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CLINICAL STUDY

Comparison between outcomes of IgA nephropathy with nephrotic-range proteinuria and nephrotic syndrome: do podocytes play a role?

Yizhen Chen[a]*, Aicheng Yang[b]*, Yuansheng Hou[a], Longhui Liu[b], Jiehua Lin[b], Xiaodan Huang[a], Jundu Li[a], Xusheng Liu[c,d], Fuhua Lu[c,e], Qizhan Lin[f], Haifeng Yang[g], Shuling Yue[h], Shujun Jiang[f], Lixin Wang[c] and Chuan Zou[c]

[a]Second Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, China; [b]Department of Nephrology, The Affiliated Jiangmen TCM Hospital of Jinan University, Jiangmen, China; [c]Department of Nephrology, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [d]State Key Laboratory of Dampness Syndrome of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [e]Guangdong-Hong Kong-Macau Joint Lab on Chinese Medicine and Immune Disease Research, Guangzhou University of Chinese Medicine, Guangzhou, China; [f]Department of Hemodialysis, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [g]Department of Pathology, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [h]Guangzhou Kingmed Diagnostic Laboratory Ltd, Guangzhou, China

ABSTRACT

Background: Nephrotic syndrome (NS) and nephrotic-range proteinuria (NRP) are uncommon in IgA nephropathy (IgAN), and their clinicopathology and prognosis have not been discussed. Podocytes may play an important role in both clinical phenotypes.

Methods: We investigated 119 biopsy-proven IgAN patients with proteinuria over 2 g/d. The patients were divided into three groups according to proteinuria level: the overt proteinuria (OP) group, NS group, and NRP group. In addition, according to the severity of foot process effacement (FPE), the patients were divided into three groups: the segmental FPE (SFPE) group, moderate FPE (MFPE) group, and diffuse FPE (DFPE) group. The outcome was survival from a combined event defined by a doubling of the baseline serum creatinine and a 50% reduction in eGFR or ESRD.

Results: Compared with the NRP group, patients in the NS group had more severe microscopic hematuria, presented with more severe endocapillary hypercellularity and had a higher percentage of DFPE. The Kaplan–Meier curve showed that MFPE patients had a better outcome in the NRP group <50% of tubular atrophy/interstitial fibrosis. In the multivariate model, the NRP group (HR = 17.098, 95% CI = 3.835–76.224) was associated with an increased risk of the combined event, while MFPE (HR = 0.260, 95% CI = 0.078–0.864; $p = 0.028$) was associated with a reduced risk of the combined event. After the addition of renin-angiotensin system inhibitors (RASi), the incidence of the combined event in the MFPE group (HR = 0.179, 95% CI = 0.047–0.689; $p = 0.012$) was further reduced.

Conclusions: NS presented more active lesions and more severe FPE in IgAN. NRP was an independent risk factor for progression to the renal endpoint, while MFPE indicated a better prognosis in NRP without obvious chronic renal lesions, which may benefit from RASi.

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IgAN; nephrotic syndrome; nephrotic-range proteinuria; podocyte

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, and approximately 30%–40% of patients progress to end-stage renal disease (ESRD) within 20–30 years [1]. The classic presentation of IgAN is episodic hematuria and proteinuria. Nephrotic syndrome (NS) is not a common manifestation of IgAN and has been reported to occur in only 5–10% of IgAN patients [2,3]. The 2021 KDIGO guidelines indicate two specific subtypes of IgAN associated with significant proteinuria, namely, NS and nephrotic-range proteinuria (NRP) [4]. Research suggests that NS

CONTACT Lixin Wang wanglixin1210@163.com Department of Nephrology, Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Road, Yuexiu District, Guangzhou, 510120, China; Chuan Zou doctorzc541888@126.com Department of Nephrology, Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Road, Yuexiu District, Guangzhou, 510120, China
*These authors contributed equally to this work.

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without minimal change disease (MCD) pathological pattern is often accompanied by more active pathological changes, such as mesangial hypercellularity, endocapillary hypercellularity and crescents [3,5]. While the KDIGO guidelines note that NRP commonly reflects coexistent secondary focal segmental glomerular sclerosis (FSGS) or the development of extensive glomerulosclerosis and tubulointerstitial fibrosis, the guidelines do not present relevant research data. In addition, proteinuria over 1 g/d is known as a risk factor for CKD progression in IgAN, and the higher the proteinuria is, the more severe the pathology [6]. However, in previous studies on IgAN with NS, the baseline proteinuria level of most patients in the control group was no more than 2 g/d [3,5], and the two groups had strong pathological heterogeneity and were not very comparable. A literature survey shows that the proportion of patients with proteinuria over 2 g/d is small, generally approximately 28% [7–9], so there are few relevant studies. To compare the difference between nephrotic-level proteinuria and moderate overt proteinuria, it is more comparable to select patients with proteinuria above 2 g/d as the control group.

In addition, studies have shown that proteinuria is positively correlated with the severity of foot process effacement (FPE) in IgAN [10]. Typical NS, including MCD, membranous nephropathy (MN) and FSGS, is characterized by diffuse FPE under electron microscopy [11]. MCD generally has a good prognosis, while FSGS may progress to ESRD [12]. The effect of FPE on renal prognosis in IgAN is unclear, especially the difference between NS and NRP.

Corticosteroid therapy is effective for NS with MCD [13,14], but current studies have been controversial regarding whether to administer corticosteroid therapy to patients with massive proteinuria without MCD. Due to the lack of relevant research evidence, IgAN patients with NS and NRP were both managed with the general protocol according to KDIGO guidelines (assessing the risks, providing supportive therapy for 90 days, and administering corticosteroid therapy for high-risk patients, 2B). However, although most patients are treated with corticosteroid combination renin-angiotensin system inhibitors (RASi) in clinical practice, the efficacy is unclear.

Therefore, we used proteinuria above 2 g/d as the baseline group to compare the clinicopathology, treatment and prognosis of IgAN with NRP and NS and explored the relationship between podocyte injury and prognosis associated with these two clinical phenotypes.

