

CONCISE REPORT

Do classic blood biomarkers of JSLE identify active lupus nephritis? Evidence from the UK JSLE Cohort Study

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Background: Lupus nephritis (LN) affects up to 80% of juvenile-onset systemic lupus erythematosus (JSLE) patients. The value of commonly available biomarkers, such as anti-dsDNA antibodies, complement (C3/C4), ESR and full blood count parameters in the identification of active LN remains uncertain. **Methods:** Participants from the UK JSLE Cohort Study, aged <16 years at diagnosis, were categorized as having active or inactive LN according to the renal domain of the British Isles Lupus Assessment Group score. Classic biomarkers: anti-dsDNA, C3, C4, ESR, CRP, haemoglobin, total white cells, neutrophils, lymphocytes, platelets and immunoglobulins were assessed for their ability to identify active LN using binary logistic regression modeling, with stepAIC function applied to select a final model. Receiver-operating curve analysis was used to assess diagnostic accuracy. **Results:** A total of 370 patients were recruited; 191 (52%) had active LN and 179 (48%) had inactive LN. Binary logistic regression modeling demonstrated a combination of ESR, C3, white cell count, neutrophils, lymphocytes and IgG to be best for the identification of active LN (area under the curve 0.724). **Conclusions:** At best, combining common classic blood biomarkers of lupus activity using multivariate analysis provides a 'fair' ability to identify active LN. Urine biomarkers were not included in these analyses. These results add to the concern that classic blood biomarkers are limited in monitoring discrete JSLE manifestations such as LN. *Lupus* (2017) 0, 1–6.

Key words: Lupus nephritis; classic biomarkers; ESR; anti-dsDNA; complement; C3; C4

Introduction

Juvenile-onset systemic lupus erythematosus (JSLE) is a heterogeneous life-threatening multi-system autoimmune disease, exhibiting a more aggressive course when onset is in childhood.¹ The value of commonly available classic biomarkers of overall JSLE activity in identifying discrete aspects of JSLE, such as lupus nephritis (LN), remains uncertain. LN is more common in JSLE than in adult counterparts, with up to 80% of JSLE patients having some renal involvement within a 5-year period.² Renal histology is the gold standard for LN identification, but is seldom repeated serially due to its invasive nature. Effective

treatment of LN relies on early recognition of the often subtle presenting features, to prevent renal damage.

Clinicians rely heavily on non-invasive markers such as proteinuria, serum creatinine and glomerular filtration rate (GFR) when monitoring JSLE patients. Following a LN flare, proteinuria has been shown to take a significant period of time to normalize, with 53% of adult LN patients requiring up to 2 years to recover and 74% recovering by 5 years.³ During this time, differentiating between proteinuria due to irreversible damage of the glomerular capillaries or a LN flare is problematic, limiting the reliability of proteinuria in ongoing monitoring. Spot albumin or protein creatinine ratio measurements are largely used as an alternative to 24-hour urinary protein quantification; however, the correlation between spot protein/creatinine ratio and 24-hour urine protein has recently been shown to be poor in those with a high or medium LN activity index score.⁴

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There have also been numerous reports of clinically silent LN in patients with biopsy defined LN but no proteinuria, normal urinalysis and normal renal function.⁵ The best calculation for GFR measurement in LN patients has been shown to be the Cockcroft–Gault equation using ideal body weight in the calculation. Deviation from this approach as part of the standard protocols used in some institutions may also influence the reliability of GFR measurements in systemic lupus erythematosus (SLE) patients.⁶

The above studies highlight uncertainties relating to conventional renal function measurements in SLE. Studies looking at the role of other routinely measured immunological, haematological and inflammatory biomarkers in active LN identification have mainly focused on adult patients. The aim of this study was therefore to use participants from the UK JSLE Cohort Study² to assess the ability of classic biomarkers of JSLE for identification of active LN, both individually and in combination.

