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Correlation analysis of cofilin-1 with renal prognosis in primary IgA nephropathy

Ruo-Bei Zhao[1†], Yuan-Shan Xu[1†], Xiao-Hua Li[1], Mei-Ju Wei[1], Yang Deng[1], Xun Peng[1] and Ling Pan[1*]

Abstract

Purpose The purpose of this study was to investigate the correlation between podocyte related biomarker cofilin-1 and renal function, and explore the value of cofilin-1 in predicting the risk of renal adverse prognosis in IgA nephropathy (IgAN).

Methods Patients with primary IgAN diagnosed by initial renal biopsy performed in our hospital from January 2019 to February 2022 were included. This study was a prospective cohort study. All IgAN patients were detected the expression of cofilin-1 and other related biomarkers (RhoA, NGAL) in urine by enzyme-linked immunosorbent assay (ELISA) and follow-up at least 6 months. We also collected baseline clinicopathologial data of IgAN. The decreased renal function group was defined as baseline eGFR < 60 ml/min/1.73m^2. Logistic and Cox regression model were used to analyze the correlation among cofilin-1 and renal prognosis.

Results 133 IgAN patients were included, with a male-to-female ratio of 1.25:1 and an age of 37.67 ± 13.78 years, as well as an average of eGFR was 71.63 (40.42,109.33) ml/min/1.73m^2. 56 patients (42.1%) had decreased renal function at baseline, with the average of eGFR was 34.07 (16.72, 49.21) ml/min/1.73 m^2. 12 of which developed to renal adverse prognosis. The average of follow-up time was 22.035 ± 8.992 months. The multivariate regression analysis showed that increased urinary cofilin-1 was an independent risk factor associated with baseline renal function decline and renal adverse prognosis in IgAN patients (*P* < 0.05). ROC curves showed great efficacy of urinary cofilin-1 levels in diagnosing baseline renal function decline and predicting renal adverse prognosis (the area under the ROC curve was 0.708 and 0.803).

Conclusion Cofilin-1 as a novel biomarker of podocyte lesion is closely related to renal function decline in IgAN. Cofilin-1 has certain clinical value in predicting the risk of renal adverse prognosis. Podocyte fusion affects the renal prognosis of IgAN.

Keywords IgA nephropathy, Podocyte fusion, Cofilin-1, Renal prognosis

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Introduction

IgA nephropathy (IgAN) is the most common primary glomerular disease among the world. Due to the diversity of its clinicopathological manifestations, the prognosis is also highly heterogeneous. Progressive IgAN is one of the main causes of chronic renal failure and end-stage renal disease (ESRD) [1]. It was previously thought that glomerular mesangial hypercellularity was the dominant pathological damage in IgAN, but in recent years, with the "Mesangial-Podocytic-Tubular Cross-Talk" theory being proposed, there has been increasing evidence that podocyte lesions also play an important role in the development of IgAN [2].

Podocytes is the important barrier of glomerular filtration membrane [3]. Damage to the podocyte structure leads to a decreased glomerular filtration rate, proteinuria leakage and impaired renal function, all of which are closely related to the severity of clinicopathology and prognosis in IgAN patients. However, podocyte lesions need to be observed by electron microscopy, and renal biopsy is an invasive test. Thus, it is difficult to perform repeated renal biopsies for monitoring, and electron microscopy is not yet available for routine implementation at all hospitals. Therefore, research on the screening of sensitive noninvasive biomarkers [4, 5] associated with podocyte injury and the assessment of their correlation with severity or renal prognosis are important for the early identification of patients at high risk of renal adverse prognosis in IgAN patients. Several podocyte biomarkers, such as nephrin, podocin, and podocalyxin, found in the current study have clinical significance in assessing the degree of renal injury [4, 5]. However, studies on the correlation between actin cytoskeletal regulatory proteins of podocytes and renal prognosis in IgAN are rarely reported. The actin cytoskeletal proteins and actin-binding proteins are essential for maintaining glomerular filtration function [6]. As an actin-binding protein, cofilin-1 binds to actin and participates in the regulation of actin depolymerization in the podocyte cytoskeleton for maintaining podocyte structure [7]. Consequently, cofilin-1 is considered a potential predictive marker for structural podocyte lesions [8]. The correlation of podocyte cytoskeleton actin-binding protein cofilin-1 with clinicopathology and renal prognosis in IgAN patients is still unclear yet.

