Original Paper

Clinicopathological Features to Predict Progression of IgA Nephropathy with Mild Proteinuria

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Key Words

IgA nephropathy • Mild proteinuria • Clinicopathological • Progression

Abstract

Background/Aims: In the past, little attention has been paid to patients with IgA nephropathy (IgAN) who had minimal proteinuria upon the onset. The aim of this study was to analyze the clinicopathological features and the prognostic factors in patients with IgA nephropathy.

Methods: Data of patients that had their first renal biopsy in our hospital and were diagnosed with primary IgAN with proteinuria <1 g/d from January 1995 to December 2014 were retrospectively examined. Clinical records of the clinicopathological features, renal function, and proteinuria were collected and investigated. The factors affecting the renal function and proteinuria were analyzed by Cox regression. The predictive efficiencies of clinical and pathological models were evaluated by Harrell concordance index (C-index). **Results:** A total of 506 patients with IgA nephropathy were included in this study. (1) Baseline proteinuria greater than 0.5 g/d was positively associated with Oxford M, S, and T lesions. eGFR less than 90 mL/min/1.73 m² were positively associated with Oxford T. (2) In the follow-up with a median of 50 months, 82 patients (16.2%) achieved complete clinical remission (CCR), whereas 54 patients (10.6%) showed an increase in creatinine by more than 50% (not progressing to end-stage renal disease). The cumulative proportion of creatinine increased >50%, and the values obtained by life-table analysis in 10, 15, and 20 years were 15%, 21%, and 22%, respectively. Significant differences were found in baseline age, proteinuria, and Oxford T between the group of creatinine increase >50% and the CCR group. (4) Multivariate COX regression showed that baseline age and proteinuria > 0.5 g/d were independent risk factors of adverse outcome. C-index suggested that the clinical model was more effective than the pathological

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models in predicting endpoint events. (5) Effect of the mean value during the follow-up on adverse endpoint events: Multivariate COX regression found that the mean proteinuria during follow-up was an independent influencing factor for the increase of creatinine by more than 50%. **Conclusion:** (1) Proteinuria > 0.5g/d and eGFR < 90 mL/min/1.73 m² may predict more severe pathological changes; (2) With the increase in age and baseline proteinuria, the risks of adverse endpoint events would increase significantly; (3) Pathology could roughly predict the adverse endpoint events but is less efficient than the clinical indicators; (4) Data during follow-up suggested that the patients should regularly test their renal function and proactively control their proteinuria.

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Introduction

IgAN is currently considered a chronic progressive disease, and more than 50% of the cases progress despite the active treatment applied [1]. Among them, approximately 20%–40% of the patients progress to end-stage renal disease (ESRD) [2, 3]. Pathological changes, including mesangial hypercellularity (M), endocapillary proliferation (E), segmental sclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescent (C), are considered independent risk factors for progression of IgAN to ESRD [4–7]. However, these results are obtained mainly in IgAN patients with urinary protein > 1 g/d. In the past, IgAN patients with proteinuria < 1 g/d were believed to have slowly progressing conditions and good prognosis [8]. Studies in Asia revealed that 7%–24% of the IgAN patients with mild proteinuria, normal renal function, and normal blood pressure progressed to renal dysfunction [9–11]. Therefore, it is important to understand the prognosis of these patients and determine the factors that lead to disease progression. This study analyzed the clinical and pathological features of IgAN patients with urinary protein level < 1 g/d and eGFR ≥ 60 mL/min/1.73 m², as well as the influencing factors for adverse renal outcomes, to provide the basis for the clinical identification of the patients with a tendency to disease progression.

Materials and Methods

Subjects

Patients that had their first renal biopsy and had been diagnosed with IgAN during their hospitalization in PLA General Hospital (Beijing, China) from January 1995 to December 2014 were included in this study. The following inclusion criteria were used: (1) 18 years of age or older, male or female; (2) 24-h urinary protein quantification at least twice before renal biopsy and urinary protein level < 1 g/d; (3) eGFR ≥ 60 mL/min/1.73 m² before the renal biopsy; (4) Number of glomeruli ≥ 8 in PAS staining of renal biopsies; (5) Not treated with corticosteroids and/or immunosuppressive agents before the renal biopsy; (6) Followed up for at least 12 months after the renal biopsy. The exclusion criteria were as follows: (1) IgAN secondary to Henoch-Schönlein purpura (HSP), rheumatoid arthritis, hepatitis B virus-associated glomerulonephritis and cirrhosis; (2) combined with other kidney diseases, such as diabetic nephropathy, interstitial nephritis, etc.; (3) combined with systemic diseases that affect the pathological manifestations and prognosis of IgAN, such as diabetes, autoimmune diseases, active tuberculosis, malignant tumor, and severe infection.

