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ORIGINAL ARTICLE

Clinical and pathological features of immunoglobulin A nephropathy patients with nephrotic syndrome

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Abstract

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. The classic manifestation of IgAN is episodic hematuria and proteinuria. Nephrotic syndrome (NS) is not very common in IgAN, reported to occur in only 5–10% of IgAN patients. However, the clinical and pathological characteristics and long-term outcomes of patients with NS-IgAN at onset remain unknown. A retrospective study was conducted, enrolling 1165 patients with biopsy-proven IgAN from West China Hospital in 2008–2015. Patients with renal biopsy of minimal change disease with mesangial IgA deposits were excluded. The renal endpoint was defined as 50% decrease in eGFR or progressing into end-stage renal disease (ESRD). A total of 1165 patients were enrolled with average age of 34.58, and 171 (14.7%) patients were presented with NS. Comparing NS and non-NS groups, significance differences were shown in hypertension (HTN), 24-h urine protein, serum albumin, serum creatine, eGFR and uric acid. NS group had severe pathological changes such as endocapillary hypercellularity, tubular atrophy or interstitial fibrosis and crescent, but less segmental glomerulosclerosis or adhesion and global sclerosis. During the average follow-up of 44.27 months, 29.8% (51/171) NS patients and 15.8% (157/994) non-NS patients progressed to the renal endpoint. 5-year renal survival rates were 73.1% and 87.8% ($P < 0.001$) in NS and non-NS groups, respectively. This study demonstrated that IgAN patients with NS had higher serum creatine, lower eGFR, lower uric acid, more acute lesions and poor prognosis. NS was an independent risk factor for progression to the renal endpoint.

Keywords IgA nephropathy · Nephrotic syndrome (NS) · End-stage renal disease (ESRD)

Introduction

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, which is characterized by mesangial proliferation and deposition of IgA in glomeruli [1]. It is well known that up to 40% of the patients would develop end-stage renal disease (ESRD) within 20 years after the diagnosis of IgAN [2].

The classic presentation of IgAN is episodic hematuria and proteinuria. Nephrotic syndrome (NS) is not a common manifestation of IgAN, which was reported to occur in only 5–10% of IgAN patients [1, 3]. Considering that massive proteinuria is highly associated with ESRD in IgAN [4], we speculate that NS may also be related to ESRD in IgAN. Although IgAN patients with NS are often treated with corticosteroids according to KDIGO guidelines [5], recent studies found that spontaneous remission (SR) of NS in IgAN patients was common with even 24% prevalence [3, 6].

However, the clinical and pathological characteristics and long-term outcomes of patients with NS at onset remain unknown. To clarify these issues, a retrospective observational study was conducted to clarify the characteristics of IgAN with NS in Chinese patients.

Materials and methods

Patients

Biopsy-proven IgAN patients from the West China Hospital between 2008 and 2015 were included in this study. The following inclusion criteria were applied: (1) IgAN diagnosed

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by a renal biopsy with predominant mesangial deposition of IgA with at least 1 + on immunofluorescent staining and electron-dense deposits within the mesangium detected by electron microscopy; (2) patients were followed for at least 3 months; and (3) patients were at least 14 years old. Patients with the following exclusion criteria were excluded from the study: (1) eGFR < 15 mL/min/1.73m2 at the time of biopsy; (2) medical history of systemic disease, such as systemic lupus erythematosus, Henoch–Schönlein purpura and liver cirrhosis; (3) history of renal replacement therapy, such as dialysis and renal transplant; (4) patients without complete renal biopsy information or clinical data; and (5) renal biopsy shows MCD with diffusion loss of podocyte foot processes, vacuolation and the appearance of microvilli. Patients with pathological results of minor glomerular abnormality (MGA) with IgA deposition, which appeared to be similar to minimal change disease (MCD) rather than IgAN, have been detailedly discussed previously [7–9]. The research was in compliance with the Declaration of Helsinki and was approved by the ethical committee of West China Hospital of Sichuan University. Written informed consents were signed by all the patients before treatment. Medication-related adverse events were carefully described to each patient. Clinical decisions were made by both doctors' advice and patients' willing. Patients refusing to take steroids or immunosuppressants were given optimal supportive therapy.

