Outcomes of Male Patients with Alport Syndrome Undergoing Renal Replacement Therapy

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Summary

Background and objectives Patients with the hereditary disease Alport syndrome commonly require renal replacement therapy (RRT) in the second or third decade of life. This study compared age at onset of RRT, renal allograft, and patient survival in men with Alport syndrome receiving various forms of RRT (peritoneal dialysis, hemodialysis, or transplantation) with those of men with other renal diseases.

Design, setting, participants, & measurements Patients with Alport syndrome receiving RRT identified from 14 registries in Europe were matched to patients with other renal diseases. A linear spline model was used to detect changes in the age at start of RRT over time. Kaplan-Meier method and Cox regression analysis were used to examine patient and graft survival.

Results Age at start of RRT among patients with Alport syndrome remained stable during the 1990s but increased by 6 years between 2000–2004 and 2005–2009. Survival of patients with Alport syndrome requiring dialysis or transplantation did not change between 1990 and 2009. However, patients with Alport syndrome had better renal graft and patient survival than matched controls. Numbers of living-donor transplantations were lower in patients with Alport syndrome than in matched controls.

Conclusions These data suggest that kidney failure in patients with Alport syndrome is now being delayed compared with previous decades. These patients appear to have superior patient survival while undergoing dialysis and superior patient and graft survival after deceased-donor kidney transplantation compared with patients receiving RRT because of other causes of kidney failure.

Clin J Am Soc Nephrol 7: 1969–1976, 2012. doi: 10.2215/CJN.02190312

Introduction

Alport syndrome is a hereditary nephropathy characterized by progressive renal failure, sensorineural deafness, and typical ocular abnormalities. It almost inevitably leads to ESRD during adolescence or early adulthood (1–3). The disease is caused by mutations in type IV collagen genes (1,4–6). Eighty-five percent of Alport families have an X-linked (*COL4A5* gene) and 15% an autosomal-recessive (*COL4A3* or *COL4A4* genes) pattern of inheritance (1,7–10). Female heterozygous X-linked Alport carriers show a large inter- and intrafamilial variability of the clinical course and a more favorable prognosis (11,12). Heterozygous *COL4A3*/*COL4A4* carriers develop thin basement membrane nephropathy (10,12,13), which may lead to an increased risk for developing progressive CKD (12). Thin basement membrane nephropathy is very common, with a prevalence ranging from 1% in the general population (13) to 5.2% in a series of transplant biopsies (14). This high prevalence of heterozygous carriers among family members might affect the rate of living kidney donation in Alport families.

Patients with Alport syndrome who undergo kidney transplantation typically have a good outcome (15). However, 2%–5% of males develop anti–glomerular basement (GBM) membrane disease early in the post-transplant period, resulting in rapid loss of the allograft (16–18). Anti-GBM disease can recur earlier and behave more aggressively in subsequent transplants. Until the late 1990s, no therapy could be offered to patients with Alport syndrome to delay onset of kidney failure. Angiotensin-converting enzyme inhibitor therapy may delay disease progression, according to studies in both animal models (19) and humans (20).

Data on patients with Alport syndrome undergoing renal replacement therapy (RRT) are scarce. Therefore, this study was launched to evaluate outcome of male patients with Alport syndrome receiving RRT using data collected by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry (21). The study examines the time trends in age at onset of RRT of patients with Alport syndrome from 1990 to 2009 and compares the

following outcomes among patients with Alport syndrome and matched controls with other renal diseases: overall patient survival during RRT, patient survival during dialysis, and patient and graft survival after renal transplantation.

Material and Methods

Data Collection

The ERA-EDTA Registry annually collects data on patients who start RRT and are listed in national and regional renal registries in Europe. Fourteen national or regional renal registries from 11 countries, which submitted individual patient data to the ERA-EDTA Registry from 1990 to 2009, participated in the study. These included the national registries of Austria, Denmark, Finland, Greece, Iceland, Norway, Sweden (from 1991), the Netherlands, and Scotland and the regional registries of Calabria in Italy (from 1997) and Andalusia (Basque country, from 1992), Catalonia, and Valencian Community (from 1992) in Spain. These registries report to cover almost 100% of the general population in their country. Moreover, after data are received, they are extensively checked within the ERA-EDTA registry (21). Further details of the ERA-EDTA database and the methods used to collect and process data have been previously reported (22).