Methods

All included medical records were reviewed. The clinical and pathological data before the renal biopsy, age at the renal biopsy, sex, and latency from the onset of the disease to time of the renal biopsy were collected. The following clinical indicators were used in the evaluation: clinical diagnosis, presence of macroscopic hematuria, presence of hypertension, blood pressure, and treatment before the renal biopsy [12]; clinical indices before the diagnosis included urine routine, 24-hour urine protein, serum creatinine, serum albumin, total cholesterol, and triglyceride. eGFR was calculated using the CKD-EPI formula for Asians [13]. Pathology was evaluated according to the Oxford classification [14].

Table 1. Baseline characteristics

Characteristics	Number	Mean ±SD
Age	34.71	± 9.46
Male (%)	276	(54.5)
Hypertension (%)	166	(32.8)
Systolic pressure (mmHg)	123.52	± 15.75
Diastolic pressure (mmHg)	79.68	± 11.83
Mean arterial pressure (mmHg)	94.3	± 12.4
Proteinuria (g/d)	0.56	± 0.26
Proteinuria <0.5g/d	214	(42.3)
Serum creatinine (umol/l)	77.99	± 18.50
CKD stage I/ II	362	/144
eGFR (mL/min/1.73 m ²)	102.12	± 19.82
Albumin (G/L)	41.42	± 3.63
Cholesterol (mmol/L)	4.39	± 0.89
Triglyceride (mmol/L)	1.58	± 1.05
ACEI/ARB (%)	404	(79.8)
Steroids (%)	69	(13.6)
Oxford Classification		
M0	351	(69.4%)
M1	155	(30.6%)
E0	480	(94.9%)
E1	26	(5.1%)
S0	154	(30.4%)
S1	352	(69.6%)
T0	423	(83.6%)
T1	75	(14.8%)
T2	8	(1.6%)
C0	413	(81.6%)
C1	93	(18.4%)

For presentation and definition of the data after the renal biopsy, time-averaged values were used to represent the blood pressure and proteinuria during the follow-up, namely, time-averaged mean arterial pressure (TA-MAP), and time-averaged urinary protein (TA-P). All time-dependent parameters were calculated as time-averaged values based on a trapezoidal rule [15]. The area under the curve formed by the repeated measurements at every visit was divided by the elapsed time up to the end of the follow-up period, yielding a single time-averaged value for a time-dependent parameter. In addition, TA-MAP was similarly calculated.

The events that were observed after the renal biopsy were as follows: (1) Complete clinical remission (CCR): 24-hour urinary protein stabilized at less than 0.2 g/d, absence of blood, normal renal function, and normal blood pressure in at least three urinary routines; (2) Serum creatinine increased by more than 50% from baseline; (3) ESRD: eGFR < 15 mL/min/1.73 m² or receiving long-term dialysis or kidney transplantation. The cumulative proportion of endpoint events in 10, 15, and 20 years was calculated by life-table analysis.

Results

Baseline clinical indices

A total of 506 patients with IgAN met the inclusion criteria during the period 1995–2014 period and were enrolled in the study (Table 1). Males accounted for 54.5% of the subjects (276 cases).; Average age at renal biopsy was 34.7 ± 9.46 years; Before renal biopsy, 165 patients (32.6%) had a history of gross hematuria, 60 patients (11.8%) had simple proteinuria, and 31 (5.1%) patients had simple hematuria; 167 patients (33.0%) had hypertension, and systolic pressure was (123.52 ± 15.75) mmHg, diastolic pressure was (79.68 ± 11.83) mmHg, and mean arterial pressure was (94.3 ± 12.4) mmHg. Average proteinuria was 0.56 ± 0.26 g/d among these patients. The results of other tests were serum creatinine 77.99 ± 18.5 umol/L, eGFR 102.1 ± 19.82 mL/min/1.73 m², albumin 41.42 ± 3.63 g/L, total cholesterol 4.39 ± 0.89 mmol/L, triglyceride 1.58 ± 1.05 mmol/L, 362 patients (71.5%) were at CKD stage I. 69 patients (13.6%) started on steroids therapy.

