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Genetic and epigenetic determinants of relapse risk in lupus nephritis

Elisabeth Skoglund ,[1] Oliver Skoglund,[2] Holme Vestin ,[1] Nina Oparina ,[1] Ahmed Sayadi,[1] Francesca Faustini ,[3] Elisabet Svenungsson ,[3] Lars Ronnblom ,[1] Maria K Svensson ,[4,5] Juliana Imgenberg-Kreuz ,[1] Iva Gunnarsson,[3] Christopher Sjöwall ,[2] Dag Leonard [1]

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[1]Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden
[2]Division of Inflammation and Infection/Rheumatology, Department of Biomedical and Clinical Sciences, Linkoping University, Linköping, Östergötland County, Sweden
[3]Rheumatology Unit, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
[4]Dept. of Medical Sciences, Renal Medicine, Uppsala University, Uppsala, Sweden
[5]Uppsala Clinical Research Center, Uppsala, Uppsala County, Sweden

Correspondence to
Dr Elisabeth Skoglund; elisabeth.skoglund@medsci.uu.se

ABSTRACT

Objective Lupus nephritis (LN) is a potentially severe manifestation of SLE, often resulting in permanent kidney damage. We investigated whether polygenic and/or epigenetic risk is associated with time to LN relapse and whether this association differs by initial therapy.

Methods Caucasian patients with biopsy-verified LN between 1974 and 2022 (n=149) were genotyped using the Illumina Global Screening Array, and DNA methylation was assessed with the Illumina HumanMethylation450k BeadChip. A weighted Polygenic Risk Score (PRS) based on 55 non-Human leukocyte antigen (HLA) SLE risk gene variants and a Methylation Risk Score (MRS) based on the 17 most differentially methylated cytosine-phosphate-guanine sites identified in SLE-control comparison were calculated. Time to LN relapse was analysed using Cox proportional hazards models, adjusted for centre, sex and year of the first LN.

Results Neither PRS nor MRS was associated with time to LN relapse in the overall cohort, irrespective of treatment (PRS: HR=1.00 (0.77–1.30); p=0.99; MRS: HR=1.01 (1.00–1.02); p=0.21). No associations were observed among cyclophosphamide (CYC)-treated patients (PRS: HR=0.81 (0.55–1.20); p=0.29; MRS: HR=1.00 (0.99–1.02); p=0.89). In non-CYC-treated patients, PRS showed a non-significant trend towards shorter time to LN relapse (HR=1.26 (0.88–1.81); p=0.21), with a similar trend for MRS (HR=1.02 (1.00–1.03); p=0.066). Adding MRS to the PRS model improved performance in this subgroup (likelihood ratio test, p=0.028), with significant associations for MRS (PRS: HR=1.56 (0.97–2.50); p=0.066; MRS: HR=1.02 (1.00–1.04); p=0.037).

Conclusions Genetic and epigenetic susceptibility appears to influence LN relapse risk in a treatment-dependent manner. The absence of an association among patients receiving CYC suggests that initial treatment with CYC may attenuate the impact of genetic and epigenetic predisposition on relapse. These findings support the potential of genetic and epigenetic profiling at LN diagnosis to improve relapse risk stratification and individualise selection of treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ All patients with lupus nephritis (LN) are treated according to a standard regime mainly based on nephritis subclass.
⇒ Relapse nephritis is common and forceful immunosuppression is associated with adverse events.
⇒ There is an urgent unmet need to better individualise LN treatment.

WHAT THIS STUDY ADDS

⇒ The results from this study suggest that LN relapse may be influenced by polygenic and epigenetic risk in a treatment-dependent manner.
⇒ Genetic and epigenetic profiling can therefore be a valuable tool at LN diagnosis to tailor treatment

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the results from this study can be replicated in prospective studies, genetic and epigenetic tools may be used in clinical practice to guide treatment.

INTRODUCTION

SLE is a heterogeneous autoimmune rheumatic disease with clinical manifestations ranging from mild to life-threatening. Lupus nephritis (LN) is a potentially serious and common organ manifestation, affecting up to 50% of patients.[1] Despite advances in immunosuppressive therapy, about 30%–50% experience a LN relapse and globally 4%–28% of patients with LN develop end-stage kidney disease (ESKD), with large differences in prevalence and severity between different cohorts,[1–3] underscoring a substantial unmet clinical need.

Current treatment strategies for LN are largely standardised and primarily guided by morphological classification.[4–6] Initial therapy typically involves aggressive immunosuppression combined with high doses of corticosteroids, which are associated with considerable toxicity and long-term adverse effects.[4–8] At present, there are no reliable prognostic biomarkers available to tailor treatment at the time of LN diagnosis. Importantly, relapse of LN has been shown to be a stronger predictor of long-term renal outcome than histological subclass, proteinuria or serum creatinine

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levels.[9] Early identification of patients at risk of relapse therefore enables improved stratification and more personalised therapeutic approaches.

