



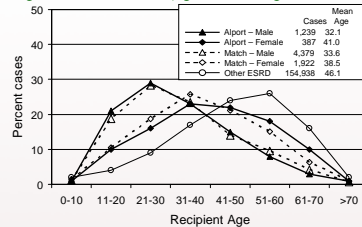
A Retrospective Examination of Kidney Transplant Outcomes in Patients with Alport Syndrome

Tariq Shah MD, Ian V. Hutchinson PhD, Robert Mendez MD, Rafael Mendez MD, and Steven Takemoto PhD

National Institute of Transplantation, Los Angeles, CA

Results

Percentage cases distributed by gender and age.



Abstract

Introduction: Alport Syndrome accounts for approximately 1% of kidney transplants. It is a hereditary cause of kidney failure associated with hearing loss, more often affecting males than females. Loss of kidney function is attributed to collagen defects in the glomerular basement membrane. Formation of antibody reactive to normal collagen in the transplanted kidney may increase the risk of graft loss.

Methods: This retrospective examination of registry data for transplants 1996-2007 used logistic regression to identify distinguishing characteristics of Alport patients (n=1,626). A cohort (n=6,301) with similar distributions of age, gender, race, graft number, donor type, insurance, co-morbidity and re-transplant status was identified.

Results: Cox proportional hazards analysis indicate that Alport recipients had 19% reduced risk of graft loss and 39% reduced risk of death when compared to the matched cohort. Registry reports did not reveal cases where graft loss in Alport recipients was attributed to antibody reactive to glomerular basement membrane. Re-transplantation and expanded criteria donors were associated with increased risk of graft loss.

Conclusion: Examination of retrospective registry data indicates that kidney transplantation provides excellent outcome for patients with Alport syndrome. There were low rates of graft loss due to disease recurrence or anti-GBM antibody; and outcomes were similar with living related and unrelated donors.

Objectives

To compare covariates and outcomes in Alport patients with patients having other causes of ESRD using a matched cohort of kidney transplant recipients.

Methods

A matched cohort was constructed to obtain a set of patients with a similar distribution of recipient age in deciles, gender, ethnicity, body-mass index (BMI) grouping, re-transplant, dialysis duration, type of insurance and type of donor.

Differences in the distribution of covariates were tested for significance using the Chi-square test.

Rates of rejection, graft loss, death-censored graft and death rates were calculated using the Kaplan-Meier product limit method with significance tested using log rank analysis.

Cox proportional hazards modelling was used to calculate hazard ratios using stepwise regression to eliminate confounders with significance less than 0.05. The initial models included recipient age, gender, ethnicity, pregnancy, panel reactive antibody (PRA), duration of dialysis prior to transplantation, diabetes, hypertension, cancer and cardiovascular conditions, type of insurance, level of HLA-A, -B -DR locus mismatch (ABDR MM), donor age, source of donor and whether tacrolimus (Tmc) was used as a calcineurin inhibitor (CNI), mycophenolate mofetil (MMF) as an antiproliferative, or induction antibody was administered.

Both primary and secondary indications as well as free text fields were examined to estimate rates of the various causes of graft loss after excluding patients who died with a functioning graft. The significance of differences was tested using the Chi-square test.

Female Alport recipients were generally older with a mean age of 41 years compared to 32 years for male. Patients with other causes of ESRD were generally older with a mean age of 46 years. The age distribution was skewed to the left for male Alport recipients and to the right for other ESRD while female Alport recipients had a more normal age distribution.

Alport recipients were more likely male, White, non-obese with body mass index (BMI) less than 25 kg/m² and unsensitized with panel reactive antibody (PRA) less than 10%. They were less likely retransplanted, had a lower comorbidity burden of diabetes, hypertension, cardiovascular disease or cancer, and less likely received an expanded criteria donor.