Cases included only male patients with ESRD due to Alport syndrome (code 51, defined as Alport's syndrome/hereditary nephritis with nerve deafness) who started RRT between January 1, 1990, and December 31, 2009, and were still alive at day 91 after start of RRT. Females with Alport syndrome (code 51) were excluded to avoid the inclusion of heterozygous female carriers of X-linked Alport syndrome, who have a different prognosis. As shown in Table 1, controls included males undergoing RRT with ESRD due to causes other than Alport syndrome, who were still alive at day 91 after start of RRT. They were matched for age (per year), year at onset of RRT (within 2 years), and RRT modality at day 91 after onset of RRT (hemodialysis, peritoneal dialysis, and kidney transplantation). For each Alport case, five male controls were randomly selected from the same age, year, and modality categories. To compare survival after the first kidney transplant, a second cohort was composed of male patients with ESRD due to Alport syndrome who received a kidney transplant between January 1, 1990, and December 31, 2009. For each of these Alport patients, five male controls with other causes of ESRD were randomly selected from the same age at transplantation (per year), year of transplantation (within 2 years), and donor kidney (living, deceased, and unknown) categories.

Statistical Analyses

Differences in patient characteristics between groups were examined using the chi-squared test. To detect points in time when the age at start of RRT increased more rapidly, a linear spline model was developed and fitted using the Transreg procedure in SAS software, version 9.2 (SAS Institute, Inc., Cary, NC). Here the dependent variable was the age at onset of RRT, and the spline transformation of the year of RRT initiation was the independent variable. The Kaplan-Meier method and Cox regression analyses were used to compare survival probabilities. Patients were followed until December 31, 2009. For the analysis of patient survival on RRT, the day at start of RRT was taken as the starting point, and the event studied was death. Reasons for censoring were recovery of renal function, loss to follow-up, and end of follow-up time. For the analysis of patient survival on dialysis, the first day on dialysis was the starting point, the event was death, and reasons for censoring were recovery of renal function, loss to follow-up, end of follow-up time, and renal transplantation. To account for renal transplantation as a competing risk for death while patients are undergoing dialysis, a competing risk analysis was also performed. For the analysis of patient and graft survival after transplantation, survival times were measured from the date of the first renal transplantation. The event of interest was death in patient survival analysis and graft failure or death in graft survival analysis. Reasons for censoring were loss to follow-up and end of follow-up time. For all models, interactions between Alport syndrome and the age at start of RRT, or the age at kidney transplantation, were examined to determine whether the association of Alport syndrome with outcome differed between younger and older patients.

Results

Between January 1, 1990, and December 31, 2009, 456 patients with ESRD due to Alport syndrome started RRT. A total of 2280 matched controls were included. Table 1 describes the characteristics of the patients with Alport syndrome and the matched controls.

Age at Start of RRT

Figure 1 shows the distribution of the age at onset of RRT during the periods 1990–1994, 1995–1999, 2000–2004, and 2005–2009. In the first decade of the study period, the distribution of age remained similar and the median age did not change. Compared with the first two periods, the median age at the onset of RRT increased by about 1 year during the period 2000–2004. In the most recent period, 2005–2009, a clear shift toward older ages occurred, as is illustrated by the increase in the median age by more than 6 years compared with the period 2000–2004. The linear spline model (Figure 2) identified the year 2000 (P=0.004) as the time point at which the mean age at initiation of RRT began to increase more rapidly.

