The association of 5-year therapeutic responsiveness with long-term renal outcome in IgA nephropathy

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Abstract

Background:

Immunoglobulin A nephropathy (IgAN) is the most common type of primary glomerulonephritis. Since most patients have a relatively benign renal prognosis, long-term follow-up is required. During such a long course of disease, relapse of IgAN is occasionally observed after upper respiratory tract infection or without any trigger. However, little is known about the impact of relapse on long-term renal outcomes.

Methods:

In this retrospective cohort study of biopsy-proven primary IgAN, we analyzed the association of 5-year therapeutic responsiveness (relapse) with the subsequent development of end-stage kidney disease (ESKD) using a 5-year landmark analysis (Cox model) and explored predictors of relapse from histological and clinical data at baseline.

Results:

Among 563 patients from the exploratory cohort, most relapses (13.7%) occurred within 5 years after treatment. Using 5-year landmark analysis, among 470 patients, 79 developed ESKD during a median follow-up period of 155 months. Even after adjustment for clinicopathological relevant confounders, hazard ratios (95% confidence intervals) in the relapse and non-responder groups compared with the remission group were 2.86 (1.41–5.79) and 2.74 (1.48–5.11), respectively. Among 250 patients who achieved remission within 5 years, proteinuria, eGFR, mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, and crescent, but not interstitial fibrosis/tubular atrophy, were independent predictors of 5-year relapse in multivariable logistic regression analysis,

Conclusions:

Both relapsers and non-responders had similarly strong association with ESKD in patients with IgAN. We also confirmed predictors of relapse 5 years after renal biopsy, which may guide the treatment strategies for patients with IgAN who occasionally relapse after remission.

Keywords: IgA nephropathy, relapse, renal survival, landmark analysis, Oxford classification

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common type of primary glomerulonephritis and occurs at a rate of 2.5/100,000 per year [1]. About 40% of patients with IgAN develop end-stage kidney disease (ESKD) within 20 years of onset [2, 3], while another significant number of patients suffer from decreased kidney function [3].

The progression of IgAN is often very slow, but the problem is that patients with IgAN are younger at onset than those with other kidney diseases. The median age of IgAN patients is about 35 years [4, 5]; in contrast, the median age of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [6] and diabetic nephropathy cohorts [7] is 55–60 years. Therefore, in some patients with IgAN, ESKD may occur more than 30 years after the onset of IgAN [8]. However, since most patients with IgAN have a relatively benign renal prognosis over the short term, many cases drop out during follow-up, making long-term observation difficult. In a recent study examining the long-term renal prognosis of IgAN patients, only 27% of cases were observed for more than 20 years [9].

During such a long course of disease, relapse of IgAN is occasionally observed after upper respiratory tract infection or without any particular trigger. There are some reports that these relapses could be reduced by tonsillectomy [10-12] or additional immunosuppressants [13] with steroid therapy. In this way, previous studies on relapse of IgAN have examined the therapeutic effect of treatments with relapse as the endpoint [10-13], and information on the subsequent renal prognosis after relapse of IgAN is very limited. Although relapse has been shown to be associated with a poor renal prognosis in lupus nephritis [14] and ANCA-associated vasculitis [6, 15], few papers have reported a link between relapse of IgAN and renal prognosis.

Indeed, transplant recipients with IgAN as the primary disease experienced 5%, 10%, and 15% relapse at 5, 10, and 15 years after transplantation, respectively [16]. Patients with relapse were twice as likely to lose their allografts compared with those without relapse [16]. The only study focusing on relapse of primary IgAN examined the short-term renal prognosis after relapse [17]. Yuan et al. reported that relapse was observed in 15.5% of patients who achieved remission and was associated with poor renal prognosis compared with those without relapse. However, the median observation period for this study was only 5 years and the long-term renal prognosis for relapse is unknown.

In this long-term retrospective cohort study with primary IgAN (median follow-up period of 155 months), we analyzed the association of 5-year relapse with subsequent long-term renal prognosis using a 5-year landmark analysis and explored predictors of 5-year relapse from histological and clinical data at the time of renal biopsy.