This study intends to analyze the relationship between urinary cofilin-1 levels and the clinicopathologic data and baseline renal function of IgAN patients, and to investigate the predictive value of cofilin-1 for renal adverse prognosis in IgAN for finding new effective biomarkers to predict the renal prognosis of IgAN.

Methods

Study population

Patients with primary IgAN diagnosed by initial renal biopsy performed at the Department of Nephrology, The First Affiliated Hospital of Guangxi Medical University from January 2019 to February 2022 were included. Exclusion criteria were as follows: (1) age<18 years; and (2) secondary IgAN, such as lupus glomerulonephritis, hepatitis B virus associated-glomerulonephritis, and Henoch-Schonlein Puroura; and (3) the patients had taken glucocorticoid and immunosuppressor before renal biopsy. Age- and sex-matched healthy people were also selected as normal controls. The present study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University (approval number:2016 (036)). The purpose of the present study was explained to all patients, who provided written informed consent. We mainly observed the impact of a single podocyte marker on renal prognosis in this study. Referring to previous studies, the prevalence of adverse renal prognosis of IgAN was about 10%–16%, therefore, we used PASS 15.0 to calculate the sample size and considered with lost rate of follow-up, thus the sample size was at least 100 cases.

Clinicopathological data collection

The general information and vital signs, demographic, clinical and pathological data were collected from patients at the baseline time of renal biopsy. Demographic, clinical and pathological data were collected at the time of renal biopsy. (1) General information: age, gender, weight, height, BMI, SBP, DBP, MAP. (2) Laboratory indicators: Hb, Scr, BUN, ALB, TG, TC, LDL, HDL, 24 h urinary protein quantity and microscopic hematuria and other indicators.The eGFR was calculated according to the patient's age, gender and Scr by using the CKD-EPI formula [9]. (3) Pathological data of renal biopsy: light, immune and electron microscope results of IgAN patients were collected. (4) We also collected important medicine records which were taken during renal biopsy (For example ACEI/ARB drugs, etc.).

Estimate the prognostic of IgAN patients

This study was a prospective cohort study. All IgAN patients were followed up at least 6 months. The clinical outcome event "renal adverse prognosis" was defined as the patient's development to ESRD (long-term renal replacement therapy or eGFR<15 ml/min/1.73m^2) or eGFR decreased by more than 50% from baseline.

Urine sample collection and the detection of podocyte related biomarkers

About 10 ml of morning urine was collected on the day of kidney biopsy from IgAN patients, and the healthy

controls from Health Examination Population in our hospital were informed to collect 10 ml of morning urine within 1 week after the results of the physical examination were reported. The expression of podocellular biomarker cofilin-1 in urine was detected by enzyme-linked immunosorbent assay (ELISA).

Definitions

Microscopic hematuria refers to urine that has been centrifuged, and then high magnification microscopic examination of the urine sediment reveals a number of >3 red blood cells per high magnification view. Massive proteinuria is defined as 24 h-UTP>3.5 g. Diagnostic criteria for IgAN was that light microscopic immunofluorescence examination showed that immunoglobulins, mainly IgA or IgA deposits, were deposited in the glomerular mesangial area in granular or mass form.

Renal function decline was defined as an eGFR<60 ml/min/1.73 m^2. IgAN patients were divided into 2 groups according to the eGFR. The decreased renal function group was defined as baseline eGFR<60 ml/min/1.73m^2, the normal renal function group was defined as baseline eGFR≥60 ml/min/1.73m^2. The "renal adverse prognosis" was defined as the patient's development to ESRD (long-term renal replacement therapy or eGFR<15 ml/min/1.73m^2) or eGFR decreased by more than 50% from baseline.

Statistical analysis

SPSS26.0 software was used for statistical analysis of the data. The measurement data were expressed as x±s if they conformed to normal distribution, and t-test was used for comparison between groups. Those that did not conform to normal distribution were expressed as M (1/4, 3/4), and the rank sum test was used for comparison between groups. Count data were expressed as number of cases and percentages (%), and the χ^2 test was used for comparison between groups. The Wilcoxon rank-sum test was used for comparison between groups for grade data. Binary multivariate Logistic regression model was used to analyze the independent risk factors affecting the dependent variable. Univariate and Multivariate Cox regression model was used to analyze the independent risk factors affecting the renal prognosis. ROC curves were used to analyze the value of urinary cofilin-1 levels in judging baseline renal function decline and estimating the renal prognosis. $p < 0.05$ was considered a statistically significant difference.

