

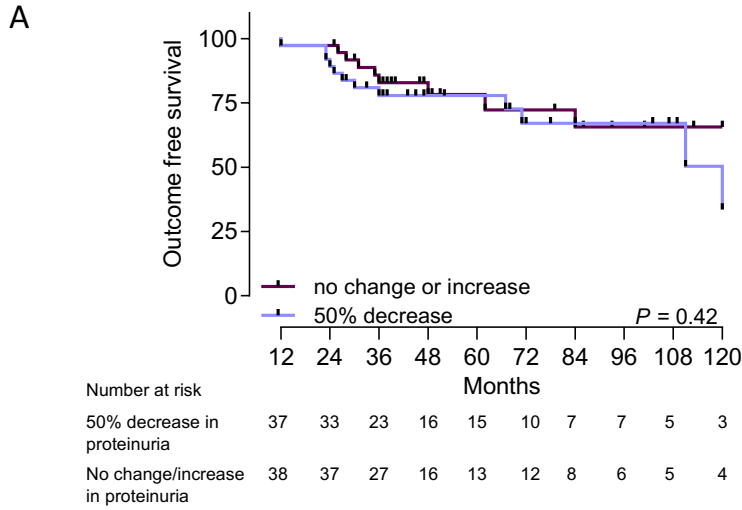
SUPPLEMENTAL DATA

Histological Predictors of Outcome in C3 Glomerulopathy and Idiopathic immunoglobulin-associated Membranoproliferative Glomerulonephritis

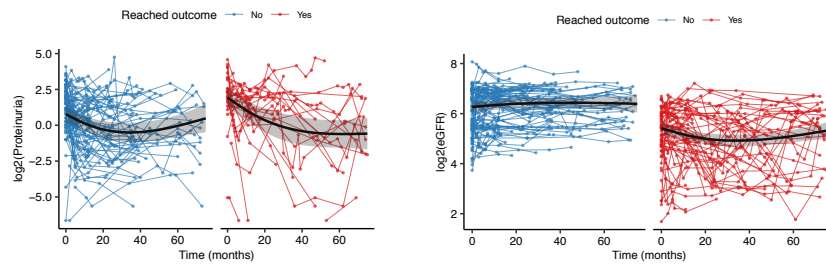
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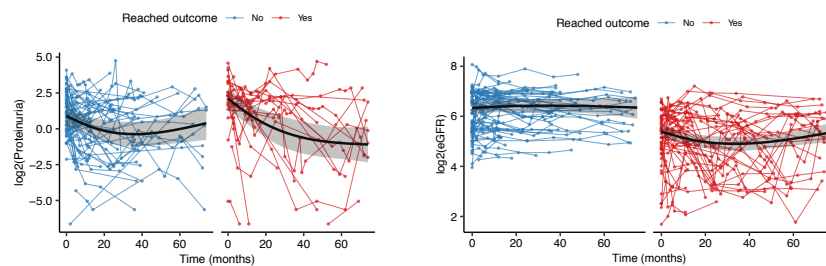
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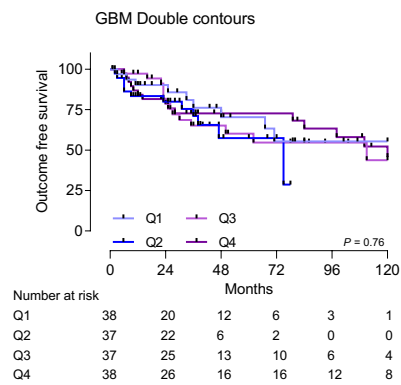
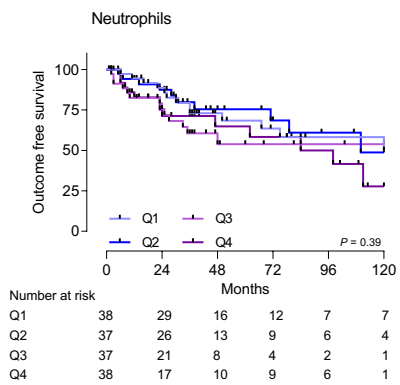
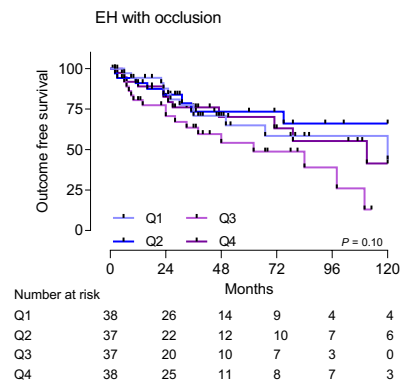
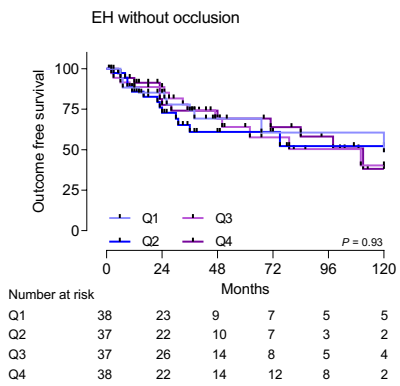
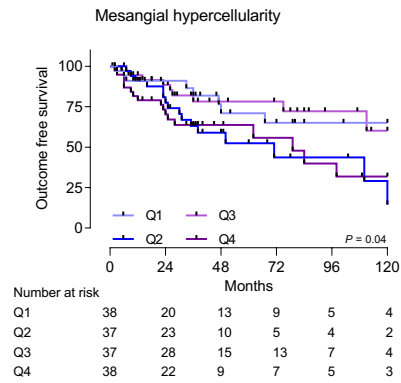
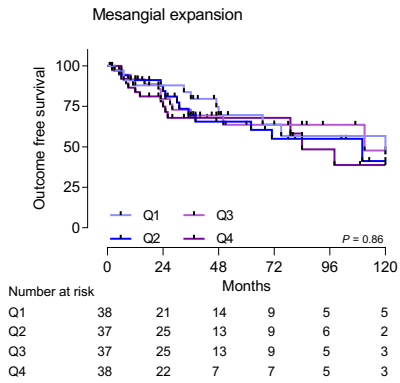
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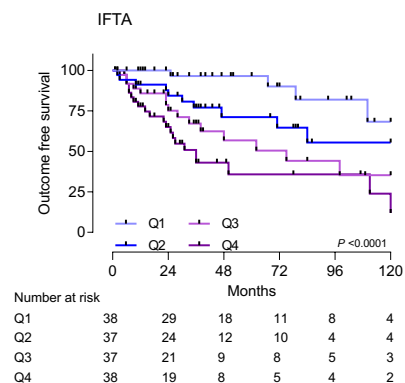
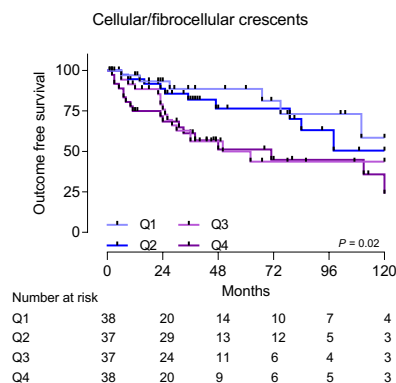
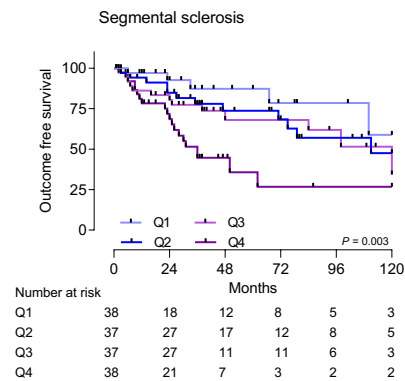
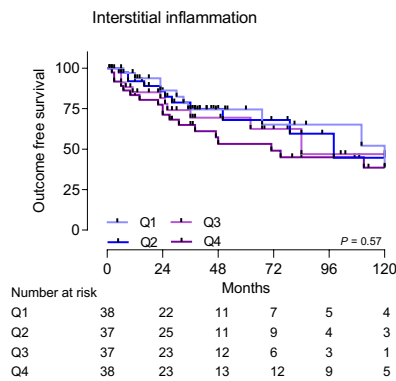
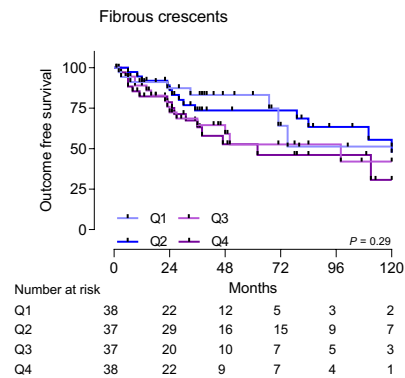
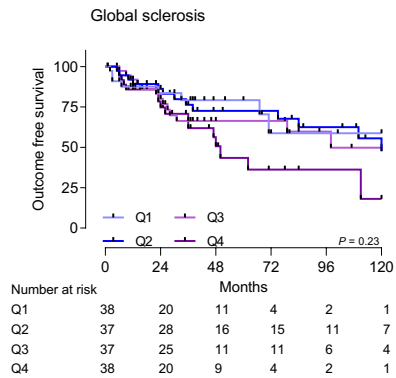
C3G COHORT



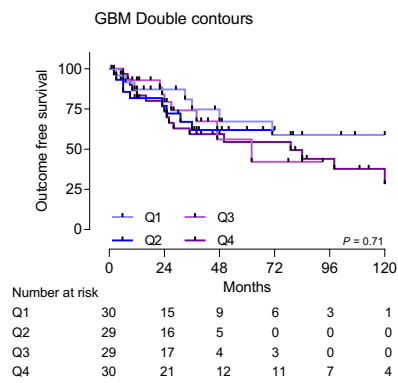
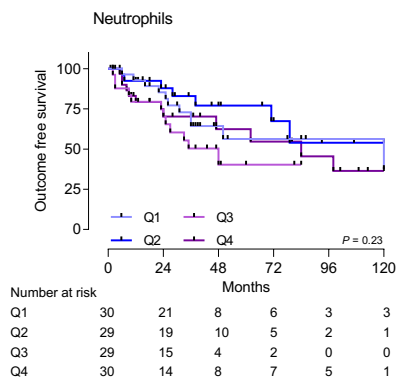
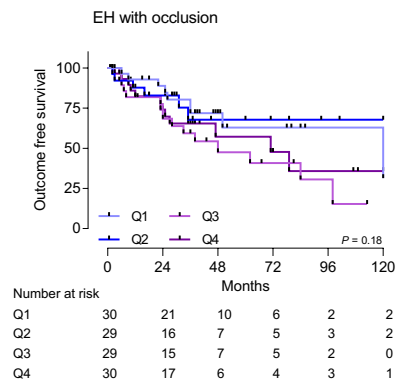
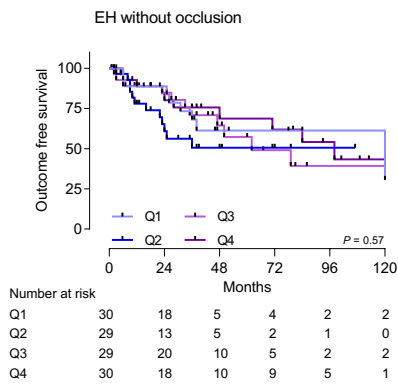
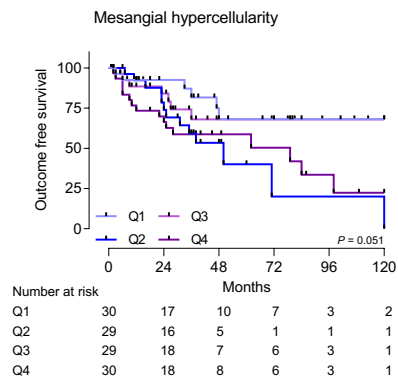
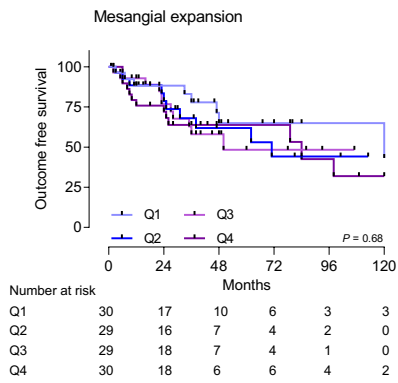
Supplemental Figure 1. Proteinuria and outcome free survival. (A) Relationship between outcome free survival and changes in proteinuria over the 12 months following baseline biopsy. Proteinuria changes were analysed in 75 patients over 12 months, all of whom had at least 2 years of follow up to reliably determine stable vs progressive disease. The patients were split into those who had a 50% reduction in proteinuria over 12 months ($n=39$) following diagnosis and those who did not ($n=42$). Progression to an outcome event was compared in these groups by survival analysis (Log-rank test). No significant differences were seen when patients who had $<1\text{g}/24\text{hr}$ of proteinuria at the time of diagnosis were removed from the analysis. (B) Subject-specific $\log_2(\text{Proteinuria})$ and $\log_2(\text{eGFR})$ over time in the whole cohort (upper panel) and C3G cohort (lower panel) grouped into those that did (red lines) and did not (blue lines) reach the composite outcome at 75 months. Using JMBayes2 package in R Quadratic splines were used to estimate the longitudinal profiles (black lines) and the 95% confidence intervals (grey shading) were estimated using joint linear mixed-effect and Cox proportional hazards models (variables included were sex, eGFR at diagnosis, diagnosis [C3GN, DDD, Ig-MPGN], age, immunosuppression use [yes/no], cellular/fibrocellular crescents and IFTA scores). Numbers analysed: Whole cohort proteinuria ($n=77$ individuals, $n=334$ time points) and eGFR ($n=109$ individuals, $n=489$ time points); C3G cohort proteinuria ($n=60$ individuals, $n=252$ time points) and eGFR ($n=90$ individuals, $n=391$ time points).