Methods

Study design and participants

We recruited patients with primary IgAN confirmed by renal biopsy at two hospitals between December 1981 and June 2015 as potential participants in this study. The exclusion criteria were as follows: follow-up duration < 1 year, not treated with steroid therapies (oral and/or steroids pulse therapy) and/or renin-angiotensin system (RAS) blockers, inadequate histological sample, missing clinical data, and/or health complicated by other renal diseases. Clinical baseline data were obtained at the renal biopsy and outcome data were obtained retrospectively until June 2017. This study was approved by the Ethic Committee of Nara Medical University Hospital (approval No. 2005-18) and registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000031121). All patients gave their "opt-out" informed consent.

Analytical approach

First, all the eligible patients were enrolled in an exploratory cohort to examine the natural course (remission, relapse, or renal death) after renal biopsy (Fig. 1). Next, we performed landmark analysis by focusing on the patients who could be followed for more than 5 years after renal biopsy. Using this cohort of patients (cohort for 5-year landmark analyses), patients were divided into three groups according to their therapeutic responsiveness during 5 years after renal biopsy (remission, relapse, and non-responder). The association of 5-year therapeutic responsiveness with renal prognosis and predictors of relapse 5 years after renal biopsy were examined in the 5-year landmark cohort (Fig. 1).

Variables

In the present study, we defined the disease status for IgAN as remission, relapse, and non-responder. Remission was defined if the following criteria were met three consecutive times or more over 6 months: proteinuria qualitative reaction: (-) to (±) or proteinuria level less than 0.3 g/day (g/g Cr) [18]. Relapse was defined if the following criteria were met three consecutive times or more over 6 months among patients who had achieved remission: proteinuria qualitative reaction: ≥ (1+) or proteinuria level more than 0.5 g/day (g/gCr). Those who could not achieve remission were defined as non-responders.

The primary end point of this study was the development of ESKD, which was defined as a requirement for renal replacement therapy or death attributed to ESKD. Deaths without ESKD were statistically processed as censored data.

Serum creatinine values (mg/dL) measured by the Jaffe method were corrected by subtracting 0.207 mg/dL for comparison to values obtained by the enzymatic method. The eGFR (mL/min/1.73 m^2 of body surface area) was calculated using the new three-variable Japanese equation for estimating glomerular filtration rate: eGFR = 194 × serum creatinine $(mg/dL)^{-1.094}$ × $age^{-0.287}$ × 0.739 (if female) [19]. Proteinuria was measured by 24-hour urine protein (or spot urine protein creatinine ratio if 24-hour urine protein was not available).

Histological evaluations

Histological evaluations were performed independently by two renal pathologists according to the Oxford MESTC scores [20, 21]. Briefly, the mesangial hypercellularity (M; M0 < 50% of glomeruli with mesangial hypercellularity, M1 > 50% of glomeruli with mesangial hypercellularity), endocapillary hypercellularity (E; E0

absent, E1 present), segmental glomerulosclerosis or adhesion (S; S0 absent, S1 present), interstitial fibrosis and tubular atrophy (IFTA) (T; T0 0%–25%, T1 26%–50%, T2 > 50%), and cellular or fibrocellular crescent (C; C0 absent, C1 0%–25%, C2 > 25%) were used to evaluate the severity of IgAN.

Statistical analyses

Categorical variables were expressed as numbers and/or percentages and were compared using the chi-square test followed by post hoc analysis adjusted with the Holm method if necessary. Continuous variables were expressed as a median with interquartile range and were compared by the analysis of variance (ANOVA) and subjected to post hoc analysis with the Tukey HSD method if necessary. Using an exploratory cohort, survival curves for the development of remission, relapse, and ESKD were obtained using the Kaplan–Meier method. We performed 5-year landmark analysis to examine the association of disease status of IgAN at 5 years (remission, relapse, or non-responder) with the development of ESKD. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence intervals (CI) for the effect of relapse and non-responder (vs. remission) on the development of ESKD. In the multivariable models, model 1 was adjusted for sex and age, model 2 was adjusted for model 1 plus eGFR, proteinuria, systolic blood pressure, body mass index (BMI), and steroid therapies, and model 3 (main model) was adjusted for model 2 plus Oxford MESTC scores. Subgroup analyses for the main model were conducted in groups stratified by possible effect modifiers (sex, age, proteinuria, eGFR, BMI, systolic blood pressure, and steroid therapies). Multivariable logistics regression analysis was performed to examine predictors of relapse 5 years after renal biopsy.

All analyses were performed using R software version 3.6.3 (R Foundation, Vienna, Austria) and EZR version 1.53 [22]. *P* values less than 0.05 were considered statistically significant in all analyses except for interaction analyses, which were considered statistically significant when *P* values were less than 0.1.

