SUPPLEMENTAL MATERIAL

Clinical and Histopathologic Associated With Renal Outcome in Lupus

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Supplemental material (1).

Histopathology definitions

Abbreviations: GBM, glomerular basement membrane; TBM, tubular basement membrane.

Definitions for glomerular lesions

Scorable glomeruli: Glomeruli that remained after excluding those which had less than 3 mesangial fields because they were too small, on the edge of the biopsy and therefore incomplete, or otherwise artefactually damaged.
Focal: Involving <50% of glomeruli.
Diffuse: Involving ≥50% of glomeruli.
Segmental: Lesion involving less than half of the glomerular area inside Bowman's capsule.
Global: Lesion involving more than half of the glomerular area inside Bowman's capsule.
Normal glomerulus: Glomerulus without a lesion. A normal glomerulus may show subtle changes as a result of ischemia.
Minimal leukocyte influx: Occurrence of <4 neutrophils, lymphocytes, or monocytes in an otherwise normal glomerulus, in the absence of endothelial cell swelling.
Global sclerosis: Sclerosis of the entire glomerulus (obliteration of the capillary lumen by increased extracellular matrix, with or without hyalinosis or foam cells).
Segmental sclerosis: Less than 100% of the glomerular is sclerosed (obliteration of the capillary lumen by increased extracellular matrix, with or without hyalinosis or foam cells).
Ischemic glomerulus: A glomerulus showing one or more of the following lesions: wrinkling of the GBM, collapse of the capillary tuft, thickening/splitting of Bowman's capsule.
Mesangial hypercellularity: Four or more nuclei in the contiguous matrix of a peripheral mesangial segment. Note: mesangial hypercellularity is scored for each glomerulus by assessing the most cellular mesangial area. Mesangial areas immediately adjacent to the vascular stalk should not be scored. Scoring categories: (0) <4 nuclei; (1) 4-5 nuclei; (2) 6-7 nuclei; (3) >7 nuclei.
Mesangial matrix expansion: Width of extracellular matrix exceeding 2 mesangial cell nuclei in ≥2 glomerular lobules.
Endocapillary hypercellularity: Hypercellularity due to an increased number of cells within glomerular capillary lumina (leukocytes or endothelial cells), causing narrowing of the lumina. Indicate whether lesion is segmental or global.
Endocapillary inflammatory infiltrate: ≥4 inflammatory cells in the glomerulus – either granulocytes, lymphocytes, or monocytes.
Endothelial cell swelling: Prominence of endothelial cells in capillary lumens with narrowing of the lumen.
Wire loop: Capillary wall thickening characterized by subendothelial immune complex deposits as demonstrated in the PAS staining.
Adhesion: Area of continuity between glomerular tuft and Bowman capsule separate from extracapillary lesion or from area of segmental sclerosis.
Crescent: one of the following lesions involving >10% of circumference of Bowman's capsule:

- **Cellular crescent**: Extracapillary cell proliferation of ≥3 cell layers with ≥50% of the lesion occupied by cells.
- **Fibrocellular crescent**: Extracapillary lesion comprising cells and extracellular matrix, with <50% cells and <90% matrix.
- **Fibrous crescent**: Extracapillary lesion composed of ≥90% matrix.
- **Segmental crescent:** Lesion occupying less than 50% of the circumference of Bowman's capsule.
- **Circumferential crescent:** Lesion occupying 50% or more of the circumference of Bowman's capsule.

Fibrinoid necrosis: Disruption of the GBM with fibrin exudation and karyorrhexis. **Karyorrhexis**: Presence of fragmented nuclei including apoptosis.
Microthrombus: A microscopic clump of fibrin, platelets, and red blood cells.
Pseudothrombus: Eosinophilic, rounded aggregates in glomerular capillaries due to immune complex precipitates rather than fibrin, also known as hyaline thrombi.
Double contour/tram track: Double layer of GBM separated by clear zone on silver or PAS stains.
Spikes/vacuoles: Extensions of glomerular basement membrane between deposits (egg racks).

Definitions of tubulointerstitial lesions

Interstitial infiltration: Inflammatory cells within the cortical interstitium in more than 5% of the cortical area. Specify dominant cell type of infiltrate: either lymphocytes, granulocytes, or other. Scoring categories: (0) <5%; (1) 5-24%; (2) 25-49%; (3) ≥50% of the cortical area.
Interstitial fibrosis: Extracellular matrix separating tubules in more than 5% of the cortical area. Scoring categories: (0) <5%; (1) 5-24%; (2) 25-49%; (3) ≥50% of the cortical area.
Focal cortical atrophy: Subcapsular ischemic cortical atrophy, sharply demarcated from normal cortex.
Tubular atrophy: Loss of cytoplasmic organelles, accompanied by a decreased diameter of tubules and thick irregular TBM. Scoring categories: (0) <5%; (1) 5-24%; (2) 25-49%; (3) ≥50% of tubules.
Acute tubular injury: Necrosis of tubular epithelial cells (coagulation necrosis, karyorrhexis, pyknosis), swelling and clear vacuolation of tubular epithelium; can be accompanied by separation/detachment of tubular epithelium from TBM.
Tubular casts: Presence of proteinaceous structures within the lumen of the tubules; may contain cellular debris; only scored when present in nonatrophic tubuli.
Tubular luminal macrophages: Presence of macrophages in tubular lumina; distinguish from sloughed epithelial cells.
Tubular regeneration: Regeneration following acute tubular injury usually characterized by presence of mitotic figures.
Tubular reabsorption droplets: PAS/silver-positive resorption droplets in the proximal tubular epithelium.
Tubulitis: Lymphocytes/other inflammatory cells within the epithelial layer of tubules.

