Very early serum creatinine as a surrogate marker for graft survival beyond 10 years

Julio Pascual[1], Roberto Marcén[1], Javier Zamora[2], Ana M. Fernández[1], Francisco J. Burgos[3], Juan J. Villafruela[1], Joaquín Ortuño[1]

[1] Nephrology Unit, Ramón y Cajal Hospital, Madrid - Spain
[2] Clinical Biostatistics Unit, Ramón y Cajal Hospital, Madrid - Spain
[3] Urology Unit, Ramón y Cajal Hospital, Madrid - Spain

ABSTRACT

***Background*: Available studies of early serum creatinine (SCr) as a surrogate marker for long-term graft loss are multicenter, registry-based or limited to 5- to 7-year survival.**

***Methods*: This was a single-center observational retrospective study. SCr during the first year post-kidney transplant as an independent variable in determining long-term (>10-year) graft survival in 754 first cadaver kidney transplants was assessed with univariate and multivariate models.**

***Results*: Kaplan-Meier survival estimates showed that recipient female sex, a transplant procedure performed after 1997, donor age under 55 years, immunosuppression including tacrolimus and/or mycophenolate mofetil and absence of acute rejection, were significantly related to better long-term graft survival. SCr at 1, 3, 6 and 12 months stratified into ≤1.5, 1.6-2 and >2 mg/dL groups was also strongly related to long-term graft survival. Multivariate Cox models showed that increased SCr at any point during the first year had a higher relative risk for ultimate graft loss.**

***Conclusions*: Early graft function is strongly correlated with long-term graft survival (≥10 years). Mild differences in SCr (1.5 vs. 1.6-2 mg/dL) are associated with highly significant impact on long-term survival, longer than previously described. However, the "hard" predictive value of SCr as an isolated tool is not strong enough. Other early surrogate end points for graft loss are needed.**

Key words: *Graft function, Serum creatinine, Surrogate end points*

INTRODUCTION

The evaluation of new therapeutic strategies in kidney transplantation is becoming of limited value because the usual end points are poor tools in the long run, and time-to-event of potentially useful end points such as graft loss is too long. Consequently, short-term variables predicting long-term evolution of kidney transplants would be very useful for patient management. The simplest and most recently defined surrogate markers are serum creatinine (SCr) levels at 6 months or 1 year and the change in SCr over the first 12 months following transplant (1). We have previously suggested that SCr at 1 month post-kidney transplant is strongly correlated to 3-year graft survival (2). Other studies that examined renal function as a predictive marker for long-term graft survival have either been in the context of acute rejection episodes or have utilized discharge SCr values or parameters of graft function from big registries (3-5). Moreover, they have examined predictive capacity for graft survival over a period of only 5 to 7 years (1, 5). The purpose of this study was to examine renal function during the first year of transplant as an independent variable in determining long-term ≥10-year) renal allograft survival. The hypothesis is that achievement of good renal function as early as 30 days and during the first year after transplant is correlated with well-maintained graft function during the subsequent 10 or more years.

SUBJECTS AND METHODS

Patient cohort

Between November 1979 and August 2003, 968 renal allograft transplants were performed by our service. To

assess a more uniform cohort, retransplants (n=89), living-donor transplants (n=14) and grafts functioning less than 1 month or never-functioning kidneys (n=111) were excluded from the analysis. The cohort was then formed from the 754 primary renal cadaver allograft transplants functioning for at least 30 days.

The database was locked in December 2005, when we had information from the 754 patients until graft loss or at least 4 potential months of follow-up in functioning kidneys. At this date, 296 (39%) kidneys were not functioning, 15 (2%) had been lost to follow-up and 443 (59%) were functioning. All graft survival analysis was based in the 296 final events. Lost-to-follow-up kidneys and patients dead with a functioning graft were included in the analysis, censored with their last functional data available.

