ORIGINAL ARTICLE

Lower donated kidney volume is associated with increased risk of lower graft function and acute rejection at 1 year after living donor kidney—a retrospective study

Filipa Silva[1], Jorge Malheiro[1], Nicole Pestana[2], Catarina Ribeiro[3], Diogo Nunes-Carneiro[4], Mariana Mandanelo[4], Joana Tavares[1], Sofia Pedroso[1], Manuela Almeida[1], Miguel Silva-Ramos[4], Leonídeo Dias[1], La Salete Martins[1] & António Castro Henriques[1]

1 Nephrology and Kidney Transplantation Department, Centro Hospitalar e Universitário do Porto, Porto, Portugal
2 Nephrology Department, Hospital Dr. Nelio Mendonça, Funchal, Portugal
3 Nephrology Department, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal
4 Urology Department, Centro Hospitalar e Universitário do Porto, Porto, Portugal

Correspondence
Filipa Silva, Largo Prof. Abel Salazar 1, 4099-001 Porto, Portugal.
Tel.: +351 222 077 500;
fax: 00351222077519;
e-mail: filipasofiasantossilva@gmail.com

SUMMARY

Kidney volume has been proven to be a surrogate marker of nephron mass and renal function. We studied 190 donor and recipient pairs undergoing living donor kidney transplantation at our institution during 9 years. Different metrics of donor kidney volume (DKV) were explored: alone or indexed to recipient's anthropometry, as body surface area (BSA). DKV/BSA (min. 49.7; P33rd 77.7; P67th 95.3; max. 176 cm^3/m^2) was chosen given its higher correlation with eGFR at 1 year, and recipients were divided according to its tertiles (T). The eGFR at 1 year was lower in T1, when compared with T2 ($P = 0.015$) and T3 ($P < 0.001$). In a multivariable model, a regression spline revealed that a DKV/BSA lower than 80 was significantly associated with an eGFR at 1 year <60. In the first 6 years, the overall annual eGFR slope was −0.90 ml/min/year. Acute rejection occurred in 19%, 11%, and 0% of patients in T1, T2, and T3, respectively ($P < 0.001$). DKV/BSA increased stepwise from cellular- ($n = 12$) to antibody-mediated ($n = 7$) AR cases and to those without AR ($n = 171$; $P = 0.002$; no AR versus cellular AR). Lower DKV/BSA ratio was associated with significantly worse graft function and higher incidence of AR. Hence, it can be a tool for better selection of donors in order to improve graft outcomes, particularly in the setting of multiple potential living donors or kidney paired exchange programs.

Transplant International 2020; 33: 1711–1722

Key words
acute rejection, kidney volume, living donor transplantation

Received: 20 June 2020; Revision requested: 21 July 2020; Accepted: 3 September 2020;
Published online: 2 October 2020

Introduction

Chronic kidney disease affects approximately 5 million people worldwide [1], and kidney transplantation offers a longer and better quality of life than dialysis [2,3]. Kidney transplantation from living donors offers many advantages, including superior graft and patient survival. The improvements of graft survival have mainly been attributed to better immunosuppressive regimens which translated into reducing acute rejection rates that are the main barrier for the short-term success of a transplantation [4–7].

On the other hand, late graft failure is more difficult to reduce because it is a multifactorial phenomenon and not only attributed to immunological activity [5,6]. Back in 1992, Brener *et al.* [8] suggested that one size

doi:10.1111/tri.13740

does not fit all with the presence of a nonimmune cause as a possible trigger of progressive to renal injury. The typical features of the response to reduced renal mass could include glomerulosclerosis, tubular atrophy, peritubular capillary rarefaction, interstitial fibrosis, hypertension, and proteinuria [9,10], leading to shortened graft survival [9,11].

Kidney volume has been proven to be a surrogate marker of nephron mass and renal function in living donors and although many studies correlate the kidney mass with renal function of the donors after donation, few studies have compared the donated kidney mass with estimated glomerular filtration rate (eGFR) in the kidney´s recipients [12,13,14,15].

Computed tomography (CT) is part of the preoperative evaluation of living kidney donors, and beside giving us information on the kidneys' anatomy, it also allows us to estimate kidney volume [12,13,16,17].

The purpose of this study was to examine the relationship between donor kidney volume and post-transplantation graft function at one year by using CT to obtain renal volumes.

Materials and methods

Study cohort

We retrospectively reviewed the clinical data off all donor and recipient pairs undergoing living donor kidney transplantation at our institution between January 2008 and December 2017 ($n = 210$). After exclusion of 20 recipients, ten whose donor CT scans were unavailable for our examination (performed outside our institution), four with primary graft nonfunction, and another six without evaluation of eGFR at 1 year, the remaining 190 recipients defined our study cohort.

Baseline data and graft outcomes

Baseline demographic, anthropomorphic, analytical, and clinical data were collected from both recipients and donors. Transplant data were also included. Serum creatinine based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to predict estimated glomerular filtration rate (eGFR). Graft biopsies were performed per indication. All acute rejection episodes were biopsy-proven, recorded at 1 year, and classified according to Banff'17 criteria. Each recipient was followed up until the end of June 2017, date of death, graft loss, or loss in follow-up.

Immunosuppression and desensitization protocols

Induction therapy was used in most patients, with an anti-IL-2 receptor monoclonal antibody (Basiliximab Novartis®, 20 mg twice at day 0 and day 4) or a polyclonal anti-thymocyte globulin (ATG Fresenius®, 3 mg/kg for 5–7 days). ATG was primarily used in HLA-incompatible KT and retransplants. All enrolled recipients had similar triple maintenance immunosuppression, consisting of oral tacrolimus, mycophenolate mofetil (MMF), and methylprednisolone (MP)/prednisolone. Tacrolimus was started at a dose of 0.1–0.15 mg/kg/day, and the dose was adjusted to maintain a trough level in whole blood between 8 and 12 ng/ml during the first month postoperatively, between 7 and 10 ng/ml during 2–3 months after transplant, and between 5 and 8 ng/ml thereafter. MMF was started at a dose of 2000 mg/day, with the dose decreasing to 1000–1500 mg/day during the first month postoperatively, depending on white blood cells count. Both tacrolimus and MMF were prescribed 7 days before transplant. Methylprednisolone was administered intravenously at doses of 500, 250, and 125 mg/day on the day of transplantation, days 1–2 and days 3–4 after the operation, respectively. Oral prednisolone was started on day 5 after the operation at the dose of 20 mg, being then tapered to 5–10 mg/day within 2–3 months after transplant.