Data collection

Demographic data, including gender, age at biopsy, date of initial presenting clinical features and date of birth, were collected. Stage of chronic kidney disease (CKD) of patients was recorded. Clinical parameters that we collected included systolic blood pressure (SBP), diastolic blood pressure (DBP), 24-h urine protein, hematuria, albumin, serum creatine, estimated glomerular filtration rate (eGFR) and uric acid. Hypertension was determined with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate eGFR [10].

Renal biopsies from all patients were reviewed by two experienced pathologists. Five pathological variables were collected: mesangial hypercellularity (M0/M1, < or equal to > 50% of glomeruli with > 4 mesangial cells/area), endocapillary hypercellularity (E0/E1, present/absent), segmental glomerulosclerosis or adhesion (S0/S1, present/absent), tubular atrophy or interstitial fibrosis (T0/T1/T2, < 25%, 25–50%, > 50%) and crescent (C0/C1/C2, no crescents/crescent in a least 1 glomerulus/crescents in at least 25% of glomeruli) according to the updated Oxford classification [11–13]. Global glomerulosclerosis was defined as hyaline deposition or scarring lesion happens in more than 50% of a single glomerulus. Global glomerulosclerosis (G) was scored according to the percentage of global glomerulosclerosis: G0 (≤ 25% of glomeruli), G1 (26–50% of glomeruli) and G2 (> 50% of glomeruli).

Treatments

The usage of angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blocker (ARB) applied to achieve the goal blood pressure (BP < 140/90 mmHg) was regarded as supportive care (SC). Corticosteroids (CS) were applied with dose of 0.5–1 mg/kg prednisone daily, tapering down within 6–8 months. Immunosuppressants (IS) was combined with the use of corticosteroids, such as cyclophosphamide 2 mg/kg daily for 3 months or mycophenolate mofetil 1–2 g daily or cyclosporine 3–5 mg/kg daily or tacrolimus 0.03–0.05 mg/kg daily for 6–8 months recorded at diagnosis.

Outcomes

Responses to therapy included complete remission (CR), partial remission (PR), no response (NR) and ESRD. Complete remission (CR) was defined as the absence of proteinuria (< 0.5 g/d). Spontaneous remission (SR) was defined as CR with NS without using corticosteroids or immunosuppressive agents. Partial remission (PR) was defined as a > 50% decrease from baseline in proteinuria. No response (NR) was defined as a < 50% decrease from baseline in proteinuria or an increase in proteinuria. ESRD was defined as eGFR < 15 ml/min/1.73m2 or the necessity for renal replacement of therapy. The renal endpoint was defined as a 50% decline of eGFR and/or progressing to ESRD.

Statistical analyses

Normally distributed data were presented as mean ± standard deviation (SD), and nonparametric data were presented as the median and interquartile range. Continuous data were compared using the *t* test or the one-way ANOVA, and categorical data were compared using Chi-square test. Unadjusted and adjusted analyses with Cox regression models were used to identify independent risk factors for poor prognosis. The probability of renal survival was analyzed using Kaplan–Meier survival curve and the log-rank test. All *P* values were two-tailed, and $P < 0.05$ was considered to be statistically significant. Statistical software SPSS 20 (SPSS, Chicago, IL, USA) was employed for statistical analysis.

