

Renal Transplantation in Patients Older Than 60 Years With High Comorbidity. Is There a Survival Benefit? A Multicenter Study in Argentina

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Background. The impact of renal transplantation (RT) in the elderly with many comorbid conditions is a matter of concern. The aim of our study was to assess the impact of RT on the survival of patients older than 60 years compared with those remaining on the waiting list (WL) according to their comorbidities. **Methods.** In this multicentric observational retrospective cohort study, we included all patients older than 60 years old admitted on the WL from 01 January 2006 to 31 December 2016. The Charlson comorbidity index (CCI) score was calculated for each patient at inclusion on the WL. Kidney donor risk index was used to assess donor characteristics. **Results.** One thousand and thirty-six patients were included on the WL of which 371 (36%) received an RT during a median follow-up period of 2.5 (1.4–4.1) years. Patient survival was higher after RT compared to patients remaining on the WL, 87%, 80%, and 72% versus 87%, 55%, and 30% at 1, 3, and 5 years, respectively. After RT survival at 5 years was 37% higher for patients with CCI ≥ 3 , and 46% higher in those with CCI < 3 , compared with patients remaining on the WL. On univariate and multivariate analysis, patient survival was independently associated with a CCI of ≥ 3 (hazard ratio 1.62; confidence interval 1.09–2.41; $P < 0.02$) and the use of calcineurin-based therapy maintenance therapy (hazard ratio 0.53; confidence interval 0.34–0.82; $P < 0.004$). **Conclusions.** Our study showed that RT improved survival in patients older than 60 years even those with high comorbidities. The survival after transplantation was also affected by comorbidities.

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INTRODUCTION

Renal transplantation (RT) is the treatment of choice for patients suffering from end-stage renal disease (ESRD).¹ It offers not only a survival benefit but also cost-effectiveness when compared with dialysis even in elderly patients.^{2–4} But as the gap between the offer and demand of organs grows wider, long waiting times make patients reach RT with a greater degree of comorbidities.⁵ This situation affects all patients but the elderly in particular as they have less life expectancy and higher degree of associated illnesses when compared with younger dialysis patients. On the other hand, patients older than 60 years represent 49.6% of all dialysis patients in Argentina, of which only 9.9% are listed for RT. Clinical heterogeneity of this group calls for assessing comorbid conditions on individual basis before entering the waitlist for RT. Such comorbid conditions appear as the main reason for not listing these patients.⁵ In an attempt to optimize organ allocation, “old for old” programs have been designed. Results, although better than dialysis in general, are hampered mainly by donor-related factor and recipients’ comorbid conditions.^{6,7} The impact of RT in the elderly with many comorbid conditions is a matter of concern.

The aim of our study was to assess the impact of RT on the survival of patients older than 60 years compared with

those remaining on the waiting list (WL) according to their comorbidities. Then, we evaluated the impact of comorbidities on graft and patient survival after transplantation.

MATERIALS AND METHODS

Study Population

In this multicenter observational retrospective cohort study, we included all patients older than 60 years on dialysis replacement therapy, admitted on the WL for deceased donor RT from 01 January 2006 to 31 December 2016. All patients were followed from the day of inclusion on the WL until their death or last follow-up on 30 April 2018. Recipients younger than 60 years, patients with history of malignancy, living donors, as well as multi-organ's recipients or retransplants were excluded.

In Argentina, patients have to be on dialysis to be listed for deceased donor RT; therefore, there were no preemptive transplants in our cohort.

Variables Analyzed

Baseline recipient's characteristics such as age at inclusion on the WL, sex, panel reactive antibodies, cause of renal disease, and time on dialysis before transplantation were recorded. Follow-up data included the following dates: WL inclusion, transplantation or WL exclusion, graft loss, death or last follow-up. The cause of death was also recorded and assigned to the WL even if this occurred after exclusion, or RT even if this occurred after returning to dialysis.