Results

General results

A total of 133 patients with IgAN were included, with a male-to-female ratio of 1.25:1 and an age of 37.67±13.78 years. The average of eGFR of IgAN patients was 71.63

(40.42, 109.33) ml/min/1.73 m^2. There were 56 patients (42.1%) with baseline renal function decreased, and the average of baseline eGFR of the renal function decreased group was 34.07 (16.72, 49.21) ml/min/1.73 m^2. A control group of 120 healthy people was included, with a male to female ratio of 1.18:1 and age of 42.57±18.49 years. The average of follow-up time was 22.035±8.992 months, 11 patients with baseline eGFR < 15 ml/min/1.73m^2 and receiving long-term replacement therapy were excluded to follow-up. 9 patients(9/133, 6.8%)were lost to follow-up. 12 patients (12/(133-11-9), 10.6%) developed to renal adverse prognosis during the follow-up period (flow diagram as shown in Fig. S1 of Supplementary material). Comparison of the differences in urinary cofilin-1 levels between the IgAN group and the normal controls using t-test showed that there were no significant differences in age and gender between the two groups (all $P > 0.05$), and urinary cofilin-1 levels was significantly higher in the IgAN group than in the normal controls (62.36±6.39 vs 55.49±8.83, $P < 0.001$).

Analysis of the relationship between urinary cofilin-1 levels and baseline renal function decline in IgAN patients

(1) Comparison of clinical and pathological features between the decreased renal function group and the normal renal function group.

Compared with normal renal function group, patients in the decreased renal function group had higher age, MAP, UA, 24 h-UTP levels and the proportions of Oxford pathological classification M1, S1, T1/2 and C1/2, as well as higher urinary cofilin-1 and NGAL levels, and lower Hb levels and lower eGFR levels (all $P < 0.05$). There were no statistically significant differences in gender, BMI, ALB, lipids, microscopic hematuria, urinary RhoA levels, and Oxford pathological classification E score between the two groups (all $P > 0.05$), as shown in Table 1.

We also analyzed the relationship between urinary cofilin-1 levels and eGFR levels among the urinary protein subgroups, and the results showed that there was no statistical significance in urinary cofilin-1 levels among the four groups ($P > 0.05$), while the eGFR levels gradually decreased with increasing urinary protein levels ($P < 0.05$), as shown in Table S1 of Supplementary material.

(2) Analysis of risk factors affecting the decline of baseline renal function in IgAN patients.

The above significant factors were included in the binary multivariate logistic regression analysis, and the results showed that the increased MAP levels, decreased Hb levels, Oxford pathological classification T1/2 and increased urinary cofilin-1 levels were independent risk factors for baseline renal function decline in IgAN patients (all $P < 0.05$), as shown in Table 2.

Table 1 Comparison of clinicopathological and urinary biomarkers of podocytes data between the IgAN group with renal function decline and the IgAN group with normal renal function

Characteristic	The normal renal function group (n=77)	Declining renal function group (n=56)	t/χ²/Z	P
Age (yr)	34.35 ± 13.16	42.23 ± 13.41	−3.383	**0.001**
Male (female)	33 (42.9)	26 (46.4)	−0.168	0.682
BMI (kg/m²)	24.27 ± 5.08	25.17 ± 5.43	−0.974	0.332
SBP (mmHg)	119.688 ± 11.861	133.625 ± 14.261	−6.141	**<0.001**
DBP (mmHg)	77.247 ± 8.440	84.714 ± 10.065	−4.643	**<0.001**
MAP (mmHg)	91.39 ± 8.68	101.02 ± 10.89	−5.665	**<0.001**
Hb (g/L)	133.18 ± 20.21	110.68 ± 24.76	5.762	**<0.001**
ALB (g/L)	30.99 ± 9.75	31.34 ± 8.05	−0.222	0.824
UA (μmol/L)	378.53 ± 110.19	464.31 ± 128.34	9.250	**0.002**
TC (mmol/L)	5.30 (4.36, 7.91)	5.17 (4.22, 6.68)	−0.542	0.588
TG (mmol/L)	1.26 (0.91, 2.10)	1.53 (1.10, 2.15)	−1.752	0.080
HDL (mmol/L)	1.20 (0.99, 1.56)	1.16 (1.04, 1.41)	−0.923	0.356
LDL (mmol/L)	3.09 (2.43, 4.98)	3.06 (2.36, 4.39)	0.633	0.526
eGFR (ml/min/1.73m²)	102.25 (81.45, 120.12)	34.07 (16.72, 49.21)	−9.825	**<0.001**
24 h-UTP (g/24 h)	0.93 (0.58, 2.04)	2.37 (1.24, 3.64)	−4.029	**<0.001**
Microscopic hematuria	33 (42.9)	28 (50.0)	−0.666	0.414
M1	19 (24.7)	31 (56.4)	13.691	**<0.001**
E1	2 (2.6)	5 (9. 1)		0.127
S1	39 (50.6)	42 (76.4)	8.948	**0.003**
T1/2	9 (11.9)	42 (76.4)	56.604	**<0.001**
C1/2	7 (9.1)	13 (23.6)	5.280	**0.022**
NGAL (ng/ml)	8.45 ± 0.76	8.80 ± 0.80	−2.468	**0.015**
RhoA (ng/L)	502.89 + 52.80	513.66 + 52.68	−1.128	0.262
Cofilin-1 (pg/ml)	60.40 ± 5.77	65.04 ± 6.27	−4.367	**<0.001**

