

Serum Albumin as a Marker for Disease Activity in Patients with Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* To determine whether serum albumin reflects disease activity in patients with systemic lupus erythematosus (SLE) with and without nephritis (LN, LNN), and whether serum albumin could be a surrogate marker of SLE disease activity overall. There is currently no clinical “gold standard” in the assessment of disease activity in SLE.

Methods. Patients with ≥ 3 clinic visits within a maximum followup period of 10 years were selected from the University of Toronto Lupus Clinic database. Subjects were divided into 3 groups: LN-B, those with nephritis defined by histological findings on renal biopsies; LN-L, those with nephritis defined by laboratory abnormalities in the absence of biopsy; and LNN, those without nephritis. In a subanalysis, the renal groups were further stratified by proteinuria status. The associations of SLE-Disease Activity Index (SLEDAI-2K) with serum albumin and dsDNA were examined using the mixed model regression analysis.

Results. A total of 1078 patients were studied: 89.1% female, 71.5% white, mean age 33.6 (SD 12.6) years, and with median baseline SLEDAI-2K of 8. Serum albumin was more significantly associated with SLEDAI in LN-B and LN-L. The association was also present but weaker in the LNN group. In all LN, the associations between serum albumin and SLEDAI-2K were stronger in those with proteinuria.

Conclusion. In patients with SLE, higher SLEDAI was associated with lower serum albumin levels. (First Release June 1 2010; J Rheumatol 2010;37:1667–72; doi:10.3899/jrheum.091028)

Key Indexing Terms:

ALBUMIN BIOMARKER LUPUS NEPHRITIS SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies and the presence of systemic inflammation. Although SLE can affect virtually any tissue or organ, there is considerable variation in presentation and organ involvement among patients.

Currently there is no universally accepted “clinical gold standard” to measure disease activity, but the measurement of serum levels of anti-double-stranded DNA antibodies (dsDNA) is widely used as it has been shown to be a good predictor of outcome in lupus nephritis (LN)¹. However, the observation of persistently elevated dsDNA antibody titers in a substantial number of patients with SLE independent of changes in disease activity, as well as dsDNA-negative titers in others, limits its value as a biomarker². Other markers including products of complement activation (e.g., C3 and C4), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and cytokines [e.g., interleukin 10 (IL-10), IL-2/IL-2 receptor, and IL-6] have also been used as indirect serological markers in SLE, but they have had varying degrees of significance and generally do not correlate well with disease activity³. Further, from a cost-analysis perspective, tests measuring CRP, C3, C4, and dsDNA antibody levels are very costly⁴. An inexpensive and clinically reliable serological marker for disease

activity would therefore be useful to guide therapy and gauge responses to treatment.

Serum albumin is routinely measured in patients with SLE as part of standard biochemical profiles. Lower than normal levels have been frequently reported in SLE^{5,6,7}. A low serum albumin level may be a result of increased albumin catabolism due to chronic inflammation and/or because of inadequate protein and caloric intake in patients with SLE⁸. In addition, nephritis, a common manifestation of SLE, may lead to nephrotic range proteinuria, which in turn lowers serum albumin levels. This rationale has prompted clinicians to use serum albumin to indirectly assess LN activity and direct its therapy⁹. Serum albumin has been shown to predict the outcome of individuals with rheumatoid arthritis, pneumonia, acute ischemic stroke, and glomerulonephritis and patients on dialysis as well as community-dwelling elderly persons and patients undergoing surgery^{10,11,12,13,14}. The purpose of this study was to determine whether serum albumin can be used as a marker of disease activity in SLE.

MATERIALS AND METHODS

Patients were selected from the patient database at the University of Toronto Lupus Clinic (UTLC). Since 1970, the UTLCL has prospectively followed patients who fulfilled at least 4 of the 1971 or 1982 American College of Rheumatology (ACR) classification criteria¹⁵, or 3 ACR criteria plus histological evidence of SLE on renal or skin biopsy. Analysis was restricted to patients who had 3 or more clinic visits within a maximum followup period of 10 years, and who were still alive at the time of the analysis. All patients gave their informed consent and were followed according to a standard protocol. The protocol has had continuous approval from the University Health Network Research Ethics Board.