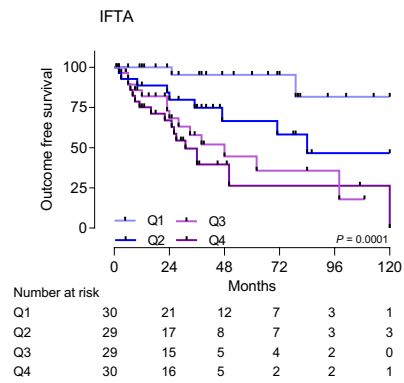
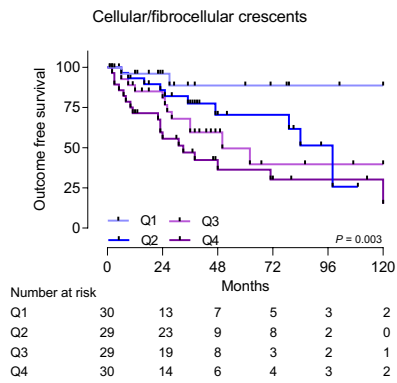
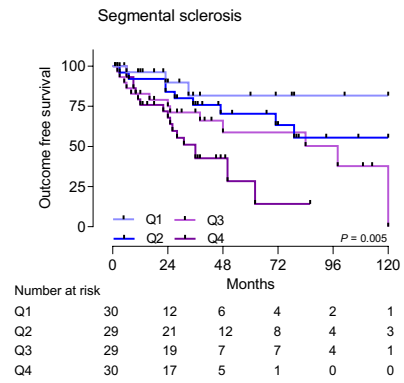
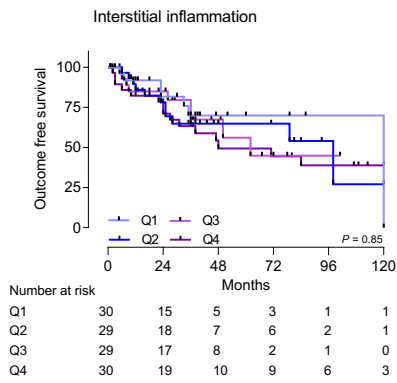
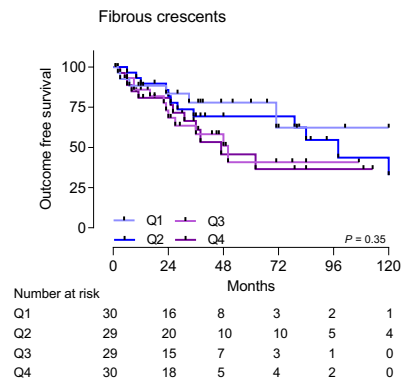
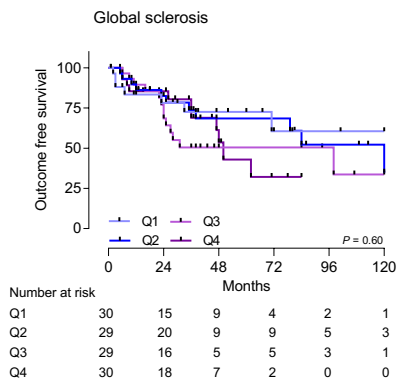
Supplemental Figure 2. Outcome free survival in the whole cohort by individual histological score quartiles. Pathology scores were divided into quartiles (Q1, 2, 3 and 4). No differences were detected for mesangial expansion, mesangial hypercellularity, EH with or without occlusion, neutrophils and GBM double contours. *P* values derived from Log-rank test. GBM – glomerular basement membrane; EH – endocapillary hypercellularity.



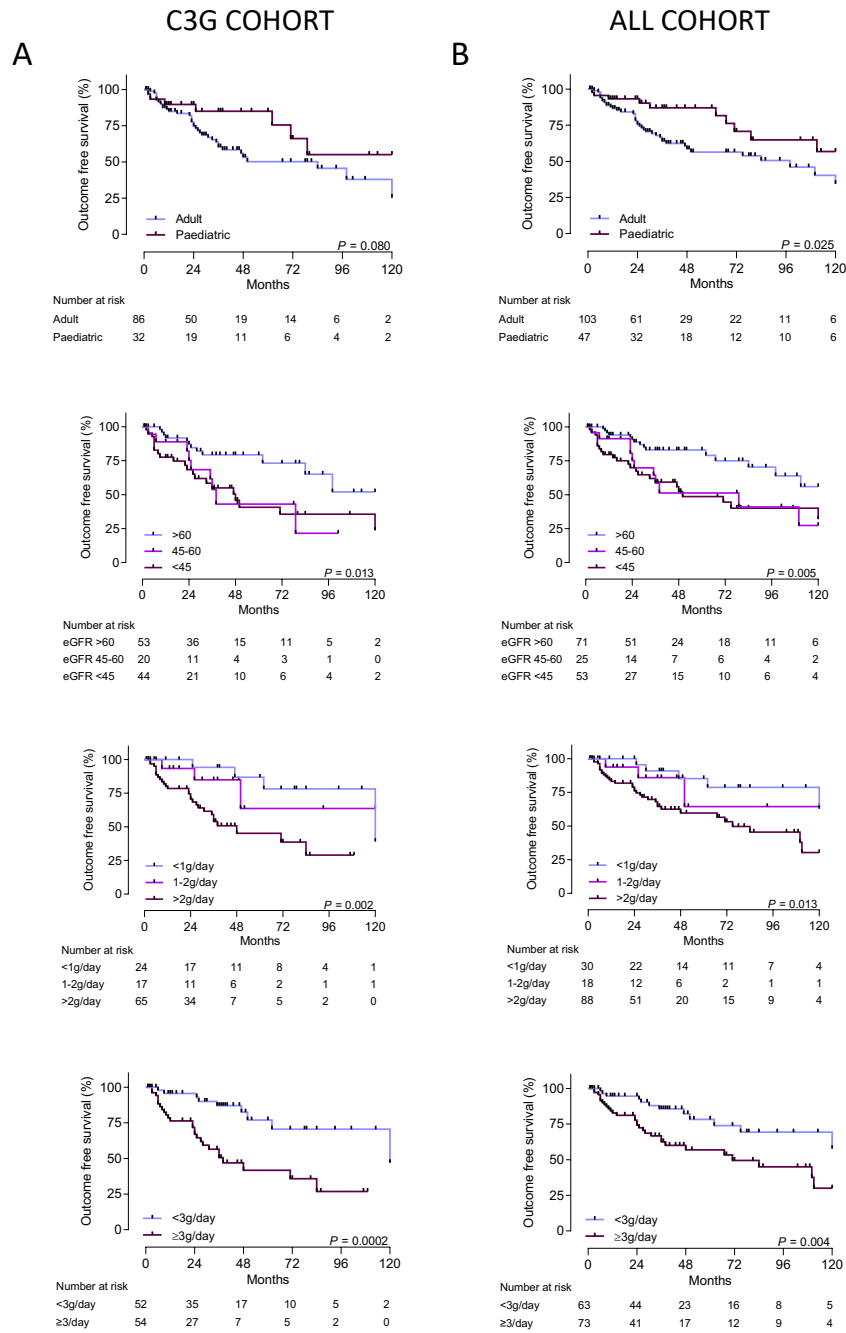
Supplemental Figure 2 (continued). Outcome free survival in the whole cohort by individual histological score quartiles. Pathology scores were divided into quartiles (Q1, 2, 3 and 4). No differences were detected for global sclerosis, fibrous crescents and interstitial inflammation. Significant differences were detected for segmental sclerosis, cellular/fibrocellular crescents and IFTA. P values derived from Log-rank test. IFTA – interstitial fibrosis and tubular atrophy.



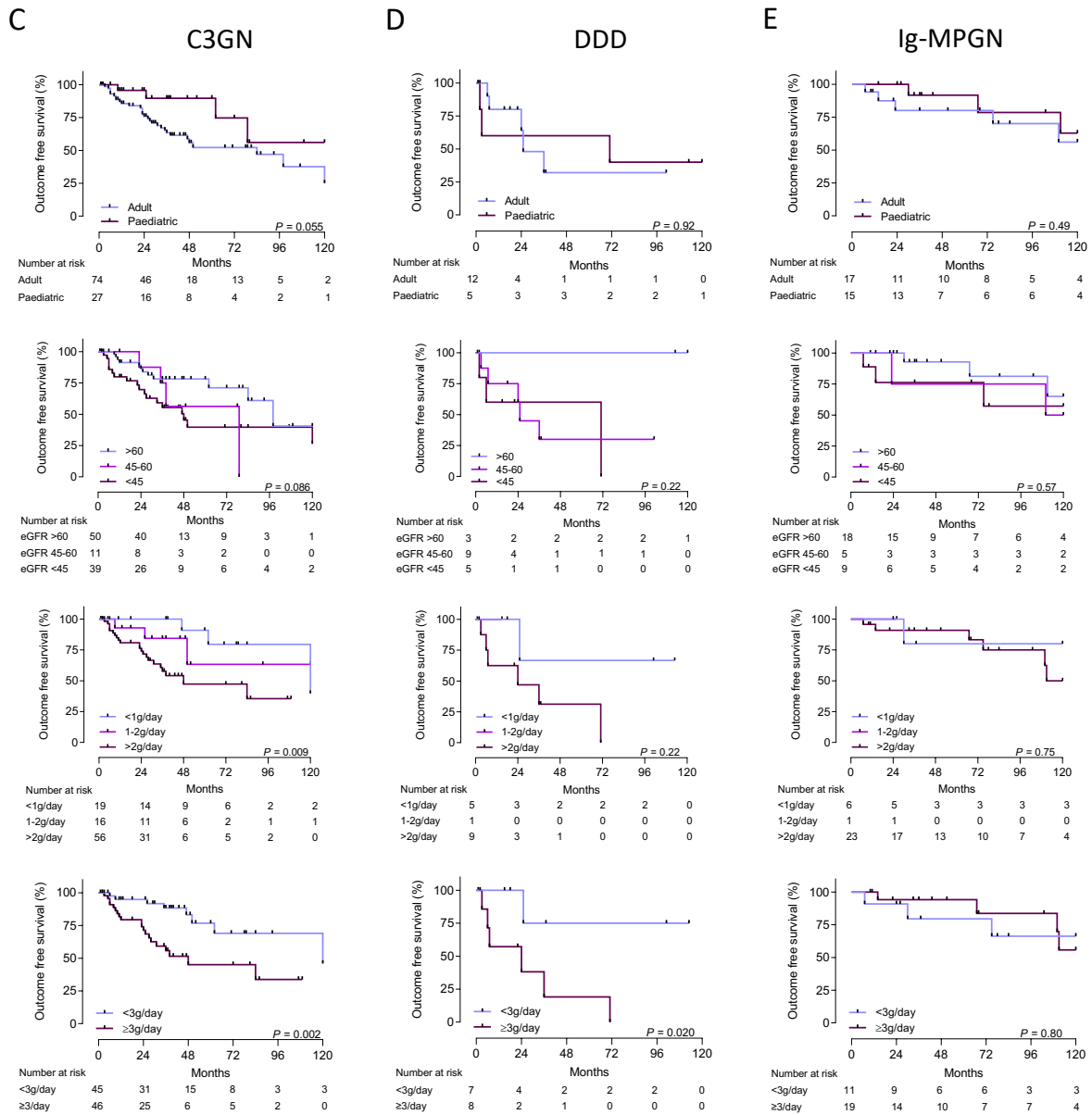
Supplemental Figure 3. Outcome free survival in the C3 glomerulopathy cohort by individual histological score quartiles. Pathology scores were divided into quartiles (Q1, 2, 3 and 4). No differences were detected for mesangial expansion, mesangial hypercellularity, EH with or without occlusion, neutrophils and GBM double contours. *P* values derived from Log-rank test. GBM – glomerular basement membrane; EH – endocapillary hypercellularity.