HLA-incompatible KT received desensitization with intravenous immunoglobulin 2 g/kg at transplant (0.5 g/kg immediately before transplant, and at days 1, 2, and 3) and 1 month after transplant (1 g/kg in two consecutive days), and a dose of rituximab (375 mg/m^2) at day 3 post-transplant. Given the strength of performed anti-HLA donor-specific antibodies and flow-cytometry cross-match results, six patients also underwent plasmapheresis every other day (first session 3 days before transplant, for a total of 6–9 sessions). Our desensitization protocol for ABO-incompatible KT was performed as previously described [18].

Volume assessment

All the living donors were submitted to one of two multidetector-row CT scans available at our institution (a 64-detector GE VCT LightSpeed® or a 16-detector GE Brightspeed®) using the same image acquisition protocols. Images were obtained prior and after to contrast, evaluating the nephrographic and excretory phases of enhancement.

The volume of the kidney selected for transplant was evaluated with CT scans using the same image

Transplant International 2020; 33: 1711–1722

acquisition protocols. Volumes were measured through the voxel counting technique (the sum resulting from the tracing of the renal contours in sequential 2.5-mm transversal CT nephrographic images, excluding the renal sinus area) using the Osirix® (Pixmeo Sarl, Geneva, Switzerland) software.

Relation between donor kidney volume (DKV) by itself or indexed to anthropometric measurements of recipient [weight (*W*), body surface area (BSA), and body mass index (BMI)] was explored. Both BMI and BSA were calculated using the DuBois formula.

Statistical analysis

Continuous data were described using mean ± standard deviation (SD) or median [interquartile range (IQR)], and categorical data were expressed as number (and percentages). Categorical data including were compared using Pearson chi-square test or Fisher exact test, and continuous variables were compared with Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Correlation between eGFR values and DKV metrics is presented as Pearson's coefficient.

Risk factors for an eGFR < 60 ml/min at 1 year were analyzed through a univariate multivariable logistic regression model and a multivariable logistic regression model. To further explore the relationship between DKV/W and the risk of an eGFR < 60 ml/min at 1 year, we used a restricted cubic regression spline basis matrix to graphically model (using the same multivariable model as above) the logistic prediction, using the adjustrcspline command of postrcspline package for Stata.

Recipient eGFR slope between 1 and 6 years after transplant was assessed by univariate and multivariable linear mixed regression models that imputed subject-specific random effects (intercept and slope defined as eGFR at 1 year and time in years, respectively) on an unstructured covariance matrix. The dependent variable was all eGFR measurements, and the independent variables were entered as 2-way interaction terms between them and the time (in years) variable. All 190 recipients were studied, and a median of 4 (IQR: 3–6) annual measurements of eGFR were available.

Graft survival curves were visualized using Kaplan–Meier method, with comparison between patients' groups being done by log-rank test. In the case of death with a functioning graft, time was censored at the time of death. Potential predictors of graft failure were explored by univariate and multivariable Cox proportional hazards models.

In all multivariable models, independent risk factors or predictors were identified using a backward elimination method, with a P-value < 0.05 necessary for retention in the model, as previously proposed [19], with the exception of the linear mixed model in which variables with a P-value < 0.150 in eGFR slope univariate analysis were included in the multivariable model.

A 2-sided P-value < 0.05 was considered as statistically significant. Statistical calculations were performed using STATA/MP, version 15.1 (Stata Corp, College Station, TX, USA).

Results

The correlation between different metrics of donor kidney volume (DKV) with eGFR at 1 year after kidney transplant was analyzed: DKV alone ($r = 0.402$, $P < 0.001$), DKV adjusted for weight ($r = 0.396$, $P < 0.001$), body mass index ($r = 0.383$, $P < 0.001$), or body surface area ($r = 0.431$, $P < 0.001$). Since DKV/BSA had the highest correlation, it was our metric of choice. Recipients were then divided into tertiles according to their DKV/BSA (cm^3/m^2): tertile 1 (DKV/BSA between 49.7 and 77.5, $n = 64$), tertile 2 (78–95.2, $n = 63$), and tertile 3 (95.4–176, $n = 63$).

Baseline characteristics

Overall baseline characteristics and their comparison between terciles are shown in Table 1. The mean age of the transplant recipients was 41.7 (±12.6) years, and they were mostly (70%, $n = 133$) male. The mean BSA and BMI were 1.78 (±0.18) m^2 and 23.9 (±3.8) kg/m^2, respectively. The most frequent dialysis before transplantation was hemodialysis ($n = 103$, 54%). In 23% of patients, the transplant was preemptive. Recipients in the lower tertile group tended to be older, men and had a higher BSA and BMI.

With regard to donors, the mean age was 48.5 (±10.1) years, they were chiefly female ($n = 138$, 73%) and had a mean BSA and BMI of 1.73 (±0.17) m^2 and 25.3 (±3.4) kg/m^2, respectively. The mean predonation eGFR was 100.0 (±13.8) ml/min/1.73 m^2, and the mean DKV was 155.4 (±31.3) cm^3. Recipients in the lower tertile received a kidney with significantly lower DKV ($P < 0.001$), and their donor had the lowest predonation eGFR ($P = 0.001$). In most of the cases, the donated kidney was the left one ($n = 155$, 82%).

Acute rejection at 12-months was significantly different between tertiles ($P < 0.001$), with no episode of acute rejection was occurred in the greatest tertile,

Table 1. Baseline characteristics based on tertiles of DKV/BSA.