Serum albumin (normal range 35–45 g/l), dsDNA (Farr assay, > 7 U/ml = abnormal), and SLE Disease Activity Index (SLEDAI-2K) score, a validated measure of lupus disease activity¹⁶, were obtained at baseline and at each followup visit. A SLEDAI-2K score of 6 or more was considered clinically active disease¹⁷. Also for each clinic visit, a modified SLEDAI-2K was calculated, removing the dsDNA item from the original SLEDAI-2K score, which served to dissociate the anti-dsDNA antibody component from the remainder of the SLEDAI-2K disease activity. The SLEDAI-2K was used for comparisons between the performance of serum albumin and that of anti-dsDNA antibody. We decided to remove the dsDNA component of the SLEDAI-2K because we presumed the correlation analysis between dsDNA and the intact SLEDAI could lead to a high correlation that would not be informative about disease activity outside of the presence or absence of dsDNA. But in fact the associations between complete SLEDAI and modified SLEDAI and dsDNA were similar. Other data retrieved from the database included age, body mass index (BMI), ethnicity, SLE duration, presence of renal involvement, and laboratory variables including serum creatinine at every visit (usually at mean intervals of 4 mo), 24-h urine protein, and presence of urinary casts when available. Since serum albumin levels have been shown to decrease with renal involvement and advanced age^{10,13,14}, the patient cohort was stratified for our purposes according to renal status and the presence of proteinuria. Age was included in the mixed model statistical analyses as a covariate. Patients were stratified by renal status into 3 groups: LN defined by histological findings on renal biopsies (denoted LN-B), LN defined by laboratory abnormalities in the absence of renal biopsy (LN-L; proteinuria > 0.5 g/24 h and/or presence of urinary cellular casts ever), and no renal abnormalities (LNN). In another analysis, the relationship between serum albumin and SLEDAI-2K was examined in LN-B and LN-L patients with and without proteinuria. Since 24-h urine protein or casts results were not available for all patients or for all visits, patients were classified as hav-

ing proteinuria or urinary cellular casts if they ever had abnormal results during their followup period.

Statistical analysis. Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA, 1983, version 12) and SAS (SAS Institute, Cary, NC, USA, version 9.1). When comparing LN and LNN, the t-test and the Wilcoxon rank-sum test were used for continuous variables, and the chi-square test and Fisher's exact test for categorical variables. The associations between SLEDAI-2K/modified SLEDAI-2K and serum albumin, as well as with dsDNA, were examined using the mixed model analysis, which accounted for multiple measures over time and within and between subject variations. As a measure of these multivariate associations, the new R^2 (R^2_{β}) statistic proposed by Edwards, *et al*¹⁸ was used, where the Kenward-Roger F and a random intercept covariance structure were considered. The square root of R^2_{β} is denoted as *r*. Various covariance structures were considered, and the final choice was based on the Akaike Information Criteria¹⁹. For all tests and CI, the significance level was set at 5%.

RESULTS

A total of 1441 patients were followed prospectively and according to a standard protocol since January 1, 1970. Of these, 1078 patients met the inclusion criteria for our study. Baseline characteristics of subjects are reported in Table 1. Women made up 89.1% (n = 961) of the cohort, and the majority of subjects were white (71.5%) followed by African Americans and Chinese. The mean followup duration was 6.1 (SD 3.4) years, and mean SLE duration at baseline was 3.9 (SD 5.7) years and at the end of the followup period 10.0 (SD 6.3) years. Patients had a mean BMI (kg/m²) of 24.4 ± 6.0 at baseline as well as a median of 14 (interquartile range 7.0–24.0) clinic visits during their followup period at the time of data analyses.

Comparison between LN and LNN. In our cohort, 529 patients were diagnosed with LN (290 LN-B + 239 LN-L) and 372 (70.3%) had proteinuria at some point during the course of their followup. LN and LNN groups were similar with respect to age distribution (Table 2). However, the LN group had sig-

Table 1. Baseline characteristics of study subjects.

