Evidence from the large VALIGA cohort validates the subclassification of focal segmental glomerulosclerosis in IgA nephropathy

see commentary on page 1165

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Evidence from the Oxford IgA nephropathy (IgAN) cohort supports the clinical value of subclassifying focal segmental glomerulosclerosis lesions (S1). Using the larger Validation in IgA (VALIGA) study cohort, we investigated the association between podocytopathic changes and higher proteinuria, kidney outcome and response to immunosuppressive therapy. All biopsies were evaluated for glomeruli with segmental capillary occlusion by matrix ("not otherwise specified", NOS lesion), simple capsular adhesion without capillary occlusion (Adh), tip lesions, and podocyte hypertrophy (PH). S1 required a NOS lesion and/or Adh. A Chi-Squared Automatic Interaction Detection method was used to identify subgroups of FSGS lesions associated with distinctive proteinuria at biopsy. We assessed survival from a combined event (kidney failure or 50% decline in estimated glomerular filtration rate). Finally, we evaluated within each subgroup if immunosuppression was associated with a favorable outcome using propensity analysis. In 1147 patients, S1 was found in 70% of biopsies. Subclassification found NOS lesions in 44%, Adh in 59%, PH in 13%, and tip lesions in 3%, with much overlap. Four subgroups were identified with progressively higher proteinuria: from lowest, S1 without NOS, S1 with NOS but without Adh/PH, to highest, S1 with NOS and Adh but without PH, and S1 with NOS and PH. These four subgroups showed progressively worse kidney survival. Immunosuppression was associated with a better outcome only in the two highest proteinuria subgroups. Propensity analysis in these two groups, adjusted for clinical and pathological findings, found a significantly reduced time-dependent hazard of combined outcome with corticosteroids. Podocyte hypertrophy and glomeruli with simple adhesions appeared to reflect active lesions associated with a response to corticosteroids, while other S1 lesions defined chronicity. Thus, our findings support subclassifying S1 lesions in IgAN.

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KEYWORDS: IgA nephropathy; podocytopathy; segmental sclerosis; subclassification

Lay Summary

IgA nephropathy (IgAN) is a common kidney disease, and patients lose proteins and blood in the urine. In a minority of patients, IgAN progresses rapidly to kidney failure. Segmental sclerosis (SS) refers to scarring of the glomerulus, the functional unit of the kidney, with loss of its normal function. SS is identified by microscopic examination of a kidney biopsy and encompasses multiple lesions, some of which have been proposed to predict clinical outcomes. In a large retrospective cohort of 1147 IgAN patients, we validated subclassifying SS into groups, and identified features in the biopsy (glomeruli with podocyte hypertrophy or simple adhesions in combination with other glomeruli with "not otherwise specified" lesions) associated with disease progression and reduced kidney survival, but also with a response to immunosuppressive treatments. Given that indications for immunosuppression are unclear, and are associated with adverse effects, these findings have important implications for managing patients with IgAN.

Focal segmental glomerulosclerosis (FSGS) as a morphologic marker of glomerular injury has been described in various diseases affecting the kidney. Its pathogenesis and significance are varied. Segmental glomerulosclerosis is a frequent finding in IgA nephropathy (IgAN), seen in ∼70% of biopsies. The Oxford Classification Study demonstrated that the presence of segmental sclerosis (SS; S1 in the classification) is an independent predictor of kidney outcome in IgAN.[1,2] S1 was correlated with a higher level of

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proteinuria at the time of biopsy and was associated with a more rapid loss of kidney function and worse kidney survival. This occurred independently of other histologic features, glomerular filtration rate, mean arterial blood pressure (MAP), initial proteinuria, and follow-up MAP and proteinuria. Subsequent studies, including the Validation in IgA (VALIGA) study, have confirmed that S1 is an independent predictor of outcome in IgAN.[3–5]

Three pathways are implicated in the pathogenesis of S1 lesions in IgAN.[6] They can result from healed inflammatory or necrotizing lesions, appearing as bland scars with broad-based adhesions. However, in both the original Oxford Classification Study and the VALIGA cohorts, no significant correlation was found between S1 and the presence of necrosis or the extent of endocapillary hypercellularity. S1 lesions also can result from hyperfiltration injury, which typically produces glomerulomegaly with perihilar sclerosis and hyalinosis. A third mechanism is podocyte injury (podocytopathy), as seen in primary FSGS[7]; in such cases, the lesion is seen initially as podocyte injury, with an adhesion between the capillary tuft and Bowman's capsule, and with time, it progresses to established SS with matrix obliteration of capillaries.

In the original Oxford classification, the morphologic spectrum of segmental sclerosing lesions, including isolated tuft adhesions without matrix obliteration of capillary lumina, were collectively classified as S1. Subsequent study of the Oxford classification cohort addressed the clinical value of subclassification of SS in IgAN. Here, markers of podocyte injury, including podocyte hypertrophy (PH) and tip lesions, were found to be associated strongly with proteinuria and worse prognosis in patients not treated with immunosuppression (IS). The 2016 revision of the Oxford classification recommended that the presence of podocytopathic features be noted in biopsies showing S1 lesions.[8] However, the consensus was that confirmation of these finding in further larger validation studies of SS was required before changes to the original definition of Oxford classification S1 could be made. In this study, using the VALIGA cohort, we sought to validate the clinical value of subclassifying segmental sclerosing lesions in IgAN.

METHODS

Study design

We performed a *post hoc* analysis of patients from the VALIGA cohort, assembled retrospectively in 2011. In brief, the study included patients from 55 European centres who were diagnosed with primary IgAN, irrespective of the level of proteinuria or the estimated glomerular filtration rate (eGFR), with a follow-up of at least 1 year, unless it progressed to kidney failure within this period. Patients with systemic diseases, including diabetes, lupus, and Henoch-Schönlein purpura, were excluded, as were those whose biopsies included less than 8 glomeruli.

We recorded the following initial and follow-up clinical assessments: eGFR, systolic and diastolic blood pressures, proteinuria, number of antihypertensive medications, including renin-angiotensin blockade (RASB) with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Immunosuppressive therapy with corticosteroids (CSs) or other agents (cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors) was reported as intention-to-treat. No information on the dosage of medication was available. We assessed the time to a combined kidney event, defined by kidney failure (eGFR $\leq$ 15 ml/min per 1.73 m^2, dialysis or transplantation) or a 50% decline in eGFR during follow-up.

Definitions

The eGFR was estimated using the Modification of Diet in Renal Disease Study formula in adults, and the Schwartz formula in children. The maximum eGFR was set at 120 ml/min per 1.73 m^2 because the accuracy of eGFR above this level is imprecise. MAP was calculated as diastolic blood pressure +1/3 of the pulse pressure. Data in children were adjusted for 1.73 m^2, or normalized as described.[3] Proteinuria, MAP, and eGFR at biopsy were the closest values within 6 months of biopsy. To determine time-averaged proteinuria, time-averaged MAP, and time-averaged blood pressure medications, we calculated the average of the mean values of each 6-month period.