	Total (N = 190)	Tertile 1 (N = 64)	Tertile 2 (N = 63)	Tertile 3 (N = 63)	P
DKV/BSA (cm^3/m^2), mean ± SD [min–max]	88.1 ± 20.0 [49.7–176.0]	67.9 ± 7.0 [49.7–77.5]	86.2 ± 5.5 [78.0–95.2]	110.5 ± 14.2 [95.4–176.0]	<0.001
Recipient					
Age, mean ± SD	41.7 ± 12.6	46.1 ± 12.9	40.2 ± 11.3	38.8 ± 12.4	0.002
Female gender, *n* (%)	57 (30)	10 (16)	19 (30)	28 (44)	0.002
BSA (m^2), mean ± SD	1.78 ± 0.18	1.86 ± 0.13	1.79 ± 0.16	1.69 ± 0.19	<0.001
BMI (kg/m^2), mean ± SD	23.9 ± 3.8	25.1 ± 3.4	24.1 ± 4.0	22.7 ± 3.8	0.001
Dialysis modality before transplantation, *n* (%)					
Preemptive	44 (23)	14 (22)	17 (27)	13 (21)	0.808
HD	103 (54)	36 (56)	34 (54)	33 (52)	
PD	43 (23)	14 (22)	12 (19)	17 (27)	
Donor					
Age, mean ± SD	48.5 ± 10.1	49.3 ± 10.7	49.0 ± 10.6	47.3 ± 8.9	0.494
Female gender, *n* (%)	138 (73)	59 (92)	49 (78)	30 (48)	<0.001
BSA (m^2), mean ± SD	1.73 ± 0.17	1.64 ± 0.13	1.74 ± 0.16	1.81 ± 0.17	<0.001
BMI (kg/m^2), mean ± SD	25.3 ± 3.4	24.4 ± 3.1	25.5 ± 3.6	25.9 ± 3.3	0.050
Predonation serum creatinine (mg/dl), median (IQR)	0.70 (0.63–0.86)	0.71 (0.66–0.83)	0.66 (0.61–0.78)	0.73 (0.61–0.90)	0.067
Predonation eGFR-SCr (ml/min/1.73 m^2), mean ± SD	100.0 ± 13.8	94.8 ± 15.7	102.2 ± 10.8	103.0 ± 13.2	0.001
Donated kidney volume (cm^3), mean ± SD	155.4 ± 31.3	126.3 ± 16.1	154.1 ± 13.3	186.4 ± 26.3	<0.001
Left kidney donated, *n* (%)	155 (82)	48 (75)	50 (79)	57 (90)	0.068
Transplant					
Living-unrelated donor, *n* (%)	78 (41)	33 (52)	21 (33)	24 (38)	0.095
Previous transplant, *n* (%)	26 (14)	12 (19)	8 (13)	6 (10)	0.306
Calculated PRA > 0%, *n* (%)	54 (28)	21 (33)	16 (25)	17 (27)	0.621
HLA-incompatible KT, *n* (%)*	19 (10)	7 (11)	6 (10)	6 (10)	0.954
AB0-incompatible KT, *n* (%)	7 (4)	3 (5)	3 (5)	1 (2)	0.703
HLA-A MM mean ± SD	0.97 ± 0.66	1.05 ± 0.63	0.95 ± 0.63	0.90 ± 0.71	0.454
HLA-B MM mean ± SD	1.17 ± 0.74	1.34 ± 0.76	1.06 ± 0.69	1.10 ± 0.76	0.073
HLA-DR MM mean ± SD	0.99 ± 0.70	1.14 ± 0.73	0.87 ± 0.66	0.95 ± 0.68	0.129
Induction, *n* (%)					
None	5 (3)	2 (3)	3 (5)	0	0.453
Basiliximab	165 (87)	57 (89)	53 (84)	55 (87)	
ATG	20 (11)	5 (8)	7 (11)	8 (13)	
DGF, *n* (%)	8 (4)	2 (3)	3 (5)	3 (5)	0.869
AR at 12 months, *n* (%)	19 (10)	12 (19)	7 (11)	0	<0.001
ACR, *n*	12	8	4	0	
AMR, *n*	7	4	3	0	

Table 1. Continued.

	Total (N = 190)	Tertile 1 (N = 64)	Tertile 2 (N = 63)	Tertile 3 (N = 63)	P
Years of follow-up, median (IQR)	4.8 (3.2–7.5)	3.8 (2.5–6.6)	5.6 (3.6–7.6)	5.7 (3.6–8.7)	0.004

ACR, acute cellular rejection; AMR, antibody-mediated rejection; AR, acute rejection; ATG, anti-thymocyte globulin; BMI, body mass index; BSA, body surface area; DGF, delayed graft function; DKV, donor kidney volume; DP, peritoneal dialysis; eGFR-SCr, estimated glomerular filtration rate with serum creatinine; HD, hemodialysis; HLA, human leukocyte antigen; MM, mismatch HLA; PRA, panel-reactive antibody.
*HLA-incompatible KT was defined as the presence of pretransplant anti-donor antibodies.

while it occurred in 19% and 11% of cases in lower and middle tertiles, respectively. No other significant differences were observed considering transplantation variables.

eGFR at 1 year after transplantation

Dispersion of eGFR at 1-year values according to DKV/BSA is shown in Fig. 1 *top*. The mean eGFR at 1 year from the tertile 1–3 was 54.9 (±15.5), 60.9 (±13.8) and 69.1 (±115.3) ml/min/1.73 m^2, respectively (Fig. 1 *bottom*). The eGFR at 1 year was significantly lower in tertile 1, when compared with both tertile 2 ($P = 0.015$) and tertile 3 ($P < 0.001$). eGFR values during the first year (at months 1, 3, 6, and 12) according to DKV/BSA tertiles, mirrored the results at 1 year, with differences between groups at each time point being all significant ($P < 0.05$) by analysis of variance, except for the comparison between tertile 1 and tertile 2 at month 6 (Fig. 2 and Table S1).

The proportion of kidney transplant recipients with an eGFR <60 ml/min/1.73 m^2 at 1 year from the first to third tertile were 64%, 46%, and 32%, respectively ($P = 0.001$). In a logistic regression analysis, we could identify significant risk factors for eGFR < 60 ml/min at 1 year (Table 2): acute rejection at 1 year (OR = 4.116, $P = 0.018$), calculated PRA >0% (OR = 2.075, $P = 0.039$), higher donor age (OR per unit = 1.033, $P = 0.047$), and peritoneal dialysis modality (in comparison with preemptive KT: OR = 3.232, $P = 0.013$). The highest tertile (in comparison with the lowest: OR = 0.306, $P = 0.004$) was protective of this outcome. Using the regression spline model, we could observe a rather linear association between DKV/BSA continuous values and the risk of eGFR < 60 ml/min at 1 year, with a DKV/BSA <80 cm^3/m^2 being significantly associated with that outcome (Fig. 3).