Results

Baseline characteristics

One thousand three hundred and seventy patients with biopsy-proven IgAN were enrolled from the West China Hospital between 2008 and 2015. The following patients were then excluded: (1) eGFR < 15 mL/min/1.73 m^2 at time of biopsy ($N = 22$); (2) medical history of acute kidney disease ($N = 2$); (3) history of renal replacement ($N = 1$), intermittent hemodialysis ($N = 2$) and continuous ambulatory peritoneal dialysis ($N = 2$); and (4) MCD with IgA deposition ($N = 171$). Therefore, a cohort of 1165 patients were included in the present study. Geographic and clinical features are shown in Table 1. The mean age of all the patients was 34.58 ± 11.14 years old, and the mean follow-up period was 44.27 ± 25.14 months. Geographic and clinical information of 171 NS-IgAN patients (14.7%) and 994 non-NS-IgAN patients (85.3%) is also listed in Table 1. No significant difference in gender or age was observed between the two groups. Clinical analyses revealed significant difference in blood pressure, proteinuria, serum albumin, serum creatinine, eGFR and uric acid at baseline between these two groups (Table 1). For pathological characteristics, patients in NS-IgAN group have higher percentage of E1, T1-2 and C1-2 and lower percentage of S1 and G (present). The NS-IgAN group had higher percentage of CKD 3b (14.6%, $P = 0.049$) and CKD 4 (17%, $P < 0.001$) than non-NS-IgAN group.

Treatments and clinical response

As shown in Table 2, the use of CS alone and CS combined with IS in NS-IgAN group was significantly higher than non-NS-IgAN group. Within NS-IgAN patients, treatments were also different. In particular, in CR group, all patients used CS alone or combined with IS as shown in Table 3.

Table 4 shows the clinical and pathological features of IgAN patients with NS grouped by different clinical responses. Sixty-five (38%) patients reached CR and 67 (39.2%) patients reached PR. However, 39 (22.8%) patients showed poor response or disease progression. No difference was revealed in gender or age, but significant difference was shown in blood pressure, serum creatine and eGFR at baseline. Proteinuria, as well as serum albumin and uric acid, had no significant difference at baseline, but revealed significant difference after treatment at the last follow-up. For pathological scores, S1 and T1 revealed significant differences between groups.

Table 1 Baseline characteristics of IgAN patients

	All patients ($n = 1165$)	NS-IgAN ($n = 171$)	Non-NS-IgAN ($n = 994$)
Clinical findings			
Male (%)	530 (45.5%)	79 (46.2%)	451 (45.4%)
Age	34.58 ± 11.135	33.12 ± 13.661	34.83 ± 10.629
SBP**	130 [119–146]	140 [120–150]	129 [118–145]
DBP**	84.67 ± 14.229	87.35 ± 15.802	84.2 ± 13.898
HTN (%)**	443 (38%)	85 (49.7%)	358 (36.1%)
MAP (mmHg)*	100.49 ± 15.406	103.90 ± 16.691	99.91 ± 15.106
Urine protein (g/24 h)***	2.73 ± 2.81	6.74 ± 4.522	2.04 ± 1.582
Serum albumin (g/dL)***	38.09 ± 11.883	26.11 ± 5.022	40.15 ± 11.499
Serum creatine (μmol/L)***	108.16 ± 56.476	130.04 ± 75.227	104.40 ± 51.705
eGFR (mL/min/1.73 m^2)**	82.53 ± 49.24	66.277 ± 45.103	77.594 ± 37.68
Uric acid (μmol/L)*	291.02 ± 192.39	271.98 ± 198.091	300.51 ± 180.373
Pathological findings			
M0/M1 (%)	124/1041 (10.6/89.4%)	14/157 (8.2/91.8%)	110/884 (11.1/88.9%)
E0/E1 (%)***	1100/65 (94.4/5.6%)	142/29 (83/17%)	958/36 (96.4/3.6%)
S0/S1 (%)*	490/675 (42.1/57.9%)	86/85 (50.3/49.7%)	404/590 (40.6/59.4%)
T0/T1/T2 (%)***	848/243/74 (72.8/20.9/6.4%)	105/45/21 (61.4/26.3/12.3%)	743/198/53 (74.7/19.9/5.3%)
C0/1/2***	834/253/778(71.6/21.7/6.7%)	107/40/24 (62.6/23.4/14%)	727/217/50 (73.1/21.8/5%)
G (absent/present)*	222/943 (19.1/80.9%)	42/129 (24.6/75.4%)	180/813 (18.1/81.9%)

