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

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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.

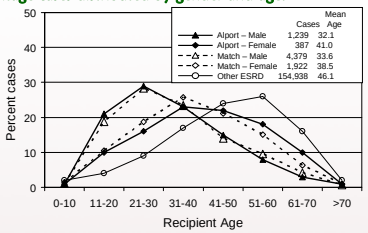
Rates of rejection, graft loss, death-censored graft and death rates were calculated using the Kaplan-Meier product limit method with significance tested using log rank analysis.

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 (Tac) 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.

Results

Percentage cases distributed by gender and age.



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

		Alport	Other	P	Matched	P
Cases		1,626	163,943		6,301	
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	12.2%	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%	
Comorbid	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	4.4%	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	Tac	51.8%	52.9%	0.389	50.4%	0.349
Anti-Proliferative	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 slighly 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	0.88	0.78	0.99	0.03
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	2.2	3.5	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	0.11	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	10.8	16.1	0.17	3.1	8.9	13.3	0.59	1.1	2.4	4.2	0.059
ReTx	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 Dialysis	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	18.6		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	3.5	10.8	18.8	0.948	3.0	10.4	18.4	0.04	0.4	0.4	0.4	<0.001
	26-40	5.6	12.2	19.2		5.0	11.3	17.4		1.3	2.2	3.7	
	>40	7.5	12.5	18.7		5.0	8.9	11.8		3.5	5.5	10.2	
Gender	Female	7.3	12.5	19.4	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	16.6	
	Living Related	3.7	7.6	13.3		3.5	6.5	12.3		0.7	2.0	2.0	
	Living Unrelated	2.0	6.0	10.3		1.6	5.0	7.4		0.8	1.4	4.4	
Primary Graft		5.4	11.5	18.2	0.01	4.2	9.9	15.3	<0.001	1.8	2.7	4.5	0.3
Retransplant		6.9	16.8	32.0		6.9	15.5	27.7		0.8	3.7	9.7	
Dialysis Preemptive		3.6	7.8	12.9	<0.001	3.4	7.6	11.5	0.01	0.6	1.0	2.8	0.001
	<1 year	4.6	9.5	16.4		4.1	8.2	13.3		1.0	1.9	4.7	
	1-3 years	5.2	14.7	23.9		3.3	13.0	20.6		2.1	2.4	4.6	
	>3 years	8.7	15.4	22.8		6.7	11.8	18.8		3.3	6.0	7.4	
CNI	CsA	4.4	10.9	16.5	0.73	3.2	9.5	14.2	0.94	1.4	2.2	3.6	0.340
	Tac	3.1	9.7	18.5		2.3	7.9	14.4		1.2	2.7	5.7	
Antiproliferative	Aza	6.0	16.9	21.8	0.8	5.1	16.1	20.1	0.49	1.7	1.7	2.9	0.423
	MMF	3.4	9.2	16.3		2.5	7.8	13.5		1.1	1.8	4.1	
Induction	No	5.8	11.7	19.9	0.83	4.8	10.4	16.7	0.990	1.5	2.6	5.8	0.899
	Yes	5.3	12.2	17.7		4.1	10.3	15.4		1.9	2.8	3.4	

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 seem to have an impact on outcome.

Causes of graft loss

	Alport	Match	P
Graft failure cases	238	1,090	
Recurrance	7 (3%)	117 (11%)	<0.001
Thrombosis	25 (11%)	103 (9%)	0.617
Hyperacute Rejection	2 (1%)	3 (0%)	0.197
Primary Failure or ATN	16 (7%)	78 (7%)	0.813
Acute Rejection	52 (22%)	267 (25%)	0.387
Chronic Rejection	116 (49%)	461 (42%)	0.069
Noncompliance	24 (10%)	107 (10%)	0.748

Rates of graft loss due to recurrent disease were higher in the matched cohort, but the rates of other causes were similar in the Alport and matched cohorts.

Our examination of causes of graft loss reported to the OPTN registry did not reveal any Alport recipients transplanted since 1998 who lost their graft due to anti-GBM antibody. Registry survey forms, however, may poorly capture this uncommon condition.

Conclusions

Alport patients are generally younger and have less burden of systemic disease when compared to those with other causes of ESRD.

Rates of graft loss and death were lower in Alport recipients.

Rejection rates were similar in Alport recipients as were rates of graft loss due to disease recurrence.

Recipients of living related and unrelated donor kidneys had similar outcomes.

There were high rates of graft loss in retransplanted recipients and those receiving a transplant from an expanded criteria donor.