Immunosuppression

Immunosuppression for primary cadaver renal transplants was based on azathioprine and prednisone without antibody induction (years 1979-1985); standard cyclosporine (Sandimmune) and prednisone (1986-1995); and microemulsified cyclosporine (Neoral) or tacrolimus (Prograf), and prednisone, with or without mycophenolate mofetil (MMF; Cellcept) (since 1996). Azathioprine was used at a dosage of 1.5-3 mg/kg per day. Standard cyclosporine dosage was initially 10-12 mg/kg per day divided into 2 doses, for blood trough levels of 400-800 ng/mL the first month, and 200-400 ng/mL thereafter. Microemulsified cyclosporine was initially given at a dosage of 8-10 mg/kg per day in 2 doses, adjusted for 200-400 ng/mL the first month and 150-250 ng/mL thereafter. Tacrolimus dosage was initially 0.2 mg/kg per day divided into 2 doses, for blood trough levels of 8-15 ng/mL the first month and 8-10 ng/mL thereafter. MMF was given at a dosage of 2 g daily (with cyclosporine) or 1 g daily (with tacrolimus).

Outcomes assessed and statistical analysis

Our electronic database was initiated in 1989, when more than 200 clinical and analytical variables were retrospectively entered, involving all transplant procedures performed between 1979 and 1988. Between 1989 and 2005, all variables were prospectively recorded in each patient file, with updates to all clinical and analytical variables regarding new events and data on a daily basis. Consequently, missing data are less than 1% for all variables and categories considered, and the quality of the data is very high.

Univariate survival analysis was performed with the Kaplan-Meier method (6), assessing the influence of the following variables on graft survival: recipient age (over or under 55 years) and sex, underlying renal disease (stratified into diabetes, hypertensive nephropathy or other), transplant period (stratified into 3 groups: 1979-1985, 1986-1996 and 1997-2005), donor age (over and under 55 years), donor sex, immediate or delayed graft function, cold ischemia time (more and less than 18 hours), immunosuppression (stratified into 3 groups: azathioprine, cyclosporine and new immunosuppressive drugs: tacrolimus and/or MMF), acute rejection during the first year post-kidney transplant and SCr at 1, 3, 6 and 12 months post-kidney transplant (stratified into 3 groups: ≤1.50, 1.51-2 and ≥2 mg/dL). The differences in SCr between month 3 and month 1 (Δ 1-3 months, mg/dL), between month 6 and month 1 (Δ 1-6 months, mg/dL) and between month 12 and month 1 (Δ 1-12 months, mg/dL) were calculated and included as categorized variables (≥0.3 mg/dL vs. ≤0.3 mg/dL). Estimated glomerular filtration rate (GFR; Modification of Diet in Renal Disease [MDRD-4] study formula) and estimated creatinine clearance (Cockcroft-Gault formula) were also assessed, but they were finally excluded due to intense colinearity with SCr. Similarly, transplant year and treatment were not included at the same time in the analysis due to the high correlation between both covariates.

Recipients with panel reactive antibodies (PRA) levels over 50%, those who were using antilymphocytic antibodies as induction therapy, those who had HLA matches for more than 3 alleles and race other than white were so infrequent in our first cadaveric kidney transplant cohort that the subgroups determined were very small. Consequently, these variables were not included in the analysis.

Median survival in years (time passed until 50% of the grafts were lost) was used to represent the influence of the studied variables on graft survival, and the log-rank test was used to compare Kaplan-Meier survival curves.

Several multivariate survival analyses were performed by means of the Cox proportional hazards method (7), adjusting the influence of early SCr (measured at different time intervals) for the above-mentioned covariates. These variables were included in the maximum multivariate model. The final, most parsimonious model was obtained by backward selection from the maximal model. The log-likelihood ratio test was used for model comparison and goodness-of-fit assessment. The proportional hazards assumption was tested by introducing time-dependent covariates into the model and by visual inspection of

log(-log(survival)) versus log(time) plots (8).
The area under the receiver operating characteristic (ROC) curve (AUC) was calculated for SCr at 1, 3, 6 and 12 months to gain additional information on the "hard" predictive capacity of those values for graft survival or loss (5). Significance was assumed at a p level of less than 5%. Calculations were made using SPSS, version 12.0, software (SPSS Inc., Chicago, IL, USA).

Ethical issues

This study was approved by the clinical investigation ethics committee within the Ramón y Cajal Hospital. No external funding or grants were given to this study.