Definitions of vascular lesions

Vasculitis: Inflammation in an arterial/arteriolar wall, characterized by presence of inflammatory cells and/or fibrinoid necrosis.
Fibrinoid necrosis: Homogeneous, fibrin-like, deeply eosinophilic area with disruption of the architecture of the arterial/arteriolar vascular wall.
Thrombosis: Total occlusion of vessel with fibrin.
Hyaline arteriolosclerosis: Accumulation of glassy, refractive, strongly PAS-positive material in the arteriolar intima and/or media.
Fibrous intimal hyperplasia: Cellular and fibroelastic intimal thickening with a fibrous intimal projection or cushion bulging into the lumen.
Arterial intimal fibrosis: Concentric thickening of the intima by deposition of collagen.

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Supplemental material (2).

Detailed study outcomes and statistical methods

Outcomes were studied in two settings: (1) the complete cohort of patients with all observed LN classes who received various therapies and (2) a subset of patients with class III/IV (±V) LN who received induction immunosuppression including cyclophosphamide (CYC), mycophenolate mofetil (MMF), or azathioprine (AZA). Prespecified variables for multivariable analyses were: variables from the reduced histopathology dataset; interaction terms of these variables with race, age, and induction immunosuppression; and the clinical variables sex, race, time since SLE diagnosis, age_0, $proteinuria_0$, $erythrocyturia_0$, MAP_0, induction immunosuppression, and decade during which the patient was biopsied. The models described below make no assumptions about the distribution of independent variables and the dependent variable, eGFR, was normally distributed; therefore, the variables were entered in the models without transformation.

Renal flare and ESRD

The outcomes "renal flare" and "ESRD" relate to time-to-event analyses. We studied the time to a first LN flare in patients who achieved (partial) remission after induction therapy. Time to first renal flare was calculated from the date of biopsy until the date of flare for patients who reached this endpoint. For patients who did not, the follow-up time was from the time of biopsy until the last follow-up or until the patient reached ESRD. The definition of ESRD was dialysis-dependence for >3 months or renal transplantation. Time to ESRD was calculated analogous to time to renal flare. Patients who reached ESRD before the last follow-up were regarded as having eGFR=0 mL/min/1.73 m^2 at the remaining time points. Outcomes were assessed using Kaplan-Meier analysis and Log-Rank tests. To ascertain independent predictors of ESRD and renal flare, multivariable Cox proportional-hazards models were designed including the prespecified variables. The multivariable models were simplified by stepwise removal of the least significant variables. Hazard ratios and 95% confidence intervals were estimated.

eGFR during follow-up

The extent by which variables were associated with irreversible nephron loss was investigated by modeling eGFR during follow-up. An adjusted average level (intercept) and rate (slope) of decline of renal function during follow-up were modeled. Baseline variables were tested for their potential to predict a change in the intercept of this adjusted average level of decline in random intercept/slope linear mixed-effects models. Variables were tested in univariable models in the complete cohort (**Table S2.1**). A full model including the prespecified variables was designed and simplified by removing the least significant variables (Wald test) and comparing the goodness of fit of nested models (maximum likelihood ratio test). The distribution of data and the homogeneity of variance were assessed using graphical evaluation of residuals.

Progressive eGFR decline

To investigate progressive eGFR decline that did not necessarily result in ESRD and/or renal flare, variables were analyzed in association with progressive eGFR decline over 1, 5, and 10 years relative to its linear prediction based upon $eGFR_0$. The linear relationship between $eGFR_0$ and the predicted eGFR at time *t* ($eGFR_{Predicted(t)}$) was defined as: $eGFR_{Predicted(t)}=eGFR_0*\beta_{(t)}+constant$. Progressive eGFR decline relative to the $eGFR_{Predicted(t)}$ was assessed by calculating the corrected eGFR ($eGFR_{CORR(t)}$), which was defined as the difference between the observed eGFR(*t*) and predicted eGFR(*t*).(1) This procedure created a corrected value that was independent of the starting value. Variables were first tested in univariable linear regression models for the outcomes $eGFR_{CORR1}$, $eGFR_{CORR5}$, and $eGFR_{CORR10}$ in the complete cohort (**Table S2.2**). For the complete cohort and the selected subset, a prediction

model for these outcomes was designed using automated backward linear regression starting with the prespecified variables.

