PREDICTORS OF CLINICAL AND HISTOPATHOLOGICAL OUTCOMES FOR IGA NEPHROPATHY AND EFFECT OF TREATMENT IN AN INDIAN COHORT

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OBJECTIVES

To evaluate clinical and histopathological outcomes in IgA nephropathy (IgAN) > To evaluate the effect of treatment (RAS) Blockade, Immunosuppression) in IgA nephropathy

METHODS

- > Retrospective cohort of IgAN patients followed at Christian Medical College, Vellore, India from 2006 to 2011.
- > We evaluated clinical and pathological predictors of renal survival (time to reach endstage renal disease requiring dialysis) by cox proportional hazards model and effect of treatment such as renin-angiotensin system blockade and immunosuppression.



Characteristics	Total patients –	Study patients –				
	(n/mean ± SD)	(n/mean ± SD ± (range))				
IgA nephropathy patients	436	315				
Demographic profiles						
Age at the time of biopsy (years)	38.5 ± 11.2 (11 – 80)	38.7 ± 11 (13 – 70)				
Male: female ratio	1.9:1	1.9:1				
Duration of follow-up in months	28.4 ± 21.2 (1 – 82)	29 ± 21 (3 – 82)				
Li	aboratory profiles					
Serum creatinine (mg/dl)	2.61 ± 2.23 (0.5 – 15.2)	2.06 ± 1.33 (0.6 – 9.2)				
e-GFR at the time of presentation (ml/min/1.73m ²)	46.43 ± 32.24 (3.22 – 182.56)	51.02 ± 30.69 (6.81 – 182.56)				
Proteinuria (mg/day)	2872 ± 2513 (40 – 17000)	2690 ± 2338 (81 – 12900)				
Systolic blood pressure (mm/Hg)	134 ± 17 (94 – 200)	133 ± 17 (94 – 200)				
Diastolic blood pressure (mm/Hg)	85 ± 10 (56 – 120)	84 ± 10 (56 – 120)				
Mean arterial pressure MAP (mm/Hg)	101 ± 11 (49 – 143)	101 ± 12 (49 – 143)				
BMI	23.5 ± 4.3 (13.8 – 44.9)	23.4 ± 4.3 (13.8 – 44.9)				
Serum albumin (g/dl)	4.0 ± 2.7 (1.2 – 4.9)	4.0 ± 2.4 (1.2 – 4.9)				
Serum cholesterol (mg/dl)	191 ± 63 (79 – 541)	191 ± 63 (79 – 541)				
Hypertension	153(35.1)	107(34)				
Dialysis requirement at the time of presentation	23(5.3)	7(2.2)				

Baseline characteristics

Histology – MEST & Others

Treatment details

		atients es]–n (%)	Study pa [315 biopsi		
(т	S	E	М	Score
	50	119	209	284	0
Immunosup	(15.9)	(37.8)	(66.3)	(90.2)	
2	135	196	106	31	1
	(42.9)	(62.2)	(33.7)	(9.8)	
Prednisone	130	-	-	-	2
alone (%)	(41.3)				
- 82 (36.8)	ents]–n (%)	Study pati 315 biopsies	;	al parameter	Histologio
	5)	33(10.5			Crescents
	6)	109(34.		tion with C3	Co-depos
		31(9.8)		tion with Ige	Co-depos
	.)	36(11.4	sits	wall IgA depo	Capillary

Treatment details (Total no. of patients – 315)				
Immunosuppres 223 (RAS blockade (ACEi/ARB) (%)			
Prednisone alone (%) - 82 (36.8)	Prednisone and MMF (%) - 89 (39.9)	232 (73.7)		

Effect of treatment in IgA nephropathy

Treatment with immunosuppression and renin-angiotensin blockade had better renal survival.





