



The Association Between Erythrocyte Sedimentation Rate, C3, C4, Anti-dsDNA Levels, and Renal Disease Activity, Based on BILAG Index in Females With Lupus Nephritis

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that involves many organs, such as the kidneys. Females are most affected and early detection of renal disease activity is very important for morbidity and mortality reduction.

Objectives: The aim of this study was to determine the relationships between ESR, C3, C4, and anti-dsDNA levels and renal disease activity, based on renal components of the British Isles lupus assessment group (BILAG) index, in females with lupus nephritis (LN).

Methods: This study retrospectively reviewed the medical files of 150 females, diagnosed as LN, who were on routine follow-up at Hafez hospital lupus clinic located in Shiraz, Southern part of Iran (during years 2014 to 2015). The BILAG index score was extracted and data was analyzed ($\alpha = 0.05$).

Results: In all 150 females with SLE, the mean (SD) age was 37.1 (10.6) years. There were significant relationships between BILAG index score and higher ESR level (P value = 0.01), positive anti-dsDNA (P value < 0.001) and low C4 level (P value = 0.003), statistically. However, the results were not significant for mild level of ESR and low level of C3.

Conclusions: This study confirmed that the BILAG index score was a valuable predictive index for renal disease involvement in females with LN; thus the authors suggest clinicians to use this index for better LN management.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, ESR, C3, C4, Anti-dsDNA, BILAG Index

1. Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory, multisystem disease with unknown etiology, with various clinical and serological manifestations. In this disease, autoantibodies are produced and females are most affected (1-4). The prevalence of SLE is different in various parts of the world, 20 to 150 per 100000 population, with different characteristics (5-7). In Iranian patients, renal involvement is more common than in other countries (4). This may depend on genetic and environmental factors (8). The prevalence of SLE is 40 per 100000 individuals in Iran (4).

In 1982, the American college of rheumatology (ACR) developed a classification criterion for diagnosis of SLE, which was updated during 1997. During the interval of observations, if a patient had 4 or more of the 11 criteria, ei-

ther serially or simultaneously, he was diagnosed with SLE (9, 10). In the US, about 35% of patients with SLE had clinical evidence of Lupus Nephritis (LN) at the time of diagnosis and during the first 10 years of disease, 50% to 60% of which developed to nephritis (11). Also, LN leads to a reduction of about 88% of 10 years' survival (12).

Laboratory tests, such as elevation of erythrocyte sedimentation rate (ESR) and anti-double stranded DNA antibodies (anti-dsDNA), and decreased serum levels of complement components (C3 and C4), are suggested for disease activity assessment, disease flares prediction, and monitoring of organ-specific complications (13-16). The elevation of ESR is strongly associated with SLE activity, as well as, high anti-dsDNA (14, 15). Low C3 and C4 levels often represent active SLE, particularly Lupus Nephritis (LN) (15). In these patients, any sign of renal involvement has an

Table 1. Cross-Tabulation of All Scores on British Isles Lupus Assessment Group Index and Erythrocyte Sedimentation Rate, C3, C4, Anti-dsDNA

	Variables	BILAG				P Value
		A	B	C	D	
ESR	Normal (< 25 mm/hour), No. (%)	12 (31.6)	22 (39.3)	14 (58.3)	25 (78.1)	< 0.0001
	Mild elevation (25 ≤ ESR < 50 mm/hr), No. (%)	9 (23.7)	15 (26.8)	7 (29.2)	6 (18.8)	
	Moderate elevation (50 ≤ ESR < 75 mm/hour), No. (%)	5 (13.2)	12 (21.4)	3 (12.5)	0 (0)	
	Marked elevation (75 mm/hour ≤), No. (%)	12 (31.6)	7 (12.5)	0 (0)	1 (3.1)	
C3	Normal (0.85 - 1.9 g/L), No. (%)	14 (36.8)	23 (41.1)	20 (83.3)	24 (75)	< 0.0001
	Low (< 0.85 g/L), No. (%)	24 (63.2)	33 (58.9)	4 (16.7)	8 (25)	
C4	Normal (0.1 - 0.4 g/L), No. (%)	10 (26.3)	19 (33.9)	19 (79.2)	28 (87.5)	< 0.0001
	Low (< 0.1 g/L), No. (%)	28 (37.7)	37 (66.1)	5 (20.8)	4 (12.5)	
Anti-dsDNA	Negative (< 30 IU/mL), No. (%)	6 (15.8)	19 (33.9)	19 (79.2)	25 (78.1)	< 0.0001
	Positive (> 35 IU/mL), No. (%)	32 (84.2)	37 (66.1)	5 (20.8)	7 (21.9)	