Genome-wide association studies have identified more than 300 genetic risk loci for SLE, several of which are associated with renal involvement and may interact with environmental factors such as smoking.[10–15] We have previously shown that a Polygenic Risk Score (PRS) based on 57 SLE risk variants is associated with an increased risk of developing LN and progression to ESKD.[16] Environmental contributions to disease risk and progression may be captured in part through epigenetic mechanisms, particularly DNA methylation, with hypomethylation of interferon-regulated genes representing a key feature of SLE.[17]

In this study, we investigated whether high polygenic and/or epigenetic risk burden in patients with SLE is associated with time to LN relapse, and whether these associations differ according to initial therapy.

METHODS

Participants and clinical data

Caucasian patients with biopsy-verified LN between 1974 and 2022 treated at Uppsala, Linköping and Karolinska University hospitals, and for whom clinical, genetic and/or epigenetic data were available (n=149), were included in the LN relapse analysis. Clinical data were retrospectively extracted from patients' medical records. Baseline was defined as the date of biopsy-verified LN, and baseline data were collected within approximately ±1 month of the first LN diagnosis. LN was classified according to WHO or International Society of Nephrology/Renal Pathology Society (ISN/RPS). Class III and IV, including subclasses, were considered proliferative. Relapse nephritis was defined by the treating physician's clinical judgement together with a concurrent change in treatment, including a change in medication, an increased dose or an escalation of prednisolone to >20 mg/day. Estimated glomerular filtration rate (eGFR) was calculated using the Lund-Malmö equation: $eGFR = e^{X-0.0158 \times age + 0.438 \times \ln(age)}$, where X was defined according to sex and serum creatinine level. For women with creatinine <150 µmol/L, X=2.50 + 0.0121 × (150 – creatinine), for women with creatinine ≥150 µmol/L X = 2.50–0.926 × ln(creatinine / 150), for men with creatinine <180 µmol/L, X=2.56 + 0.00968 × (180 – creatinine), and for men with creatinine ≥180 µmol/L: X=2.56–0926 × ln(creatinine / 180). For individuals who underwent kidney transplant during follow-up due to ESKD, serum creatinine was set to 1000 µmol/L for the purpose of eGFR calculation. Hypertension was defined as a blood pressure above 140/90 mm Hg. Data on initial treatment, including cyclophosphamide (CYC), mycophenolate mofetil (MMF), rituximab (RTX) or azathioprine (AZA), were extracted from medical charts. Seventeen patients, predominantly diagnosed with class II or V LN, received no or alternative initial treatments (online supplemental table 1). Six individuals received initial treatment with both CYC and an additional immunosuppressant (three also received MMF, one RTX, one AZA and one patient received MMF+RTX the first month and thereafter CYC). Data on use of antimalarials were extracted from medical charts at the time of methylation blood sampling.

Genotyping and PRSs

Genotyping was performed using the Illumina's Global Screening Array (GSA), SNP&SEQ Technology platform at Science for Life Laboratory in Uppsala, Sweden. Quality control (QC) was performed as previously described.[18] Briefly, preimputation QC was followed by imputation using Sanger Imputation Service. The post-imputation QC was conducted at both variant and sample levels. Single nucleotide variants (SNVs) showing significant differential missingness between cases and controls (PLINK (test-missing), p<0.001) were excluded to reduce potential technical artefacts.

A failure in the Hardy-Weinberg equilibrium test ($p<1\times10^{-4}$), minor allele frequency under 0.01, SNVs with missingness >2% and imputation quality (imputation information score, INFO) <0.8 were excluded. At the sample level, principal component analysis (PCA) was performed jointly with reference populations from the International HapMap Project. Individuals located more than ±5 SD from the centroid of the European reference cluster in PCA space were excluded and considered to be of non-European ancestry. Samples with a call rate below 95%, excess heterozygosity (±5 SD), samples with a pairwise identity by descent over 0.1875 and samples with mismatch in registered sex and the inbreeding coefficient F, calculated on the X chromosome (>0.2 for women or <0.8 for men), were also removed.

Polygenic Risk Score

The PRS was calculated as previously described by Reid *et al*.[16] Briefly, for each individual, the natural logarithm of the OR for each SNV was multiplied by the number of SLE risk alleles, yielding one score per SNV. The PRS was calculated as the sum of all individual SNV scores. SNV selection was based on the ImmunoChip gene score reported by Reid *et al*.[16] If a specific SNV was not available on the GSA, a proxy SNV in linkage disequilibrium (LD; $r^2 \geq 0.8$) was used. Two SNVs could not be included due to missingness. The final PRS comprised 55 of the original 57 SNVs (see online supplemental tables 2 and 3). The Pearson correlation coefficient between the original 57 SNV PRS (ImmunoChip-based) and the 55 SNV PRS (GSA-based) was 0.91. Genotype data for all 55 SNVs were available for all individuals included.

Methylation analysis and methylation risk score

DNA methylation was measured using the Infinium HumanMethylation450 BeadChip (HM450k, Illumina, San Diego, California, USA), covering 485 577 cytosine-phosphate-guanine (CpG) sites, previously described by Imgenberg-Kreuz *et al*. The R Minfi package was used

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for QC and normalisation.[17 19 20] Methylation levels were expressed as beta values (range 0–1), corresponding to 1%–100% methylation, and were used to calculate the Methylation Risk Score (MRS) as described below.