Results

Incidence of remission and relapse after renal biopsy in the exploratory cohort

Among 791 patients with biopsy-proven primary IgAN, those who did not meet the criteria were excluded. Main reasons for the exclusion of patients were <1 year of follow-up periods (n=102) and not receiving active treatment of RAS inhibitors or steroids (n=102). Supplemental table 1 shows baseline characteristics between exploratory cohort of this study and excluded patients. Obviously, excluded patients had less clinical and histological changes compared to cohort patients, and no one received steroids or immunosuppressants. To examine the natural course (remission, relapse, and ESKD) after renal biopsy, the remaining 563 patients were included in the exploratory cohort (Fig. 1). The cumulative rate of remission at 1 year, 3 years, 5 years, and 20 years after renal biopsy was 42.2%, 51.9%, 55.8%, and 76.4%, respectively. The cumulative rate of relapse at 3 years, 5 years, and 20 years after renal biopsy was 3.9%, 13.7%, and 25.1%, respectively (Fig. 2). The overall proportion of renal outcomes over the follow-up period is shown in Supplemental Fig. 1 where it is evident that renal outcomes were confirmed in 44% of patients 15 years after renal biopsy. The incidence of remission increased sharply within a year after renal biopsy (treatment), then reached a plateau with a gradual increase (Fig. 2 and Supplemental Fig. 1). Similarly, most relapses occurred within 5 years and then reached a plateau. Only 6 patients developed ESKD during the 5 years after renal

biopsy. Based on these observations that most relapses and few cases of ESKD were observed during 5 years after renal biopsy, a 5-year landmark analysis was performed to evaluate the relative risk of ESKD among patients with 5-year therapeutic responsiveness, including those in the remission, relapse, and non-responder groups. Among 563 patients included in the exploratory cohort, 93 patients with a follow-up period of less than 5 years were excluded and the remaining 470 patients were included in the final analysis (Fig. 1).

Baseline characteristics in the cohort for 5-year landmark analyses

According to their therapeutic responsiveness during 5 years after renal biopsy, 470 patients were divided into three groups (remission, relapse, and non-responder). Five years after renal biopsy, 197 patients remained in remission of proteinuria, 53 patients experienced relapse after remission, and 220 patients had persistent proteinuria (non-responder). Among remission group, 142 (72%), 35 (18%), and 20 (10%) patients had non-hematuria, relapse after remission of hematuria, and persistent hematuria, respectively. Among relapse group, 2 (4%), 30 (57%), and 21 (40%) patients had non-hematuria, relapse after remission of hematuria, and persistent hematuria, respectively. Among non-responder group, 47 (21%), 11 (5%), and 162 (74%) patients had non-hematuria, relapse after remission of hematuria, and persistent hematuria, respectively. These prevalences varied significantly between groups (*P* value <0.001). Baseline clinical and pathological data at renal biopsy are shown in Table 1. The patients in the non-responder group received less oral steroid and/or steroid pulse therapy compared with patients with other two groups. The most patients treated with immunosuppressants received mizoribine (n=101) and only one patient received cyclosporine and another one patient received

combination of mizoribine and cyclosporine. The relapse group had more immunosuppressant users and decreased renal function, more urinary protein excretion, and urinary red blood cell casts compared with the other two groups. Histological findings revealed that the relapse group had severe endocapillary hypercellularity, segmental glomerulosclerosis, and cellular/fibrocellular crescent formation compared with the other two groups, but there was not a statistically significant difference in segmental glomerulosclerosis between the relapse and non-responder groups.

The association of relapse and non-responder groups with ESKD

Among 470 patients, 79 developed ESKD during a median follow-up period of 155 (106–216) months. Of the 79 ESKD patients, 15, 21, and 43 were found in the remission, relapse, and non-responder groups, respectively. The HRs for ESKD in the relapse and non-responder groups compared with the remission group are shown in Table 2. The unadjusted HRs (95% CIs) for ESKD in the relapse and non-responder groups compared with the remission group were 6.26 (3.23–12.16) and 2.16 (1.20–3.90), respectively. The fully adjusted survival curves among the three groups are shown in Fig. 3. Even after adjustment for clinicopathological relevant confounders (Model 3: main model), the HRs (95% CIs) in the relapse and non-responder groups remained statistically significant and were 2.86 (1.41–5.79) and 2.74 (1.48–5.11), respectively (Table 2 and Fig. 3). Fig. 4 shows the subgroup analyses used to determine the association of relapse and non-responder with ESKD across specified groups of patients. Age, sex, body mass index, systolic blood pressure, and eGFR did not modify the association of 5-year therapeutic responsiveness (relapse and non-responder) with ESKD (each *P* value for