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Table S2.1 Univariable predictions of eGFR during follow-up up in 105 LN patients.

eGFR in mL/min/1.73 m^2 during follow-up†		β (95% CI)
Clinical variables		
Female sex		−5.5 (−21.5; 10.4)
Age_0 (y)		−0.8 (−1.3; −0.4)*
Race	*Caucasian*	0.5 (−13.1; 14.1)
	Asian	−0.8 (−16.3; 14.7)
	Afro-Caribbean	0.3 (−19.3; 20.0)
Years since diagnosis SLE_0		−1.2 (−2.3; 0.0)*
$Proteinuria_0$ (g/24h)		−0.4 (−2.1; 1.4)
$Erythrocyturia_0$ >1+		−11.9 (−42.3; 18.5)
MAP_0 (mm Hg)		−0.5 (−0.9; −0.1)*
ACE inhibitor (after Bx)		−2.2 (−19.1; 14.7)
Cytotoxic immunosuppressive (after Bx)		−13.1 (−39.0; 12.8)
Biopsied after 2000		15.4 (2.5; 28.3)*
Glomerular variables		
% Normal glomeruli/minimal leukocyte influx§		0.4 (0.2; 0.7)*
% Global sclerosis		−0.8 (−1.2; −0.4)*
% Segmental sclerosis		3.3 (−0.3; 6.9)
% Ischemic glomeruli		−0.7 (−1.1; −0.2)*
% Mesangial hypercellularity		0.0 (−0.1; 0.1)
% Mesangial matrix expansion		0.1 (−0.3; 0.4)
% Endocapillary hypercellularity	*Any*	0.0 (−0.2; 0.2)
	Segmental	0.1 (−0.2; 0.4)
	Global	−0.1 (−0.3; 0.1)
% Endocapillary infiltration	*Lymphocytes*	0.0 (−0.2; 0.2)
	Monocytes	0.0 (−0.3; 0.2)
	Granulocytes	0.1 (−0.4; 0.6)
% Crescents	*Cellular/fibrocellular*§	−0.4 (−0.6; −0.1)*
	Fibrous	−1.6 (−2.8; −0.4)*
% Wire loops		0.0 (−0.3; 0.2)
% Adhesions		−0.4 (−1.1; 0.3)
% Fibrinoid necrosis		−0.2 (−1.1; 0.6)
% Karyorrhexis		−0.1 (−0.6; 0.3)
% Double contours		−0.1 (−0.5; 0.2)
% Spikes/vacuoles		0.1 (−0.2; 0.3)
Tubulointerstitial variables		
IF/TA	*5–24%*	−3.9 (−14.0; 11.1)
	25–49%	−37.5 (−60.8; −14.2)*
	≥50%	−50.1 (−82.4; −17.7)*
Interstitial infiltration	*5–24%*	−11.8 (−25.2; 1.6)
	25–49%	13.1 (−20.7; 46.9)
	≥50%	−34.1 (−57.8; −10.5)*
Tubular casts		−19.5 (−32.0; −7.1)*
Tubular macrophages		−15.7 (−32.4; 0.9)
Tubular reabsorption droplets		−10.2 (−23.2; 2.8)
Arterial intimal fibrosis		−44.7 (−67.6; −21.7)*

β represents the mean change in the level of eGFR decline over time with one unit change of the variable. * P<0.05. † univariable random intercept/random slope mixed-effects models. § The composite variables "normal glomeruli/minimal leukocyte influx" and "extracapillary 2" were used rather than their individual components, as effect sizes of components were in strong accordance (data not shown).
Abbreviations: Bx, biopsy; IF/TA, interstitial fibrosis or tubular atrophy; MAP, mean arterial pressure.

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Table S2.2 Univariable predictions of progressive eGFR decline (in mL/min/1.73 m^2) over 1, 5, and 10 years follow-up in 105 LN patients.