Methylation Risk Score

The top differentially methylated CpG sites in the SLE-control comparison in the study by Imgenberg-Kreuz *et al* were initially selected (n=32, |delta-beta|>0.1 between SLE and controls, p<0.0001).[17] When multiple CpG sites mapped to the same locus, the site with the largest effect size (ie, absolute delta-beta in the original study) was retained, resulting in a total of 17 CpG sites (online supplemental table 4). The MRS was calculated using the formula: Z-score = $(value_{individual} - mean_{controls})/SD_{controls}$. For each individual, the Z-scores were derived from DNA methylation levels (beta-values) at the selected CpG sites, using the mean and SD of the control group for standardisation. Z-scores of CpG sites hypomethylated in SLE were multiplied by −1. The MRS was then calculated as the sum of all 17 CpG sites.

Patient and public involvement

No patient partner has been involved in the design, recruitment or conduct of this study. Our patient partner will be involved in dissemination of the results.

Statistical analysis

All numerical variables are presented as mean and SD or range; all categorical variables as counts and percentages. For statistical testing, linear model analysis of variance was used for continuous variables, Pearson's χ^2 test for categorical variables and Fisher's exact test for categorical variables with few (<5) observations in the cross table.

For LN relapse, Cox proportional hazards models were used with relapse (yes/no) and time to relapse or last follow-up (years) as the outcome variable. Three different models were used: one for all patients regardless of treatment (n=137 for PRS, n=121 for MRS, n=109 for PRS and MRS combined), one for CYC-treated patients (n=64 for PRS, n=62 for MRS, n=54 for PRS and MRS combined) and one for non-CYC-treated patients (n=73 for PRS, n=59 for MRS, n=55 for PRS and MRS combined). The models included sex (male/female), year of the first nephritis and centre (Uppsala, Linköping, Stockholm) as covariates. Centres were included in the model due to numerical differences in LN relapse rates and for variations in clinical practice regarding the timing of repeated biopsies across the participating university hospitals. To assess the predictive contribution of the MRS in addition to PRS, the PRS was evaluated alone and in combination with the MRS using a likelihood ratio test. Schoenfeld residuals were visually assessed without any obvious