interaction > 0.10). The associations of relapse with ESKD were synergistically increased among patients with proteinuria < 1 g/day or who were not treated with steroid therapies. Similar results were yielded when defining a renal outcome as 1.5-fold increase in serum creatinine. The HRs for 1.5-fold increase in serum creatinine in the relapse and non-responder groups compared with the remission group are shown in supplemental Table 2. The fully adjusted survival curves among the three groups are shown in supplemental Fig. 2. In the main model, the HRs (95% CIs) in the relapse and non-responder groups remained statistically significant and were 4.71 (2.75,8.09) and 2.88 (1.81,4.56), respectively.

Clinicopathological predictors for relapse 5 years after renal biopsy

Using a logistic regression analysis, the predictors of relapse 5 years after renal biopsy were examined among baseline clinicopathological factors (Table 3). Among 250 patients who achieved remission within 5 years, increase in proteinuria, endocapillary hypercellularity, segmental sclerosis, IFTA, and crescent and decrease in eGFR were the significant predictors of relapse 5 years after renal biopsy in univariate analysis. In multivariable analysis, increase in proteinuria, endocapillary hypercellularity, segmental sclerosis, and crescent and decrease in eGFR and mesangial hypercellularity, but not IFTA were independent predictors of relapse 5 years after renal biopsy.

Discussion

In this study, we examined the therapeutic responsiveness including remission and relapse after treatment with steroid therapies and/or RAS inhibitors among patients with IgAN. In the exploratory cohort, the cumulative remission rate at 1 year

increased sharply to 42.2% and gradually increased to reach 76.4% in 20 years. In contrast, the 5-year cumulative relapse rate reached 13.7% with a steep increase until 5 years and gradually increased to reach 25.1% in 20 years. Approximately 55% of total events (at 20 years) in remission/relapse were observed during the period of steep increase. Although there is little information on the natural history of relapse after remission of IgAN [10-13], Yuan et al. [17] reported that 15.5% of patients experienced relapse during a median follow-up period of 66 months (5.5 years), which is generally consistent with the results of this study (13.7% relapse at 5 years). Next, we examined the impact of relapse on ESKD using a 5-year landmark analysis and confirmed the robust association of relapse with ESKD compared with remission, which is as strong as that of a non-responder. In previous studies, Yuan et al. only investigated the association between relapse of IgAN and ESKD in a short observation period of 5 years [17]. Because all cases of relapse observed during the entire observation period were defined as the relapse group, some cases have relapse and renal death occurring at about the same time. Therefore, the impact of the causal relationship between the relapse (intermediate event) and ESKD (final event) is biased [17]. To elucidate this problem, we performed landmark analysis to examine the association between the 5-year relapse and ESKD with a long-term follow-up period (median follow-up period of 155 months). Of note, we set the cutoff for landmark analysis to 5 years considering that most relapses were observed within 5 years and only a few renal deaths (6 ESKD; 1.1%) were observed during that period.

In subgroup analyses, we found that the associations of relapse with ESKD appeared to be stronger among patients without steroid therapies (oral and/or pulse) and with proteinuria < 1 g/day. In fact, these subgroups share a very similar subset

