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Influence of donor age on graft survival

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ABSTRACT

Introduction: In 2007 in Spain 43% of donors were older than 60 years. This produces a worse graft quality and probably a worse survival.

Objective: Our objective is to analyze the influence of donor age on graft survival.

Material and methods: We analyze retrospectively 216 renal consecutive transplants realized between 2000 and 2008. A univariate and multivariate study (Cox regression) was performed and Kaplan-Meier test with log rank for graft survival.

Results: Follow-up mean of 40 months ($\pm 33,4$ SD). The univariate analysis of graft survival showed that donor age had a significative influence on graft survival. (OR=1.03; 95% CI 1.01-1.05) (p: 0.009).

Studying the relation between donor and recipient age we find an inverse correlation (Pearson's Correlation: 0.55. $p < 0.0001$), but there are significative differences after the adjustment for recipient age. (OR: 1.02; 95% CI 1.01-1.04) (p: 0.04). Optimal cut-point value determined by the ROC analysis was 60 years.

The graft survival of donors over 60 years is 79% (95% CI; 74-84%) and 71% (95% CI; 65-77%) at 3 and 5 years in contrast with 94% (95% CI; 94-96%) and 90% (95% CI; 88-92) in donors under 60 (p: 0.002).

The multivariate study of the influential factors on graft survival reveals that donor age dichotomized in older or younger than 60, the presence of a surgical immediate reintervention and a delayed graft function were independent influence factors.

Conclusions: Donor age over 60 years has a negative and independent prognostic influence on graft survival.

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Edad del donante y su influencia en la supervivencia del injerto

R E S U M E N

Palabras clave:

Trasplante renal

Edad del donante

Supervivencia del injerto

Introducción: En 2007 en España el 43% de los donantes tuvo más de 60 años, lo que supone peor calidad del injerto y probablemente peor supervivencia.

Objetivo: Nuestro objetivo es analizar la influencia de la edad del donante en la supervivencia del injerto.

Material y métodos: Analizamos retrospectivamente 216 trasplantes renales consecutivos realizados entre 2000-2008. Valoramos la influencia de la edad del donante sobre la supervivencia del injerto y buscamos el mejor punto de corte.

Para el estudio de la supervivencia actuarial del injerto se ha utilizado el método de Kaplan Meyer. Para la comparación de curvas de supervivencia utilizamos el test de log-rank. Para el estudio de los factores influyentes en la supervivencia hemos utilizado los modelos de regresión de Cox en forma de estudio univariado y multivariado.

Resultados: La media de seguimiento fue de 48 meses ($\pm 33,4$ DE) y la mediana de seguimiento fue de 48 meses (rango de 0-166 meses).

El análisis univariado de la supervivencia del injerto nos mostró que la edad del donante como variable continua influye significativamente en la supervivencia del injerto (odds ratio: 1,03; intervalo de confianza [IC] 95%: 1,01-1,05; $p = 0,009$).

Al estudiar la relación entre la edad del donante y el receptor evidenciamos una correlación inversa significativa (correlación de Pearson: 0,55; $p < 0,0001$), pero a pesar de esto, la significación se mantiene si se ajusta con la edad de los receptores (odds ratio: 1,02; IC 95%: 1,01-1,04) ($p = 0,04$). El mejor punto de corte corresponde a 60 años.

La supervivencia actuarial del injerto en donantes mayores de 60 años es del 79 (95% IC: 74-84) y del 71% (IC 95%: 65-77) en 3 y 5 años frente al 94 (IC 95%: 94-96%) y al 90% (IC 95%: 88-92) en los receptores de riñones de donantes menores de 60 años ($p = 0,002$).

El estudio multivariado de los factores influyentes en la supervivencia del injerto revela que la edad del donante dicotomizada en mayor y menor de 60 años, la presencia de reintervenciones quirúrgicas inmediatas y la función diferida eran los factores de influencia independiente en la supervivencia del injerto.

Conclusiones: La edad del donante mayor de 60 años influye negativamente en la supervivencia del injerto renal con valor pronóstico independiente.

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Introduction

According to the National Transplant Organization, individuals over the age of 70 years represented 11.2% of donors in Spain in 1999, and 23.4% in 2008; individuals under the age of 30 changed from 11.2% to 23.7% of donors. In 2007, 72% of donors were older than 45 years, and 43% were older than 60.