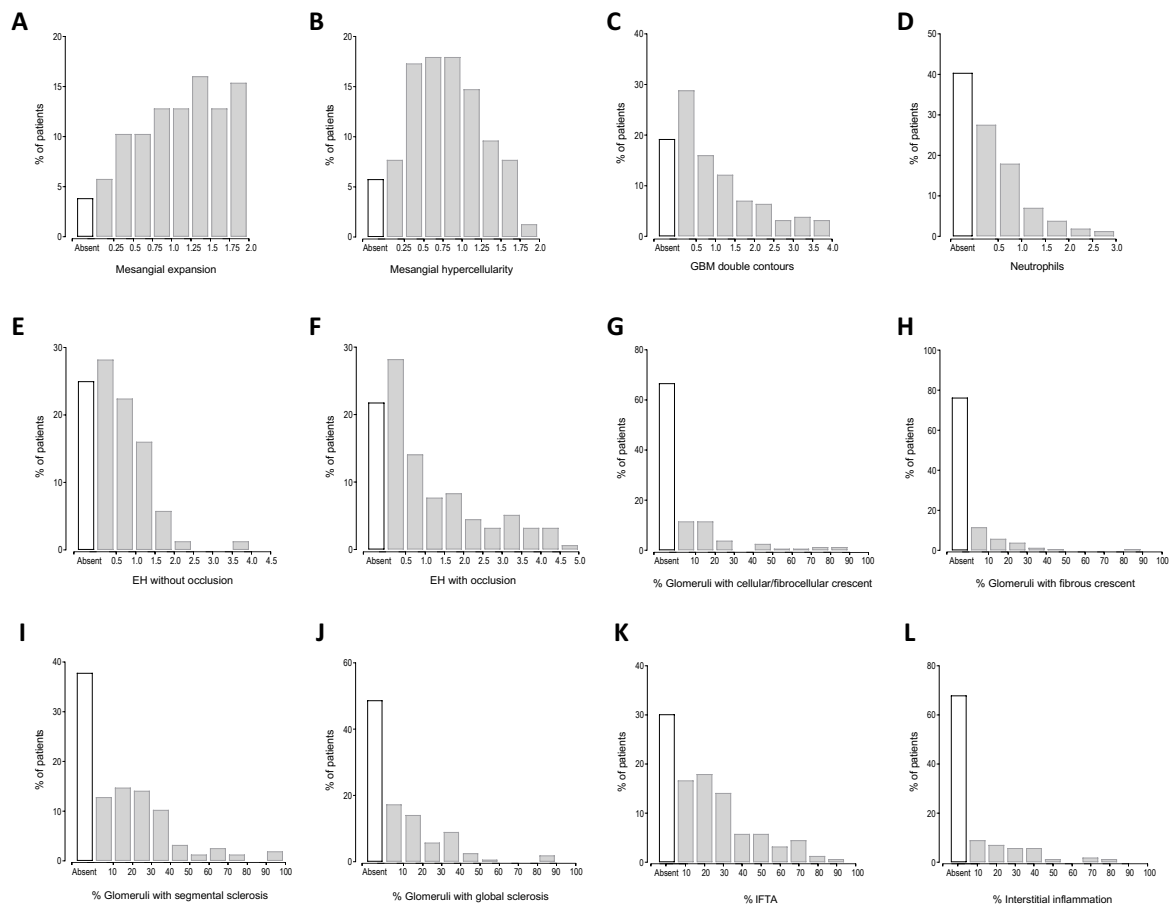
Supplemental Figure 3 (continued). Outcome free survival in the C3 glomerulopathy cohort by individual histological score quartiles. Pathology scores were divided into quartiles (Q1, 2, 3 and 4). No differences were detected for global sclerosis, fibrous crescents and interstitial inflammation. Significant differences were detected for segmental sclerosis, cellular/fibrocellular crescents and IFTA. *P* values derived from Log-rank test. IFTA – interstitial fibrosis and tubular atrophy.



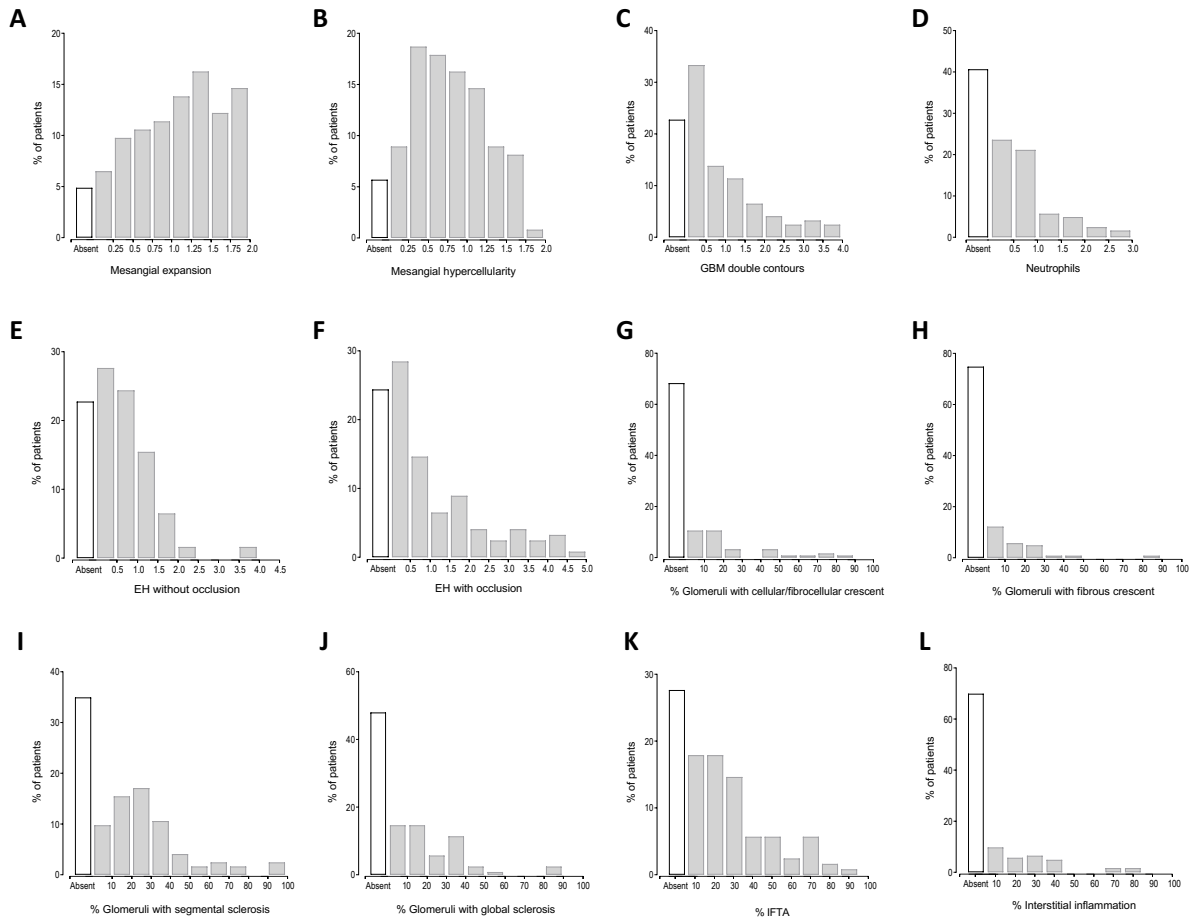
Supplemental Figure 4. Progression to a combined outcome event. This was assessed in (A) the C3G cohort, (B) the whole cohort, (C) the C3GN cohort, (D) the DDD cohort and (E) the Ig-MPGN cohort and stratified by age (adult vs. paediatric); eGFR and proteinuria. *P* values derived from Log-rank test. Proteinuria analysis n=136. eGFR analysis n=149, n=6 excluded due to ESKD at baseline. eGFR - estimated glomerular filtration rate; C3G - C3 glomerulopathy (C3 glomerulonephritis and Dense Deposit Disease); Ig-MPGN, idiopathic immunoglobulin-associated membranoproliferative glomerulonephritis.



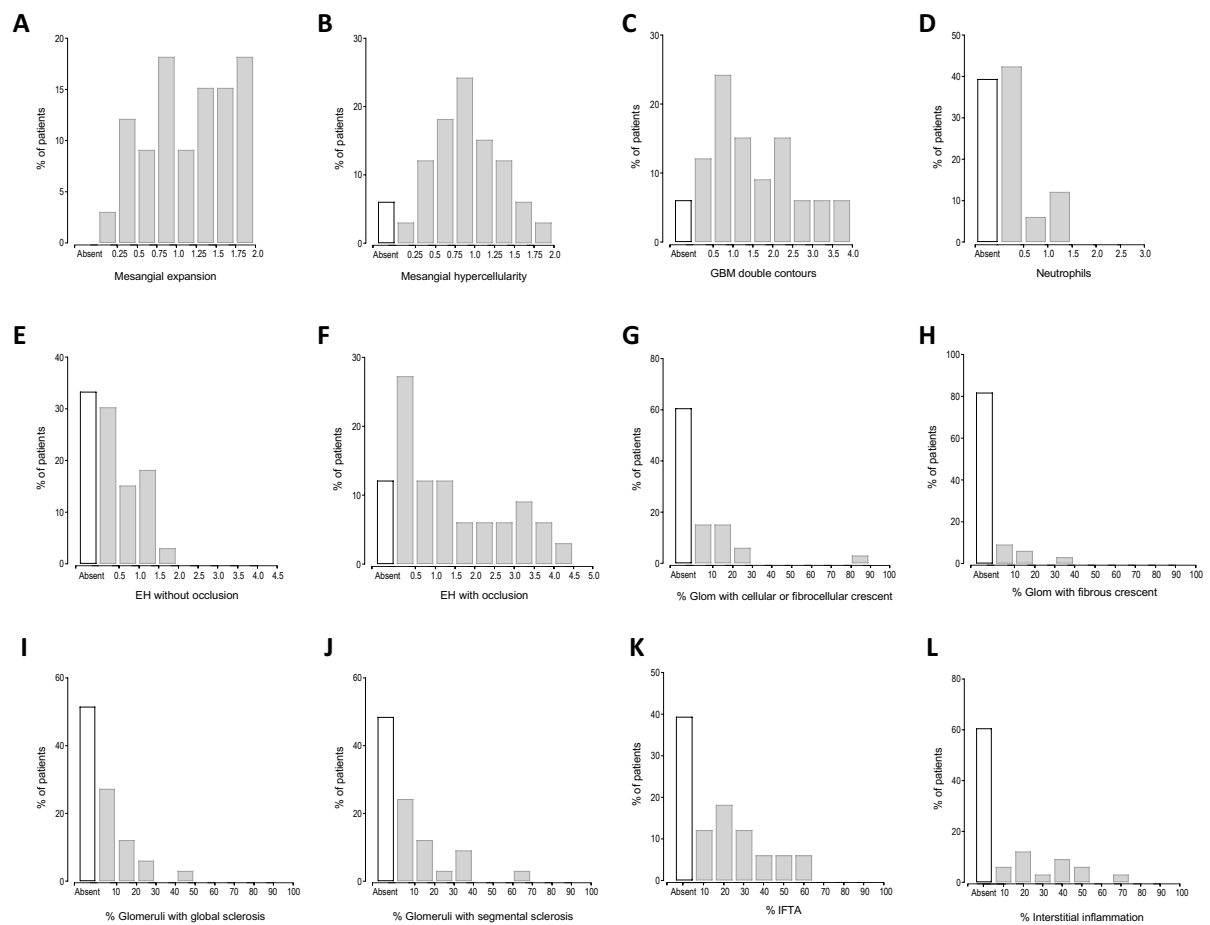
Supplemental Figure 4 (continued). Progression to a combined outcome event. This was assessed in (A) the C3G cohort, (B) the whole cohort, (C) the C3GN cohort, (D) the DDD cohort and (E) the Ig-MPGN cohort and stratified by age (adult vs. paediatric); eGFR and proteinuria. P values derived from Log-rank test. Proteinuria analysis $n=136$. eGFR analysis $n=149$, $n=6$ excluded due to ESKD at baseline. eGFR - estimated glomerular filtration rate; C3G - C3 glomerulopathy (C3 glomerulonephritis and Dense Deposit Disease); Ig-MPGN, idiopathic immunoglobulin-associated membranoproliferative glomerulonephritis.