Results

Univariate Kaplan-Meier survival estimates

In univariate analysis (Tabs. I and II), age at transplant did not influence censored graft survival. Female recipients showed a longer graft survival than male recipients (median graft survival 19.6 vs. 12.4 years, respectively; p=0.036). Underlying renal disease did not influence graft survival. Transplant performance period was significantly correlated with graft survival, and transplants performed during the first period (1979-1985) showed significantly less survival than those performed during the second and third periods. Furthermore, graft survival for organs transplanted between 1986 and 1996 showed worse survival than those performed after 1997. Donor age over 55 years was associated with worse graft survival than donor age younger than 55 years (median graft survival 8.3 vs. 14.1 years, respectively; p=0.031). Donor sex did not influence graft survival. Cold ischemia time was not associated with graft survival (median graft survival 14.3 years if >18 hours vs. 12 years if <18 hours, p=0.270). There were no differences when stratification was at 12 or 24 hours (data not shown). Graft half-life was influenced by immunosuppressive drugs used, with an obvious relationship with transplant periods. The improvement in long-term function achieved by cyclosporine was only modest in comparison with azathioprine (p=0.047). Five-year graft survival and projected half-life was better with the new drugs tacrolimus and/or MMF than with cyclosporine plus steroids. Immediate graft function was not associated with significantly better long-term graft survival than delayed graft function (median graft survival 14.1 vs. 12.9 years, respectively; p=0.174). The presence of acute rejection during the first posttransplant year was very strongly related to worse survival, and median graft survival was almost doubled in the absence of this complication.
In Table II we can observe the influence of SCr during the first year, on graft survival estimates. A SCr of 1.5 mg/dL or less at 1 month did not predict better graft survival than a SCr of 1.6-2 mg/dL at 1 month. SCr of 1.5 mg/dL or less predicted significantly better survival for the graft than SCr over 2 mg/dL at any time point ($p<0.00001$, for all comparisons). SCr of 1.5 mg/dL or less at 3, 6 and 12 months predicted better graft survival than SCr 1.6-2 mg/dL at 3, 6 and 12 months, in the univariate analysis. SCr of 1.6-2 mg/dL was associated with longer graft survival than SCr over 2 mg/dL at any point ($p<0.01$, for all comparisons).
Estimated GFR (MDRD-4 formula) and estimated creatinine clearance (Cockcroft-Gault formula) were also assessed, but the association with graft loss was less intense than that for SCr values (data not shown).
Early 1-month SCr could be increased due to a reversible process of ischemia reperfusion during the recovery phase. To rule out possible confusion with acute tubular necrosis we have compared graft survival between patients with or without delayed graft function in each of the 3 SCr categories (1 month SCr ≤1.5, 1.6-2 or >2 mg/dL). Kaplan-Meier estimates were similar for patients with or without delayed graft function in each of the 3 strata.

ROC curves

In Table III the AUCs for SCr during the first year after kidney transplant are summarized. The best fit was achieved with 12-month SCr, with an AUC of 0.631.

Multivariate Cox proportional hazard models

Multivariate analyses with Cox proportional hazard models showed that SCr values at 1, 3, 6 and 12 months are independent significant predictors of graft survival beyond 10 years, after adjustment for other known prognostic factors. Change (Δ) SCr over 0.3 mg/dL was a strong factor for graft loss at 6 and 12 months. The 4 models are depicted in Table IV. We have tried to address the true impact of acute rejection by including another Cox regression multivariate analysis stratifying the patients into 2 subgroups, with and without rejection during the first year, and assessing the possible different impact of SCr at 1, 3, 6 and 12 months. Including only patients with acute rejec-

TABLE I

INFLUENCE OF SOME CLINICAL VARIABLES ON UNIVARIATE KAPLAN-MEIER ESTIMATES FOR GRAFT SURVIVAL IN 754 PRIMARY CADAVER RENAL ALLOGRAFT RECIPIENTS WITH A FUNCTIONING GRAFT FOR AT LEAST 1 MONTH

