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Letter to the Editor

LETTER TO THE EDITOR

Individualizing immunosuppressive therapy decision in immunoglobulin A nephropathy and application in a Southeast Asian cohort

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Immunoglobulin A nephropathy (IgAN) affects 25–40% of Asians with primary glomerulonephritis and can cause kidney failure in 5–30% [1, 2]. Kidney histology in the form of the Oxford MEST-C score can prognosticate kidney failure in IgAN [3], but its role in guiding immunosuppression remains uncertain [4]. We previously reported that among our multi-ethnic Southeast Asians with biopsy-proven IgAN with crescents, immunosuppressive therapy tended to lower the risk of rapid kidney disease progression [50% reduction in estimated glomerular filtration rate (eGFR) or kidney failure at 12 months] and significantly reduced kidney failure [5]. While other studies have also explored the impact of immunosuppressants on kidney outcomes according to the presence and extent of crescents [6, 7], Itami *et al*. extended the use of kidney histology in individualizing the decision for immunosuppressants by developing the steroid responder score (SRS) and steroid nonresponder score (SNRS) [8]. Among Japanese patients with IgAN, immunosuppression with steroids for high SRS (presence of three or more of the M, E, S and C components of the Oxford MEST-C score) improved renal survival. The potential utility of the SRS to guide immunosuppressive therapy was recently validated in a propensity-derived cohort from the Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) study [9]. Although the group with high SRS was small ($n = 26$) and possibly underpowered, chronic kidney disease progression (either 50% decline in eGFR or kidney failure at 10 years) was more frequent in those without steroid therapy (82 versus 17%).

In our dataset of 66 IgAN with complete clinical and histological data [5], SRS were low, medium and high in 4 (6%), 33 (50%) and 29 patients (44%), respectively. The median age was 46.8 (interquartile range 36.6, 58.5) years and systolic and diastolic blood pressures were 128 (119, 140) and 71 (70, 80) mmHg, respectively. Most patients (97%) received renin-angiotensin-aldosterone system blockers (RASB) and 56% received immunosuppressants, among which the most frequent immunosuppressive treatment regimens were glucocorticosteroid alone (59%), and combined glucocorticosteroid and cyclophosphamide (14%). Kidney failure occurred in 6% during the median follow-up of 21.5 (10.0, 35.1) months. Table 1 compared 29 patients with high SRS and 33 patients with medium SRS by immunosuppressant treatment. Among those with high SRS, the baseline clinical parameters were not significantly different and high SNRS tended to be more frequent in the immunosuppressant group, yet kidney failure was less frequent among those treated with immunosuppressants than those without immunosuppressants (0 versus 30%, $P = 0.03$; Figure 1). Immunosuppressive therapy did not significantly affect rapid kidney disease progression in both high and medium SRS groups, nor kidney failure in the medium SRS group. Although the small sample size limited the power to detect small differences in effect size and for regression analyses to control for confounders, our real-world data suggest that the Oxford MEST-C score may guide individualized immunosuppressive treatment in Southeast Asians.

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Table 1. Clinical characteristics and kidney outcomes among individuals with IgAN categorized by steroid responder score