Note BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *Hb* hemoglobin, *ALB* blood albumin, *UA* blood uric acid, *TC* blood cholesterol, *TG* blood triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate, *24 h-UTP* 24-hour urine protein, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental glomerulosclerosis, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *NGAL* neutrophil gelatinase-associated lipocalin, *RhoA* Ras homology family member A. MAP defined as (systolic blood pressure+2×diastolic blood pressure)/3

Analysis of risk factors affecting the renal adverse prognosis in IgAN patients

Univariate Cox regression model was used to analyze the clinicopathological data, and the results showed that there was statistically significant differences in Hb, BUN, Scr, eGFR, Oxford pathological classification T1/2, Microscopic hematuria and Cofilin-1 levels (all *P*<0.05). The above significant factors were included in the Multivariate Cox regression model, the results showed that after correcting for confounding factors, the increased urinary cofilin-1 levels and Scr were independent risk factors for renal adverse prognosis in IgAN patients who were follow-up for at least 6 months (*P*<0.05), as shown in Table 3.

Table 2 Binary logistic regression model was used to analyze the influencing factors of baseline renal function decline in IgAN patients

Characteristics	Wald	OR	95%CI	P
Age (yr)	2.114	1.042	0.986 ~ 1.102	0.146
Increased MAP (mmHg)	11.691	1.184	1.075 ~ 1.304	**0.001**
Hb (g/L)	6.914	0.955	0.922 ~ 0.988	**0.009**
UA (μmol/L)	0.446	1.002	0.996 ~ 1.008	0.504
24 h-UTP (g/24 h)	0.535	1.106	0.844 ~ 1.450	0.464
M1	2.769	4.160	0.776 ~ 22.301	0.096
S1	0.584	0.473	0.070 ~ 3.224	0.445
T1/2	10.322	19.487	3.184 ~ 119.274	**0.001**
C1/2	1.825	3.727	0.553~25.133	0.177
NGAL (ug/ml)	0.015	1.059	0.423 ~ 2.650	0.903
cofilin-1 (pg/ml)	5.955	1.195	1.036 ~ 1.378	**0.015**

Note Increased MAP, mean arterial pressure>105 mmHg; *Hb* hemoglobin, *UA* blood uric acid, *24 h-UTP* 24-hour urine protein, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental glomerulosclerosis, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *NGAL* neutrophil gelatinase-associated lipocalin

The value of urinary cofilin-1 levels in diagnosing baseline renal function decline and renal adverse prognosis in IgAN patients

(1) The value of cofilin-1 in estimating baseline renal function decline in IgAN patients.

To explore the ability of urinary cofilin-1 levels to predict baseline renal function decline, we plotted ROC curves, and the results showed that the AUC was 0.708 (*P*<0.001), with a cut-off value was 65.49 pg/ml, sensitivity was 0.537, and specificity was 0.853. The ability of urinary cofilin-1 levels combined with clinicopathological data (MAP, Hb, Oxford pathological classification T, *P*<0.05 in the above logistic regression model) to judge baseline renal function decline, the AUC was 0.942 (*P*<0.001), with a sensitivity was 0.870 and specificity was 0.867, as shown in Fig. 1.

(2) The value of cofilin-1 in estimating renal adverse prognosis in IgAN patients.

ROC curves were plotted to analyze the ability of urinary cofilin-1 levels to evaluate the risk of renal adverse prognosis, and the results showed AUC was 0.803 (*P*=0.001), cut-off value was 65.122 pg/ml, sensitivity was 0.833, and specificity was 0.711, as shown in Fig. 2.

