Accepted: 17 June 2017

DOI: 10.1111/ctr.13036

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

How does age affect the outcome of kidney transplantation in elderly recipients?

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Abstract

The aging of the on-dialysis population raises the issue of whether to propose elderly patients for kidney transplantation and how to manage their immunosuppression. This study aimed to analyze the outcome of kidney transplantation on an Italian series of elderly recipients. We included in this retrospective study all patients over 60 years, receiving a deceased-donor kidney transplantation from January 2004 to December 2014 in two north Italian Centers. We analyzed the correlation of recipient age with graft's and patient's survival, delayed graft function, acute cellular rejection (ACR), surgical complications, infections, and glomerular filtration rate. Four hundred and fifty-two patients with a median age of 65 years were included in the study. One-, 3-, and 5-year patient's and graft's survival were, respectively, of 98.7%, 93%, 89% and 94.4%, 87.9%, 81.4%. The increasing recipient age was an independent risk factor only for the patient's (P=.008) and graft's survival (P=.002). ACR and neoplasia were also associated to a worse graft survival. The reduced graft survival in elderly kidney recipients seems to be related more to the increasing recipient's age than to the donor's features. In this population, the optimization of organ allocation and immunosuppression may be the key factors to endorse improvements.

KEYWORDS

elderly recipients, extended criteria donors, kidney allocation, kidney transplantation, survival advantage

1 | INTRODUCTION

In the Western countries, the increase in prevalence of chronic renal failure is greater than the increase in its incidence;[1] thus, the population on dialysis is rapidly aging.[2]

The kidney transplantation still represents the best replacement therapy for renal failure as it improves patient's long-term survival and quality of life and substantially reduces the dialysis-related costs.[3] Despite the mean age of renal transplant recipients having increased in the recent years,[4] the survival advantage of the renal transplantation in these older recipients has not been clarified yet. Although the initial reports of the years 1980-2000 showed a reduced patient and graft survival for recipients older than 60 compared to younger patients,[5] more recent studies have partially reversed this conclusion analyzing the death-censored graft survival.

Many age-related factors can jeopardize the outcome of the renal transplantation.

The first issue concerns the different pharmacokinetics of the immunosuppressive medications occurring in this population together with a weaker immune system. These two peculiar aspects of the older recipients increase their susceptibility to opportunistic infections and neoplasia.[6,7]

Secondly the cardiac and metabolic comorbidities make older patients more prone to cardiovascular events,[8] which may accelerate the transplant failure and, sometimes, the exitus.

Finally, the use of expanded criteria donors (ECD) organs[9] bears an increased risk of transplant loss in the elderly population of recipients compared to kidneys from standard criteria or living donors.[10]

In the last decade, several authors have reported contrasting findings about the outcome of kidney transplantation in elderly recipients. Initial papers reflected the fear of increasing the mortality of older kidney recipients due to their burden of comorbidities.[11] More recent reports about the comparison of the patient survival between older renal transplantation recipients versus peer patients on dialysis have clearly showed the survival advantage for the transplanted group.[12]

However, the analysis of the outcome of renal transplantation in older kidney recipients is hindered by multiple factors. The first issue is the difficulty of finding an adequate population of comparison. Younger transplanted patients have the advantage given by the biological privilege and by the selection of optimal organs, especially in the last years when organs from expanded criteria donors have been preferentially allocated to older recipients. Elderly patients with end-stage renal disease who are not transplanted often remain on dialysis because of comorbidities which contraindicate any surgical procedure. On the contrary, peer elderly adults who are not on dialysis lack the comorbidities due to the end-stage renal disease and the replacement treatment. Both these populations are not good terms of comparison for the survival analysis of elderly recipients of kidney transplantation.

Although a survival benefit has been shown for the transplanted population of any age versus staying on dialysis, still the convenience of this therapeutic option in the elderly population needs to be better explored and possibly maximized through the optimization of allocation procedures and immunosuppressive protocols.

The Italian population is among the oldest in Europe, and this demographic trend influences the population of both kidney recipients and donors. At the best of our knowledge, no Italian studies have been published about the outcome of kidney transplantation in the elderly population. The aim of this study was to analyze how the recipient age affected the outcome of renal transplantation in patients above the age of 60.