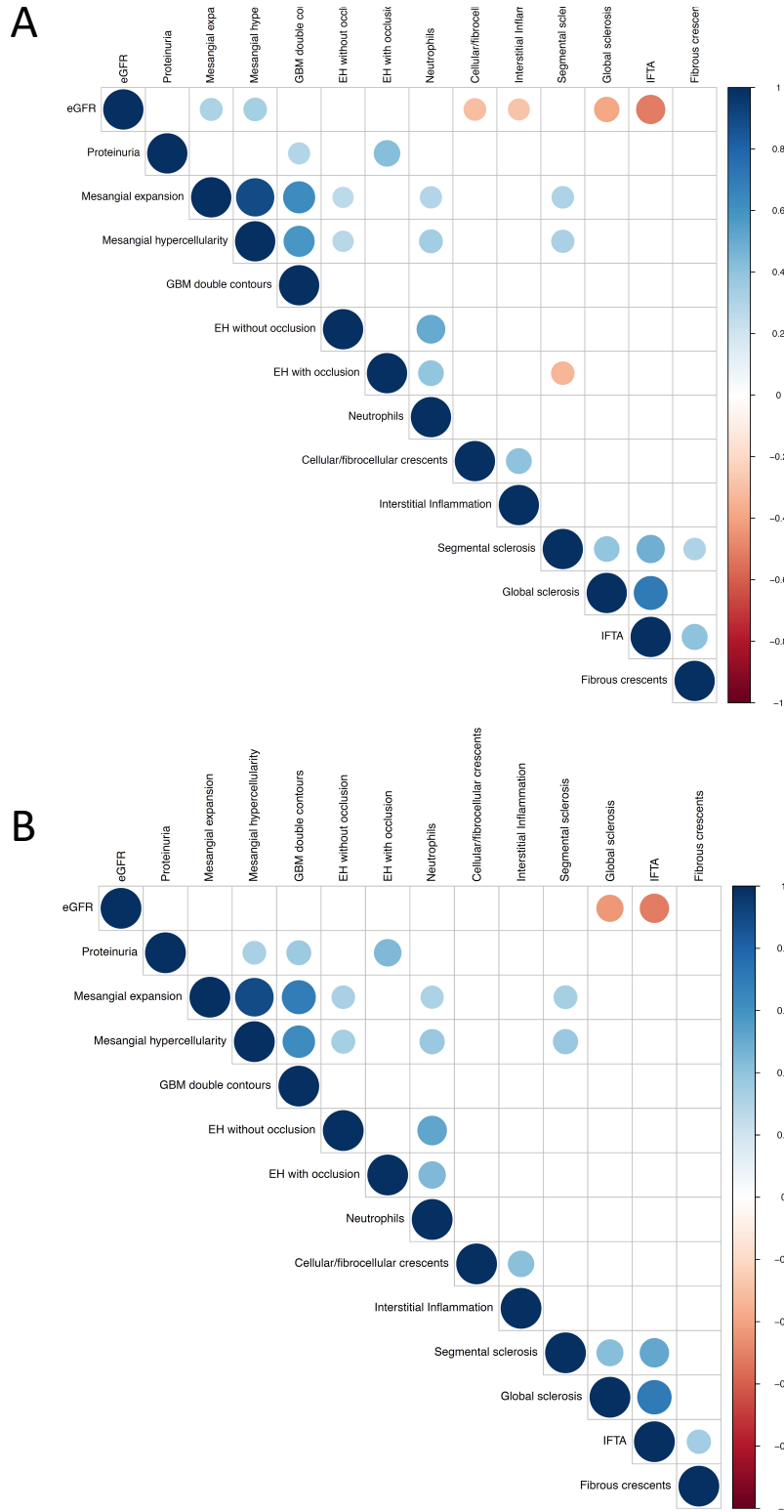
Supplemental Figure 5. Histograms of the histological scores in 156 baseline kidney biopsies. (A) Mesangial expansion; (B) Mesangial hypercellularity; (C) Glomerular basement membrane double contours; (D) Neutrophils; (E) Endocapillary hypercellularity without occlusion; (F) Endocapillary hypercellularity with occlusion; (G) Cellular/fibrocellular crescent; (H) Fibrous crescent; (I) Segmental sclerosis; (J) Global sclerosis; (K) Interstitial fibrosis and tubular atrophy and (L) Interstitial inflammation. GBM, glomerular basement membrane; EH, endocapillary hypercellularity; IFTA, Interstitial fibrosis and tubular atrophy.



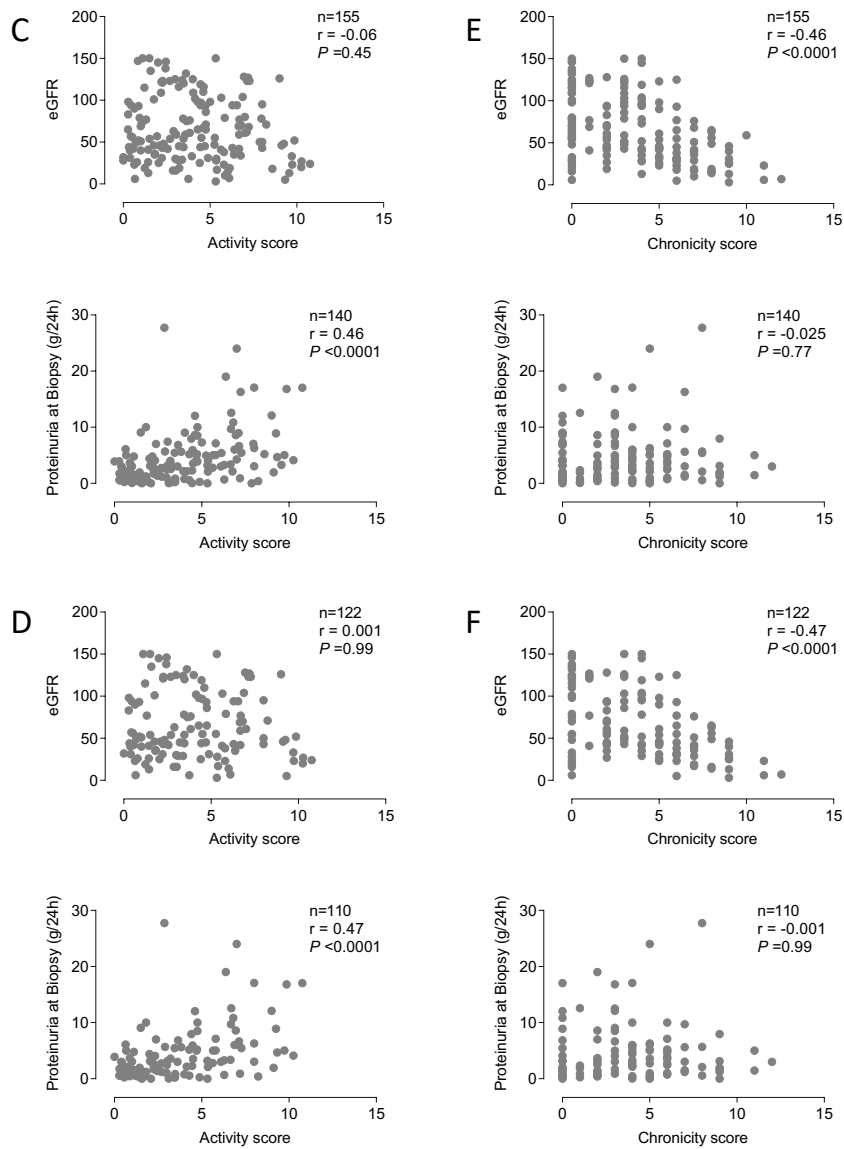
Supplemental Figure 6. Histograms of the histological scores in 123 baseline kidney biopsies with C3G. (A) Mesangial expansion; (B) Mesangial hypercellularity; (C) Glomerular basement membrane double contours; (D) Neutrophils; (E) Endocapillary hypercellularity without occlusion; (F) Endocapillary hypercellularity with occlusion; (G) Cellular/fibrocellular crescent; (H) Fibrous crescent; (I) Segmental sclerosis; (J) Global sclerosis; (K) Interstitial fibrosis and tubular atrophy and (L) Interstitial inflammation. GBM, glomerular basement membrane; EH, endocapillary hypercellularity; IFTA, Interstitial fibrosis and tubular atrophy.



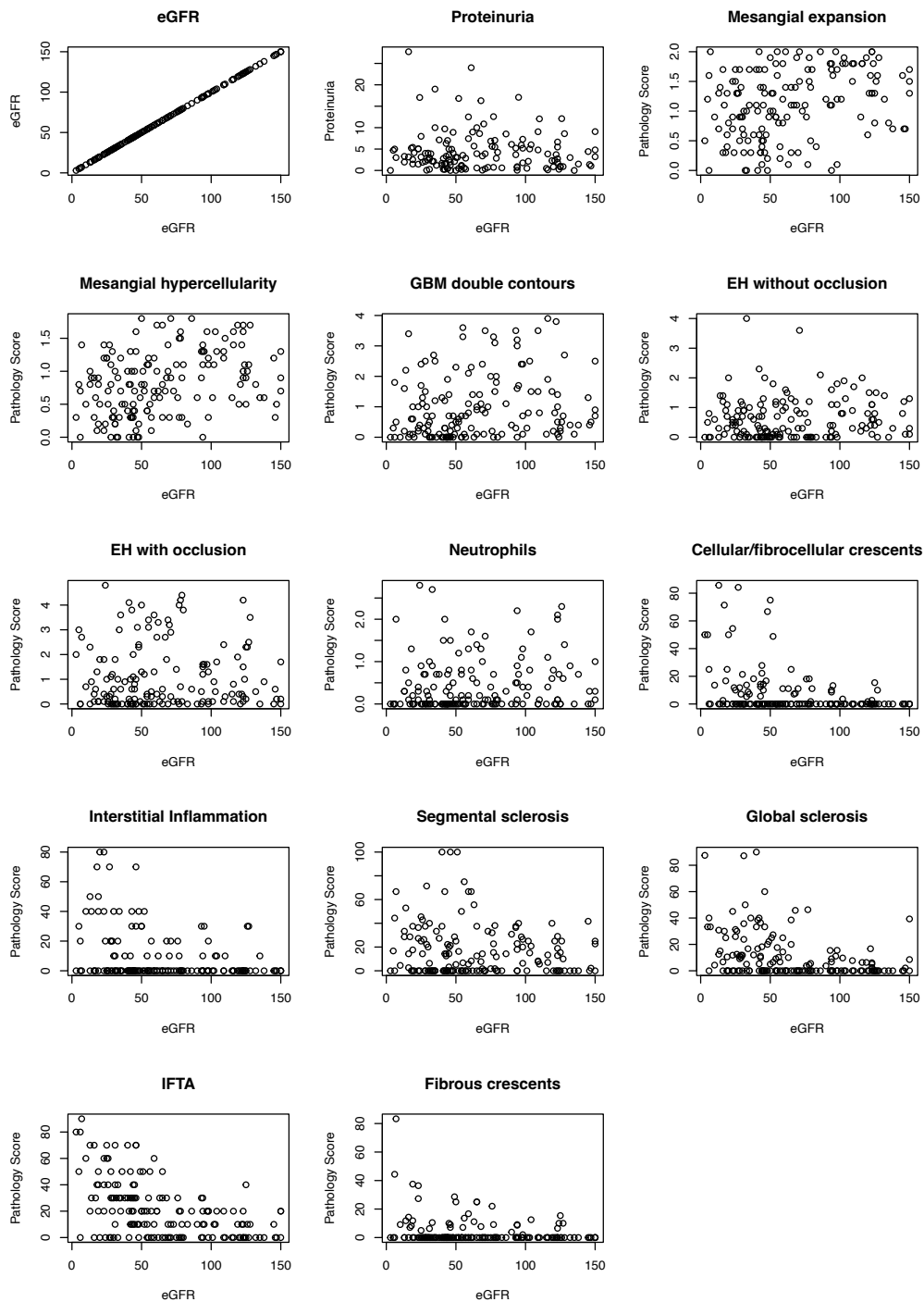
Supplemental Figure 7. Histograms of the histological scores in 33 baseline kidney biopsies with Ig-MPGN. (A) Mesangial expansion; (B) Mesangial hypercellularity; (C) Glomerular basement membrane double contours; (D) Neutrophils; (E) Endocapillary hypercellularity without occlusion; (F) Endocapillary hypercellularity with occlusion; (G) Cellular/fibrocellular crescent; (H) Fibrous crescent; (I) Segmental sclerosis; (J) Global sclerosis; (K) Interstitial fibrosis and tubular atrophy and (L) Interstitial inflammation. GBM, glomerular basement membrane; EH, endocapillary hypercellularity; IFTA, Interstitial fibrosis and tubular atrophy.