Patient Survival on RRT

The total follow-up time of the 456 Alport patients was 3179 years; 38 patients died within the study period (1.20 deaths per 100 patient-years). The 2280 matched controls had a total follow-up time of 14,746 years, and 405 patients died (2.75 deaths per 100 patient-years). Only four (0.9%) of the Alport patients and 21 (1.1%) of the controls were censored because of loss to follow-up. Survival of patients with Alport syndrome was better than for the matched controls (Figure 3A and Table 2; $P<0.001$). The distribution of causes of death did not differ significantly between the two groups (Table 3), with cardiovascular disease and infections being the most common causes. Although we found a statistically significant interaction between Alport syndrome as primary renal disease and the age at start of

Table 1. Characteristics of patients with Alport syndrome and matched controls who started renal replacement therapy or received their first kidney transplant

Patients' Characteristics	Alport Patients Starting RRT	Matched Controls Starting RRT[a]	Alport Patients Receiving Transplant	Matched Controls Receiving Transplant[b]
Patients (*n*)	456	2280	408	2040
Median age at start of RRT (yr)	27.9 (21.7–40.5)	28.0 (21.6–40.2)	25.7 (20.5–35.9)	26.3 (20.4–36.0)
Median age at first transplant (yr)	28.0 (22.1–38.0)	27.4 (21.7–36.7)	27.9 (22.3–37.6)	27.9 (22.5–37.7)
Median year at start of RRT	2000 (1995–2004)	2000 (1995–2004)	1998 (1993–2002)	1998 (1993–2002)
Median year of first transplant	2003 (1998–2006)	2003 (1998–2007)	1999 (1995–2004)	2000 (1995–2005)
Treatment modality at day 91, *n* (%)				
Hemodialysis	264 (57.9)	1320 (57.9)	226 (56.4)	1216 (60.2)
Peritoneal dialysis	131 (28.7)	655 (28.7)	114 (28.4)	520 (25.7)
Kidney transplantation	61 (13.4)	305 (13.4)	61 (15.2)	284 (14.1)
Primary renal disease, *n* (%)				
Alport syndrome	456 (100)	—	408 (100)	—
GN/sclerosis	—	685 (30.0)	—	694 (34.0)
Congenital anomalies of kidney and urinary tract	—	377 (16.5)	—	376 (18.4)
Cystic kidney disease	—	168 (7.4)	—	147 (7.2)
Diabetes	—	278 (12.2)	—	181 (8.9)
Hypertension/renal vascular disease	—	134 (5.9)	—	120 (5.9)
Multisystem diseases	—	159 (7.0)	—	144 (7.1)
Miscellaneous	—	129 (5.7)	—	105 (5.2)
Unknown/missing,	—	350 (15.4)	—	273 (13.4)
Median time to first transplant (yr)			1.4 (0.6–2.7)	1.3 (0.6–2.6)
Kidney donor source, *n* (%)	—	—		
Deceased donor	—	—	257 (63.0)	1285 (63.0)
Living donor	—	—	98 (24.0)	490 (24.0)
Unknown type of donor	—	—	53 (13.0)	265 (13.0)

Medians are expressed with 25th, 75th percentiles. RRT, renal replacement therapy.
[a]Matched for age at start of RRT, year at start of RRT (2-year period), RRT modality at day 91 (hemodialysis, peritoneal dialysis, or transplant).
[b]Matched for age at first transplant, year at first transplant (2-year period), transplant donor source (deceased, living, or unknown donor).

RRT (P=0.026), the survival advantage of patients with Alport syndrome compared with matched controls was consistent in both younger and older patients starting RRT (Figure 3B and Table 2). In addition, when stratified by period of RRT initiation, patients with Alport syndrome showed superior survival in both 1990–1999 and 2000–2009 (Figure 3C and Table 2). However, in neither group was there a statistically significant difference in patient survival between patients who started RRT in 2000–2009 and those who started it in 1990–1999 (Figure 3C; Alport patients: hazard ratio [HR] for 2000–2009, 0.76 [95% confidence interval [CI], 0.35–1.67], P=0.498; matched controls: hazard ratio for 2000–2009, 0.79 [95% CI, 0.63–1.01], P=0.057; data adjusted for differences in age over time).

