for renal function. To our knowledge there are no standards governing whether donors with increased urinary microalbumin secretion should be permitted to donate their kidneys
- Donors with a preoperatively increased UACR require close observation, even if the level is within the normal range, because there may be a greater possibility of MA developing after donation, which is one of the predictive factors of CKD. Moreover higher UACR levels are associated with histological abnormalities

Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate

N Engl J Med 2016;374:411-21.
DOI: 10.1056/NEJMoa1510491

Morgan E. Grams, M.D., Ph.D., Yingying Sang, M.S., Andrew S. Levey, M.D., Kunihiro Matsushita, M.D., Ph.D., Shoshana Ballew, Ph.D., Alex R. Chang, M.D., Eric K.H. Chow, M.Sc., Bertram L. Kasiske, M.D., Csaba P. Kovesdy, M.D., Girish N. Nadkarni, M.D., M.P.H., Varda Shalev, M.D., M.P.A., Dorry L. Segev, M.D., Ph.D., Josef Coresh, M.D., Ph.D., Krista L. Lentine, M.D., Ph.D., and Amit X. Garg, M.D., Ph.D., for the Chronic Kidney Disease Prognosis Consortium*

- Kidney donation probably increases the risk of ESRD, but the increase in risk according to predonation characteristics is difficult to quantify reliably with the use of existing data
- We developed an online risk tool to help evaluate, counsel, and accept living kidney-donor candidates (www .transplantmodels .com/esrdrisk). Using population-based data, we derived equations that quantify the combined effect of 10 routinely available demographic and health characteristics to estimate the risk of ESRD among kidney-donor candidates over a 15-year time horizon
- We compared risk projections with the observed 15-year incidence of ESRD among living kidney donors, hypothesizing, on the basis of recent reports, that the incidence of ESRD among persons who donate kidneys would be at least four times as high as the projected incidence in the absence of donation
- We considered 13 distinct demographic and health characteristics: age, race, sex, eGFR, urinary albumin-to-creatinine ratio, systolic blood pressure, the presence or absence of noninsulindependent diabetes mellitus, the use or nonuse of antihypertensive medication, smoking status, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), total cholesterol level, low-density lipoprotein (LDL) cholesterol level, and history of kidney stones. All the models were adjusted for an interaction between age and race

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- We applied the risk equations to 57,508 living kidney donors assembled from the U.S. Organ Procurement and Transplantation Network between January 1, 2005, and July 2, 2014. After the exclusion of 4510 donors who were missing predonation data on serum creatinine level or systolic blood pressure, 52,998 donors were included
- The urinary albumin-to-creatinine ratio was imputed as 4 (measured in milligrams of albumin to grams of creatinine) for participants with urinalysis results reported as “negative,” “not done,” or “unknown” and as 30 for those with results reported as “positive”
- Higher urinary albumin-to-creatinine ratio associated with a higher risk of ESRD (hazard ratio per increase of 10×, 2.94; 95% CI, 0.99 to 8.75)

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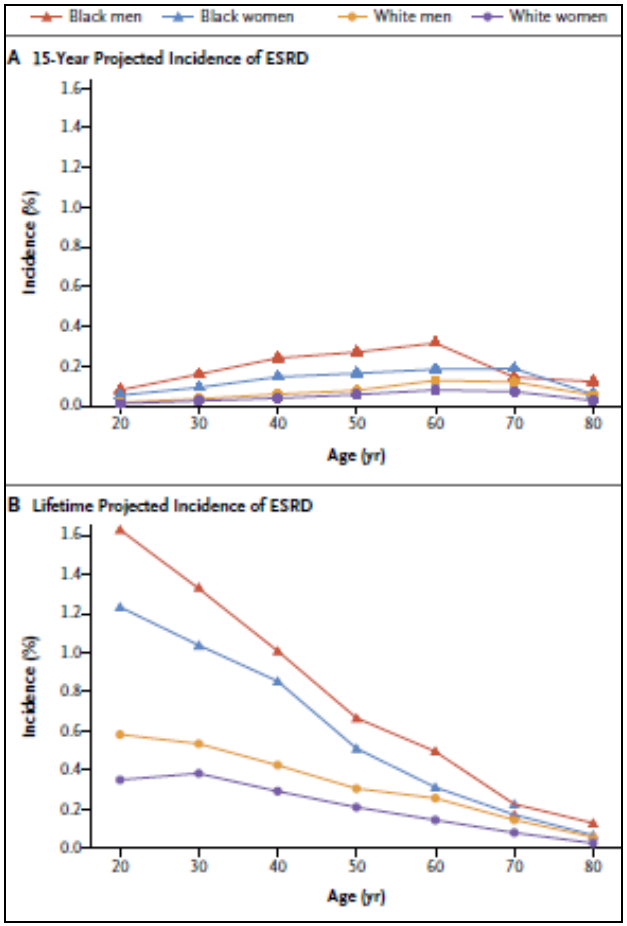

Figure 1. Projections of the Incidence of End-Stage Renal Disease (ESRD) in the United States According to Age, Race, and Sex for the Base-Case Scenario.