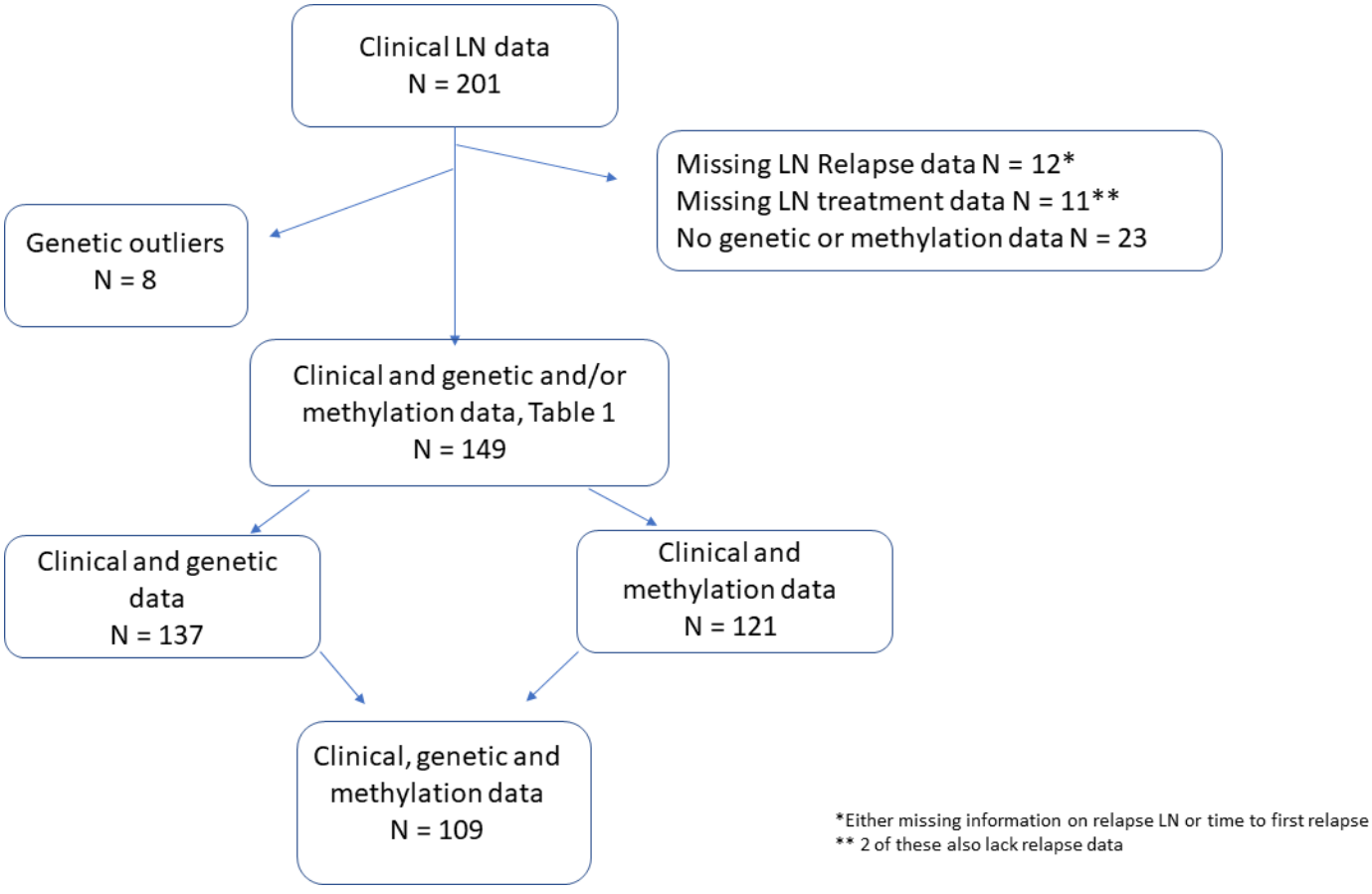

Figure 1 Flow chart over included individuals. LN, lupus nephritis.

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violation of the proportional hazards assumption. RStudio V.2025.09.0+387 was used for the analysis. In total 149 individuals were included in the study; see figure 1.

All patients gave informed consent.

RESULT

The mean age at SLE diagnosis was 33 years, with a mean interval of 3 years until the first episode of LN (table 1). At LN onset, 64% of patients had proliferative nephritis. Initial LN therapy comprised CYC in 48% of patients, MMF in 22%, AZA in 22% and RTX in 7%. At LN onset, 51% of patients were on antihypertensive treatment, including 45% who were prescribed an ACE inhibitor or an angiotensin II receptor blocker. Over a mean follow-up of 17 years, 33% (n=49) experienced at least one LN relapse after an average of 8 years (range 0–34 years).

Patients with relapsing LN received their SLE and LN diagnoses earlier than those without relapse, with mean year of SLE and LN diagnosis 1996 and 1999, respectively, compared with 2001 and 2005 in the non-relapsing group (p<0.01 for both). The mean duration of follow-up was longer among patients with relapsing LN (20 years) than among those without relapse (16 years; p=0.02). No significant differences were observed between the groups with respect to sex distribution, LN class, hypertension treatment or double-stranded DNA (dsDNA) antibodies. Patients with relapsing LN were less frequently treated with MMF than those without relapse (12% vs 27%; p=0.04), and there was a trend towards greater use of AZA in the relapsing group (31% vs 17%; p=0.06), table 1. Data on the use of antimalarials at the time of methylation blood sampling were available for 118 individuals. There were no differences in antimalarial use between the groups (44% in relapsing LN and 43% in non-relapsing LN; p=0.91). For baseline characteristics of CYC and non-CYC treated patients see online supplemental table 5.

PRS and LN relapse

We first examined the association between PRS and time to LN relapse in the full cohort, regardless of treatment. In this analysis, PRS was not related to time to relapse (HR=1.00 (0.77–1.30); p=0.99). Given the important role of treatment in LN progression, we next evaluated whether the association between PRS and relapse differed by initial therapy. Noteworthy, patients receiving CYC showed a different response pattern compared with those treated with other regimes (online supplemental figure 1). We therefore stratified patients into two groups based on whether they received CYC as part of their initial treatment or not. Among the CYC-treated patients, PRS did not differ between relapsing and non-relapsing patients (PRS=8.4 in relapse and 8.6 in non-relapse; p=0.45). In contrast, in the non-CYC group, relapsing patients exhibited a nominally higher PRS than non-relapsing patients (PRS=9.1 in relapse LN and PRS=8.5 in non-relapse; p=0.06) (figure 2). Similarly, PRS was not associated with time to LN relapse in the CYC-treated group (HR=0.81 (0.55–1.20); p=0.29). In the non-CYC group, however, the CI suggested a potential, though non-significant, association between higher PRS and shorter time to relapse (HR=1.26 (0.88–1.81); p=0.21).

MRS and LN relapse

Next, we analysed MRS and time to LN relapse regardless of treatment in the complete cohort. As for PRS, MRS was not associated with time to LN relapse (HR=1.01 (1.00–1.02); p=0.21) in this group. Since the relationship between MRS and LN relapse followed the same pattern as for PRS, where CYC-treated patients differed in their relationship to MRS compared with the other initial treatments (online supplemental figure 2), we stratified the group into CYC-treated and non-CYC-treated patients. Among CYC-treated patients, MRS was similar in relapsing and non-relapsing individuals (MRS=51.9 in relapse and MRS=54.0 in non-relapse; p=0.78). In contrast, within the non-CYC group, relapsing patients exhibited a nominally higher MRS than responders (MRS=67.8 in relapse LN and MRS=53.6 in non-relapse; p=0.09) (figure 2). Correspondingly, MRS was not related to time to LN relapse in the CYC-treated patients (HR=1.00 (0.99–1.02); p=0.89), but a trend was observed in the non-CYC-treated group (HR=1.02 (1.00–1.03); p=0.066). These results indicate a potential treatment-specific influence of MRS on LN relapse.