indication for first renal biopsy, in order to achieve pathological assessment (17). In 2003, the international society of nephrology/renal pathology society (ISN/RPS) published a classification system for LN (18). Approximately, 10% to 30% of patients with LN progressed to end stage renal disease (ESRD) during 15 years of diagnosis, which enforced them to dialysis or transplantation (17). Quality of life in patients on hemodialysis are worse than the normal population (19).

Therefore, assessing SLE disease activity is important, however, there is no agreement on meaning of disease activity and how it is measured (20). There are 6 indexes for assessing SLE activity (21), one of which is the British Isles lupus assessment group (BILAG) index. This is an easy and quick ordinal scale index, which is based on 9 group manifestations evaluation over the previous 4 weeks, and it was updated in 2005 (21-23). The test reliability was evaluated and high sensitivity (87%), specificity (99%), and positive predictive values (80%) were reported (23). In the BILAG index, the activity of each organ system is scored as: A, most active disease; B, intermediate activity; C, mild, stable disease; D, previous involvement, currently inactive, and E, no previous activity. Also, the BILAG index is used to evaluate the occurrence of flares: severe flare is defined as score A, new appearance and a moderate flare as B, and recurrence as D or E (21). Therefore, it was decided to determine the relationships between ESR, C3, C4, anti-ds-DNA levels and renal disease activity, based on renal components of the BILAG index, in females with lupus nephritis.

2. Methods

This study was approved by the vice-chancellor of research and technology, as well as the ethics committee (IR.SUMS.MED.REC.1394.s491) of Shiraz University of Medical Sciences. This was a cross-sectional study (from April 2014 to December 2015) that was conducted on medical files of patients at the lupus clinic of Shiraz Hafez hospital, as a governmental and biggest referral clinic in Southern Iran.

The study included all females, who were referred to this clinic between 2003 and 2015, and diagnosed as SLE, according to updated American college of rheumatology (ACR) criteria (9-10), and their disease was classified by one specific rheumatologist. Their laboratory tests were done at least 2 times. All patients were excluded from the study if they were pregnant, had an infectious disease, were ESRD according to pathology reports (LN class VI), without biopsy, and had a malignancy (24, 25). Among all patients with SLE on routine follow up at this clinic, patients with renal involvement, who had a renal biopsy (diagnosed as LN), were selected (18). The researchers used a data collecting form including all data required for determining the BILAG index score, such as complete urine analysis, 24-hour urine protein, blood urea nitrogen (BUN), Creatinine (Cr), blood pressure, glomerular filtration rate (GFR), renal biopsy, erythrocyte sedimentation rate (ESR), C3, C4, and anti-dsDNA levels. All patient information was kept confidential.

By using the NCSS PASS software for Windows, version 11 ($\beta = 10\%$, confidence interval = 95%, effect size = 0.35, and $df = 6$), it was determined that at least 145 patients were required as the sample size (according to 4 main variables: C3, C4, ESR and anti-ds DNA) (26), yet 150 patients were se-

lected considering drop outs. From 1200 medical files, one patient was selected from every 8 medical files, by using systematic random sampling. If the patient met the exclusion criteria, the next medical file was selected. It is noticeable that all medical files were assessed by one of the researchers.

Only renal disease activity was assessed with the BILAG index, thus 4 categorical scores were possible (A, B, C and D) (21). The ESR, C3, C4, and anti-dsDNA levels were the variables of this study. For the purpose of statistical analysis, variables were divided to ordinal categories: for ESR, the categories were normal (0 to 25 mm/hour), mildly elevated (25 to 50 mm/hour), moderately elevated (50 to 75 mm/hour), and markedly elevated (more than 75 mm/hour). For C3 and C4 levels, the categories were normal and low. For anti-dsDNA level, the categories were normal and positive. All data were analyzed by the SPSS software for Windows, version 22, and using descriptive and analytical tests, such as analysis of variance (ANOVA), Chi-square test for trend, univariate and multivariate ordinal logistic regression and Chi-square tests for contingency tables. P values of less than 0.05 were considered significant.

