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Recipient age as a determinant factor of patient and graft survival

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Abstract

Background. Age of renal transplants has been related to death, alloimmune response and graft outcome. We reviewed the influence of patient age on transplant outcome in three cohorts of patients transplanted in Spain during the 1990s.

Methods. Patient age was categorized into four groups (I, 18–40; II, 41–50; III, 51–60; and IV, >60 years). Risks factors for acute rejection were evaluated by logistic regression adjusting for transplant centre and transplantation year, while a Cox proportional hazard model was employed for analysing patient and graft survival.

Results. Older patients had a higher death rate (I, 3.5%; II, 7.7%; III, 13.2%; and IV, 16.9%; $P < 0.001$), but a lower standardized mortality index (I, 7.6; II, 7.0; III, 5.8; and IV, 4.1; $P = 0.0019$). Older patients had the lowest risk of acute rejection [odds ratio (OR) 0.79 and 95% confidence interval (CI) 0.66–0.97 for group II; OR 0.75 and 95% CI 0.62–0.91 for group III; OR 0.43 and 95% CI 0.33–0.56 for group IV). Death-censored graft survival was poorer in patients older than 60 years (relative risk 1.40; 95% CI 1.09–1.80), but this result was not explained by any combination of patient age with donor age, delayed graft function or immunosuppression.

Conclusions. Patient age is a main determinant of transplant outcome. Although death rate is higher for older patients, standardized mortality was not. Thus, the efforts to reduce mortality should be also implemented in younger patients. Old patients have a low risk of acute rejection but a poorer death-censored graft survival. This last result was not explained by any controlled variable in our study.

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Introduction

During the last two decades the clinical outcome of renal transplantation has progressively improved since the rate of acute rejection episodes and infective complications have decreased with the arrival of new immunosuppressive drugs [1]. On the other hand, the age of end-stage renal failure patients has steadily increased with the mean age of patients suitable for transplantation to be near 50 years at 2000 in Spain. Moreover, donor age has increased with donors older than 70 years being accepted and the main cause of donor death has moved from traumatic to cerebrovascular events.

This modification of the clinical scenario would be associated with different outcomes from different subgroups of patients. As in the general population, elderly patients have a higher rate of cardiovascular complications and, thus, a high risk of patient death due to cardiovascular events [2,3]. Moreover, elderly patients may have a higher incidence of infectious complications, especially when powerful immunosuppression is employed [4]. On the other hand, it has been proposed that elderly patients need less immunosuppression to avoid acute and chronic rejection since they are less immunologically active [4]. However, it has also been demonstrated that there is no relevant effect of recipient age on immunological reactivity and it has even been suggested that increased recipient age is an independent risk factor for the development of chronic renal allograft failure [5,6].

Thus, patient age plays an important role in renal transplantation outcome and it would be helpful to analyse its effect taking into account the interaction between donor and recipient variables. Accordingly, we will analyse the effects of patient age on patient survival and death-censored graft survival adjusting for other

confounding variables in three cohorts of patients transplanted in Spain over the last decade.

Patients and methods

Cox regression analysis performed with the entire cohort showed that until the fourth decade no risk for death-censored graft failure was associated with patient age. For this reason, in order to analyse the relationship between patient age and graft outcome the following categories of age were considered: from 18 to 40 years, from 41 to 50 years, from 51 to 60 years and older than 60 years. Unfortunately, few patients older than 70 years were available in this cohort of patients and so, in order to maintain statistical power, this last decade was not evaluated separately. In order to detect any interaction between donor age and recipient age, donor age was categorized in the same way as recipient age.

The cause of patient death after the first year was recorded as cardiovascular, infection, malignancy, liver shortage or other. Cardiovascular risk factors, defined by standard criteria, were analysed at 1 year after transplantation. Diabetes mellitus at 1 year was considered as pre-transplant diabetes mellitus or post-transplant diabetes defined as at least two determinations of fasting serum glucose levels higher than 140 mg/dl or any anti-diabetic therapy. Standardized mortality index (SMI) was calculated according to the Spanish population mortality in the year 2000 in the different age categories as follows:

$$\text{SMI} = \text{observed deaths}/(\text{yearly mortality rate} * \text{years of follow up} * \text{patients})$$

The comparison between age groups was performed by means of log-linear Poisson regression, employing (yearly mortality rate * years of follow up * patients) as an offset variable. Also, relative risk (RR) of patient age was evaluated including the offset in the Cox regression according to the following expression:

$$\text{Offset} = \log(\text{RR})_{\text{expected}} = \log\left[\frac{\text{yearly mortality rate in a certain age group}}{\text{yearly mortality rate in the reference group}}\right]$$

Immunosuppressive treatment for the present work was evaluated only taking into consideration the use of polyclonal or monoclonal anti-lymphocyte induction therapy and mycophenolate mofetil (MMF). Since the majority of patients were treated with anticalcineuric agents, any attempt to analyse its effect was done.