2 | PATIENTS AND METHODS

2.1 | Study design

This retrospective observational study included all consecutive patients over the age of 60 who underwent a kidney transplantation from deceased donors in two north Italian centers (Unit of Kidney Transplantation, S. Orsola Hospital Bologna, and Kidney and Pancreas Transplantation Unit, Hospital of Padua from January 2004 to December 2014). Patients were followed up from the date of transplantation until the last follow-up visit or the loss of graft function or the patient's death.

We excluded from the analysis all the combined transplantations (with liver or heart) and the transplantation from living donors.

Data on recipients and donors' characteristics, on transplantation procedure, immunosuppressive therapy, and clinically relevant outcomes were collected. The outcomes were graft function (DGF), acute cellular rejection (ACR), surgical complications, new-onset diabetes after transplant (NODAT), viral or bacterial infections, tumors, glomerular filtration rate (GFR) at 1, 3, and 5 years and patient and graft survival.

A DGF was defined as the need of dialysis in the first week after transplantation. We defined the occurrence of ACR either when biopsy proven or when the clinical suspicion lead to the start of an anti-rejection therapy.

All vascular, urologic, or lymphatic complications that caused an operative intervention (either radiologic or surgical) were counted in the analysis. NODAT was diagnosed when a glycemic impairment, not present before the transplantation, required the beginning of oral hypoglycemic drugs or insulin administration. For viral infections, we considered all symptomatic infections with opportunistic viruses and the asymptomatic reactivations of opportunistic viral infections, for which a sustained antiviral therapy was needed for more than 3 months. Among the bacterial infections, we included all the pulmonary, gastrointestinal, and dermatologic bacteria-driven infections in the post-transplant period, which were treated with specific antibiotics.

Patients' survival and death-censored graft survival were also evaluated. Graft loss was defined as return to dialysis.

2.2 | Donor and recipients characteristics

According to the regional allocation policy, kidneys from 60- to 69-year-old donors, without risk factors were considered for single transplantation (SKT). Organs from donors over 70 years of age or from 60 to 69 with at least two risk factors (creatinine clearance ≤60 mL/min, hypertension treated with at least two drugs, history of diabetes and cardiovascular complications) were histologically assessed. The biopsies were analyzed according to the Remuzzi score;[13,14] from 2004 to 2010, the grafts with scores from 4 to 6 were used for double kidney transplantation, the grafts with scores <4 were allocated to single kidney transplantations and grafts with score ≥7 were discarded. From 2010, we reconsidered the cutoff scores for the allocation of these marginal grafts using score of 4 for single kidney transplantation.

Patients were considered eligible for kidney transplantation when they met all the standard criteria for admission to waiting list for kidney transplantation, regardless of the effective age.

2.3 | Immunosuppressive therapy

The immunosuppressive regimen differed according to the center preferences.

In the Bologna center, the induction therapy was mainly basiliximab 20 mg at the moment of transplantation and in 4th post-operative day. The maintenance therapy was with calcineurin inhibitor (CNI) plus mycophenolic acid or mTOR inhibitors. When cyclosporine was used, the

target serum level at 2 hours ranged from 800 to 1200 ng/mL in the first 3 months and from 500 to 700 ng/mL subsequently. When tacrolimus was used, the serum level was kept 8-12 ng/mL in the first 3 months and 5-8 ng/mL subsequently.

In the Padua center, the induction therapy consisted of Thymoglobulin (mean cumulative dose 5.19 mg/kg) for transplantations with ECD donors.

The maintenance immunosuppressive scheme has changed in the years.

From 2003 to 2007, the recipients of ECD grafts were treated with mTOR inhibitors (sirolimus at the target serum level of 10-15 ng/mL in the first 3 months and then 5-10 ng/mL) plus mycophenolic acid. From 2008, the protocol was slightly changed as previously described[15,16] with low dosage of calcineurin inhibitor plus low dosage of everolimus.

When cyclosporine was adopted, the serum level at 2 hours was 500-700 ng/mL for the first 3 months and 400-600 ng/mL afterwards. The tacrolimus level was 4-7 ng/mL up to 3 months after transplantation and 2.5-5 ng/mL afterwards. The everolimus levels were 4-8 ng/mL.