	Graft survival estimates by year						Median survival (years)	Log-rank test (p Value)
	1	3	5	10*	15*	20*		
Age at transplant								
>50 years (%)	79.2	73.0	65.5	50.7	35.4	--	10.2	
<50 years (%)	80.5	73.1	67.2	53.4	42.1	36.0	12.1	0.222
Recipient sex								
Male (%)	91.6	82.5	73.6	57.9	41.6	34.7	12.4	
Female (%)	89.3	82.3	77.8	63.8	55.8	47.2	19.6	0.036
Underlying renal disease								
DM or hypertension (%)	86.4	83.8	77.5	61.3	40.7	--	14.1	0.983 (vs. a) 0.946 (vs. b)
Polycystic or GN (%) (a)	91.4	81.8	73.0	61.9	45.8	36.6	13	0.940 (vs. b)
Other (%) (b)	90.4	82.8	76.8	58.0	48.2	42.3	14.7	
Transplant period								
Years 1979-1985 (%) (I)	78.3	67.5	63.7	51.6	40.7	34.3	10.3	0.043 (vs. II) <0.00001 (vs. III)
Years 1986-1996 (%) (II)	91.0	83.9	76.6	60.3	47.1	--	13.3	0.037 (vs. III)
Years 1997-2005 (%) (III)	97.8	90.4	81.1	--	--	--	17†	
Donor age								
>55 years (%)	91.8	82.3	69.2	36.4	--	--	8.3	
<55 years (%)	90.1	82.3	75.7	61.3	47.4	40.5	14.1	0.031
Donor sex								
Male (%)	89.7	82.2	75.8	60.3	45.7	40.3	13.9	
Female (%)	91.7	82.4	73.5	58.7	47.4	38.2	13.3	0.826
Cold ischemia time								
>18 hours (%)	90.4	81.9	74.5	61.6	48.9	40.3	14.3	
<18 hours (%)	89.5	81.7	75.4	54.2	38.9	33.9	12.0	0.270
Immunosuppression								
Azathioprine + St (%) (c)	78.6	67.9	64.1	51.6	40.8	34.4	10.3	0.047 (vs. d) <0.00001 (vs. e)
Cyclosporine + St (%) (d)	91.4	83.9	75.6	60.1	46.8	--	13.3	0.006 (vs. e)
Tacrolimus or MMF (%) (e)	97.4	91.9	84.5	--	--	--	18.3†	
Delayed graft function								
Yes (%)	88.3	81.3	74.2	56.9	45.8	37.1	12.9	
No (%)	92.0	83.3	76.0	63.0	46.6	41.7	14.1	0.174
Acute rejection first year								
Yes (%)	82.4	72.6	66.9	50.6	37.4	32.8	10.2	
No (%)	97.5	91.5	82.7	70.2	58.2	43.6	18.9	<0.00001

DM = diabetes mellitus; GN = glomerulonephritis; St = steroids.

*Empty cells denote a small number of patients (<10%) at risk at some points for some subgroups, thus excluding Kaplan-Meier estimates as a reliable tool at these time points.

†Projected half-life.

tion, the model for SCr remained very similar to that obtained with the whole patient series. When we considered only patients without acute rejection, the model for SCr remained very significant, but the variables immunosuppression, donor age and immediate function lost their significance.

TABLE II
INFLUENCE OF SERUM CREATININE (SCr) AT 1, 3, 6 AND 12 MONTHS, ON UNIVARIATE KAPLAN-MEIER ESTIMATES FOR GRAFT SURVIVAL IN 754 PRIMARY CADAVER RENAL ALLOGRAFT RECIPIENTS WITH A FUNCTIONING GRAFT FOR AT LEAST 1 MONTH

	Graft survival estimates by year						Median survival (years)	Log-rank test (p Value)
	1	3	5	10	15	20*		
SCr at 1 month								
≤1.5 mg/dL (%) (a)	95.3	86.2	82.1	68.8	53.7	45.4	18.6	0.717 (vs. b) <0.00001 (vs. c)
1.6–2 mg/dL (%) (b)	95.9	89.7	81.1	63.7	53.1	39.7	17.2	<0.00001 (vs. c)
>2 mg/dL (%) (c)	78.7	70.6	61.1	43.9	31.4	29.1	7.8	
SCr at 3 months								
≤1.5 mg/dL (%) (d)	96.9	88.6	84.0	67.9	54.4	46.6	19	0.038 (vs. e) <0.00001 (vs. f)
1.6–2 mg/dL (%) (e)	96.8	87.7	78.2	60.0	45.8	--	12	0.003 (vs. f)
>2 mg/dL (%) (f)	81.4	74.6	62.7	48.2	29.2	--	9.9	
SCr at 6 months								
≤1.5 mg/dL (%) (g)	98.8	91.5	84.7	71.2	57.0	47.9	19.2	0.005 (vs. h) <0.00001 (vs. i)
1.6–2 mg/dL (%) (h)	98.6	89.1	84.5	61.0	42.3	--	13.4	0.006 (vs. i)
>2 mg/dL (%) (i)	88.2	78.1	62.1	43.1	32.2	--	7.8	
SCr at 12 months								
≤1.5 mg/dL (%) (j)	100	95.4	90.5	75.5	59.9	48.9	19.7	0.007 (vs. k) <0.00001 (vs. l)
1.6–2 mg/dL (%) (k)	100	92.8	84.5	61.8	42.3	--	13.3	0.0001 (vs. l)
>2 mg/dL (%) (l)	100	73.1	57.5	36.4	29.1	--	6.5	

*Empty cells denote a small number of patients (<10%) at risk at 20 years, for the SCr 1.6-2 mg/dL and >2 mg/dL subgroups, thus excluding Kaplan-Meier estimates as a reliable tool at this point.

