Development of an Index to Non-invasively Quantify Lupus Nephritis Chronicity in Children

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Background: The current gold standard for assessing chronic changes in Lupus Nephritis (LN) is a kidney biopsy interpreted using the International Societies for Nephrology & Renal Pathology (ISN/RPS) Classification. However, kidney biopsies are invasive, costly and unsuited for close surveillance of LN. The objective of this study was to develop a non-invasive Index to measure LN chronicity or damage, considering both traditional measures of LN (LN-TM) and recently discovered renal biomarkers (RBM).

Methods: In this ongoing prospective study, 70 children with LN were studied at the time of the kidney biopsy for the LN-TM [GFR, anti-dsDNA antibodies, urinary protein/creatinine ratio] and the urine concentrations of the RBM (see Table 1) were measured. Histological findings were rated by a single nephropathologist who provided the NIH chronicity index (NIH CI; range 0-12) which served as the Criterion Standard. Prior to statistical analysis, RBM levels were normalized by urine creatinine and logarithmically transformed. NIH-CI scores ranged from 0 to 12. LN damage was categorized as low (NIH-CI <3) or moderate (NIH-CI >3). LN-TM and the RBM that showed significance in univariate logistic analysis at a p-value<0.20 were considered in exploratory stepwise multivariate logistical regression models as candidate predictors, using the NIH CI as dependent variable (outcome) to assess the combinatorial character of the candidate predictors.

Results: The means and percentages of the values of the LN-TM and RBM levels are summarized (Table1). Based on multivariate logistical regression modeling levels of TGFB, NGAL and GFR (or serum creatinine) but not protein excretion (urinary protein/creatinine ratio) were found to be combinatorial biomarkers of LN damage. Results on the RBM liver-type fatty acid binding protein (LFABP), Kidney Injury Molecule-1 (KIM1) and the receiver operating characteristic curve analyses will be presented.

Conclusion: NGAL, TGBF and GFR are good potential components for Children a Lupus Nephritis Index for Damage (C-LID) to non-invasively measure chronic histological changes in LN in the glomeruli, interstitium and tubules. Further studies with larger numbers of patients are required for further evaluation and confirmation of our finding.

Table1 Comparisons of LN biomarkers between NIH CI Groups

	NIH CI Score		
LN biomarkers	**< 3**	**≥ 3**	p
Protein/ Cr ratio*	1.85 (1.32, 2.59)	3.73 (1.94, 7.18)	0.065
GFR*	***104.39 (90.12, 120.91)***	***72.00 (54.34, 95.40)***	***0.025***
Serum Cr*	0.71 (0.62, 0.81)	1.04 (0.80, 1.35)	0.012
NGAL	***0.33 (0.21, 0.53)***	***0.83 (0.33, 2.08)***	***0.089***
CP	175 (102, 301)	302 (104, 876)	0.377
MCP1	11.37 (7.22, 17.90)	10.86 (4.45, 26.49)	0.930
AGP	929 (416, 2,075)	395 (102, 1,534)	0.298
TGFB*†	***0.69 (0.49, 0.96)***	***3.37 (1.41, 8.06)***	***0.005***
ADI	0.17 (0.07, 0.42)	0.29 (0.05, 1.64)	0.591

HEPCIDIN	0.62 (0.33, 1.17)	0.47 (0.14, 1.56)	0.695
LPGDS	3.76 (2.30, 6.15)	3.92 (1.49, 10.30)	0.942
TF	0.12 (0.07, 0.18)	0.17 (0.07, 0.43)	0.470
VDBP	6.20 (2.94, 13.06)	4.98 (1.15, 21.54)	0.796
HPX	26.57 (15.11, 46.72)	20.24 (7.12, 57.57)	0.657

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

**: Values in the cells are %;

†: N=16, too small sample size for Step 2 analysis.

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.