Pathology review

MEST-C scoring (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis and/or adhesion; T, tubular atrophy and interstitial fibrosis; and C, cellular or fibrocellular crescents) according to the Oxford classification of IgAN has been described previously.[5] We used the original assessment of the 2 central pathologists, excluding the local pathologist's assessment. M1 defined mesangial hypercellularity of $\geq$4 cells in one or more mesangial area present in >50% of glomeruli. Endocapillary hypercellularity (E) was scored as absent (0) or present (1). Interstitial fibrosis and tubular atrophy were scored according to the percentage of cortex showing interstitial fibrosis and tubular atrophy, as follows: T0 ($\leq$25% of cortex), T1 (26%–50%), and T2 (>50%). Crescents were scored according to the proportion of glomeruli showing cellular and/or fibrocellular crescents: C0 (0%), C1 (1%–24%), and C2 ($\geq$25%).

For this study, all slides were reviewed by a single pathologist (SSB) for subclassifying segmental sclerosing (S1) lesions, with a second pathologist (ISDR) reviewing lesions for which S score differed from that of the local pathologists, besides those associated with diagnostic difficulty or uncertainty. For each glomerulus, the presence of the following lesions was recorded: lesions with occlusion of capillaries by matrix, with or without adhesion to Bowman's capsule but lacking other features below ("not otherwise specified" [NOS]); capsular adhesions without associated occlusion of the capillaries by matrix (simple adhesions or ADH); PH; tip lesion; perihilar sclerosis; hyalinosis; collapsing lesions; resorption droplets within podocytes; and endocapillary foam cells. The presence of S1 required either the NOS lesion or simple adhesions. These features were found to have a good reproducibility in our previous assessment of the Oxford data (kappa $\geq$ 0.6), except for PH with a kappa of 0.52[9]; S1 was defined according to the Oxford classification determined by the presence of at least one glomerulus with SS or adhesion. The glossary of terms provided in the Columbia Working Group classification[10] of FSGS was used to define the individual lesions. Pathologists were blinded to the clinical data. The spectrum of segmental sclerosing lesions in IgAN is illustrated in Supplementary Figure S1.

Statistical analysis

Normally distributed variables are presented as mean ± SD and were compared using an independent *t* test or a one-way analysis of variance, as appropriate. Nonparametric continuous variables are presented as a median with interquartile range ([IQR]: 25th and 75th percentiles) and were compared using a Mann–Whitney *U* test or a Kruskal–Wallis test, as appropriate. Categorical variables are summarized using proportions and were compared using the Pearson χ^2 test. Trend tests were performed using Pearson or Spearman's rank correlation, as appropriate. The proportions of glomeruli showing S1, NOS, and simple adhesions are presented as continuous variables. Other pathology variables were infrequent and are presented as present or absent.

We tested which FSGS lesions were associated with the initial proteinuria using the χ^2 automatic interaction detection (CHAID) method.[11] This decision-tree analysis creates subgroups with distinctive proteinuria levels. This approach first identifies the FSGS lesion most associated with proteinuria and splits the cohort accordingly. The subsequent FSGS lesion most associated with proteinuria is then determined separately for each group. This process is repeated until no remaining FSGS lesion is associated with proteinuria in all the groups created. In the end, each branch (or terminal node) represents an FSGS subgroup with a statistically different proteinuria. We compared these subgroups and tested whether they experienced a different survival from a combined event using Kaplan–Meier curves.

Once we defined how to best classify FSGS lesions, we addressed in each subgroup whether the use of any IS was associated with greater survival from a combined event. We performed time-dependent Cox proportional hazard regressions, considering the survival time before the initiation of therapy, to address lead-time bias and any eGFR change from the time of biopsy to the start of treatment. Given the study's retrospective nature, where IS choices were unstandardized, patients with versus without therapy were likely to differ in risk factors of progression. To compare outcomes in treated patients to those of controls at similar risk, we then derived a propensity score to match individuals with an equal likelihood of receiving IS. This analysis was done in only the FSGS subgroups in which IS appeared to confer a benefit. Two methodological choices were made and applied:

- Subjects receiving IS without CSs were excluded from the propensity-matched analysis. However, we did include individuals given both CSs and another immunosuppressive agent, to avoid a selection bias, as these subjects may have received the additional agent based on a higher-risk profile or after the failure of CSs.
- Only patients receiving RASB were considered, and RASB had to be given before or at the start of administration of CSs.

Next, we calculated the predicted probability (propensity score) of receiving CSs in each patient, using logistic regression. The variables included in the model were age, initial proteinuria, prior use of IS, M, E, T, and C lesions (expressed as T0 vs. T1–2, and C0 vs. C1–2), time-averaged proteinuria, MAP, and blood pressure medications. We used time-averaged measurements prior to the administration of CSs in the CSs + RASB group, as treatment may impact these measurements. We then matched each patient treated with CSs + RASB to a control subject on RASB only, using the closest propensity score ± 0.25 • SD of the propensity score, which was 0.050.[12] Finally, we performed time-dependent Cox proportional hazard regression comparing CSs + RASB to RASB.

All *P* values were 2-tailed, and values less than 0.05 were considered statistically significant. Confidence intervals included 95% of predicted values. SPSS 27 statistical software (IBM Corporation) was used for all analyses.

RESULTS

Cohort characteristics

The VALIGA cohort included 1147 participants, of whom 73% were men and 97% were Caucasian. At the biopsy, their age was 36 ± 16 years, with an eGFR of 73 ± 30 ml/min per 1.73 m^2, proteinuria of 1.3 (IQR: 0.6–2.6) g/d, and a MAP of 98 ±13 mm Hg (Table 1). Ten percent of patients had received prior IS, and 15% were aged <18 years at the time of kidney biopsy. Patients were followed for a median of 4.7 years (IQR: 2.4–7.9), during which 16% experienced a combined event, and 12% progressed to kidney failure. Overall, the amount of missing data was low. The initial proteinuria measurement was missing in 3.6% of cases, and all other variables were missing in <1% of cases.

Table 1 | Baseline clinical and pathologic findings of the study of 1147 patients with IgA nephropathy

Variables	
Initial assessment	
Age, yr	36 ± 16
Female	314 (27)
Proteinuria, g/d	1.3 (0.6–2.6)
MAP, mm Hg	98 ± 13
Number of BP medications	1 (0–1)
eGFR, ml/min per 1.73 m^2	73 ± 30
Prior immunosuppression treatments	10
MEST-C score	
M1	320 (28)
E1	123 (11)
S1	796 (69)
T0, T1, T2	903 (79), 203 (18), 41 (3)
C0, C1, C2	1025 (89), 100 (9), 22 (2)
S lesions	
NOS lesion	502 (44)
Simple adhesion	672 (59)
Podocyte hypertrophy	149 (13)
Tip lesion	29 (3)
Protein resorption droplet	48 (4)
Hyalinosis	18 (2)
Follow-up	
Length of follow-up, yr	4.7 (2.4–7.9)
Exposure to immunosuppression	46
Time-averaged proteinuria, g/d	0.8 (0.4–1.6)
Time-averaged BP, mm Hg	96 ± 9
Time-averaged number of BP medications	1.0 (0.8–2.0)
Combined event	16
Kidney failure	12

BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; M1, mesangial hypercellularity of ≥4 cells in 1 or more mesangial area present in >50% of glomeruli; E1, presence of endocapillary hypercellularity; NOS, not otherwise specified; S1, presence of segmental glomerulosclerosis and/or adhesion; T0–T2, percentage of cortex showing tubular atrophy and interstitial fibrosis: T0 (≤25% of cortex), T1 (26%–50%), and T2 (>50%); C0–C2, proportion of glomeruli showing cellular and/or fibrocellular crescents: C0 (0%), C1 (1%–24%), and C2 (≥25%). There were no collapsing lesions.
Initial proteinuria, eGFR, MAP and number of BP medications were missing in 42, 10, 11, and 78 of the 1147 patients, respectively. Exposure to immunosuppression was missing in 2. No other data were missing.
Values are mean ± SD, n (%), median (IQR), or %.