Patient Survival during Dialysis

At day 91 after the start of RRT, 395 of the 456 patients with Alport disease were receiving dialysis (hemodialysis, 264; peritoneal dialysis, 131) (Table 1). Survival of patients with Alport syndrome during dialysis was superior to that of matched controls, for both hemodialysis and peritoneal dialysis (Figure 4 and Table 2). Of 131 Alport patients receiving peritoneal dialysis who were included in the analysis, only 2 died, compared with 91 of 655 matched controls; therefore, a reliable HR could not be calculated. Competing risk analysis with transplantation as the competing event confirmed these results ($P<0.001$). For patient survival with hemodialysis, we found a statistically significant interaction between Alport syndrome as primary renal disease and age at start RRT (P=0.020). However, we

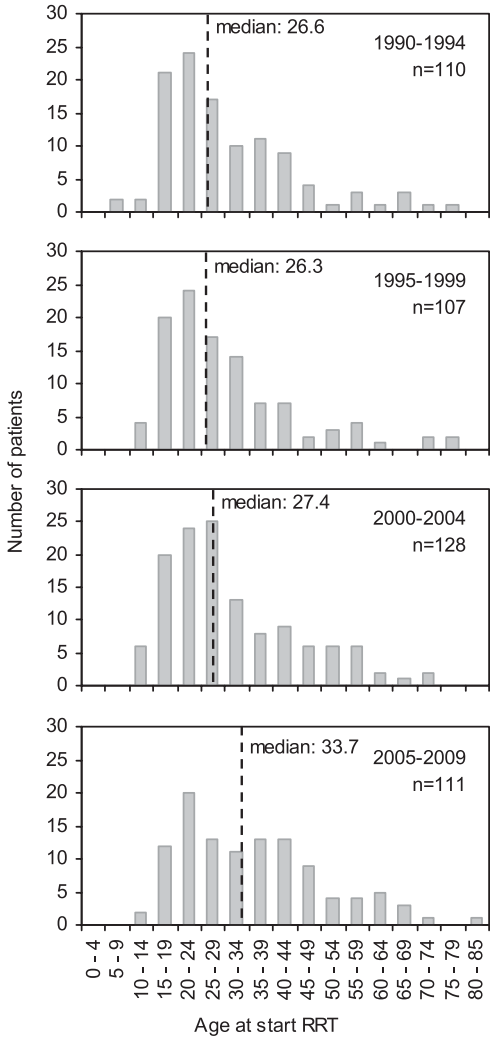

Figure 1. | Distribution of the age and median age at onset of renal replacement therapy (RRT) during the periods 1990–1994, 1995–1999, 2000–2004 and 2005–2009 in patients with Alport syndrome.

found no relevant difference in outcomes for patients younger than 25 years of age (HR, 0.61 [95% CI, 0.37–0.99]) or 25 years of age or older (HR, 0.55 [95% CI, 0.35–0.86]) at the start of RRT.

Patient and Graft Survival after Kidney Transplantation

Between January 1, 1990, and December 31, 2009, a total of 408 patients with Alport syndrome underwent kidney transplantation. These patients were matched for age, year of transplantation, and kidney donor source with 2040 kidney transplant recipients with other renal diseases. Figure 5 and Table 2 demonstrate that patients with Alport syndrome had superior patient and graft survival. There was no statistically significant interaction between Alport syndrome as primary renal disease and age at kidney transplantation for graft and patient survival after transplantation. Patients with Alport syndrome received a kidney from a living donor less often than did matched controls (data not shown). Stratified analyses (Table 2) revealed no statistically significant difference in patient and graft survival between patients with Alport syndrome and matched controls after living-donor transplantation. In contrast, patient and graft survival were statistically significantly better in patients with Alport syndrome after deceased-donor transplantation (Table 2).

Discussion

To our knowledge, this is the first study to investigate the epidemiology of ESRD due to Alport syndrome by using a large data set from the ERA-EDTA Registry, including individual data from European patients receiving RRT. Several outcome measures were evaluated, including patient survival on RRT and survival after kidney transplantation as the most relevant endpoints.