TABLE III
AREA UNDER THE RECEIVER OPERATING CHARACTERISTIC CURVE (AUC) FOR SERUM CREATININE (SCr) AT 1, 3, 6 AND 12 MONTHS FOR 754 PRIMARY CADAVER RENAL ALLOGRAFT RECIPIENTS WITH A FUNCTIONING GRAFT FOR AT LEAST 1 MONTH

Variable	AUC	95% Confidence interval	p Value
SCr at 1 month	0.592	0.551-0.632	<0.0001
SCr at 3 months	0.559	0.518-0.600	0.005
SCr at 6 months	0.591	0.549-0.633	<0.0001
SCr at 12 months	0.631	0.589-0.673	<0.0001

TABLE IV
COX PROPORTIONAL HAZARD MODELS ASSESSING THE INFLUENCE OF SERUM CREATININE (SCr) AT 1, 3, 6 AND 12 MONTHS ON LONG-TERM GRAFT SURVIVAL

	Hazard ratio	95%Confidence interval	p Value
SCr at 1 month			
Azathioprine + steroids	1		
Cyclosporine + steroids	0.60	0.45-0.81	0.001
Tacrolimus and/or MMF	0.25	0.14-0.45	<0.001
Donor age >55 years	1.76	1.22-2.54	0.002
Immediate function	0.77	0.60-0.99	0.040
Acute rejection 1st year	1.46	1.12-1.91	0.005
SCr ≤1.5 mg/dL	1		
SCr 1.6-2 mg/dL	1.26	0.91-1.76	0.163
SCr >2 mg/dL	2.62	1.90-3.59	<0.001
SCr at 3 months			
Azathioprine + steroids	1		
Cyclosporine + steroids	0.81	0.59-1.11	0.196
Tacrolimus and/or MMF	0.29	0.15-0.55	<0.001
Donor age >55 years	1.69	1.14-2.51	0.008
Acute rejection 1st year	1.43	1.09-1.87	0.011
SCr ≤1.5 mg/dL	1		
SCr 1.6-2 mg/dL	1.34	0.99-1.82	0.061
SCr >2 mg/dL	1.99	1.38-2.88	<0.001
Δ SCr (1-3 months) >0.3 mg/dL	1.45	0.99-2.14	0.059
SCr at 6 months			
Azathioprine + steroids	1		
Cyclosporine + steroids	1.08	0.78-1.50	0.639
Tacrolimus and/or MMF	0.43	0.22-0.83	0.013
Female sex	0.66	0.50-0.88	0.005
Donor age >55 years	1.75	1.15-2.68	0.009
Acute rejection 1st year	1.40	1.06-1.86	0.019
SCr ≤1.5 mg/dL	1		
SCr 1.6-2 mg/dL	1.18	0.85-1.64	0.323
SCr >2 mg/dL	1.59	1.08-2.34	0.018
Δ SCr (1-6 months) >0.3 mg/dL	2.14	1.45-3.15	<0.001
SCr at 12 months			
Female sex	0.73	0.54-0.98	0.035
Donor age >55 years	1.59	1.05-2.43	0.030
Acute rejection 1st year	1.46	1.11-1.92	0.007
SCr ≤1.5 mg/dL	1		
SCr 1.6-2 mg/dL	1.24	0.89-1.74	0.204
SCr >2 mg/dL	2.23	1.53-3.25	<0.001
Δ SCr (1-12 months) >0.3 mg/dL	2.09	1.46-3.00	<0.001

MMF = mycophenolate mofetil.