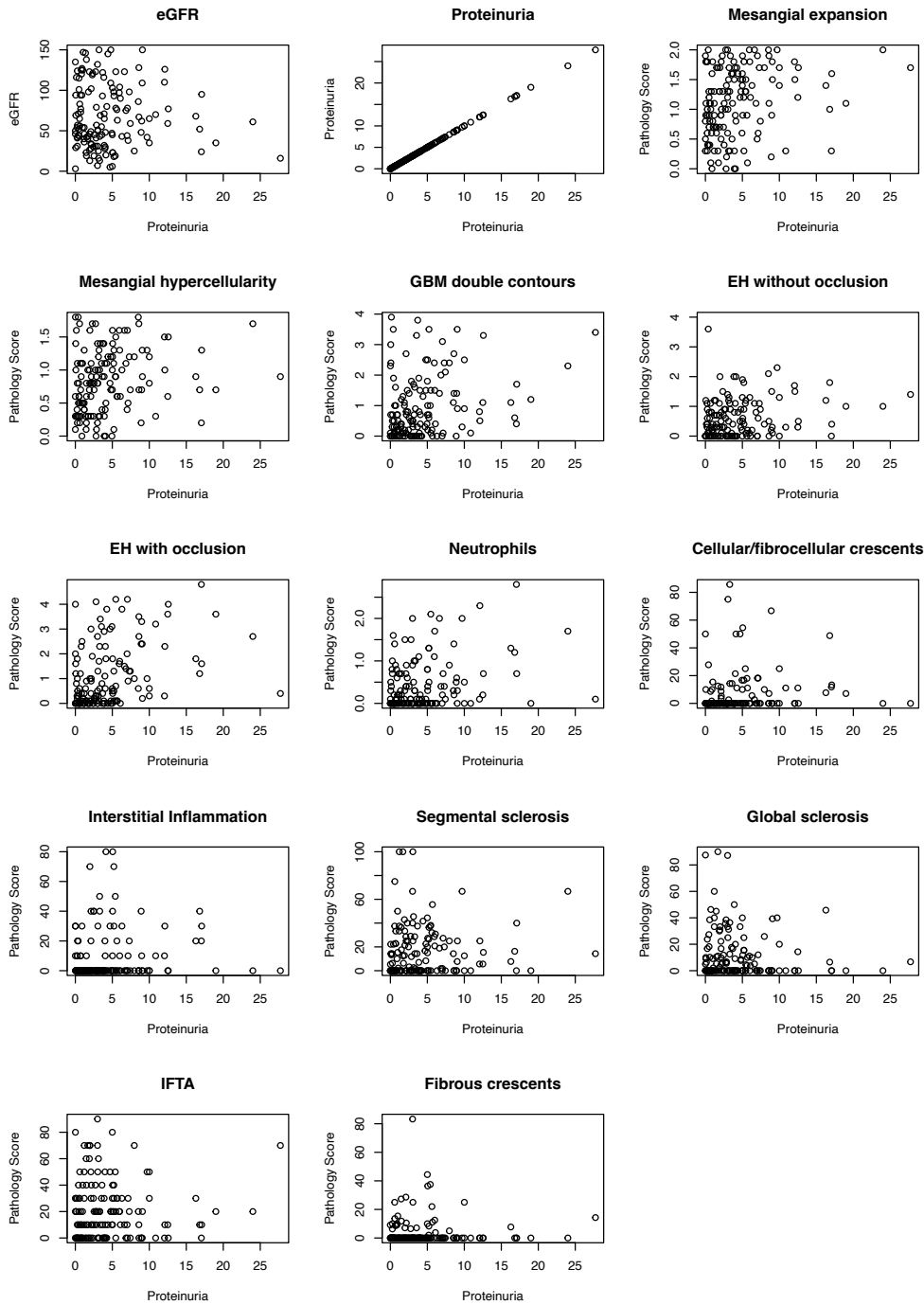
Supplemental Figure 8. Correlation between histological variables, eGFR, proteinuria, activity and chronicity scores. The correlograms for (A) the whole and (B) the C3G cohort represent Spearman's rho rank correlation coefficients for all possible pair-wise comparisons below the statistical threshold (Holm-Sidak adjusted P value; 0.00078 and 0.00072 respectively). Circle areas represent rho values with positive coefficients in blue and negative coefficients in red. EH - endocapillary hypercellularity; GBM - glomerular basement membrane; IFTA - interstitial fibrosis and tubular atrophy; eGFR - estimated glomerular filtration rate. Coefficients, P values and number of pairwise comparisons are listed in Supplemental Tables 5 and 6.



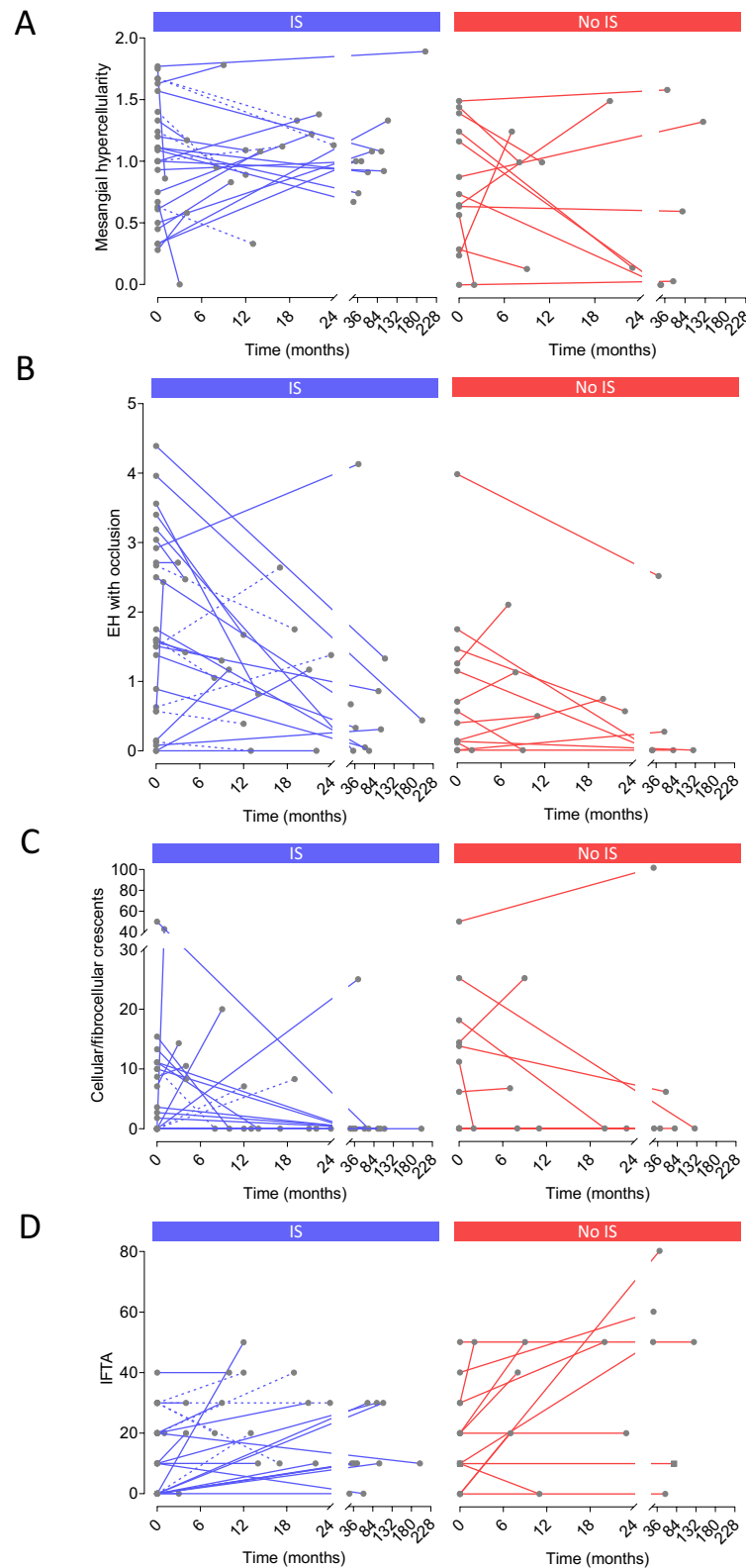
Supplemental Figure 8 (continued). Correlation between histological variables, eGFR, proteinuria, activity and chronicity scores. Correlations between baseline biopsy activity and chronicity scores and eGFR and proteinuria at the time of biopsy in (C and E) the whole cohort and (D and F) the C3G cohort. Data derived from the Spearman rank correlation; r represents Spearman's rho. C3G - C3 glomerulopathy; eGFR - estimated glomerular filtration rate in ml/min/1.73m².



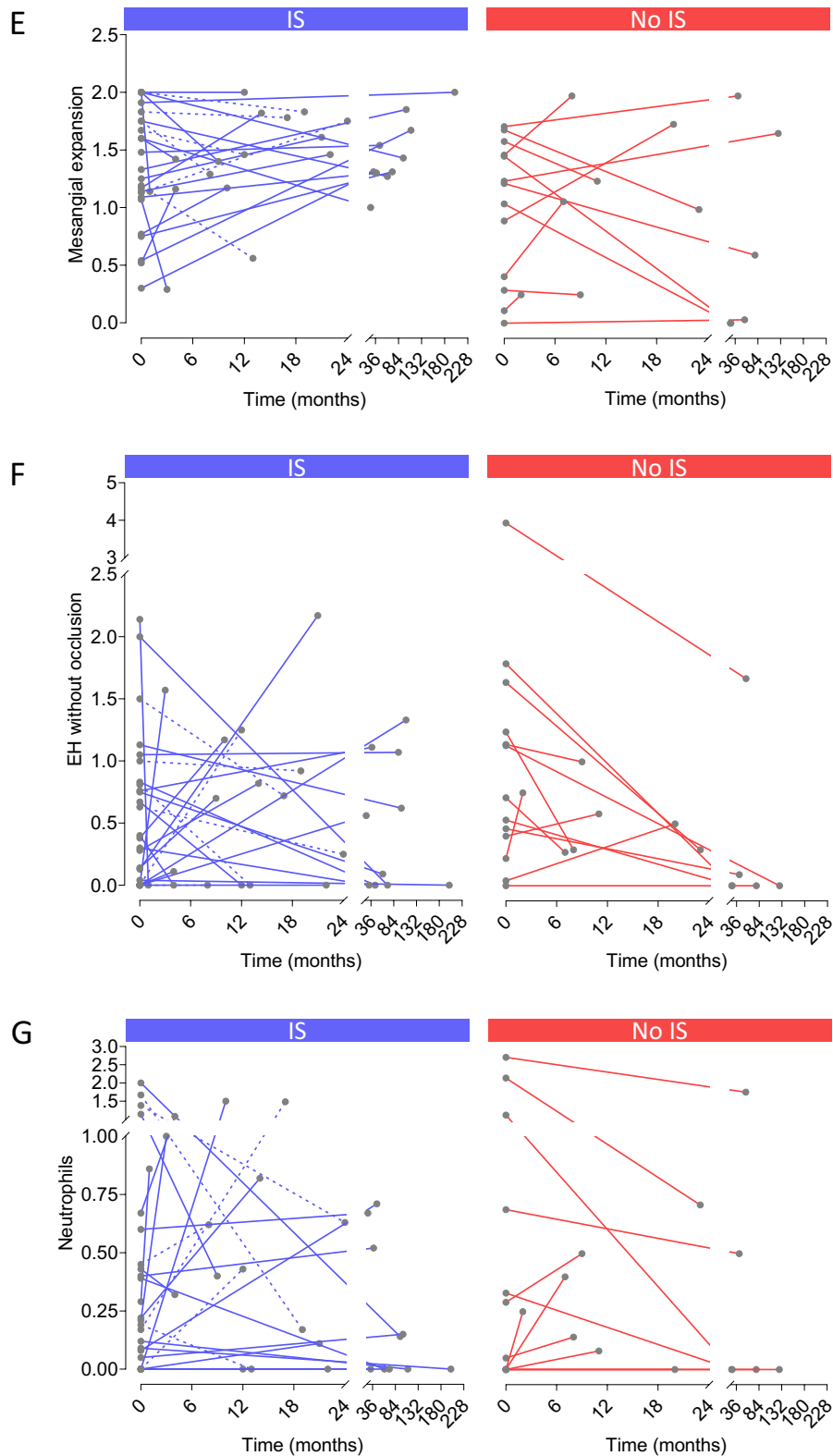
Supplemental Figure 9. Scatterplots of eGFR vs Proteinuria and histological features in the whole cohort. Interstitial fibrosis and tubular atrophy, fibrous crescents, interstitial inflammation, Cellular/fibrocellular crescents and mesangial hypercellularity were significantly associated with eGFR in a multivariate analysis (See Table 3). Due to strong correlation between mesangial hypercellularity and mesangial expansion, mesangial expansion was not included in the multivariate analysis. EH – endocapillary hypercellularity; IFTA – interstitial fibrosis and tubular atrophy; GBM – glomerular basement membrane; eGFR – estimated glomerular filtration rate.