Patients and methods

Patient cohort

Children participating in the UK JSLE Cohort Study² between 2005 and 2015, aged under 16 years at the time of diagnosis, meeting four of more of the American College of Rheumatology (ACR) SLE classification criteria were recruited. Disease activity and classic biomarker data were collected using the paediatric British Isles Lupus Assessment Group (BILAG; pBILAG2004) disease activity score.⁷ Written patient assent/consent and parental consent was obtained, and the study had full ethical approvals in place from the National Research Ethics Service North West, Liverpool East (REC reference 06/Q1502/77). The research was carried out in accordance with the Declaration of Helsinki.

Patient groups

Patients were categorized according to the renal domain of pBILAG2004 disease activity score, defined as follows: pBILAG2004 grade A/B: severe, moderate renal disease respectively; grade C: mild renal disease; grade D: inactive disease but previous renal system involvement; grade E: renal system has never been involved. The composite renal domain of the BILAG score consists of six items including renal function (deterioration based on serum creatinine and GFR), proteinuria (defined by urine dipstick, or urine protein/albumin creatinine ratio (UPCR/UACR), or 24 hour

protein levels), nephrotic syndrome, active urinary sediment, hypertension and histological evidence of active nephritis in the previous 3 months. Different cut-offs for the above clinical investigations correspond to the different renal BILAG disease activity categories.⁷ Patients were then grouped as follows:

- Active LN: if they had a renal pBILAG2004 of A or B.
- Inactive LN: if they had a renal pBILAG2004 of D or E.

Patients who were graded ‘C’ were excluded from analysis. The study was undertaken on a cross-sectional basis. Individual patient visits were selected when the clinical data were most complete.

Classic blood biomarkers investigated

Anti-dsDNA, C3, C4, ESR, CRP, haemoglobin, total white cell count (WCC), neutrophils, lymphocytes, platelets and immunoglobulin (IgG, IgA, IgM) levels were compared between patients with active and inactive LN. As our definition of active LN was based on the composite renal BILAG score, calculated from proteinuria, GFR, blood pressure, active urine sediment, plasma creatinine and recent biopsy findings, we could not investigate the performance of these classic renal biomarkers.

Statistical analysis

Demographic and classic biomarker data were not normally distributed and therefore were expressed as median values and interquartile ranges (IQR). Mann–Whitney U tests were used to compare the distribution of the classic biomarker levels between active and inactive LN patients (Bonferroni correction method applied to account for multiple testing, 17 comparisons). A binary logistic multiple regression model was fitted to assess for association between a combination of classic biomarkers and LN status (outcome: LN active 1; non-LN JSLE 0). All classic biomarkers (log-transformed) excluding those contributing to the renal BILAG score (UACR, UPCR, GFR, plasma creatinine) were included in an initial model and the ‘stepAIC’ function in R⁸ applied to select a final model. This function compares different models based on all possible combinations of biomarkers and chooses the model with the minimum Akaike information criterion (AIC) value. The AIC is a measure of the relative quality of a model relative to each of the other models, with a lower value representing better quality. The area under the curve (AUC) for the final model was calculated. AUC values of 1.0–0.9, 0.9–0.8, 0.8–0.7, 0.7–0.6 and 0.6–0.5 were considered

‘excellent, good, fair, poor and fail’, respectively. Data analysis and was undertaken using R version 3.1.1.⁸ Where Bonferroni adjustment was made to account for multiple testing, the Bonferroni corrected P value, P_c is reported.

Results

Patient demographics

The study cohort consisted of 370 JSLE patients, 191 active LN patients and 179 inactive, with a median age of 12.7 and 12.8 years, respectively, at diagnosis (Table 1). All patients fulfilled at least four ACR classification criteria at diagnosis. At the time of analysis, disease duration for active and inactive LN patients was 0.5 and 0.6 years, respectively. The female to male gender ratio was 5.0:1 for active LN patients and 4.8:1 for inactive LN patients. The most commonly self-reported patient ethnicity in both groups was Caucasian (54% active group and 51% inactive group), followed by Indian, Pakistani or Bangladeshi (21% active group and 21% inactive group). No statistically significant differences were observed on comparing any of the reported demographics between the active and inactive groups ($P_c > 0.05$ for all, see Table 1).