Subdivision of FSGS lesions and correlations with clinical presentation

The median number of glomeruli per biopsy was 16 (IQR: 12–23), and M1, E1, and S1 were found in 28%, 11%, and 69%, respectively. Tubular atrophy and interstitial fibrosis were present in 18% (T1) and 3% (T2). Crescents were found in 9% (C1) and 2% (C2). Upon review, the S score, defined by the presence of either NOS lesion or simple adhesions, was reclassified in 1% of biopsies; 3 biopsies classified initially as S0 in 2012 were then considered to be S1, and 14 biopsies classified initially as S1 became S0.

Biopsies presented at least one NOS lesion in 502 of 1147 patients (44%), simple adhesion in 672 (59%), and PH in 149 (13%; Table 1). The overlap between the presence of these lesions is illustrated in Figure 1. When present in a biopsy, S1 was found in 18% (10%–30%) of glomeruli, NOS in 24% (13%–36%), and simple adhesions in 13% (8%–21%; Figure 2). These lesions were associated strongly with higher proteinuria, higher blood pressure despite more antihypertensive medications, reduced eGFR, and older age (Table 2). In addition, the proportion of these lesions had a graded effect on proteinuria level (Figure 3). NOS lesions and simple adhesions were associated with proteinuria independently of each other, as the graded response still existed when the other lesion was absent.

The proportions of the cohort presenting tip lesion, protein resorption droplets, or hyalinosis were only 3%, 4% and 2%, respectively, and they were not associated with proteinuria or blood pressure, except for biopsies showing protein resorption droplets that had a proteinuria of 1.7 g/d (IQR: 0.9–2.7), compared to 1.3 g/d (IQR: 0.6–2.6) g/d in those without droplets ($P = 0.03$). All 3 lesions were associated with a lower eGFR. The spectrum of segmental sclerosing lesions in IgAN is illustrated in Supplementary Figure S1. Only 6 individuals presented ischemic glomeruli.

All FSGS lesions showed associations with the M, E, T, and C scores, except for hyalinosis (Supplementary Table S1). No FSGS lesion was correlated with sex.

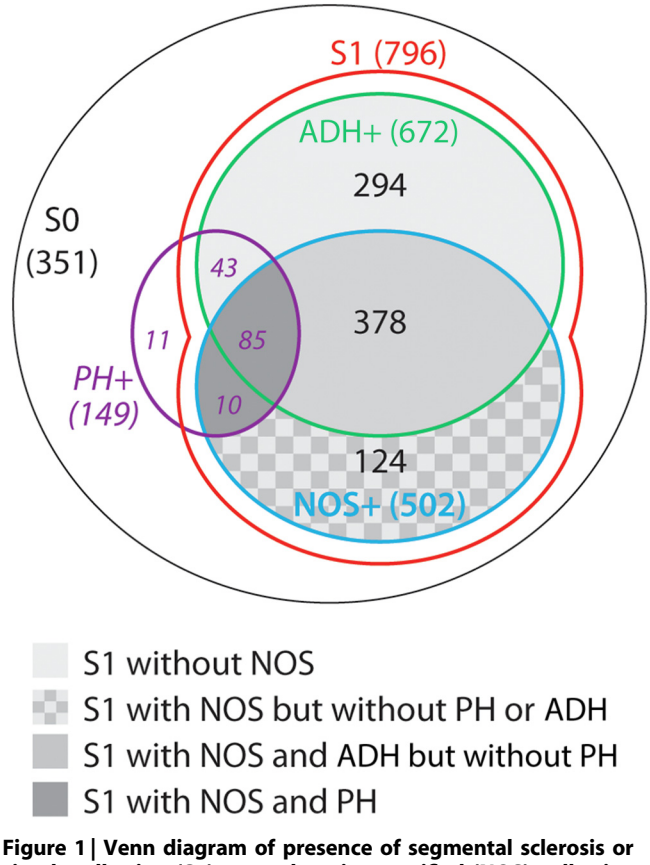


Figure 1 | Venn diagram of presence of segmental sclerosis or simple adhesion (S1), not otherwise specified (NOS), adhesions (ADH), and podocyte hypertrophy (PH) in the European Validation Study of the Oxford Classification of IgAN (VALIGA) cohort (n = 1147).

Subgrouping of FSGS lesions

To address the clinical value of subclassification of SS, we first created subgroups with distinctive proteinuria levels using the χ^2 automatic interaction detection method (Figure 4). We found that the pathology finding that discriminated the level of proteinuria the most was the NOS lesion, dividing the cohort into those with S1 without NOS with 1.2 g/d (IQR: 0.5–2.3), compared to those with S1 with NOS with 1.7 g/d (IQR: 0.9–3.2; $P < 0.001$). Categorizing S1 without NOS further had no value. As shown in Figure 1, S1 without NOS included, by definition, the presence of ADH with or without PH. By contrast, the category of S1 with NOS could be further subdivided by the presence of PH, with subjects with S1 with NOS and PH displaying the highest level of proteinuria, at 2.2 g/d (IQR: 1.1–4.2). Finally, the remaining subjects could be split by the existence of simple adhesions: those with S1 with NOS but without ADH or PH being associated with proteinuria of 1.2 g/d (IQR: 0.7–2.5) compared to those with S1 with NOS and ADH but without PH showing proteinuria of 1.8 g/d (IQR: 1.0–3.2; $P = 0.01$). In all, we found 4 distinct S1 FSGS subgroups with progressively higher proteinuria, 2 subgroups with lower proteinuria levels—those with S1 without NOS, and those with S1 with NOS but without ADH or PH—and 2 subgroups with higher proteinuria levels—those with S1 with NOS and ADH but without PH and those with S1 with NOS and PH (Figure 1).

Associations of classes of FSGS with other clinical characteristics and with outcome

To further validate whether the proposed FSGS classification was clinically relevant, we compared other biopsy findings and the initial and follow-up assessments among FSGS subgroups (Supplementary Table S2). In parallel to the increasing severity of FSGS lesions, the initial eGFR decreased, and the initial and follow-up blood pressures increased, despite more use of antihypertensive, RASB, and immunosuppressive drugs. We also found a stepwise reduction in the survival from a combined event with each subgroup severity increase, supporting the proposed classification (Figure 5). However,