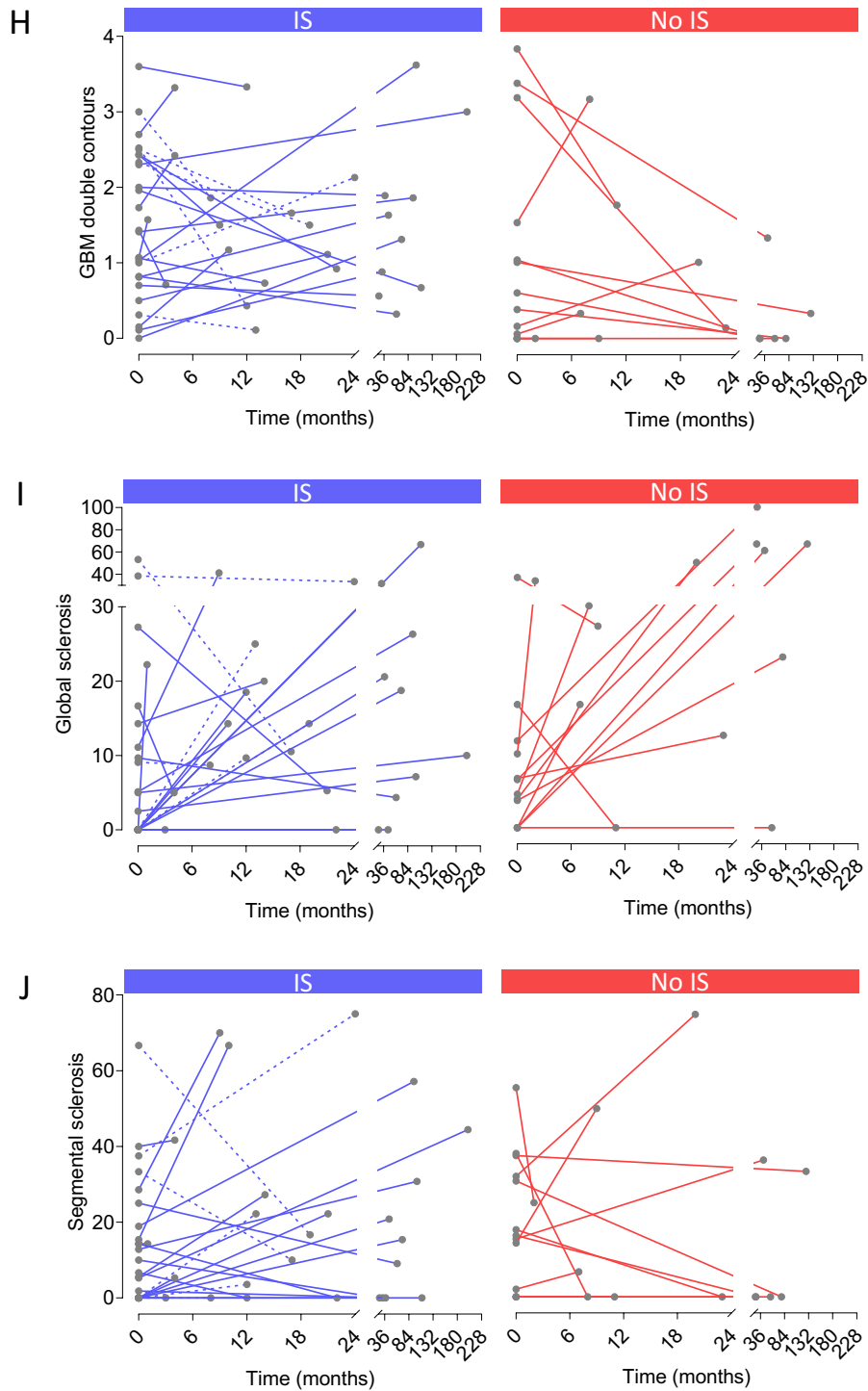
Supplemental Figure 10. Scatterplots of Proteinuria vs eGFR and histological features in the whole cohort. Endocapillary hypercellularity with occlusions, endocapillary hypercellularity without occlusions and GBM double contours were significantly associated with eGFR in a multivariate analysis (See Table 3). Due to strong correlation, mesangial hypercellularity and mesangial expansion, mesangial expansion was not included in the multivariate analysis. EH – endocapillary hypercellularity; IFTA – interstitial fibrosis and tubular atrophy; GBM – glomerular basement membrane; eGFR – estimated glomerular filtration rate.



Supplemental Figure 11. Biopsy features over time. Histopathology features scored in both baseline and first repeat native biopsies were grouped into patients who had (blue, n=26) or had not (red, n=13) received any form of immunosuppressive therapy. (A) Mesangial hypercellularity; (B) endocapillary hypercellularity (EH) with occlusion; (C) cellular/fibrocellular crescents and (D) interstitial fibrosis and tubular atrophy (IFTA). Each graph indicates the time between baseline and second biopsies which varied between patients, dashed lines represent patients with stable disease. Data compared by Fisher's exact test.

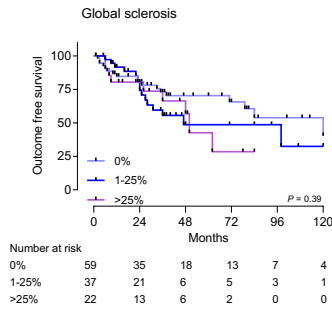


Supplemental Figure 11 (continued). Biopsy features over time. Histopathology features scored in both baseline and first repeat native biopsies were grouped into patients who had (blue, n=26) or had not (red, n=13) received any form of immunosuppressive therapy. (E) Mesangial expansion; (F) endocapillary hypercellularity (EH) without occlusion; (G) neutrophils. Each graph indicates the time between baseline and second biopsies which varied between patients, dashed lines represent patients with stable disease. Data compared by Fisher's exact test.

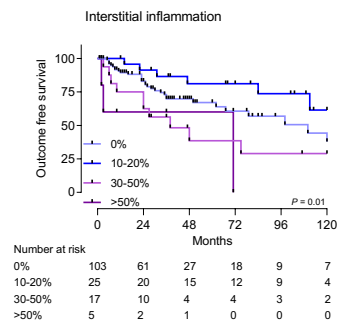
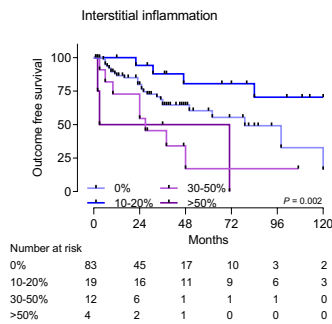
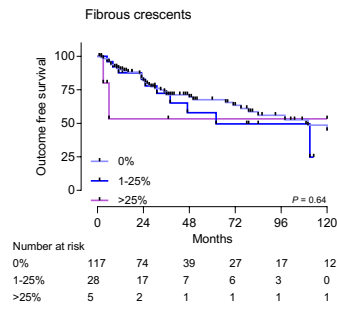
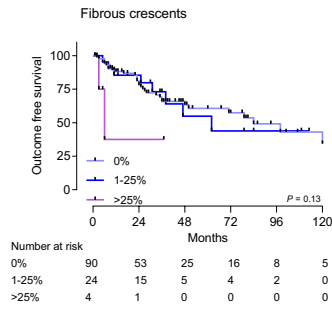
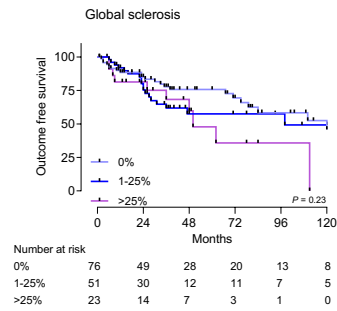


Supplemental Figure 11 (continued). Biopsy features over time. Histopathology features scored in both baseline and first repeat native biopsies were grouped into patients who had (blue, n=26) or had not (red, n=13) received any form of immunosuppressive therapy. (H) GBM double contours; (I) global sclerosis; (J) segmental sclerosis. Each graph indicates the time between baseline and second biopsies which varied between patients, dashed lines represent patients with stable disease. Data compared by Fisher's exact test.

C3G COHORT



ALL COHORT



Supplemental Figure 12. Outcome free survival in the whole and C3G cohort using a categorical histological scoring system. Based on score distribution we grouped scores using a scale of either 0, 1-25 >25% (cellular/fibrocellular crescents; segmental sclerosis; global sclerosis; fibrous crescents) or 0, 10-20, 30-50, >50% (IFTA, interstitial inflammation). Data for cellular/fibrocellular crescents; segmental sclerosis; and IFTA are shown in Figure 4, main manuscript. *P* values derived from Log-rank test. IFTA – interstitial fibrosis and tubular atrophy; C3G – C3 glomerulopathy.

Glomerular Definition (A glomerulus is large enough to score if it contains at least 3 mesangial areas)	Score
<i>Unscorable:</i> A glomerulus that is too small to score (Yes=1/No=0).	0/1
<i>Normal:</i> A glomerulus that does not have any of the specific abnormal features listed below (Yes=1/No=0).	0/1
<i>Minimally abnormal glomerulus:</i> A glomerulus that is nearly normal without any of the specific features scored below. The abnormality is noted.	
<i>Ischemic changes:</i> Global tuft collapse and capillary wall wrinkling with or without thickening of Bowman's capsule. May also show fibrosis inside Bowman's space. May be present with other lesions detailed below (Present=1/Absent=0).	0/1
<i>Mesangial expansion:</i> An increase in the extracellular material in the mesangium. Scored as follows:	
0 - absent	0/1/2
1- increase in the extracellular material in the mesangium such that the width of the mesangium exceeds two mesangial cell nuclei in at least two glomerular lobules.	
2- increase in the extracellular material in the mesangium such that the width of the mesangium exceeds four mesangial cell nuclei in at least two glomerular lobules.	
<i>Mesangial hypercellularity:</i> Four or more nuclei in a mesangial area away from the hilum and not adjacent to an area of sclerosis or endocapillary hypercellularity. N.B. Feature not scored in sclerotic areas or areas with endocapillary hypercellularity (not assessable/absent/4-7/>7).	-1/0/1/2
<i>Endocapillary hypercellularity</i> (2 categories):	
1. <u>Cells in the lumens without occlusion</u> (0, 1 cell per glomerulus, >1 cell in 1-10% lumens, 11-25%, 26-50%, 50-75%, >75%).	0/1/2/3/4/5/6
2. <u>Increased cells in capillary lumens with occlusion</u> (0, 1-10%, 11-25%, 26-50%, 50-75%, >75% of loops involved).	0/1/2/3/4/5
<i>Neutrophils:</i> In any location within the glomerulus (0, 1, 2-3, 4-10, >10).	0/1/2/3/4
<i>Necrosis:</i> Disruption of the glomerular basement membrane, fibrin and karyorrhexis. At least two of these three lesions need to be present to meet the criteria for necrosis (Present=1/Absent=0).	0/1
<i>Glomerular basement membrane (GBM) duplication:</i> A double contour of the GBM with or without endocapillary hypercellularity (0, 1-25%, 26-50%, 51-75%, >75% of capillary loops involved).	0/1/2/3/4
<i>Segmental sclerosis:</i> Obliteration of the capillary lumens by increased extracellular matrix with or without hyalinosis, with or without foam cells, involving part of but not the whole tuft. Percentage of glomeruli with feature was determined.	Percentage
Extracapillary lesions (sub-classified as follows):	
<i>Cellular crescent:</i> Extracapillary cell proliferation of more than two cell layers, more than 75% cells and fibrin and less than 25% fibrous matrix. This is further classified by the percentage of the glomerular circumference involved. Percentage of glomeruli with feature was determined.	Percentage
<i>Fibrocellular crescent:</i> Part of the circumference of Bowman's capsule covered by a combination of cells and extracellular matrix, with 25-75% cells and fibrin and the remainder fibrous matrix. This lesion is often associated with disruption of Bowman's capsule. Ischemic, obsolescent glomeruli should be excluded. This is further classified by the percentage of the glomerular circumference involved. Percentage of glomeruli with feature was determined.	Percentage
<i>Fibrous crescent:</i> More than 10% of the circumference of Bowman's capsule covered by a lesion composed of <u>more than 75% fibrous matrix and less than 25% cells and fibrin</u> . This is further classified by the percentage of the glomerular circumference involved. Percentage of glomeruli with feature was determined.	Percentage
A glomerulus may be involved with more than one type of crescent.	
<i>Visceral epithelial cell hypertrophy:</i> Prominent enlargement of the cytoplasm in a cluster of at least 3 cells, with or without cytoplasmic vacuoles or protein droplets, and/or nuclear enlargement with or without nucleoli (Present=1/Absent=0).	0/1
<i>Tip Lesion:</i> A segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule). The tubular pole must be identified in the defining lesion. The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck. Tip lesion may be cellular or sclerosing (Present=1/Absent=0).	0/1
<i>Global sclerosis:</i> The entire glomerular tuft involved with sclerosis (Present=1/Absent=0).	0/1
<i>An adhesion:</i> An extracellular matrix attachment in a glomerulus without segmental sclerosis, or a fibrous or fibrocellular crescent (Present=1/Absent=0)	0/1
<i>Thrombosis:</i> A mass of fibrin and platelets within capillary lumens (0, 1-25%, 26-50%, 51-75%, >75% of the glomerulus involved)	0/1/2/3/4
<i>Mesangiolysis:</i> Dissolution or attenuation of the mesangial matrix and degeneration of mesangial cells (0, 1-25%, 26-50%, 51-75%, >75% of the glomerulus involved).	0/1/2/3/4
Tubulointerstitial definitions	
<i>Tubular atrophy:</i> Thick irregular tubular basement membranes with decreased diameter of tubules, or the appearance of thyroidisation. It is scored according to the percent of cortical area involved rounded to the closest 10% (ie <5% = 0%).	0/10/20/30/40/50 /60/70/80/90/100
<i>Interstitial fibrosis:</i> Increased extracellular matrix separating tubules in the cortical area, excluding the subcapsular area. It is scored as percentage involvement rounded to the closest 10% (ie <5% = 0%)	0/10/20/30/40/50 /60/70/80/90/100
<i>Interstitial inflammation:</i> Inflammatory cells within the cortical interstitium. It is scored as percentage involvement in non-scarred areas rounded to the closest 10% (ie <5% = 0%).	0/10/20/30/40/50 /60/70/80/90/100
<i>Note if substantial inflammation in scarred areas</i> (Present=1/Absent=0).	0/1
<i>Note if tubulitis present</i> (Present=1/Absent=0).	0/1
Additional tubular lesions are noted as follows:	
<i>Red blood cells:</i> The presence of numerous red blood cells, defined as tubules completely filled with red blood cells with or without casts, is noted as a lesion when it involves ≥20% of tubules. Score cortex and medulla separately (Present=1/Absent=0).	0/1
<i>Acute tubular injury</i> of the proximal tubular epithelium is defined by simplification of the epithelium without tubular basement membrane thickening or widespread sloughing of cells and/or cell cytoplasm into tubular lumens. Scored as percentage of non-atrophic tubules involved (0, 5-10%, 11-25%, 26-50%, >50%)	0/1/2/3/4
<i>Foam cells:</i> Presence of foam cells in the biopsy is scored (absent, scanty, many).	0/1/2
Vascular definitions	
<i>Arterial lesions</i> are scored based on the most severe lesions. Interlobular and larger arteries are scored separately. Intimal thickening is scored by comparing the thickness of the intima to that of the media in the following categories: (0, <50%, >50%).	0/1/2
<i>Arteriolar lesions</i> are scored as follows:	
<i>Non-hyaline arteriolar sclerosis</i> (Present=1/Absent=0)	0/1
<i>Arteriolar hyaline:</i> Marked hyaline in one or lesser hyaline in more than one. (Present=1/Absent=0)	0/1
Of note: Other vascular lesions including thrombosis or TMA changes can be noted on the scoring form in the "comments/other" box.	
Immunofluorescence and Electron Microscopy data collected only for diagnosis	

Supplemental Table 1. Definitions of histological features standardised and scored in the study.