The base-case scenario for the 15-year projected risk (Panel A) is the following: an age-specific estimated glomerular filtration rate (114, 106, 98, 90, 82, 74, and 66 ml per minute per 1.73 m2 for an age of 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure of 120 mm Hg, a urinary albumin-to-creatinine ratio of 4 (as measured in milligrams of albumin to grams of creatinine), a BMI of 26, and no diabetes mellitus or use of antihypertensive medication. These factors were selected as being representative of living kidney donors in the United States

The lifetime projections (Panel B) were based on 15 years of follow-up data and were calibrated to the incidence of ESRD in the low-risk population in the United States and thus lack precision. All the estimates reflect the U.S. population average for unmeasured characteristics; individual risk may be higher or lower. Confidence intervals were obtained from simulations that were sampled from the distribution of coefficientsderived from the meta-analysis

Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate

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Table 3. Projected Incidence of ESRD in the United States among Hypothetical Donor Candidates in the Absence of Kidney Donation.*

Scenario	Age	Race	eGFR	Urinary Albumin: Creatinine Ratio†	Systolic Blood Pressure	Smoking Status	15-Yr Projection (95% CI)	Model-Based Lifetime Projection (95% CI)
	yr		*ml/min/1.73 m²*		*mm Hg*			
1	20	Black	115	4	130	Never	0.1 (0.1–0.1)	1.9 (1.2–2.5)
2	20	Black	115	4	130	Current	0.2 (0.1–0.2)	3.4 (2.0–4.8)
3	20	Black	115	4	140‡	Current	0.3 (0.1–0.4)	5.4 (2.9–8.5)
4	20	Black	115	30	140‡	Current	0.7 (0.2–1.5)	13.3 (4.8–27.0)
5	60	White	80	4	140	Never	0.2 (0.1–0.3)	0.4 (0.2–0.6)
6	60	White	60	4	140	Never	0.4 (0.2–0.6)	0.7 (0.3–1.2)
7	60	White	60	4	140‡	Never	0.5 (0.2–0.8)	1.0 (0.5–1.7)
8	60	White	60	30	140‡	Current	2.2 (1.1–3.6)	4.4 (2.1–7.0)

- The projected risk of ESRD was higher among persons with additional risk factors, particularly a high albumin-to-creatinine ratio, than among those without additional risk factors

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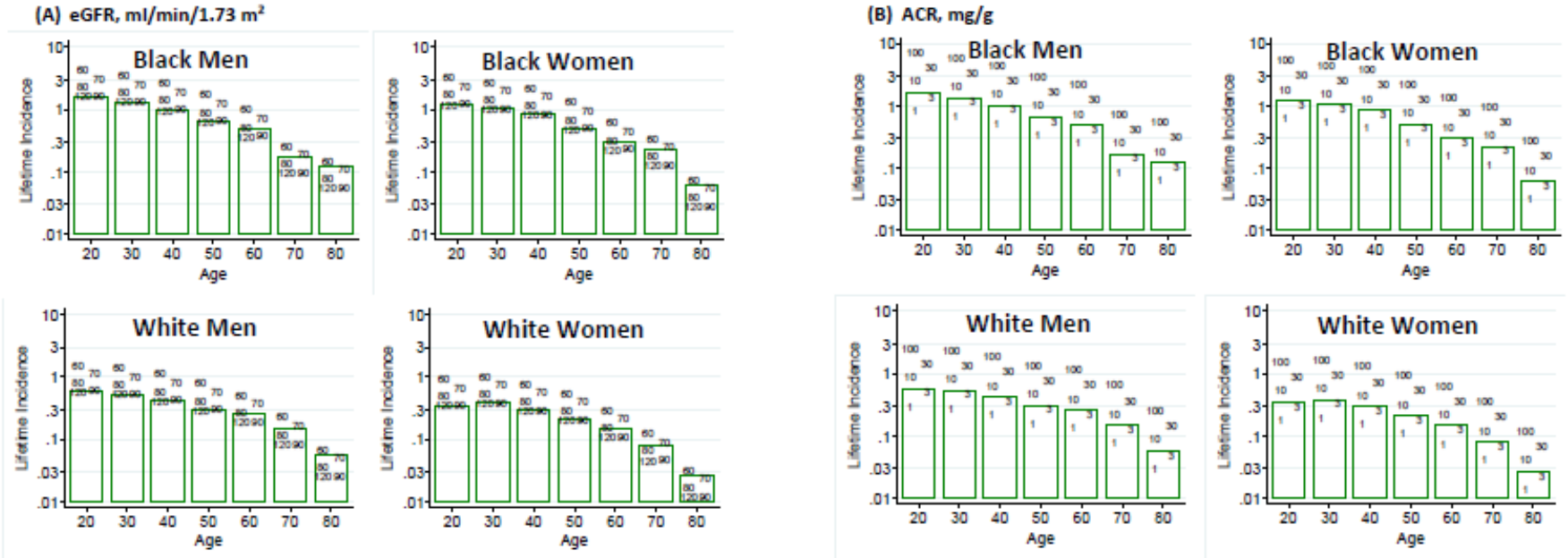
Figure S2: Lifetime incidence (%) of ESRD in the United States in the absence of kidney donation for the "base-case" scenario (green bars) with alteration of a single risk factor