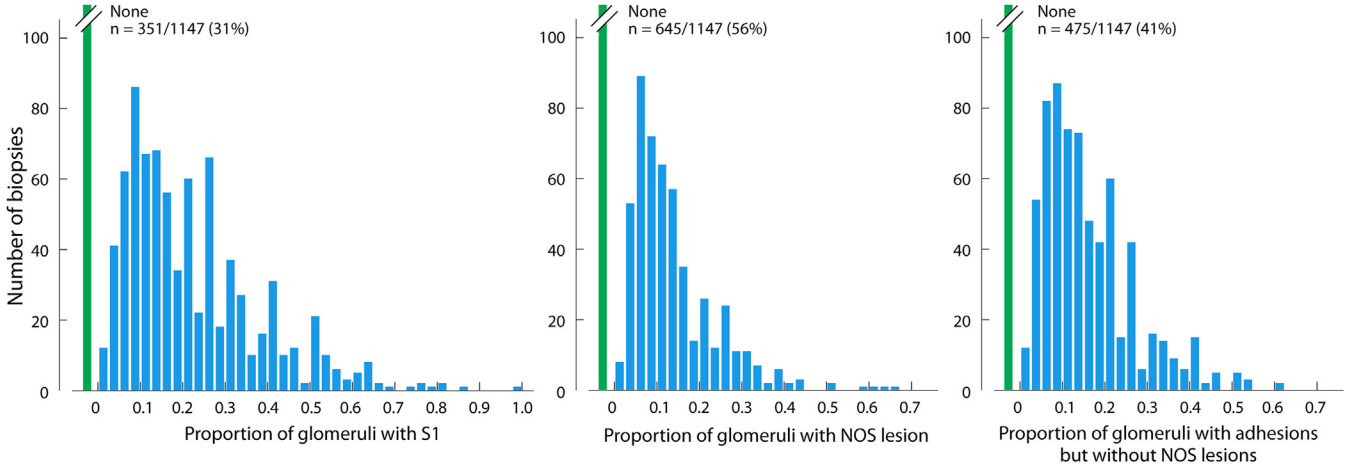


Figure 2 | Proportions of glomeruli within each biopsy showing presence of segmental sclerosis or simple adhesion (S1), not otherwise specified (NOS), and adhesion lesions.

FSGS subgroups also showed progressively more M, E, T, and C lesions.

Influence of immunosuppressive therapy within each FSGS subgroup

In addition to proposing a classification of SS associated with different outcomes, we studied the associations between subgroups of S1 and response to immunosuppressive therapy. We first compared the survival from a combined outcome in those who received any IS to those who never received any IS in each FSGS subgroup (Figure 6). A time-dependent survival analysis was used to account for the lead-time bias from biopsy to the start of therapy, and the loss of eGFR during that time. We found an apparent benefit of IS in only the 2 subgroups with the highest initial proteinuria level (those with S1 with NOS and ADH but without PH and those with S1 with NOS and PH).

We then compared the clinical and pathology characteristics of treated versus untreated patients within these 2 FSGS subgroups combined (Table 3). Those who received IS were younger, had received prior IS more often, and presented more crescents and a higher proteinuria level than those who received no IS.

Finally, we performed a propensity study, to match patients who received CSs and RASB to those with a similar risk of progression who received only RASB. We limited this analysis to the subgroups in which unmatched findings were associated with a benefit of IS. Matched subjects

Table 2 | Clinicopathologic associations with FSGS lesions

Variables	Age, yr	Sex (% Female)	Proteinuria (g/d)	MAP mm Hg	# of BP Meds	eGFR ml/min per 1.73 m^2
S0 (351)	32 ± 17	25	0.7 (0.4–1.6)	95 ± 13	0 (0–1)	88 ± 27
S1 (796)	38 ± 16	28	1.5 (0.8–2.9)	100 ± 13	1 (0–2)	67 ± 30
P	<0.001	0.26	<0.001	<0.001	<0.001	<0.001
NOS– (645)	35 ± 17	27	0.9 (0.4–2.0)	96 ± 13	0 (0–1)	81 ± 28
NOS+ (502)	38 ± 15	28	1.7 (0.9–3.2)	101 ± 13	1 (0–2)	64 ± 31
P	<0.001	0.54	<0.001	<0.001	<0.001	<0.001
Adhesion– (475)	34 ± 17	26	0.9 (0.4–2.0)	96 ± 12	0 (0–1)	82 ± 29
Adhesion+ (672)	38 ± 16	28	1.6 (0.8–3.0)	100 ± 14	1 (0–2)	67 ± 29
P	<0.001	0.42	<0.001	<0.001	<0.001	<0.001
P-hypertrophy– (998)	36 ± 16	27	1.2 (0.5–2.4)	98 ± 13	1 (0–1)	75 ± 30
P-hypertrophy + (149)	37 ± 16	30	2.0 (1.0–4.0)	100 ± 13	1 (0–2)	60 ± 31
P	0.48	0.53	<0.001	0.12	<0.001	<0.001
Tip lesion– (1118)	36 ± 16	27	1.3 (0.6–2.6)	98 ± 13	1 (0–1)	74 ± 30
Tip lesion+ (29)	40 ± 16	41	1.5 (0.9–3.6)	98 ± 13	1 (0–1)	62 ± 27
P	0.25	0.14	0.11	0.98	0.58	0.04
PRD– (1099)	36 ± 16	27	1.3 (0.5–2.6)	98 ± 13	1 (0–1)	74 ± 30
PRD+ (48)	35 ± 16	31	1.7 (0.9–2.7)	99 ± 14	1 (0–2)	62 ± 30
P	0.66	0.54	0.03	0.65	0.15	0.01
Hyalinosis– (1129)	36 ± 16	27	1.3 (0.6–2.6)	98 ± 13	1 (0–1)	74 ± 30
Hyalinosis+ (18)	41 ± 18	22	2.1 (0.7–2.6)	103 ± 14	1 (1–3)	57 ± 23
P	0.26	0.62	0.63	0.12	0.22	0.007

–, absence; +, presence; eGFR, estimated glomerular filtration rate; BP, blood pressure; meds, medications; FSGS, focal segmental glomerulosclerosis; P, podocyte; PRD, protein resorption droplet; NOS, not otherwise specified; S0, no glomerulus with segmental sclerosis or simple adhesion; S1, glomeruli with segmental sclerosis or simple adhesion present.