Patient survival on RRT (dialysis or kidney transplantation) was found to be superior for patients with Alport syndrome compared with matched controls with other diseases. One explanation for this superior outcome is the absence of other essential organ system involvement; this absence leads to less morbidity than do, for example, diabetes and systemic inflammatory diseases that cause kidney failure. Such inflammatory diseases, including lupus nephritis and vasculitis, are likely to be responsible for the inferior survival during dialysis and after kidney transplantation (23). Further, these diseases require more aggressive pharmacologic therapy, potentially resulting in more severe adverse effects. In patients with congenital anomalies of the urinary tract and kidney, ESRD may also be associated with increased morbidity due to surgical procedures and infectious complications, which can be life-threatening. Patients with these and several other renal diseases have an increased risk for serious complications from the illness itself or adverse treatment effects, possibly with fatal consequences. Furthermore, patients with Alport syndrome are thought to benefit from the nonrecurrent character of their disease in their kidney allografts.

Of note, patients with Alport syndrome seem to do particularly well with peritoneal dialysis. Among these patients, the potentially better outcome associated with peritoneal dialysis compared with hemodialysis requires further study. The absolute risk for death in patients with Alport syndrome is lower than in matched controls. However, the relative distribution of causes of death from cardiovascular disease, infection, and suicide did not differ between patients with Alport syndrome and matched controls. The similar risk for death from cardiovascular disease is notable because previous unpublished work suggested that patients with Alport syndrome have an increased risk for vascular events; this elevated risk is presumably due to a less stable architecture of their vascular basement membranes, which lack the disulfide-bonds of the $\alpha3/\alpha4/\alpha5$ type IV collagen chains. This notion is supported by the observation of an increased risk for premature stroke in patients with mutations in the $\alpha1$ chain type IV collagen (24).

The relatively low rate of living-donor kidney transplants in patients with Alport syndrome is probably due to the genetic cause of disease, resulting in other affected family members and small family sizes. Nevertheless, overall kidney graft and patient survival after kidney transplantation were better in patients with Alport

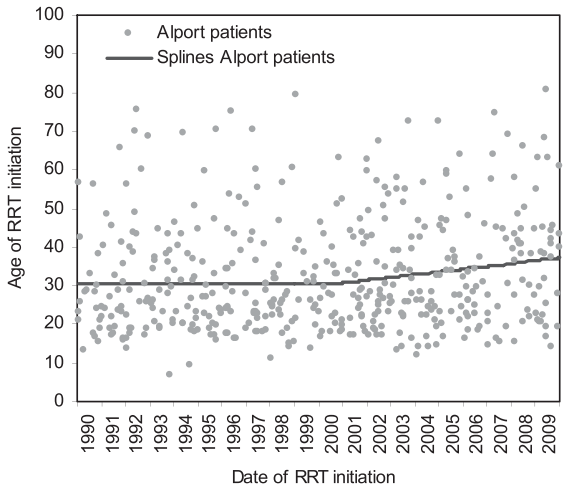

Figure 2. | Linear splines model of the age and of median age at onset of renal replacement therapy (RRT) during 1990–2009 in patients with Alport syndrome.

syndrome than in matched controls. However, patients with Alport syndrome who receive a transplant run the risk of developing post-transplant anti-GBM nephritis caused by circulating alloantibodies against the "normal" donor-kidney GBM containing $\alpha3/\alpha4/\alpha5$ type IV collagen chains. The immune system of patients with Alport syndrome recognizes these chains as foreign. Anti-GBM disease, which occurs in 2%–5% of patients with Alport syndrome who receive a transplant (15–18), might contribute to a possible lack of superior graft survival in patients with this syndrome compared with controls in the first 2 years after transplantation. In fact, the graft survival curve begins to diverge from that of controls approximately 3 years after transplantation (Figure 5B). An overall superior survival of patients with Alport syndrome after kidney transplantation in general is thought to be caused by a better preservation of general health (due to a lower burden of comorbid conditions and treatment complications) compared with patients with other underlying renal diseases, in addition to an enhanced graft survival. The median graft survival in 56 patients with Alport syndrome from the European Alport registry (20) was 19 years (unpublished data). Superior graft survival can be partly explained by the nonrecurrence of the genetic kidney disease in Alport syndrome.