The cause of graft failure was recorded as death with a functioning graft (DWFG), chronic allograft nephropathy (CAN) either with or without histological confirmation, irreversible acute rejection, non-treatment compliance, *de novo* glomerulonephritis, primary recurrent disease or other.

Results

Patient survival

The overall patient mortality for this cohort of patients was 8.9% at the end of follow-up. As expected, older patients had a poorer patient survival (Figure 1), but the SMI was higher for younger patients. Although younger recipients tended to die less frequently due to cardiovascular events, causes of patient death were distributed in a similar way in the four studied groups of patients (Table 1).

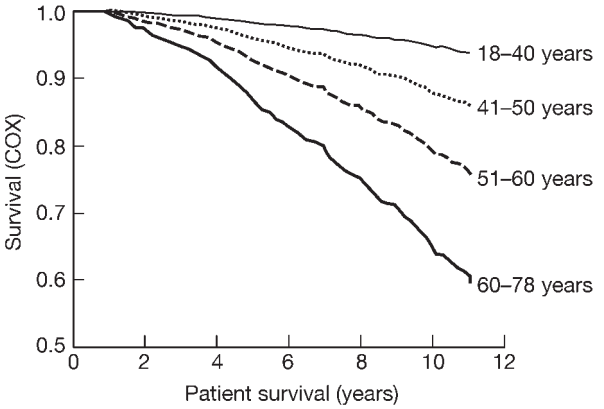

Fig. 1. Patient survival according to patient age ($P < 0.0001$).

The cardiovascular profile was worse in the older groups. These patients showed a higher proportion of diabetes mellitus, had elevated total serum cholesterol levels and showed systolic hypertension 1 year after transplantation (Table 2). Moreover, older patients had a lower diastolic blood pressure. No differences in serum triglycerides or serum creatinine levels were detected (Table 2).

No relationship was observed between immunosuppressive treatment (use of anti-lymphocyte induction therapy or MMF) and the cause of patient death.

After adjusting for the year of transplantation and for the centre effect, patient age [RR 2.23 and 95% confidence interval (CI) 1.50–3.32 for patients 41–50 years; RR 4.02 and 95% CI 2.80–5.79 for patients 51–60 years; RR 7.97 and 95% CI 5.34–11.90 for patients older than 60 years], donor age (RR 1.47 and 95% CI 1.07–2.02 for donors 41–50 years; RR 1.64 and 95% CI 1.17–2.30 for donors 51–60 years; RR 1.54 and 95% CI 1.04–2.30 for donors older than 60 years) and positive hepatitis C serology (RR 1.35 and 95% CI 1.01–1.81) were the only independent pre-transplant variables associated with patient survival. We did not observe any additional effect when the interaction between donor and recipient age was considered. However, this effect of patient age on patient survival is not observed when it is considered as RR associated with the standardized mortality.

Immunosuppression and clinical events after transplantation

Anti-lymphocyte induction therapy was employed more frequently in high-risk young recipients. It is important to remark that MMF was employed more frequently in older patients since this drug was not introduced in Spain in 1990 and 1994. Older recipients also displayed a higher incidence of cytomegalovirus infection that is not related to MMF treatment (Table 3).

Table 1. Cause of patient death according to patient age

	18–40 years	41–50 years	51–60 years	61–78 years	*P*
N	1177	828	846	461	
Patient death	41 (3.5%)	64 (7.7%)	112 (13.2%)	78 (16.9%)	<0.001
SMI	7.6	7.0	5.8	4.1	0.0019
Cause of death					
Cardiovascular	6 (16.2%)	17 (29.3%)	38 (36.2%)	21 (28.0%)	
Infection	7 (18.9%)	9 (15.5%)	10 (9.5%)	11 (14.7%)	
Neoplasia	8 (21.6%)	12 (20.7%)	26 (24.8%)	17 (22.7%)	
Liver failure	1 (2.7%)	4 (6.8%)	6 (5.7%)	5 (6.7%)	
Other	15 (40.5%)	16 (27.6%)	25 (23.8%)	21 (28%)	NS
Missing data	4	6	7	3	

SMI, standardized mortality index.