NS-IgAN patients with nephrotic syndrome; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *HTN* hypertension; *MAP* mean arterial pressure; *eGFR* estimated glomerular filtration rate; *M* mesangial hypercellularity; *E* endocapillary hypercellularity; *S* segmental glomerulosclerosis or adhesion; *T* tubular atrophy/interstitial fibrosis; *C* crescents; *G* global glomerulosclerosis

P value: *0.01 = <*P* < 0.05, **0.001 = <*P* < 0.01, ***$P < 0.001$

Table 2 Treatments and endpoints of IgAN patients

	NS-IgAN ($n=171$)	Non-NS-IgAN ($n=994$)	P values
Treatment			
SC	14 (8.2%)	434 (43.7%)	< 0.001
GC alone	76 (44.4%)	318 (32%)	0.001
GC and IS	81 (47.4%)	242 (24.3%)	< 0.001
Endpoints			
eGFR 50% off	49 (28.7%)	154 (15.5%)	< 0.001
ESRD	43 (25.1%)	116 (11.7%)	< 0.001
Renal Endpoint	51 (29.8%)	157 (15.8%)	< 0.001

SC supportive care; *CS* corticosteroids; *IS* immunosuppressants; *ESRD* end-stage renal disease

Table 3 Treatments and endpoints of NS-IgAN patients

	CR ($n=65$)	PR ($n=67$)	NR ($n=39$)	P values
Treatment				
SC	0	6 (9%)	8 (21.1%)	0.001
GC alone	42 (63.6%)	25 (37.3%)	9 (23.7%)	< 0.001
GC and IS	24 (36.4%)	36 (53.7%)	21 (55.3%)	0.073
Endpoints				
eGFR 50% off	0	20 (29.9%)	29 (74.4%)	< 0.001
ESRD	0	16 (23.9%)	27 (69.2%)	< 0.001
Renal Endpoint	0	21 (31.3%)	30 (76.9%)	< 0.001

SC supportive care; *CS* corticosteroids; *IS* immunosuppressants; *ESRD* end-stage renal disease

Long-term clinical outcomes

In total, 208 (17.8%) patients reached the renal endpoint. Within the 208 patients, 203 (17.4%) patients lost 50% eGFR and 159 (13.6%) patients progressed to ESRD. 29.8% (51/171) NS-IgAN patients and 15.8% (157/994) non-NS-IgAN patients progressed to our endpoint as shown in Table 2. Kaplan–Meier analysis showed that renal survival was significantly different between two groups ($P<0.001$, Fig. 1). 5-year renal survival rates were 73.1% versus 87.9% ($P<0.001$) in two groups, respectively. NS-IgAN group showed significantly lower renal survival probability compared with non-NS-IgAN group. No NS-IgAN patient in CR group reached our endpoint, but 21 (31.3%) and 30 (76.9%) in PR and NR groups reached the endpoint, respectively. 5-year renal survival rates were 100%, 71.6% and 23.1% ($P<0.001$) in CR, PR and NR groups. Renal survival between these three groups was significantly different ($P<0.001$, Fig. 2).

Factors related to the renal endpoint

Factors related to progressing to eGFR 50% off or ESRD in all IgAN patients are shown in Table 5. Unadjusted analyses showed that male (HR: 1.43, $P=0.010$), M1 (HR: 2.80, $P=0.023$), E1 (HR: 1.86, $P=0.017$), S1 (HR: 1.94, $P<0.001$), T1 (HR: 10.11, $P<0.001$), T2 (HR: 30.29, $P<0.001$), C2 (HR: 2.04, $P=0.001$), G (present) (HR: 28.555, $P<0.001$), hypertension (HR: 6.50, $P<0.001$), NS (HR: 2.28, $P<0.001$), serum creatine (HR: 1.02, $P<0.001$) and CS/SC (HR: 0.57, $P<0.001$) were significantly associated with poor renal prognosis (Table 5). However, adjusted analyses showed that male (HR: 0.721, $P=0.35$), T1 (HR: 3.453, $P<0.001$), T2 (HR: 6.471, $P<0.001$), C1 (HR: 0.659, $P=0.048$), C2 (HR: 2.070, $P=0.005$), G (present) (HR: 8.518, $P=0.003$), hypertension (HR: 2.189, $P<0.001$), NS (HR: 1.518, $P=0.25$), serum creatinine (HR: 1.01, $P<0.001$), IS/SC (HR: 0.553, $P=0.001$) were independent risk factors of poor renal outcome.