Two reasons explain the increase in the age of donors: In the first place, there is a change in the causes of death of the donor. In 1992, 52% of donor deaths were from head trauma, and 39% were from cerebrovascular accident. Last year, 65.4% of donors died from cerebrovascular accident and 19.5% from head trauma. The second reason for the increased donor age is the expansion of selection criteria, of which donor age is a key point. The Scientific Registry of Transplant Recipients (SRTR) of 2007 recognizes age as the most significant variable in the expanded criteria donor (ECD) group.¹ The influence of age is so heavy that some groups have even submitted

that the donor's age correlates better with survival than the preoperative biopsy findings.²

In this changing panorama, the influence of the criteria expansion on graft survival must be determined in order to make better decisions when selecting donors. Most studies assess all variables characterizing the "ECD kidney" as a whole.

The objective of this study is to assess the impact of donor age on graft survival, based on the understanding that age is the variable that most accurately defines this type of kidney.

Material and methods

We conducted a retrospective analysis of 216 consecutive kidney transplants between 2000 and 2008.

The variables obtained for the study were: donor's and recipient's age, donor's stay at the ICU, time of cold ischemia, residual diuresis, proteinuria, cause of recipient's

kidney failure, immunosuppressive regimens received, type of dialysis, percentage of surgical complications (major and minor), and reinterventions during the immediate postoperative period and for delayed graft function.

Surgical technique and follow-up

In all transplants, the donor's renal artery and vein were anastomosed terminolaterally (with 6-0 monofilament suture) to the recipient's external iliac artery and vein, respectively. The Campos-Freire technique with subsequent ureteral catheterization was used systematically for ureteral reimplantation. The ureterovesical anastomosis completed with a 6/0 reabsorbable braided suture (PDS), and the bladder was closed in one layer. A retroperitoneal aspiration drain was placed in all cases. A Foley catheter was left in place for five days. Renal function was monitored daily with plasma creatinine determinations; a Doppler ultrasound of the graft and a diuretic renal scintigraphy were conducted within the first 24 hours after transplantation.

Statistical analysis

An actuarial survival analysis was done for the group; whether the donor's age had an influence was determined initially using age as a quantitative variable in a univariate test using Cox models. Recipients of older donors are usually of a similar age, and this determines graft survival; now, the influence of the donor's age on graft survival was assessed by adjusting it to the recipient's age.

The best cutoff point was sought for donor age by doing an initial approximation with ROC curves and finding which one provided a larger area under the curve. This point was then evaluated with a survival analysis in order to verify the difference in survival between the two resulting groups.

Lastly, a univariate and a multivariate study (Cox models) were used to determine which variables affect graft survival. The variables included in the univariate analysis were: surgical complications, reinterventions during the immediate postoperative period, delayed graft function, and donor age over 60 years.

The event in the survival analysis was graft dysfunction or initiation of dialysis.

All statistical analyses were done with the Statistical Product and Services Solutions package version 15.0 (SPSS Inc., Chicago, Illinois, USA). A *p* value under 0.05 was required for statistical significance.

Results

We conducted a retrospective analysis of 216 consecutive kidney transplants between 2000 and 2008. The mean follow-up was 48 months (SD: ± 33.4), and the median was 48 months (range: 0-166 months). The donors' mean age was 48 years (SD: ± 17.47), and the recipients' mean age was 49 years (SD: ± 13.39). Table 1 describes the other sample variables (table 1).

At the median follow-up of 40 months, 36/216 patients (17%) had lost the graft. The group's actuarial 3- and 5-year survival is 90 ± 2 and $83 \pm 3\%$, respectively.

Table 1 – Demographic and clinical parameters of the study group

Parameter	Mean \pm SD
Recipient age (years)	49.7 \pm 13
Donor age (years)	48.9 \pm 17
Days in ICU	2.8 \pm 3.3
Donor BMI (kg/m ²)	25.1 \pm 3.4
Recipient BMI (kg/m ²)	25.1 \pm 4.1
Cold ischemia time (min)	813 \pm 512
Residual diuresis (cm ³)	873 \pm 731
Proteinuria (mg/dL)	55 \pm 101
Parameter	Percentage of total (n=216)
Functioning grafts	82.9
Delayed graft function	23
Surgical complications	38
Immediate reinterventions	10.6
<i>Causes of kidney failure in recipients</i>	
Glomerulonephritis	22.2
Polycystic kidney disease	20.8
Diabetic nephropathy	7.9
Obstructive uropathy	5.6
Autoimmune disease	2.8
Chronic pyelonephritis	7.4
Nephroangiosclerosis	8.3
Tubulointerstitial nephritis	7.9
Idiopathic	13.4
<i>Immunosuppressive regimens</i>	
Tacrolimus, mycophenolate mofetil, and corticosteroids	60.2
Cyclosporine, mycophenolate mofetil, and corticosteroids	26.9
Cyclosporine, sirolimus, and corticosteroids	5.6
Cyclosporine, everolimus, and corticosteroids	4.6
Other	2.7
<i>Type of dialysis</i>	
Predialysis	8.8
Peritoneal	25.5
Hemodialysis	60.6
Both	5.1
SD: Standard Deviation; BMI: Body Mass Index; ICU: Intensive Care Unit.	