Table 2. Cardiovascular risk factors 1 year after transplantation

	18–40 years	41–50 years	51–60 years	61–78 years	*P*
Diabetes mellitus	86 (7.3%)	92 (11.1%)	131 (15.5%)	92 (20%)	<0.001
Cholesterol (mg/dl)	225 ± 49	237 ± 49	240 ± 49	232 ± 50	<0.001
Triglycerides (mg/dl)	153 ± 72	157 ± 72	153 ± 71	149 ± 73	NS
SBP (mmHg)	136 ± 17	139 ± 18	143 ± 19	145 ± 19	<0.001
DBP (mmHg)	83 ± 12	83 ± 11	82 ± 10	79 ± 10	<0.001
Creatinine (mg/dl)	1.7 ± 0.8	1.7 ± 0.7	1.6 ± 0.7	1.6 ± 0.6	NS
Proteinuria (g/day)	0.4 ± 1.0	0.4 ± 0.9	0.3 ± 0.8	0.3 ± 0.7	0.0042

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Immunosuppression and clinical events after transplantation

	18–40 years	41–50 years	51–60 years	61–78 years	*P*
MMF	288 (25.4%)	235 (29.1%)	244 (29.6%)	117 (42.7%)	<0.001
Antibodies	372 (32.8%)	217 (26.9%)	235 (28.5%)	138 (30.4)	0.0313
CMV infection	268 (25.7%)	162 (21.9%)	220 (28.5%)	117 (29.3%)	0.0105
DGF	332 (30.3%)	225 (28.9%)	239 (29.8%)	135 (30.5%)	NS
AR	444 (37.9%)	274 (33.1%)	266 (31.6%)	96 (21.1%)	<0.001

MMF, mycophenolate mofetil; CMV, cytomegalovirus; DGF, delayed graft function; AR, acute rejection.

The incidence of delayed graft function after transplantation was similar in the four groups. It is important to remark that older recipients had a lower incidence of acute rejection after transplantation (Table 3). The logistic regression analysis shows that the lower incidence of acute rejection in the older group was independent of the use of MMF after adjusting for centre and transplant year [odds ratio (OR) 0.79 and 95% CI 0.66–0.97 for patients 41–50 years; OR 0.75 and 95% CI 0.62–0.91 for patients 51–60; OR 0.43 and 95% CI 0.33–0.56 for patients older than 60 years).

Death-censored graft survival

The proportion of patients with graft failure was similar in the four age groups**,** but while in younger recipients the main cause of graft failure was CAN (group I, 62.8%; group II, 52.4%; group III, 38.5%; and group IV, 27.5%), in older recipients the main cause of graft failure was DWFG (group I, 11.1%; group II, 28.1%; group III, 44.8%; and group IV, 56.5%).

Death-censored graft survival was not different in the four groups, but adjusting for year of transplantation and centre effect, death-censored graft survival was poorer in patients older than 60 years than in patients younger than 60 years (RR 1.40; 95% CI 1.09–1.80). Taking into consideration only pre-transplant variables, patient age was not included in the final model. However, when pre- and post-transplant variables were included, patient age was an independent predictor of death-censored graft survival (RR 1.7 and 95% CI 1.3–2.2).

We analysed whether there existed any interaction between donor age and recipient age. Recipients older than 60 years who receive kidneys harvested from donors older than 60 years have the highest risk for late graft failure, although the combined variable donor age ∗ recipient age did not reach statistical significance (Table 4). In the same way, no relationship was detected between the use of MMF and outcome in the four recipient age groups. Finally, death-censored graft survival adjusting for transplant centre and year of transplantation was analysed in the subset of patients

Table 4. Risk factors associated with graft survival

	RR	95% CI	*P*
Recipient age (reference <40 years)	1		
Donor age (reference <40 years)	1		
Donor age (41–50 years)	2.12	1.50–2.99	<0.0001
Donor age (51–60 years)	2.33	1.63–3.34	<0.0001
Donor age (>60 years)	1.96	1.11–1.34	0.0209
Recipient age (41–50 years)	1.16	0.84–1.58	NS
Donor age (reference <40 years)	1		
Donor age (41–50 years)	0.97	0.65–1.43	NS
Donor age (51–60 years)	1.17	0.76–1.81	NS
Donor age (>60 years)	2.01	1.19–3.41	0.0093
Recipient age (51–60 years)	1.19	0.87–1.63	NS
Donor age (reference <40 years)	1		
Donor age (41–50 years)	1.35	0.91–2.03	NS
Donor age (51–60 years)	1.38	0.92–2.06	NS
Donor age (>60 years)	1.98	1.30–3.02	0.0015
Recipient age (>60 years)	1.14	0.68–1.89	NS
Donor age (reference <40 years)	1		
Donor age (41–50 years)	1.79	1.02–3.15	0.0421
Donor age (51–60 years)	1.44	0.80–2.58	NS
Donor age (>60 years)	2.76	1.81–4.19	<0.0001

Cox regression analysis for the interaction between patient and donor age adjusting by centre and year of transplantation. *P*-values: recipient age, 0.69; donor age, <0.0001; and recipient age∗donor age, 0.31.

older than 60 years. In this analysis, once again, donor age was the only independent predictor of graft survival, while immunosuppression, CMV infection and hepatitis C virus infection did not reach statistical significance.