Steroids at the moment of induction therapy with a following tapering until a life-long baseline of 4 mg/d of prednisolone was adopted for all the patients unless the discontinuation of steroids was needed for clinical reasons.

2.4 | Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and categorical variables as number and percentage. The association between recipient age and continuous variables was assessed using Spearman's rank correlation, while Mann-Whitney test and Kruskal-Wallis test were used when categorical variables were analyzed. Logistic regression models were estimated to evaluate the association of recipient age and clinical outcomes, adjusting for a set of clinically relevant confounders: donor age, cause of donor death, ECD, cold ischemia time and center for DGF as dependent variable; donor age, ECD, induction therapy, maintenance therapy and center for ACR as dependent variable; maintenance therapy, dialytic age, type of transplantation (double kidney transplantation, retransplantation) and center for surgical complications as dependent variable; dialytic age, ECD, induction therapy, maintenance therapy and center for post-transplant diabetes, infections and neoplasia as dependent variables. A linear mixed effect model was used to assess the association between recipient age and GFR levels during follow-up, accounting for the longitudinal structure of the data (GFR were evaluated at 6 months and 1, 2, 5 years after transplantation). Time and an age-by-time interaction term were also included in the model. Patients' survival and death-censored graft survival were evaluated using Kaplan-Meier method. Cox regression models were estimated to evaluate the association of recipient age with patients' survival and death-censored graft survival, adjusting for donor age, ECD, double kidney transplantation, CIT, induction therapy, maintenance therapy, DGF, ACR, surgical complications, NODAT, viral infections, bacterial infections, and neoplasia. Proportional hazard assumption was tested using the package "Survival" of R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Competing risk analysis based on Fine and Gray method was performed for death censored graft survival, in order to check for consistency with the findings of cause-specific survival analysis. Subhazard ratios (SHRs) with corresponding 95% confidence intervals (CIs) were reported for the Fine and Gray model, while hazard ratios (HRs) were presented for cause-specific analysis. A *P*-value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS (SPSS Base 23; Application Guide, SPSS Inc., Chicago, IL, USA, 2014).

3 | RESULTS

3.1 | Sample characteristics

A total of 452 patients (median age 65 years, IQR: 62-68) were included in the study. Recipients' and donors' characteristics are shown in Table 1. Double kidney transplantations were performed in 37.6% of patients. The induction therapy was achieved with Thymoglobulin in the majority of cases (58.4%), and the preferred maintenance therapy adopted was calcineurin inhibitors with mycophenolate mofetil (47.6%).

The association between recipient age and patients' characteristics is shown in Table 2. Older recipient age was associated to older donor age (*P*<.0001), induction therapy with Thymoglobulin (*P*<.0001) and maintenance therapy with CNI and everolimus (*P*<.0001).

3.2 | Clinical outcomes

DGF occurred in 140 patients (31%), and ACR in 57 cases (12.6%). We observed 60 surgical complications of which 40% lymphoceles, 36.6% ureteral, 16.7% vascular, and 6.7% hemorrhages. NODAT occurred in 65 cases (14.4%), while the viral and bacterial infections were, respectively, 69 (15.3%) and 86 (19%). We recorded 60 de novo tumors (13.3%).

At multivariable analysis, the recipient age was not associated to DGF, ACR, surgical complications, post-transplant diabetes, viral or bacterial infections and tumors, adjusting for relevant confounders (see Methods). Full results of multivariable analysis are shown in Table 3.

3.3 | GFR

Median GFR was 144.15 μmol/L (IQR: 106-168) at 6 months, 139 μmol/L (IQR: 102.7-164) at 1 year, 145 μmol/L (IQR: 106-161) at 3 years and then reached a plateau of 143.18 μmol/L (IQR: 106-171) at 5 years. GFR levels decreased with increasing age (age beta: -1.19, SE: 0.23; *P*<.0001), with no interaction with time (age×time: *P*=.14).

3.4 | Survival

Median follow-up was 47.86 months (IQR: 22.7-81.13). Seventy-nine patients died during follow-up, most of them due to cardiovascular accidents (32%), sepsis (25%), and neoplasms (11%). Overall patients' survival was 98.7%, 98.7%, 93%, and 89% at 6, 12, 36, and 60 months from transplantation (Figure 1A).