Simultaneously, we using the QxMD International IgA Nephropathy Risk Prediction Tool [10] to calculate the risk of renal adverse prognosis for dividing into the medium-high risk group and the low risk group. We compared the real ability of cofilin-1 in evaluating actual event occurrence with the prediction ability of International IgAN prediction tool in predicting event occurrence. Comparison of clinicopathological index and urinary biomarkers between medium-high risk group and low-risk group by calculated from **QxMD** International IgAN prediction tool was showed in Table S2. The significant factors of Table S2 were further included

Zhao *et al. BMC Nephrology*   (2024) 25:289

Page 5 of 9

Table 3 Univariate and Multivariate Cox regression model was used to analyze the risk factors of renal adverse prognosis in IgAN patients

Characteristics	Univariate			Multivariate		
	HR	95%CI	*P*	HR	95%CI	*P*
Age (yr)	0.976	0.930–1.024	0.315			
Gender	0.741	0.238–2.303	0.604			
BMI (kg/m^2)	1.003	0.899–1.120	0.957			
SBP (mmHg)	1.021	0.990–1.053	0.179			
DBP (mmHg)	1.024	0.978–1.071	0.314			
MAP (mmHg)	1.025	0.985–1.068	0.223			
Hb (g/L)	0.965	0.941–0.990	**0.007**	0.982	0.939–1.026	0.411
UA (µmol/L)	1.002	0.998–1.006	0.305			
BUN (mmol/L)	1.188	1.080–1.307	**<0.001**	0.844	0.632–1.128	0.252
ALB (g/L)	0.998	0.931–1.049	0.691			
Scr (umol/L)	1.012	1.007–1.018	**<0.001**	1.022	1.000-1.044	**0.047**
eGFR (ml/min/1.73m^2)	0.962	0.940–0.986	**0.002**	1.034	0.982–1.090	0.204
TC (mmol/L)	0.946	0.760–1.178	0.622			
TG (mmol/L)	1.011	0.767–1.332	0.938			
HDL (mmol/L)	0.685	0.161–2.926	0.610			
LDL (mmol/L)	0.955	0.715–1.277	0.759			
24 h-UTP (g/24 h)	1.118	0.929–1.344	0.237			
Microscopic hematuria	0.242	0.065–0.894	**0.033**	0.313	0.072–1.362	0.122
M1	0.575	0.185–1.784	0.338			
E1	0.239	0.051–1.107	0.067			
S1	0.274	0.060–1.253	0.095			
T1/2	0.094	0.021–0.429	**0.002**	0.381	0.017–8.763	0.546
C1/2	0.495	0.134–1.834	0.293			
Number of glomerulosclerosis	1.063	0.989–1.142	0.096			
Nephrin (ug/ml)	1.544	0.972–2.453	0.066			
NGAL (ng/ml)	1.091	0.519–2.293	0.819			
RhoA (ng/L)	1.010	0.999–1.021	0.085			
Cofilin-1 (pg/ml)	1.209	1.077–1.357	**0.001**	1.194	1.014–1.407	**0.034**
ACEI/ARB	3.573	0.461–27.704	0.223			

Note BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *Hb* hemoglobin, *ALB* blood albumin, *UA* blood uric acid, *BUN* Blood Urea Nitrogen, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *TC* blood cholesterol, *TG* blood triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *24 h-UTP* 24-hour urine protein, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental glomerulosclerosis, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *NGAL* neutrophil gelatinase-associated lipocalin, *RhoA* Ras homology family member A. MAP defined as (systolic blood pressure+2×diastolic blood pressure)/3

in the binary multivariate logistic regression analysis in Table S3. The predicting ability of logistic regression model resulted from Table S3 for medium-high risk of renal adverse prognosis was presented in Fig. S2 which was conducted by ROC curve analysis. The results were detailed in Tables S2, S3 and Fig. S2 of Supplementary material. We also analyzed the relationship between cofilin-1and the risk of renal adverse prognosis among the urinary protein subgroups, the results were shown in Fig. S3 of Supplementary material.

Discussion

Podocytes are terminally differentiated mesenchymal cells that constitute the final gatekeeper of the glomerular filtration barrier. Foot processes of podocytes contain an actin-based cytoskeleton that is linked to the GBM, foot processes of podocytes form a highly branched interconnected network with those of neighboring podocytes, which are connected by Slit diaphragm. Therefore, podocyte lesions mainly lead to damage of the glomerular filtration barrier, which affects urinary protein loss and its filtration function.