Characteristics	Cohort, n = 1078
Women, n (%)	961 (89)
Race, n (%)	
White	737 (71)
African Americans	107 (10)
Chinese	100 (10)
Filipino	31 (3)
Other/missing	103 (6)
Age, yrs. (range)	33.6 ± 12.6 (13.4–81.1)
Patients > 50 yrs, n (%)	124 (12)
SLE duration, yrs. (range)	3.9 ± 5.7 (0–51.8)
SLEDAI-2K, median (IQR)	8.0 (4.0–13.0)
Serum albumin, g/l (range)	39.0 ± 7.1 (11–78)
Patients with lupus nephritis, n (%)	529 (49)
Biopsy-proven	290 (27)
By laboratory criteria	239 (22)
Anti-ds-DNA antibody by Farr assay, U/ml, median (IQR)	17.0 (6.0–41.0)

SLEDAI-2K: SLE Disease Activity Index 2000.

Table 2. Characteristics of patients with and without lupus nephritis (LN). Results are mean (SD) or percentage unless stated otherwise.

	LN by Biopsy, n = 290	LN, n = 529 LN by Laboratory Results, n = 239	All LN, n = 529	LNN, n = 549	p Between LN and LNN
Age at baseline, yrs	30.6 ± 10.8	34.9 ± 12.8	32.5 ± 11.9	34.6 ± 13.2	0.008
Patients age ≥ 50 yrs, %	5.5	14.6	9.6	13.3	0.060
Women, %	87.6	80.4	84.3	93.8	0.0001
SLE duration at last visit, yrs	10.4 ± 5.4	10.9 ± 7.3	10.6 ± 6.3	9.4 ± 6.3	0.0013
Followup, yrs	6.9 ± 3.1	6.4 ± 3.3	6.7 ± 3.2	5.6 ± 3.4	0.0001
Baseline SLEDAI, median (IQR)	10.0 (6.0, 16.0)	8.0 (4.0, 13.0)	9.0 (6.0, 15.0)	6.0 (4.0, 10.0)	0.0001
Baseline serum albumin, g/l	36.3 ± 7.8	37.6 ± 7.4	36.9 ± 7.6	41.0 ± 5.9	0.0001
Baseline ds-DNA, U/ml, median (IQR)	24.0 (10.0, 58.0)	22.0 (6.0, 51.0)	22.0 (8.0, 53.0)	12.0 (4.0, 34.0)	0.0001

nificantly more women, longer followup periods, longer SLE duration, higher baseline SLEDAI-2K, and higher baseline dsDNA levels compared to LNN (Table 2). Baseline serum albumin was lower in LN compared to LNN (Table 2). Further, patients with LN who had proteinuria had lower serum albumin levels compared to those with LN without proteinuria (35.2 ± 7.6 vs 40.9 ± 6.1 g/l; $p < 0.0001$). LN-B and LN-L groups were similar in duration of followup, SLE duration at last visit, baseline dsDNA, and baseline albumin. However, the LN-B group was significantly younger and had a higher baseline SLEDAI compared to the LN-L group.

Associations. Based on the mixed model approach, while including age as a covariate, there were significant ($p < 0.01$) associations between serum albumin and SLEDAI-2K in all LN-B ($r = -0.62$) and all LN-L ($r = -0.59$) as well as in LN-B

($r = -0.62$) and LN-L ($r = -0.63$) with proteinuria. Although statistically significant, these associations were weaker in LN-B ($r = -0.43$) and in LN-L ($r = -0.41$) without proteinuria, and in those without LN ($r = -0.30$).

Figure 1 represents the mixed model output showing the relationships between serum albumin and SLEDAI-2K in LN-B, LN-L, and LNN, adjusted for age at each visit. Serum albumin was significantly associated with SLEDAI-2K in LN-B ($\beta = -0.30$, $p < 0.0001$) and LN-L ($\beta = -0.28$, $p < 0.0001$) and less so in LNN ($\beta = -0.10$, $p < 0.0001$). Our results for the same association between serum albumin and the modified SLEDAI-2K did not differ qualitatively or markedly quantitatively (data not shown).