The positive predictive values of each DKV/BSA tertile for the *optimal* outcome of an eGFR ≥ 60 ml/min/1.73 m^2 at 12 months from the third to the first tertiles were 68.2% (95% CI: 57.9–77.1%), 53.9% (95% CI: 43.8–63.7%), and 35.9% (95% CI: 26.8–46.1%), respectively.

Acute rejection at 1 year

Acute rejection (AR) at 1 year was observed in 19 recipients (10%), with 12 cases of acute cellular rejection (Banff grades: IA 4, IB 1, IIA 6, and IIB 1) and seven of antibody-mediated rejection. No case of acute cellular

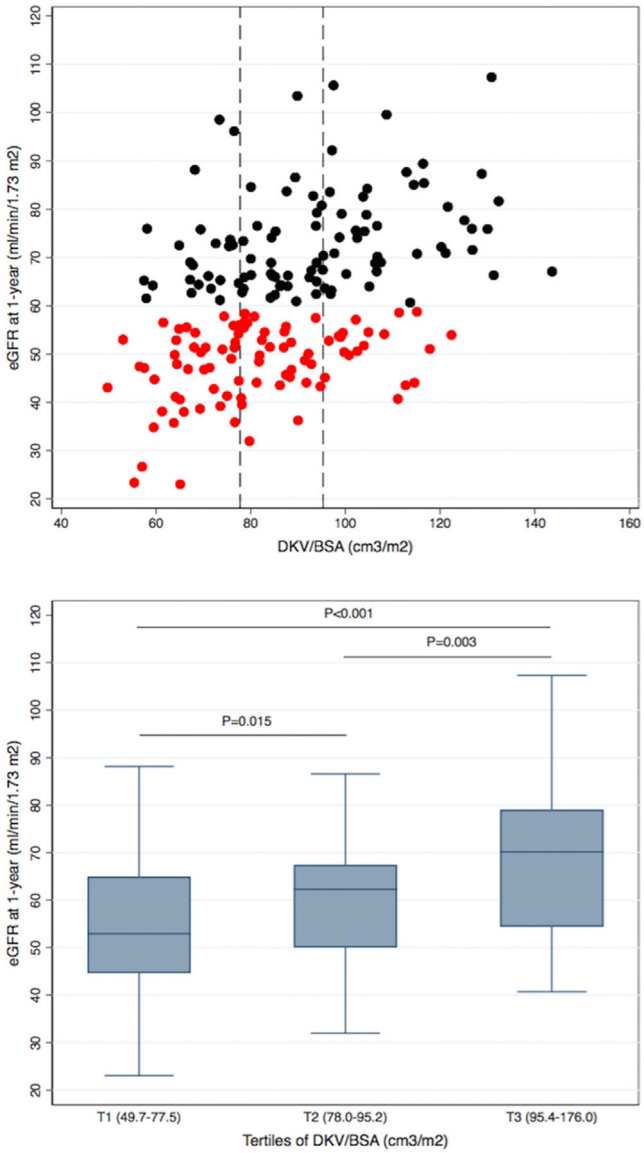

Figure 1 eGFR at 1-year (ml/min/1.73 m^2) according to terciles of DKV/BSA (cm^3/m^2). BSA, body surface area; DKV, donor kidney volume; eGFR-SCr, estimated glomerular filtration rate with serum creatinine.

rejection was observed in recipients of an HLA-incompatible or ABO-incompatible KT. Differently, antibody-mediated rejection was associated with anti-HLA donor-specific antibodies in six cases (two preformed and four *de novo*), while one case occurred in an ABO-incompatible KT. Moreover, at 1 year, there was only one additional patient with detectable *de novo* anti-HLA donor-specific antibodies that did not experience AR.

Patients that experienced AR had significantly lower DKV/BSA (median DKV of 87.5 (IQR: 75.9–102.2) cm^3/m^2 in patients without rejection and 73.6 (IQR: 65.0–86.4) cm^2/m^2 in patients with rejection, $P = 0.002$), particularly those with acute cellular rejection (median of DKV/BSA of 70.4 (IQR: 58.2–84.1) cm^3/m^2, $P = 0.002$ versus no rejection) when compared with 77.5 (IQR: 73.6–88.3) cm^3/m^2 in patients with antibody-mediated rejection ($P = 0.213$ versus no rejection; Fig. 4). Given this significant difference considering DKV/BSA, we explored the risk factors for acute cellular rejection at 1 year by logistic regression model (Table S2). DKV/BSA was the most important risk factor, both in univariable (OR 0.937, $P = 0.005$) and in multivariable (OR 0.939, $P = 0.007$) analyses, with for every 1 cm^3/m^2 more in DKV/BSA, there was a 40% reduction in the risk of acute cellular rejection. Considering these results, we explored the hypothesis that the significant higher risk of an eGFR

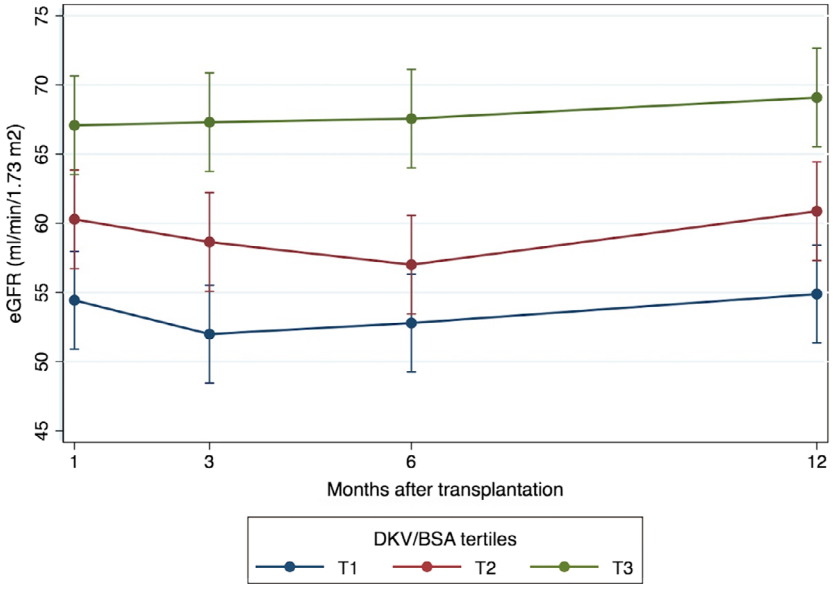

Figure 2 eGFR between groups at 1, 3, 6, and 12 months after transplantation. BSA, body surface area; DKV, donor kidney volume; eGFR-SCr, estimated glomerular filtration rate with serum creatinine.