The univariate analysis of graft survival shows that the donor's age as a continuous variable has a significant influence on graft survival (Odds ratio: 1.03; 95% confidence interval: 1.01-1.05; *p*=0.009).

An examination of the relationship between the donor's age and the recipient's age shows a significant inverse correlation (Pearson's correlation: 0.55; *p*<0.0001), and the significance is maintained when the recipients' age is adjusted (odds ratio: 1.02; 95% confidence interval: 1.01-1.04; *p*=0.04).

The best cutoff point is 60 years. One hundred and fifty patients received a graft from a donor younger than 60 years, and 65 patients from a donor older than 60. The two groups are homogeneous in terms of donor's creatinine and time of cold ischemia. There is a significant difference between the

Table 2 – Clinicopathological variables of groups of donors older and younger than 60 years of age

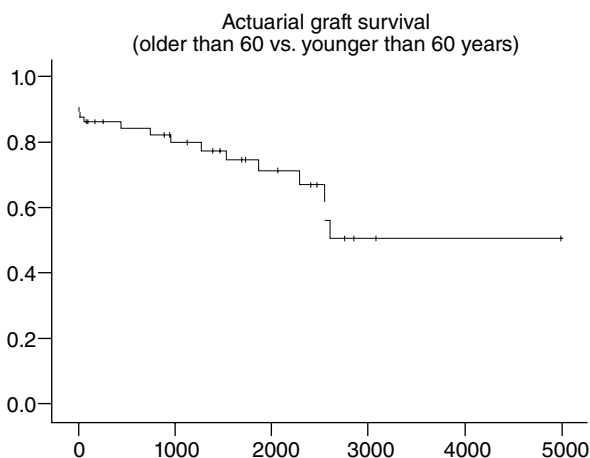
	Donors younger than 60 years (\pm SD)	Donors older than 60 years (\pm SD)	p
Creatinine (mg/dL)	1.04 (\pm 0.4)	1.06 (\pm 0.3)	>0.05
Cold ischemia time (min)	789 (\pm 575)	868 (\pm 319)	>0.05
ICU stay before extraction (days)	3.2 (\pm 3)	1.8 (\pm 1)	<0.001
BMI (kg/m^2)	24.5 (\pm 3.4)	26.5 (\pm 3)	0.02
Recipient age (years)	45 (\pm 12)	59 (\pm 10)	0.0001

Student's t-test used for statistical analysis.
BMI: Body Mass Index; ICU: Intensive Care Unit.

Table 3 – Univariate analysis of graft survival

	3-year graft SRV (95% CI)	5-year graft SRV (95% CI)	p
Donor younger than 60 years	94% (93-95)	90% (88-92)	(0.002)
Donor older than 60 years	79% (74-84)	71% (65-77)	

Kaplan Meyer test (log-rank) used for survival analysis.
CI: Confidence Interval; SRV: Survival.

**Figure 1 – Actuarial graft survival (older than 60 vs. younger than 60 years).**

age of recipients in the two groups (35 vs. 59 years; $p=0.001$). The body mass index is higher for the >60 years group ($p<0.001$). Pre-extraction ICU stay is longer for those under 60 years of age ($p<0.02$) (table 2).

The 3- and 5-year graft survival of organs from donors over 60 years of age is 79 ± 5 and $71\pm 6\%$, vs. 94 ± 1 and $90\pm 2\%$ for kidneys from donors under the age of 60. The differences are significant ($p=0.002$) (table 3).

Figure 1 shows that cumulative survival over time is longer in the under-60 group.

The multivariate analysis of factors influencing graft survival reveals that the donor's age dichotomized in over-

60 and under-60 years, the presence of immediate surgical reinterventions, and delayed function are independent factors influencing graft survival (table 4).