Figure 2 represents the mixed model output showing the relationships between serum albumin and SLEDAI-2K in

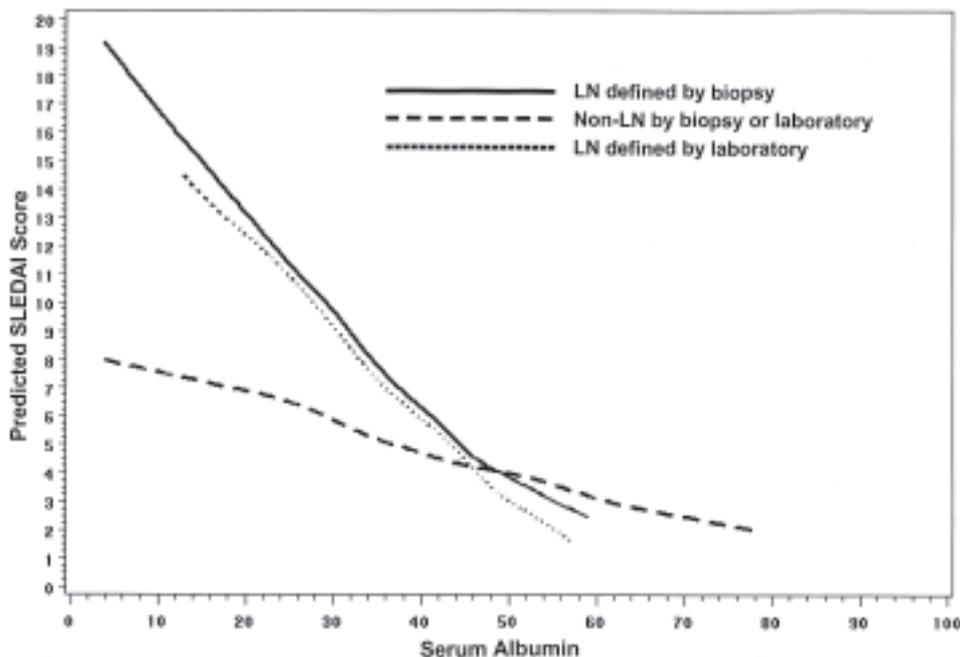


Figure 1. Relationship between serum albumin and SLEDAI-2K stratified by renal status.

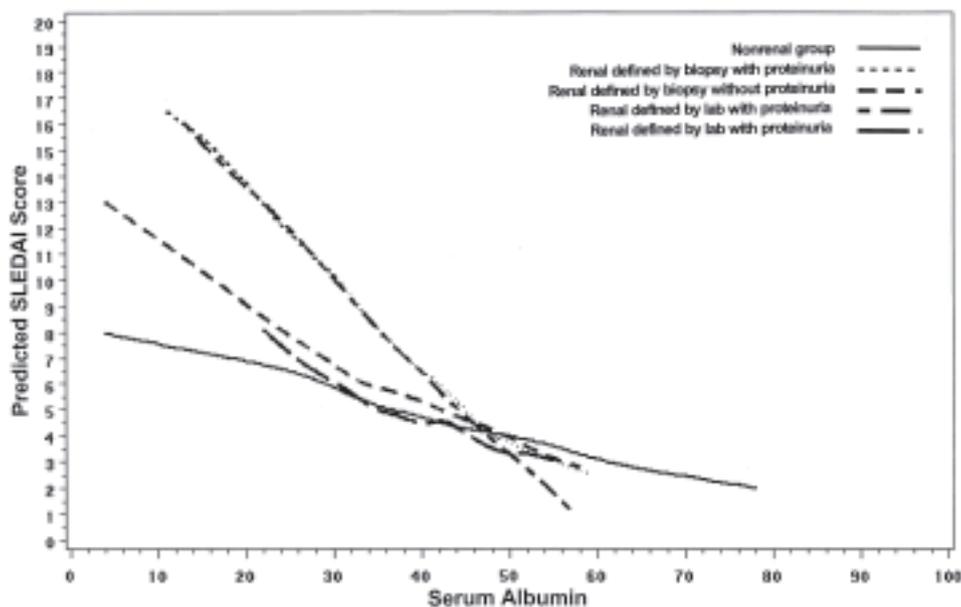


Figure 2. Relationship between serum albumin and SLEDAI-2K stratified by renal status and proteinuria.