3. Results

Out of all patients, 38 (25.3%) patients had a BILAG index score of A, 56 patients (37.3%) B, 27 patients (16%) C, and 32 patients (21.3%) D. The distribution of the patients' BILAG index score is shown in Table 1. The mean (SD) age of the patients was 37.1 (10.6) years (minimum = 18 and maximum = 70 years). The mean (SD) age of the patients in different groups of the BILAG index had no significant differences according to the analysis of variance (ANOVA) test (P value = 0.24). Because of the small number of patients with moderate and marked elevation of ESR, these amounts were combined for analytical assessment. By using the univariate ordinal logistic regression, there was a significant association between BILAG index score and ESR level, statistically (P value < 0.0001). This means that the patients with more active disease, according to BILAG index score, had higher levels of ESR.

The association between C3 and BILAG index scores was analyzed by the Chi-square test for trend. There was a significant association between BILAG index score and C3 level (P value < 0.0001), statistically. Results of this analysis showed that based on the BILAG index score, the patients with more active disease, had lower levels of C3.

The Chi-square test was used for trend, and a significant association between BILAG index score and C4 level was found, statistically (P value < 0.0001). This means that patients with more active disease based on the BILAG index score had lower levels of C4.

By using the Chi-square test for trend, a statistically significant association was found between the BILAG index score and anti-dsDNA level (P value < 0.0001). This means that based on the BILAG index score, the patients with more active disease had higher levels of anti-dsDNA (Table 1).

All variables were then entered to multivariate ordinal logistic regression. The results showed that the patients with moderate and marked elevated ESR would be in worse conditions 2.9 times of patients with normal ESR (OR = 2.93, P value = 0.01). Also, the odds that the patients with lower C4 level would be in worse conditions was 3.8 times those, who have normal C4 (OR = 3.77, P value = 0.003). The odds that the patients with positive anti-dsDNA would be in the worse conditions was 4 times of the patients with negative results (OR = 4.14, P value = 0.00). This association was not significant for C3, mild ESR level, and age (Table 2).

4. Discussion

According to high prevalence of SLE disease in Iran (8), especially renal involvement, and considering that LN leads to 88% reduction of 10 years' survival (12), SLE disease activity evaluation is important. Therefore, renal assessment is very important in response to the treatment and remission or disease flare evaluation. The most common factors, such as ESR, anti-dsDNA, complements like C3 and C4, are useful tests for assessing and predicting SLE disease activity, yet the relationship is not absolute and is in controversy, for example, anti-dsDNA may be elevated without any clinical manifestations (15, 17, 27, 28). Also, there is controversy about ESR elevation and SLE disease activity (16).

There are several indices for SLE disease activity assessment, with the BILAG index being one of them. The BILAG index evaluated 9 groups of manifestations over the previous 4 weeks (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological) by scoring factors in each group. Also, it is used for occurrence of SLE disease flare. In the renal component, these factors are assessed by systolic blood pressure, diastolic blood pressure, accelerated hypertension, urine dipstick protein, urine albumin-creatinine ratio, urine protein-creatinine ratio, 24-hour urine protein, nephrotic syndrome, creatinine (plasma/serum), GFR, active urinary sediment, and active nephritis (21). Although BILAG index is easy, quick and valid (22, 23, 26), specialist rarely use it.

The aim of the current study was to determine the associations between ESR, C3, C4, and anti-ds-DNA levels and renal disease activity, based on renal components of the BILAG index, in lupus nephritis patients. Only one similar study was found in Iran that was done with fewer patients (26) and no such study was conducted in Shiraz, Fars

Table 2. Results of Multivariate Ordinal Logistic Regression

		Odds Ratio (OR)	Standard Error (SE)	P Value	CI95%
Age		1.02	0.015	0.27	0.99, 1.05
ESR	Normal	1	.	.	.
	Mild elevation	1.14	0.38	0.75	0.52, 2.48
	Moderate and marked elevation	2.93	0.42	0.01	1.29, 6.65
C3	Low	0.9	0.42	0.8	0.4, 2.04
	Normal	1	.	.	.
C4	Low	3.77	0.44	0.003	1.57, 9.02
	Normal	1	.	.	.
Anti-dsDNA	Negative	1	.	.	.
	Positive	4.14	0.39	< 0.001	1.93, 8.87

Province. Therefore, it was decided to emphasize the importance of this index and suggest it for better LN management.