Clinical and pathological predictors of renal survival

Parameters		Median/*Mean survival ± SE	p-value	Hypertension >140/90 mmHg (NO vs. YES)	Serum uric acid (<7.1 vs. >7.1 mg/dL)
Age (years)	≤39	56.94 ± 3.00	0.109		
	>39	64.49 ± 2.76	_	Survival Functions	Survival Functions
ex	Male	$60.82 \pm 2.46^*$	0.898	1.0- Hyperfension at presentation	1.0- 1.0-
	Female	55.78 ± 2.67 [*]	_		
MI	≤23.1	57.62 ± 3.04	0.101		₽°° ⁻
	>23.1	63.68 ± 2.63	_		
ypertension	No	63.52 ± 2.31 [*]	0.015#		3 04
	Yes	55.80 ± 3.65*	_	0.2-	0.2-
/AP (mmHg)	≤99	76.83 ± 14.50	0.125	0.0-	0.0-
	>99	68.29 ± 5.26	_	0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00 Time in months from renal biopsy	0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00 Time in months from renal biopsy
/lacroscopic hematuria	No	$60.41 \pm 2.15^*$	0.291	Mean survival	Median survival
	Yes	$59.44 \pm 4.45^*$	_	No - 63.52 ± 2.31 months, Yes - 55.80 ± 3.65 months	UA <7.1 - 64.75 ± 3.28 months, UA >7.1 - 47.43 ± 3.74 months
erum uric acid (mg/dl)	≤7.1	64.75 ± 3.28	0.000#		
	>7.1	47.43 ± 3.74	_	Proteinuria (< 2 vs. > 2 gm/day)	e-GFR at presentation (< 43.4 vs. > 43
erum cholesterol (mg/dl)	≤182	60.99 ± 3.45	0.638		
	>182	61.47 ± 3.08	_		Survival Experience
GFR at presentation(ml/min/1.73m ²)	≤ 43.39	54.58 ± 6.30	0.000#	Survival Functions	
	>43.39	79.06 ± 15.66	-	1.0- 24 hours urine protein 22 gm/day 22 gm/day	
4 hours proteinuria (mg/day)	< 2000	76 83 + 0 00	0.000#		0.8-
nouis proteinuna (mg/ auy)	>2000	57.00 ± 6.16			<u>8</u> 00-
efore bionsy RAS blockade	No	76 83 + 7 65	0 598		
	Yes	68 28 + 5 21			
fore biopsy Immunosuppressant drugs	No	60 91 + 2 18	0.689	02-	0.2-
	Yes	55 03 + 3 55	_ 0.005	0.0-	0.0- 0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00
locangial proliferation	100	76.92 ± 6.20	0.079	0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00 Time in months from renal biopsy	Time in months from renal biopsy
resangial promeration		70.83 ± 0.20		Median survival	Median survival
adosanillary hyporsollularity	E0	59.97 ± 9.27	0.000#	Proteinuria <2 gm/day - 76.83 ± 0.00 months,	GFR<43.4 ml/min/1.73m ² - 54.58 ± 6.30 months, GFR >43.4- 79.06 ± 15.66 months
ndocapiliary hypercentiarity	EU E1	77.50 ± 5.98	0.009"	> 2 gm/day – 57.00 ± 6.16 months	
amontal colorosis	EI	50.09 ± 8.07	0.006#		
egmental scierosis	51	68 22 ± 5 00	0.000	Endocapillary proliferation	Segmental sclerosis
ubular atraphy/Interstitial fibrasis	51	68.23 ± 5.90	0.000#	(E0 vs. E1)	(S0 vs. S1)
ubular atrophy/interstitial librosis	T1	00.20 ± 1.14	0.000″	Survival Functions	Survival Functions
		70.35 ± 2.51	_	1.0- endocapillary proliferation	10 Segme
	12	47.17 ± 3.07			
rescents	No	76.83 ± 4.79	0.164		
	Yes	56.81 ± 0.00			
o- deposition with C3	No	57.33 ± 2.40	0.094	S ^{ov} −	б Б 0.4-
	Yes	66.20 ± 3.25		0.2-	
o-deposition with IgG	No	77.56 ± 10.41	0.431		
	Yes	76.83 ± 0.00		0.0	0.0- 0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00
apillary wall IgA	No	76.83 ± 4.82	0.818	Time from renal biopsy in months	Time from renal biopsy in months
	Yes	56.81 ± 0.000		Median survival E0 - 77.56 ± 5.98 months,	Median survival S0 – 77.56 ± 8.16 months,
reatment with RAS blockade	No	47.15 ± 12.56	0.000#	E1 – 56.09 ± 8.07 months	S1 – 68.23 ± 5.90 months
	Yes	79.07 ± 8.66			
reatment with Immunosuppressant drugs	No	50.83 ± 4.25*	0.000#	Tubular atrophy/Interstit	tial fibrosis (T0 vs. T1 vs. T2)
	Yes	$64.08 \pm 2.14^{\circ}$			
Cox proportion Haza independent risk fa	ard rat	io model or renal s	for urviva	Survival Functions	Mean survival $T0 - 60.26 \pm 1.14$ months, $T1 - 70.35 \pm 2.51$ months, $T2 - 47 17 \pm 2.07$ months
Parameter Sig Exp(B)	95.0% CI fo	or Exp(B)		Ğ 0.4-	12 - 47.17 ± 5.07 months
Farameter Sig. Exp(B)	Lower	Upper		0.2-	
Age .004 .94	1 .903	.980		0.0-	
				0.00 12.00 24.00 36.00 48.00 60.00 72.00 84.00	
Hypertension .0036 1.049	9 1.003	1.097		nine nom renar propsy in months	