LNN, LN-B, and LN-L with and without proteinuria, adjusted for age at each visit. Within this analysis, serum albumin was significantly associated with SLEDAI-2K in LN-B + proteinuria ($\beta = -0.32$, $p < 0.0001$), LN-L + proteinuria ($\beta = -0.33$, $p < 0.0001$); LN-B without proteinuria ($\beta = -0.17$, $p < 0.0001$), LN-L without proteinuria ($\beta = -0.13$, $p < 0.0001$), and less so in LNN ($\beta = -0.10$, $p < 0.0001$). Based on these relationships, a suboptimal albumin level of 30 g/l would be associated with a SLEDAI of 10 in LN+ proteinuria, 7 in LN- proteinuria, and 6 in LNN. Given that SLEDAI-2K ≥ 6 reflects active disease, we can appreciate that a serum albumin level of 30 g/l would be expected to be associated with clinically active SLE in patients with nephritis, but not necessarily so in patients without nephritis.

With regard to dsDNA, there were also significant ($p < 0.01$) moderate associations at each visit between serum dsDNA and SLEDAI-2K in LN-B ($r = 0.62$), LN-L ($r = 0.57$), and in LNN ($r = 0.43$).

Figure 3 represents the mixed model output showing the relationships between modified SLEDAI-2K and dsDNA, in LN-B, LN-L, and LNN groups adjusted for age at each visit. The mixed model analysis also showed that dsDNA was significantly associated with the modified SLEDAI-2K in LN-B patients ($\beta = 0.06$, $p < 0.0001$), LN-L ($\beta = 0.04$, $p < 0.0001$), and LNN patients ($\beta = 0.02$, $p < 0.0001$). Using the complete SLEDAI, there were also significant associations between SLEDAI-2K and dsDNA in all 3 groups (data not shown).

DISCUSSION

We found a significant inverse association between serum albumin and disease activity assessed by SLEDAI-2K, with lower serum albumin levels associated with higher levels of SLE disease activity. The clinical implications of these results

are that hypoalbuminemia alone will not be the ideal biomarker to identify disease activity in SLE. It may, however, be a useful screening test and guide in patients with LN. Hypoalbuminemia is common in patients with SLE^{5,6,7} and it has been correlated to poorer prognoses in SLE and other diseases such as ischemic heart disease, diabetes mellitus, and hypertension^{7,20}. The association between SLEDAI-2K and serum albumin was strongest for subjects with SLE who had LN compared to those without LN, and especially in LN with proteinuria. Clinicians have traditionally based LN activity and its therapy on the results of urinary protein excretion and creatinine clearance⁹. A reliable measure of proteinuria such as that derived from a 24-h urine collection was not routinely done in every patient and therefore could not be used to differentiate how much of the hypoalbuminemia was attributable to the proteinuria and how much to the inflammatory disease. Hence, the clinical utility of serum albumin as a marker for disease activity in SLE-related nephritis has not been studied. Our results suggest that serum albumin may be a good screening test that would prompt the ordering of a 24-h urine collection for proteinuria in patients with SLE.

Several factors may affect the serum albumin level. Serum albumin has been reported to decline with advanced age and is shown to be a reliable predictor of all-cause mortality in the elderly^{13,14}. Based on this, we included age as a covariate in our mixed model analysis. Severe protein deficiency and energy-protein malnutrition can also contribute to a low serum albumin level. However, in our study, all patients had a Western diet and had a BMI > 18 and therefore a low serum albumin level due to malnutrition was unlikely. Proteinuria is another factor that can influence serum albumin level. However, proteinuria is part of the SLE disease process and reflects renal disease activity. It was our intention to deter-