It is encouraging that the age at which patients with Alport syndrome in Europe require RRT increased slightly starting in 2000 and has increased even more from 2005 onward (Figures 1 and 2). It is conceivable that increasing use of renoprotective therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers over the past two decades may have been beneficial in adolescents with Alport syndrome (12,20). In addition, earlier diagnosis and increased awareness of possible therapeutic options for Alport syndrome in recent years may have delayed the onset of RRT and improved outcome. Nevertheless, the data provide no evidence that the delay in onset of RRT is due to changes in clinical practice resulting in a later start of dialysis. Patient survival after initiation of RRT did not change over the two different periods (1990–1999 versus 2000–2009) in patients with Alport syndrome or in controls.

In this study, the controls were selected from the same age, year, and modality categories as patients with Alport syndrome. Although it would have been preferable to match with respect to comorbidity as well, these data were not available. Moreover, a previous study has shown that once age, sex, and primary renal disease are included in models for patient survival on RRT, comorbidity may add relatively little to the explanation of the variance in mortality (25).

In conclusion, our data suggest that renal failure in patients with Alport syndrome may be delayed compared with previous decades. Patient survival with RRT did not improve over time, suggesting that patients with Alport syndrome may benefit most from pharmacologic treatments that contribute to the postponement of ESRD. However, the good prognosis of these patients on RRT found in our study should be balanced against the risk-benefit ratio of future therapies (26,27). Nevertheless, compared with patients who have other renal diseases,

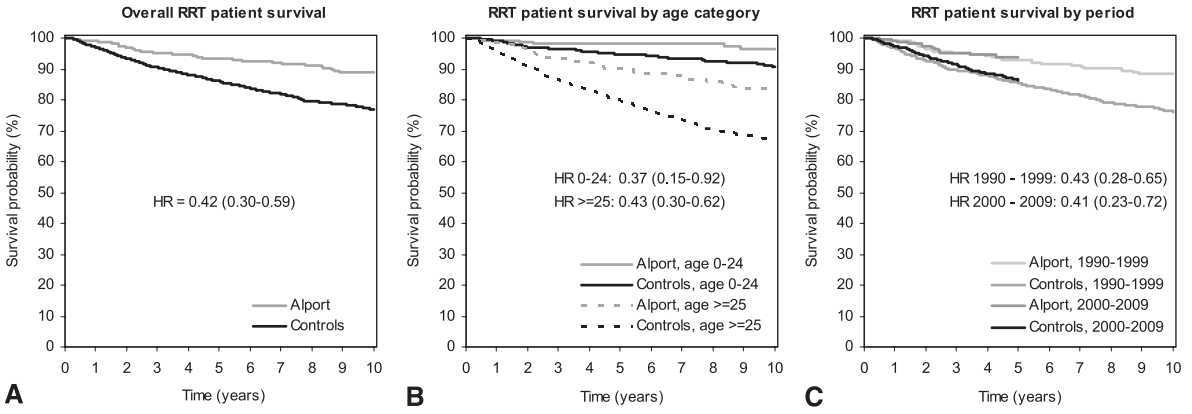

Figure 3. | Patient survival among patients with Alport syndrome receiving renal replacement therapy (RRT) compared with matched controls. Numbers in parentheses are 95% confidence intervals. HR, hazard ratio.