TABLE 1 Characteristics of the donor and the recipient

Recipient characteristics (n=452)	
Recipient age (y)	65 (62-68)
Recipient gender (male)	287 (63.5%)
Recipient BMI	25.19 (23.1-27.64)
ESRD etiology	
ADPKD	91 (20.1%)
Nephroangiosclerosis	65 (14.4%)
Interstitial nephritis	47 (10.4%)
Diabetic nephropathy	27 (6%)
Other	222 (49.1%)
Dialytic treatment	
Hemodialysis	304 (67.3%)
Peritoneal dialysis	134 (29.6%)
Pre-emptive	14 (3.1%)
Time on dialysis (mo)	31.21 (18.51-57.46)
In list waiting time (mo)	12.18 (6-27.34)
Donor characteristics (n=434)	
Donor age (y)	71 (66-76)
Donor gender (male)	217 (50%)
Donor BMI	25.6 (23.51-27.68)
Brain death donors	
CVA	335 (77.2%)
Trauma	78 (18%)
Anoxic	16 (3.7%)
Other	5 (1.1%)
ECD	392 (90.3%)
Cold ischemia time (min)	900 (755-1070)
Transplant factors	
Double kidney transplantation	170 (37.6%)
Retransplantation	8 (1.8%)
Induction	
Basiliximab	188 (41.6%)
Thymoglobulin	264 (58.4%)
Maintenance therapy	
CNI+ever	183 (40.5%)
CNI+MMF	215 (47.6%)
Sirolimus+MMF	54 (11.9%)
Follow-up (mo)	47.86 (22.7-81.13)

Continuous variables were expressed as median (IQR) while the categorical variables were expressed with the number and the percentage.

TABLE 2 Correlation between the recipient age and characteristics related to recipient, donor, and transplantation factors

	Recipient age (IQR)	*P* value
ESRD etiology		
ADPKD	64.15 (62-66)	.188
Nephroangiosclerosis	65 (62-68)	
Interstitial nephritis	64 (61-68)	
Diabetic nephropathy	65.5 (61.7-68)	
Other	65 (62-68)	
Dialytic treatment		
Hemodialysis	65 (62-68)	.118
Peritoneal dialysis	65 (62-68)	
Pre-emptive	67 (65-71)	
Time on dialysis (mo)[a]	−0.099	.038
Waiting time (mo)[a]	−0.154	.001
Donor age[a]	0.288	<.0001
ECD		
No	61.8 (61-63.65)	<.0001
Yes	65 (62-68)	
Double kidney transplantation		
No	64.27 (62-67)	.1
Yes	65 (62-68)	
Retransplantation		
No	65 (62-68)	.081
Yes	61.73 (61.29-64.8)	
Induction		
Simulect	64 (61.4-66.8)	<.0001
ATG	65 (62-68)	
Maintenance therapy		
CNI+ever	66 (63-69)	<.0001
CNI+MMF	64 (62-67)	
Sirolimus+MMF	65 (62.5-68)	

Data expressed as median (IQR) or [a]Spearman corr. coeff.

The graft losses were 113 due to the death of the patients (64%), rejection (10%), functional exhaustion (9%), and technical issues (7%). Overall death-censored graft survival was 95.3%, 94.4%, 87.9%, and 81.4% at 6, 12, 36, and 60 months from transplantation (Figure 1B).

Multivariable analysis (Table 4) identified recipient age as significant risk factor of patients' survival (*P*=.008; HR: 1.083, 95% CI 1.021-1.15) and of death-censored graft survival (*P*=.002, HR: 1.149, 95% CI: 1.054-1.252). There was no evidence to contradict the proportional hazard assumption for both overall survival (*P*=.99) and graft loss (*P*=.10). ACR and surgical complications were also identified as significant risk factors of death-censored graft survival (Table 4). Competing-risks analysis based on Fine and Gray's method confirmed the role of recipient age (*P*=.03, SHR: 1.098, 95% CI: 1.011-1.191), ACR (*P*=.0004, SHR: 3.3434, 95% CI: 1.733-6.805), and surgical complications (*P*=.0007, SHR: 3.399, 95% CI: 1.675-6.899).

4 | DISCUSSION

The present study aimed to analyze the outcome of kidney transplantation in a series of aged recipients.