		eGFR decline over 1 year ($eGFR_{CORR1}$)‡ β	eGFR decline over 5 years ($eGFR_{CORR5}$)‡ β	eGFR decline over 10 years ($eGFR_{CORR10}$)‡ β
Clinical variables				
Female sex		−9.0 (−22.1; 4.1)	6.1 (−13.1; 25.2)	−6.2 (−32.5; 20.1)
Age_0 (y)		−0.5 (−0.9; −0.1)*	−0.9 (−1.5; −0.4)*	−1.2 (−1.9; −0.4)*
Race	*Caucasian*	10.2 (−0.8; 21.3)	11.2 (−7.1; 29.6)	13.7 (−11.2; 38.6)
	Asian	−2.9 (−15.7; 9.8)	5.3 (−10.8; 21.3)	3.5 (−18.6; 25.5)
	Afro-Caribbean	−16.6 (−32.6; −0.7)*	−28.5 (−50.9; −6.1)*	−28.5 (−59.1; 2.2)
Years since diagnosis SLE_0		−1.0 (−2.0; −0.1)*	−2.4 (−3.6; −1.2)*	−2.2 (−3.9; −0.5)*
$Proteinuria_0$ (g/24h)		0.2 (−1.3; 1.6)	−0.5 (−2.5; 1.5)	1.2 (−1.5; 3.8)
$Erythrocyturia_0$ >1+		1.6 (−23.5; 26.8)	−2.8 (−41.1; 35.5)	−10.2 (−98.6; 78.2)
MAP_0 (mm Hg)		−0.1 (−0.4; 0.2)	−0.3 (−0.8; 0.2)	−0.9 (−1.4; −0.3)*
ACE inhibitor (after Bx)		0.0 (−13.9; 14.0)	2.1 (−17.9; 22.1)	9.9 (−18.9; 38.7)
Cytotoxic immunosuppressive (after Bx)		1.2 (−20.3; 22.7)	4.4 (−27.2; 36.0)	13.4 (−27.3; 54.1)
Biopsied after 2000		7.6 (−3.3; 18.5)	10.2 (−5.2; 25.6)	7.0 (−14.3; 28.2)
Glomerular variables				
% Normal glomeruli/minimal leukocyte influx§		0.0 (−0.2; 0.2)	0.1 (−0.2; 0.4)	0.1 (−0.3; 0.5)
% Global sclerosis		−0.5 (−0.8; −0.2)*	−0.7 (−1.1; −0.2)*	−0.7 (−1.3; −0.1)*
% Segmental sclerosis		−0.8 (−3.9; 2.3)	2.3 (−2.3; 6.8)	3.0 (−2.5; 8.5)
% Ischemic glomeruli		−0.2 (−0.6; 0.2)	−0.3 (−0.9; 0.3)	−0.6 (−1.5; 0.3)
% Mesangial hypercellularity		−0.1 (−0.2; 0.1)	−0.1 (−0.2; 0.1)	0.0 (−0.2; 0.2)
% Mesangial matrix expansion		−0.1 (−0.3; 0.2)	−0.1 (−0.4; 0.3)	0.0 (−0.5; 0.5)
% Endocapillary hypercellularity	*Any*	0.2 (0.0; 0.3)	0.2 (−0.1; 0.4)	0.3 (0.0; 0.6)
	Segmental	0.0 (−0.3; 0.2)	0.1 (−0.3; 0.4)	0.4 (−0.1; 0.8)
	Global	0.2 (0.0; 0.4)	0.2 (−0.1; 0.5)	0.1 (−0.3; 0.5)
% Endocapillary infiltration	*Lymphocytes*	0.1 (−0.1; 0.3)	0.1 (−0.2; 0.3)	0.4 (0.0; 0.7)
	Monocytes	0.2 (0.0; 0.4)	0.2 (0.0; 0.5)	0.4 (0.0; 0.7)*
	Granulocytes	0.4 (0.0; 0.8)*	0.6 (0.0; 1.1)*	0.7 (−0.1; 1.5)
% Crescents	*Cellular/fibrocellular*§	−0.1 (−0.3; 0.2)	−0.1 (−0.5; 0.2)	−0.1 (−0.6; 0.3)
	Fibrous	−0.6 (−1.6; 0.5)	−0.9 (−2.4; 0.7)	−1.0 (−3.2; 1.2)
% Wire loops		0.2 (−0.1; 0.4)	0.3 (0.0; 0.6)	0.3 (−0.1; 0.8)
% Adhesions		−0.1 (−0.8; 0.5)	−0.4 (−1.2; 0.5)	−0.1 (−1.3; 1.0)
% Fibrinoid necrosis		−1.0 (−1.7; −0.3)*	−1.0 (−2.0; 0.1)	−0.2 (−1.8; 1.5)
% Karyorrhexis		0.2 (−0.2; 0.5)	0.0 (−0.7; 0.6)	−0.6 (−1.7; 0.5)
% Double contours		0.0 (−0.3; 0.3)	−0.2 (−0.7; 0.3)	−0.1 (−0.7; 0.4)
% Spikes/vacuoles		0.0 (−0.3; 0.2)	−0.1 (−0.5; 0.2)	0.0 (−0.4; 0.4)
Tubulointerstitial variables				
IF/TA	*5–24%*	3.2 (−9.3; 15.6)	−6.4 (−23.8; 10.9)	−13.5 (−37.0; 10.0)
	25–49%	−17.1 (−37.0; 2.8)	−26.5 (−57.6; 4.6)	−35.5 (−79.9; 9.0)
	≥50%	−27.9 (−55.4; −0.5)*	−33.7 (−71.4; 3.9)	−48.2 (−98.7; 2.3)
Interstitial infiltration	*5–24%*	−2.5 (−13.8; 8.8)	0.7 (−15.2; 16.5)	−5.5 (−27.0; 16.0)
	25–49%	9.3 (−18.7; 37.2)	4.7 (−33.6; 42.9)	35.5 (−26.9; 98.0)
	≥50%	−11.7 (−31.8; 8.3)	−22.5 (−53.8; 8.7)	−30.2 (−81.6; 21.1)
Tubular casts		−9.8 (−20.4; 0.9)	−14.1 (−29.1; 0.9)	−11.3 (−32.5; 9.8)
Tubular macrophages		8.4 (−5.8; 22.5)	−3.6 (−23.6; 16.4)	10.6 (−16.3; 37.6)
Tubular reabsorption droplets		−5.9 (−16.7; 5.0)	−17.0 (−32.2; −1.9)*	−15.9 (−37.1; 5.3)
Arterial intimal fibrosis		−34.5 (−53.7; −15.3)*	−38.0 (−64.7; −11.3)*	−31.1 (−63.5; 1.4)

Interpretation $eGFR_{CORR1/5/10}$ (in mL/min/1.73 m^2): β represents the change in $eGFR_{CORR}$ with one unit change of the variable. * P<0.05. ‡ univariable linear regression models. § The composite variables "normal glomeruli/minimal leukocyte influx" and "extracapillary 2" were used rather than their individual components, as effect sizes of components were in strong accordance (data not shown).
Abbreviations: Bx, biopsy; IF/TA, interstitial fibrosis or tubular atrophy; MAP, mean arterial pressure.