because patients with higher proteinuria levels are more likely to receive steroid therapies. A total of 39.4% of patients with low proteinuria levels (< 1 g/day) received steroid therapies, while 70.9% of patients with high proteinuria levels (1 g/day or more) received steroid treatment (chi-square test; $P < 0.001$). These results suggest that even patients with low proteinuria levels (< 1 g/day) may have a worse renal prognosis if they relapse without steroid therapies on board. In other words, steroid therapies can contribute to renal protection by preventing relapse in patients with low proteinuria levels. In a recent STOP-IgAN trial, a randomized placebo control trial was performed to examine the effect of steroid monotherapy (based on the Pozzi protocol [23]) or combination therapy with immunosuppressants in patients with IgAN whose proteinuria levels were > 0.75 g/day after 6 months of supportive care including RAS inhibitors [24]. In this study, immunosuppressive therapy including steroids showed a significant reduction in proteinuria, but failed to prevent the progression of renal failure over a short-term observation period of 3 years [24] and even over a long-term observation of 10 years [25]. However, a recent systematic review from the Cochrane Database revealed that steroid therapy probably prevents the progression to ESKD compared with placebo or standard care in patients with IgAN (eight studies; 741 participants: relative risk 0.39, 95% CI 0.23–0.65; moderate certainty evidence) [26]. Taken together, this suggests that steroid therapy may be effective in patients whose proteinuria levels decreased to 0.75 g/day or less with standard care including RAS inhibitors. In addition to previously reported risk factor for poor renal prognosis, including clinical findings [27], histological findings [20, 21, 28], and biomarkers [29], we have newly confirmed that 5-year relapse is a significant risk factor for the development of ESKD in patients with IgAN.

Finally, we identified increased proteinuria levels and decreased eGFR from clinical factors, and decreased mesangial hypertrophy (M lesions), increased endocapillary hypertrophy (E lesions), increased segmental sclerosis (S lesions), and increased crescent formation (C lesions) from histological factors as a significant predictor of 5-year relapse from renal biopsy using a multivariable logistic regression analysis. According to clinical factors, it is not surprising that increased proteinuria levels and decreased eGFR at baseline were significant predictors of relapse. However, in terms of histological factors, there was some discrepancy between predictors of renal prognosis (ESKD) and those of relapse. The original Oxford study cohort and subsequent validation studies have shown that M, S, T (IFTA), and C lesions each provide reliable prognostic information. In particular, T lesions were a consistent predictor of renal prognosis with more variable results for M, S, and C lesions [20, 21, 30]. Specifically, T lesions, which were a consistent predictor of renal prognosis, were not identified as a predictor of relapse. In contrast, E lesions, which yielded less reproducible results as a predictor of renal prognosis, were identified as a significant predictor of relapse. However, it is also not surprising that E and C lesions were active cellular lesions that may be associated with disease activity and relapse as it has been confirmed for lupus nephritis that patients with crescentic glomerulonephritis had higher incidence of relapse than those without crescents [31]. In contrast, T lesions merely reflect the stage of the disease, which is associated with chronic damage and shorter time to ESKD rather than disease activity. It is worth noting that E, S, and C lesions share some common pathways. Hisano et al. noted that the degree of lysis of the glomerular basement membrane and/or crescent was positively and closely correlated with the degree of distribution of endocapillary proliferation [32]. Using 100 serial sections from each patient with IgAN, another

study showed that cellular crescents were formed adjacent to the segmental lesions [33]. Although it is well known that S lesions in IgAN may also reflect a response to podocyte injury (podocytopathy) [34] as well as the organization of segmental necrotizing or endocapillary inflammatory lesions (post-inflammatory scarring) [35], E, S, and C lesions were associated with each other to some extent in patients with IgAN. We unexpectedly found that decrease in mesangial hypercellularity, which was not significant in univariate analysis, was an independent predictor for 5-year relapse after multivariate analysis. It would be very difficult to interpret this result from the viewpoint of the mechanisms. Further verification is needed to conclude this result.

This study has several limitations. The non-responder group had a lower use of steroid therapies than the remission and relapse groups and had less severe renal histological changes than the relapse group, suggesting that the non-responder group might include patients with mild IgAN who are judged by their doctor to not require steroid treatment (selection bias). However, similar results were obtained in a stratified model (subgroup analysis) in which the analysis target was restricted to patients who received steroid therapies. Another limitation is that this study included only Japanese patients. It has been reported that patients with IgAN have epidemiological and geographic heterogeneities as a result of differences in race and gender because of several molecular mechanisms [36]. Thus, the results should be confirmed in IgAN patients of other races.

In conclusion, among 5-year therapeutic responsiveness, both the relapse and non-responder groups had similarly strong association with ESKD in patients with IgAN. Proteinuria, eGFR, mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, and crescent, but not IFTA were independent predictors of relapse 5 years after renal biopsy. This information may help the treatment strategies

for patients with IgAN who occasionally relapse after remission during a long-term observation.

Compliance with ethical standards

Conflict of interest: The authors have declared that no conflict of interest exists.

Ethical approval: This study was approved by the Ethic Committee of Nara Medical University Hospital (approval No. 2005-18) and registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000031121).