Table 1 Key demographic data for the JSLE patients studied

	Inactive LN (n = 179) ^a	Active LN (n = 191) ^a	P_c value ^b
Age at diagnosis (years)	12.7 (10.1–14.3)	12.8 (10.8–14.5)	1.000
Disease duration (years)	0.6 (0–1.7)	0.5 (0–2.6)	1.000
Gender (F:M ratio)	4.8:1	5:1	1.000
ACR criteria at diagnosis	4 (4–5)	5 (4–5)	1.000
Patient ethnicity (n, %) ^c			
• Caucasian	95 (54%)	95 (51%)	
• African	12 (6%)	12 (6%)	
• Caribbean	6 (3%)	10 (5%)	
• Mixed race	14 (8%)	14 (7%)	0.717
• Indian/Pakistani/ Bangladeshi	38 (21%)	40 (21%)	
• Chinese	3 (2%)	8 (4%)	
• Other Asian	11 (6%)	12 (6%)	

^aResults expressed as median values and interquartile ranges. Chi squared and Mann–Whitney U tests used to assess for differences in demographic/clinical factors between different patient groups as appropriate.

^b P value_c: Bonferroni-corrected P values.

^cEthnicity data are patient reported.

JSLE: juvenile-onset systemic lupus erythematosus; LN: lupus nephritis; F:female; M: male; ACR: American College of Rheumatology.

Individual classic biomarkers

Table 2 summarizes the median and interquartile ranges for renal and non-renal classic biomarker concentrations in the active and inactive LN patient groups separately. Univariate analysis of the association between each classic biomarker and LN status revealed a statistically significant difference in concentration of C3, C4, ESR, haemoglobin, UACR and UPCR between patients with active LN and those with inactive LN (all $P_c < 0.05$). The concentration of serum creatinine, anti-dsDNA, neutrophils, eGFR, CRP, WCC, lymphocyte/platelet counts and IgG, IgA and IgM did not differ between patient groups (all $P_c > 0.05$).

Strength of non-renal classic biomarkers in combination for identifying active LN

A binary multiple logistic regression model was fitted including all classic biomarkers which do not contribute to the renal BILAG score, and then applying the R ‘StepAIC’ function.⁸ The final selected model included six classic biomarkers including ESR, C3, WCC, neutrophils, lymphocytes and IgG (see Table 3). The AUC corresponding to this final model was 0.724, demonstrating this optimal combination of classic

Table 2 Classic biomarker measurements in active versus inactive LN patients

	n ^a	Inactive LN ^b	Active LN ^b	P_c value ^c
Anti-dsDNA (IU/L)	308	29 (7–154)	77 (13–261)	0.068
C3 (g/L)	339	0.99 (0.75–1.23)	0.78 (0.43–1.08)	<0.001
C4 (g/L)	338	0.15 (0.08–0.20)	0.10 (0.05–0.19)	0.017
ESR (mm/h)	327	18 (6–40)	40 (11–80)	<0.001
CRP (mg/L)	306	5 (3–7)	5 (3–7)	1.000
Haemoglobin (g/dl)	367	12.1 (10.8–13.2)	11.5 (9.9–12.8)	0.014
White cells ($\times 10^9/L$)	365	5.4 (4.2–7.1)	5.7 (4.0–8.8)	1.000
Neutrophils ($\times 10^9/L$)	365	3.2 (2.1–4.3)	3.6 (2.4–6.4)	0.053
Lymphocytes ($\times 10^9/L$)	365	1.3 (0.9–1.9)	1.3 (0.9–1.9)	1.000
Platelets ($\times 10^9/L$)	364	270 (207–325)	261 (196–335)	1.000
IgG (g/L)	291	13.7 (10.9–18.6)	12.0 (9.2–18.1)	1.000
IgA (g/L)	289	1.8 (1.2–2.4)	1.9 (1.2–2.8)	1.000
IgM (g/L)	287	1.2 (0.8–1.7)	1.0 (0.6–1.6)	1.000
UACR (mg/mmol Cr)	130	0.9 (0.5–2.2)	23.9 (2.5–109.7)	<0.001
UPCR (mg/mmol Cr)	141	11 (5–15)	102 (60–325)	<0.001
eGFR (ml/min/m ²)	267	116 (99–130)	108 (87–108)	1.000
Serum creatinine (μ mol/L)	318	54 (46–54)	61 (48–57)	1.000

^aNumber of patients contributing to analysis for each laboratory parameter.