It has been proved that no single test can predict SLE disease activity and among all combinations, ESR, anti-dsDNA, C3, and C4 are the most useful laboratory tests in patients with LN (27, 29, 30). Although all these 4 laboratory tests are associated with the BILAG index score, the current results showed that high ESR level, low C4 level, and positive anti-dsDNA had a positive and significant relationship with renal disease activity in females with LN, according to the multivariate analysis. This means that patients with more active disease according to the BILAG index, have higher ESR levels, positive anti-dsDNA, and low level of C4. However, this relationship was not found for C3 level and mild ESR. It is noticeable that ESR will be increased under other conditions, such as pregnancy, malignancy, infection, and ESRD (24, 25), so these patients were excluded from the study. As mentioned above, the number of patients were small in moderate and marked elevation ESR, thus they were combined for the statistical analysis and this class had a significant relationship between disease activity, based on BILAG index, which was proved previously, as well as positive anti-dsDNA (14, 15). However, it was expected that low level of C3 would have a relationship with increased scores of BILAG index, as previous studies (15). Also, no significant statistical relationship was found with age.

Nasiri et al. conducted a similar cross-sectional study on 100 SLE patients in Iran, and they reported that an increasing ESR level correlated with higher disease activity (elevated (31 - 60 mm/h) with OR = 1.9 (CI95% = 1.2 - 2.6) and markedly elevated (> 60 mm/h) with OR = 2.6 (CI95% = 1.2 - 4.3)). Although there was a different categorization for ESR

in the current study, ESR higher than 50 mm/hour (moderate and marked elevation of ESR) had a stronger positive significant correlation with the BILAG index (OR = 2.93, CI95% = 1.29, 6.65). Also, they found a correlation between low C3 level (very low (less than or equal to half the LLN) with OR = 4.8 (CI95% = 1.4 - 15.1) and low with OR = 2.3 (CI95% = 1.5 - 3.1) and higher disease activity, which was not found in the current study's multivariate ordinal logistic regression analysis (26). This difference maybe because of the difference in number of patients under study, C3 categorization definition or patients' characteristics. Unlike the current study, they did not find any significant correlation between C4 and anti-dsDNA.

Narayana et al. reported that anti-dsDNA, C3, and C4 levels were the most useful laboratory tests for assessing SLE disease activity. They found an increasing titre of anti-dsDNA in all renal flare in SLE patients, as well as low C3 and C4 in most of them. Also, they showed a negative significant prediction for C3 and C4 levels and SLEDAI scores (an index for SLE disease activity evaluation), and a positive significant correlation between anti-dsDNA titre and this index (31).

4.1. Limitation

The limitation of this study was that a cross-sectional method was used, and a cohort is suggested for future researches. Also, because of the small number of patients with moderate and marked elevation of ESR, these groups were combined for analytical assessment; this problem could have been solved if a greater sample size was considered.

4.2. Conclusion

The results of this study revealed that all C3, C4, anti-dsDNA, and ESR were significant usefulness factors in renal involvement assessment in females with LN, and they increased in renal flare. Also, the current study showed that there were significant associations between progression of renal disease activity (based on BILAG index) and higher levels of ESR, positive anti-dsDNA, and lower levels of C4 in females with LN, yet there was no significant association between low C3 level and mild ESR, in the multivariate analysis. Finally, this study confirmed that the BILAG index is a valuable predictive index for renal disease involvement in females with LN. Although it is suggested that calculation of BILAG is a useful clinical tool for better LN management, a cohort or clinical trial is recommended with a greater sample size to better clarifying this index and C3 level. Also, more studies about BILAG index, according to the LN classification are recommended.

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Footnotes

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