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- In model-based lifetime projections, young persons, particularly those of black race, were at the highest risk
- Many older persons had low estimates of the long-term risk of ESRD, even in the presence of health characteristics that are often considered to be contraindications to donation, such as low eGFR or mild hypertension
- Use of the online risk tool in kidney donor–acceptance protocols may help to minimize the number of living kidney donors in whom ESRD develops after donation, support donation among people whose long-term risk was previously misunderstood, and enhance informed consent and shared decision making with donor candidates
- Although the risk tool was developed specifically for the United States, the methods that we used to generate robust estimatesmay be adapted to other countries with the use of local data sources

Long-term Safety of Living Kidney Donation in an Emerging Economy

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Transplantation 2016;100: 1284–1293

Multivariate risk factor analysis for postdonation impaired renal function, proteinuria and hypertension

Factors	Odds Ratio	*P*
(A) CrCl < 60 mL/min per 1.73 m^2		
Age at donation (>40 y ≤ 40 y)	2.8	<0.001
Predonation CrCl (≤80 vs >80 mL/min)	1.7	0.03
(B) Persistent proteinuria >300 mg/24 hr		
Pre donation protein (>150 vs ≤150)	2.1	0.006
Male sex	1.8	0.006
Smoking	2.3	0.001
Postdonation hypertension	2.3	0.001
Nephrectomy donation (>10 yr vs ≤10 yr)	3.5	<0.001
(C) Hypertension		
Age at donation (>40 vs ≤40)	1.5	0.002
Predonation BMI (≥25 vs <25)	1.7	<0.001
Predonation systolic BP (>130 vs ≤130)	1.8	<0.001
Predonation diastolic BP (>80 vs ≤80)	1.6	0.001
Nephrectomy period (>5 yr vs ≤5 yr)	4.8	<0.001

CrCl < 60 was adjusted for time since donation >5 years, persistent proteinuria was adjusted for systolic BP >130, diastolic BP >80 and CrCl < 80 at donation. Hypertension was adjusted for Cr Cl <80 at donation.

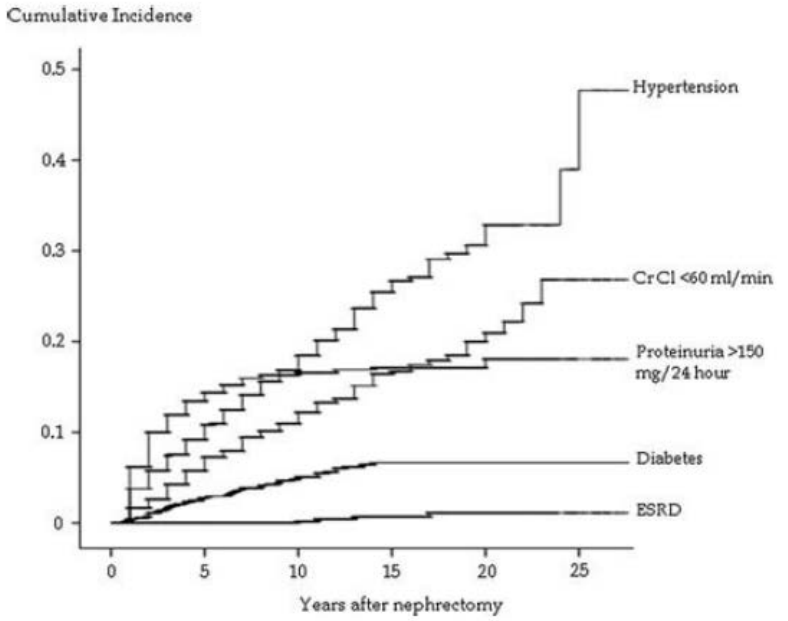

FIGURE 3. Cumulative incidence of comorbidity and ESRD after nephrectomy.

- Postdonation hypertension and proteinuria did not impact on the development of CrCl less than 60
- Persistent proteinuria was associated with: higher predonation proteinuria, male sex, smoking, postdonation hypertension, and longer duration of follow-up

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- Previously reported risk factors for development of proteinuria greater than 300 mg/24 hours were duration of nephrectomy and female sex to which we add predonation proteinuria greater than 150 mg/24 hours, male sex, smoking, and hypertension but not age