A Renal Activity Index May Predict Histological Activity in Lupus Nephritis in Children

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Background: Lupus Nephritis (LN) occurs in up to 80% of childhood-onset Systemic Lupus Erythematosus (cSLE) and it has a worse prognosis than adults. The current gold standard for diagnosing LN and assessing its activity is a kidney biopsy interpreted using the International Societies for Nephrology & Renal Pathology (ISN/RPS) classification. Kidney biopsies are invasive and too costly to assess the course of LN. The objective of this study is to develop and initially validate for Children a Renal Activity Index (C-RAI) to non-invasively monitor LN activity, considering both traditional measures of LN (LN-TM) and recently discovered renal biomarkers (RBM).

Methods: In this ongoing prospective study, 83 children with LN were studied at the time of the kidney biopsy; LN-TM [GFR, complements, anti-dsDNA antibodies, urinary protein/creatinine ratio], clinical indices [Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS), renal domain score of BILAG (BILAG-R) and SLEDAI (SLEDAI-R)] were all obtained, and the RBM (see Table 1) were measured. Histological findings were rated by a single nephropathologist who provided ISN/RPS class, NIH Glomerular Activity Index (GLAI; range 0-24) and Tubulointerstitial Activity Index (TIAI; range = 0-21) scores (Criterion Standards). Prior to statistical analysis, RBM levels were normalized by urine creatinine and logarithmically transformed. LN-TM, RBM and clinical indices that showed significance in univariate analysis at a p-value<0.10 were considered in stepwise multivariate logistical regression models as C-RAI candidate predictors, using the GLAI and TIAI as dependent variable (outcome). The accuracy of the C-RAI of predicting and discriminating LN activity was assessed by receiver-operating characteristic curve (ROC) analysis.

Results: Means and percentages of the values of LN-TM, clinical indices and RBM levels are summarized inTable1. Based on multivariate logistical regression modeling, histological activity measurement does not necessitate consideration of clinical indices but rather select LN-TM and RBM. Levels of C3, NGAL, CP, MCP1 and TF were found to be candidate C-RAI's for predicting high LN activity (GLAI>10) with outstanding accuracy [area under the ROC curve (AUC) = 0.9]. NGAL and HPX were excellent predictors of high interstitial inflammation with active LN (TIAI > 5; AUC = 0.88) (Figure1).

Conclusion: C3 level, NGAL, CP, MCP1, TF, and HPX are good potential components for C-RAI to measure histological LN activity in the glomeruli and interstitium. Confirmation in a larger data set is required.