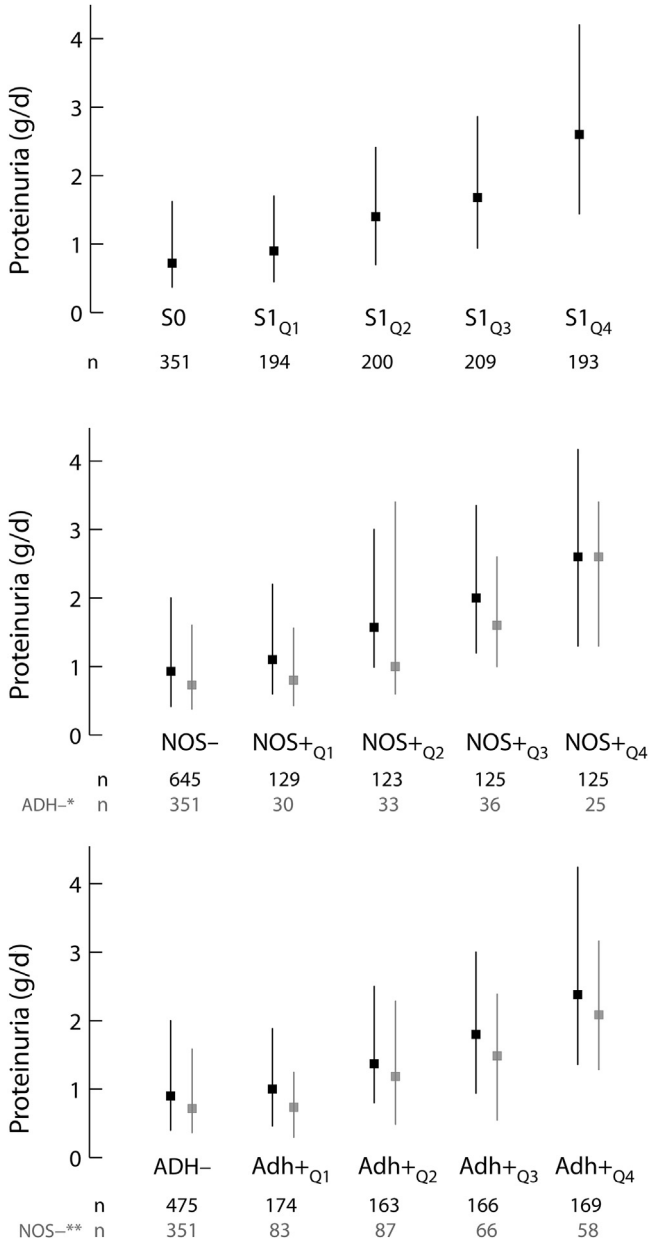


Figure 3 | Relationship between proteinuria and proportions of glomeruli in presence of segmental sclerosis or simple adhesion (S1), not otherwise specified (NOS) lesions, and adhesions (ADH). *Gray values refer to NOS lesions restricted to biopsies without glomeruli with simple adhesion. **Gray values refer to glomeruli with simple adhesion restricted to biopsies without NOS lesions.

showed similar risk factors of progression (Table 2). We found a greater survival rate from a combined outcome with CSs and RASB, with a time-dependent hazard of 0.30 (95% confidence interval, 0.14–0.68, $P = 0.004$) in reference to RASB only (Figure 7). This analysis also was statistically significant when it was done on the 2 subgroups with the highest initial proteinuria level separately (data not shown).

DISCUSSION

In IgAN, SS is associated with greater initial proteinuria, independent of other glomerular lesions. On further subclassifying these S1 lesions in the Oxford classification cohort, we identified tip lesions and PH as the strongest determinants of proteinuria. In this study of the VALIGA cohort, very few biopsies showed tip lesions, but SS with PH again was found to be associated with the highest levels of initial proteinuria, the most-rapid decline in kidney function, and the worst outcome from a combined event. The presence of SS, with some glomeruli showing isolated capsular adhesions, also was associated with more proteinuria than SS without this, but less proteinuria than that associated with PH. More importantly, these 2 groups with the highest initial proteinuria level were associated with the

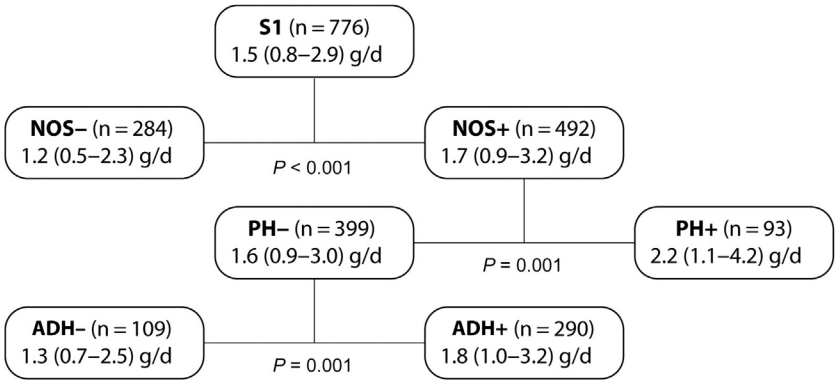
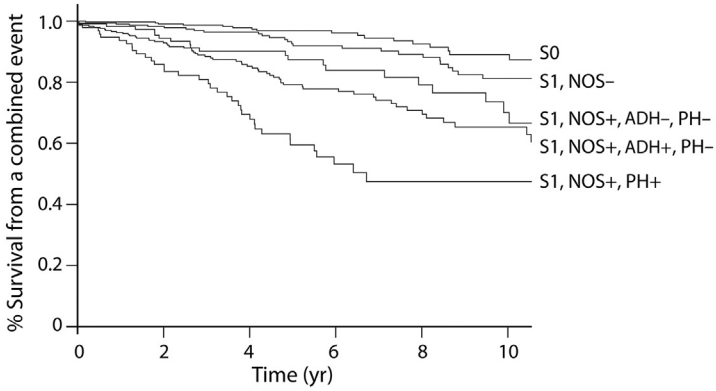


Figure 4 | Decision-tree analysis of focal segmental glomerulosclerosis lesions associated with proteinuria. The classification was derived using the χ^2 automatic interaction detection (CHAID) methodology. Patients without presence of segmental sclerosis or simple adhesion (S0) had a proteinuria level of 0.7 (0.4–1.6) g/d. The initial proteinuria level was missing in 42 of the 1147 patients. +, presence; –, absence; ADH, simple adhesion; NOS, not otherwise specified; PH, podocyte hypertrophy; S1, presence of segmental sclerosis or simple adhesion.

best response to CSs, even when other risk factors were taken into account by propensity-score matching.

FSGS is a morphologic pattern of injury with multiple etiologies and pathogenetic pathways.[13] In the absence of immune complex deposition in the glomeruli, nephrotic FSGS can develop as a result of genetic abnormalities,[14] or racial predisposition,[15,16] in addition to podocyte injury associated with viral infections,[17] drugs,[18] and ischemia.[19,20] Elevated levels of certain soluble permeability factors have been implicated in the development of primary FSGS.[21] In addition to post-inflammatory scars and hyperfiltration, podocyte injury is implicated in the development of SS in IgAN, with histologic features similar to those of other podocytopathies, and evidence from animal models.[22–24] Morphologically, features favoring podocytopathy include tip lesions, PH, endocapillary foam cells, and collapsing lesions.[10] Although podocyte injury via mesangial-podocyte cross-talk initiates these lesions as isolated adhesions between the capillary tuft and Bowman's capsule, the development of matrix obliteration of capillary lumina is orchestrated by activated parietal epithelial cells.[25] We use the term PH by convention to describe the cells overlying segmental sclerosing lesions, reflecting their visceral epithelial location, although these typically show a parietal epithelial phenotype. We describe these lesions in the context of IgAN as "podocytopathic" features. Although S1 lesions with adhesions or PH show good response to IS, biopsies with pure NOS-type lesions showed poor response to IS, the latter representing an irreversible injury (podocytopathic or otherwise).

No phenotypes of FSGS are specific to either primary or secondary forms, including those associated with immune complex glomerulonephritis. The Oxford Classification Study demonstrated that the presence of SS is an independent prognostic marker,[2] in addition to mesangial hypercellularity (M), endocapillary hypercellularity (E), and tubular atrophy/interstitial fibrosis (T). An interesting point to note is that a higher proportion of S1 lesions show evidence of podocyte



S0	351	286	214	131	89	53
S1, NOS–	294	239	168	115	86	54
S1, NOS+, ADH–, PH–	114	91	71	44	31	20
S1, NOS+, ADH+, PH–	293	227	149	94	56	33
S1, PH+	95	72	43	22	9	1

Figure 5 | Survival from a combined event according to groups of focal segmental glomerulosclerosis lesions, (S0, no glomerulus with segmental sclerosis or simple adhesion; S1, presence of glomeruli with segmental sclerosis or simple adhesion). ADH, simple adhesions; NOS, not otherwise specified; PH, podocyte hypertrophy.