Materials and methods

Study population and design

In this retrospective study, 119 biopsy-proven IgAN patients were collected from Guangdong Provincial Hospital of Chinese Medicine between May 2006 and October 2020. The inclusion criteria were as follows: (1) age >16 years; (2) diagnosis of primary IgAN by renal biopsy; (3) 24-h urine protein excretion over 2 g/d at the time of renal biopsy; and (4) patients were followed up for >6 months. The exclusion criteria were as follows: (1) insufficient clinical and pathological data; (2) suffering from other glomerular diseases or systemic diseases (including but not limited to patients with systemic lupus erythematosus, rheumatism, liver disease, and diabetes); and (3) renal biopsy showing MCD, with pathological results of minor glomerular abnormality with IgA deposition, which appeared to be similar to MCD rather than IgAN.

The patients were divided into three groups according to the 24-h urinary protein excretion at renal biopsy: an overt proteinuria (OP) group with proteinuria between 2 and 3.5 g; an NS group defined as proteinuria >3.5 g/d and hypoalbuminemia; and an NRP group defined as proteinuria >3.5 g/d but without NS.

Clinical data collection

In this study, all clinical data were obtained for all patients during renal biopsies, including gender, age, mean arterial pressure (MAP) defined as diastolic pressure plus one-third of the pulse pressure, 24-h urinary protein excretion, serum albumin (ALB), body mass index (BMI), total cholesterol (TC), triglyceride (TG), serum creatinine (Scr) and eGFR (calculated by the CKD-EPI equation). The urine protein-to-creatinine ratio (UPCR) was recorded at 6 months and the last follow-up. In terms of medication, regardless of the duration and dose, immunosuppression was defined as treatment with corticosteroids and/or immunosuppressant (cyclophosphamide, tacrolimus, mycophenolate, etc.). RASi was defined as treatment with angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin-receptor-blockers (ARB) after renal biopsy.

Pathology data review

Renal biopsies were reviewed by a pathologist and a nephrologist and were scored according to the updated Oxford Classification (MEST-C) [15]. The degree of IgA deposition was semiquantitatively evaluated as 1+, 2+, and 3+. IgG, IgM, C1q and Co-deposition of

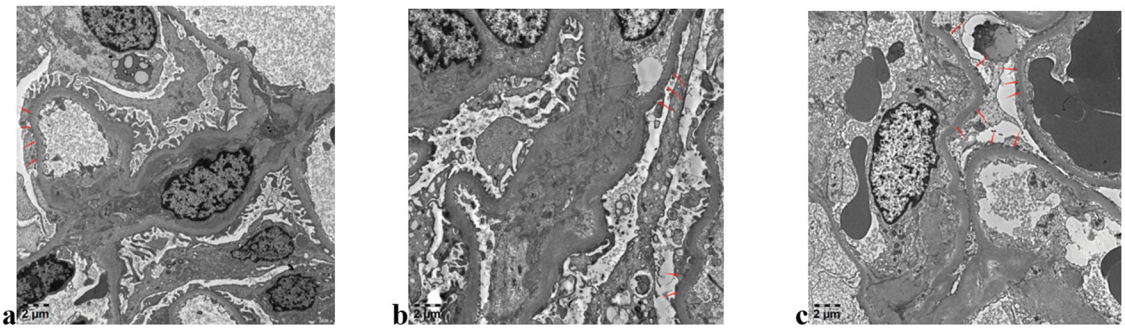

Figure 1. Representative images of electron microscopy of (a) segmental, (b) moderate, and (c) diffuse foot process effacement. Red arrows represent lesions with foot process effacement (× 6000).

complement 3 (C3) was described as negative(0), 1+, 2+ and 3+.

The severity of FPE was determined based on the extent of FPE by electron microscopy (EM) and established by visual inspection using a semiquantitative method, with 1–3 glomeruli observed in each patient's specimen. The glomerular basement membrane of each capillary loop was observed under EM to assess the overall proportion of FPE. When more than 75% of the capillaries exhibited FPE, we defined the severity as 'diffuse' (DFPE). If FPE was observed in more than half (but not exceeding 75%) of the total glomerular capillary length, it was defined as 'moderate' (MFPE); if not (i.e. FPE was observed in less than half of the total glomerular capillary length), it was described as 'segmental' (SFPE) (Figure 1).

Clinical outcome

Short-term remission (SR) was defined as (1) $a > 50\%$ reduction in proteinuria within 6 months and an absolute reduction in proteinuria less than 3.5 g/d or 2 g/d (OP group); (2) ALB > 35 g/L; and (3) Scr within 6 months not increased by 15% more than baseline. No response (NR) was defined as failure to meet the above criteria. The outcome was survival from a combined event defined by a doubling of the baseline serum creatinine and a 50% reduction in eGFR or ESKD (eGFR < 15 mL/min per 1.73 m^2).

Statistical analysis

SPSS(version 26.0) was used for statistical analysis. Normally distributed continuous data were presented as mean ± SD, and one-way ANOVA or Kruskal-Wallis test was used for multiple groups comparison. Nonnormally distributed continuous data were presented as a median and interquartile range, compared across the groups using the Kruskal-Wallis test. The categorical data were presented as numbers (percentage) and analyzed using the Chi-Square test or Fisher's test. p values were adjusted by the false discovery rate (FDR) test. Kaplan-Meier survival curve and log-rank test were performed to compare renal survival rates among the different groups. Multivariate Cox regression analysis was applied to identify the independent risk factors for poor renal prognosis ($p < 0.05$ indicated statistical significance).

Results

Characteristics of the cohort

A total of 119 patients were enrolled in this study. At the time of renal biopsy, the patients had a urinary protein excretion of 3.51 (2.5–4.55) g/24 h and an eGFR of 55.69 (35.10–76.85) mL/min/1.73 m^2. Regarding FPE, 53.8% were 'SFPE', 23.5% were 'MFPE', and 22.7% were 'DFPE'. The patients were followed up for a median of 40 (24–86) months. Of these patients, 52 (43.7%) were in the OP group, 33 (27.7%) were in the NS group, and 34 (28%) were in the NRP group. The clinicopathological features of the three groups are shown in Table 1.

Subgroup characteristics

Compared with the OP group, patients in the NS and NRP groups had increased proteinuria levels [4.55 (3.72–5.41), 4.08 (3.64–5.02) vs. 2.42 (2.14–2.78) g/24 h]. Compared with the NRP group, the ALB levels in the NS group were lower [28 (25–29.5) vs. 36.5 (33.95–38.42) g/L], the urine red blood cell level [113 (38–359) vs. 37.5 (7.22–81.5)/μl] were higher. The remission rates of proteinuria were no significant difference between the two groups.