Covariate distribution

Cases	Alport		Overall		Matched	
	1,626	163,943	P	6,301	P	
Recipient Factors						
Male	76.2%	59.6%	<0.001	69.5%	<0.001	
Age						
0-25	32.0%	11.0%	<0.001	27.7%	0.003	
26-40	36.2%	23.2%		39.2%		
>40	31.8%	65.6%		33.1%		
Race						
White	79.6%	57.7%	<0.001	77.8%	0.271	
Black	6.6%	23.6%		7.0%		
Hispanic	11.1%	12.4%		11.7%		
Other	2.6%	6.3%		3.5%		
BMI						
<=25	63.2%	43.8%	<0.001	60.5%	0.112	
26-30	24.6%	31.6%		26.8%		
>30	12.6%	24.6%		12.8%		
Regraft	7.9%	9.5%	0.015	8.1%	0.238	
PRA						
0-10%	80.5%	76.3%	0.001	78.5%	0.181	
11-30%	7.3%	8.9%		8.6%		
>30%	12.3%	14.8%		13.0%		
Dialysis						
Preemptive	24.5%	18.4%	<0.001	22.7%	0.349	
<1 year	25.9%	19.8%		25.4%		
1-3 yr	27.0%	31.5%		28.3%		
>3 yr	22.6%	30.4%		23.7%		
Comorbidity						
Diabetes	0.1%	21.9%	<0.001	0.0%		
Hypertension	75.2%	80.9%	<0.001	74.5%	0.577	
Cardiovascular	4.0%	9.8%	<0.001	6.4%	0.522	
Cancer	1.4%	3.0%	<0.001	1.9%	0.215	
Private Insurance	51.5%	41.0%	<0.001	53.6%	0.118	
Donor Source						
Deceased	51.2%	51.2%	<0.001	49.9%	<0.001	
Expanded criteria	5.1%	9.4%		5.1%		
Living related	25.6%	27.4%		31.5%		
Living unrelated	17.5%	12.0%		13.6%		
Immunosuppression						
CNI						
Anti-Proliferative	51.8%	52.9%	0.389	50.4%	0.349	
MMF	71.3%	69.8%	0.182	69.2%	0.102	
Induction Antibody	43.6%	41.2%	0.052	42.6%	0.461	

Univariate outcomes

Endpoint	Cohort	6 Months	1 Year	3 Years	5 Years	P
Rejection	Alport	6.2	15.0	23.6		
	Match	6.0	15.5	24.7		0.123
	Other ESRD	5.5	12.8	20.4		0.034
Graft Loss	Alport	4.0	5.5	11.9	18.9	
	Match	5.1	6.8	14.4	22.6	0.001
	Other ESRD	5.9	8.2	17.5	27.9	<0.001
Death Censored Graft Loss	Alport	3.3	4.4	10.2	16.0	
	Match	4.1	5.3	11.6	17.8	0.035
	Other ESRD	4.0	5.4	11.6	18.8	0.012
Death	Alport	1.3	1.7	2.7	4.8	
	Match	1.5	2.2	4.8	8.0	<0.001
	Other ESRD	2.6	4.0	8.8	14.7	<0.001

Rates of transplant rejection for Alport patients and the matched cohort were similar but slightly higher than patients with other causes of ESRD.

Rates of graft loss, death censored graft loss and death were significantly lower in Alport patients compared both to the matched and other ESRD cohorts.

Multivariate outcomes

	Reference - Other ESRD				Reference - Matched Cohort			
	Haz. Ratio	95% CI	P		Haz. Ratio	95% CI	P	
Rejection	1.02	0.92 - 1.13	0.696		0.97	0.89 - 1.06	0.503	
Graft loss	0.81	0.72 - 0.91	<0.001		0.81	0.72 - 0.93	0.002	
Death-censored graft loss	0.92	0.80 - 1.04	0.177		0.86	0.74 - 0.99	0.034	
Death	0.51	0.40 - 0.65	<0.001		0.61	0.47 - 0.79	<0.001	

The risk of rejection was 12% lower for Alport vs. matched patients but was similar to rejection in patients with other causes of ESRD.

Alport patients had a 19% lower risk of graft loss compared to matched and 29% lower than other ESRD patients, and a lower risk of death (39% vs 49%, respectively).

Subset analyses comparing Alport patients to the matched cohort

		Graft loss				Death-Censored				Death			
		1yr	3yr	5yr	P	1yr	3yr	5yr	P	1yr	3yr	5yr	P
Age 0-25	Alport	3.5	10.8	18.8		3.0	10.4	18.5		0.4	0.4	0.4	
	Match	5.9	15.1	23.7	0.01	5.1	13.6	21.7	0.06	1.1	2.4	4.2	0.001
Male	Alport	4.9	11.7	18.8		3.9	10.3	16.1		1.5	2.3	4.1	
	Match	6.7	14.1	22.4	<0.001	5.2	11.3	17.7	0.31	2.1	4.6	7.4	<0.001
Deceased Donor	Alport	6.2	13.4	21.1		4.7	11.7	17.4		2.1	3.0	5.9	
	Match	8.1	16.2	25.7	0.001	6.3	12.9	20.0	0.02	2.7	5.9	9.8	<0.001
Living Donor	Alport	3.7	7.6	13.3		3.5	6.5	12.3		0.7	2.0	2.0	
	Match	4.1	10.7	18.4	0.17	3.1	8.9	13.3	0.59	1.1	2.4	4.2	0.059
RxTx	Alport	6.9	16.8	32.0		6.9	15.5	27.7		2.1	6.5	8.5	
	Match	8.2	19.8	28.1	0.99	6.8	16.4	23.7	0.75	0.8	3.7	9.7	0.49
Preemptive Dialysis	Alport	3.6	7.8	12.9		3.4	7.6	11.5		0.6	1.0	2.8	
	Match	4.6	10.3	17.6	0.06	3.9	8.4	14.1	0.22	0.9	2.6	5.2	0.051
>3 Years	Alport	8.7	15.4	22.8		6.7	11.8	18.8		3.3	6.0	7.4	
	Match	10.3	20.0	30.2	0.03	7.7	15.4	22.8	0.09	4.1	8.3	13.5	0.061
Tacrolimus	Alport	3.1	9.7	16.4		2.3	7.9	14.4		1.2	2.7	5.7	
	Match	5.0	13.4	21.0	0.01	3.8	10.5	16.0	0.07	1.7	4.0	7.0	0.052
MMF	Alport	3.4	9.2	16.3		2.5	7.8	13.5		1.1	1.8	4.1	
	Match	5.3	12.8	21.2	<0.001	3.9	10.2	16.2	0.02	1.9	4.4	7.9	<0.001