Combining polygenic and MRS and LN relapse

To assess the effect of adding MRS to the PRS model, both variables were included in the same model. Among non-CYC-treated patients, a trend was observed for PRS (HR=1.56 (0.97–2.50); p=0.066), while the MRS was significantly associated with shorter time to LN relapse (HR=1.02 (1.00–1.04); p=0.037, figure 3). Inclusion of MRS significantly improved model performance compared with PRS alone, as assessed by the likelihood ratio test (p=0.028). In contrast, in an analysis including all patients, regardless of treatment, neither PRS nor MRS was associated with time to LN relapse (PRS: HR=1.06 (0.79–1.43); p=0.70; MRS: HR=1.01 (1.00–1.02), p=0.21). Similarly, in CYC-treated patients, neither PRS nor MRS was associated with time to LN relapse (PRS: HR=0.76 (0.48–1.23); p=0.27; MRS: HR=1.00 (0.99–1.02); p=0.66). All models were adjusted for centre, sex and the year of first nephritis. Collectively, the data support a potential treatment-dependent contribution of combined genetic and epigenetic risk on LN relapse.

Because combined PRS-MRS analyses required availability of both genetic and methylation data, fewer patients were included compared with models evaluating PRS and MRS separately. In the combined non-CYC-treated group, AZA use was numerically more frequent than in the PRS-only group (26 patients (47%) vs 29 patients (40%)) and slightly higher than in the MRS-only group (26 patients (46%)). In addition, 15 patients (27%) did not receive any of the specified initial treatments in the combined PRS and MRS group, compared with 15 (21%) in the

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Table 1 Baseline characteristics at time of first lupus nephritis (LN) diagnosis

	Non-relapsing LN (n=100)	Relapsing LN (n=49)	Total (n=149)	P value
Centre				0.01
Uppsala	37 (37.0%)	23 (46.9%)	60 (40.3%)	
Linköping	42 (42.0%)	9 (18.4%)	51 (34.2%)	
Stockholm	21 (21.0%)	17 (34.7%)	38 (25.5%)	
Sex				0.74
Female	73 (73.0%)	37 (75.5%)	110 (73.8%)	
Male	27 (27.0%)	12 (24.5%)	39 (26.2%)	
Age at SLE diagnosis*				<0.01
Mean (SD)	35 (18)	27 (13)	33 (17)	
Range	7–80	10–61	7–80	
Age at LN diagnosis				<0.01
Mean (SD)	39 (18)	31 (13)	36 (17)	
Range	11–84	12–61	11–84	
Year of First LN				<0.01
Mean (SD)	2005 (10)	1999 (9)	2003 (10)	
Range	1979–2022	1974–2021	1974–2022	
Nephritis class *				0.93
II	16 (16.3%)	7 (15.2%)	23 (16.0%)	
III	22 (22.4%)	9 (19.6%)	31 (21.5%)	
III+IV	2 (2.0%)	1 (2.2%)	3 (2.1%)	
III+V	6 (6.1%)	1 (2.2%)	7 (4.9%)	
IV	34 (34.7%)	17 (37.0%)	51 (35.4%)	
IV+V	2 (2.0%)	2 (4.3%)	4 (2.8%)	
V	16 (16.3%)	9 (19.6%)	25 (17.4%)	
Induction treatment				
Cyclophosphamide	45 (45.0%)	27 (55.1%)	72 (48.3%)	0.25
Mycophenolate mofetil	27 (27.0%)	6 (12.2%)	33 (22.1%)	0.04
Rituximab	9 (9.0%)	1 (2.0%)	10 (6.7%)	0.17
Azathioprine	17 (17.0%)	15 (30.6%)	32 (21.5%)	0.06
Hypertension*	39 (45.9%)	9 (30.0%)	48 (41.7%)	0.13
Hypertension treatment*	48 (51.6%)	18 (50.0%)	66 (51.2%)	0.87
ACE inhibitors or angiotensin II receptor blocker*	42 (45.2%)	17 (45.9%)	59 (45.4%)	0.94
dsDNA antibodies*	64 (74.4%)	30 (85.7%)	94 (77.7%)	0.18
Estimated glomerular filtration rate (mL/min)*				0.55
Mean (SD)	75 (26)	72 (25)	74 (25)	
Range	13–142	26–114	13–142	
Follow-up, years				0.02
Mean (SD)	16 (10)	20 (10)	17 (10)	
Range	0–44	1–40	0–44	
Year to first relapse				
Mean (SD)	NA	8 (7)	8 (7)	
Range	NA	0–34	0–34	

*Data are missing, included number of individuals; year of diagnosis and age at SLE diagnosis n=148, nephritis class n=144, hypertension (blood pressure above 140/90 mm Hg) n=115, hypertension treatment n=129, ACE inhibitors or angiotensin II receptor blocker n=130, double-stranded DNA (dsDNA) antibodies and estimated glomerular filtration rate n=121. Nephritis class according to WHO or International Society of Nephrology/Renal Pathology Society (ISN/RPS). For statistical testing linear model analysis of variance was used for continuous variables, Pearson's χ^2 test for categorical variables and Fisher's exact test for categorical variables with few (<5) observations in the cross table.