Elderly patients would have not been considered for kidney transplantation up to a decade ago.[17] Only in the recent years, the

TABLE 3 Effect of recipient age on clinically relevant outcomes

Outcome	Observed recipient age (y): median (IQR)	Multivariable analysis: OR (95% CI)	Multivariable analysis: *P*-value
DGF			
Yes	64.12 (61-67.86)	0.97 (0.92-1.03)[a]	.312[a]
No	65 (62-68)		
Rejection			
Yes	64 (61-67)	0.926 (0.853-1.006) [b]	.068[b]
No	65 (62-68)		
Surgical complications			
Yes	64 (62-68)	1.014 (0.939-1.094)[c]	.726[c]
No	65 (62-68)		
Post transplant diabetes mellitus			
Yes	65 (61.5-67)	0.995 (0.925-1.070)[d]	.893[d]
No	65 (62-68)		
Viral infections			
Yes	64.65 (62.13-67.03)	1.044 (0.973-1.120)[d]	.235[d]
No	65 (62-68)		
Bacterial infections			
Yes	65 (62-68)	1.004 (0.94-1.072)[d]	.902[d]
No	65 (62-67.79)		
Neoplasia			
Yes	65 (62.11-68)	1.044 (0.969-1.125)[d]	.257[d]
No	65 (62-68)		

[a]Adjusted for donor age, cause of donor death, ECD, cold ischemia time, and center.
[b]Adjusted for donor age, ECD, induction therapy, maintenance therapy, and center.
[c]Adjusted for maintenance therapy, dialytic age, type of transplantation (double kidney transplantation, retransplantation) and center.
[d]Adjusted for dialytic age, ECD, induction therapy, maintenance therapy, and center.

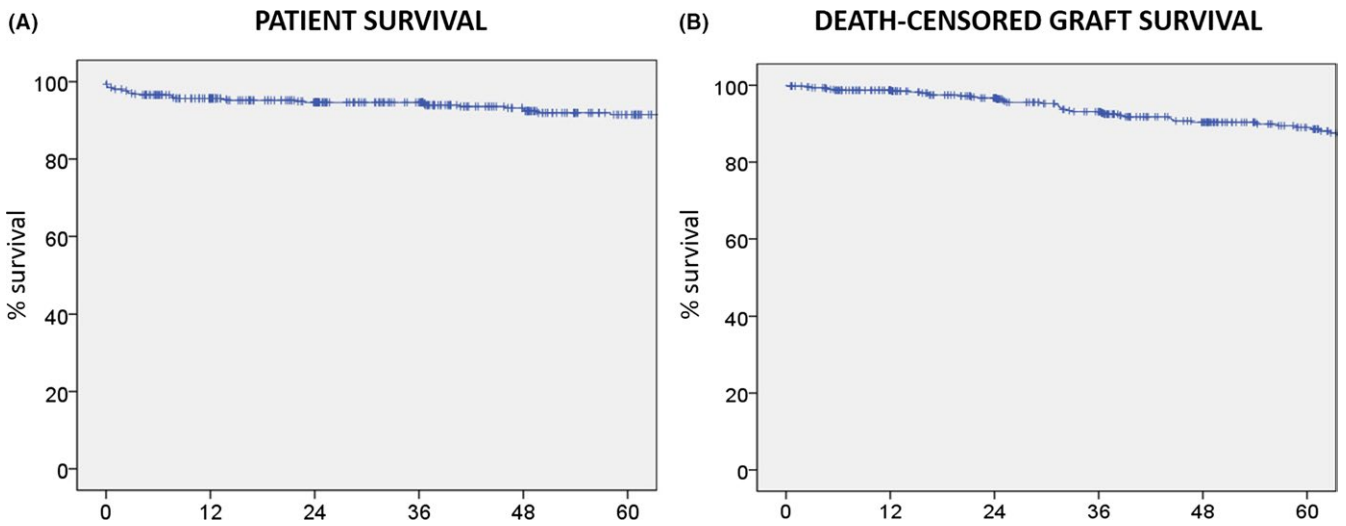

FIGURE 1 Overall patients' survival (A) and death-censored graft survival (B)

transplantation centers have started including older recipients in the waiting list.