At the time of renal biopsy, the patients in the NS had a higher proportion of E1 (60.6% vs. 25%, 23.5%) and C2 (24.2% vs. 5.8%, 14.7%). The patients in the NRP group had a higher proportion of T2 than the OP group (41.2% vs. 11.5%). The NS group had a higher

Table 1. Baseline cohort characteristics.

Variable	Overall ($n = 119$)	OP group ($n = 52$)	NS group ($n = 33$)	NRP group ($n = 34$)	P value
Age, years	35 (28–49)	36 (28.25–46.75)	44 (28.50–53.50)	31.5 (26–42.5)	0.193
Female, *n* (%)	59 (49.6)	23 (44.2)	20 (60.6)	16 (47.1)	0.345
MAP, mm Hg	105 ± 13.12	102.41 ± 12.65	103.81 ± 12.59	108.98 ± 13.67	0.115
BMI, kg/m2	23.05 (20.78–25.21)	22.48 (20.68–25.0)	23.05 (20.74–25.03)	23.68 (21.75–26.35)	0.387
Urinary protein, g/24 h	3.51 (2.5–4.55)	2.42 (2.14–2.78)	4.55 (3.72–5.41)[a]	4.08 (3.64–5.02)[a]	<0.001
Scr, μmol/L	123 (96–171)	112 (93.25–149)	123 (89.2–191.25)	134 (106–245.5)	0.182
eGFR, mL/min/1.73 m2	55.69 (35.10–76.85)	59.4 (48.2–76.81)	50.2 (30.16–83.41)	52.09 (25.45–75.28)	0.227
Urine red blood cells, counts/μL	52 (14–149.92)	44.5 (11–149)[b]	113 (38–359)	37.5 (7.22–81.5)[b]	0.008
TC, mmol/L	5.34 (4.5–6.2)	4.88 (4.16–6.15)[b]	5.8 (5.31–6.97)	5.15 (4.49–5.93)[b]	0.019
Tg, mmol/L	1.89 (1.28–2.58)	1.89 (1.13–2.56)	1.65 (0.98–2.20)	1.96 (1.53–2.78)	0.241
ALB, g/L	34.3 (29.2–38.3)	37.2 (32.5–41.7)[b]	28 (25–29.5)	36.5 (33.95–38.42)[b]	<0.001
α2-MG	6.6 (2.66–9.16)	4.84 (2.6–9.16)[b]	9.16 (6.07–10.65)	4.11 (2.43–9.16)[b]	0.002
UPCR, g/g (6 months)	1 (0.5–2)	0.68 (0.3–1)	1.87 (1.00–3.00)[a]	1.73 (0.84–2.19)[a]	<0.001
UPCR, g/g (Last follow-up)	0.91 (0.31–2)	0.5 (0.23–1)	1 (0.5–2)[a]	1.33 (0.35–3)[a]	0.003
SR, *n* (%)	84 (70.6)	41 (78.8)	21 (63.6)	22 (64.7)	0.252
Oxford classification, *n* (%)					
M1	119 (100)	52 (100)	33 (100)	34 (100)	/
E1	41 (34.5)	13 (25)[b]	20 (60.6)	8 (23.5)[b]	0.003
S1	85 (71.4)	33 (63.5)	26 (78.8)	26 (76.5)	0.266
T0/T1/T2	34(28.6)/56(47.1)/29(24.4)	18(34.6)/28(53.8)/6(11.5)	8(23.5)/16(35.3)/9(27.3)	8/(24.2)12(35.3)/14(41.2)	0.072
C0/C1/C2	39(32.8)/64(53.8)/16(13.4)	17 (32.7)/32 (61.5)/3(5.8)	10 (30.3)/15(45.5)/8 (24.2)	12(35.3)/17(50)/5(14.7)	0.227
FPE, *n* (%)					<0.001
SFPE	64 (53.8)	33 (63.5)	15 (45.5)	16 (47.1)	
MFPE	28 (23.5)	11 (21.2)	3 (9.1)	14 (41.2)	
DFPE	27 (22.7)	8 (15.4)	15 (45.5)	4 (11.8)	
With immunosuppression	90 (75.6)	42 (80.8)	33 (100)	27 (79.4)	0.019
With RASi	102 (85.7)	44 (84.6)	25 (75.8)	21 (61.8)	0.106

OP, overt proteinuria; NS, nephrotic syndrome; NRP: nephrotic range proteinuria; FPE: foot process effacement; SFPE, segmental FPE; MFPE, moderate FPE; DFPE: diffuse FPE; TC, Cholesterol; Tg, triglyceride; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; α2-MG:α2-macroglobulin of urine; RASi, renin-angiotensin system inhibitors. a Compared to OP group, $p < 0.05$. b Compared to NS group, $p < 0.05$.

Table 2. Baseline subgroup characteristics.

Variable	SFPE group ($n = 64$)	MFPE group ($n = 28$)	DFPE group ($n = 27$)	P value
Age, years	36 (28.25–49)	32.5 (26.75–43.75)	36 (26–53)	0.744
MAP, mm Hg	105.53 ± 14.38	107.16 ± 12.41	100.42 ± 9.76	0.145
Urinary protein, g/24 h	3.15 (2.26–4.32)	3.51 (2.74–4.76)	3.65 (2.85–4.9)	0.078
BMI, kg/m2	23.11 (21.11–25.63)	24.07 (20.65–27.31)	21.64 (19.1–24)[b]	0.037
Scr, μmol/L	112 (93–162.75)	119 (95.95–156.25)	165 (104–196)	0.243
eGFR, mL/min/1.73 m2	57.79 (43.00–79.18)	63.34 (43.08–77.51)	43.15 (28.44–74.19)	0.109
ALB, g/L	34.55 ± 6.74[b]	36.35 ± 5.30	31.20 ± 6.92[b]	0.013
OP/NS/NRP, *n* (%)	33 (51.6)/15 (23.4)/16 (25)	11 (39.3)/3 (10.7)/14 (50)	8 (29.6)/15 (55.6)/4 (14.8)[a,b]	<0.001
SR, *n* (%)	43 (67.2)	21 (75)	20 (74.1)	0.678
Oxford classification, *n* (%)				
M1	1	1	1	1
E1	20 (31.3)[b]	6 (21.4)	15 (55.6)[b]	0.019
S1	44 (68.8)	20 (71.4)	21 (77.8)	0.711
T0/T1/T2	21 (32.8)/30 (46.9)/13 (20.3)	8 (28.6)/9 (32.1)/11 (39.3)	5 (18.5)/17 (63)/5 (18.5)	0.112
C0/C1/C2	22 (34.4)/38 (59.4)/4 (6.3)	10 (35.7)/14 (50)/4 (14.3)	7 (25.9)/12 (44.4)/8 (29.6)	0.073
With immunosuppression	52 (81.3)	24 (85.7)	26 (96.3)	0.193
With RASi	49 (76.6)	19 (67.9)	22 (81.5)	0.51