The Charlson comorbidity index (CCI) score was calculated for each patient at inclusion on the WL. This index has been adapted for its use in ESRD patients. This version excludes renal insufficiency from the score as it is present in all patients.⁸⁻¹⁰ Briefly, it includes the following variables and scoring: age (1 point every 10 y ≥ 50 y), myocardial infarction (1), congestive heart failure (1), peripheral vascular disease (1), cerebrovascular disease (1), dementia (1), pulmonary disease (1), rheumatologic disease (1), ulcer disease (1), mild liver disease (1), moderate-severe liver disease (3), diabetes (1), diabetes with end-organ disease (2), hemiplegia (2), lymphoma, leukemia, or solid tumor without metastasis (2), metastatic solid tumor (6), and acquired immunodeficiency syndrome (6).

Kidney donor profile index/kidney donor risk index (KDPI/KDRI) was used to assess donor characteristics. This index is used by Organ Procurement and Transplantation Network to assess the risk of graft failure by certain donor characteristics which includes: age, sex, weight, height, race, cause of death, history of hypertension or diabetes, serum creatinine before procurement, hepatitis c virus status, and donation after circulatory death.¹¹ For the analysis of patients and graft survival after transplantation, we also recorded donor type (single versus multiple organ), mismatch HLA (locus A, B, and DR), use of induction therapy (T cell depleting and nondepleting agents were included), immunosuppressive maintenance therapy used: calcineurin-based therapy (CNI) versus calcineurin-free therapy (CNI-free), and 1-year graft loss.

Data Collection

Baseline recipients and donors characteristics were obtained from the National procurement and

transplantation registry in Argentina, SINTRA (Sistema Nacional de Información de Procuración y Trasplante de la República Argentina).⁵ Each of the 8 centers participating in the study received a template with the baseline information. CCI score was completed by each center according to the information on medical records at inclusion on the WL. Follow-up information and causes of death, although present on the registry information, were revisited and updated accordingly by the participating centers.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation or median interquartile range (25th–75th percentile) according to their distribution. Categorical variables were expressed as frequency and percentage. Mann–Whitney or *t* test were used to compare continuous variables according with their distribution. For categorical data, Fisher's exact test or χ^2 test with Yates correction was used accordingly; $P < 0.05$ was considered significant. Propensity score (PS) matching model was developed to account for potential confounding factors, reduce the effect of selection bias, and to derive 2 matched groups for comparative outcomes analysis. We implemented a nearest neighbor PS matching ratio 1:1 to construct a balance sample. Kaplan–Meier curves and long-rank test were used for survival estimation. To assess the impact of RT on patient survival, univariate and multivariate Cox regression models were built. We also analyzed graft survival by Cox regression models. Data were analyzed with STATA 13.

RESULTS

Baseline Characteristics

One thousand one hundred thirty-three patients were included on the WL, after excluding 97 patients with history of malignancy, 1036 were left for the analysis of which 371 (36%) received an RT during a median follow-up period of 2.5 (1.4–4.1) years. The most frequent causes of ESRD were nephroangiosclerosis and diabetes (Figure 1). After PS matching, a sample of 351 patients on WL and 351 RT was constructed. Table 1 summarizes the baseline characteristics of all patients and after PS matching. Mean CCI score for the whole cohort was 3.74 ± 84 (median 3;

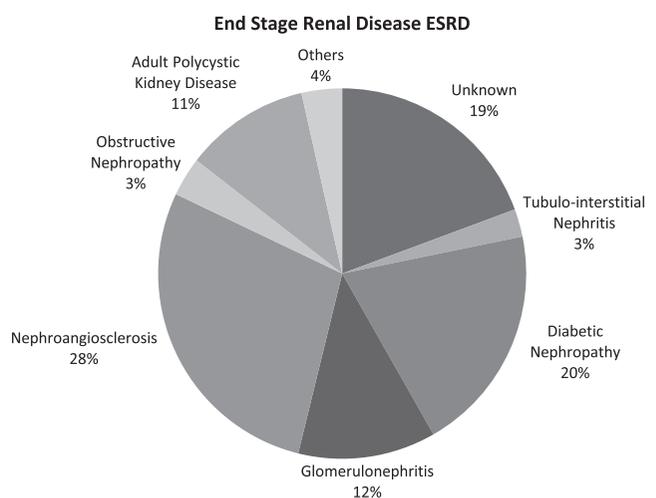


FIGURE 1. Etiology of ESRD. ESRD, end-stage renal disease.