Discussion

To date, NS is uncommon in IgAN which was reported to occur in only 5–10% of IgAN patients [1, 3]. Few studies have investigated the clinical and pathological features of IgAN with NS [3, 14]. To our knowledge, our cohort was the first one analyzing Chinese NS-IgAN adult patients, which provided valuable and a lot of clinical and pathological information.

One important finding in our study was the high proportion of NS presented in IgAN adult patients. Our cohort had 208 (17.8%) NS-IgAN patients even though 171 MCD-IgAN patients were all excluded. MCD with IgA deposition is a special group in IgAN typically with nephrotic syndrome and has been demonstrated to have favorable prognosis and be well responded to corticosteroid in several studies [7–9, 15, 16]. MCD-IgAN was suggested to be treated as MCD according to 2012 KDIGO [5]. Accordingly, patients with MCD with IgA deposition were excluded in our study. Rauen et al. [17] reported a prevalence of 7.0% of NS in IgAN in German. 8.3–10.2% IgAN patients were investigated to present NS in Korean cohorts [3, 15]. A Chinese study surprisingly showed 83.4% IgAN patients with MCD had more than 3.5 g/d proteinuria [9]. As we know, prevalence of IgAN in the world is variable and is more common in Asia and Pacific areas [18]. Geographic variability, genetic differences and renal biopsy timings [19, 20] may possibly explain the differences.

For the clinical features between two groups in our study, gender and age revealed no difference, but prevalence of hypertension, serum creatinine and eGFR were significantly different, regarding that the clinical features at biopsy of

Table 4 Baseline characteristics of IgAN-NS patients

	CR ($n=65$)	PR ($n=67$)	NR ($n=39$)
Clinical findings			
Male (%)	29 (44.6%)	31 (46.3%)	18 (48.7%)
Age	33 [23.75–47.25]	27 [21–40]	29 [24–37.25]
SBP**	129.44 ± 21.917	140.21 ± 22.052	144.42 ± 19.267
DBP***	81.38 ± 12.321	91.01 ± 16.003	91.26 ± 17.890
HTN (%)***	18 (27.7%)	38 (56.7%)	29 (74.4%)
MAP (mmHg)***	97.4 ± 14.635	107.41 ± 17.270	108.98 ± 15.731
Pre-proteinuria (g/24 h)	5.265 [4.095–7.815]	6.38 [2.8–8.71]	4.645 [3.731–6.235]
Pre-albumin (g/dL)	25.11 ± 5.012	27.05 ± 5.364	26.18 ± 4.125
Post-serum creatine (μmol/L)***	75.5 [62.75–93]	122 [84–340]	432.5 [221.25–800.05]
Pre-eGFR (mL/min/1.73 m^2)***	92.229 ± 38.229	69.284 ± 36.725	46.118 ± 31.072
Pre-urine acid (μmol/L)	247.5 [58–357.5]	321.5 [43.5–467.75]	364 [58.25–496.75]
Last follow-up			
Post-proteinuria (g/24 h)***	0.2 [0.13–0.3475]	1.1 [0.7–2.27]	2.05 [3.075–5.05]
Post-albumin (g/dL)***	41.99 ± 6.339	38.89 ± 6.176	31.99 ± 5.492
Pre-serum creatine (μmol/L)***	82.5 [65–111.25]	103 [80–198]	174 [128.75–221.25]
Post-eGFR (mL/min/1.73 m^2)***	101.9 [70.575–118.075]	55 [15.9–89.1]	12.8 [5.45–28.15]
Post-urine acid (μmol/L)***	258 [37–315.5]	379.5 [76.25–494.5]	486 [195–621]
Pathological findings			
M0/M1 (%)	4/61 (6.2/93.8%)	9/58 (13.4/86.6%)	1/38 (2.6/97.4)
E0/E1 (%)	55/10 (84.6/15.4%)	57/10 (85.1/14.9%)	30/9 (76.9/23.1%)
S0/S1 (%)***	47/18 (72.3/27.7%)	23/44 (34.3/65.7%)	16/23 (41/59%)
T0/T1/T2 (%)***	58/7/0 (89.2/10.8/0%)	39/20/8 (58.2/29.9/11.9%)	8/18/13 (20.5/46.2/33.3%)
C0/1/2	42/16/7 (64.6/24.6/10.8%)	43/16/8 (64.2/23.9/11.9%)	22/7/10 (56.4/17.9/25.6%)
G (absent/present)***	31/34 (47.7/52.3%)	8/59 (11.9/88.1%)	3/36 (7.7/92.3%)