FPE: foot process effacement; SFPE: segmental FPE; MFPE: moderate FPE; DFPE: diffuse FPE; SR: Short-term remission.
[a]Compared to SFPE group; [b]Compared to MFPE group, $p < 0.05$.

proportion of DFPE (45.5% vs. 11.8%) and a lower proportion of MFPE (9.1% vs. 41.2%) than the NRP group. All NS groups were treated with immunosuppression.

To further explore the role of FPE in IgAN, the clinicopathological features based on the severity of FPE are shown in Table 2. Compared with the SFPE and MFPE groups, the DFPE group had a higher proportion of E1 (55.6% vs. 32.3% vs. 18.5%). Compared with the DFPE group, patients in the MFPE group had an increased BMI [24.07 (20.65–27.31) vs. 21.64 (19.1–24)]. In terms of T and C, although the difference was not statistically significant, MFPE had a higher proportion of T2 (39.3% vs. 18.5%) and a lower proportion of C2 (14.3% vs. 29.6%) than DFPE. In terms of immunofluorescence, the patients in the DFPE group had a higher degree of mesangial IgM (2+) deposition (33.3% vs. 7.1%, 9.4%, $p = 0.031$) (Table 3).

Short-term outcomes and long-term prognosis

The Kaplan–Meier survival curve (Figure 2) showed that in the overall cohort and among patients receiving

Table 3. Immunofluorescent findings according to the severity of FPE.

Variable	SFPE group ($n = 64$)	MFPE group ($n = 28$)	DFPE group ($n = 27$)	P value
IgA				0.936
2+	9 (14.1)	3 (10.7)	3 (11.1)	
3+	56 (85.9)	24 (89.3)	24 (88.9)	
IgG				0.608
–	62 (96.9)	26 (96.4)	26 (96.3)	
+	2 (3.1)	0	1 (3.7)	
2+	0	1 (3.6)	0	
IgM				0.031
–	34 (53.1)	18 (64.3)	7 (25.9)*	
+	19 (29.7)	7 (25)	8 (29.6)	
2+	6 (9.4)	2 (7.1)	9 (33.3)*	
3+	5 (7.8)	1 (3.6)	3 (11.1)	
C3				0.754
–	5 (7.8)	1 (3.6)	1 (3.7)	
+	8 (12.5)	2 (7.1)	4 (14.8)	
2+	15 (23.4)	6 (21.4)	3 (11.1)	
3+	36 (56.3)	19 (67.9)	9 (70.4)	
C1q				0.17
–	56 (87.5)	26 (92.9)	19 (70.4)	
+	6 (9.4)	2 (7.1)	6 (22.2)	
2+	2 (3.1)	0	2 (7.4)	

*$p < 0.05$ compared to the MFPE group.

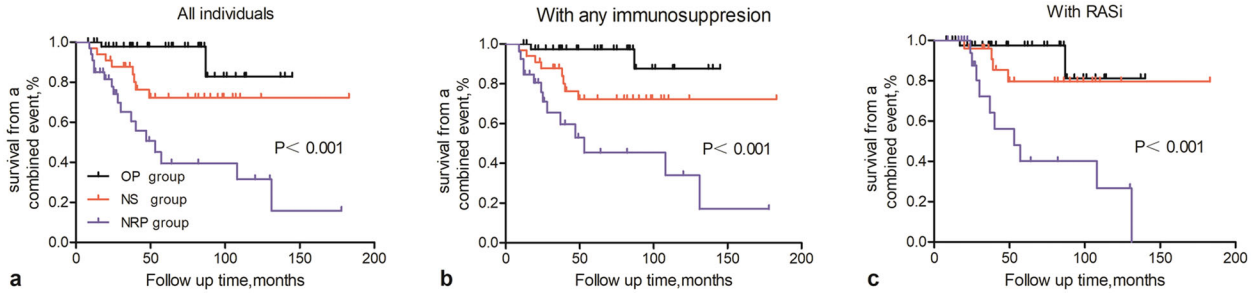

Figure 2. Kaplan-Meier curve of the survival from a combined event for patients in each group: (a) all patients ($P_{NRP\ vs\ NS} = 0.012$, $P_{NS\ vs\ OP} = 0.039$, $P_{NRP\ vs\ OP} < 0.001$), (b) patients receiving immunosuppression ($P_{NRP\ vs\ NS} = 0.027$, $P_{NS\ vs\ OP} = 0.033$, $P_{NRP\ vs\ OP} < 0.001$), (c) and those receiving RASi ($P_{NRP\ vs\ NS} = 0.007$, $P_{NS\ vs\ OP} = 0.375$, $P_{NRP\ vs\ OP} < 0.001$).

immunosuppressants and RASis, the cumulative renal survival in the NRP group was significantly lower than that in the other two groups, with significant differences among the three groups ($p < 0.001$).

Further analysis of the use of different treatments revealed that there were no statistically significant differences in long-term prognosis between patients treated with and without immunosuppression (Figure 3). Patients treated with RASi had a better long-term prognosis than those not treated with RASi in the overall cohort, and patients treated with RASi had a lower incidence of composite endpoints in the NS group; however, the difference was not statistically significant ($p = 0.055$) (Figure 4).