Discussion

A retrospective registry analysis of more than 105,000 renal transplants undertaken between 1988 and 1998 in the United States identified renal function within the first year posttransplant as an important predictor of long-term transplant outcome, with SCr concentrations ≤1.5 mg/dL at 6 or 12 months being associated with the highest rate of 5-year graft survival (1). Interestingly, data obtained from our own center between 1996 and 2000 in 216 transplant procedures showed that SCr concentrations may be predictive of long-term outcome as early as 1 month posttransplant, with values above 2 mg/dL at this time point being associated with significantly ($p<0.01$) worse 3-year graft survival versus SCr concentrations ≤2 mg/dL (2). Our current study confirms and extends these findings in a larger series of 754 primary cadaveric kidney allograft recipients with organs functioning at least 30 days. SCr determined at 1, 3, 6 and 12 months showed independent predictive value for long-term graft survival. Previous reports had concluded that SCr values at 6 or 12 months were able to discriminate between grafts functioning at 5 years and grafts lost at 5 years, and calculated only *projected* half-life for kidneys stratified by SCr at 6 or 12 months (1). Other studies have examined renal function as a predictive marker for long-term graft survival in the context of acute rejection episodes (3) or have utilized discharge SCr values (4). An important study from the US Renal Data System (USRDS) registry assessed the value of serum creatinine at 1 year and other renal function parameters in their relationship with graft survival up to 7 years (5). In our cohort, we have a very extended follow-up, enough to determine actual median renal allograft half-life for the 3 levels of early SCr in which we categorized our patients and for other important clinical variables.

In the univariate analysis, recipient female sex, a transplant procedure performed after 1997, donor age under 55, immunosuppression including tacrolimus and/or MMF and absence of acute rejection, were all significantly related to long-term graft survival. However, and consistent with our previous reports, age at transplant did not influence censored-for-death graft survival (9), and delayed graft function was not associated with long-term graft loss (10). When we distribute our 754 primary cadaver kidney allograft procedures into 3 consecutive time periods, the improvement in graft survival is highly significant. However, this improvement is very pronounced only in the most recent period, when the new drugs MMF and tacrolimus were predominantly used in our unit. As we reported previously, the improvement seen in the cyclosporine era in long-term graft survival was only modest in comparison with the azathioprine period before 1986 (11, 12). A recent study in cadaver kidney recipients by Gourishankar et al showed that the rate of decline in graft function improved between 1990 and 2000 (13), and these results have been confirmed and extended by pooling data derived from more than 10,000 patients at 5 transplant centers in the United States (14).

One of the most striking findings in our univariate study with Kaplan-Meier estimates is that median graft survival in cadaver renal allograft transplants is 19 years when 1-month SCr is 1.5 mg/dL or lower and decreases to less than 8 years when 1-month SCr is 2 mg/dL or over. Similar results are obtained when using SCr at 3, 6 or 12 months, and it is worth noting the very low half-life of 6.5 years for kidneys showing SCr over 2 mg/dL at 12 months. Early SCr of 2-2.5 mg/dL is usually considered as an indicator of an acceptable functional level, and our data indicate that this might not be the case.

Cox proportional hazards analysis confirmed that early SCr influences the rate of graft failure. With this method, the influence of all the other variables considered is taken into consideration, and adjustments for interaction were easily made. The independent predictive value of the Δ SCr in our models is noteworthy. After SCr level, the increase in SCr between 1 and 6-12 months was the most relevant risk factor for long-term graft loss. A Δ for 1 to 6 or 1 to 12 months of more than 0.3 mg/dL was associated with double the risk for long-term graft loss. This confirms and extends similar results from the USRDS registry (1). Immunosuppressive drugs used showed a significant influence on 1-month SCr predictive value, and this influence decreased over time. Transplant period showed a strong relationship with graft survival, but this association disappeared when immunosuppressive drugs were included in the multivariate Cox model (Tab. IV). In other words, when we include transplant period in the model, the significance of the immunosuppressive drugs used disappeared and vice versa (data not shown). The clear relationship between periods and drugs confounds this issue and does not allow us to distinguish their effects consistently. Interestingly, the influence of immunosuppressive drugs on the early SCr value to predict graft loss disappeared when we considered only patients without acute rejection.