TABLE 1.
Baseline patient's characteristics

Variables	All patients		P (χ^2 or t test)	PS matched		P (χ^2 or t test)
	Patients on the WL (n = 665)	Transplant patients (n = 371)		Patients on the WL (n = 351)	Transplant patients (n = 351)	
Age	66.62 ± 4.9	66.22 ± 4.56	0.18	66.66 ± 4.91	66.31 ± 4.59	0.5
Female sex	285 (42%)	146 (39%)	0.27	138 (39%)	144 (41%)	0.64
Myocardial infarction	108 (16%)	39 (11%)	0.01	36 (10%)	38 (11%)	0.9
Diabetes	195 (29%)	83 (22%)	0.015	77 (22%)	77 (22%)	1
Diabetes with organ disease	179 (27%)	67 (18%)	0.001	64 (18%)	64 (18%)	1
Congestive heart failure	203 (31%)	85 (23%)	0.009	90 (26%)	82 (23%)	0.48
Peripheral vascular disease	204 (31%)	83 (22%)	0.004	80 (23%)	81 (23%)	0.92
Cerebrovascular disease	56 (8%)	342 (9%)	0.91	20 (6%)	20 (9%)	0.14
Dementia	7 (1%)	8 (2%)	0.26	6 (2%)	6 (2%)	1
Pulmonary disease	75 (11%)	440 (11%)	0.8	43 (12%)	32 (11%)	0.55
Rheumatologic disease	19 (3%)	10 (3%)	0.88	9 (3%)	10 (3%)	0.81
Ulcer disease	35 (5%)	24 (7%)	0.42	22 (6%)	17 (5%)	0.41
Mild liver disease	18 (3%)	10 (3%)	0.99	11 (3%)	9 (3%)	0.65
Moderate–severe liver disease	5 (1%)	3 (1%)	0.92	3 (1%)	3 (1%)	1
Hemiplegia	11 (2%)	3 (1%)	0.25	2 (1%)	3 (1%)	0.65
Acquired immunodeficiency syndrome	1 (0.5%)	2 (0.5%)	0.26	1 (0.3%)	0 (0%)	0.31
CCI score	4.22 ± 2	3.76 ± 1.89	<0.0001	3.76 ± 1.83	3.73 ± 1.85	0.8
CCI score ≥3	486 (73%)	258 (70%)	0.22	233 (66%)	240 (68%)	0.57
Dialysis (y)	5 ± 2.43	4.64 ± 2.66	0.03	4.74 ± 2.27	4.65 ± 2.64	0.61
Hypersensitized (PRA > 50%)	50 (7%)	9 (3%)	<0.0001	11 (3%)	9 (3%)	0.65
PS	0.34	0.39	<0.0001	0.38	0.38	0.81

All patients and PS-matched sample.
CCI, Charlson comorbidity index; PRA, panel reactive antibody; PS, propensity score; WL, waiting list.

interquartile 2–5); hence, patients were divided into those with CCI score <3 and ≥3 for survival analysis purposes.

Patient Survival on WL Versus RT

Patient survival was higher after RT compared to patients remaining on the WL, 87%, 80%, and 72% versus 87%, 55%, and 30% at 1, 3, and 5 years, respectively (Figure 2). After stratifying patients in those with baseline CCI score <3 and ≥3, the former's survival at 1, 3, and

5 years was 90%, 85%, and 78% after RT versus 85%, 57%, and 32% on the WL, and for those with baseline CCI score ≥3 survival was 84%, 73%, and 64% after RT versus 90%, 52%, and 27% on the WL (Figure 3). We did the same analysis including only recipients of donors older than 60 years (old for old scenario) obtaining similar results (data not shown). The main known cause of death on the WL was cardiovascular disease (52%) while after RT was infectious (46%). In multivariate analysis, RT had

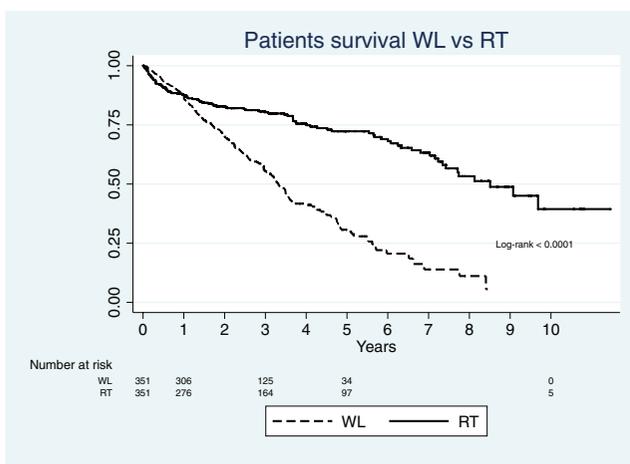


FIGURE 2. Kaplan–Meier patient survival curves. RT, renal transplantation; WL, waiting list.