The actin-based cytoskeleton of podocytes is an important component in maintaining the structural and functional stability of podocytes, and the actin-blinding protein can regulate podocyte cytoskeletal movement and structural integrity by binding to actin-based cytoskeleton of podocytes. It has been shown that cofilin-1 could cause actin disorganization and podocyte foot process spreading following podocyte injury via the CMIP/Fyn/RhoA/cofilin-1 signaling pathway [11]. Garg et al. [7] found that nephrin co-localized with cofilin-1 on the cell membrane of podocytes. Nephrin activation induced cofilin-1 dephosphorylation via intermediaries

Zhao *et al. BMC Nephrology*　　　(2024) 25:289

Page 6 of 9
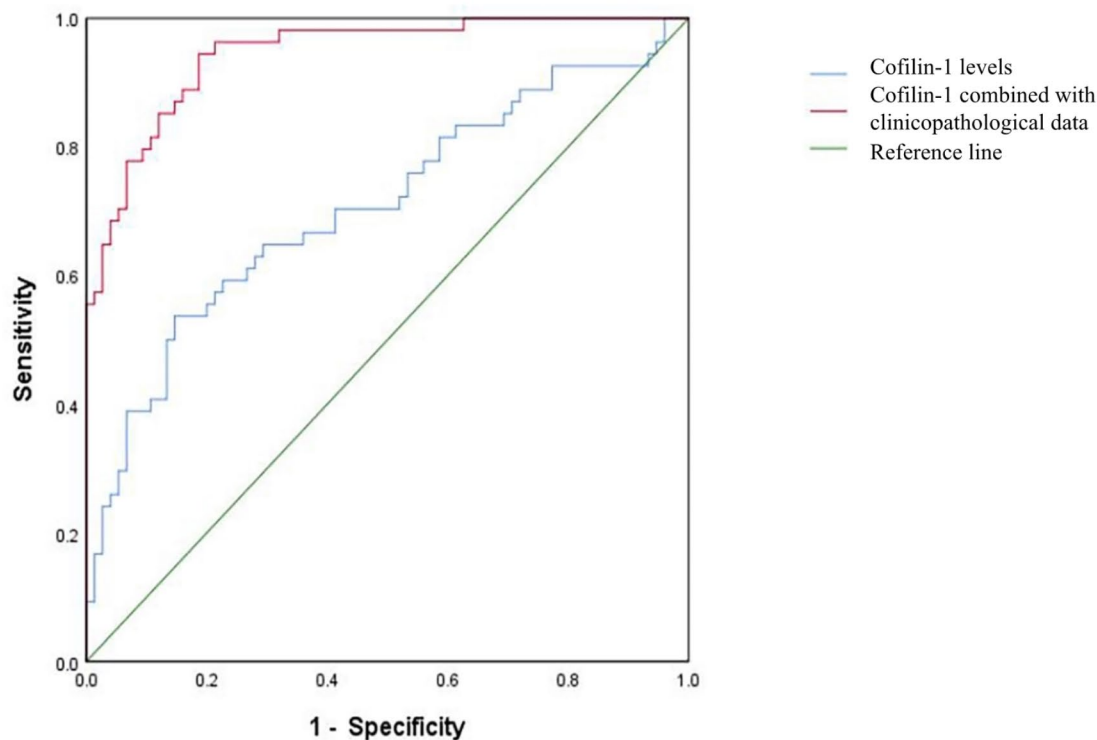
Fig. 1 ROC curve of urinary cofilin-1 levels and clinicopathological combined urinary cofilin-1 levels for the prediction of baseline renal function decline. The blue line indicates the cofilin-1 levels, and the red line indicates the cofilin-1 combined with clinicopathological data. The AUC of cofilin-1 levels and cofilin-1 levels combined with clinicopathological data was 0.708 and 0.942, $P<0.001$

that include phosphatidylinositol 3-kinase, SSH1, 14-3-3, and LIMK in a cell culture model. Cofilin-1 is necessary for maintenance of normal podocyte architecture and for actin structural changes that occur during induction and recovery from podocyte injury. In addition, asparagine endopeptidase (AEP) maintains the podocyte cytokinetics by cleaving cofilin-1 to keep cofilin-1 dephosphorylated during the progression of diabetic nephropathy [12]. All the above results indicated that cofilin-1 was closely associated with podocyte lesions, therefore, cofilin-1 was considered as one of the potential biomarkers of podocyte lesions, which may be closely related to the clinical manifestation, renal function and prognosis of IgAN.