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Supplemental material (3).

Correlations between histopathologic variables

To prevent the inclusion of strongly correlated variables in our analyses of the various outcomes, we assessed correlations between 29 glomerular and 9 tubulointerstitial variables (occurring in >5 patients), excluding normal glomeruli. Significant correlation coefficients between histopathologic variables after Bonferroni correction are shown in **Table S3.1** below. The following variables that were strongly correlated with other variables (r/ ρ >0.8) were dropped: "mesangial 1" and "extracapillary 3/5" because of relatively laborious scoring; "endocapillary 3" because "minimal leukocyte influx" was encompassed by "normal glomeruli/minimal leukocyte influx"; "endothelial swelling", "endocapillary inflammatory infiltrate", and "endocapillary monocytes" because they were encompassed by "endocapillary 1/2/4"; "extracapillary 1" because cellular crescents were encompassed by "extracapillary 2"; and "interstitial lymphocytes" because they were encompassed by "interstitial infiltration". "Interstitial fibrosis" and "tubular atrophy" were combined (whichever was the higher value) into a composite variable: "interstitial fibrosis/tubular atrophy" (IF/TA). Thus, 29 histopathologic variables remained to be tested in relation to outcomes.

Table S3.1. Because 666 comparisons were assessed, the significance was set to $P=8\cdot10^{-5}$ by Bonferroni correction ($P=0.05/666$). Only correlation coefficients with $P<8\cdot10^{-5}$ are shown. Numbers in the cells represent Pearson/Spearman correlation coefficients. Correlation coefficients >0.8 are bold-printed. Abbreviations: DC, double contours; End1/2/3: endocapillary 1/2/3; EndInf, endocapillary inflammatory infiltrate; EndGran, endocapillary granulocytes; EndLym, endocapillary lymphocytes; EndMon, endocapillary monocytes; EndSw: endothelial cell swelling; Extr1/2/3/4/5: extracapillary 1/2/3/4/5; GlobGS, global sclerosis; IF, interstitial fibrosis; ArtIF, arterial intimal fibrosis; IntInf, interstitial infiltration; IntLym, interstitial lymphocytes; IntGran, interstitial granulocytes; Mes1/2/3: mesangial 1/2/3; MinLeu, minimal leukocyte influx; TA, tubular atrophy; WL, wire loops.

	Mes2	End2	End3	EndSw	EndInf	EndGran	EndLym	EndMon	WL	Extr1	Extr2	Extr3	Extr5	Necr	DC	TubAt	IntInf	IntLym	IntGran	IF	ArtIF
GlobGS			-0.5													0.5				0.5	0.4
Isch																0.5				0.4	
Mes1	**0.9**														0.4						
Mes3										0.3	0.4	0.4									
MinLeu		-0.4			-0.4																
End1		0.5	0.6	0.5	0.5									0.3							
End2		–	**0.8**	**0.99**	**0.9**	0.5	0.7	**0.8**	0.5												
End3			–	**0.8**	**0.8**		0.6	0.6	0.5												
EndSw				–	**0.9**	0.5	0.7	**0.8**	0.5		0.4										
EndInf					–	0.5	**0.8**	**0.8**	0.4												
EndGran						–		0.4													
EndLym							–	0.6													
EndMon								–	0.5												
Extr1											**0.9**	**0.8**					0.4				
Extr2											–	**0.9**					0.4				
Extr3												–					0.4				
Extr4													**0.97**								
TA															–					**0.8**	
IntInf																	–	**0.9**			