<60 ml/min/1.73 m^2 at 1 year in the lowest DKV/BSA tertile resulted chiefly from its association with acute rejection. Hence, we repeated the univariate and multivariate logistic regressions presented in Table 2, imputing a full interaction term between these two variables, and found no significant interaction between (Table S3), ascertaining that the association between lower DKV/BSA and the risk of eGFR < 60 ml/min at 1 year was independent from the occurrence of acute rejection.

eGFR slope after 1 year

Through mixed linear regression models, recipient annual eGFR slope from 1 to 6 years after transplantation was analyzed (Table S4), with an overall annual eGFR slope of −0.90 ml/min/year. Marginal prediction of mean eGFR (Fig. 5 left) showed that its correlation with DKV/BSA tertiles remained fairly stable from 1 to 6 years after transplant, with an estimated mean eGFR at 6 years of around 60, 55, and 45 ml/min from the third to the first tertiles. Moreover, although annual eGFR slope (Fig. 5 right) was negative in all tertiles, this decrease was more pronounced in T1 (−1.61 ml/min/year), followed by T3 (−0.85 ml/min/year) and T2 (−0.46 ml/min/year), with a significant difference between T1 and T2 ($P = 0.035$) being detected. Recipient age (slope per unit: +0.09 ml/min/year; $P < 0.001$), gender (slope difference female vs male: −1.21 ml/min/year; $P = 0.016$), and donor age (slope per unit: −0.05 ml/min/year; $P = 0.034$) were also significant predictors of eGFR slope.

Graft survival

The median follow-up was 4.8 (IQR: 3.2–7.5) years. There were 10 graft failures during the follow-up period, mostly after 6 years. Censored graft survival from first to third tertiles at 10 years was 59.3%, 91.3%, and 91.1%, respectively (Fig. 6; P for trend 0.034). Independent predictors of graft failure (Table S5) were HLA-incompatible KT (HR 11.130, $P = 0.002$) and acute rejection at 12 months (HR 5.580, $P = 0.044$), while DKV/BSA tertiles were not.

Discussion

It has been known that the loss or diminish renal mass leads to adverse effects on the remaining kidney with progressive glomerular damage [8,9,20], suggesting that the number of viable nephrons is crucial to long-term success or failure of renal allograft recipients [20]. Kasiske *et al.* related that donor–recipient size mismatch, in deceased kidney transplantation, was associated with graft failure, resulting from compensatory changes in glomerular capillary pressures and flows that could lead, in a directly or indirectly way, to progressive kidney injury. These changes could act as a pro-inflammatory stimulus leading to an alloantigen-dependent kidney damage [21,22].

In living donor transplantation, this question is even more important being fundamental to the identification of clinical or analytical variables that could improve

Table 2. Risk factors for eGFR < 60 ml/min/1.73 m^2 at 1 year by logistic regression.

	Univariate			Multivariable*		
	OR	95% CI	*P*	OR	95% CI	*P*
Recipient						
Age	1.025	1.002–1.049	0.036	–	–	–
Female gender	1.106	0.594–2.058	0.751	–	–	–
BMI	1.030	0.956–1.110	0.440	–	–	–
Dialysis modality before transplantation						
Preemptive	Ref.			Ref.		
HD	1.121	0.548–2.293	0.755	1.178	0.546–2.542	0.677
PD	2.438	1.029–5.773	0.043	3.232	1.277–8.181	0.013
Donor						
Age	1.031	1.001–1.061	0.043	1.033	1.000–1.067	0.047
Female gender	1.476	0.773–2.818	0.238	–	–	–
BMI	1.035	0.951–1.127	0.426	–	–	–
Transplant						
DKV/BSA tertiles						
T1	Ref.		<0.001†	Ref.		0.004†
T2	0.478	0.235–0.975	0.042	0.536	0.253–1.135	0.103
T3	0.261	0.125–0.545	<0.001	0.306	0.138–0.679	0.004
HLA-A MM	0.775	0.501–1.201	0.255	–	–	–
HLA-B MM	0.921	0.627–1.351	0.673	–	–	–
HLA-DR MM	0.955	0.634–1.438	0.826	–	–	–
Previous transplant	0.945	0.412–2.167	0.894	–	–	–
Living-unrelated donor	1.196	0.670–2.134	0.544	–	–	–
Calculated PRA > 0%	1.759	0.930–3.326	0.082	2.075	1.037–4.154	0.039
HLA-incompatible KT‡	2.044	0.767–5.443	0.153	–	–	–
AB0-incompatible KT	2.882	0.545–15.241	0.213	–	—	–
DGF	1.902	0.441–8.195	0.388	–	–	–
Induction						
None	Ref.			–	–	–
Basiliximab	0.569	0.093–3.497	0.543			
ATG	0.815	0.111–5.987	0.840			
AR at 12 months	3.500	1.207–10.150	0.021	4.116	1.277–13.269	0.018

AR, acute rejection; ATG, anti-thymocyte globulin; BMI, body mass index; BSA, body surface area; DGF, delayed graft function; DKV, donor kidney volume; DP, peritoneal dialysis; HD, hemodialysis; HLA, Human Leukocyte Antigen; MM, mismatch HLA; PRA, panel-reactive antibody.

*Model *C*-statistics (AUC): 0.730, Hosmer–Lemeshow X^2: 5.86 $P = 0.663$.

†*P* for trend.

‡HLA-incompatible KT was defined as the presence of pretransplant anti-donor antibodies.

graft outcome. In the presence of more than one compatible living donor or in the setting of kidney paired exchange program, the choice for one of them could be optimized in order to favor the donor with the highest renal volume and with the minor anatomical variants of the renal vessels. Besides of that, this evaluation is extremely important in order to choose the kidney with lower volume for nephrectomy, assuming to be the one with the lowest renal mass and the best renal function. All measures that protect and benefit the donor must be taken and under no circumstances should it be harmed.