Table 2. Hazard ratios comparing survival of patients with Alport syndrome receiving renal replacement therapy and matched controls

Survival Type	Hazard Ratio (95% CI)	*P* Value
Overall RRT patient survival[a]	0.42 (0.30–0.59)	0.000
RRT patient survival by age at start of RRT[a]		
0–24 yr[a]	0.37 (0.15–0.92)	0.03
≥25 yr[a]	0.43 (0.30–0.62)	0.000
RRT patient survival by period[a]		
1990–1999[a]	0.43 (0.28–0.65)	0.000
2000–2009[a]	0.41 (0.23–0.72)	0.002
Patient survival during dialysis[a]	0.48 (0.32–0.72)	0.000
Hemodialysis[a]	0.57 (0.37–0.87)	0.010
Peritoneal dialysis[a]	NA[b]	NA[b]
Patient survival after transplantation[c]	0.46 (0.29–0.74)	0.001
Deceased donor[d]	0.51 (0.30–0.87)	0.013
Living donor[d]	0.42 (0.10–1.79)	0.24
Graft survival after transplantation[c]	0.75 (0.60–0.93)	0.008
Deceased donor[d]	0.69 (0.52–0.90)	0.007
Living donor[d]	0.87 (0.54–1.40)	0.57

CI, confidence interval; RRT, renal replacement therapy; NA, not available.
[a]Adjusted for age at start of RRT and year at start of RRT.
[b]Number of events too low to perform Cox regression analyses.
[c]Adjusted for age at transplantation, year of transplantation, and kidney donor source.
[d]Adjusted for age at transplantation and year of transplantation.

Table 3. Distribution of causes of death among patients with Alport syndrome and matched controls

Causes of Death	Patients with Alport Syndrome (*n*=38)	Matched Controls (*n*=405)	Chi-Squared *P* Value
Cardiovascular	12 (31.6)	125 (30.9)	0.93
Infection	7 (18.4)	60 (14.8)	0.55
Suicide/treatment refusal/ withdrawal/cachexia	4 (10.5)	27 (6.7)	0.37
Malignancies	3 (7.9)	30 (7.4)	0.91
Miscellaneous	5 (13.2)	98 (24.12)	0.12
Unknown/unavailable	7 (18.4)	65 (16.1)	0.71

Values are the numbers (percentages) of patients.

patients with Alport syndrome appear to have superior patient survival with dialysis and superior patient and renal allograft survival after deceased-donor kidney transplantation.

Acknowledgments

We would like to thank the patients and staff of all the dialysis and transplant units who have contributed data *via* their national and regional renal registries. Furthermore, we gratefully acknowledge the following registries and persons for their participation in the data collection: P. Castro de la Nuez and M.A. Pérez Valdivia (Andalusian Renal Registry); J. Aranzabal, J. Arrieta, I. Lampreabe, Á. Magaz, I. Moina, and M. Rodrigo (Basque Country Renal Registry); E. Arcos, J. Comas, P.À. Montserrat, and J. Twose (Catalan Renal Registry and Catalan Transplant Organisation); A. Hemke (Dutch End-Stage Renal Disease Registry); C. Grönhagen-Riska (Finnish Registry for Kidney Diseases); G.A. Ioannidis (Greek National Renal Registry); T. Leivestad (Norwegian Renal Registry); K. Simpson (Scottish Renal Registry); L. Bäckman, K.G. Prütz, S. Schön, A. Seeberger, and B. Rippe (Swedish Renal Registry [SNR]); and M. Ferrer Alamar (Registro de Enfermos Renales de la Comunidad Valenciana). Registry committee members and national registries not listed as authors are included here. The authors wish to thank Christoph Wanner, ERA-EDTA Registry chairman, for giving us the access to the ERA-EDTA Registry.

The project Access to the ERA-EDTA Registry for the European Alport Registry was funded by the European Renal Association (to O.G.). The European Alport Registry was supported by the Association pour l'Information et la Recherche sur les Maladies Rénales Génétiques (to O.G.) and the KfH Foundation Preventive Medicine (Fritz-Scheler Stipendium of the German Society of Nephrology) (to O.G.).

Parts of the registry data were made public in abstract form at the annual meetings of the German and American Societies of Nephrology, the German Association of Internal Medicine, the European Renal Association, the German Society of Pediatric Nephrology, and the International Pediatric Nephrology Association.