NS-IgAN patients with nephrotic syndrome; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *HTN* hypertension; *MAP* mean arterial pressure; *eGFR* estimated glomerular filtration rate; *M* mesangial hypercellularity; *E* endocapillary hypercellularity; *S* segmental glomerulosclerosis or adhesion; *T* tubular atrophy/interstitial fibrosis; *C* crescents; *G* global glomerulosclerosis

P value: *$0.01 =< P < 0.05$, **$0.001 =< P < 0.01$, ***$P < 0.001$

IgAN with NS showed severer at baseline. However, NS-IgAN group had lower uric acid than IgAN group. It may be associated with protein loss from kidney and poor purines or nucleotides intake from edematous gastrointestinal mucosa due to nephrotic syndrome [21]. Although high uric acid has been reported to be associated with CKD progression and cardiovascular diseases, recent studies believed that uric acid had a J-shaped association with poor renal survival in IgA nephropathy and more studies were needed to explore the relationship between uric acid and kidney diseases [22, 23].

As for pathological features, E1, S1, T1-2, C1-2 and G (absent/present) showed significant difference between two groups. In particular, NS-IgAN group had lower percentage of S1 and G (present), which represented chronic lesions of kidney, so the NS-IgAN group showed more acute kidney lesions. Yuko et al. also reached the same conclusion that IgAN patients with NS were presented with highly active acute lesions [14]. It may be caused by obvious symptom of edema, which urged patients to visit doctors as soon as possible. The pathological factors related to a 50% decline of eGFR and/or progressing to ESRD by adjusted Cox regression analysis were T1-2, C1-2 and G (present). Consistently, a recent review revealed that tubular atrophy/interstitial fibrosis is the strongest predictor of renal survival and crescent portion (C) was added to update Oxford scores because of its strongly prediction of renal survival by accumulating evidence from studies [13, 24]. Interestingly, in this study, global sclerosis was also more common in NS-IgAN group. Although global sclerosis was not included in the Oxford scores, it was demonstrated as a risk factor for renal failure and had emphasized potential to predict long-term renal outcome in IgAN [25, 26]. Zhang et al. showed global sclerosis was possible risk factors for AKI [27]. Therefore, it is believed that NS-IgAN patients had more active acute lesions.

Another major finding in the present study was that the long-term outcomes of IgAN with NS were worse than non-NS-IgAN group. 29.8% (51/171) NS-IgAN patients and

