

## ABNORMALITIES IN COMPLEMENT SYSTEM ARE RELATED TO DISEASE SEVERITY INDEX IN SYSTEMIC LUPUS ERYTHEMATOSUS

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## ABSTRACT

### PURPOSE

We sought to evaluate the relationships between low complement C3 and C4 proteins, abnormal complement activation (cell-bound complement activation products [CB-CAPs]), and a Lupus Severity Index (LSI) instrument recently developed.

### METHODS

The study was multi-centered and enrolled 500 SLE subjects (mean age 41.0±0.6 [SEM] years; 91% female; mean disease duration 10.9±0.4 years), all fulfilling the 1982 American College of Rheumatology (ACR) criteria revised in 1997. LSI was determined using the ACR criteria and sub-criteria elements collected from medical records as described (Bello et al., Lupus Science & Medicine 2016; 3:e000136). Serum C3 and C4 levels were determined using standard immunochemistry techniques. Complement activation was assessed by quantitative flow cytometry, and abnormal activation was defined as levels of C4d bound to erythrocyte (EC4d) or B-lymphocytes (BC4d) above the 99th percentile of a control group of normal healthy individuals (>14 and >60 net mean fluorescence intensity [MFI], respectively). Multivariate linear regression analysis was used to evaluate the contributions of low complement and abnormal CB-CAPs to LSI, with age and disease duration as covariates. Pearson's Chi-Square and Kruskal Wallis ANOVA tests were used as appropriate for group comparisons.

### RESULTS

In this cohort, median LSI score was 0.596 points (range 0.327 - 0.938 points, first tertile: 0.544; second tertile: 0.792). Multivariate linear regression analysis revealed that higher LSI scores were associated with abnormal CB-CAPs (estimate = 0.063 ± 0.015 points; p < 0.01), low complement (estimate

= 0.030 ± 0.015; p = 0.048), younger age (estimate = -0.026 ± 0.001 per 10-years increment; p < 0.01), and longer disease duration (estimate = 0.027 ± 0.003 per 10-years increment, p < 0.01) (Global R<sup>2</sup> = 0.13). Altogether, subjects presenting with both low complement and abnormal CB-CAPs had higher LSI (median [IQ range]: 0.785 [0.558 - 0.839]) than those presenting with either abnormality (median [IQ range]: 0.591 [0.526 - 0.817]) or those presenting with normal complement and normal CB-CAPs (median [IQ range]: 0.546 [0.481 - 0.703]) (p < 0.001). Figure 1 illustrates the higher frequencies of low complement (p < 0.01) and abnormal CB-CAPs (p < 0.01) by LSI tertiles and shows that abnormal CB-CAPs is more prevalent than low complement at all LSI levels (p < 0.01).

### CONCLUSION

These data indicate that abnormalities in the complement system are associated with increased LSI.

## DEMOGRAPHICS

N = 500 Patients with SLE	
<b>Age (yr)</b>	Median 39.5 (IQR: 29-51)
<b>Female Gender</b>	N = 455 (91%)
<b>Disease Duration (yr)</b>	Median 9 (IQR: 3-16)
<b>Race and Ethnicity</b>	N = 214 white N = 145 black N = 90 Hispanic N = 38 Asian N = 13 other

## LUPUS DISEASE INDEX

$$\text{Lupus severity index} = \frac{k}{1 + \exp(-\sum_j \hat{\beta}_j x_j)}$$

k: constant; set = 1 in this analysis  
(LSI min = 0; LSI max = 1)

x<sub>j</sub>: ACR criterion or sub-criterion; can be 0 (if absent) or 1 (if present)  
β̂<sub>j</sub>: weight of each criterion or sub-criterion  
(Table S2 of Bello et al., 2016)

### EXAMPLE

Patient fulfills ACR criteria or subcriteria of

- Malar rash (β̂<sub>j</sub> = 0.020)
- Oral ulcers (β̂<sub>j</sub> = 0.093)
- Arthritis (β̂<sub>j</sub> = -0.289)
- Immunologic (β̂<sub>j</sub> = 0.447)

### FORMULA

- Multiply the criteria/subcriteria present by their β̂<sub>j</sub> and sum:  
(1x0.020) + (1x0.093) + (1x(-0.289)) + (1x0.447) = 0.271
- Make the negative of that value = -0.271
- Elevate e to the power of that value: 2.781<sup>^</sup>(-0.271) = 0.7626
- Add 1 = 1.7626
- LSI = 1 / 1.7626 = **0.567**

Bello et al., Lupus Science & Medicine 2016; 3:e000136

## MULTIVARIATE ANALYSIS LSI PREDICTORS

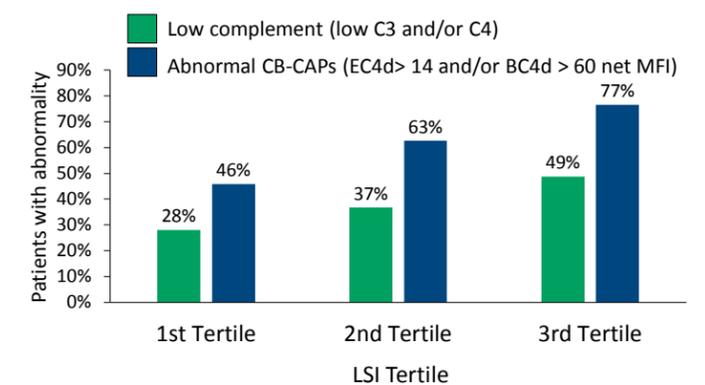
	Beta Coefficient	SE of beta Coefficient	P value
<b>Intercept</b>	0.677	0.026	
<b>Abnormal CB-CAPs (*)</b>	0.063	0.015	< 0.01
<b>Low complement (**)</b>	0.030	0.015	0.048
<b>Age (yr)</b>	-0.0026	0.001	< 0.01
<b>Duration of disease (yr)</b>	0.0027 per 10-yr increment	0.001	< 0.01

(\*) Abnormal CB-CAPs: blood levels of C4d bound to erythrocyte (EC4d) and/or B-lymphocytes (BC4d) above the 99th percentile of a control group of normal healthy individuals (EC4d > 14 and BC4d > 60 net mean fluorescence intensity [MFI]).

(\*\*) Low complement: serum levels of complement proteins C3 and/or C4 below cutoff.

## LSI BY TERTILES

- Frequency of low complement (p < 0.01) and high CB-CAPs (p < 0.01) increase with increasing lupus severity index (LSI).
- Abnormal CB-CAPs is more prevalent than low complement at all LSI levels (p < 0.01).



## CONCLUSION

These data indicate that abnormalities in the complement system are associated with increased LSI.