Pathology

Oxford classification: For mesangial cell proliferation (M), 155 cases (30.6%) were classified as M1; for endocapillary proliferation (E), 26 cases (5.1%) were classified as E1; for segmental glomerulosclerosis/glomerular adhesions (S), 352 cases (69.6%) were classified as S1; and for tubular atrophy/interstitial fibrosis (T), 76 cases (14.8%) were classified as T1 and eight cases were classified as T2. In assessment of glomerular crescents, 413 of the cases (81.6%) showed no crescents (C0), 93 of the cases (18.4%) showed crescents of C1, and none of the cases showed crescent in over 25% of glomeruli (C2).

Correlation between baseline clinical indices and pathology

Proteinuria greater than 0.5 g/d was positively correlated with Oxford M, S, and T lesions, whereas stage 2 CKD was positively correlated with T lesions (see Table 2).

Outcomes

No patients progressed to ESRD. 54 patients with creatinine increased by greater than 50%. The cumulative proportion of creatinine increased >50% in 10, 15, and 20 years were 15%, 21% and 22%, respectively (see Table 3). Based on the endpoint proteinuria and creatinine during follow-up, all patients were divided into three groups: Complete clinical remission (group1), including 82 patients with proteinuria less than 0.2 g and no increase in creatinine; group 2, including 370 patients with proteinuria greater than 0.2 g and creatinine increased by less than 50%; and group 3, including 54 patients with creatinine increased by greater than 50%.

Baseline Clinicopathological Differences between Patients in the CCR Group and group with creatinine increased > 50%

As for baseline clinicopathological data, compared with creatinine increased > 50% group, the CCR group had smaller age, lower baseline proteinuria, slighter T lesions in Oxford classification; the difference was statistically significant ($P < 0.05$) as shown in Table 4. Neither steroids nor ACEI/ARB was statistically significant between CCR group and creatinine increased > 50% group ($P > 0.05$).

Table 2. Correlation between baseline clinical indices and Oxford classification. ** $P < 0.01$

Baseline clinical indices		M	E	S	T	C
Proteinuria > 0.5 g/d	correlation coefficient	0.118**	0.018	0.121**	0.131**	0.086
	P	0.008	0.685	0.007	0.003	0.053
CKD II	correlation coefficient	-0.020	-0.067	-0.011	0.206**	-0.017
	P	0.653	0.130	0.802	0.000	0.710

Table 3. The cumulative proportion of creatinine increased > 50% in 10, 15, and 20 years by life-table analysis

	10 years	15 years	20 years
Creatinine increased > 50%	15%	21%	22%
Complete clinical remission	23%	28%	32%

Table 4. Baseline Clinicopathological Differences Between Patients in CCR Group and creatinine increased >50% Group

Characteristics	CCR (n = 82)		Creatinine increased >50% (n = 54)		P
Sex (female/male)	46	/36	37/17		0.156
Age	32.65	± 9.23	35.93	±10.37	0.039
Proteinuria (g/d)	0.39	± 0.23	0.60	±0.27	<0.001
Systolic pressure (mmHg)	118.54	± 13.39	122.33	± 14.64	0.148
Diastolic pressure (mmHg)	75.06	± 9.53	77.86	± 11.69	0.094
Mean arterial pressure (mmHg)	89.55	± 9.97	92.68	±12.03	0.092
Serum creatinine (umol/L)	68.65	± 15.54	67.38	±19.17	0.281
eGFR (mL/min/1.73m ²)	113.10	± 16.74	109.17	± 20.42	0.514
Albumin (G/L)	40.92	± 3.49	39.62	± 3.68	0.055
Cholesterol (mmol/L)	4.16	± 0.92	4.42	± 0.78	0.056
Triglyceride (mmol/L)	1.44	± 0.82	1.44	± 0.85	0.981
ACEI/ARB	Yes	24	15		1
	No	58	39		
Steroids	Yes	11	8		0.837
	No	71	46		
Oxford classification					
Oxford M	M0	67	38		0.092
	M1	15	16		
Oxford E	E0	77	52		0.423
	E1	5	2		
Oxford S	S0	33	16		0.14
	S1	49	38		
Oxford T	T0	79	47		0.431
	T1	3	7		
Oxford C	C0	66	42		0.431
	C1	16	12		