	High SRS, $n = 29$			Medium SRS, $n = 33$		
	No IS $n = 10$	IS $n = 19$	P-value[a]	No IS $n = 18$	IS $n = 15$	P-value[a]
Clinical parameters						
Age, years	48.5 (33.8, 52.2)	41.4 (34.3, 47.3)	0.49	48.2 (35.9, 59.6)	52.9 (38.4, 61.7)	0.64
Male, *n* (%)	4 (40.0)	5 (26.3)	0.67	6 (33.7)	7 (46.7)	0.43
Systolic BP, mmHg	140 (118, 152)	130 (120, 150)	0.80	124 (110, 134)	125 (116, 140)	0.33
Diastolic BP, mmHg	75 (70, 84)	72 (70, 80)	0.50	70 (60, 81)	75 (70, 80)	0.44
eGFR, mL/min/1.73 m^2	63 (20, 83)	51 (37, 81)	0.76	59 (35, 78)	55 (34, 101)	0.73
Proteinuria, g/g	3.5 (1.7, 4.2)	4.6 (2.7, 6.9)	0.28	1.7 (1.0, 1.9)	2.0 (1.4, 3.1)	0.04
RASB, *n* (%)	10 (100)	18 (94.7)	1.00	18 (100)	15 (100)	–
SNRS			0.13			0.95
Low, *n* (%)	7 (70.0)	7 (36.8)		11 (61.1)	9 (60.0)	
High, *n* (%)	3 (30.0)	12 (63.2)		7 (38.9)	6 (40.0)	
Global sclerosis, %	32.5 (23.4, 53.5)	25.0 (13.8, 38.4)	0.11	25.0 (14.4, 37.3)	33.3 (11.1, 46.1)	0.42
Kidney outcomes						
Rapid progression	3 (30.0)	1 (5.3)	0.10	1 (5.6)	1 (6.7)	1.00
Kidney failure, *n* (%)	3 (30.0)	0	0.03	1 (5.6)	0	1.00
Follow up, months	18.5 (9.4, 33.1)	17.2 (6.7, 29.6)	0.55	19.5 (9.9, 35.0)	32.7 (21.6, 66.3)	0.07

BP, blood pressure; IS, immunosuppressant; RASB, renin-angiotensin-aldosterone system blocker; SRS, steroid responder score; SNRS, steroid non-responder score. Rapid progression was defined as 50% reduction in estimated glomerular filtration rate or kidney failure at 12 months.

[a]Comparison between IS and no IS groups by Pearson Chi-squared or Fisher's exact test as appropriate for categorical variables and Mann–Whitney U test for continuous variables.

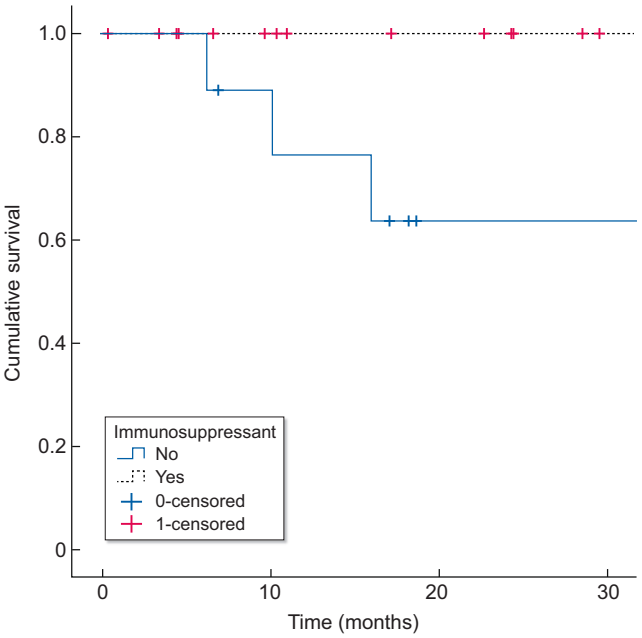

FIGURE 1: Kaplan Meier survival curve showing that kidney failure was reduced in IgAN with high steroid responder score (SRS) treated with immunosuppressant (log rank p = 0.02).

It is therefore timely that the proposed Clinical Study in IgA nephropathy (CLIgAN) trial will consider histological activity, in addition to kidney function and proteinuria, to individualize treatment decisions [10]. As current knowledge is based on data from the pre-sodium glucose co-transporter-2 inhibitors (SGLT2i) era [5, 7, 9], future immunosuppressant trials for IgAN with active histological lesions will also need to consider if optimized RASB and SGLT2i will alter the benefit conferred by immunosuppression.

DATA AVAILABILITY STATEMENT

Data available upon reasonable request and subject to institutional approval.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part. The study was reviewed by the SingHealth Centralized Institutional Board (CIRB 2016/3072) and waiver of informed consent was approved for this retrospective medical record review. All authors declare no potential conflict of interest.

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