SR had different effects on long-term prognosis in the two clinical phenotype groups (Figure 5). All patients were treated with immunosuppression in the NS group, and patients who achieved SR had better long-term prognosis than those who exhibited NR; however, SR was not associated with long-term renal outcome in patients treated with RASi in the NS group. In the NRP group, achievement of SR was associated with a better long-term prognosis in patients treated with RASi than NR, but there was no association with long-term renal outcome in patients treated with immunosuppression. In addition, our data show that in the NS group, patients with SR had a lower Scr (105 (79–142) vs. 197.5 (125.25–250.5), $p = 0.002$), higher urine RBC count (130 (85.5–421) vs. 47 (23.5–262.25), $p = 0.043$), and lower proportion of C0 (C0/C1/C2: 3/11/7 vs. 7/4/1, $p = 0.024$) than the patients with NR, but there were no significant differences in urine protein, blood pressure, ALB and FPE between the two groups (see Supplementary Material, Table S1).

The severity of FPE had different effects on prognosis in the two clinical phenotype groups (Figure 6). The FPE group had a better long-term prognosis in NRP with T0/1, but there was no significant difference in NS-IgAN. Stratified Cox regression models were used to compare the prognosis of the two groups in each subgroup. The NRP group had a better prognosis in those

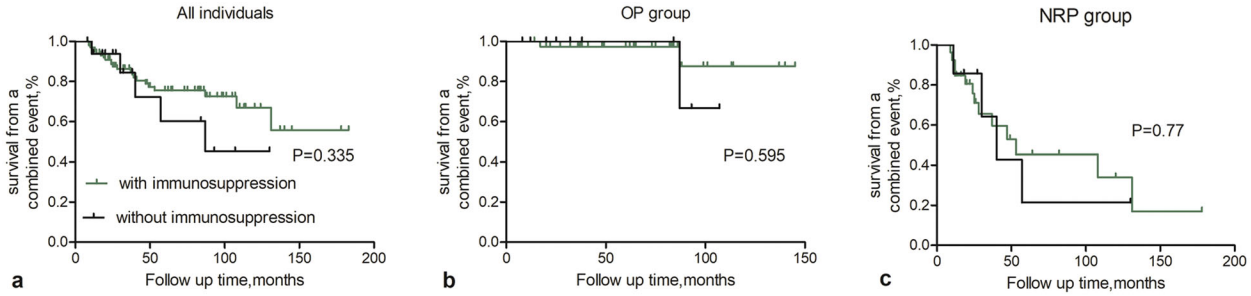

Figure 3. Kaplan-Meier curve of the survival from a combined event for patients whether or not use immunosuppression in each group: (a) all patients, (b) patients in the OP group, (c) patients in the NRP group.

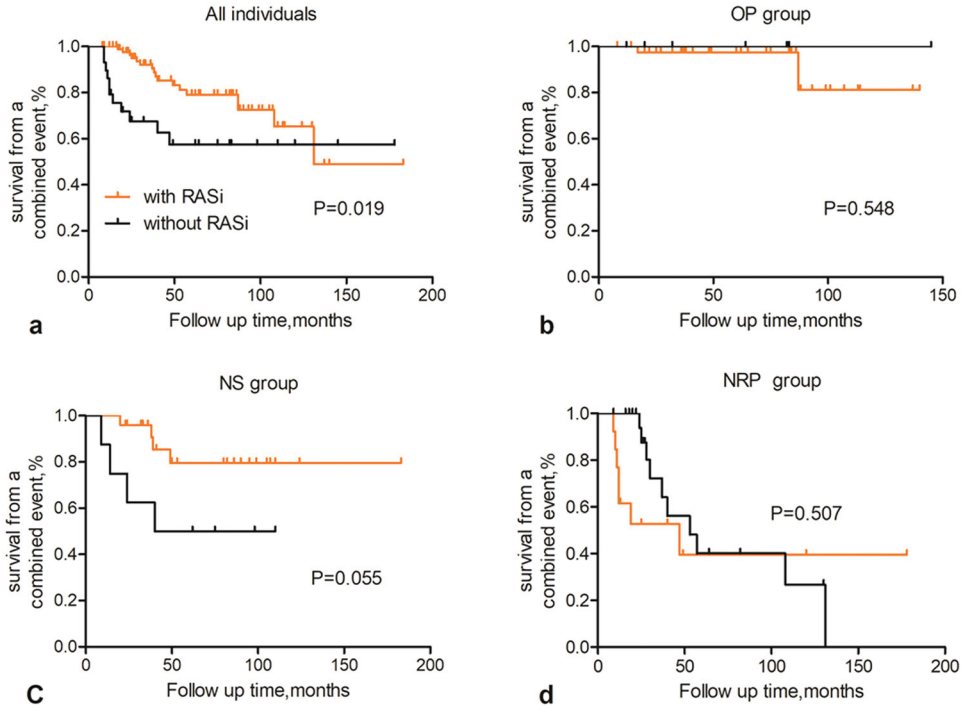

Figure 4. Kaplan-Meier curve of the survival from a combined event for patients whether or not to use RASi in each group: (a) all patients, (b) patients in the OP group, (c) patients in the NS group, (d) patients in the NRP group.

with MAP >100 mm Hg, BMI >23 kg/m^2, absence of T2 and C2 than the NS group (Figure 7).

Factors related to the renal endpoint

Univariate Cox regression identified NRP, NS, Scr, proteinuria, and T2 as risk factors (Table 4). The multivariate Cox regression model (Model 1) further verified that NRP (HR = 17.098, 95% CI 3.835–76.224; $p < 0.001$), NS (HR = 7.949, 95% CI 1.299–48.658; $p = 0.025$), Scr (HR = 1.018, 95% CI 1.01–1.026; $p < 0.001$), and T2 (HR = 4.868, 95% CI 1.669–14.199; $p = 0.004$) were independent risk factors for the renal endpoint, while MFPE was a protective factor. After the addition of a RASi (Model 3), the incidence of a combined event for MFPE was further reduced (HR = 0.179, 95% CI = 0.047–0.689; $p = 0.012$).

