An anti-dsDNA fluorescence enzyme immunoassay (FEIA) demonstrates diagnostic test specificity ≥ 90 % according to the 2019 EULAR/ACR classification criteria for Systemic Lupus Erythematosus

Reference: Orme ME, Voreck A, Aksouh R et al., accepted for publication 2021 Autoimmunity Reviews.

Summary

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical features associated with multiple autoantibodies. A positive antinuclear antibodies (ANAs) test is currently defined as the entry criterion for SLE classification[1] mostly followed by testing for antibodies against dsDNA. Testing for anti-dsDNA antibodies is crucial for disease diagnosis and classification but also important for prognosis, progression and therapeutic decisions.[2] In the evolution of anti-dsDNA testing a diversity of techniques including fluorescence enzyme immunoassays (FEIA), chemiluminescence immunoassays (CLIA), crithidia luciliae indirect immunofluorescence tests (CLIFT), enzyme-linked immunosorbent assays (ELISA), Farr radioimmunoassays (FARR-RIA) and multiplex immunoassays (MIA) was introduced to detect different types of anti-dsDNA antibodies. Anti-double helix antibodies are the most specific anti-dsDNA antibodies compared to other anti-dsDNA antibody types including anti-backbone or anti-bases antibodies.[3] The comprehensive range of methodologies affects harmonization of anti-dsDNA antibody tests and complicates the comparability of the different test systems and their performance regarding specificity and sensitivity. Therefore, the 2019 classification criteria for SLE developed by the European League Against Rheumatism (EULAR) and the American Rheumatism Association (ACR) introduced a new benchmark for anti-dsDNA tests considering the usage of “an immunoassay with demonstrated ≥ 90 % specificity for SLE against relevant disease controls”.

Based on this novelty a systemic literature review of anti-dsDNA tests was performed including data from January 2001 to August 2019 to investigate FEIA dsDNA tests’ sensitivity and their performance with respect to the ≥ 90 % specificity benchmark to identify classified SLE patients against disease control groups. Data achieved against healthy control groups were excluded because this comparison may result in overestimated test specificity. Furthermore, a pooled estimate of specificity was determined by means of a quantitative meta-analysis.

Results

Using the Quality Assessment Tool for Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist six FEIA dsDNA studies were identified to fulfill the quality criteria for quantitative meta-analysis. All of the included studies were based in Europe and used the EliA™ dsDNA test. Sensitivity for EliA dsDNA across the studied SLE populations (totally 1,977 studied patients, 47 % SLE) was estimated to be 52.41 % (95% CI 36.43 %, 67.92 %; figure 1). A difference of sensitivity between active (87.32 %; 95 % CI 77.51 %, 93.23 %) and inactive (45.64 %; 95 % CI 35.36 %, 56.31 %) SLE was observed.

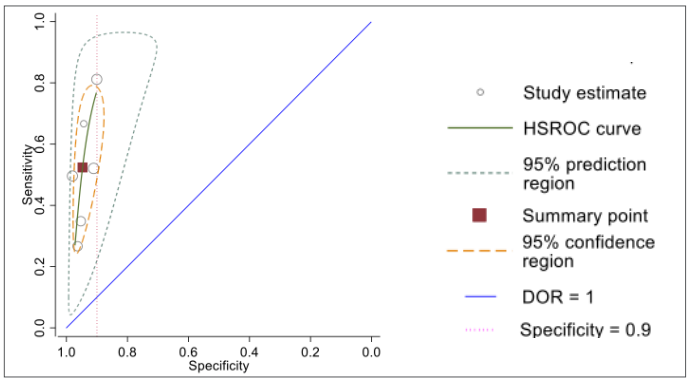

Figure 1: HSROC plot representing sensitivity versus specificity of the EliA dsDNA test. HSROC: hierarchical summary receiver operating characteristic; DOR: Diagnostic Odds Ratio, Blue line is DOR = 1; below this line the test is uninformative and is of no clinical value.

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Table 1: Predicted results per 1,000 patients tested using sensitivity (52.4 %) and specificity (94.7 %) from the meta-analysis * Number rounded

	Number of results per 1,000 patients tested								
Prevalence of SLE in tested population	**5 %**	**10 %**	**20 %**	**25 %**	**30 %**	**40 %**	**47.3 %**	**50 %**	**60 %**
SLE cases per 1,000 tested	50	100	200	250	300	400	473	500	600
Correctly identified as SLE	26	52	105	131	157	210	248	262	314
Corrently identified as not SLE	900	852	758	710	663	568	499	474	379
Corrently identified	**926**	**905***	**862***	**841**	**820**	**778**	**747**	**736**	**693**

* number rounded

Metaanalysis yielded specificity estimates of 94.7 % (95 % CI 91.67 %, 96.67 %; figure 1). Predicted results per 1,000 patients tested using sensitivity and specificity from the meta-analysis are presented in table 1.

Conclusions

The meta-analysis demonstrated specificity of EliA dsDNA ≥ 90% for SLE, against relevant disease controls, and therefore performs in accordance with the 2019 EULAR/ACR classification criteria for SLE.

Comment

The presented study highlights the value of systematic assessment of test accuracy especially in the diagnosis of heterogenous diseases like SLE. Given that there can be a very low proportion of patients with SLE in the population referred for testing in some settings, it is vital to ensure that the anti-dsDNA test used has proven specificity.

References

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