Alport patients had lower rates of graft loss in younger, male and deceased donor cohorts as well as those treated with tacrolimus or mycophenolate mofetil.

Rates of death were significantly lower in Alport patients who were young, male, in receipt of a graft from a deceased donor or treated with mycophenolate.

Subset analysis of Alport patients

		Graft loss				Death-Censored				Death			
		1yr	3yr	5yr	P	1yr	3yr	5yr	P	1yr	3yr	5yr	P
Recipient Age 0-25	Alport	3.5	10.8	18.8	0.948	3.0	10.4	18.4	0.04	0.4	0.4	0.4	<0.001
	Match	5.6	12.2	19.2		5.0	11.3	17.4		1.3	2.2	3.7	
>40	Alport	7.5	12.5	18.7		5.0	8.9	11.8		3.5	5.5	10.2	
	Match	8.9	17.4	25.8		6.0	10.2	15.8	0.68	2.5	3.9	6.7	0.015
Gender	Female	7.3	12.5	18.4	0.793	6.0	10.2	15.8	0.68	2.5	3.9	6.7	0.015
	Male	4.9	11.7	18.8		3.9	10.3	16.1		1.5	2.3	4.1	
Donor type	Deceased	6.3	13.5	22.0	<0.001	4.7	11.5	18.2	<0.001	2.2	3.1	5.5	0.001
	Expanded Criteria	18.2	37.7	45.7		15.8	35.8	41.1		5.3	7.5	18.6	
Living Related	Alport	3.7	7.6	13.3		3.5	6.5	12.3		0.7	2.0	2.0	
	Match	2.0	6.0	10.3		1.5	5.0	7.4		0.8	1.4	4.4	
Living Unrelated	Alport	2.0	6.0	10.3		1.5	5.0	7.4		0.8	1.4	4.4	
	Match	5.4	11.5	18.2	0.01	4.2	9.9	15.3	<0.001	1.8	2.7	5.3	0.3
Retransplant	Alport	6.9	16.8	32.0		6.9	15.5	27.7		0.8	3.7	9.7	
	Match	8.2	19.8	28.1	0.99	6.8	16.4	23.7	0.75	0.8	3.7	9.7	0.49
Dialysis Preemptive	Alport	3.6	7.8	12.9		3.4	7.6	11.5		0.6	1.0	2.8	
	Match	4.6	10.3	17.6	0.06	3.9	8.4	14.1	0.22	0.9	2.6	5.2	0.051
>3 Years	Alport	8.7	15.4	22.8		6.7	11.8	18.8		3.3	6.0	7.4	
	Match	10.3	20.0	30.2	0.03	7.7	15.4	22.8	0.09	4.1	8.3	13.5	0.061
Tacrolimus	Alport	3.1	9.7	16.4		2.3	7.9	14.4		1.2	2.7	5.7	
	Match	5.0	13.4	21.0	0.01	3.8	10.5	16.0	0.07	1.7	4.0	7.0	0.052
MMF	Alport	3.4	9.2	16.3		2.5	7.8	13.5		1.1	1.8	4.1	
	Match	5.3	12.8	21.2	<0.001	3.9	10.2	16.2	0.02	1.9	4.4	7.9	<0.001

Graft survival rates were similar in young and older recipients, but death rates were increased and censored rates were decreased with age.

Rates of graft loss high with ECD and re-transplant and lower with reduced duration of pretransplant dialysis improved outcome rates.

Recipients of living related and unrelated kidneys had similar rates of outcome. Choice of CNI, antiproliferative agent and induction antibody did not