Discussion

IgAN is a chronic progressive glomerular disease, and the clinical phenotype is related to pathology and can indicate the necessary treatment. It is impossible for each patient to have a repeated renal puncture at any time. Therefore, it is necessary to study different clinical phenotypes and compare their pathology to provide evidence for individualized treatment. NS and NRP are two different clinical phenotypes in IgAN. Most previous studies only compared NS and non-NS, which involved a subset of patients with MCD-like features and mild proteinuria [3,5], but no study has explored the difference between NS and NRP. Our study demonstrated that IgAN with massive proteinuria was associated with more severe clinical and pathological manifestations, and the prognosis was worse. Compared with the NRP

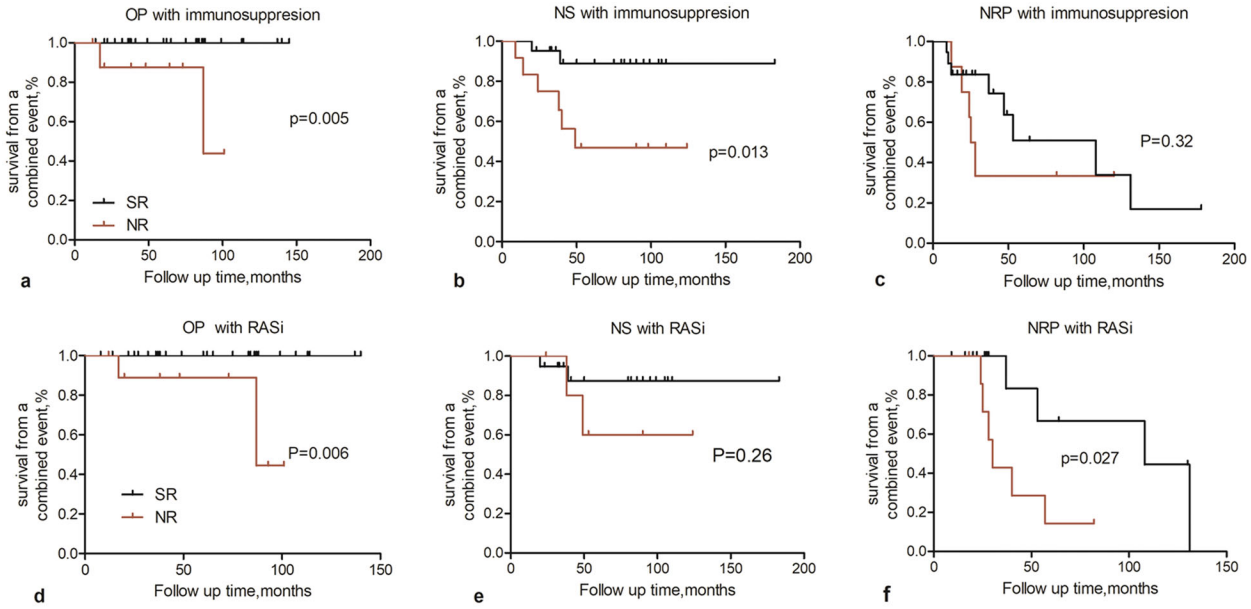

Figure 5. Kaplan-Meier curve of the survival from a combined event for patients whether or not reach SR in each group: (a) patients with immunosuppression in OP group, (b) patients with immunosuppression in NS group, (c) patients received with immunosuppression in NRP group, (d) patients with RASi in OP group, (e) patients with RASi in NRP group, (f) patients with RASi in NRP group.

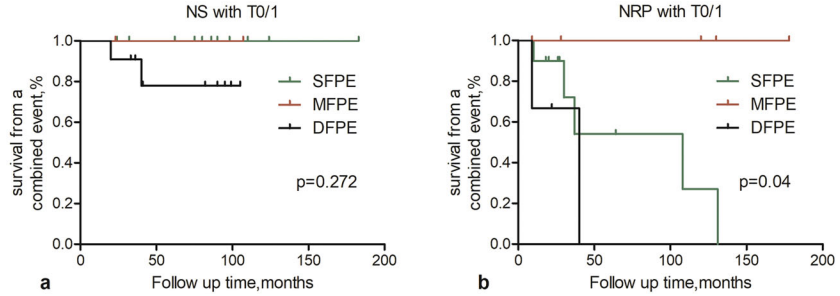

Figure 6. Kaplan-Meier curve of the survival from a combined event for severity of FPE in each group (a) NS with T0/1 ($P_{SFPE\ vs\ DFPE} = 0.131$, $P_{MFPE\ vs\ DFPE} = 0.569$), (b) patients in the NRP with T0/1 ($P_{MFPE\ vs\ SFPE} = 0.043$, $P_{MFPE\ vs\ DFPE} = 0.034$, $P_{SFPE\ vs\ DFPE} = 0.271$).

group, the NS group had higher urine red blood cells, lower ALB and a higher proportion of E1. Although there was no significant difference, the proportion of T2 was higher and the proportion of C2 was lower in the NRP group. The results suggest that NS in patients with IgAN is always associated with active acute lesions in renal pathology. Moriyama T et al. also reached the same conclusion [16]. As observed previously, the presence of hypoalbuminemia is associated with acute and severe lesions in renal pathology. On the other hand, NRP reflects chronic lesions, the course of the disease is usually relatively long and accompanied by activation of renin-angiotensin system (RAS). Which forced proteinuria to leak, but the protein loss was chiefly other proteins rather than albumin [17]. So NRP results from a chronic course and may show a normal range of serum albumin.

Several repeat biopsy studies [18–20] have consistently shown the reversal of active lesions (M, E, C) following immunosuppressive therapy or progression to chronic lesions. Therefore, we hypothesized that NRP and NS are two different states that may be interchangeable. Immunosuppressive therapy may restore the active lesions of NS-IgAN, but if immunosuppressive therapy is not administered in a timely manner, the active lesions may progress to chronic disease with NRP; NRP may also transform into NS if severe and acute lesions occur again in the presence of chronic lesions. Therefore, the ratio of active to chronic lesions needs to be further studied in the future.