Effect of combined steroid and MMF therapy on rate of decline in GFR

KM survival curve – Steroid alone vs. along with MMF



Spearman rho -0.092, p 0.230



Mean survival Steroid monotherapy – 71.02 ± 3.02 months, Combined steroid & MMF therapy – 69.91 ± 2.89 months

Parameter	Sig.	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Age	.004	.941	.903	.980
Hypertension	.0036	1.049	1.003	1.097
Macroscopic hematuria	.015	.154	.034	0.692
e-GFR at presentation	.000	.925	.892	.959
Enocapillary proliferation E1	.000	4.534	2.006	10.246
Segmental sclerosis S1	.058	2.651	.968	7.258
Tubular atrophy T2	.041	2.891	0.927	13.578
Treatment with RAS blockade	.026	0.353	0.141	0.883
Treatment with Immunosuppressant drugs	.000	0.163	0.065	0.405

Rate of decline in GFR

Parameters	Univariate	analysis	Multivariate analysis	
	Spearman's correlation co-efficient	p-value	ExpB (95% CI)	p-value
Age (years)	-0.138	0.014	-	-
Sex (Female)	0.011	0.848	-	-
BMI	-0.134	0.017	-	-
Hypertension	-0.021	0.712	-	-
MAP (mmHg)	-0.015	0.789	-	-
Macroscopic hematuria	-0.044	0.436	-	-
Serum uric acid	-0.012	0.863	-	-
Serum cholesterol (mg/dl)	0.101	0.122	-	-
e-GFR at presentation(ml/min/1.73m ²)	0.030	0.596	-	-
24 hours proteinuria (mg/day)	0.219	0.000	-	-
Before biopsy RAS blockade	32(20)	0.335	-	-
Before biopsy Immunosuppressant drugs	17(10.8)	0.461	-	-
Mesangial proliferation (M1)	-0.029	0.612	-	-
Endocapillary hypercellularity (E1)	0.060	0.287	-	-
Segmental sclerosis (S1)	0.063	0.268	-	-
Tubular atrophy/Interstitial fibrosis (T0 & T1 vs.T2)	0.159	0.005	2.166(0.0.019 – 0.386)	0.031
Crescents	- 0.039	0.489	-	-
Co- deposition with C3	-0.106	0.060	-	-
Co-deposition with IgG	0.001	0.985	-	-
Capillary wall IgA	0.095	0.093	-	-
Treatment with RAS blockade	-0.123	0.029	-	-
Treatment with Immunosuppressant drugs	-0.078	0.167	-	-

 \succ In clinical parameters, the independent predictors of poor renal survival were young age, hypertension, baseline renal dysfunction, > Whereas macroscopic hematuria was found to have good prognosis.

> > Among MEST score, independent histological predictors of poor renal survival were endocapillary proliferation (E1), segmental sclerosis (S1) and tubular atrophy/interstitial fibrosis (T2).

Especially T2 had accelerated rate of decline in renal function where as E1 and S1 did not independently predict rate of decline of GFR. Interestingly mesangial codeposition of C3 along with IgA was an independent predictor of slow progression of renal disease.

Effect of combined steroid & MMF therapy on secondary outcomes

Percentage reduction	Steroid alone	Steroid & MMF	p-value
ΔProteinuria (%)	-41.41 ± 104.30	-49.51 ± 79.73	0.570
ΔМАР (%)	-5.18 ± 11.51	-3.64 ± 12.27	0.401

Combined steroid and MMF therapy did not have any improvement in outcome (such as better renal survival, proteinuria reduction, BP control) over steroid monotherapy.

By linear regression by using backward method, using the following dependent variables age, BMI, 24 hours proteinuria, MEST, treatment with RAS blockade were analyzed.

CONCLUSION

> In the Indian cohort, apart from clinical parameters such as young age, baseline hypertension and renal dysfunction, Oxford histological score E1, S1, T2 had poor renal survival and aid in predicting prognosis.

> Treatment with immunosuppression had better renal survival in Indian patients in contradictory with other studies.

Combined steroid and MMF therapy did not have any improvement in outcome

•Keywords: IgA nephropathy (IgAN), Oxford classification, MEST score (Mesangial hypercellularity, Endocapillary proliferation, Segmental sclerosis, Tubular atrophy/interstitial fibrosis)









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