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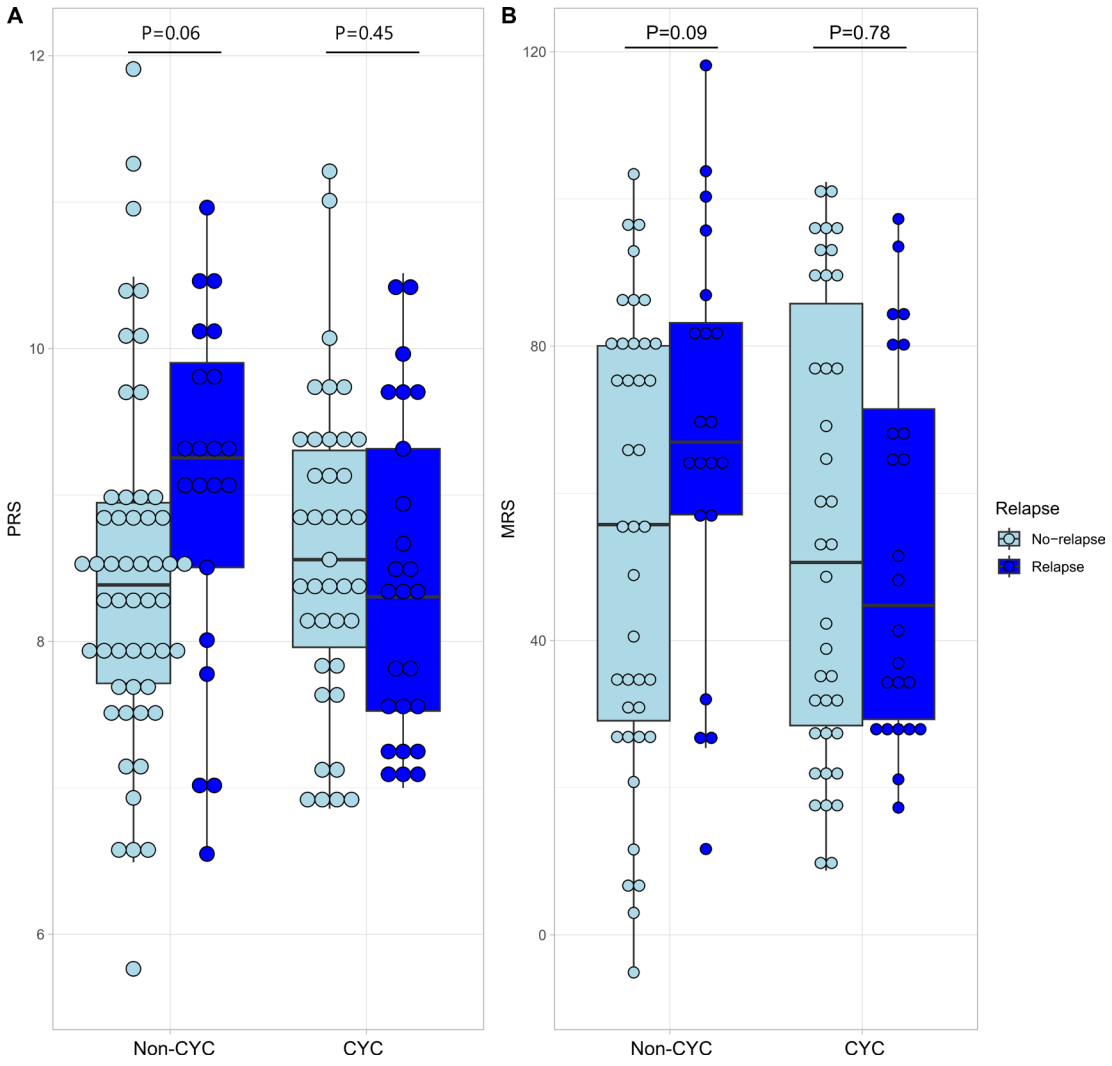

Figure 2 Boxplots of Polygenic Risk Score (PRS) and lupus nephritis (LN) relapse, treated without cyclophosphamide (non-CYC) or with cyclophosphamide (CYC) (A). Boxplots of Methylation Risk Score (MRS) and LN relapse treated without cyclophosphamide (non-CYC) or with cyclophosphamide (CYC) (B). Hinges indicates first and third quartiles, the whisker extends to smallest/largest value or 1.5 IQR. All individual data points are indicated by blue or light blue dots.

PRS group and 17 (29%) in the MRS group (see online supplemental information). These differences should be considered when interpreting results from the combined models

DISCUSSION

In this exploratory study of Caucasian patients with SLE, we show that genetic and epigenetic risk may influence time to LN relapse in a treatment-dependent manner. In patients treated with initial therapy with CYC, no association was observed, suggesting that this therapy can overcome differences in individual risk. Among patients not receiving CYC, higher genetic and epigenetic risk tended to predict shorter time to relapse. Adding epigenetic risk to the genetic risk model improved the predictive capacity, with significant association for the MRS and a similar trend for the PRS. If confirmed prospectively, these findings suggest that low-risk patients might be managed with less intensive therapy, and that genetic and epigenetic profiling at LN diagnosis could help tailor treatment.