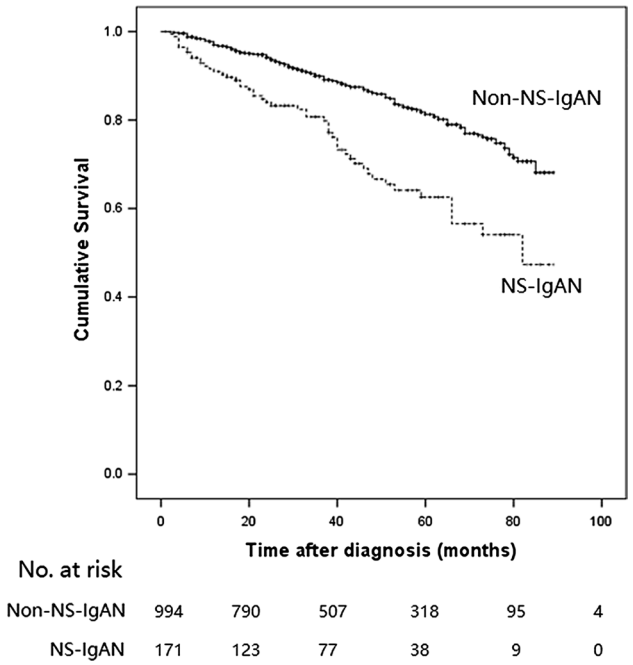

Fig. 1 Probability of renal survival in IgAN patients ($P < 0.001$)

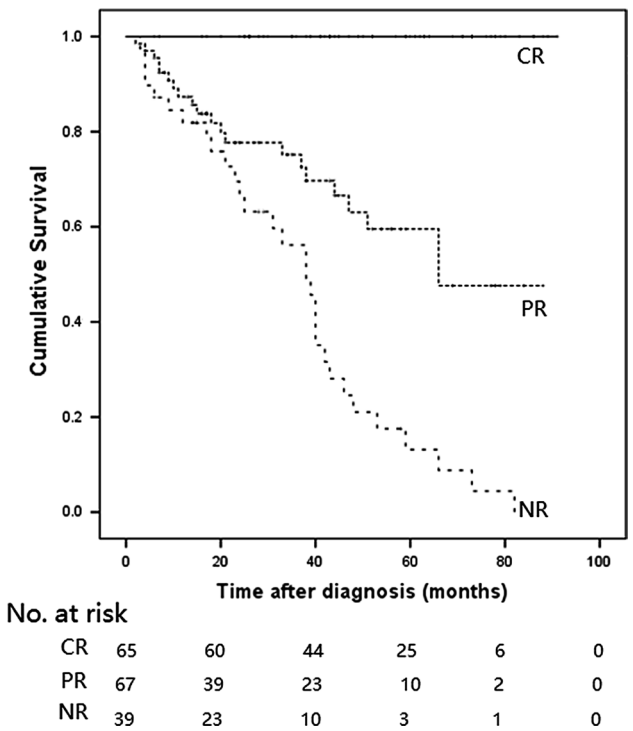

Fig. 2 Probability of renal survival in IgAN-NS patients ($P < 0.001$). *CR* complete remission, *PR* partial remission, *NR* no response

15.8% (157/994) non-NS-IgAN patients progressed to our endpoint, and the Kaplan–Meier analysis revealed significant difference ($P < 0.001$). In the adjusted cox regression analysis, NS was significantly correlated with progressing to ESRD and eGFR 50% off (HR: 1.518, $P = 0.025$). Therefore, NS was an independent risk factor for processing to eGFR 50% off or ESRD of IgAN. Excessive proteinuria is the typical clinical feature of NS, and several studies demonstrated that proteinuria could be an important predicting factor for IgAN progression [4, 19, 28–30]. Remission of proteinuria was one important goal in IgAN treatment. In our cohort, 66 patients achieved CR and 67 achieved PR. In the CR group, no patient reached the endpoint, while 21 (31.3%) of PR patients reached that endpoint. However, 30 (76.9%) patients with no proteinuria remission or progression reached the endpoint. Kim JK et al. demonstrated that the protein remission after treatment was the prognostic factor for renal survival in NS-IgAN patients, although MCD-IgAN patients were not excluded in this study [3]. Reich et al. [30] also revealed that remission of proteinuria in IgAN patients in treatment progression was important for favorable long-term renal outcome. Renal survival analysis showed significant difference in renal outcome between CR, PR and NR. Proteinuria had been demonstrated to be a risk factor for renal outcome and could be applied to predict long-time renal prognosis of IgAN patients [28, 29, 31]. Recent study showed that intermedin can significantly reduce proteinuria and ameliorated renal pathomorphological changes by diminishing oxidative stress and suppressing inflammation, which may be a potential candidate for remission treatment of IgAN [32]. Consistently, the present study showed the same results with those previous studies, proving that remission of proteinuria could improve renal prognosis, regardless of complete or partial remission of proteinuria.