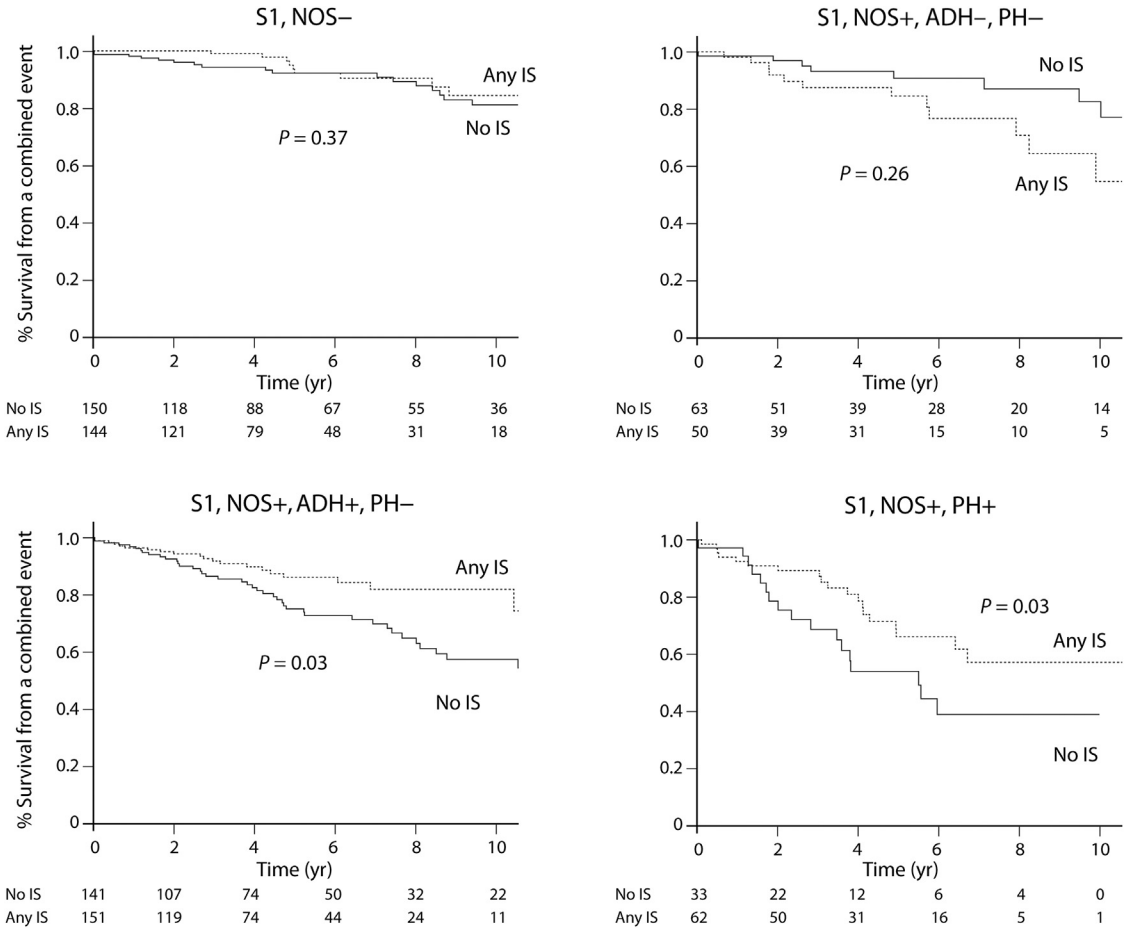


Figure 6 | Survival from a combined event according to treatment in groups of focal segmental glomerulosclerosis lesions. *P* values were derived using a time-dependent survival analysis to account for the lead time bias prior to the start of therapy and the loss of estimated glomerular filtration rate during that time. Immunosuppressive therapy during follow-up data were missing in 2 subjects. +, presence; –, absence; ADH, simple adhesions; IS, immunosuppression; NOS, not otherwise specified; PH, podocyte hypertrophy; S1, presence of segmental sclerosis or simple adhesion.

injury in IgAN than in lupus nephritis, despite the fact that they are both immune complex glomerulonephritis.[26,27] Hill *et.al.*[27] observed that adhesions without inflammation in glomerular tuft occurred most commonly in primary FSGS (69%), followed by IgAN (41%), and they were least common in lupus nephritis (8%). They hypothesized that podocyte injury similar to primary FSGS is an important contributing factor to sclerosis in IgAN, in addition to glomerular inflammation, as in other immune complex glomerulonephritis, including lupus nephritis. Previous studies[26,27] have demonstrated focal loss of podocyte markers glomerular epithelial protein (GLEPP-1) and nephrin, particularly at sites of capsular adhesion where they acquire parietal epithelial cell phenotype, as evidenced by positive staining for paired box antigen 2 (PAX 2) and cytokeratin at sites of adhesions and overlying sclerosed segments, as seen in primary FSGS. Also, evidence indicates that mesangial-podocyte cross-talk occurs, along with release of mediators causing podocyte injury.[28] This finding is consistent with earlier studies demonstrating that IgA stimulates mesangial cell proliferation with release of mediators that cause podocyte injury.[29,30] In addition, excretion of podocytes in the urine reflects disease progression.[31]

To improve the level of interobserver agreement, isolated adhesions and SS, with matrix obliteration of capillaries, were grouped together as S1 lesions in the Oxford classification. Together, these lesions involved 76% of the biopsy specimens from 265 patients in the Oxford classification cohort.[1] However, further subclassification was not undertaken at the time of initial publication. A schema for subclassification of primary FSGS—the Columbia classification[10]—which is widely used, has been shown to be of prognostic value.[32,33] Patients with tip variant FSGS have the highest frequency of remission after steroid therapy and a better long-term outcome, whereas patients with a collapsing variant are most likely to progress to end-stage chronic kidney disease. In the Oxford Classification Study cohort, tip lesions and PH were associated with higher levels of initial proteinuria, supporting the role of podocyte injury in IgA.[9] In the VALIGA cohort, the presence of SS with luminal obliteration by matrix, in association with PH and/or other glomeruli in the biopsy showing isolated adhesions, was associated with higher levels of initial proteinuria and good response to IS. We did not try to validate the Columbia classification in IgAN, because simply applying the schema would require incorrect

Table 3 | Comparisons of individuals showing NOS lesions with PH or ADHs combined receiving immunosuppressive therapy