Discussion

The kidney is an eminently vascular organ that is very sensitive to aging, which provokes structural and functional changes. These changes result in glomerular hyalinization and glomerular sclerosis with a decrease of functioning nephrons; as of the third decade of life there is a physiologic decrease in the glomerular filtration rate of about $1 \text{ mL}/\text{min}/\text{year}$.³

A central problem in current renal transplantation is the scarcity of organs and a growing number of elderly patients on the waiting lists. As a result, more grafts from elderly donors are transplanted, assigned preferably to older recipients. The increase in the age of patients on waiting lists and of donors has resulted in the development of the ECD program in the United States (and the Eurotransplant Senior Program [Old-for-Old] in Europe).⁴ However, our understanding of the influence of donor and recipient age is still limited and requires more research.

While the issue is still controversial, most authors report poorer long-term survival outcomes with kidneys from elderly donors; this includes sub-optimal, borderline, and marginal organs, although there is currently no consensus on the definition of these terms.³

ECDs include deceased donors over the age of 60 years or over 50 with two of the following characteristics:

Table 4 – Multivariate analysis of graft survival per Cox model

	OR	95% CI	p
Donor age >60 years	2.7	1.2-6.5	<0.012
Immediate surgical reintervention	3.1	1.2-8.4	<0.0001
Delayed graft function	4.7	2.3-10.1	<0.0001
CI: Confidence Interval; OR: Odds Ratio.			

hypertension, creatinine higher than 1.5 mg/dL, or death from cerebrovascular accident. It is clear that age is key when potential donors are selected.

The main problem with the definition of extended donor criteria is that the lower age limit is clearly defined (60-65 years), but the upper limit is not. We must therefore ask what is the maximum acceptable age of cadaveric donors.⁵

Between 30 and 40% of "ECD kidneys" initially considered suitable end up being rejected, especially after they undergo bank surgery assessment and biopsy.⁴ In the past, grafts from elderly donors were rejected if creatinine was under 60 mL/min or the biopsy revealed glomerular sclerosis exceeding 15%.⁹ The current trend is more permissive, and other negative factors such as arterial hylinosis and interstitial fibrosis are given more weight. Recent studies question the notion that the most relevant pattern is glomerular sclerosis¹⁰⁻¹² and suggest that the donor's age is a better predictor of graft function.^{2,13} The utility of a biopsy is increasingly questioned, and the age of the donor is emerging as the main predictor of graft survival.

Other studies have highlighted the influence of cardiac arrest as the cause of death, hypertension, and prior renal function as determinants of graft survival in ECD patients.^{14,15} Some studies have assessed recipient age as a possible factor influencing graft survival, and concluded that the recipient's age is not a good predictor.¹⁶

Most multicenter studies admit that "ECD kidneys" have a shorter long-term survival than standard criteria donor (SCD) kidneys.⁶ In the 2007 SRTR report, recipients of an expanded criteria kidney had a risk of graft failure 77% higher than those who received a conventional transplant. Year-adjusted graft survival of ECD kidneys was 83.6% vs. 90.4% for standard criteria transplant. Donor advanced age is the most significant variable defining ECD in this study.¹

A literature review by Pascual et al shows that donor age has a negative impact on graft survival; only a few single-center studies with a low power did not find differences when they compared ECD to standard donor grafts.⁶ Three SRTR analyses support the notion that it is worthwhile waiting for an SCD kidney and avoiding an ECD kidney transplant for young recipients. A recipient/donor age ratio higher than 1.10 (donor older than 55 years and receptor of 50 years of age or younger) was associated with a three-fold graft loss in the first study.⁷

However, it is also clear that ECD graft transplants improve survival compared to patients with long waiting times on dialysis. Patients 40-years-old and older, especially those

with diabetic or non-diabetic nephropathy, with a long waiting time to transplant have a better survival with an ECD kidney than those on dialysis. Some authors set the waiting limit at 4 years. If waiting times were longer, a better survival would be obtained with ECD transplants.⁸

Based on available evidence, the conclusion is that patients younger than 40 and those requiring a new transplant should not receive an ECD kidney.⁸ However, the question is where the cutoff point is for patients over that range. Knowing the effect of donor age as an independent variable for graft survival is vital in order to stratify donor candidates. Collini et al compared the survival of grafts from donors over the age of 75 years (ultra old) to the remaining younger ECD group patients. Their outcomes were worse in terms of survival and complications in the over-75-years group, but they are still acceptable and promising for this age group.⁹