In our study, we were able to confirm that DKV adjusted to recipient BSA was a strong predictor of allograft eGFR at 1 year after transplantation. More than that, we were able to verify that lower volumes, specifically DKV/BSA < 80 cm^3/m^2 correlate with an eGFR < than 60 ml/min/1.73 m^2 at 1 year. This is an important finding since in the presence of potential donors with renal volumes lower than 80 cm^3/m^2, it is necessary to rethink to proceed with the transplant. This cutoff should act as a warning sign for the development of early dysfunction in the short term. In fact, the

Transplant International 2020; 33: 1711–1722

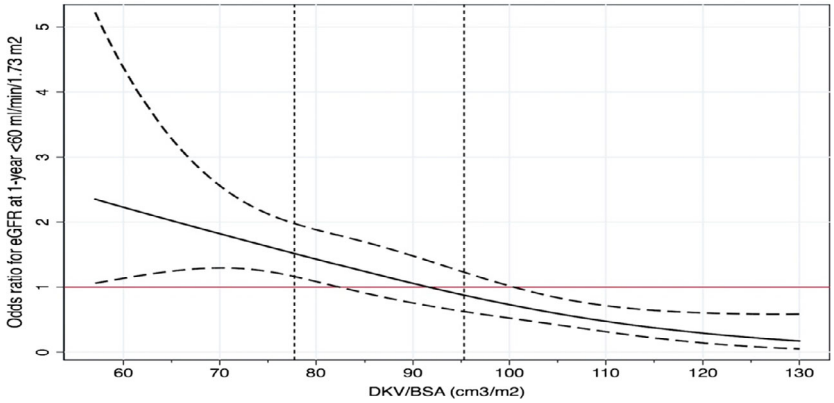

Figure 3 Correlation of DKV/BSA with eGFR at 1 year in a continuously way, by regression spline. BSA BSA, body surface area; DKV, donor kidney volume; eGFR-SCr, estimated glomerular filtration rate with serum creatinine.

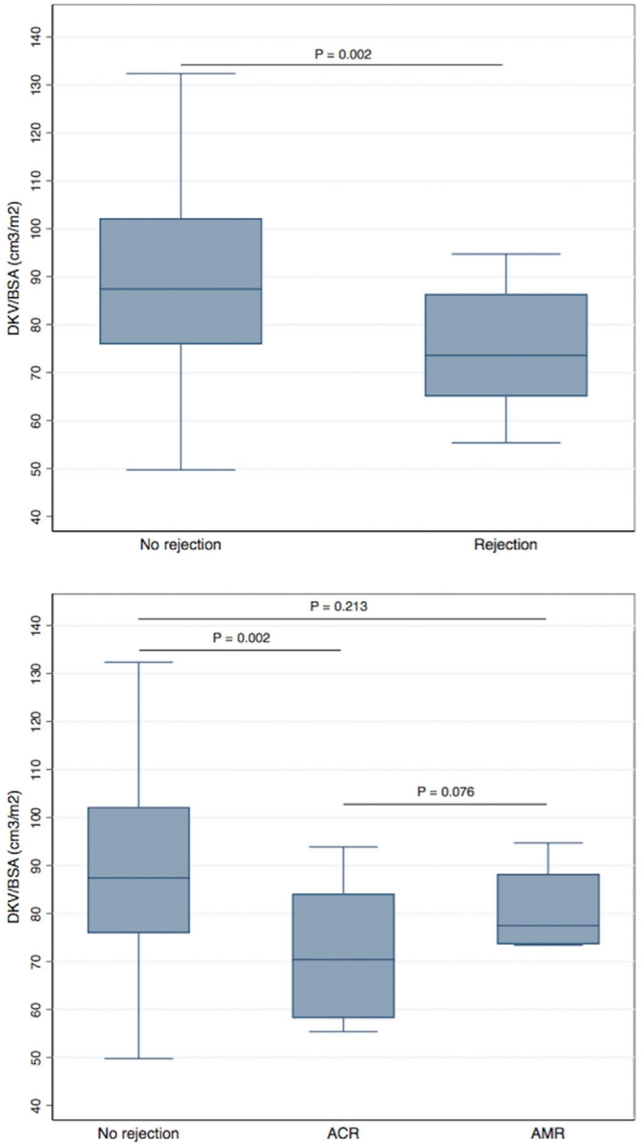

Figure 4 Relation between acute rejection and DKV/BSA until 12 months of follow-up. BSA, body surface area; DKV, donor kidney volume.