^bExpressed as median values and interquartile ranges.

^c P value_c: Bonferroni-corrected P values.

LN: lupus nephritis; UACR: urinary albumin to creatinine ratio; UPCR: urinary protein creatinine ratio; eGFR: estimated glomerular filtration rate.

Table 3 Binary logistic regression model for identification of active LN using classic biomarkers

<i>Final model fitted by including all biomarkers in a multiple logistic regression model and applying 'StepAIC' function</i>				
<i>Biomarkers</i>	<i>Coefficient</i>	<i>Standard Error</i>	<i>P value</i>	<i>AUC</i>
ESR	0.019	0.007	0.003	0.724
C3	-1.035	0.488	0.034	
White cells	-0.699	0.423	0.098	
Neutrophils	0.795	0.427	0.06	
Lymphocytes	0.735	0.503	0.144	
IgG	-0.061	0.026	0.017	

StepAIC function: step Akaike Information Criterion function, 185 patients (88 active lupus nephritis (LN) and 97 inactive LN) included in this model as patients excluded when classic biomarker measurements were missing.

AUC: area under the curve.

non-renal biomarkers to have 'fair' ability for active LN identification.

Discussion

Using a cross-sectional national cohort of paediatric patients recruited to the UK JSLE Cohort Study, the aim of this study was to assess the ability of classic immunological and haematological biomarkers of JSLE to identify active LN compared to inactive LN, both individually and in combination. Previous studies have largely focused on individual biomarkers and adult-onset SLE populations.

This study univariately showed ESR, C3, C4, haemoglobin, UACR and UPCR to differ significantly between active and inactive LN patients (all $P_c < 0.05$). When all classic biomarkers which do not contribute to the renal BILAG score were considered within a binary multiple logistic regression model, ESR, C3, WCC, neutrophils, lymphocytes and IgG were shown to contribute significantly to the optimal model for the identification of active LN. The accuracy of these tests for identifying active LN was assessed using area under the receiver operating characteristic curve analysis, with the area measuring discrimination, i.e. the ability of the test to classify correctly those with and without LN. AUC values of 1.0–0.9, 0.9–0.8, 0.8–0.7, 0.7–0.6 and 0.6–0.5 correspond to a test being 'excellent, good, fair, poor and failing'. Although ESR, C3, WCC, neutrophils, lymphocytes and IgG levels differed significantly, their accuracy as a test for active LN fell in the 'fair' range when considered in combination (AUC 0.724).

These results complement those of an adult-onset SLE study which showed decreases in C3 to be associated with renal disease activity, despite inconsistent performance for predicting global SLE activity.⁹ In a prospective study serially monitoring C3/C4 levels in adult SLE patients, C4 was demonstrated to deteriorate before C3, starting 25 and 20 weeks, respectively, before the LN flare becoming clinically detectable.¹⁰ Together with anti-dsDNA antibody levels, C3/C4 levels have been shown to have a good negative predictive value for active LN in a 6-year prospective study of 228 LN patients.¹¹ Complement fragments C3d-CIC and C5a have previously been shown to be significantly higher in active compared to inactive JSLE patients,¹² but these data are not collected by the UK JSLE Cohort Study, and therefore could not be included in these analyses.