Variable	NOS+ with PH or ADH			Matched NOS+ with PH or ADH		
	No IS (n = 174)	IS (n = 213)	*P*	RASB (n = 71)	RASB + CS (n = 71)	*P*
Clinical characteristics at biopsy						
Age, yr	41 ± 14	36 ± 15	<0.001	39 ± 14	27 ± 15	0.40
Female, %	29	29	0.98	28	25	0.71
African, Asian, Indian, Caucasian, %	0, 0, 2, 98	1, 2, 1, 96	0.07	0, 0, 99, 1	0, 3, 97, 0	0.22
eGFR, ml/min per 1.73 m^2	61 ± 28	63 ± 31	0.52	60 ± 26	62 ± 30	0.63
MAP, mm Hg	102 ± 14	100 ±14	0.21	100 ± 12	98 ± 11	0.30
Number of antihypertensive medications	1 (0–2)	1 (0–2)	0.21	1 (0–1)	1 (1–2)	0.009
Proteinuria, g/d	1.7 (0.8–3.0)	2.1 (1.2–4.0)	0.007	1.7 (0.7–3.1)	1.5 (1.0–2.7)	0.84
RASB, %	42	43	0.74	39	54	0.09
Prior IS, %	2	15	<0.001	1	0	0.32
Biopsy findings, %						
M1	40	45	0.34	41	46	0.50
E1	16	15	0.77	14	13	0.81
T0, T1, T2	60, 34, 6	64, 31, 5	0.64	65, 30, 36	55, 35, 10	0.42
C0, C1, C2	89,11,0	81, 15,5	0.009	83, 17, 0	86, 13, 1	0.48
Follow-up[a]						
Length of follow-up, y	3. 7 (2.1–7.7)	3.6 (2.4–6.5)	0.30	4.0 (2.0–7.3)	4.2 (2.9–7.0)	0.45
MAP, mm Hg[a]	98 ± 10	100 ± 13	0.09	99 ± 9	98 ± 10	0.55
Number of antihypertensive medications[a]	1.7 (1.0–2.3)	1.0 (0.5–2.0)	0.002	1.3 (0.8–2.1)	1.0 (1.0–2.0)	0.77
RASB[a]	88	81	0.05	100	100	By design
CS, CS pulse, CS oral	—	98, 36, 93	By design	—	100, 32, 96	By design
Azathioprine, cyclophosphamide, MMF, CNI	—	17, 19, 10, 3	By design	—	13, 13, 13, 0	By design
Time-averaged proteinuria[a]	1.1 (0.6–2.3)	2.1 (1.2–3.7)	<0.001	1.3 (0.8–2.7)	1.4 (0.9–2.42)	0.64

ADH, adhesion; CNI, calcineurin inhibitor; CS, corticosteroid; C0–C2, proportion of glomeruli showing cellular and/or fibrocellular crescents: C0 (0%); C1 (1%–24%); C2 (≥25%). eGFR, estimated glomerular filtration rate; E1, endocapillary hypercellularity; IS, immunosuppression; M1, mesangial hypercellularity; MAP, mean arterial pressure; MMF, mycophenolate mofetil; NOS, not otherwise specified; PH, podocyte hypertrophy; RASB, renin-angiotensin blockade; T0–T2, percentage of cortex showing interstitial fibrosis and tubular atrophy: T0 (≤25% of cortex), T1 (26%–50%), and T2 (>50%).
[a]Prior to IS in the treated groups. Immunosuppressive therapy during follow-up was missing in 2 subjects.

assumptions to be made and would entail the risk of loss of valuable information from the histologic analysis. We therefore chose to score the individual histologic features seen within segmental sclerosing lesions, including those that form the basis of the Columbia schema.

El Karoui *et al.*[26] subclassified the S1 lesions in their IgAN cohort using the hierarchical system of the Columbia classification, but they applied a modification for their NOS-subtype to avoid SS resulting from inflammatory scarring. They included only those sclerotic lesions that showed proliferation of parietal epithelial cells or hyalinosis, with the assumption that these features were not seen in post-inflammatory scars. They reported a collapsing variant in 11 of 128 cases, a cellular variant in 27 cases, a perihilar variant in 7 cases, tip lesions in 6 cases, and FSGS not otherwise specified in 52 cases. Both collapsing and cellular variants

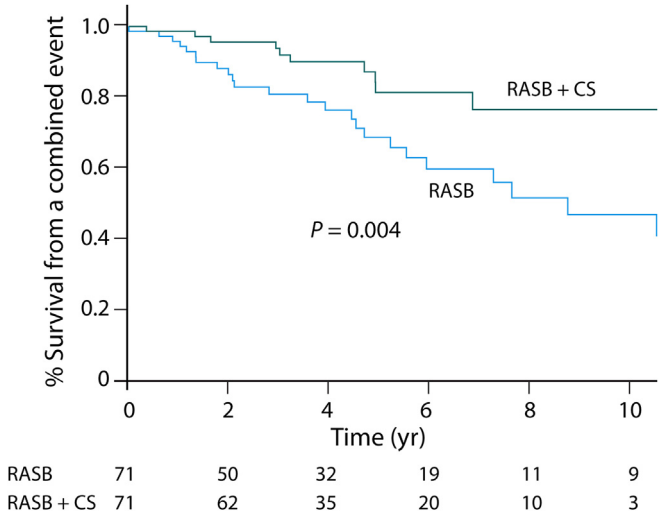


Figure 7 | Response to corticosteroids (CSs) and renin–angiotensin system blockade (RASB), compared with that to RASB alone, in propensity-matched individuals displaying glomeruli with not otherwise specified (NOS) lesions and podocyte hypertrophy or isolated adhesions.

were associated with particularly poor prognosis, with most patients progressing to end-stage disease, whereas the tip variant was associated with a relatively good prognosis. Although tip lesions were noted to be one of the adverse prognostic factors in the Oxford classification cohort, in the VALIGA cohort, the number of biopsies with tip lesions was too small to infer any statistical relevance; no biopsy specimens showed collapsing lesions in either of these cohorts. In the Hill *et al.* group,[27] the criteria for inclusion under the cellular variant was the presence of hyperplastic epithelium overlying the areas of endocapillary hypercellularity, which in the Oxford classification and the VALIGA cohorts would be categorized as E1 rather than S1. Furthermore, in the VALIGA cohort, although we used the same criteria as were used in the Oxford Classification Study cohort to subclassify S1 lesions, the proportions of biopsies with tip lesions, protein resorption droplets, and hyalinosis constituted a mere 3%, 4%, and 2%, respectively. To make the subclassification clinically relevant, we had to further regroup using the χ^2 automatic interaction detection method (Figure 3). The difference in the frequency of lesions between the study of El Karoui *et al.*[26] and ours emphasizes the importance of consistent interpretation of histology. In our previous study of the Oxford Classification Study cohort,[9] 2 pathologists (SSB & OV) subclassified the S1 lesions independently, and the classification was found to be reproducible. In this study of the VALIGA cohort, all slides were reviewed by a single pathologist (SSB) for subclassifying S lesions, with a second pathologist (ISDR) reviewing lesions for which S differed from that of the local pathologists, besides those associated with diagnostic difficulty or uncertainty. The level of reproducibility of subclassification of S1 lesions among pathologists working in different units around the world would be expected to be lower; the introduction of digital pathology in recent years will enable this issue to be tested using online scoring of whole slide images.

Our observational study has limitations. Histology was correlated with severity of proteinuria, but clinical data regarding the presence of nephrotic syndrome were not available for our patient cohort. Given that this cohort was pan-European, our findings might require further validation in cohorts from other ethnic groups. Also, unlike kidney biopsy reporting in real time, for which multiple levels and sections are available, here, we had more-limited material available for review. A periodic acid–Schiff–stained slide was available for review for 99% of biopsies, but slides stained with hematoxylin and eosin, and silver, were available for only around half the biopsies, and a trichrome was available for a third of them. We also were unable to correlate the light-microscopic findings with the severity of podocyte foot process effacement or the immunophenotype of epithelial cells associated with SS, as electron microscope images and tissue blocks were not available to study. Finally, treatment allocation was not randomized, and propensity-score adjustments could not take into account unmeasured variables.