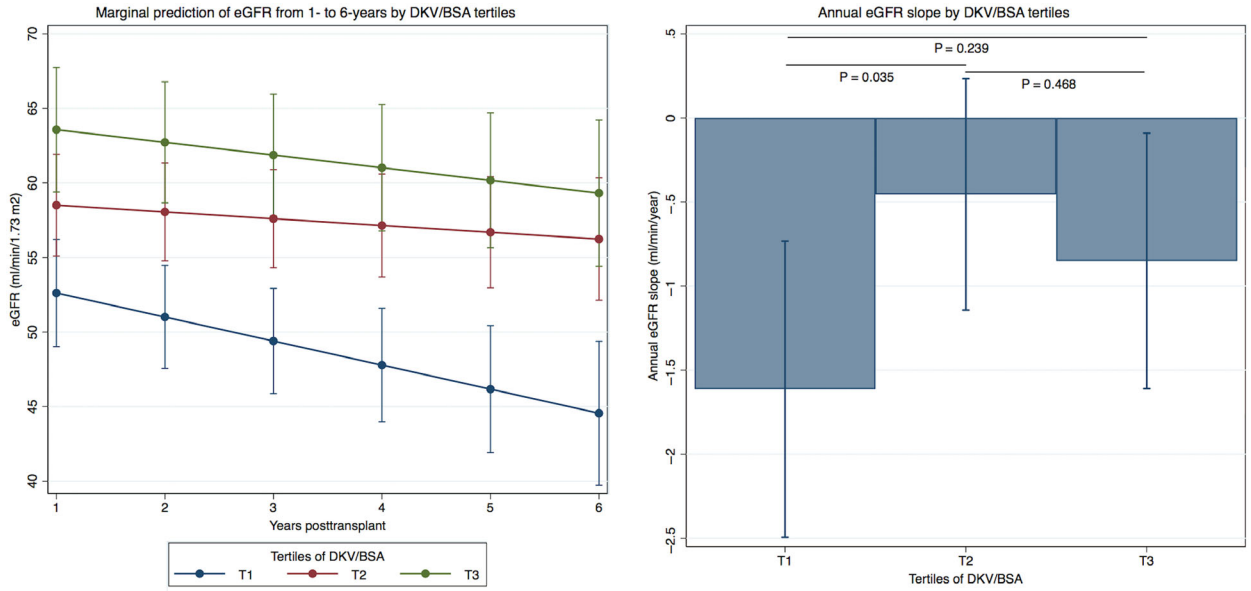

Figure 5 eGFR slope from 1 to 6 years after transplant. Left, marginal mean prediction of eGFR at 1–6 years by DKV/BSA tertiles. Right, annual eGFR slope by DKV/BSA tertiles. BSA, body surface area; DKV, donor kidney volume; eGFR-SCr, estimated glomerular filtration rate with serum creatinine.

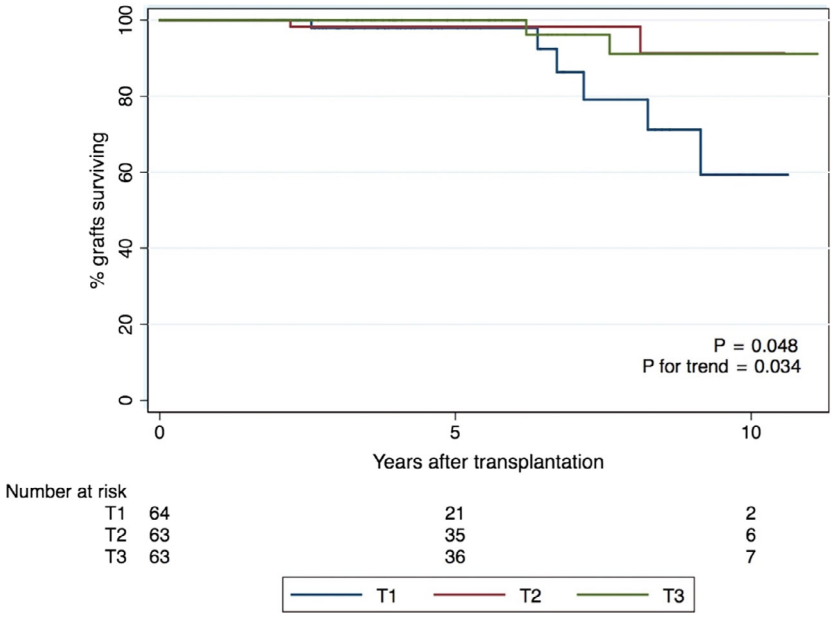

Figure 6 Censored graft survival graph by DKV/BSA terciles.

positive predictive values of each DKV/BSA tertile for the *optimal* outcome, considered an eGFR ≥ 60 ml/min/1.73 m^2 at 12 months, are substantially superior in third tertile (68.2%) when compared with second (53.9%) or the first one (35.9%). We also could identify other significant risk factors for eGFR < 60 ml/min at 1 year, namely the presence of AR at 1 year, calculated PRA >0%, higher donor age, and peritoneal dialysis modality.

In our study, 10% of the recipients (n = 19) developed AR at 1 year with acute cellular rejection (n = 12) being the most frequent. Interesting, we found that the patients who experienced AR had significantly lower DKV/BSA (median DKV of 73.6 cm^2/m^2) particularly those with acute cellular rejection.

Other reports have shown that the graft size in capable of influence the development of AR episodes and

consequently post-transplant graft function [23–27]. Our data are consistent with these studies, suggesting that the higher DKV/BSA may be protective of AR episodes, particularly cell-mediated cases. Importantly, this is the first study that shows this association, although its motif is still unclear. We speculate that in living donor transplantation giving the lack of cold ischemia, the occurrence of delayed graft function is reduced but that does not mean that in small kidneys, there is no territory that can enhance the occurrence of ischemia-reperfusion injury, that although not resulting in delayed graft function, may nonetheless correlate with its known detrimental effects as allo-mediated inflammation and fibrosis, which could explain the higher incidence of cell-mediated rejection and lower graft function in recipients with lower DKV/BSA. Moreover, He *et al.* [28], based on studies in murines, raise a hypothesis that graft size affects susceptibility to immune-mediated injury. Their results showed that there was an important interrelationship between T-cell frequency and the size of a target organ with graft function being better in larger tissue mass than in recipients of allografts with smaller tissue mass [28].

Regarding to eGFR after transplantation, we found that in the first 6 years, the overall annual eGFR slope was −0.90 ml/min/year. Moreover, although annual eGFR slope was negative in all tertiles, this decrease was more pronounced in T1 (−1.61 ml/min/year). Also, recipient age, gender, and donor age were significant predictors of eGFR slope. As far as we know, we are the first report to show the annual decrease in eGFR in this kind of patients.

With these results, we can say that the DKV/BSA of donated kidneys seems to have an impact not only on kidney function at 1 year, but also on the preservation of kidney function in the long term.

Regarding to graft survival, the association between volumes was not independent: In the multivariate model, the independent predictors were rejection and HLA-incompatible transplantation (i.e., with preformed DSA). This favors the multiple publications that state that the main cause of graft loss, even in the long run, is rejection phenomena.

Our study had some limitations. First, our cohort consisted only in Caucasians, which does not allow inferring the results for other populations. Second, we recognize that eGFR by estimation equations to assess graft function, had, for itself, limitations. However, the CKD-EPI has been shown, in epidemiological studies, to perform a more pertinent CKD diagnosis and staging [29] and most of the studies published used an equation from Modification of Diet in Renal Disease (MDRD). Third, potential correlations between immunosuppression exposure with AR occurrence were not explored, given the absence of longitudinal data on tacrolimus through levels. Fourth, the number of rejection episodes is relatively small and the estimates may be unreliable. Besides that, an added value of our study cohort is its larger size and longer follow-up when compared with other cohorts.