Definition	Reproducibility	Test
<i>Glomerular lesion</i>		
Mesangial hypercellularity	0.86	ICC
Increased cells in lumen	0.79	ICC
Increased cells in lumen with loop distension	0.56	ICC
Neutrophils	0.78	ICC
GBM double contours	0.67	ICC
Segmental sclerosis	0.8	ICC
Mesangiolytic	0.12	ICC
Cellular crescents	0.57	ICC
Fibrocellular crescents	0.79	ICC
Fibrous crescents	0.6	ICC
Normal glomeruli	0.17	Kappa
Ischemic changes	0.32	Kappa
Increased mesangial matrix	0.34	Kappa
Karyorrhexis	0.23	Kappa
Visceral epithelial cell hypertrophy	0.07	Kappa
Global sclerosis	0.84	Kappa
An adhesion	0.18	Kappa
<i>Tubulointerstitial lesion</i>		
Interstitial fibrosis	0.88	ICC
Tubular atrophy	0.91	ICC
Acute tubular injury	0.75	ICC
Interstitial inflammation (non-scarred areas)	0.84	ICC
Interstitial inflammation (scarred areas)	0.19	Kappa
Tubulitis	0.32	Kappa
<i>Vascular lesion</i>		
Interlobular intimal thickening	0.38	ICC
Larger artery intimal thickening	0.54	ICC
Arteriolar hyaline	0.24	Kappa
Non-hyaline arteriolar sclerosis	0.09	Kappa

Score reproducibility was assessed using intra-class correlation coefficients (ICC) or the Fleiss Kappa test (Kappa)

Supplemental Table 2. Reproducibility of histology scores.

Active Score feature (max score = 24)	Definition	Score
Mesangial hypercellularity	Four or more nuclei in a mesangial area away from the hilum and not adjacent to an area of sclerosis or endocapillary hypercellularity	0 = none 1 = 4-7 2 = >7
Endocapillary hypercellularity without occlusion	Increased cells in capillary lumens, without occlusion (% of capillary loops involved)	0 = none 1 = 1 cell 2 = 1-10% 3 = 11-25% 4 = 26-50% 5 = 51-75% 6 = >75%
Endocapillary hypercellularity with occlusion	Increased cells in capillary lumens, with occlusion (% of capillary loops involved)	0 = none; 1 = 1-10%; 2 = 11-25%; 3 = 26-50%; 4 = 51-75%; 5 = >75%
Neutrophils	Neutrophils located in any location within the glomerulus. Number of neutrophils per glomerulus	0 = none; 1 = 1; 2 = 2-3; 3 = 4-10; 4 = >10
Cellular/fibrocellular crescents	% of glomeruli with cellular/fibrocellular crescents	0 = none; 1 = 1-10%; 2 = 11-25%; 3 = 26-50%; 4 = >50%
Interstitial inflammation	% of cortical area involved with interstitial inflammation	0 = 0%; 1 = 10-20%; 2 = 30-50%; 3 = >50%
Chronic Score feature (max score = 12)		
Glomerular sclerosis	% of glomeruli with global or segmental sclerosis	0 = <10%; 1 = 10-25%; 2 = 26-50%; 3 = >50%
Fibrous crescents	% of glomeruli with fibrous crescents	0 = 0; 1 = <25%; 2 = 26-50%; 3 = >50%
Interstitial fibrosis	% of cortical area involved with interstitial fibrosis	0 = 0%; 1 = 10-20%; 2 = 30-50%; 3 = >50%
Tubular atrophy	% of cortical area involved with tubular atrophy	0 = 0%; 1 = 10-20%; 2 = 30-50%; 3 = >50%

Scoring of chronic changes informed by: Sethi S, D'Agati VD, Nast CC, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int* 2017; 91: 787-789.

Supplemental Table 3. Definitions of Activity and Chronicity scores.

Supplemental Table 4. Joint model showing longitudinal change in proteinuria and the hazard of reaching an outcome event

ALL COHORT						
Predictor	Reference	log(OR) Estimate	log(OR) SD	log(OR) 95% CI	P value	OR
Gender	Female	0.925	0.867	-0.728 - 2.673	0.276	
eGFR	NA*	-0.026	0.013	-0.052 - -0.003	0.022	0.975
Diagnosis	C3GN	-	-	-	-	-
DDD		0.887	0.966	-1.028 - 2.789	0.355	
Ig-MPGN		-0.249	0.810	-1.927 - 1.250	0.780	
Age	NA*	-0.020	0.019	-0.057 - 0.020	0.301	
Immunosuppression use	No immunosuppression use	1.401	0.996	-0.371 - 3.543	0.130	
IFTA	0%	-	-	-	-	-
10-20%		2.746	0.962	0.963 - 4.745	0.002	15.579
30-50%		2.500	1.023	0.562 - 4.574	0.012	12.183
>50%		2.952	1.481	0.105 - 5.946	0.042	19.144
Cellular/fibrocellular Crescent	0%	-	-	-	-	-
1-25%		0.872	0.696	-0.467 - 2.257	0.204	
>25%		-1.716	1.513	-4.788 - 1.151	0.249	
Value (Proteinuria)		0.683	0.296	0.192 - 1.349	0.002	1.980
C3G COHORT						
Predictor	Reference	log(OR) Estimate	log(OR) SD	log(OR) 95% CI	P value	OR
Gender	Female	1.162	0.945	-0.597 - 3.116	0.205	
eGFR	NA*	-0.024	0.013	-0.051 - -0.002	0.030	0.976
Diagnosis	C3GN	-	-	-	-	-
DDD		-0.109	1.090	-2.341 - 1.971	0.939	
Age	NA*	-0.003	0.022	-0.046 - 0.042	0.881	
Immunosuppression use	No immunosuppression use	1.714	1.041	-0.124 - 3.941	0.069	
IFTA	0%	-	-	-	-	-
10-20%		4.475	1.380	1.931 - 7.359	0.000	87.784
30-50%		4.224	1.432	1.551 - 7.186	0.002	68.278
>50%		4.477	1.688	1.313 - 7.938	0.006	87.932
Cellular/fibrocellular Crescent	0%	-	-	-	-	-
1-25%		0.820	0.786	-0.653 - 2.458	0.280	
>25%		2.297	2.097	-1.664 - 6.586	0.261	
Value (Proteinuria)		0.590	0.343	0.088 - 1.430	0.014	1.804

NA* - numerical values were used for age and eGFR rather than categories. eGFR - estimated glomerular filtration rate; DDD - dense deposit disease; C3GN - C3 glomerulonephritis
IFTA - interstitial fibrosis and tubular atrophy; Ig-MPGN - immunoglobulin-associated membranoproliferative glomerulonephritis; OR - odds ratio; HR - hazard ratio; SD - standard deviation; CI - confidence interval

Supplemental Table 4. Joint model showing longitudinal change in proteinuria and the hazard of reaching an outcome event.

Spearman rho														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	1													
Proteinuria	0.001	1												
Mesangial expansion	0.336	0.262	1											
Mesangial hypercellularity	0.334	0.247	0.900	1										
GBM double contours	0.233	0.292	0.629	0.589	1									
EH without occlusion	0.104	0.233	0.269	0.273	0.123	1								
EH with occlusion	0.077	0.225	0.249	0.240	0.248	0.095	1							
Neutrophils	0.157	0.214	0.296	0.342	0.174	0.302	0.308	1						
Cellular/fibrocellular crescents	-0.307	0.252	-0.256	-0.196	-0.193	-0.043	0.265	0.026	1					
Interstitial inflammation	-0.287	0.128	-0.104	-0.026	-0.079	0.158	0.174	0.114	0.402	1				
Segmental sclerosis	-0.084	0.099	0.304	0.322	0.190	0.037	-0.331	0.019	-0.065	-0.063	1			
Global sclerosis	-0.388	-0.093	0.018	-0.030	-0.058	-0.179	-0.195	-0.051	-0.109	-0.083	0.396	1		
IFTA	-0.519	-0.007	0.081	0.037	0.000	-0.141	-0.229	-0.100	0.000	-0.017	0.484	0.703	1	
Fibrous crescents	-0.147	-0.028	0.010	0.013	-0.077	0.005	-0.081	0.095	0.132	0.113	0.304	0.209	0.408	1

P-value														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	NA													
Proteinuria	0.994	NA												
Mesangial expansion	0.000	0.002	NA											
Mesangial hypercellularity	0.000	0.003	0.000	NA										
GBM double contours	0.004	0.000	0.000	0.000	NA									
EH without occlusion	0.198	0.006	0.001	0.001	0.126	NA								
EH with occlusion	0.339	0.000	0.002	0.003	0.002	0.236	NA							
Neutrophils	0.050	0.011	0.000	0.000	0.030	0.000	0.000	NA						
Cellular/fibrocellular crescents	0.000	0.003	0.001	0.014	0.016	0.590	0.001	0.749	NA					
Interstitial inflammation	0.000	0.133	0.195	0.751	0.326	0.049	0.030	0.158	0.000	NA				
Segmental sclerosis	0.297	0.246	0.000	0.000	0.017	0.644	0.000	0.813	0.417	0.434	NA			
Global sclerosis	0.000	0.273	0.827	0.711	0.473	0.026	0.015	0.526	0.177	0.304	0.000	NA		
IFTA	0.000	0.933	0.317	0.646	0.996	0.080	0.004	0.215	0.999	0.832	0.000	0.000	NA	
Fibrous crescents	0.068	0.746	0.905	0.873	0.340	0.951	0.915	0.237	0.102	0.162	0.000	0.009	0.000	NA

Number of pair-wise comparisons														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	155													
Proteinuria	140	140												
Mesangial expansion	155	140	156											
Mesangial hypercellularity	155	140	156	156										
GBM double contours	155	140	156	156	156									
EH without occlusion	155	140	156	156	156	156								
EH with occlusion	155	140	156	156	156	156	156							
Neutrophils	155	140	156	156	156	156	156	156						
Cellular/fibrocellular crescents	155	140	156	156	156	156	156	156	156					
Interstitial inflammation	155	140	156	156	156	156	156	156	156	156				
Segmental sclerosis	155	140	156	156	156	156	156	156	156	156	156			
Global sclerosis	155	140	156	156	156	156	156	156	156	156	156	156		
IFTA	155	140	156	156	156	156	156	156	156	156	156	156	156	
Fibrous crescents	155	140	156	156	156	156	156	156	156	156	156	156	156	156

Light green shaded cells denotes significant P values before correction for multiple comparison testing; dark green shaded cells denote significant P values after adjusting for multiple comparison testing using Holm-Sidak procedure (α=0.0078)

eGFR - estimated glomerular filtration rate; EH - endothocillary hypercellularity; GBM - glomerular basement membrane; IFTA - interstitial fibrosis and tubular atrophy

Supplemental Table 5. Correlations between eGFR and Proteinuria and histology features in the whole cohort.