In this study, we found that age, MAP, Hb, UA, eGFR, 24 h-UTP, urinary NGAL levels and Oxford pathological classification M, S, T, and C were associated with baseline renal function decline, and increased MAP, decreased Hb, and T1/2 were independent risk factors for baseline renal function decline. While MAP, Hb, UA, TG, 24 h-UTP, urinary RhoA levels, urinary NGAL levels and Oxford pathological classification M1, S1, T1/2 were associated with increased risk of renal adverse prognosis

in IgAN patients, and increased MAP, massive proteinuria, Oxford pathological classification T1/2 were independent risk factors for increased risk of renal adverse prognosis in IgAN patients, and all these results were consistent with previous studies [13].

This study also suggested that urinary cofilin-1 levels were associated with baseline eGFR and risk of renal adverse prognosis in IgAN patients, and that increased urinary cofilin-1 levels was an independent risk factor for baseline renal function decline and increased risk of renal adverse prognosis in IgAN patients. Furthermore, the performance of cofilin-1 levels in diagnosing renal function decline and the increased risk of renal function progression is better, especially when combined with clinicopathological indicators, the predictive performance is significantly higher. The AUC results of our study indicated that cofilin-1 was a great evaluation biomarker for predicting renal adverse prognosis. Ashworth et al. [14] also showed that a large accumulation of actin fibers was seen after silencing of cofilin-1, and the migration ability of podocytes was significantly decreased, renal function damage can be observed in cofilin-1 deficient mice, suggesting that cofilin-1 is associated with podocyte
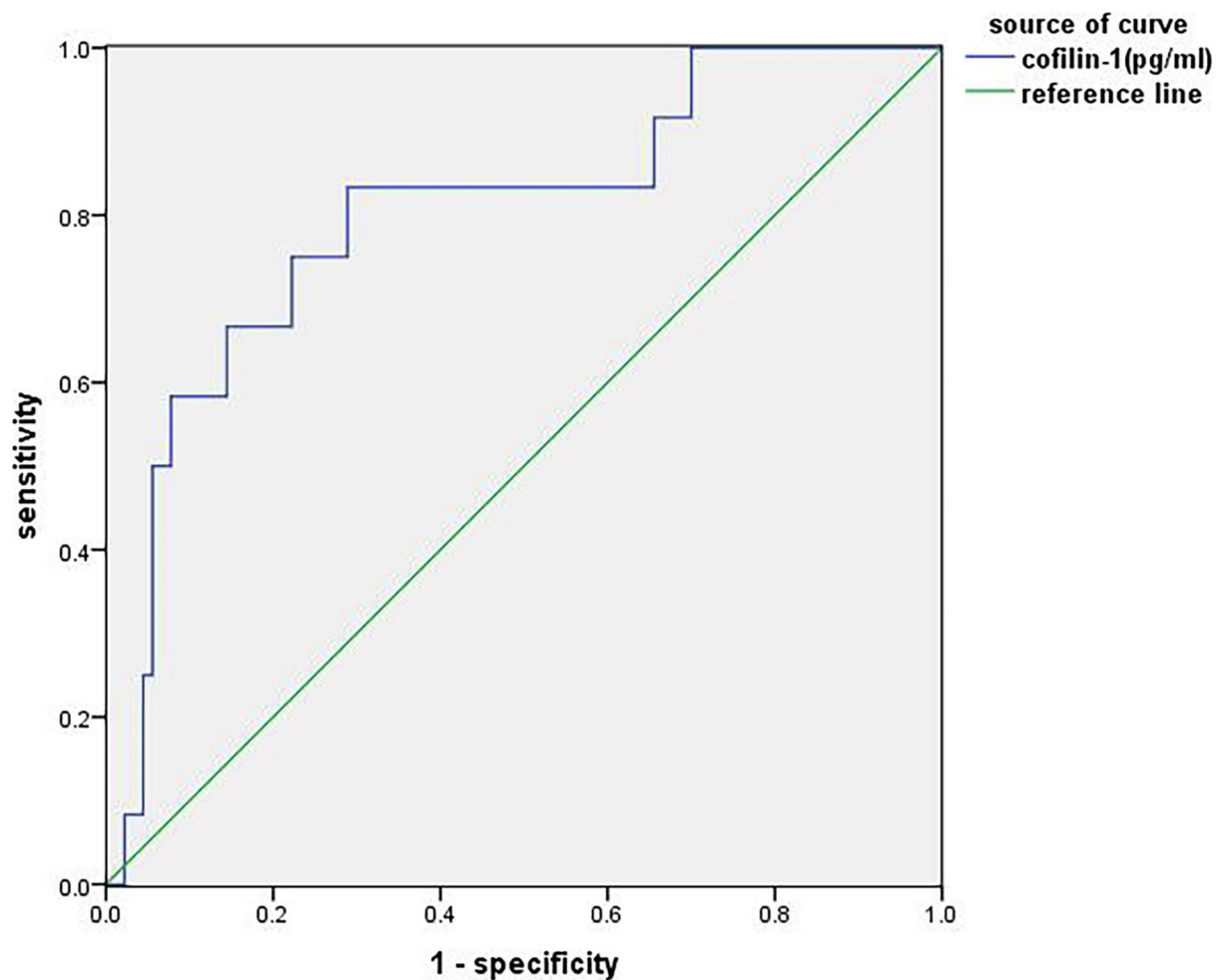
Fig. 2 ROC curves of urinary cofilin-1 levels for the prediction of renal adverse prognosis. The AUC of cofilin-1 levels was 0.803, $P=0.001$

