Accuracy of Laboratory Measures and Clinical Renal Activity Indices for Reflecting Biopsy-proven Lupus Nephritis (LN) Activity

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Background: LN is common in childhood-onset Systemic Lupus Erythematosus (cSLE). Kidney biopsies are impractical to assess the course of LN given their invasiveness and cost. Therefore, traditional laboratory measures [GFR, complement levels, anti-dsDNA antibodies, serum creatinine and urinary protein/creatinine ratio] are used and several clinical indices [Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS), renal domain score of the BILAG (BILAG-R) and SLEDAI (SLEDAI-R)] have been developed: The objective of this study was to validate these traditional non-invasive measures of LN activity in cSLE, using histological activity & severity of LN as criterion standard.

 Methods: The traditional laboratory measures were measured in 83 children with LN at time of the kidney biopsy. The biopsy specimens were rated by a single nephropathologist for LN severity as per International Societies for Nephrology & Renal Pathology (ISN/RPS) class, the NIH glomerular activity Index (GLAI; range 0-24) and the tubulointerstitial activity index (TIAI, range 0-21). For the statistical analysis, LN severity is categorized as Class I/II vs. III/IV vs. V; GLAI score ($\leq$10 vs. >10), or TIAI score ($\leq$5 vs. >5) in fixed effect models and logistical models, respectively.

 Results: Of the 83 kidney biopsies, 12%, 60% and 28%, of the patients had class I/II, III/IV and V, respectively. The median scores of the GLAI and TIAI are summarized (Table 1). SLEDAI-R and SLICC-RAS, but not BILAG-R was positively associated to the ISN/RPS classification (Table 2). In particular, higher SLEDAI-R and serum creatinine level and lower GFR level was found in patients with LN inflammatory activity (GLAI > 10 or TIAI >5). Similar patterns were also noticed in patients with ISN/RPR Class III/IV being compared against those with ISN/RPR Class V.

Conclusion: Of the currently used measures to assess LN in routine daily practice, the SLEDAI-R and the GFR appears to best reflect inflammatory LN activity in both the glomerulus and the interstitium of pediatric populations.

Table1. Summary of GLAI, TIAI and ISNPR CLASS in cSLE Cohort

Score	Stat Type	Statistics
GLAI score	Median (range)	6 (0, 22)
	Freq (%) of score>10	27/71 (38.0%)
TIAI score	Median (range)	4 (0, 11)
	Freq (%) % of score>5	14/55 (25.5%)
ISNPR CLASS	I/II	10 (12.05%)
	III/IV	50 (60.24%)
	V	23 (27.71%)

Table2 Traditional LN measures validated by LN biopsy

Traditional LN measure	ISNRP Class			GLAI Score		AITI Score	
	I/II	III/IV	V	≤ 10	> 10	≤ 5	> 5
SLEDAI-R*	6.80 (3.75, 9.85)	10.20 (8.84, 11.56)#	6.78 (4.77, 8.79)	7.45 (6.06, 8.84)	11.93 (10.15, 13.70)‡	8.20 (6.75, 9.64)	11.43 (8.96, 13.90)‡
BILAG-R*	10.10 (8.26, 11.94)	11.20 (10.38, 12.02)	9.86 (8.62, 11.11)	10.37 (9.52, 11.23)	11.56 (10.48, 12.63)	10.93 (10.02, 11.83)	10.86 (9.33, 12.38)
SLICC-RAS*	3.11 (0.45, 6.67)	6.96 (5.42, 8.50)	5.83 (3.32, 8.35)	4.38 (2.75, 6.02)	7.58 (5.57, 9.58)	5.20 (3.47, 6.92)	5.92 (2.86, 8.98)
Protein/ Cr ratio*	1.89 (0.79, 4.56)	1.93 (1.35, 2.75)	3.05 (1.77, 5.25)	1.79 (1.20, 2.67)	2.85 (1.74, 4.67)	1.98 (1.31, 2.97)	2.67 (1.31, 5.42)
Urine Random Protein*	177 (31, 1,030)	246 (139, 434)	278 (48, 1,612)	186 (102, 339)	424 (206, 871)	185 (107, 321)	542 (221, 1,327)
GFR*	111 (79, 158)	84 (72, 98)	133 (105, 168)†	115 (97, 136)	76 (61, 93)‡	108. (94, 125)	70 (55, 88)‡
Serum Cr*	0.56 (0.41, 0.76)	0.90 (0.78, 1.03)#	0.60 (0.49, 0.73)	0.63 (0.55, 0.74)	0.99 (0.82, 1.20)‡	0.66 (0.58, 0.76)	1.06 (0.85, 1.33)‡
C3 level*	55.65 (38.31, 80.84)	47.77 (40.28, 56.64)	73.12 (56.51, 94.60)†	64.28 (53.79, 76.82)	41.94 (33.44, 52.60)‡	53.31 (43.72, 65.01)	52.35 (37.43, 73.22)
C3 (Low)**	40.00%	27.08%	57.14%†	47.62%	15.38%†	30.00%	28.57%
C4 level*	7.42 (4.77, 11.54)	7.17 (5.86, 8.78)	12.29 (9.06, 16.66)†	9.95 (7.92, 12.50)	6.35 (4.80, 8.41)‡	7.63 (6.04, 9.64)	7.67 (5.17, 11.39)
C4 (Low)**	20.00%	12.24%	52.38%†	30.95%	14.81%	25.00%	21.43%
DSDNA (Positive)**	0.00%	10.64%	36.84%†	16.67%	8.00%	11.43%	9.09%

*: Values in the cells are mean (95% CI);
**: Values in the cells are %;
#: The ISNRP Class=III/IV group is different from other two groups;
†: The ISNRP Class=V group is different from the III/IV group;
‡: The GLAI Score > 10 (or AITI >5) group is different from the GLAI Score ≤ 10 (or TIAI Score ≤ 5) group.