Different outcomes of renal transplantation in elderly patients have been reported in the last twenty years, mainly for the great heterogeneity of the donor population, and partly for the dispersion of these studies along different age periods, which implies a different definition of old age along time periods, and changes in the immunosuppressive protocols.

TABLE 4 Multivariate analysis of survival

	Patient survival		Death-censored graft survival	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
Recipient age (y)	.014	1.078 (1.015-1.144)	.012	1.114 (1.024-1.211)
Donor age (y)	.503	–	.759	–
ECD	.601	–	.587	–
Yes				
No				
Double kidney transplantation	.667	–	.362	–
Yes				
No				
CIT	.27	–	.191	–
Induction therapy	.126	–	.071	–
ATG				
Simulect				
Maintenance therapy	.581	–	.156	–
CNI+ever				
CNI+MMF				
Sirolimus+MMF				
DGF	.214	–	.238	–
Yes				
No				
ACR	.97	–	<.0001	
Yes				3.78 (1.857-7.695)
No				Reference
Surgical complications	.863	–	.002	
Yes				3.345 (1.582-7.072)
No				Reference
PTDM	.743	–	.421	–
Yes				
No				
Viral infections	.629	-	.198	–
Yes				
No				
Bacterial infections	.254	–	.464	–
Yes				
No				
Neoplasia	.918	–	.068	–
Yes				
No				

The "old-to-old" allocation system in the Eurotransplant community has showed effective in increasing the number of transplantations.[9] The analysis of this policy outlined the survival advantage offered to elderly patients through the transplantation with ECD kidneys. This benefit was significantly higher for diabetic recipients and for those who had a high probability of long wait times on dialysis.[18-20]

To our knowledge, the present study is the first Italian report of the outcome of kidney transplantation in elderly recipients. As the Italian population is among the oldest in Europe, this study well highlights the impact of recipient age on the success of the kidney transplantation, in particular within the Eurotransplant community and the old-to-old program.

We showed that older patients received grafts from older donors and therefore more ECD grafts. The overall patient and graft survival observed at 1 year in the population of this study was, respectively, 98% and 95%, perfectly consistent with the national reports of outcome of adult recipients of kidney transplantation.

Older patients are obviously more prone to die sooner, but the survival benefit conferred by kidney transplantation over dialysis persists even when organs from ECD are used. The inclusion in waiting list for older recipients seems therefore sustained by scientific evidence. However, this extension will further increase the waiting list for kidney transplantation, exacerbating the discrepancy between the need for transplantation and the organ supply. In this scenario, we need to balance the equity and utility of kidney transplantation; older candidates should access to the waiting list, but the chances of the younger adults to receive an organ should also be preserved.

The use of ECD grafts and the program of old-to-old allocation bring excellent results, yet some age-related issues may compromise the success of kidney transplantation.

In 2001, Meier-Kriesche et al.[6] first outlined the increased risk of infection-related death for older recipients compared to younger patients; nevertheless, the survival advantage conferred by renal transplantation over dialysis was maintained for all age groups.

From a survey analyzing data from the US Renal Data System (USRDS) between 1988 and 1997, the recipient age appeared to be independently associated to an increased graft loss. The interaction of greater recipient and donor age was significantly detrimental for the graft survival.[21] However, when this analysis was performed on the OPTN database from 1995 to 2000, the results were exactly opposite. The death-censored graft survival increased with the recipient age. In this study, the incidence of chronic allograft nephropathy was highest for the youngest recipients.[22] This result was supported by a later paper reporting death as the main cause of graft loss in the geriatric population.[23]

More recently, American studies have confirmed a comparable death-censored graft survival between the adult and the geriatric population of kidney transplant recipient; the major cause of graft failure for the geriatric population again seemed to be death with functioning graft.[23-25]

Within the European experience, the Norway group reported the relevance of rejection events in decreasing grafts' and patients' survival in elderly recipients. From their analysis, the presence of pretransplant comorbidities was not predictive of mortality, at least in recipients over 70 years.[26]

These studies outlined the impact of donor selection, organ allocation, and immunosuppressive management in the outcome of renal transplantation in the elderly population.