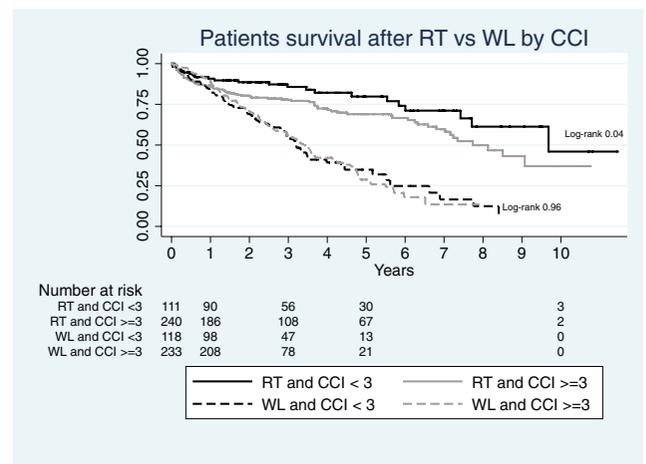


FIGURE 3. Patient survival after RT by CCI, WL, and RT. CCI, Charlson comorbidity index; RT, renal transplantation; WL, waiting list.

a protective effect on patient survival (hazard ratio [HR] 0.35; confidence interval [CI] 0.27-0.45; $P < 0.0001$) independent of the CCI score (HR 1.05; CI 0.98-1.11; P 0.16).

Survival After RT

Table 2 summarizes recipients and donor characteristics. Donors older than 60 years represented 52% of all donors. Mean KDPI/KDRI was $69 \pm 28.60/1.35 \pm 0.46$.

Patient Survival After RT

Patient survival after RT was 90%, 85%, and 78% in those with CCI <3 versus 84%, 73%, and 64% in those with CCI ≥ 3 at 1, 3, and 5 years (log-rank test: P : 0.02). On univariate and then multivariate analysis, patient survival had a negative association with a CCI ≥ 3 (HR 1.62; CI 1.09-2.41; $P < 0.02$) and a positive association with the use of CNI maintenance therapy (HR 0.53; CI 0.34-0.82; $P < 0.004$) (Table 3). CCI components negatively associated with patient survival were age (HR 1.09; CI 1.04-1.13; $P < 0.001$), myocardial infarction (HR 1.87; CI 1.05-3.17; P 0.03), and cerebrovascular disease (HR 2.57; CI 1.50-4.40; P 0.001) (Table 4).

Graft Survival After RT

On univariate and then multivariate analysis, CCI score did not affect graft survival which was otherwise negatively associated with KDRI (HR 2.55; CI 1.34-4.85; $P < 0.004$), HLA mismatch (HR 1.32; CI 1.05-1.66; $P < 0.02$), particularly on locus DR (HR 0.45; CI 0.24-0.83; P 0.01) and locus A (HR 0.30; CI 0.01-0.99; P 0.04), CNI maintenance therapy had a positive association (HR 0.41; CI 0.23-0.76; P 0.005) (Table 5).

DISCUSSION

The survival benefit of RT in the elderly has been shown in many studies;¹²⁻¹⁵ nevertheless, it is still unclear whether

TABLE 2.