Risk factors of creatinine increased > 50% and predictive effect of baseline clinicopathological indicators on patient's outcome

Univariate COX regression [16] indicated that age, baseline proteinuria, Oxford T were the influencing factors of the adverse endpoint event of creatinine increased >50% from baseline. However, multivariate COX regression showed that only age and baseline proteinuria were independent influencing factors of such adverse endpoint event ($P < 0.05$). See Table 5. These results suggested that the baseline pathological indicators might be not as effective in predicting disease progression. By further calculating C-Index, it was found that Oxford classification was less effective than the clinical indicators in predicting the adverse endpoint events for IgAN patients with minor proteinuria (see Table 6).

Correlation Between Adverse Endpoint and Clinical Indicators During Follow-up

The clinical data during follow-up were compared between patients in the CCR group and creatinine increased > 50% group. Results showed that time-averaged blood pressure and time-averaged proteinuria (TA-P) were significantly different between the two groups ($P < 0.001$) as shown in Table 7. Univariate COX regression suggested that the time-averaged mean arterial pressure (TA-MAP), diastolic pressure (TA-DBP), and time-averaged proteinuria (TA-P) were correlated with creatinine increased by greater than 50%. However, multivariate COX regression suggested that only TA-P was an independent risk factor of creatinine increased by greater than 50% (Table 8).

Table 5. Baseline characteristic to predict creatinine increased >50%. HR: Hazard Ratio

Characteristics	univariate COX			multivariate COX		
	HR	95% CI	P	HR	95% CI	P
Sex (male vs female)	0.32	(0.17–0.59)	0.065	0.35	NS	
Age (per decade.)	1.66	(1.14–2.42)	0.009	1.74	(1.25–2.42)	0.001
Hypertension(yes vs no)	1.53	(0.75–3.14)	0.241		NS	
CKD I vs CKD II	0.86	(0.41–1.78)	0.066		NS	
Proteinuria > 0.5 g/d	3.31	(1.07–12.65)	0.039	2.43	(1.36–4.36)	0.003
Cholesterol (mmol/L)	1.49	(0.93–1.51)	0.161		NS	
Triglyceride (mmol/L)	0.75	(0.60–1.49)	0.826		NS	
ACEI/ARB (yes vs no)	0.91	(0.41–2.02)	0.808		NS	
Steroids	1.42	(0.66–3.03)	0.379		NS	
Oxford classification					NS	
M (M1 vs M0)						
E (E1 vs E0)	1.11	(0.52–2.34)	0.789		NS	
S (S1 vs S0)	0.72	(0.1–5.33)	0.752		NS	
(T1 + T2) vs T0	0.80	(0.99–1.67)	0.044		NS	
C1 vs C0	1.67	(0.89–4.07)	0.065		NS	

Table 6. C-index of clinical model, Oxford classification. Clinical model: age + baseline proteinuria >0.5 g/d

	C-index (95% CI)	P (VS Clinical model)
clinical model	0.65 (0.57–0.73) ^a	
Oxford classification	0.58 (0.50–0.66)	0.012

Table 7. Differences of time-averaged clinical data between patients in CCR Group and creatinine increased > 50% Group. TA-P: time-averaged proteinuria; TA-SBP time-averaged systolic pressure; TA-DBP: time-averaged diastolic pressure; TA-MAP: time-averaged mean arterial pressure; CCR: Complete clinical remission

	CCR (n = 82)		Creatinine increased >50% (n = 54)		P
TA-P	0.15	± 0.07	0.68	± 0.37	<0.001
TA-SBP	115.85	± 9.54	123.78	± 11.58	<0.001
TA-DBP	73.37	± 6.95	78.39	± 6.87	<0.001
TA-MAP	87.54	± 7.20	93.51	± 7.91	<0.001

Table 8. Correlations between time averaged clinical indicators and creatinine increased >50%. TA-P: time-averaged proteinuria; TA-SBP time-averaged systolic pressure; TA-DBP: time-averaged diastolic pressure; TA-MAP: time-averaged mean arterial pressure; HR: Hazard Ratio