Spearman Rho														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial Inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	1													
Proteinuria	0.008	1												
Mesangial expansion	0.273	0.315	1											
Mesangial hypercellularity	0.298	0.329	0.895	1										
GBM double contours	0.228	0.364	0.691	0.629	1									
EH without occlusion	0.109	0.174	0.376	0.338	0.224	1								
EH with occlusion	0.100	0.447	0.245	0.255	0.245	0.178	1							
Neutrophils	0.188	0.231	0.315	0.375	0.230	0.520	0.446	1						
Cellular/fibrocellular crescents	-0.258	0.247	-0.299	-0.194	-0.205	-0.024	0.217	-0.026	1					
Interstitial Inflammation	-0.179	0.130	-0.073	0.011	-0.108	0.174	0.152	0.130	0.412	1				
Segmental sclerosis	-0.104	0.151	0.332	0.378	0.281	-0.035	-0.283	-0.006	-0.054	-0.061	1			
Global sclerosis	-0.434	-0.081	0.006	-0.041	-0.079	-0.235	-0.219	-0.131	-0.160	-0.147	0.429	1		
IFTA	-0.510	0.027	0.098	0.051	0.028	-0.217	-0.244	-0.180	-0.065	-0.151	0.514	0.708	1	
Fibrous crescents	-0.083	-0.073	0.029	0.044	0.001	-0.098	-0.049	0.039	0.076	0.069	0.297	0.171	0.349	1

P-value														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial Inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	NA													
Proteinuria	0.935	NA												
Mesangial expansion	0.002	0.001	NA											
Mesangial hypercellularity	0.001	0.000	0.000	NA										
GBM double contours	0.011	0.000	0.000	0.000	NA									
EH without occlusion	0.234	0.068	0.000	0.000	0.013	NA								
EH with occlusion	0.273	0.000	0.006	0.004	0.006	0.048	NA							
Neutrophils	0.038	0.015	0.000	0.000	0.011	0.000	0.000	NA						
Cellular/fibrocellular crescents	0.004	0.009	0.001	0.031	0.023	0.792	0.016	0.773	NA					
Interstitial Inflammation	0.048	0.176	0.424	0.905	0.233	0.054	0.092	0.151	0.000	NA				
Segmental sclerosis	0.254	0.116	0.000	0.000	0.002	0.704	0.001	0.945	0.556	0.502	NA			
Global sclerosis	0.000	0.400	0.947	0.651	0.386	0.009	0.015	0.150	0.076	0.105	0.000	NA		
IFTA	0.000	0.780	0.278	0.573	0.763	0.016	0.007	0.046	0.472	0.095	0.000	0.000	NA	
Fibrous crescents	0.365	0.448	0.748	0.629	0.990	0.279	0.592	0.665	0.404	0.440	0.001	0.059	0.000	NA

Number of pair-wise comparisons														
VARIABLE	eGFR	Proteinuria	Mesangial expansion	Mesangial hypercellularity	GBM double contours	EH without occlusion	EH with occlusion	Neutrophils	Cellular/fibrocellular crescents	Interstitial Inflammation	Segmental sclerosis	Global sclerosis	IFTA	Fibrous crescents
eGFR	122													
Proteinuria	110	110												
Mesangial expansion	122	110	123											
Mesangial hypercellularity	122	110	123	123										
GBM double contours	122	110	123	123	123									
EH without occlusion	122	110	123	123	123	123								
EH with occlusion	122	110	123	123	123	123	123							
Neutrophils	122	110	123	123	123	123	123	123						
Cellular/fibrocellular crescents	122	110	123	123	123	123	123	123	123					
Interstitial Inflammation	122	110	123	123	123	123	123	123	123	123				
Segmental sclerosis	122	110	123	123	123	123	123	123	123	123	123			
Global sclerosis	122	110	123	123	123	123	123	123	123	123	123	123		
IFTA	122	110	123	123	123	123	123	123	123	123	123	123	123	
Fibrous crescents	122	110	123	123	123	123	123	123	123	123	123	123	123	123

Light green shaded cells denotes significant P values before correction for multiple comparison testing; dark green shaded cells denote significant P values after adjusting for multiple comparison testing using Holm-Sidak procedure ($\alpha=0.00072$)
eGFR - estimated glomerular filtration rate; EH - endocapillary hypercellularity; GBM - glomerular basement membrane; IFTA - interstitial fibrosis and tubular atrophy

Supplemental Table 6. Correlations between eGFR and Proteinuria and histology features in C3G cohort only.

ALL COHORT		eGFR (ml/min per 1.73m ² ; n=155)			Proteinuria (g/24hr; n=140)			
Biopsy Feature	Univariable - B (95% CI)	P value	Multivariable - B (95% CI), r ² = 0.505	P value	Univariable - B (95% CI)	P value	Multivariable - B (95% CI), r ² = 0.255	P value
Global sclerosis	-0.780 (-1.113 - -0.448)	<0.0001	0.094 (-0.274-0.462)	0.62	-0.032 (-0.076-0.012)	0.15		
Mesangial expansion	20.773 (10.610-30.936)	<0.0001			1.975 (0.624-3.327)	0.00		
Mesangial hypercellularity	25.932 (13.754-38.109)	<0.0001	29.206 (18.044-40.369)	<0.0001	2.076 (0.441-3.710)	0.01	-0.814 (-2.767-1.140)	0.41
EH without occlusion	4.503 (-4.551-13.558)	0.33			1.657 (0.434-2.880)	0.01	1.624 (0.331-2.918)	0.01
EH with occlusion	0.341 (-4.572-5.255)	0.89			1.444 (0.860-2.028)	<0.0001	1.273 (0.640-1.907)	<0.0001
Neutrophils	6.757 (-3.263-16.777)	0.19			2.391 (1.086-3.695)	<0.0001	0.738 (-0.743-2.219)	0.33
GBM Double contours	7.039 (1.202-12.877)	0.02	-2.681 (-7.933-2.570)	0.32	1.316 (0.568-2.063)	0.00	1.082 (0.218-1.945)	0.01
Segmental sclerosis	-0.247 (-0.531- 0.037)	0.09			0.008 (-0.029-0.046)	0.66		
Crescent (C or FC)	-0.754 (-1.107- -0.400)	<0.0001	-0.439 (-0.759- -0.119)	0.01	0.037 (-0.016-0.089)	0.17		
IFTA	-0.926 (-1.170- -0.682)	<0.0001	-1.032 (-1.356- -0.708)	<0.0001	-0.001 (-0.037-0.035)	0.95		
Interstitial Inflammation	-0.697 (-1.032- -0.362)	<0.0001	-0.483 (-0.786- -0.180)	0.00	0.022 (-0.024-0.069)	0.35		
Fibrous crescents	-0.834 (-1.428- -0.240)	0.01	0.220 (-0.295-0.736)	0.40	-0.007 (-0.082-0.068)	0.85		
C3G COHORT		eGFR (ml/min per 1.73m ² ; n=122)			Proteinuria (g/24hr; n=110)			
Biopsy Feature	Univariable - B (95% CI)	P value	Multivariable - B (95% CI), r ² = 0.486	P value	Univariable - B (95% CI)	P value	Multivariable - B (95% CI), r ² = 0.295	P value
Global sclerosis	-0.829 (-1.182- -0.477)	<0.0001	0.076 (-0.339-0.492)	0.72	-0.047 (-0.095-0.002)	0.06		
Mesangial expansion	18.850 (7.199-30.500)	0.00			2.317 (0.738-3.897)	0.00		
Mesangial hypercellularity	23.734 (9.562-37.906)	0.00	25.773 (14.525-37.020)	<0.0001	2.718 (0.796-4.641)	0.01	-0.217 (-2.437-2.004)	0.85
EH without occlusion	4.361 (-5.714-14.436)	0.39			1.408 (-0.034-2.849)	0.06		
EH with occlusion	1.058 (-4.787-6.903)	0.72			1.749 (1.033-2.465)	<0.0001	1.373 (0.607-2.139)	0.00
Neutrophils	7.903 (-3.005-18.811)	0.15			2.312 (0.833-3.791)	0.00	0.643 (-0.948-2.234)	0.43
GBM Double contours	5.738 (-1.646-13.123)	0.13			2.185 (1.231-3.139)	<0.0001	1.873 (0.775-2.971)	0.00
Segmental sclerosis	-0.256 (-0.571-0.058)	0.11			0.009 (-0.033-0.052)	0.66		
Crescent (C or FC)	-0.705 (-1.112- -0.297)	0.00	-0.396 (-0.776- -0.017)	0.04	0.047 (-0.018-0.112)	0.16		
IFTA	-0.936 (-1.210- -0.663)	<0.0001	-1.093 (-1.473- -0.713)	<0.0001	-0.002 (-0.043-0.040)	0.94		
Interstitial Inflammation	-0.536 (-0.948- -0.124)	0.01	-0.503 (-0.880- -0.126)	0.01	0.03 (-0.028-0.089)	0.31		
Fibrous crescents	-0.731 (-1.382- -0.080)	0.03	0.246 (-0.316-0.807)	0.38	-0.018 (-0.103-0.067)	0.68		

Supplemental Table 7. Regression of histological features with eGFR and proteinuria at time of biopsy

Indication for second biopsy (B2)	No of patients
Deterioration while taking immunosuppression	13 (33%)
Deterioration without taking immunosuppression	20 (51%)
Stable while taking immunosuppression	4 (10%)
Other/stable without taking immunosuppression	2 (5%)

Supplemental Table 8. Indications for repeat (B2) biopsy in 39 patients

Participant	B1 indication	B2 indication	Time between B1 and B2 (months)
Case #1	Nephrotic syndrome following flu-like illness.	Decreasing C3 level, rising creatinine.	4
Case #2	Presented with nephrotic syndrome, previously well.	No improvement since initial biopsy, second opinion sought.	38
Case #3	Acute renal failure, active urinary sediment, recent upper respiratory tract infection.	Clinical concern for relapse.	21

Supplemental Table 9. Indications for native kidney baseline (B1) and repeat (B2) biopsy where diagnosis changed from Ig-MPGN to C3G.

ALL COHORT									
Biopsy Feature	eGFR (ml/min per 1.73m ² ; n=37)				Proteinuria (g/24hr; n=30)				
	Univariate - B (95% CI)	P value	Multivariate - B (95% CI), r ² = 0.550	P value	Univariate - B (95% CI)	P value	Multivariate (NA)	P value	
Global sclerosis	-0.462(-0.872-0.052)	0.028	0.112(-0.321-0.546)	0.601	0.017(-0.093-0.127)	0.755			
Mesangial expansion	14.010(3.341-31.361)	0.110			-0.098(-3.543-3.348)	0.954			
Mesangial hypercellularity	9.686(-10.792-30.164)	0.344			0.576(-3.255-4.407)	0.76			
EH without occlusion	8.326(-10.195-26.848)	0.368			-0.397(-4.118-3.323)	0.828			
EH with occlusion	-8.168(-18.149-1.778)	0.104			1.135(-0.736-3.007)	0.224			
Neutrophils	0.853(-23.960-25.665)	0.945			0.181(-3.737-4.099)	0.925			
GBM Double contours	3.112(-6.635-12.860)	0.521			-0.225(-2.110-1.660)	0.809			
Segmental sclerosis	-0.175(-0.597-0.247)	0.405			-0.020(-0.096-0.057)	0.602			
Crescent (C or FC)	-0.600(-1.160-0.040)	0.036	-0.406(-0.838-0.025)	0.064	0.013(-0.247-0.273)	0.918			
IFTA	-0.779(-1.240-0.318)	0.002	-0.873(-1.397-0.348)	0.002	-0.001(-0.102-0.100)	0.986			
Interstitial Inflammation	-0.772(-1.299-0.245)	0.005	-0.839(-1.259-0.419)	<0.0001	0.09(-0.017-0.196)	0.095			
Fibrous crescents	-0.586(-2.363-1.190)	0.507			0.037(-0.278-0.352)	0.812			
C3G COHORT									
Biopsy Feature	eGFR (ml/min per 1.73m ² ; n=29)				Proteinuria (g/24hr; n=110)				
	Univariate - B (95% CI)	P value	Multivariate - B (95% CI), r ² = 0.485	P value	Univariate - B (95% CI)	P value	Multivariate (NA)	P value	
Global sclerosis	-0.545(-1.017-0.073)	0.025	0.051(-0.461-0.563)	0.840	0.017(-0.110-0.144)	0.786			
Mesangial expansion	13.580(-5.485-32.646)	0.155			0.752(-3.221-4.724)	0.7			
Mesangial hypercellularity	5.276(-19.091-29.643)	0.660			2.322(-2.284-6.927)	0.309			
EH without occlusion	12.163(-9.106-33.433)	0.251			-1.894(-6.346-2.558)	0.389			
EH with occlusion	-4.227(-19.044-10.591)	0.563			1.211(-1.531-3.953)	0.371			
Neutrophils	8.895(-18.518-36.309)	0.511			-0.697(-5.055-3.661)	0.744			
GBM Double contours	4.167(-7.133-15.466)	0.456			-0.071(-2.183-2.041)	0.945			
Segmental sclerosis	-0.179(-0.638-0.279)	0.430			-0.019(-0.103-0.065)	0.648			
Crescent (C or FC)	-0.518(-1.107-0.071)	0.082			-0.059(-0.402-0.284)	0.727			
IFTA	-0.909(-1.412-0.407)	0.001	-0.853(-1.443-0.262)	0.006	-0.001(-0.115-0.114)	0.992			
Interstitial Inflammation	-1.051(-1.945-0.266)	0.011	-0.892(-1.591-0.194)	0.014	0.138(-0.056-0.331)	0.155			
Fibrous crescents	-0.436(-2.315-1.443)	0.638			0.033(-0.301-0.367)	0.841			

Supplemental Table 10. Regression of histological features with eGFR and proteinuria at the time of a first repeat native biopsy.