Table1 Comparisons of LN biomarkers between NIH GLAI and TIAI classes

	GLAI Score			TIAI Score		
LN biomarkers	**≤ 10**	**> 10**	**p**	**≤ 5**	**> 5**	**p**
SLEDAI-R*	7.45 (6.06, 8.84)	11.93 (10.15, 13.70)	0.000	8.20 (6.75, 9.64)	11.43 (8.96, 13.90)	0.031
BILAG-R*	10.37 (9.52, 11.23)	11.56 (10.48, 12.63)	0.096	10.93 (10.02, 11.83)	10.86 (9.33, 12.38)	0.940
SLICC-RAS*	4.38 (2.75, 6.02)	7.58 (5.57, 9.58)	0.019	5.20 (3.47, 6.92)	5.92 (2.86, 8.98)	0.686
Protein/ Cr ratio*	1.79 (1.20, 2.67)	2.85 (1.74, 4.67)	0.156	1.98 (1.31, 2.97)	2.67 (1.31, 5.42)	0.474
Urine Protein*	185.74 (101.62, 339.49)	423.73 (206.08, 871.27)	0.106	185.43 (107.15, 320.90)	541.85 (221.27, 1,326.88)	0.076
GFR*	115.07 (97.38, 135.97)	75.53 (61.04, 93.47)	0.003	108.48 (94.32, 124.78)	69.64 (54.81, 88.48)	0.003
Serum Cr*	0.63 (0.55, 0.74)	0.99 (0.82, 1.20)	0.001	0.66 (0.58, 0.76)	1.06 (0.85, 1.33)	0.001
C3 level*	64.28 (53.79, 76.82)	41.94 (33.44, 52.60)	0.005	53.31 (43.72, 65.01)	52.35 (37.43, 73.22)	0.928
C3 (Low)**	47.62%	15.38%	0.010	30.00%	28.57%	0.920
C4 level*	9.95 (7.92, 12.50)	6.35 (4.80, 8.41)	0.018	7.63 (6.04, 9.64)	7.67 (5.17, 11.39)	0.982
C4 (Low)**	30.95%	14.81%	0.137	25.00%	21.43%	0.788
DSDNA (Positive)**	16.67%	8.00%	0.334	11.43%	9.09%	0.828
NGAL	0.25 (0.15, 0.43)	0.65 (0.36, 1.17)	0.027	0.30 (0.17, 0.50)	0.93 (0.35, 2.42)	0.052
CP	118 (64, 215)	334 (173, 645)	0.028	199 (108, 367)	266 (87, 813)	0.661
MCP1	5.88 (3.85, 8.97)	24.04 (15.16, 38.10)	0.000	8.99 (5.42, 14.91)	30.25 (12.01, 76.23)	0.033
AGP	561 (232, 1,359)	1,101 (397, 3,057)	0.337	593 (232, 1,516)	3,752 (402, 35,064)	0.153
TGFB*	0.42 (0.26, 0.69)	1.27 (0.86, 1.86)	0.004	0.73 (0.46, 1.17)	1.56 (0.83, 2.91)	0.083
ADI	0.09 (0.03, 0.23)	0.51 (0.17, 1.49)	0.023	0.11 (0.04, 0.28)	1.35 (0.22, 8.33)	0.024
HEPCIDIN	0.55 (0.26, 1.15)	0.66 (0.29, 1.47)	0.753	0.56 (0.26, 1.21)	0.70 (0.15, 3.28)	0.802
LPGDS	2.71 (1.56, 4.70)	5.74 (3.15, 10.48)	0.080	3.24 (1.84, 5.69)	8.04 (2.87, 22.51)	0.141
TF	0.09 (0.05, 0.15)	0.17 (0.10, 0.31)	0.083	0.11 (0.07, 0.19)	0.18 (0.07, 0.45)	0.395
VDBP	5.43 (2.26, 13.07)	6.19 (2.38, 16.14)	0.844	3.95 (1.72, 9.08)	30.18 (6.62, 137.64)	0.030
HPX	17.15 (9.01, 32.65)	35.64 (17.97, 70.70)	0.138	17.52 (9.76, 31.45)	109.68 (35.05, 343.16)	0.010

*: Values in the cells are mean (95% CI);

**: Values in the cells are %.

NGAL: neutrophil gelatinase associated lipocalin, **MCP1**: monocyte chemoattractant protein-1, **CP**: ceruloplasmin**, AGP:** alpha1-acid glycoprotein, **TF:** transferrin**, LPDGS:** lipocalin-like prostaglandin-D Synthase, **ADI:** adiponectin, **HPX:** hemopexin, **TGFB:** TGF-beta, **, VDBP:** vitamin D binding protein.

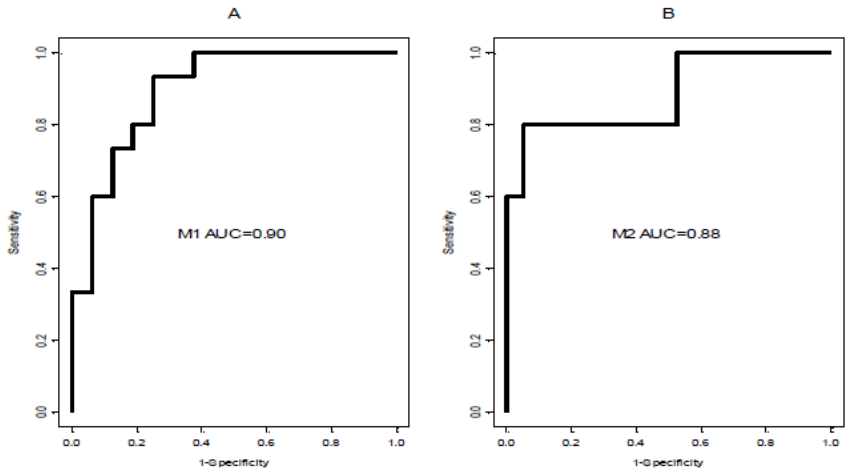

Figure 1 ROC curves of using panels of LN biomarkers to predict LN activity

A. LN activity is defined by GLAI>10. The panel of LN biomarkers is selected through a multivariate logistic model (M1) in the following
   Logit(GLAI>10) = -1.57* Ln(C3)-0.79*Ln(NGAL/Cr)+0.83*Ln(CP/Cr)+1.94*Ln(MCP1/Cr)+0.79*Ln(TF/Cr)+1.88
B. LN activity is defined by TIAI>5. The panel of LN biomarkers is selected through a multivariate logistic model (M2) in the following
   Logit(TIAI>5) = 1.09*Ln(NGAL/Cr)+0.89*Ln(HPX/Cr)-4.14