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Table 1 Baseline variables associated with LLDAS achievement based on multivariable Cox models

Characteristics	Model 1		Model 2		Model 3	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age at disease onset, years	1.010 (1.003-1.016)	0.005	1.009 (1.002-1.016)	0.010	1.010 (1.003-1.017)	0.004
Treatment-naïve	1.346 (1.105-1.641)	0.003	1.425 (1.161-1.749)	0.001	1.484 (1.204-1.830)	<0.001
Nephritis	0.776 (0.641-0.939)	0.009	1.066 (0.820-1.385)	0.634	0.925 (0.737-1.160)	0.498
SLEDAI			0.968 (0.950-0.987)	0.001		
PGA					0.685 (0.551-0.853)	0.001
Daily prednisone (or equivalent) dose, mg/d			1.003 (0.998-1.007)	0.266	1.005 (0.999-1.010)	0.093
HQC	1.638 (1.263-2.123)	<0.001	1.713 (1.318-2.225)	<0.001	1.664 (1.284-2.157)	<0.001

Figure 1 Matrix model for time to LLDAS.

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THU0248 **GLOMERULAR AND TUBULOINTERSTITIAL LESIONS IN PER-PROTOCOL REPEAT BUT NOT BASELINE KIDNEY BIOPSY PORTEND RELAPSE AND LONG-TERM RENAL FUNCTION IMPAIRMENT, RESPECTIVELY, IN INCIDENT CASES OF PROLIFERATIVE LUPUS NEPHRITIS**

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Background: In patients with lupus nephritis (LN), clinical response to treatment and renal histopathology have been shown to be discordant. No clinical or laboratory markers have to date been shown to reliably portend renal prognosis, in particular renal function impairment.
Objectives: To investigate whether per-protocol repeat renal biopsies are predictive of LN relapses and long-term impairment of renal function.
Methods: Forty-two patients with an incident biopsy-proven active proliferative (class III/IV ± V) LN from the LN database of the Université catholique de Louvain were included in the present retrospective study. Per-protocol repeat kidney biopsies were performed in all patients after a median time of 24.3 (IQR: 21.3–26.2) months. The NIH activity index (AI) and chronicity index (CI) scores were assessed in both baseline and repeat biopsies. We defined acute glomerular lesions as cellular proliferation, fibrinoid necrosis or karyorrhexis, cellular crescents, hyaline thrombi or wire loops, and leucocyte infiltration, and chronic glomerular lesions as glomerular sclerosis and fibrous crescents, in alignment with the NIH activity and chronicity indices. Similarly, we defined acute

tubulointerstitial lesions as mononuclear cell infiltration and chronic tubulointerstitial lesions as interstitial fibrosis and tubular atrophy.
Results: Despite a moderate correlation between urinary protein/creatinine (U-P/C) ratios and AI scores at repeat biopsy ($r=0.48$; $P=0.001$), ten patients (23.8%) with U-P/C ratios <1.0 g/g still had a high degree of histological activity (AI score >3). High AI scores in repeat (but not baseline) kidney biopsies were associated with an increased probability and/or shorter time to renal relapse ($N=11$) following the repeat biopsy (HR: 1.2; 95% CI: 1.1–1.3; $P=0.007$), independently of proteinuria levels. This association remained significant for the NIH activity index items within the glomerular but not the tubulointerstitial compartment of the kidney biopsies. High NIH CI scores in repeat (but not baseline) kidney biopsies were associated with a sustained increase in serum creatinine levels corresponding to $\geq 120\%$ of the baseline value (HR: 1.8; 95% CI: 1.1–2.9; $P=0.016$) through a median follow-up time of 131.5 (IQR: 73.8–178.2) months, being the case also for acute and chronic tubulointerstitial lesions in repeat but not baseline kidney biopsies.
Conclusion: Our results highlight the usefulness of per-protocol repeat biopsies as an integral part of the treatment evaluation, also in patients who have shown adequate clinical response. Glomerular lesions consistent with active renal disease portend LN relapses, while tubulointerstitial lesions consistent with active disease and chronic damage portend long-term renal function impairment.
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THU0249 **CLINICAL FEATURES AND RENAL PROGNOSIS IN LUPUS NEPHRITIS PATIENTS UNDERGOING A REPEATED BIOPSY: RESULTS OF 103 RE-BIOPSIES IN 438 PATIENTS**