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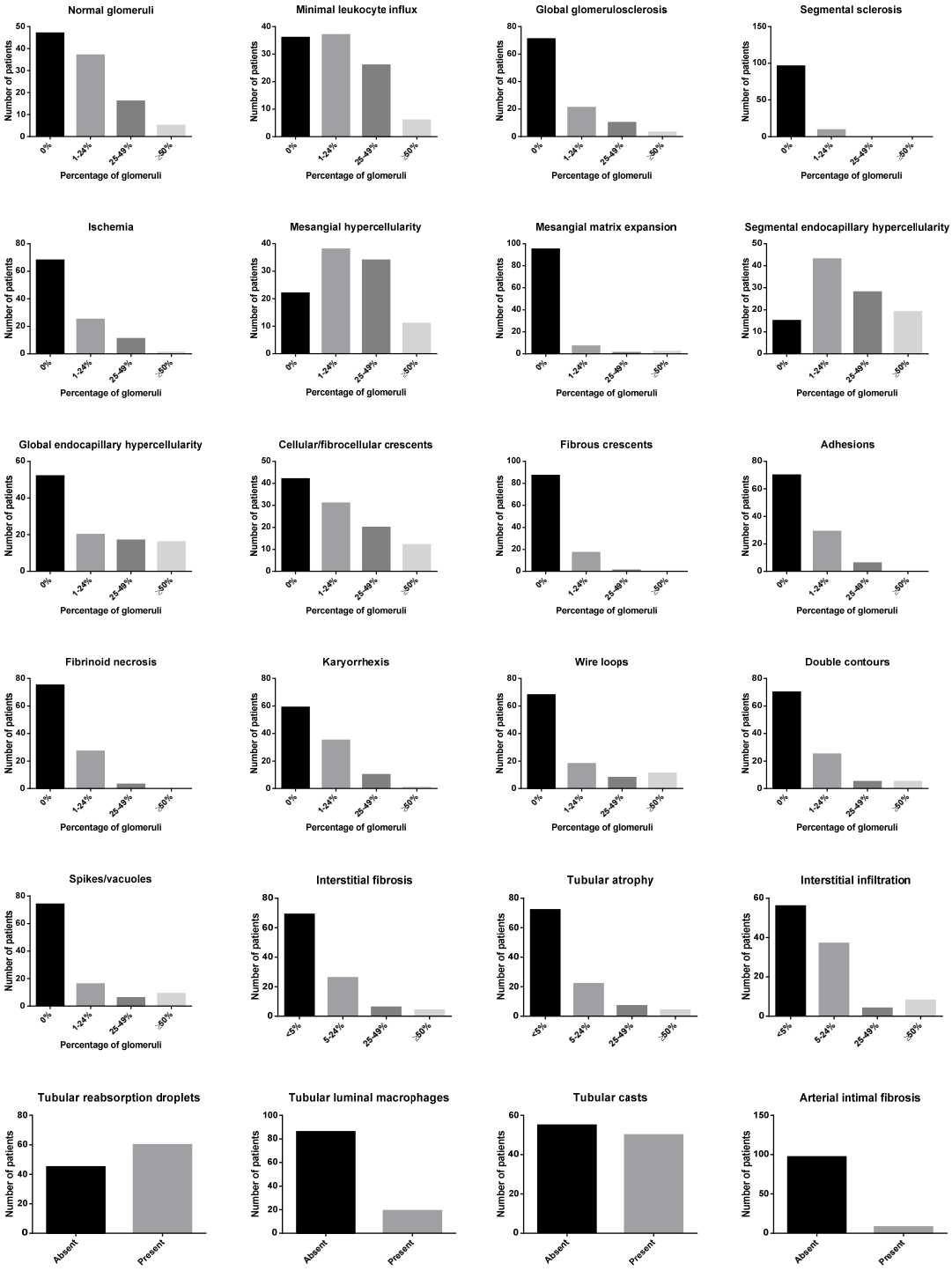
Supplemental material (4).

Distribution of histopathologic lesions across patients with LN



Correlations between histopathologic variables and the number of scorable glomeruli

None of the glomerular or tubulointerstitial variables were correlated with the number of scorable glomeruli. Patients who did not have more (≥) than 10 scorable glomeruli in their renal biopsies – as is the minimum biopsy requirement according to the ISN/RPS – had 5 (n=5), 6 (n=3), 7 (n=2), 8 (n=6), or 9 (n=3) scorable glomeruli. A comparison between patients with fewer (<) or more (≥) than 10 scorable glomeruli revealed that only the distribution of karyorrhexis, endocapillary granulocytes, and monocytes was different between the groups (all $P<0.05$; higher scores in patients with ≥10 scorable glomeruli). Following these results we decided to uphold our initial threshold of ≥5 scorable glomeruli. Karyorrhexis, endocapillary granulocytes, and endocapillary monocytes were not univariably associated with any of the outcomes studied. These variables were not incorporated in our statistical models.

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Supplemental material (5).

Correlations between histopathologic variables and mean arterial pressure (MAP), eGFR, and proteinuria at the time of renal biopsy ($_0$) in 105 patients with LN.

		$eGFR_0$, mL/min/1.73 m²		$Proteinuria_0$, g/24h		MAP_0, mm Hg	
Glomerular variables		r	*P*	r	*P*	r	*P*
% Normal glomeruli		0.3	<0.001*	−1.1	0.31	−0.2	0.02*
% Minimal leukocyte influx		0.3	<0.001*	−0.2	0.06	−0.3	0.007*
% Normal glomeruli/minimal leukocyte influx		0.4	<0.001*	−0.2	0.05*	−0.3	0.001*
% Global sclerosis		−0.2	0.02*	0.0	0.78	0.1	0.27
% Ischemic glomeruli		−0.2	0.01*	0.0	0.82	0.0	0.78
% Endocapillary hypercellularity	*Any*	−0.2	0.11	0.2	0.02*	0.3	<0.001*
	Segmental	0.1	0.36	0.0	0.85	0.2	0.08
	Global	−0.3	0.008*	0.3	0.007*	0.3	0.009*
% Wire loops		−0.1	0.20	0.2	0.11	0.2	0.02*
% Cellular/fibrocellular crescents		−0.2	0.03*	0.2	0.10	0.2	0.02*
Tubulointerstitial/vascular variables		ρ	*P*	ρ	*P*	ρ	*P*
IF/TA		−0.3	0.001*	0.1	0.67	0.2	0.03*
Interstitial infiltration		−0.3	0.002*	0.4	<0.001*	0.1	0.23
Tubular reabsorption droplets		−0.1	0.34	0.2	0.07	0.2	0.03*
Tubular casts		−0.3	0.007*	0.2	0.10	0.2	0.14
Tubular macrophages		−0.3	0.008*	0.3	0.005*	0.1	0.18
Arterial intimal fibrosis		−0.2	0.03*	0.0	0.78	0.2	0.04*

Only variables with any significant correlation with $eGFR_0$, $proteinuria_0$, and/or MAP_0 are shown.*P<0.05. IF/TA, interstitial fibrosis or tubular atrophy; r, Pearson's correlation coefficient; ρ, Spearman's correlation coefficient.