Conclusion

Our study demonstrates that transplantation of donor–recipient pairs with lower DKV/BSA ratio was associated with significantly worse graft function and higher incidence of AR. These data suggest that a larger mass of nephrons remaining adjusted to recipient's weight seems to predict a better long-term eGFR. This method can be useful in order to identify patients at risk for a low eGFR after KT and, in cases of multiple potential donors, optimize donor selection.

Authorship

FS and JM: involved in research design, acquisition of the data, data analysis, and paper writing. NP, CR, DN-C, MM, JT, SP, MA, LD and LSM: contributed to acquisition of the data and data analysis. MS-R and AC-H: involved in research design and paper writing.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of eGFR between terciles at 1, 3, 6 and 12 months after transplantation.

Table S2. Risk factors for acute cellular rejection at 1-year by logistic regression.

Table S3. Prediction of an eGFR < 60 ml/min/1.73 m^2 at 1-year by logistic regression, considering a full interaction term between DKV/BSA terciles and acute rejection.

Table S4. eGFR intercept (at 1-year post-transplant) and annual slope (ml/min/year) from 1- to 6-years post-transplant by linear mixed regression.

Table S5. Independent predictors of censored graft failure.

REFERENCES

1. Garg AX, Levey AS, Kasiske BL, Cheung M, Lentine KL, KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors Work Group and Evidence Review Team. Application of the 2017 KDIGO guideline for the evaluation and care of living kidney donors to clinical practice. *Clin J Am Soc Nephrol* 2020; **15**: 896.
2. Liyanage T, Ninomiya T, Jha V, *et al*. Worldwide access to treatment for end-stage kidney disease: a systematic review. *The Lancet* 2015; **385**: 1975.
3. Tonelli M, Wiebe N, Knoll G, *et al*. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes: systematic review of kidney transplantation. *Am J Transplant* 2011; **11**: 2093.
4. Coemans M, Süsal C, Döhler B, *et al*. Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int* 2018; **94**: 964.
5. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; **342**: 605.
6. Sayegh MH, Carpenter CB. Transplantation 50 years later – progress, challenges, and promises. *N Engl J Med* 2004; **351**: 2761.
7. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 2004; **351**: 2715.
8. Brenner BM, Cohen RA, Milford EL. In renal transplantation, one size may not fit all. *J Am Soc Nephrol* 1992; **3**: 162.
9. Brenner BM, Milford EL. Nephron underdosing: a programmed cause of chronic renal allograft failure. *Am J Kidney Dis* 1993; **21**: 66.
10. Grady RW, Novick AC. Hyperfiltration of renal injury: pathophysiology and clinical implications. *Urology* 1996; **47**: 273.
11. Miles AMV, Sumrani N, John S, *et al*. The effect of kidney size on cadaveric renal allograft outcome. *Transplantation* 1996; **61**: 894.
12. Hugen CM, Polcari AJ, Farooq AV, Fitzgerald MP, Holt DR, Milner JE. Size does matter: donor renal volume predicts recipient function following live donor renal transplantation. *J Urol* 2011; **185**: 605.
13. Dias J, Malheiro J, Almeida M, *et al*. CT-based renal volume and graft function after living-donor kidney transplantation: is there a volume threshold to avoid? *Int Urol Nephrol* 2015; **47**: 851.
14. Saxena AB, Busque S, Arjane P, Myers BD, Tan JC. Preoperative renal volumes as a predictor of graft function in living donor transplantation. *Am J Kidney Dis* 2004; **44**: 877.
15. Lee JH, Won JH, Oh C-K. Impact of the ratio of graft kidney volume to recipient body surface area on graft function after live donor kidney transplantation: graft kidney volume and graft function. *Clin Transplant* 2011; **25**: E647.
16. Halleck F, Diederichs G, Koehlitz T, *et al*. Volume matters: CT-based renal cortex volume measurement in the evaluation of living kidney donors. *Transpl Int* 2013; **26**: 1208.
17. Sikora MB, Shaaban A, Beddhu S, *et al*. Effect of donor kidney volume on recipient outcome: does the "dose" matter? *Transplant J* 2012; **94**: 1124.
18. Serviço de Nefrologia – Centro Hospitalar de Vila Nova de Gaia/ Espinho, Ribeiro C, Silva N, *et al*. ABO-incompatible living donor kidney transplantation in Portugal. *Port J Nephrol Hypert* 2020; **34**: 26.
19. Heinze G, Dunkler D. Five myths about variable selection. *Transpl Int* 2017; **30**: 6.
20. Brenner BM, Mackenzie HS. Nephron mass as a risk factor for progression of renal disease. *Kidney Int Suppl* 1997; **63**: S124.
21. Terasaki PI, Koyama H, Cecka JM, Gjertson DW. The hyperfiltration hypothesis in human renal transplantation. *Transplantation* 1994; **57**: 1450.
22. Kasiske BL. Inadequate donor size in cadaver kidney transplantation. *J Am Soc Nephrol* 2002; **13**: 2152.
23. Chertow GM, Brenner BM, Mori M, MacKenzie HS, Milford EL. Antigen-independent determinants of graft survival in living-related kidney transplantation. *Kidney Int Suppl* 1997; **63**: S84.
24. Kim YS, Moon JI, Kim DK, Kim SI, Park K. Ratio of donor kidney weight to recipient bodyweight as an index of graft function. *The Lancet* 2001; **357**: 1180.
25. Giral M, Nguyen JM, Karam G, *et al*. Impact of graft mass on the clinical outcome of kidney transplants. *J Am Soc Nephrol* 2005; **16**: 261.
26. Poggio ED, Hila S, Stephany B, *et al*. Donor kidney volume and outcomes following live donor kidney transplantation: graft volume in living kidney donation. *Am J Transplant* 2006; **6**: 616.
27. Han SS, Yang SH, Oh YJ, *et al*. Graft volume as the surrogate marker for nephron number affects the outcomes of living-donor kidney transplantation: graft volume and transplant outcome. *Clin Transplant* 2011; **25**: E327.
28. He C, Schenk S, Zhang Q, *et al*. Effects of T cell frequency and graft size on transplant outcome in mice. *J Immunol* 2004; **172**: 240.
29. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604.