Informed consent: Written informed consent was not required because of the retrospective observational study design. All patients gave their "opt-out" informed consent.

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Tables

Table 1 Baseline characteristics at renal biopsy in the 5-year landmark analysis cohort

Variable		Group			*P*
		Remission	Relapse	Non-responder	
Number of patients		197 (42%)	53 (11%)	220 (47%)	—
Demographics					
Observational period, months		155 [111, 200]	119 [83, 205]	162 [113, 230]*†	<0.01
Age, years		38 [27, 49]	38 [26, 52]	41 [28, 49]	0.69
Sex, male		43%	45%	50%	0.32
BMI, kg/m^2		21.7 [20.2, 23.4]	22.4 [21.2, 23.5]	21.8 [20.1, 23.1]	0.13
Systolic BP, mmHg		126 [112, 144]	126 [114, 156]	128 [112, 140]	0.53
Steroids: oral and/or pulse therapy		65%	79%	41%*†	<0.001
Steroid pulse therapy		40%	47%	24%*†	<0.001
Immunosuppressants		21%	47%*	16%†	<0.001
Tonsillectomy		6%	9%	4%	0.29
RAS blockers		93%	94%	91%	0.64
Laboratory					
Serum total protein, g/dL		7.0 [6.5, 7.3]	6.7 [6.1, 7.2]	6.9 [6.3, 7.4]	0.21
Serum albumin, g/dL		4.1 [3.9, 4.4]	4.0 [3.7, 4.4]	4.2 [3.8, 4.4]	0.53
Serum creatinine, mg/dL		0.80 [0.70, 1.00]	0.99 [0.80, 1.20]*	0.89 [0.70, 1.10]*	0.001
eGFR, mL/min/1.73m^2		74.5 [58.9, 93.6]	58.5 [45.2, 75.4]*	69.7 [49.5, 90.4]	<0.01
Proteinuria, g/day		0.96 [0.76, 1.31]	1.28 [1.01, 1.56]*	1.04 [0.80, 1.27]†	<0.001
Hematuria	1+	38%	30%	38%	0.051
	2+	25%	47%	27%	
	3+	36%	23%	35%	
Urinary RBC cast		13%	30%*	15%†	0.01
LDL cholesterol, mg/dL		116 [90, 143]	122 [82, 145]	108 [81, 137]	0.10
IgA, mg/dL		321 [259, 387]	339 [265, 389]	329 [260, 399]	0.69
C3, mg/dL		107 [96, 124]	106 [91, 118]	111 [93, 122]	0.75
C3/IgA ratio		2.75 [2.31, 3.61]	3.07 [2.54, 4.08]	3.13 [2.42, 3.64]	0.34
Serum C-reactive protein, mg/dL		0.10 [0.10, 0.30]	0.10 [0.10, 0.20]	0.10 [0.10, 0.30]	0.77
Histological findings					
Global sclerosis, %		6.7 [0.0, 20.0]	9.1 [0.0, 33.3]	6.6 [0.0, 19.1]	0.25
Mesangial hypercellularity	M1	33%	25%	35%	0.34
Endocapillary hypercellularity	E1	7%	30%*	11%†	<0.001
Segmental glomerulosclerosis	S1	45%	72%*	59%*	<0.001
Tubular atrophy and interstitial fibrosis	T1	17%	26%	18%	0.25
	T2	6%	11%	9%	
Cellular or fibrocellular crescent	C1	29%	60%*	37%†	<0.001
	C2	5%	19%	6%	

Note.
Results shown as the median [interquartile range] for contentious variables or percentage for prevalence.
Histological findings are evaluated according to the Oxford classification of IgA nephropathy. Segmental glomerulosclerosis includes segmental sclerosis and adhesion.
Post hoc test (Holm method for chi-square test and Tukey HSD method for ANOVA): *$P < 0.05$ vs. remission group, †$P < 0.05$ vs. relapse group.
Abbreviations: BMI: body mass index; BP: blood pressure; RAS: renin angiotensin aldosterone system; IgA: immunoglobulin A; C3: complement 3; LDL cholesterol: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate.