The Old-for-Old Eurotransplant Program allocation scheme offers a different line of results. The use of old grafts in old recipients without HLA matching did not produce survival differences with the control group thanks to a brief ischemia time. In order to ensure an acceptable rate of success, kidneys are transplanted with a shorter cold ischemia time and only non-immunized first-time recipients are included. The data suggest that if care is taken to avoid the accumulation of additional risk factors, a long cold ischemia time, and a new transplant, the Old-for-Old allocation scheme may yield satisfactory results.^{17,18}

Multi- and single-center observational studies confirm that kidney transplantation in elderly patients is associated with a long graft survival because patient survival is often the limiting survival factor for the grafted kidney.⁶ The main cause for graft loss in elderly patients is death with a functioning graft. This means that older patients are the ideal candidates to receive sub-optimal kidneys with a shorter durability than conventional ones. However, when patients with end-stage renal disease are allotted a graft, they already have many more cardiovascular risks than healthy patients of the same age. This situation must make us question the indication for the transplant and the use of chronic immunosuppression that sometimes unbalance the above-mentioned factors; we must always bear in mind that for a transplant to be effective, the recipient must survive the surgery and live for a significant time with a functioning graft.⁴ For all these reasons, the screening of high-risk patients is essential and will help to minimize morbidity and mortality in the immediate postoperative period. Although the ECD program has clear advantages for certain populations, patient

survival is limited when the ECD transplant is performed on high-risk recipients. A sedentary life-style, low functional capacity, long periods on dialysis, and delayed function are independent factors that affect the outcome of renal transplantation in elderly patients. A history of ischemic heart disease and a left ventricular function under 30% also clearly affect the outcome negatively.¹⁹ Patients of 60 years of age or older with comorbidities have sub-optimal survival outcomes when they receive an ECD transplant, compared to an SCD transplant.²⁰ Thus, ECD renal transplantation offers a longer survival than dialysis in the elderly patient, but SCD transplant offers the best survival.

When using an ECD kidney, we must take into consideration that these grafts tend to present delayed function and an overall worse course. Recipients have a longer, more costly, and more complex hospital stay.²¹ In any case, most ECD kidney recipients have an adequate, if diminished, renal function. All these features indicate that the best candidates for this kind of kidney are elderly, low-risk recipients, and that high-risk recipients with important comorbidities should avoid this type of graft. The combination of marginal kidney and elderly, high-risk donor usually results in delayed graft function and long and complicated hospital stays. In some programs this policy has caused an elevation in early postoperative mortality in elderly transplanted patients.²² A recent study in the United States revealed that the 5-year graft survival for donors over the age of 60 is 50% vs. 70% for donors of 19-45 years of age.²³ Even living donors older than 55 years pose a higher risk of graft failure.²⁴

Kauffman et al²⁰ reported a one-year mortality of 14.4% after ECD kidney transplant in patients aged 60 or older, and that any comorbidity increases that rate. Some centers report an increase in surgical urinary complications in patients receiving an ECD kidney, but this does not cause graft loss.²⁵ The main cause of mortality in these patients is cardiovascular disease (57% of deaths), followed by infections (24% of deaths), and cancer.²⁶ Mortality from infection is higher during the first year post-transplantation (40-50% of all deaths). This may be associated with excessive immunosuppression, which should be monitored.

In sum, the growing demand for organ transplants requires the use of grafts from elderly living donors and also a detailed analysis of risk factors present in the donor and the recipient.²⁷ Transplant of elderly or ECD organs is associated with reduced comorbidity and with an improved life expectancy, but requires careful donor assessment and recipient selection. The advantages of elderly donor transplants are a better survival compared to dialysis, and a better quality of life.²⁸ In this type of program, an adequate selection of patients is essential, and factors that result in poorer outcomes should be kept in mind. Excessive immunosuppression and delayed graft function should be avoided, for they result in longer and more complex hospital stays.

Conclusions

Donor age is a quantitative variable that affects graft survival. In our series the cutoff point is 60 years. A donor age of more

than 60 years has an independent negative influence on graft survival.

Donation criteria should be as detailed as possible in order to learn the cutoff point at which a patient on a waiting list ceases to benefit from a transplant. For this purpose, ECD kidney characteristics (including donor age) and their effect on graft and patient survival should continue to be researched.

Conflict of interest

The authors state that they have no conflicts of interest.

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