Our findings relating to ESR are also in keeping with those of a recent adult SLE study that showed ESR to be correlated with renal involvement and fatigue according to the lupus activity index visual analogue scales (VAS), the overall safety of estrogen in lupus national assessment–systemic lupus erythematosus disease activity index (SELENA–SLEDAI) score and physician global assessment (PGA). ESR was also correlated with haematuria and proteinuria during the current visit. Over time, a change in ESR between two visits was highly correlated with a concurrent change in the PGA and renal VAS but not changes in overall disease activity.¹³ ESR is clearly an easily accessible and inexpensive test, which has some utility in monitoring renal and global disease activity but is very non-specific in separating renal and global disease activity.

Anti-dsDNA antibody levels did not feature in the final multiple logistic regression model. Similar results have previously been reported in a study assessing anti-dsDNA antibody and C3/C4 levels, in 53 adult SLE patients 3–9 months preceding a flare. For all three tests, sensitivity and specificity for predicting renal and non-renal flares was in the region of 50% and 75%, respectively, with positive and negative likelihood ratios being close to 1.0, suggesting little clinical value as a routine test.¹⁴ In contrast, high titres of anti-dsDNA have been shown to differentiate proliferative from non-proliferative LN at the time of renal biopsy,¹⁵ with some studies concluding that increased anti-dsDNA antibody levels should prompt preemptive treatment due to the strong ability of anti-dsDNA to predict SLE flares.¹⁶ These conflicting results may be due to differences in sample size, disease activity measures and the frequency of biomarker testing.

This study is the largest to date in children and young people with JSLE looking at the performance of classic biomarkers for LN identification. We recognize that there are certain limitations to this work, which should be addressed in future studies. In this study we were interested in the performance of biomarkers not considered of classic renal origin (e.g. anti-dsDNA antibodies, C3/C4, ESR, full blood count parameters, etc.) as our definition of active LN was based on the composite renal BILAG score (calculated from proteinuria, blood pressure, serum creatinine, GFR, active urine sediment and recent biopsy findings). To look more closely at all classic biomarkers available to the clinician, including those involved in calculation of the composite renal BILAG score, further large prospective longitudinal studies are warranted using different outcome measures (e.g. renal biopsy defined LN). Such future analysis would indicate the diagnostic value of the full range of urine and blood tests which are available to the clinician. It would also be of interest to explore the effect of combining classic blood and urine biomarkers with novel urine biomarkers, as such novel biomarkers have been shown to be extremely useful in the identification of active LN.¹⁷

Patient episodes in which a renal BILAG score of C was scored were not included in this current study. Renal BILAG C patients can be a rather heterogeneous group of patients with mild LN (scoring a C on the basis of a urine dipstick value of $\geq 1+$) or with slowly improving renal disease in which the urine protein-creatinine ratio can still in fact be very high, but can have improved by 25% or greater in the previous 4 weeks. The renal BILAG score has been shown to be most sensitive for the detection of new-onset LN and a significant improvement of renal disease activity,¹⁸ therefore, this current study included a more dichotomous group of patients with clearly defined active versus inactive LN (renal BILAG A/B vs. D/E). Such a renal BILAG score definition of active LN has previously been utilized within a large number of studies looking at the ability of urine and serum biomarkers to differentiate active and inactive LN.^{19–23} A further analysis of the role of classic biomarkers in renal BILAG C patients would be of interest.

Conclusions

JSLE patients have significant renal involvement and the potential to develop irreversible renal

damage as a result of unrecognized LN relapses. At best, combining ESR, C3, WCC, neutrophils, lymphocytes and IgG provided a ‘fair’ ability to identify active LN. In contrast, novel urine biomarkers have been shown to be ‘excellent’ for identifying active LN (AUC up to 0.92), in the UK JSLE Study Cohort.¹⁷ In the future, to optimize the effective management of LN, easily measured novel biomarkers are anticipated to add to the information gained from classic biomarkers.

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Author contributions

EMDS and MWB participated in the conception, design of the study and acquisition of data. All authors participated in interpretation of the data. EMDS and ALJ performed the statistical analysis. MWB is chief investigator of the UK JSLE Cohort Study. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. They have also all read and given final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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