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Supplemental material (6).

Analysis of progressive eGFR decline

Results

Results for the complete cohort and the subset were comparable (**Table S2.2**). In the complete cohort, a decline of eGFR over 1 and 5 years was independently predicted by non-Caucasian race (1 year: −17.7 mL/min/1.73 m^2; 5 years: −17.8 mL/min/1.73 m^2), age_0 (1 year: −0.5 mL/min/1.73 m^2/year; 5 years: −0.9 mL/min/1.73 m^2/year), fibrinoid necrosis (1 year: −1.4 mL/min/1.73 m^2/%glomeruli; 5 years: −1.5 mL/min/1.73 m^2/%glomeruli), fibrous crescents (1 year: −1.2 mL/min/1.73 m^2/%glomeruli; 5 years: −1.6 mL/min/1.73 m^2/%glomeruli), and the presence of IF/TA ≥25% (1 year: −21.7 mL/min/1.73 m^2; 5 years: −30.3 mL/min/1.73 m^2). Over 10 years follow-up, MAP_0 was associated with eGFR decline (−1.1 mL/min/1.73 m^2/mm Hg), and endocapillary lymphocytes and wire loops were associated with eGFR recovery (both +0.4 mL/min/1.73 m^2/%glomeruli).

Table S6.1 Multivariable prediction models for progressive eGFR decline in mL/min/1.73 m^2.

	ISN/RPS Class I–V (N=105)	**ISN/RPS Class III/IV (±V)‡** (N=91)
Progressive eGFR decline over 1 year ($eGFR_{CORR1}$)† (N=99)		
Variables	β (95% CI)	β (95% CI)
(Constant)	30.6 (17.0; 44.1)	33.1 (18.2; 47.9)
Non–Caucasian	−17.7 (−27.7; −7.7)	−21.1 (−32.2; −10.0)
Age_0, years	−0.5 (−0.9; −0.2)	−0.5 (−0.9; -0.1)
% Fibrinoid necrosis (glomerular)	−1.4 (−2.0; −0.8)	−1.4 (−2.0; −0.8)
% Fibrous crescents	−1.2 (−2.1; −0.2)	−1.3 (−2.3; −0.2)
IF/TA ≥25%	−21.7 (−36.2; −7.2)	−25.2 (−40.8; −9.5)
Tubular macrophages present	9.7 (−2.6; 21.9)	11.1 (-2.1; 24.4)
Variables	β (95% CI)	β (95% CI)
(Constant)	45.7 (26.2; 65.2)	45.2 (24.4; 66.0)
Non-Caucasian	−17.8 (−33.0; −2.7)	−22.9 (−39.1; −6.6)
Age_0, years	−0.9 (−1.5; −0.4)	−0.8 (−1.4; −0.3)
% Fibrous crescents	−1.6 (−3.0; −0.2)	−1.7 (−3.3; −0.1)
% Fibrinoid necrosis (glomerular)	−1.5 (−2.5; −0.5)	−1.5 (−2.6; −0.5)
IF/TA ≥25%	−30.3 (−52.5; −8.1)	−31.7 (−54.4; −9.1)
Variables	β (95% CI)	β (95% CI)
(Constant)	91.1 (40.4 ; 141.8)	93.6 (35.6; 151.6)
MAP_0, mm Hg	−1.1 (−1.6; −0.6)	−1.1 (−1.7; −0.6)
% Endocapillary lymphocytes	0.4 (0.0; 0.7)	0.4 (0.0; 0.7)
% Wire loops	0.4 (0.0; 0.9)	0.5 (0.0; 0.9)

$eGFR_{CORR(t)}$ is the renal function deterioration (or improvement) in ml/min/1.73 m^2 at *t* years relative to the expected value based on the eGFR at baseline and the unadjusted mean decline of eGFR over *t* years. $eGFR_{CORR(t)} = eGFR_{Observed(t)} - eGFR_{Predicted(t)}$. For a given patient, the eGFR at time *t* is given by: $eGFR_{Predicted(t)} + eGFR_{CORR(t)}$. Estimations of $eGFR_{Predicted(t)}$ were: $eGFR_{Predicted(1\ year)} = 29.9 + 0.67*eGFR_0$; $eGFR_{Predicted(5\ years)} = 42.0 + 0.53*eGFR_0$; and $eGFR_{Predicted(10\ years)} = 33.9 + 0.50*eGFR_0$. Estimations of $eGFR_{CORR(t)}$ are given in **Table S6.1** (above); e.g., $eGFR_{CORR1}$ = Constant + $\beta_{Age0}*Age_0$ + $\beta_{\%fibrous\ crescents}$*%fibrous crescents + $\beta_{\%fibrinoid\ necrosis}$*%fibrinoid necrosis + $\beta_{non\text{-}Caucasian}$ (if Non-Caucasian) + $\beta_{IF/TA\ \geq 25\%}$ (if IF/TA ≥25%).