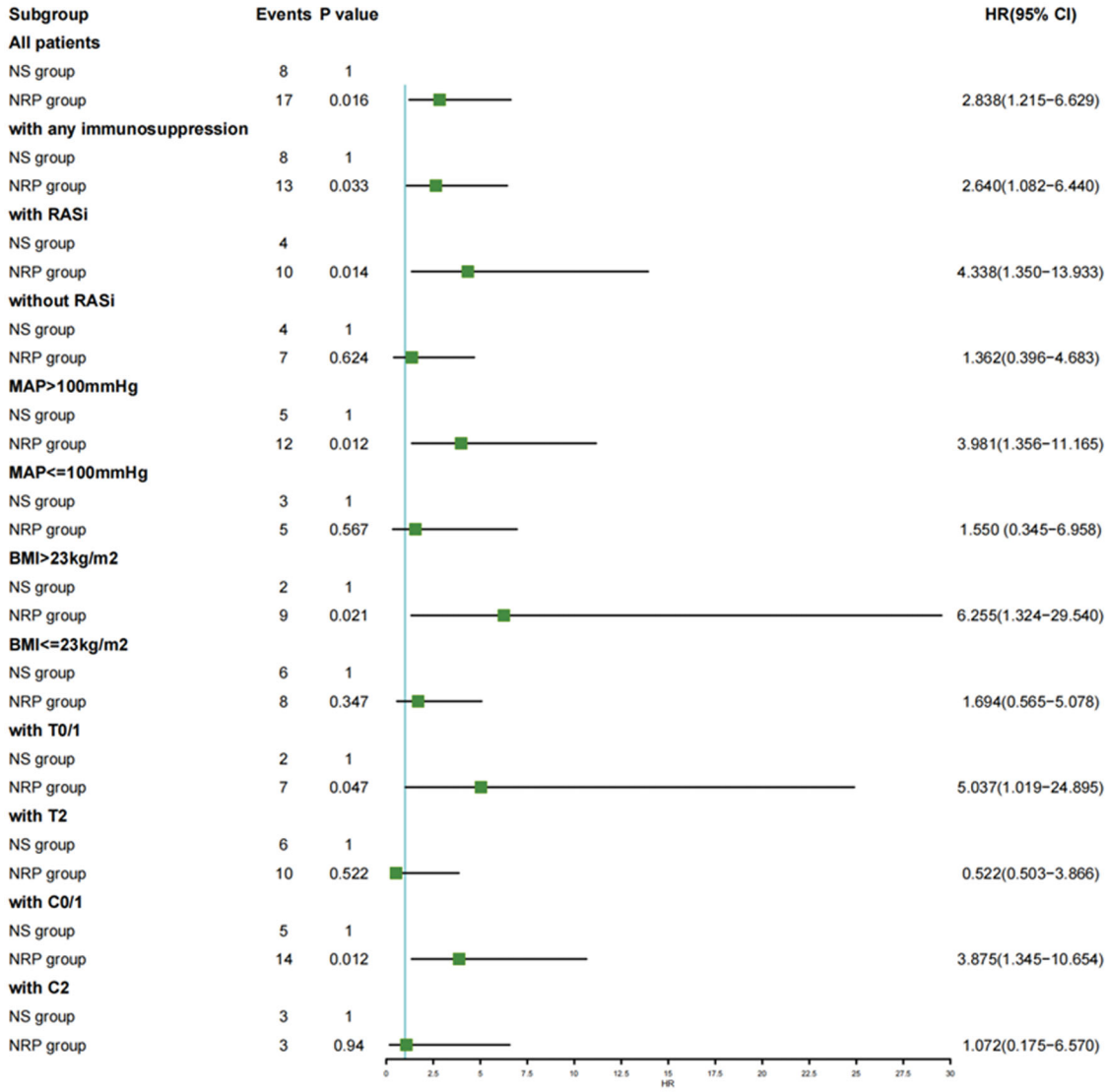

Figure 7. Stratified Cox regression models were used to compare the prognosis of two groups in each subgroup.

Regarding treatment, the role of RASi in IgAN is well established, and the KDIGO guidelines suggest that ACEI/ARB should be used in all patients with proteinuria persisting above 0.5 g/d. Stop-IgAN showed that immunosuppressive therapy reduced proteinuria, but no additional benefit was observed at either 3 years or up to 10 years of follow-up [21,22]. This is consistent with our findings that immunosuppressive therapy did not improve long-term renal outcomes in patients with significant proteinuria, although proteinuria was reduced during the follow-up.

In addition, a meta-analysis of 11 randomized trials showed that early reduction of proteinuria was associated with a lower clinical risk [23], and more research supports the use of proteinuria reduction as a reasonably likely surrogate endpoint for a treatment's effect on progression in IgAN [24]. In our study, all patients were treated with immunosuppressive therapy in the NS group, and patients who achieved an early reduction in proteinuria had a better renal function, more severe hematuria, a higher proportion of crescents, and a better long-term prognosis, which is consistent with the results of previous studies [3,5]. However, in NRP-IgAN, achieving an early reduction in proteinuria was associated with a better long-term prognosis in NRP with RASi but was not associated with long-term prognosis in patients with immunosuppression. Combined with the previous results, steroids and immunosuppressive drugs may be effective in the NS group because these cases showed active lesions and are in the acute phase. On the other hand, ACEi has renoprotective effects by reducing glomerular hyperfiltration and urinary protein excretion. Therefore, these drugs are probably more suitable for patients with advanced IgAN

Table 4. Multivariate determinants of survival from a combined event.

	Univariable		Model 1		Model 2		Model 3	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years	0.993 (0.962–1.025)	0.659						
Female, %	1.240 (0.588–2.614)	0.572						
MAP, mm Hg	1.023 (0.994–1.053)	0.120	1.011 (0.969–1.055)	0.621	1.020 (0.976–1.067)	0.373	1.009 (0.966–1.054)	0.694
Urinary protein, g/24 h	1.233 (1.042–1.436)	0.014	0.866 (0.667–1.123)	0.277	0.840 (0.645–1.094)	0.196	0.861 (0.663–1.118)	0.261
Urine red blood cells, counts/μL	0.997 (0.993–1.001)	0.109	0.994 (0.988–1.001)	0.073	0.994 (0.988–1.000)	0.063	0.994 (0.987–1.001)	0.073
Scr, μmol/L	1.019 (1.014–1.025)	<0.001	1.018 (1.01–1.026)	<0.001	1.018 (1.009–1.026)	<0.001	1.018 (1.010–1.026)	<0.001
E1, %	0.77 (0.352–1.684)	0.513						
S1, %	1.529 (0.523–4.467)	0.438						
T0 + T1, %	Reference		Reference		Reference		Reference	
T2, %	35.08 (3.565–269.58)	0.001	4.868 (1.669–14.199)	0.004	4.544 (1.555–13.282)	0.006	4.847 (1.676–14.019)	0.004
C0, %	Reference		Reference		Reference		Reference	
C1, %	0.965 (0.412–2.262)	0.935	1.779 (0.558–5.678)	0.330	1.700 (0.508–5.688)	0.389	1.876 (0.569–6.184)	0.301
C2, %	2.116 (0.745–6.015)	0.159	2.266 (0.628–8.173)	0.211	2.181 (0.604–7.880)	0.234	2.564 (0.609–10.792)	0.199
SFPE, %	Reference		Reference		Reference		Reference	
MFPE, %	0.837 (0.306–2.289)	0.728	0.260 (0.078–0.864)	0.028	0.179 (0.047–0.689)	0.012	0.274 (0.082–0.922)	0.037
DFPE, %	1.012 (0.416–2.464)	0.979	0.977 (0.262–3.639)	0.973	0.982 (0.253–3.815)	0.979	0.916 (0.236–3.551)	0.898
OP group	Reference		Reference		Reference		Reference	
NS group	3.886 (1.025–14.586)	0.046	7.949 (1.299–48.658)	0.025	7.370 (1.208–44.956)	0.030	8.657 (1.334–55.771)	0.023
NRP group	11.315 (3.305–38.73)	<0.001	17.098 (3.835–76.224)	<0.001	15.270 (3.423–68.123)	<0.001	16.378 (3.636–73.779)	<0.001
RASi	0.414 (0.193–0.886)	0.023			0.449 (0.152–1.324)	0.147		
Immunosuppression	0.623 (0.236–1.648)	0.341					0.779 (0.219–2.764)	0.669