Recipients' and donors' characteristics

Variables	Mean (SD)/n (%)
Recipient's age (y)	66 \pm 4.59
Female sex	144 (41%)
CCI score	3.73 \pm 1.85
CCI score ≥ 3	145 (41%)
PRA > 50%	9 (3%)
Time on dialysis (y)	4.64 \pm 2.64
HLA MM	3.39 \pm 1.56
0 MM locus DR	129 (36%)
0 MM locus A	55 (16%)
0 MM locus B	33 (9%)
Induction therapy	334 (95%)
CNI therapy	262 (75%)
1-y graft loss	36 (10%)
Donor's age (y)	54 \pm 15.66
Donor's age ≥ 60 y	182 (52%)
Single organ donor	155 (44%)
KDPI	69 \pm 28.60
KDRI	1.35 \pm 0.46

CCL, Charlson comorbidity index; CNI, calcineurin-based therapy; KDPI, kidney donor profile index; KDRI, kidney donor risk index; MM, mismatch; PRA, panel reactive antibody; SD, standard deviation.

TABLE 3.

Univariate and multivariate Cox regression analysis

Variables	Univariate analysis		
	HR	95% CI	P
Recipient's age (y)	1.09	1.04-1.13	<0.0001
Female sex	1.42	0.92-2.16	0.09
CCI score	1.1	0.99-1.21	0.06
CCI score ≥ 3	1.61	1.10-2.57	0.04
PRA > 50%	0.26	0.036-1.86	0.18
Time on dialysis (y)	0.98	0.92-1.05	0.99
HLA MM	1.14	1-1.31	0.06
0 MM locus DR	0.76	0.50-1.16	0.2
0 MM locus A	0.79	0.44-1.39	0.42
0 MM locus B	0.61	0.28-1.33	0.21
Induction therapy	0.61	0.30-1.22	0.16
CNI therapy	0.53	0.34-0.81	0.004
1-y graft loss	1.51	0.86-2.67	0.15
Donor's age (y)	1.01	0.99-1.03	0.07
Donor's age ≥ 60 y	1.15	0.77-1.73	0.48
Single organ donor	1.37	0.92-2.03	0.12
KDPI	1.01	0.99-1.01	0.1
KDRI	1.38	0.87-2.11	0.17
	Multivariate analysis		
CNI therapy	0.53	0.34-0.82	0.004
CCI score ≥ 3	1.62	1.09-2.41	0.02

Probability of death after RT. Recipient's age is included in CCI score.

CCL, Charlson comorbidity index; CI, confidence interval; CNI, calcineurin-based therapy; HR, hazard ratio; KDPI, kidney donor profile index; KDRI, kidney donor risk index; MM, mismatch; PRA, panel reactive antibody; RT, renal transplantation.

this benefit includes patients with high comorbid conditions. In this multicenter study, RT improved the survival of patients older than 60 years independently of the degree of comorbidities present at inclusion on the WL. Patients remaining on the WL had a significantly higher CCI score than patients undergoing RT, but after PS matching we were able to demonstrate that patients with a high CCI score ≥ 3 had a 37% survival benefit compared with similar patients remaining on the WL. Results were similar when

TABLE 4.

Cox regression multivariate

CCI components	HR	CI 95%	P
Recipient's age (y)	1.09	1.04-1.13	<0.0001
Myocardial infarction	1.87	1.05-3.17	0.03
Diabetes	0.12	0.69-1.80	0.63
Diabetes with organ disease	1.16	0.87-1.55	0.29
Congestive heart failure	1.17	0.74-1.84	0.50
Peripheral vascular disease	0.98	0.61-1.57	0.92
Cerebrovascular disease	2.57	1.50-4.40	0.001
Dementia	1.06	0.26-4.33	0.92
Pulmonary disease	0.94	0.48-1.80	0.84
Rheumatologic disease	0.72	0.17-2.94	0.65
Ulcer disease	0.77	0.28-2.10	0.61
Mild liver disease	0.31	0.44-2.25	0.25
Moderate-severe liver disease	1.97	0.48-.8	0.34
Hemiplegia	1.22	0.17-8.79	0.84

Probability of death after RT according to CCI components.

CCL, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; RT, renal transplantation.