In the PRS model, CIs suggested a potential effect on shorter time to LN relapse in non-CYC-treated patients. This effect was stronger and borderline significant in the combined PRS-MRS model. Similarly, the MRS-only model showed borderline significance, whereas the combined PRS-MRS model reached significance. Although the combined group was smaller, it included a numerically higher proportion of AZA-treated patients compared with the PRS-only or MRS-only groups, suggesting that the relationship between PRS and MRS and time to relapse may be most pronounced in patients receiving less aggressive treatment. Our patient cohort is too small to perform subgroup analyses by treatment, which could further refine patient stratification. High PRS has previously been linked to kidney disease in patients with SLE,[16 21] making it challenging to stratify high-genetic-risk individuals by relapse risk. Additionally, relapse is

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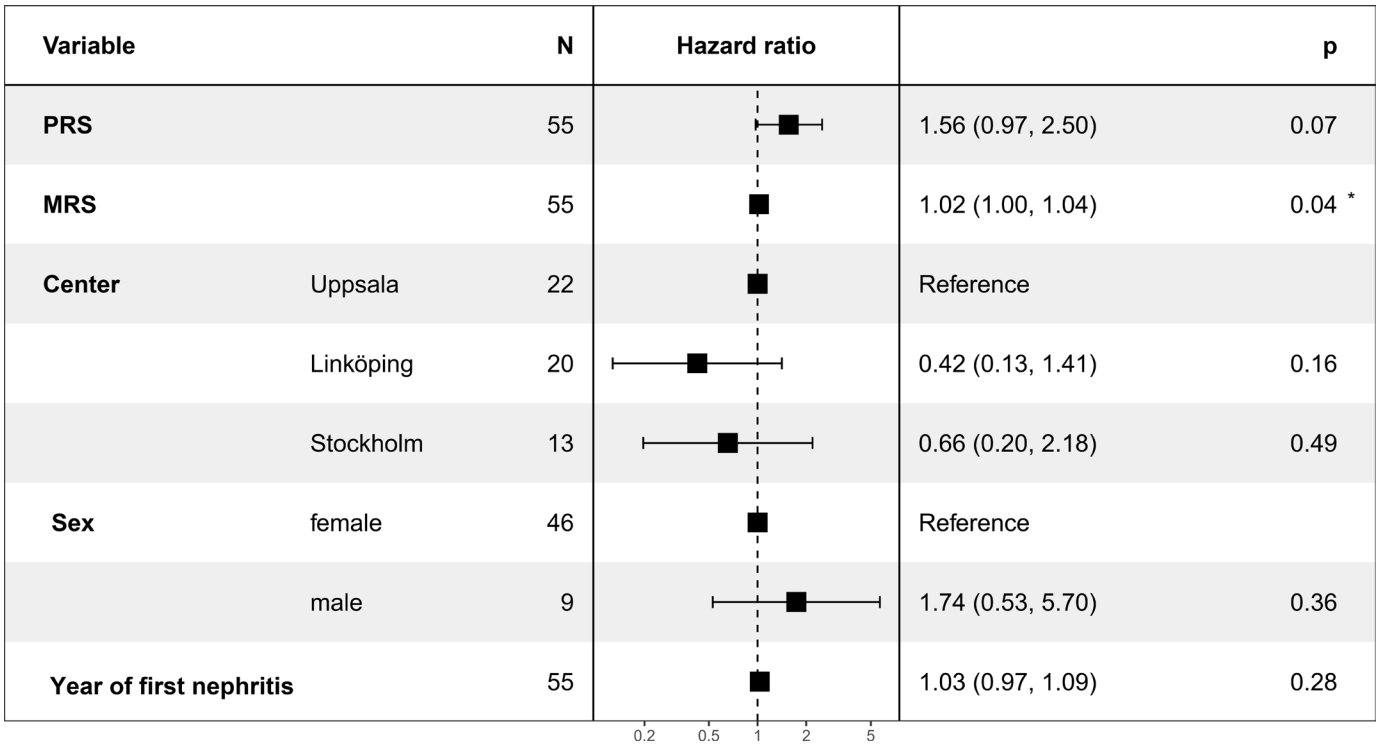

Figure 3 Forest plot of Polygenic Risk Score (PRS) and Methylation Risk Score (MRS) in non-cyclophosphamide-treated patients in the combined model with PRS and MRS. *Indicates p<0.05.

also influenced by other factors,[22] which may attenuate detectable genetic and epigenetic effects. Together with the relatively small sample size, this likely explains the borderline significant results.

It is possible that treatment influenced DNA methylation. We have previously observed an association between glucocorticoid treatment and methylation status in SLE. However, these results are difficult to interpret, as most glucocorticoid-related sites also differ significantly in patients with SLE not treated with glucocorticoids compared with controls.[17] Only two individuals with relapsing nephritis had methylation data obtained before LN diagnosis, making subgroup analysis on these individuals impossible. DNA methylation changes in patients with SLE are generally considered stable over time,[23] though eight of our CpG sites have been found to change during follow-up.[24 25] In addition, interferon-regulated sites may be more prone to change.[24] Thus, we cannot exclude the possibility that the MRS used here may change over time. However, the parallel patterns observed for genetic and epigenetic risk scores in relation to treatment and LN relapse suggest that the MRS does not simply reflect treatment effects. Validation of the MRS in untreated patients will be necessary to confirm its predictive value.