In our series, we failed to observe a correlation between the recipient age and the incidence of delayed graft function, immunologic reactions, or opportunistic infections. On the other hand, we found that the recipient age negatively affected not only patient's but also death-censored graft's survival, independently from the quality of the graft and from the donor's age. We acknowledge that donors included in this study were all very old and extended criteria donors, and this factor may have prevented the observation of any statistical difference in the outcome of these organs. Interestingly the recipients of the study were also homogeneously old, featuring a small range of age, but this condition does not invalidate the correlation between recipient's increasing age and a reduced graft survival.

The episodes of rejections, surgical complications, and neoplasms, together with the recipient age, were associated to a reduced graft survival, but independently from the donor age. Apart from the patient's death, which accounted for the greatest number of graft losses, the other causes of graft failure were rejection and functional exhaustion, which we think may be more connected to the intrinsic biological organ aging and to the drug-induced nephrotoxicity, than to immunologic factors accounting for the classical phenomenon of chronic rejection.

This observation suggests that the management of the graft, with an adequate immunosuppressive regimen, might be of particular importance in the success of the transplantation of extended criteria organs in elderly recipients.

The importance of an adequate immunosuppressive therapy for older patients was first outlined in 2001 by Meier-Krieshe et al.,[27] who reported not only an increased susceptibility of this population to infections, but also a particular vulnerability to rejections.[21] Although not frequent, the incidence of acute cellular rejection can seriously threaten the survival of ECD grafts, which are generally allocated to elderly recipients; this observation was confirmed in following studies from all around the world.[26,28,29] The selection of the optimal immunosuppressive regimen is a key point in the reduction of the rate of acute cellular rejection.

An American report of 2011 suggested that induction with Thymoglobulin may be advantageous for elderly recipients receiving kidneys from high risk donors[30] as it protects from rejection without significantly increasing the risk of opportunistic infections and malignancies.[31,32]

While calcineurin inhibitors are essential in protecting the graft from immunological events, their nephrotoxic potential can hasten a graft failure especially in ECD kidneys.[33,34]

While using Thymoglobulin allows a delay in the introduction of CNI, with the association of everolimus, we can keep lower doses of immunosuppressive drugs also in the long term, minimizing their side effects. In our study, we did not find an association between the graft survival and the use of any particular induction or maintenance immunosuppressive regimens. Possibly the long time range of this study (10 years, from 2004 to 2014), during which many factors related to the surgical and pharmacological management of the transplanted patients have changed and evolved, made it difficult to isolate the influence of the immunosuppressive drugs on the outcome of the renal transplantation.

The strengths of the study rely on the sample size and the long follow-up assessment. An additional merit of this study is to analyze the outcome of organs procured from exceptionally old donors, which is not commonly reported by the American and European published multicentric studies.

The present study has some limitations. First, the long study period might have affected the results (ie, changes in immunosuppressive protocol and surgery). However, the regimen of induction therapy and maintenance therapy was included in multivariable analysis as confounders. In addition, the surgical team and technique did not substantially change in the two centers during the study period. Second, organ allocation was not homogeneous among all patient, because older donors were matched to older recipients, as discussed before. However, the association of donor age and death-censored graft survival was not statistically significant.

Finally, we acknowledge that the number of donors and of recipients do not match exactly as some of the donors gave the two organs to two different recipients. This gap accounts for only 18 cases over a total of 452 recipients. Such a small number did not allow any meaningful statistical adjustment.

In conclusion, our study indicates that the kidney transplantation is a safe procedure in the elderly population and bears overall good results in term of graft survival, comparable with those of the general adult population. From our analysis, the donor age and the "suboptimal quality" of the grafts do not seem the most relevant factors in the graft survival. Although we could not show a direct correlation of any immunosuppressive drugs employed with the outcome of the transplantation, we think that a tailored immunosuppressive regimen could be of paramount importance for the population of elderly kidney transplant recipients.

Specific clinical trials designed for elderly recipients are necessary, in order to better investigate how to maximize the protection from rejection, reduce the calcineurine inhibitor-related nephrotoxicity and the risk of opportunistic infections and de novo neoplasms.

CONFLICT OF INTEREST

None.

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How to cite this article: Neri F, Furian L, Cavallin F, et al. How does age affect the outcome of kidney transplantation in elderly recipients? *Clin Transplant*. 2017;e13036.
https://doi.org/10.1111/ctr.13036