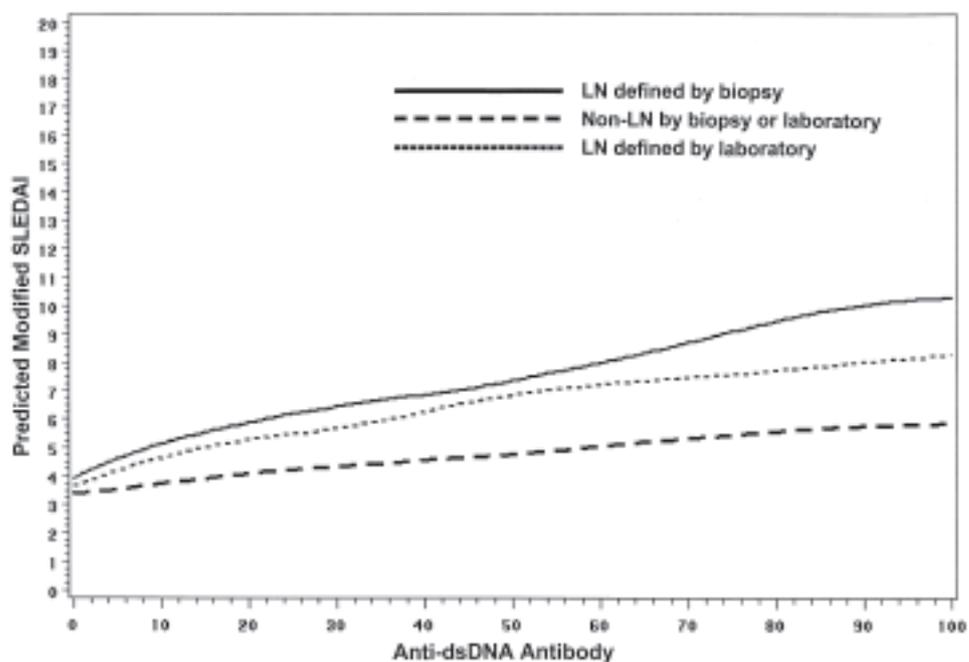


Figure 3. Relationship between anti-double-stranded DNA antibody and modified SLEDAI-2K (dsDNA excluded) stratified by renal status.

mine whether serum albumin level correlates with proteinuria and coincides with SLE disease activity. Our study in fact showed a stronger inverse relationship between serum albumin and SLEDAI-2K in patients with LN who had proteinuria.

Studies on the use of albumin in measuring SLE disease activity have primarily focused on urinary albumin. However, its validation as a biomarker has not been successful to date. In one study that aimed to identify potential markers in active pediatric LN, albuminuria was identified within the urinary protein signature, but further assessment was limited due to difficulties in protein extraction⁹. It has also been reported that albumin excretion rates have failed to reflect renal histology in patients with LN, and microalbuminuria was inadequate to predict subsequent development of clinical LN in subjects who initially did not have renal disease^{21,22,23}. Finally, albuminuria appeared to be more costly and offered no advantage over total proteinuria in diagnosing proteinuric renal flares in SLE because protein-creatinine and microalbumin-creatinine were highly correlated over the designated ranges for SLE glomerulonephritis flares²³.

Our study has some limitations. Data on 24-h urine protein were not available for every patient and/or at every clinic visit and therefore the categorization of proteinuria was based on the presence of abnormal 24-h urine protein ever during the followup period, which may not truly reflect renal disease activity at every visit. In addition, the graphical representations generated by the mixed model apply an average correlation within each subgroup. This means that a serum reading

would only provide an estimate of SLE disease activity based on a group average, but this should not override clinical judgment in the interpretation of these results. Perhaps a change in serum albumin would provide more useful information on disease activity rather than the absolute levels of serum albumin. Further, the subjects for this study were selected from those attending an academic hospital center and therefore these results may not be generalizable to the entire SLE population, such as those followed in community practices or in particular those seen in developing countries where protein-energy malnutrition is a common problem. However, our clinic includes patients from the community, as our center has been the sole resource for a large urban area for almost 30 years.

In our study, we found weak but significant associations between serum albumin and SLEDAI-2K in patients without renal disease. Further, we observed a clear demarcation between the 2 LN groups and the LNN group with mutual exclusion of the respective CI of the regression coefficients. Similarly, dsDNA was most significantly associated with disease activity in the LN groups. Using a modified SLEDAI-2K excluding dsDNA or the original complete SLEDAI-2K did not significantly alter the results of these association studies. Currently, dsDNA is widely used as a marker for disease activity in SLE, but it is expensive to measure and there is little consensus on its value as a biomarker because of inconsistent findings in its association with disease activity^{1,4}. On the other hand, serum albumin is routinely measured and is an inexpensive test to perform⁴.

We demonstrated that serum albumin is inversely associat-

ed with SLE disease activity and this association was stronger in those with LN and especially in those with proteinuria. Future studies are needed to assess the clinical utility of serum albumin as a marker for global SLE and/or renal disease activity.

