CELL-BOUND COMPLEMENT ACTIVATION PRODUCTS IN COMBINATION WITH LOW COMPLEMENT C3 OR C4 HAVE HIGH DIAGNOSTIC YIELD IN SYSTEMIC LUPUS ERYTHEMATOSUS

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BACKGROUND

Cell-bound complement activation products (CB-CAPs), are a stable form of classical complement activation ex-vivo, and sensitive and specific biomarkers of SLE. In the present study, we sought to compare the performances of CB-CAPs to the gold standard, low complement.

OBJECTIVES

- Evaluate the performance characteristics of CB-CAPs (EC4d and BC4d) in SLE and compare them to the gold standard, low complement proteins C3 and C4.
- Calculate a composite score that comprises the 4 complement abnormalities evaluated in this study: low C3, low C4, elevated EC4d, and elevated BC4d.
- Evaluate the performance characteristics of the composite score in SLE.

METHODS

SUBJECTS

All subjects (n=1200) were adults (≥18 years) and enrolled from multiple academic centers in the United States. All SLE fulfilled the 1997 ACR criteria for SLE (n=498).

Patients with other rheumatic diseases (n=450) consisted of 189 rheumatoid arthritis, 88 Sjogren's, 90 fibromyalgia and 83 patients with other connective tissues diseases. A group of healthy normal individuals was also enrolled (n=252).

BIOMARKERS

Abnormal CB-CAPs status (EC4d or BC4d>99th percentile of normal) was determined using flow-cytometry. Complement C3 and C4 levels were determined using immunoturbidimetry (Binding Site, San Diego, CA).

STATISTICAL ANALYSIS

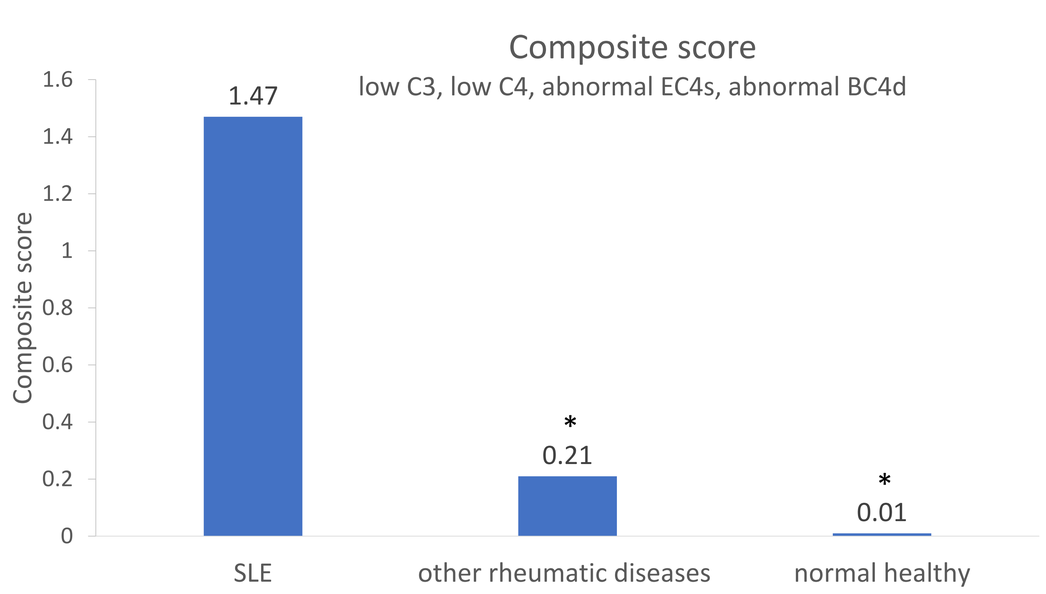
Performances of the markers, either alone or in combination, to distinguish SLE from other rheumatic diseases and controls were established using sensitivity, specificity, odds ratio (OR) and area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Youden Index (sensitivity + specificity - 100) and Akaike information criteria (AIC) were also calculated. The combination of 4 complement marker abnormalities was also evaluated using logistic regression and unweighted composite score cumulating the presence of these abnormalities was calculated.

RESULTS

Abnormal CB-CAPs status yielded 62% sensitivity with 88% specificity in distinguishing SLE from the group of patients with other diseases. Youden index was 0.492±0.027. Low C3/C4 status yielded 38% sensitivity and 93% specificity in distinguishing SLE from the group of patients with other diseases. Youden index for low C3 or C4(0.313±0.025) was significantly lower than Youden index associated with abnormal CB-CAPs ($p<0.01$). Specificity of low C3/C4 and abnormal CB-CAPs in distinguishing SLE from normal healthy individuals was 93% and 99%, respectively. AUC was also significantly higher with BC4d (0.718) than with low C3 (0.620; $p<0.01$), low C4 (0.618; $p<0.01$) and low C3 and/or C4 status (0.656; $p<0.01$) (Table).

	Sens (%)	Spec (%)	Youden Index	AUC (95% CI)	OR (95% CI)	AIC
Low C3 (<81 mg/dL)	27	97	0.240	0.620 (0.599-0.641)	10.9 (6.28-18.91	1200
Low C4 (<12.9 mg/dL	27	97	0.235	0.618 (0.596-0.639)	9.57 (5.67-16.15)	1206
Low C3 and/or low C4	38	93	0.313	0.656 (0.632-0.681)	8.34 (5.55-12.53)	1174
Abnormal EC4d (>14 net MFI)	43	92	0.350	0.675 (0.650-0.700)	8.67 (5.9-12.72)	1153
Abnormal BC4d (>60 net MFI)	50	94	0.436	0.718 (0.693-0.743)	14.95 (9.81-22.77)	1082
Abnormal ED4d and/or BC4d	62	88	0.492	0.746 (0.719-0.722	11.05 (7.95-15.37)	1067

A composite score (unweighted) cumulating all 4 abnormalities was higher in SLE than disease control group and normal healthy individuals (Figure). The complement scoring system yielded higher AUC (0.812), higher OR (36.0 CI95%: 18.8-69.0), lower AIC (1037) and greater R^2 (0.403) than any other combinations.



CONCLUSION

- Our data suggests that CB-CAPs have greater diagnostic yield than low complement (C3 and/or C4).
- The combination of these 4 complement abnormalities in a composite complement score has high yield in distinguishing SLE from other rheumatic diseases and normal healthy individuals.