The favorable impact of immediate graft function was only significant for the 1-month model, when SCr values could be falsely elevated due to slowly recovered acute tubular necrosis, high cyclosporine or tacrolimus levels or cellular

acute rejection. Immediate function lost its predictive value from 3 months on. To rule out any important influence of delayed graft function on the elevated SCr, we compared graft survival in patients with immediate versus delayed function and found there were no significant differences in any of the 3 SCr categories. Advanced donor age also had a significant influence on long-term graft failure in the 1-, 3- and 6-month models. However, considering SCr at 12 months, donor age did not itself influence graft prognosis. The only variable that always remained significant in the Cox model of SCr predictive value for long-term graft survival was acute rejection. Patients with acute rejection had 37% to 50% more risk of graft failure than patients without it, in each of the 4 models we constructed. In contrast to the results in the registry study by Hariharan et al (1), acute rejection did not lose its significance when early SCr was included in the regression model. Thus, in the setting of acute rejection, early preservation of renal function was not the only important factor; the rejection itself was also important. The magnitude of this association was intermediate between those for SCr 1.6-2 mg/dL and SCr >2 mg/dL; in other words, an acute rejection had a similar impact to a SCr of 1.6-2 mg/dL for prognosis, but the association of an early SCr over 2 mg/dL was much more important. In agreement with our data, Salvadori et al, in an observational study including more than 10,000 patients on cyclosporine, have observed that donor age, delayed graft function, acute rejection and donor type significantly increased the risk for serum creatinine >130 μmol/L at 1 year posttransplant, and 1-year SCr was the strongest predictor of 5-year renal function (15). Similar results were confirmed using estimated GFR (16).

Our analysis confirms all others that demonstrate the importance of graft function as a risk factor for death-censored graft loss (1-5). However, SCr does not have enough predictive value to be applied as a reliable predictive test for graft loss, as is shown by the low values for the AUCs (Tab. III), which supports the view of Kaplan et al (5). Using 1-month SCr for prediction of graft loss, we will only succeed in 59.2% of cases, given that AUC of 0.592; this percentage increases up to 63.1% for 12-month SCr. A very important number of grafts will survive despite high 12-month SCr, and some others will be lost despite low early SCr values. Depending on the time we perform early SCr, at 1, 3, 6 or 12 months, we can state that a given patient will have a twofold to threefold increase in their hazard risk for graft failure, but not whether this single patient will lose the graft or not.

Our study has some potential limitations. The first of these could be the use of SCr as an estimate of graft function. Many authors advocate calculated GFR (17) or several formulae derived from the MDRD study (18, 19) or other cohorts (20) to accurately assess renal graft function, but SCr is without doubt the simplest analytical parameter used mostly in outpatient clinical visits to assess posttransplant kidney function. Some of the derived formulae are very simple and include a small number of variables available in our database. However, they do not exclude factors other than renal function affecting SCr. Consequently, and despite its limitations because of the variability resulting from recipient age, sex and body weight (21), we used it in looking for an early surrogate end point which was both simple and widely used in clinical practice. Furthermore, when we applied these formulae to our analyses, no improvement was detected in comparison with the simple SCr.

The second limitation is that we have assessed a database of only 754 patients, far fewer than the numbers seen in similar recent studies (1, 5). This limitation is in our view an advantage, as our cohort is probably more homogeneous, excluding living-donor transplants and retransplants, and it reproduces with high reliability some of the main results of bigger cohorts (1, 5). Finally, our multivariate statistical method (Cox model) could be questioned as to whether it is the most appropriate tool. In a recently published analysis from the USRDS, the predictive capacity of SCr in renal transplantation was studied with univariate and multivariate logistic regression analysis (5). With this method, the occurrence of graft failure was studied within a fixed time frame without considering time as a variable. However, the time of the event (in this case "graft failure") is an important variable along with the occurrence itself, and multivariate analysis in long-term renal allograft survival can be undertaken with the Cox regression models.

We have been able to support a claim that early SCr establishes robust associations to 10- and even 15-year graft survival. Stratification between apparently similar cohorts (patients with SCr ≤1.5 mg/dL and patients with SCr 1.6-2 mg/dL) allowed us to observe striking differences in survival, thus supporting the view that mild early graft function improvement carries great advantages for the future. Transplant physicians should foster protocols (e.g., preventative measures, renoprotective immunosuppressive regimens and concomitant treatments) to obtain excellent SCr levels as soon as possible in the posttransplant evolution, as this seems critical to long-term survival.

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Address for correspondence:
Julio Pascual
Servicio de Nefrología
Hospital Ramón y Cajal
Carretera de Colmenar km 9,100
28034 Madrid, Spain
jpascual.hrc@salud.madrid.org

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