Table 2 Association of relapse and non-responder with ESKD

	Hazard Ratio (95% confidence interval) for ESKD			
	Crude	**Model 1**	**Model 2**	**Model 3**
Remission	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Relapse	6.26 (3.23,12.16)	6.75 (3.46,13.16)	4.54 (2.29,8.98)	2.86 (1.41,5.79)
Non-responder	2.16 (1.20,3.90)	2.13 (1.18,3.85)	3.52 (1.91,6.47)	2.74 (1.48,5.11)

N = 470 patients and 79 events (end-stage kidney disease; ESKD)

Model 1 adjustments: age, sex

Model 2 adjustments: model 1 + BMI, proteinuria level, eGFR, SBP, steroid therapies

Model 3 adjustments: model 2 + histological findings (MESTC score)

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure.

Table 3 Predictors of relapse 5 years after renal biopsy

Variables	**Univariate**		**Multivariate**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Clinical factors				
Age, per 10-year	1.09 (0.89-1.34)	0.41	0.82 (0.61-1.11)	0.20
Sex male (vs. female)	0.90 (0.49-1.65)	0.73	0.52 (0.23-1.14)	0.10
Proteinuria, per 1g/day	3.48 (1.73-6.98)	<0.001	2.51 (1.09-5.80)	0.03
eGFR, per 10 mL/min/1.73m^2	0.80 (0.70-0.92)	<0.01	0.75 (0.61-0.92)	<0.01
Systolic blood pressure, per 10 mmHg	1.06 (0.93-1.21)	0.41	0.99 (0.83-1.17)	0.89
Histological factors				
Mesangial hypercellularity, M1 (vs M0)	0.68 (0.34-1.35)	0.27	0.38 (0.16-0.87)	0.02
Endocapillary hypercellularity, E1 (vs. E0)	5.65 (2.54-12.60)	<0.001	2.96 (1.15-7.60)	0.02
Segmental glomerulosclerosis, S1 (vs. S0)	3.14 (1.62-6.07)	<0.001	2.85 (1.31-6.19)	<0.01
Tubular atrophy/interstitial fibrosis, T1 or 2 (vs. T0)	2.05 (1.07-3.91)	0.03	0.71 (0.29-1.76)	0.46
Cellular or fibrocellular crescent, C1 or 2 (vs. C0)	7.58 (3.66-15.70)	<0.001	6.16 (2.74-13.90)	<0.001

N = 250 patients (who achieved remission) and 53 events (relapse)

Abbreviations: eGFR: estimated glomerular filtration rate; OR: odds ratio; CI: confidence interval.

Figure legends

Fig. 1 STROBE diagram illustrating the selection criteria for the study samples

Fig. 2 Cumulative incidence of remission, relapse, and renal death after renal biopsy in the exploratory cohort (N = 563)
Note: During 5 years after renal biopsy, 314 (55.8%) patients achieved remission and 77 (13.7%) patients developed relapse but only 6 (1.1%) patients reached renal death. At last observation (20 years after renal biopsy), 430 (76.4%) patients achieved remission, 141 (25.1%) patients developed relapse, and 91 (16.1%) patients reached renal death.

Fig. 3 Renal survival curves adjusted for clinically relevant factors in the 5-year landmark analysis cohort (N = 470)
Note: N = 470 patients and 79 events (end-stage kidney disease; ESKD). Renal survival curves adjusted for age, sex, body mass index, estimated glomerular filtration rate, proteinuria level, systolic blood pressure, steroid therapies, and pathological findings, including mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, cellular and/or fibrocellular crescent.

Fig. 4 Association of relapse/non-responder with ESKD stratified by possible effect modifiers
Note: Separate models for each group; all models were adjusted for age, sex, body mass index, estimated glomerular filtration rate, proteinuria level, systolic blood pressure, steroid therapies, and pathological findings including mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and cellular and/or fibrocellular crescent.
We reported the number of patients (N) and event (ESKD) from the observed dataset.
The *P* values described for the interaction were reported for each relapse or non-responder.
Abbreviation: ESKD: end-stage kidney disease.

Supplemental figure legends

Supplemental Fig. 1 Prevalence of renal outcomes during follow-up after renal biopsy in the exploratory cohort (N = 563)

Supplemental Fig. 2 Survival curves for 1.5-fold increase in serum creatinine adjusted for clinically relevant factors in the 5-year landmark analysis cohort Note: N = 458 patients and 139 events (1.5-fold increase in serum creatinine from baseline). Survival curves adjusted for age, sex, body mass index, estimated glomerular filtration rate, proteinuria level, systolic blood pressure, steroid therapies, and pathological findings, including mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, cellular and/or fibrocellular crescent.