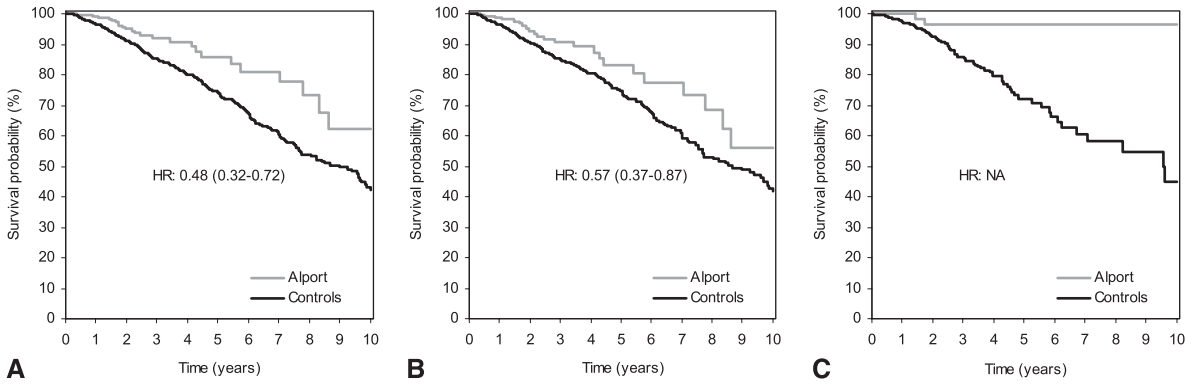

Figure 4. | **Patient survival among patients with Alport syndrome during dialysis compared with matched controls**. (A) Patient survival on dialysis, (B) patient survival on hemodialysis, and (C) patient survival on peritoneal dialysis. Numbers in parentheses are 95% confidence intervals. HR, hazard ratio.

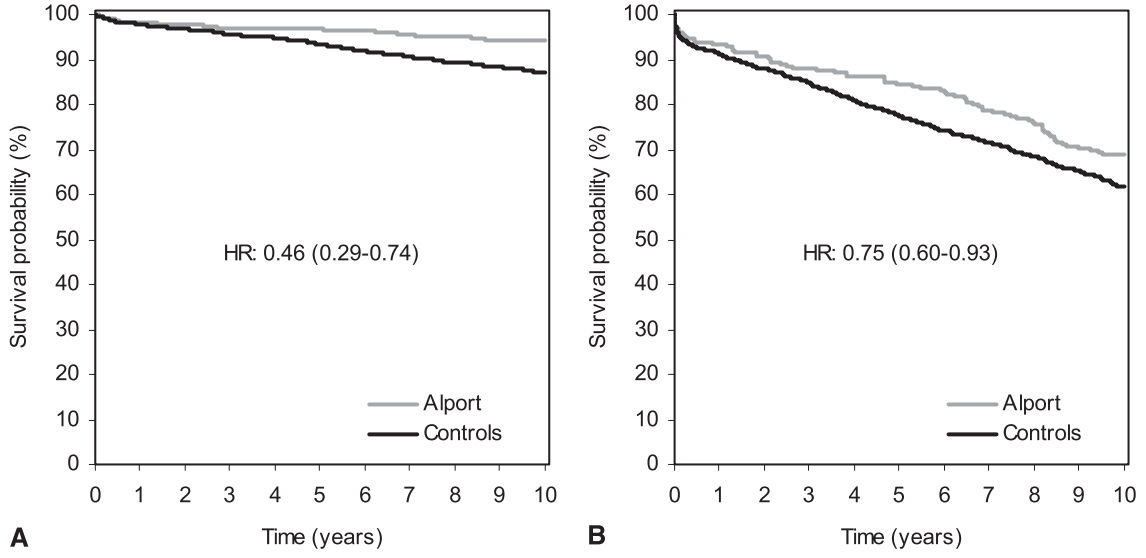

Figure 5. | **Patient and graft survival among patients with Alport syndrome after kidney transplantation compared with matched controls**. (A) Patient survival after transplantation, (B) graft survival after transplantation. Numbers in parentheses are 95% confidence intervals. HR, hazard ratio.

Disclosures

None.

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Received: March 1, 2012 **Accepted:** August 27, 2012

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.02190312/-/DCSupplemental.