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Background: Indications to repeat renal biopsy (RB) in lupus nephritis (LN) are not unanimously acknowledged.
Objectives: To evaluate the renal outcome of patients with LN undergoing a second RB.
Methods: We retrospectively analyzed prospectively collected data of patients with LN followed up in four Italian referral centres for systemic lupus erythematosus. Serological and clinical information were retrieved according to a shared database. RB were classified according to ISN/RPS 2003 classification; chronicity (CI) and activity indexes (AI) were defined according to Austin et al. The primary renal outcome was renal failure, defined as serum creatinine (Scr) >1.0 mg/dL with eGFR <60 ml/min. Non-parametric tests were used for statistics. Patients repeating RB due to renal remission were excluded from the analysis.
Results: Four-hundred and thirty-eight patients were recruited. One-hundred and three patients repeated RB after 6.1 ± 4.7 (mean $\pm$ SD) years from the first due to: protocol biopsy due to renal remission (Group 1, $n=8$); proteinuric flare (Group 2, $n=51$); worsened renal function (Group 3, $n=26$); partial renal response (Group 4 $n=18$). Patients undergoing a second RB were younger ($p<0.001$), had lower serum C3 at LN diagnosis ($p<0.001$) and displayed more frequently class IV and higher AI at first RB ($p=0.0038$ and $p=0.043$, respectively). At the end of follow-up, patients who repeated RB had more frequently renal failure ($p=0.003$). At the second RB, the histological class was unchanged in 55% of patients. CI increased at second RB compared to the first (3.6 ± 2.4 vs. 1.7 ± 1.7 ; $p<0.001$). Overall, 26 out of 103 patients (25%) developed renal failure: 0 from group 1, 10 from group 2, 14 from group 3, 2 from group 4 ($p<0.001$). Uncontrolled hypertension at LN diagnosis, increased Scr and increased proteinuria at second RB predicted renal failure (Table).
Conclusion: Patients undergoing a repeated RB had more aggressive clinical and histological features already at first RB and developed renal failure more frequently. Among baseline features, uncontrolled hypertension had the strongest association with renal failure, thus suggesting that control of blood pressure since early stages is highly advisable.
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Table . Comparison of patients undergoing 2nd RB according to development of renal failure

	Renal failure (n=26)	No renal failure (n=69)*	p
Total FU (years), mean (SD)	21 (10.4)	16.5 (9.39)	0.002
SCr (mg/dl) at 2° RB, mean (SD)	1.7 (1)	0.98 (0.35)	0.001
Proteinuria (g/24h) at 2° RB, mean (SD)	4.7 (3.9)	2.99 (2.63)	0.022
Class IV and IV+V at 2° RB, %	76.9	54.5	0.07
Hypertension at onset, %	84.6	32.4	<0.001
HCO intake at 2° RB, %	9.5	52	<0.001
Glucocorticoids at 2° RB %	84	87	ns
Immunosuppressants at 2° RB %	40	58	ns
AI at onset, mean (SD)	7.14 (3.95)	7.02 (3.86)	ns
AI at 2° RB, mean (SD)	5.37 (4.12)	4.02 (3.71)	ns
CI at onset, mean (SD)	2.05 (1.88)	1.56 (1.64)	ns
CI at 2° RB, mean (SD)	3.87 (3.08)	3.52 (2.16)	ns
Years between 2° RB and end of FU, mean (SD)	14.1 (10.5)	9.3 (8.84)	ns

*Group 1 excluded

RB, renal biopsy; AI, activity index; CI, chronicity index; SCr serum creatinine; FU, follow-up; SD, standard deviation.

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THU0250 URINE AND SERUM S100 PROTEINS ASSOCIATE WITH LUPUS NEPHRITIS AND RESPONSE TO TREATMENT

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune/inflammatory disease. Approximately 30% of SLE patients develop lupus nephritis (LN) that affects treatment and prognosis. Easily accessible biomarkers do not exist to reliably predict renal disease¹. Recently, calcium-binding S100 proteins have been suggested as biomarkers in systemic inflammatory conditions, including SLE^{2,3}.

Objectives: The MASTERPLANS Consortium aims to identify indicators of treatment responses in SLE. This study tested the applicability of S100 proteins in serum and urine as biomarkers for disease activity and response to treatment with rituximab in LN.