Treatments were analyzed between different groups, and significant differences were observed in the treatment choices. The use of GC and IS was significantly more frequent in NS group. In contrast, more people in non-NS-IgAN group were provided with support care, such as the use of ACEI/ARB. All of the complete remission patients obtained treatment of glucocorticoids alone and/or combined with immunosuppressants. No spontaneous remission of proteinuria of NS-IgAN was presented in our study, although Kim et al. [3] reported 24% IgAN patients with NS showing spontaneous remission at 2012. IgAN patients with NS were always treated with glucocorticoids as MCD in previous studies and showed favorable therapy response [7, 8]. Although our study had a larger cohort and more IgAN-NS patients, none of them presented complete remission of proteinuria unless using glucocorticoids. Combined with the previous results, it is safe to say IgAN patients with excessive proteinuria might be suitable for more aggressive treatment in order to get a complete or partial remission for the purpose of protecting kidney function.

Several limitations of this study should not be neglected. First, our cohort came from a single center,

Table 5 Analyses of factors related to ESRD and eGFR 50% off in IgAN patients using Cox regression

	Unadjusted			Adjusted		
	HR	95% confidence interval	*P* value	HR	95% confidence interval	*P* value
Male/female	1.430	1.088–1.879	0.010	0.721	0.532–0.978	0.035
M1/M0	2.801	1.149–6.831	0.023	1.961	0.800–4.807	0.141
E1/E0	1.864	1.117–3.111	0.017	1.236	0.641–2.385	0.527
S1/S0	1.939	1.445–2.603	< 0.001	0.967	0.701–1.333	0.838
T (present/absent)			< 0.001			0.000
T1/T0	10.011	7.025–14.265	< 0.001	3.453	2.289–5.208	0.000
T2/T0	30.293	20.426–44.927	< 0.001	6.471	3.951–10.599	0.000
C (present/absent)			0.001			0.000
C1/C0	0.750	0.512–1.099	0.140	0.659	0.436–0.996	0.048
C2/C0	2.041	1.319–3.158	0.001	2.070	1.248–3.434	0.005
G (present/absent)	28.555	7.091–114.997	< 0.001	8.518	2.044–35.491	0.003
HTN	6.501	4.725–8.944	< 0.001	2.189	1.541–3.112	0.000
NS	2.276	1.657–3.126	< 0.001	1.518	1.055–2.185	0.025
Serum creatine	1.017	1.016–1.019	< 0.001	1.010	1.008–1.013	0.000
(CS + IS)/SC			0.007			0.004
CS/SC	0.568	0.400–0.807	0.002	0.644	0.431–0.963	0.032
IS/SC	0.389	0.870–0.633	0.389	0.553	0.386–0.791	0.001

M mesangial hypercellularity; *E* endocapillary hypercellularity; *S* segmental glomerulosclerosis or adhesion; *T* tubular atrophy/interstitial fibrosis; *C* crescents; *G* glomerulosclerosis; *HTN* hypertension; *NS* nephrotic syndrome; *SC* supportive care; *CS* corticosteroids; *IS* immunosuppressants

making it difficult to extrapolate the results. A Germany trial discussed that two hemispheres might have heterogeneity in clinical features and response to therapy of IgAN [19]. Multicenter and multiracial IgAN patients would be discussed in future. Second, the average follow-up duration was 44.27 months which may not be long enough to observe the long-time renal survival. Considering the slow progression of IgAN, continuing follow-up of our cohort is needed.

In conclusion, a prevalence of 14.7% of NS was presented in IgAN patients in our study. IgAN with NS patients had higher serum creatine, lower eGFR, lower uric acid, more acute lesions and worse renal outcomes. NS was an independent risk factor for progression to the renal endpoint. It was also proved that the remission of proteinuria could improve renal prognosis, regardless of complete or partial remission of proteinuria. Multicenter perspective studies with large patient size are required to validate our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The research was in compliance with the Declaration of Helsinki and was approved by the ethical committee of West China Hospital of Sichuan University.

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Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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