Discussion

The present work reviews the role of recipient age on renal transplant outcome in three cohorts of patients transplanted in Spain during the last decade. We have focused our analysis on patient mortality and death-censored graft survival.

We observed that older patients have an apparent higher risk of mortality, but this risk is more pronounced in younger recipients when the standardized mortality is analysed**.** We believe that it is important to keep this result in mind, because the efforts to reduce patient mortality should not be only focused in the older patient but also, and probably more specially, in young recipients who will be at risk for longer periods of time. Obviously, this high mortality of elderly transplanted patients should be compared with the mortality of this group of patients on dialysis to be sure that transplantation is the most suitable option for these patients [7]. In an analysis done with the UNOS database, it has been shown that even transplantation of a marginal kidney is associated with a significant survival benefit when compared with maintenance dialysis [8].

We have analysed classical cardiovascular risk factors and, as expected, it was observed that older patients have a poorer cardiovascular profile. It has been reported that the role of classical cardiovascular risk factors in transplanted patients is more pronounced than in the general population [9] and therefore, taking into account that end-stage renal failure patients have a higher incidence of cardiovascular risk factors, it should be expected that the accurate management of these factors may reduce cardiovascular mortality.

We have also observed, as has been previously described [10], a higher incidence of cytomegalovirus infection and infectious deaths in patients older than 60 years than in younger recipients. However, we were not able to show any relationship between MMF use and death due to infection. Some retrospective analyses have supported that MMF in older patients is a less safe treatment than azathioprine since it is associated with a higher rate of infection and a poorer patient survival due to a higher rate of infection-related deaths [11,12]. In our study, renal transplants older than 60 years treated with MMF did not show an increased risk for death compared with patients managed with other immunosuppressants, suggesting that this treatment is safe also in older patients. We have also evaluated the safety of anti-lymphocyte induction therapy, and were also not able to detect a special risk for older patients, as has been suggested [13].

In our study, the rate of acute rejection episodes was lower in older patients, supporting that they are less immunologically active than young recipients [4]. Furthermore, we were able to demonstrate that this effect is due to patient age independently of the MMF treatment.

Patients older than 60 years have a lower incidence of acute rejection and received MMF treatment more frequently than younger recipients, but death-censored graft survival was poorer in this group of patients. A similar result was also reported recently by

Meier-Kriesche *et al*. [6], who observed that recipient age is associated with chronic allograft failure, independently of all known donor factors as well as other baseline recipient factors. In our work, we tried to explore this subgroup of patients who have a poorer death-censored graft survival analysing the interaction of patient age with other variables like donor age, immunosuppression and delayed graft function.

The allocation policy of organs in Spain, like in other areas [14], tends to match donor and recipient age in order to improve transplant outcome for organs harvested from old donors [15]. This policy may be associated with a special risk for older patients, since they receive poorer organs that may be more susceptible to ischaemia-reperfusion injury, which in turn may trigger alloimmune response. Moreover, older kidneys may have a reduced number of functioning nephrons leading to hyperfiltration injury, which may contribute to CAN [16]. Although recipients older than 60 years transplanted with kidneys harvested from donors older than 60 years have the poorest results (Table 4), we were not able to demonstrate an additional effect of the interaction between donor and recipient age independent of both variables *per se*.

Finally, the analysis of patients older than 60 years shows that death-censored graft survival of this group of patients only depends on donor age, and we are not able to detect other variables available at the time of transplantation that impair graft survival for these patients. Obviously, some non-controlled data in our study or a different response of older patients to different injuries may explain this result [6].

In summary, our study shows that patient age is a main determinant of transplant outcome. Death rate is higher in older patients, but standardized mortality is similar for all patients. Thus, the efforts to improve the cardiovascular profile and to reduce mortality should also be implemented in younger patients. Patients older than 60 years have the lowest risk of acute rejection but a poorer death-censored graft survival**.** This last result was not explained by any controlled variable in our study.

Conflict of interest statement. None declared.

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