Methods: S100A8/A9 and S100A12 proteins were quantified in the serum and urine of 243 SLE patients from the BILAG-BR study and 48 matched controls using MSD technology to determine whether they perform as biomarkers for active LN (n=85 SLE patients) and/or may be used to predict response to treatment with rituximab. Renal disease activity and response to treatment was based on BILAG-BR scores and changes in response to treatment^{4,5}.

Results: Serum S100A12 (p<0.001), and serum and urine S100A8/A9 (p<0.001) are elevated in SLE patients. While serum and urine S100 levels do not correlate with global SLE disease activity (SLEDAI), levels in urine and urine/serum ratios are elevated in SLE patients with active LN (S100A8/A9: urine p>0.005, urine/serum p<0.05; S100A12: urine p<0.05, serum/urine p<0.005). S100 proteins perform better as biomarkers for active LN involvement in SLE patients positive for anti-dsDNA antibodies. Lastly, binary logistic regression and AUC analysis suggests the combination of serum S100A8/A9 and S100A12 to predict response to RTX treatment in LN after 6 months.

Conclusion: Findings from this study show promise for clinical application of S100 proteins to predict active renal disease in SLE and response to treatment with rituximab. Significantly overlapping values between groups currently prohibit the definition of cut-off values and prospective studies are required to validate findings.

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THU0251 IMMUNOPHENOTYPIC CLUSTERS OF SLE PATIENTS REVEAL SUBGROUPS WITH SEVERE DISEASE RESISTANT TO CONVENTIONAL THERAPY

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Background: Biomarkers to predict response to rituximab include plasmablasts and, in the current MASTERPLANS consortium, Sm/U1RNP antibodies and high expression of IFN Score B (a subset of interferon-stimulated genes that predict more clinical outcomes than a classic interferon signature). The relationships amongst these biomarkers and their association with response to conventional therapies are less well described.

Objectives: To analyse the inter-relationships amongst immune biomarkers in two independent SLE cohorts in association with disease activity and stage of therapeutic pathway.

Methods: CONVAS is a cohort of unselected SLE patients; data available include current and historic disease activity, use of biologic therapy, flow cytometry, gene expression (IFN Score A and IFN Score B), and immunoprecipitation for autoantibodies (n=91). BILAG-BR is a British registry study for SLE patients commencing biologics; data available include current and historic disease activity, gene expression (IFN Score A and IFN Score B) and immunoprecipitation for autoantibodies (n=112). In both cohorts, biologics were only prescribed to patients with active disease (BILAG 1 x A or 2 x B) and failure of either cyclophosphamide or mycophenolate. Given the mixture of continuous and categorical variables, data were clustered using Gower distance and Partitioning Around Medoids. K was chosen using silhouette coefficient and clusters visualised with t-Distributed Stochastic Neighbor Embedding (t-SNE).

Results: There were 6 clusters. In rituximab-naïve patients:

1. Sm/U1RNP+, Ro60-, highest IFN Score A, low CD4⁺ T cells, low NK cells, high plasmablasts
2. Sm/U1RNP-, Ro60+, medium IFN Score A, low CD4⁺ T cells, high NK cells, high plasmablasts
3. Sm/U1RNP-, Ro60-, lowest IFN Score A, high CD4⁺ T cells, low NK cells, low plasmablasts

Other antibody subtypes and flow cytometric markers did not improve the accuracy of clustering. In rituximab-treated patients, 3 equivalent clusters for antibody subtypes and IFN Score A were observed but differentiated due to flow cytometry findings, as expected after rituximab treatment. Overall, the patients in the cluster defined by Sm/U1RNP antibodies and high IFN Score A were notable for a higher rate of prior disease activity in the renal, neurological and general BILAG domains (Table 1).

Table 1 : Clinical features in unselected SLE patients (CONVAS)

System affected (ever)	Sm/U1RNP & high IFN Score A (n=27)	Other (n=92)	p value
General	14/27 (52%)	24/92 (26%)	0.02
Mucocutaneous	23/27 (85%)	73/92 (79%)	0.50
Neuro	10/27 (37%)	17/92 (19%)	0.04
MSK	25/27 (93%)	83/92 (90%)	0.71
Cardiorespiratory	9/27 (33%)	20/92 (22%)	0.22
Renal	12/27 (44%)	15/92 (16%)	0.005
Haematology	25/27 (93%)	67/92 (73%)	0.03