OP, overt proteinuria; NS, nephrotic syndrome; NRP: nephrotic range proteinuria; FPE: foot process effacement; SFPE, segmental FPE; MFPE, moderate FPE; DFPE: diffuse FPE; RASi: renin-angiotensin system inhibitors.

who show marked glomerular hyperfiltration due to a reduction in the number of nephrons by glomerulosclerosis, than for patients with acute phase and active lesions [25]. NRP with glomerular hypertension and hyperfiltration is occurred due to chronic course. So, NRP is less likely to respond to immunosuppressive drugs and rather RASi may be effective. However, in severe cases of NRP, due to the small number of residual glomeruli, it is necessary to rely on the contraction of efferent arteriole to maintain glomerular hypertension and hyperfiltration to compensate [26]. ACEi may significantly worsen renal function. So, RASi may be effective in mild cases of NRP.

One important finding in our study was that NS-IgAN had a higher proportion of DFPE and NRP-IgAN had a higher proportion of MFPE. Further exploration revealed that DFPE patients had a higher BMI, a higher proportion of E1 and a higher degree of mesangial IgM deposition. Katafuchi et al. [27] found that IgM deposition showed a significant association with crescent and mesangial hypercellularity, as well as that it may occur in the early stage of inflammation and remains until the late sclerotic stage. Previous studies suggested that Obesity-Related Glomerulopathy is a type of obese kidney injury, and glomerular hyperfiltration induces compensatory hypertrophy and reorganization of the cytoskeleton, which can lead to focal segmental glomerulosclerosis (FSGS) [28]. We speculate that the mechanisms of NS and NRP in IgAN are different; NS suggests more active lesions, and activation of intrinsic proinflammatory signaling in podocytes, such as the NF-κB signaling pathway, aggravates podocyte injury [29]. Thus, FPE is secondary to an inflammatory response dominated by hyperplasia. NRP results in more chronic lesions and activation of the RAS, and podocytes are particularly sensitive to glomerular hyperfiltration, which directly causes mechanical damage to podocytes. In addition, activation of RAS directly leads to increased angiotensin II (Ang II) levels, and Ang II signaling mediates podocyte injury through the following aspects: directly inducing podocyte apoptosis [30,31]; decreasing the expression of zonula occludens (ZO)-1 and nephrin (main proteins of SD) to result in foot process injury [32]; and upregulating the expression of $p27^{Kip1}$ protein to cause cell phenotypic transformation and hypertrophy [33].

Previous studies have proven that FPE is associated with renal function but have not yet found an influence on prognosis [34]. Our study revealed that MFPE indicates a better prognosis in NRP without obvious chronic renal lesions. In a multivariate model, the incidence of a combined event for MFPE was further reduced after the addition of RASi. This may be due to the mechanisms of podocyte injury described above. In the absence of severe chronic disease, patients with NRP have compensatory dilatation of podocytes. ACEI/ARB can reduce glomerular perfusion pressure, improve glomerular hemodynamics, reduce mechanical damage of podocytes by blocking the RAS and directly inhibit the expression of AngII to block signaling pathways

that mediate podocyte injury. In addition, REIN and AASK studies showed that the higher the urinary protein level, the more significantly ACEI delayed the deterioration of renal function in CKD [32,33]. RASi can reduce proteinuria and protect renal function by regulating blood pressure and improving local hemodynamics in NRP; however, in patients with NS-IgAN with active lesions, the degree of FPE has little significance for treatment and prognosis. It is important to emphasize that MFPE was associated with good prognosis in the absence of obvious chronic disease. This also explains why the prognosis was worse in the NRP group than in the NS group even though the NRP group had a higher ratio of MFPE.

Several limitations should be considered when interpreting our study. First, this study was a retrospective study, and the proportion of patients with massive proteinuria in IgAN was small. Thus, the sample size included in our study was limited, and no role of FPE in chronic disease was observed. Second, due to the lack of transmission electron microscopy data, there are limited indicators of podocyte injury that could be observed, such as the width of the foot process and the number of podocytes. In the future, the sample size should be further expanded to explore more podocyte lesions.

Conclusion

In this study, we found that NS presents more active lesions and more severe FPE in IgAN. NRP was an independent risk factor for the progression to the renal endpoint, while MFPE indicated a better prognosis in NRP without obvious chronic renal lesions. This finding may be related to the compensation of intact nephrons, which is also the reason for the benefit of RASi.

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Ethics statement

This study complies with the principles of the Helsinki Declaration and was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (YE2021-326). Informed consent was exempted since the study only involved an analysis of anonymized existing data and records.

Author contributions

Research idea, study design, article writing, and guidance on revision: CZ; Data analysis, article writing, revision and submission: YC and AY; data collection, collation, and summary: HS, LL, JH, XH, JL, and SJ; medical records and renal biopsy specimens: XL, FL, QL, and LX; pathological diagnosis: HY and SY.

Disclosure statement

The authors report there are no competing interests to declare.

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Data availability statement

The data used to support the findings of this study are restricted by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine to protect patient privacy. Data are available from Guangdong Provincial Hospital of Chinese Medicine for researchers who meet the criteria for access to the data.

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