In this study of the large VALIGA cohort, we demonstrated the clinical value of subclassifying SS in IgAN, validating findings from the original Oxford Classification Study cohort. Not only were the S1 subgroups associated with significantly different kidney outcomes, but also, the presence of PH or glomeruli with simple adhesions was associated with a reduced risk of disease progression with CSs, suggesting that these features are indicative of an active and potentially reversible disease process. In contrast, other FSGS lesions were unresponsive to IS, indicative of chronic irreversible lesions. Overall, evidence from the VALIGA study supports further subclassification of segmental sclerosing lesions into categories that are associated with treatment responsiveness, as follows: S1 with matrix obliteration of capillaries (NOS lesions) + podocyte hyperplasia and/or isolated adhesions, and S1 lesions unlikely to be treatment-responsive (S1 NOS lesions without isolated adhesions or podocyte hyperplasia). These findings should be validated in non-European cohorts, particularly in IgAN patients of East Asian origin who show a different distribution of histologic features with more-frequent active inflammatory and crescentic lesions.

APPENDIX

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DISCLOSURE

IR reports receiving consulting fees from Novartis and Travere Therapeutics, and participating in an advisory board from Novartis. All the other authors declared no competing interests.

DATA STATEMENT

The initial ethics review board in 2009 did not address placing the data in an openly available repository, but ancillary studies can be submitted to the corresponding author, and additional analyses can be done by the coordination center.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Figure S1. The spectrum of segmental sclerosing lesions in IgAN.

Supplementary Table S1. Correlations between FSGS lesions and other components of the MEST-C score.

Supplementary Table S2. Clinical characteristics of FSGS subgroups. STROBE Statement.

REFERENCES

1. Roberts IS, Cook HT, Troyanov S, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int*. 2009;76:546–556.

2. Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int*. 2009;76:534–545.
3. Coppo R, Troyanov S, Bellur S, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int*. 2014;86:828–836.
4. Coppo R, D'Arrigo G, Tripepi G, et al. Is there long-term value of pathology scoring in immunoglobulin A nephropathy? A validation study of the Oxford Classification for IgA Nephropathy (VALIGA) update. *Nephrol Dial Transplant*. 2020;35:1002–1009.
5. Bellur SS, Roberts ISD, Troyanov S, et al. Reproducibility of the Oxford classification of immunoglobulin A nephropathy, impact of biopsy scoring on treatment allocation and clinical relevance of disagreements: evidence from the VALidation of IGA study cohort. *Nephrol Dial Transplant*. 2019;34:1681–1690.
6. Cook HT. Focal segmental glomerulosclerosis in IgA nephropathy: a result of primary podocyte injury? *Kidney Int*. 2011;79:581–583.
7. Sethi S, Glassock RJ, Fervenza FC. Focal segmental glomerulosclerosis: towards a better understanding for the practicing nephrologist. *Nephrol Dial Transplant*. 2015;30:375–384.
8. Trimarchi H, Barratt J, Cattran DC, et al. Oxford classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017;91:1014–1021.
9. Bellur SS, Lepeytre F, Vorobyeva O, et al. Evidence from the Oxford classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy. *Kidney Int*. 2017;91:235–243.
10. D'Agati VD, Fogo AB, Bruijn JA, et al. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis*. 2004;43:368–382.
11. Miller B, Fridline M, Liu PY, et al. Use of CHAID decision trees to formulate pathways for the early detection of metabolic syndrome in young adults. *Comput Math Methods Med*. 2014;2014:242717.
12. Olmos A, Govindasamy P. Propensity scores: a practical introduction using R. *J MultiDisciplin Eval*. 2015;11:68–88.
13. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2017;12:502–517.
14. Rood IM, Deegens JK, Wetzels JF. Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. *Nephrol Dial Transplant*. 2012;27:882–890.
15. Friedman DJ, Pollak MR. APOL1 nephropathy: from genetics to clinical applications. *Clin J Am Soc Nephrol*. 2021;16:294–303.
16. Friedman DJ, Pollak MR. APOL1 and kidney disease: from genetics to biology. *Annu Rev Physiol*. 2020;82:323–342.
17. Muehlig AK, Gies S, Huber TB, et al. Collapsing focal segmental glomerulosclerosis in viral infections. *Front Immunol*. 2021;12:800074.
18. Markowitz GS, Nasr SH, Stokes MB, et al. Treatment with IFN-alpha, -beta, or -gamma is associated with collapsing focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2010;5:607–615.
19. Salvatore SP, Reddi AS, Chandran CB, et al. Collapsing glomerulopathy superimposed on diabetic nephropathy: insights into etiology of an under-recognized, severe pattern of glomerular injury. *Nephrol Dial Transplant*. 2014;29:392–399.
20. Canaud G, Bruneval P, Noel LH, et al. Glomerular collapse associated with subtotal renal infarction in kidney transplant recipients with multiple renal arteries. *Am J Kidney Dis*. 2010;55:558–565.
21. Reiser J, Nast CC, Alachkar N. Permeability factors in focal and segmental glomerulosclerosis. *Adv Chronic Kidney Dis*. 2014;21:417–421.
22. Kriz W. The pathogenesis of 'classic' focal segmental glomerulosclerosis—lessons from rat models. *Nephrol Dial Transplant*. 2003;18(suppl 6):vi39–vi44.
23. Kriz W, Lemley KV. The role of the podocyte in glomerulosclerosis. *Curr Opin Nephrol Hypertens*. 1999;8:489–497.
24. Wiggins JE, Goyal M, Sanden SK, et al. Podocyte hypertrophy, "adaptation," and "decompensation" associated with glomerular enlargement and glomerulosclerosis in the aging rat: prevention by calorie restriction. *J Am Soc Nephrol*. 2005;16:2953–2966.
25. Moeller MJ, Smeets B. Role of parietal epithelial cells in kidney injury: the case of rapidly progressing glomerulonephritis and focal and segmental glomerulosclerosis. *Nephron Exp Nephrol*. 2014;126:97.
26. El Karoui K, Hill GS, Karras A, et al. Focal segmental glomerulosclerosis plays a major role in the progression of IgA nephropathy. II. Light microscopic and clinical studies. *Kidney Int*. 2011;79:643–654.
27. Hill GS, Karoui KE, Karras A, et al. Focal segmental glomerulosclerosis plays a major role in the progression of IgA nephropathy. I. Immunohistochemical studies. *Kidney Int*. 2011;79:635–642.
28. Menon MC, Chuang PY, He JC. Role of podocyte injury in IgA nephropathy. *Contrib Nephrol*. 2013;181:41–51.
29. Lai KN, Leung JC, Chan LY, et al. Podocyte injury induced by mesangial-derived cytokines in IgA nephropathy. *Nephrol Dial Transplant*. 2009;24:62–72.
30. Coppo R, Fonsato V, Balegno S, et al. Aberrantly glycosylated IgA1 induces mesangial cells to produce platelet-activating factor that mediates nephrin loss in cultured podocytes. *Kidney Int*. 2010;77:417–427.
31. Hara M, Yanagihara T, Kihara I. Cumulative excretion of urinary podocytes reflects disease progression in IgA nephropathy and Schonlein-Henoch purpura nephritis. *Clin J Am Soc Nephrol*. 2007;2:231–238.
32. Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int*. 2006;69:920–926.
33. D'Agati VD, Alster JM, Jennette JC, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol*. 2013;8:399–406.