	Univariate COX			Multivariate COX		
	HR	95% CI	P	HR	95% CI	P
TA-MAP	1.07	(1.03–1.11)	0.001	NS		
TA-SBP	1.05	(0.96–1.15)	0.054	NS		
TA-DBP	1.01	(1.00–1.05)	0.001	NS		
TA-P	8.84	(4.32–18.08)	0.001	6.82	(2.87–16.22)	<0.001

Discussion

Patients with proteinuria less than 1 g/d and eGFR not below 60 mL/min/1.73 m² during the percutaneous renal biopsy were included in this study. We found that the level of baseline proteinuria was correlated with M, T, and S lesions, whereas the level of baseline CKD was correlated with T lesion. This result suggest that the clinical indicators could predict pathology. For patients with proteinuria greater than 0.5 g and eGFR less than 90 mL/min/1.73 m², the pathology might be severe. Therefore, these patients should timely undergo percutaneous renal biopsy for identification of the degree of pathological changes.

After the renal biopsy performed in this study, 79.8% of the patients received ACEI/ARB therapy and had an average systolic pressure of (123.5 ± 15.7) mmHg and average diastolic pressure of (79.6 ± 11.8) mmHg. Therefore, the treatment program in this study was more standardized and closer to the KDIGO guidelines [17] than those of previous studies [8].

The role of steroids in IgA nephropathy (IgAN) is controversial. In our study, 69 patients (13.6%) received steroids therapy, but there was no statistically difference between group 1 and group 3 (Table 4). As can be seen in Table 5, steroids could not be an influencing factor for the increase in creatinine levels by >50%. These results do not support the possibility that steroids therapy may improve the outcomes of IgAN patients with mild proteinuria. The KDIGO [18] guideline support our result, which recommended that steroids therapy should be used only in IgAN patients with proteinuria >1g/d, since there was no powerful evidence to support that steroids could improve outcomes of IgAN patients with mild proteinuria. The STOP-IgAN Trial [19] included 162 IgAN patients with proteinuria >0.75 g/d. The result showed that the rate of endpoints (GFR decrease >30 ml/min per 1.73 m², Onset of ESRD, absolute GFR changes at month 36) did not differ between patients receiving corticosteroid monotherapy and supportive care. However, In patients with proteinuria >1g/d, TESTING trial [20] showed that compare with placebo, methylprednisolone could decrease rate of endpoints(40% eGFR decrease, ESRD) and increase rate of adverse events(infection). Therefore, in patients with mild proteinuria, whether steroids be used or not should be carefully considered.

No case progressed to ESRD, and 54 cases showed an increase of 50% or greater in the levels of creatinine; urinary protein of ≥1 g/d was persistently present in 45 cases (8.8%). The cumulative proportion of creatinine increased by >50% as determined through the life-table analysis, and the values predicted in 10, 15, and 20 years were 15%, 21%, and 22%, respectively. Gutiérrez, et al. [8] reported that during a follow-up with a median value of 108 months in a study with 141 Caucasians, the IgAN patients with mild proteinuria showed good prognosis. Their serum creatinine increased by >50% in five patients (3.5%); the pathological changes were mild, tubulointerstitial injury was rare, and progression to ESRD was not observed. This discrepancy was attributed mainly to the inclusion criteria (baseline proteinuria <0.5 g/d), the small sample size, or the interracial differences. An earlier gene study revealed that the differences between races influence the susceptibility [21, 22] to and progression of IgAN [23-26]. Barbour SJ, et al. [27] analyzed the data of a cohort of 202 IgAN patients of self-reported Pacific-Asian origin and 467 of other origin obtained from the Toronto GN Registry (Toronto, Ontario, Canada) that were followed up for a median of 46.4 months. Their results showed that the individuals of Pacific-Asian origin exhibited a higher risk of eGFR decline, which indicated the racial origin should be considered in risk evaluation.

Age is another important factor for patient outcome. Many literature sources suggest that age is also a prognostic factor; and old age is correlated with poor prognosis [28, 29]. A previous study compared patients of different ages (≥ 50 and <50 years old) and found a higher incidence of arterial intimal thickening in the elder group, but no differences in the degree of other pathological changes; the follow-up for 41 months showed no difference in survival [30].