TABLE 5.
Univariate and multivariate analysis

Variables	Univariate analysis		
	HR	95% CI	P
Recipient's age (y)	1.02	0.96-1.09	0.42
Female sex	0.72	0.33-1.06	0.09
CCI score	1.12	0.97-1.29	0.11
CCI score ≥ 4	1.31	0.74-2.31	0.34
Time on dialysis (y)	0.98	0.89-1.08	0.72
HLA MM	1.41	1.14-1.75	0.001
0 MM locus DR	0.45	0.24-0.83	0.01
0 MM locus A	0.3	0.01-0.99	0.04
0 MM locus B	0.63	0.23-1.77	0.33
Induction therapy	0.79	0.28-2.21	0.65
CNI therapy	0.42	0.23-0.77	0.005
Donor's age (y)	1.04	1.02-1.07	<0.0001
Donor's age ≥ 60 y	3.38	1.82-6.27	<0.0001
Single organ donor	1.34	1.82-6.29	0.24
KDPI	1.03	1.002-1.04	0.001
KDRI	3.83	1.71-53	<0.0001
Multivariate analysis			
HLA MM	1.32	1.05-1.66	0.02
KDRI	2.55	1.34-4.85	0.004
CNI therapy	0.41	0.23-0.76	0.005

Probability of graft loss. Donor's age is included in KDRI/KDPI.

CCL, Charlson comorbidity index; CI, confidence interval; CNI, calcineurin-based therapy; HR, hazard ratio; KDPI, kidney donor profile index; KDRI, kidney donor risk index; MM, mismatch.

only recipients from donors older than 60 years (52% of the donor population) were compared their WL counterpart mimicking an old for old scenario. In the literature, only Sørensen et al, using data merged from the Danish Nephrology Registry and Scandiatransplant, compared patient survival on WL versus RT according to CCI score along a wide recipient's age range. They found that RT had a protective effect independent of age and degree of comorbidity analyzed separately.¹⁶ To our knowledge, our study adds to the existing literature by analyzing the impact of RT in elderly patients according to their comorbidities.

This study also highlights the impact of comorbidities after RT. Patients transplanted with a CCI score ≥ 3 had 14% lower survival rate at 5 years compared to those transplanted with a CCI score < 3 , independent of other variables known to affect survival such as HLA mismatch, panel reactive antibody, immunosuppression, and donor characteristics. Wu et al also found comorbidities to be associated with patient survival after RT in deceased donor's recipients but not in those receiving a kidney from a living donor which were not included in our study.¹⁷

Remarkably, we could not find a difference in the survival of patients remaining on the WL stratified by CCI score ≥ 3 or < 3 as we did in the RT cohort. One hypothesis for this lack of a difference is the high event rate and the low number of patients remaining for analysis in this cohort.

This study has several limitations. Owing to the retrospective nature of our study, a potential selection bias likely explains the difference in CCI score between patients "selected" for RT versus those remaining on the WL which had higher dialysis vintage and cardiovascular events. A PS matching was done to overcome this problem. In Argentina

Organ allocation is regional, this multicenter study including centers from both central and intra-country regions, public and private practice minimizes potential bias.

Also for survival purposes, we used an intention-to-treat analysis. This approach could have generated the bias of overestimating the benefits of RT for patients dying on WL who were no longer eligible for RT, and underestimating it for patients dying after RT who were already back on dialysis for a while and therefore death could no longer be related to RT. Nevertheless, including only "on-treatment" patients would have generated a bias in the opposite direction.

Although comorbidities did not seem to have an impact on graft survival which was mostly affected by HLA mismatch, donor characteristics, and immunosuppression, this finding needs to be further investigated including variables known to impact graft survival such, rejections, readmission and infections which were not included in our study.

Finally as we do not have in Argentina a reliable index to evaluate donor quality we used the KDPI/KDRI index generated in the US population, its principal component the donor's age, correlated with patient and graft survival in this study.

Taken together and with its limitations, our findings suggest that RT is beneficial in elderly patients in spite of high comorbidity measured by CCI score. Nevertheless, CCI score components and its impact before and after RT need further analysis. Mortality in dialysis was very high independent of the CCI score, and we could not distinguish 1 component being more important than other, after transplantation mortality was significantly associated with myocardial infarction, cerebrovascular accident, and age.

Our study suggests that patients over 60 years should not be precluded from listing and transplantation according to their CCI score.

In conclusion, this study showed that RT improved survival in patients older than 60 years even in those with high comorbidities measured by CCI score. A high score should not preclude patients from transplantation. Patient survival after transplantation was affected by comorbidities and needs to be further investigated.

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