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Supplemental material (7).

Interactions between histopathologic variables and race

Compared with patients with Afro-Caribbean race, spikes/vacuoles were more positively associated with eGFR in patients with Caucasian or Asian race (β=0.9 mL/min/1.73 m^2 for each percent of glomeruli [95% CI, 0.2; 1.5]). Moreover, the relationship between tubular reabsorption droplets on eGFR was different between ethnicities: Caucasian and Asian patients with tubular reabsorption droplets had a higher average eGFR than Afro-Caribbean patients β=55.6 mL/min/1.73 m^2 [95% CI, 16.8; 94.4]).

Interactions between histopathologic variables and age

Age at the time of renal biopsy was significantly correlated with endocapillary granulocytes (r=−0.22, *P*=0.026), IF/TA (ρ=0.21, *P*=0.04), tubular casts (ρ=0.26, *P*=0.008) and arterial intimal fibrosis (ρ=0.31, *P*=0.001). A comparison between children (age <18 years) and adults revealed that children showed significantly less global glomerulosclerosis (*P*<0.001) and ischemia (*P*=0.03), and more endocapillary granulocytes (*P*<0.001). No differences in tubulointerstitial/vascular parameters were noted. No interactions between age and histopathologic variables were found.

Interactions between histopathologic variables and therapy

To study whether cytotoxic immunosuppressive therapy influenced the predictive value of histopathologic lesions, induction therapy was divided in three categories: (1) no therapy/prednisolone only; (2) guideline-recommended therapy (2-4) including intravenous cyclophosphamide or mycophenolate mofetil (MMF); and (3) azathioprine with prednisolone. No differences in the predictive value of histopathologic variables were noted between the treatment categories in mixed models for eGFR and in linear regression models for renal function recovery/deterioration in the complete cohort. In the subset of patients with class III/IV LN treated with cytotoxic drugs, analysis by treatment category for the outcomes ESRD and renal flare revealed no differences between predictive values of pathology variables, with one exception. Global glomerulosclerosis was significantly associated with ESRD for patients treated with azathioprine (HR 1.03 per %glomeruli, *P*=0.01), whereas in patients who received cyclophosphamide or MMF it was not. Time to first renal flare was not different between patients in each treatment category during 10 years follow-up (*P*=0.5). Twenty-five of 53 patients with ≥10 years follow-up did not experience a first renal flare during 10 years follow-up: of these, 3 patients who received induction immunosuppression with azathioprine (n=10) and none of the patients in the other treatment categories (n=11) experienced a first renal flare after this period (*P*=0.2).

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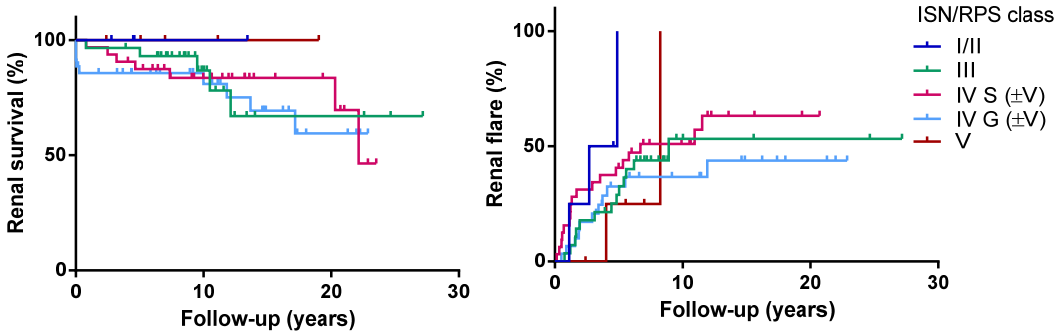
Supplemental material (8).

ISN/RPS classes in relation to outcome

Renal flare and ESRD

ISN/RPS classes were not significantly associated with overall renal survival (Log Rank test, *P*=0.7) and renal flare (Log Rank test, *P*=0.3) by Kaplan-Meier analysis (Figures below).



eGFR during follow-up

The ISN/RPS class of LN (either I/II, III, IV-S (±V), IV-G (±V), or V) was significantly associated with the mean eGFR during follow-up (*P*<0.05). The lowest mean eGFR during follow-up was found in class IV-S LN (**Table S8.1**).

Table S8.1. eGFR during follow-up adjusted for ISN/RPS class (Mixed model analysis). *Class V is the reference category; e.g., eGFR in class IV-S LN is on average 36.6 mL/min/1.73 m^2 lower than eGFR in class V LN (which is 105.1 mL/min/1.73 m^2 at the time of biopsy). "

eGFR during follow-up in mL/min/1.73 m^2	
	β (95% CI)
(Intercept)	105.1 (76.3; 114.0)
(Time, years)	−0.7 (−1.5; 0.02)
ISN/RPS class	
I/II	−10.2 (−53.4; 33.0)
III	−18.3 (−49.5; 12.9)
IV-S	−36.8 (−67.6; −6.0)
IV-G	−21.9 (−52.9; 9.1)
V	–

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