Proteinuria has always been an important prognostic factor for patients with IgAN. In this study, proteinuria in the patients was significantly lower in the CCR group than in the group with the increase in creatinine by > 50%. Multivariate regression showed that a baseline proteinuria greater than 0.5 g/d was an independent influencing factor for the increase in creatinine by more than 50%. This finding indicates that the increase in the baseline proteinuria might worsen patients' prognosis. The mean proteinuria per unit of time reflected the long-term control of patients on proteinuria during the follow-up, and this measurement was significantly correlated with the adverse endpoint events. The HR value significantly increased with the rise in TA-P, indicating that the patients in this study had minor proteinuria, which, however, could not be ignored. The risk of progression of renal function would be higher if intervention was not proactively taken.

Pathology has been regarded as an important influencing factor for the prognosis of IgAN. Reportedly [7, 31-34], according to the Oxford classification, the M, E, S, T, and C lesions are partially related to the prognosis. Barbour SJ [31] found that M/T lesions were independently associated with renal outcome. The results of Bellur SS [35] support the S score of the Oxford Classification in patients without immunosuppression. Trimarchi, et al. [36] reviewed the current classification parameters of the Oxford classification and put forward the revised MEST-C score. However, the results of these examinations were primarily derived from patients with proteinuria greater than 1 g/d. In this study, we established that for patients with minor proteinuria, only the T lesions were correlated pathologically with the adverse endpoint events. According to the results of the multivariate regression analysis, after the clinical indicators were corrected, pathology could not be used as an independent factor to predict the endpoint events. This suggested that pathological changes do not possess higher predictive ability than clinical indicators in predicting adverse endpoint events. Other studies [31, 35-38] in IgAN patients seem to have obtained different results. However, there are no conflicts with our results, because some differences, such as the inclusion criteria, stratification, and correction factors of multivariate analysis or definition of outcomes, might have led to variations in the results. Coppo R, et al. [38] analyzed 1,147 IgAN patients in the VALIGA cohort and suggested that M/S/T independently predicted renal outcome (50% reduction in renal function and/or ESRD). However, in a subgroup of 219 patients with minimal proteinuria, no MEST score predicted renal outcome in the multivariate analysis, which supports our results. Another examination, conducted by Coppo R [37], failed to confirm that MEST scores had a predictive value in a subgroup of 174 children (<18 years) in the VALIGA cohort. These results indicated that the evaluation of the Oxford classification should be stratified.

We further calculated the C-index that reflects the predictive value of the models, and found that the models based on clinical indices had a C-index that was significantly higher than that of the Oxford classification, indicating that clinical indices possessed a higher prognostic value than pathological changes. These results may be attributed to the relatively mild pathological changes in the patients with a urinary protein level lower than 1 g/d. In addition, the prompt treatment might, at least partially, have reversed the pathological changes and thus further diminished their influence. Other studies also could not verify that the MEST score had higher C-index than clinical data in predicting the renal outcome. Barbour SJ, et al. [31] calculated the C-index in 901 IgAN patients with average baseline proteinuria of 1.5 g/d (0.8–2.6 g/d). There was no evidence that the C-index of the MEST score was higher than that of clinical data. Only the combination of MEST score and clinical data increased the C-index by 0.05.

Several limitations of this study should be noted. The data were obtained from a single institution in China. The generalizability for populations of other races might have been limited. Second, patients with higher proteinuria and more advanced pathologic findings were likely to receive more aggressive treatment. In addition, the dosage and course of steroids was individualized. The effects of the therapeutic intervention on the progression need to be confirmed in a larger number of clinical studies. Third, the follow-up of the IgA

nephropathy clinical endpoints of ESRD was relatively short. We will perform a prospective study with longer a follow-up period in the future.

Conclusion

(1) Proteinuria > 0.5g/d and eGFR <90 mL/min/1.73 m² may predict more severe pathological changes; (2) With the increase in age and baseline proteinuria, the risks of adverse endpoint events increase significantly; (3) Pathology could roughly predict the adverse endpoint events but was less efficient than the clinical indicators; (4) The data collected during the follow-up period suggested that the patients should regularly check their renal function and proactively control their proteinuria.

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Disclosure Statement

The authors declared that there were no conflicts of interest in either conducting the study or analyzing the results.

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