CYC is a potent treatment for LN and has been shown to induce broad alterations in the blood transcriptome of patients with SLE, reflecting widespread effects on the immune system.[26] It is recommended for organ-threatening and/or life-threatening manifestations of SLE.[4] Previously, CYC was regarded as first-line therapy before the more widespread use of MMF and biologics. Current LN treatment is primarily guided by histological findings, although other factors such as ethnicity and disease severity are also considered.[4–6] Recent European Alliance of Associations for Rheumatology, American College of Rheumatology and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend combination therapy, adding belimumab (to CYC or MMF), a calcineurin inhibitor, or obinutuzumab (to MMF) for proliferative nephritis, although it is still unknown which patients will benefit most from early combination therapy.[4–6] Our results indicate that individuals with the lowest genetic and epigenetic risk may not relapse even when they are treated with less potent therapies. Incorporating this information at diagnosis may help identify patients who may not require early combination therapy, potentially reducing exposure to the adverse effects of aggressive treatment.

To our knowledge, no studies have yet investigated the relationship between PRS and treatment response in LN, although several studies have examined individual genetic variants in relation to drug metabolism, side effects and treatment response in LN and patients with SLE.[27–31] Our 55-SNV risk score includes a variant in the Fcγ receptor gene (*FCGR*) associated with SLE, whereas other *FCGR* variants have been linked to CYC treatment response in LN.[29] The PRS variant is not in high LD with the CYC-response-associated SNVs (r^2<0.15). Incorporating SLE risk variants with genetic polymorphisms that influence drug metabolism or treatment response could enable the development of refined PRS specifically designed to predict treatment response outcomes in LN. In addition,

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we used an MRS built on the most differentially methylated sites in patients with SLE compared with controls. Previous studies have identified methylation sites associated with LN, and these sites may be used to further refine the MRS.[32 33]

Ding *et al* recently developed a 112-SNV PRS that predicted LN development in a Chinese SLE cohort. Patients with low clinical risk but high genetic risk had a significantly higher likelihood of developing LN compared with those with both low clinical and genetic risk.[34] This highlights that incorporating genetic information at diagnosis can improve risk stratification, providing additive value beyond clinical information. In our study, treating physicians did not have access to genetic information and based treatment decisions on all available clinical and laboratory information. In retrospect, it is evident that some patients with high genetic and epigenetic risk received less aggressive therapies, such as AZA, and our results indicate that they had a greater risk of LN relapse. Thus, even in our study, the genetic and epigenetic information appears to add value to clinical assessment, although this was not the primary focus of the study and was not formally evaluated.

The main strengths of this study include a well-characterised cohort with comprehensive clinical data extracted from medical charts and a long follow-up period. To our knowledge, this is also one of the largest cohorts of patients with SLE for which both genome-wide genetic and DNA methylation data are available. However, several limitations should be acknowledged. Clinical data were collected retrospectively, and treatment strategies evolved over the study period, which may have introduced heterogeneity in patient management. In addition, no objective measures of treatment adherence were available, a factor reported to be both common and associated with SLE flares.[35 36] Another limitation is that sampling for DNA methylation analysis did not coincide with the time of LN diagnosis in most cases and consequently observed methylation patterns may be influenced by ongoing treatment. An additional strength of the study is the use of real-world clinical data. Although this may introduce variability, it likely reflects clinical practice and enhances generalisability of our findings.

In conclusion, our findings suggest that genetic and epigenetic profiling at LN diagnosis may help distinguish patients who could be managed with less aggressive therapy from those who may benefit from intensive treatment. These results require replication in independent cohorts, and the risk scores could potentially be refined further by incorporating known genetic variants associated with treatment response and adverse drug reactions.

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Contributors ESk, DL, MKS, IG and CS designed the study. LR, ESv, DL, CS and IG contributed to funding acquisition and inclusion of patients. ESk, OS, FF, IG and CS collected patient data. NO, AS, HV and JIK developed the PRS and MRS. ESk performed the statistical analysis with inputs from AS, NO, JIK and DL. ESk drafted the manuscript together with DL. DL is the guarantor. All authors read and approved the final version of the manuscript. R studio was used as the statistical program. AI (Chat GTP and Gemini) was asked for suggestions for R-code and sometimes to help find mistakes/errors in the code. All R code was then manually checked by two of the authors.

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ORCID iDs
Elisabeth Skoglund https://orcid.org/0000-0003-4243-9575
Holme Vestin https://orcid.org/0009-0005-6622-8897
Nina Oparina https://orcid.org/0000-0003-3179-1258
Francesca Faustini https://orcid.org/0000-0002-6753-7107
Elisabet Svenungsson https://orcid.org/0000-0003-3396-3244
Lars Ronnblom https://orcid.org/0000-0001-9403-6503
Maria K Svensson https://orcid.org/0000-0001-7545-5585
Juliana Imgenberg-Kreuz https://orcid.org/0000-0002-7230-8990
Christopher Sjöwall https://orcid.org/0000-0003-0900-2048
Dag Leonard https://orcid.org/0000-0002-6275-7282

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