REFERENCES

1. Illei GG, Tackey E, Lapteva L, Lipsky PE. Biomarkers in systemic lupus erythematosus – II. Markers of disease activity. *Arthritis Rheum* 2004;50:2048-65.
2. Horak P, Scudla V, Hermanova Z, Pospisil Z, Faltynek L, Budikova M, et al. Clinical utility of selected disease activity markers in patients with systemic lupus erythematosus. *Clin Rheumatol* 2001;20:337-44.
3. Boehme MWJ, Raeth U, Galle PR, Stremmel W, Scherbaum WA. Serum thrombomodulin — a reliable marker of disease activity in systemic lupus erythematosus (SLE): advantage over established serological parameters to indicate disease activity. *Clin Exp Immunol* 2000;119:189-95.
4. Shojania K. *Rheumatology: 2. What laboratory tests are needed?* *Can Med Assoc J* 2000;162:1157-63.
5. Wallace DJ, Hahn BH. Serum and plasma protein abnormalities and other clinical laboratory determinations in systemic lupus erythematosus. In: Wallace DJ, Hahn BH, Quismorio FP Jr, Klinenberg JR, editors. *Dubois' lupus erythematosus*. Philadelphia: Lippincott Williams & Wilkins; 2006:911-9.
6. Sule SD, Fadrowski JJ, Fivush BA, Gorman G, Furth SL. Reduced albumin levels and utilization of arteriovenous access in pediatric patients with systemic lupus erythematosus (SLE). *Pediatr Nephrol* 2007;22:2041-6.
7. Huang ST, Chen GY, Wu CH, Kuo CD. Effect of disease activity and position on autonomic nervous modulation in patients with systemic lupus erythematosus. *Clin Rheumatol* 2008;27:295-300.
8. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial* 2004;17:432-7.
9. Suzuki M, Wiers K, Brooks EB, Greis KD, Haines K, Klein-Gitelman MS, et al. Initial validation of a novel protein biomarker panel for active pediatric lupus nephritis. *Pediatr Res* 2009;65:530-6.
10. Margaron MP, Soni N. Serum albumin: touchstone or totem? *Anaesthesia* 1998;53:789-803.
11. Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome. *Stroke* 2004;35:E156-8.
12. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum-albumin level and physical disability as predictors of mortality in older persons. *JAMA* 1994;272:1036-42.
13. Gomi I, Fukushima H, Shiraki M, Miwa Y, Ando T, Takai K, et al. Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. *J Nutr Sci Vitaminol* 2007;53:37-42.
14. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 1999;134:36-42.
15. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. Special Article – the 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
16. Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. *J Rheumatol* 2002;29:288-91.
17. Abrahamowicz M, Fortin PR, du Berger R, Nayak V, Neville C, Liang MH. The relationship between disease activity and expert physician's decision to start major treatment in active systemic lupus erythematosus: A decision aid for development of entry criteria for clinical trials. *J Rheumatol* 1998;25:277-84.
18. Edwards LJ, Muller KE, Wolfinger RD, Qaqish BF, Schabenberger O. An R2 statistic for fixed effects in the linear mixed model. *Stat Med* 2008;27:6137-57.
19. Littell RC, Stroup WW, Freund RJ. *SAS for linear models*. 4th ed. Cary, NC: SAS Institute Inc.; 2002.
20. Straub RH, Zeuner M, Lock G, Rath H, Hein R, Scholmerich J, et al. Autonomic and sensorimotor neuropathy in patients with systemic lupus erythematosus and systemic sclerosis. *J Rheumatol* 1996;23:87-92.
21. Battle-Gualda E, Martinez AC, Guerra RA, Pascual E. Urinary albumin excretion in patients with systemic lupus erythematosus without renal disease. *Ann Rheum Dis* 1997;56:386-9.
22. de Almeida RV, de Carvalho JGR, de Azevedo VF, Mulinari RA, Ioshhi SO, Utiyama SD, et al. Microalbuminuria and renal morphology in the evaluation of subclinical lupus nephritis. *Clin Nephrol* 1999;52:218-29.
23. Birmingham DJ, Rovin BH, Shidham G, Bissell M, Nagaraja HN, Hebert LA. Relationship between albuminuria and total proteinuria in systemic lupus erythematosus nephritis: Diagnostic and therapeutic implications. *Clin J Am Soc Nephrol* 2008;3:1028-33.