lesions and the renal function decline, so cofilin-1 plays an important role in a variety of clinical conditions associated with renal injury. On the other hand, Yu et al. [11] detected significantly increased levels of phosphorylation inactivated cofilin-1 in podocytes after puromycin aminonucleoside (PA) treatment and in glomeruli isolated from rats with PA-induced nephropathy. In the pathogenesis of hypertension-induced renal damage, cofilin-1 mediated the upregulation of ETA and ETB2 receptors through regulation of NF-κB in renal tubular epithelial cells, which increased renal artery constriction, leading to nephrovascular spasm and nephroischemia, ultimately leading to renal injury, it is an important pathogenesis of hypertension causing renal damage [15, 16]. In addition, up-regulation of cofilin-1 levels was also found in patients with diabetic nephropathy and acute kidney injury [17, 18]. All of these results suggested that cofilin-1 is closely associated with kidney damage and can identify higher risk IgAN patients early.We compared the real

ability of cofilin-1 in evaluating actual event occurrence with the prediction ability of International IgAN prediction tool in predicting event occurrence. The International IgA Nephropathy Prediction Tool is the preferred method in the 2021 KDIGO guidelines. Our study indicated Cofilin-1 has certain clinical value in predicting the risk of renal adverse prognosis, and international prediction tool is also suitable for predicting the risk of renal adverse prognosis according baseline situation, The AUC value between them is close and fine.

Cofilin-1 was a actin regulating protein of the actin cytoskeleton in podocytes that act in the regulation of actin dynamics. The remodeling of the actin cytoskeleton is a response to several cellular and morphological changes, including motility, migration, growth, differentiation, and cell death. The actin cytoskeleton is regulated by a number of complex signaling pathways and key molecules, multiple actin regulating proteins are necessary for remodeling the actin cytoskeleton by

specifically tuning the assembly and disassembly of actin [19]. As a member of actin regulating proteins, cofilin-1 bound to action, and promoted the depolymerization of filamentous-actin into globular-actin, while the polymerization of globular-actin into filamentous-actin is inhibited, allowing the recycling of actin microfilaments. In addition, the affinity of cofilin with ADP-bound actin filaments was higher than that of ATP-bound actin filaments, which then induced selective disassembly of "aged actin filaments". With cofilin-1 deficiency, filamentous-actin fibers accumulated in the podocyte, the ability of the podocyte actin cytoskeleton to remodel is impaired, its skeletal structure was changed, and the filtration barrier was impaired, resulting in decreased renal function. In this study, urinary cofilin-1 levels were significantly higher in patients with IgAN than in healthy controls, suggesting that cofilin-1 may be a potential biomarker for the diagnosis of IgAN, but it cannot be excluded that cofilin-1 is also expressed in other podocyte-associated glomerular diseases, and further studies are needed to demonstrate.

It was found that cofilin-1 silenced or knockout mice can develop massive proteinuria [14], and cyclosporin A can stabilize the actin cytoskeleton of podocytes by upregulating cofilin-1 expression, which acts to reduce proteinuria [20]. While our results showed that the bivariate correlation analysis between cofilin-1 levels and urinary protein levels was not statistically significant. it was also found that the performance of urinary cofilin-1 to predict the risk of renal adverse prognosis decreased as urinary protein levels increased, suggesting that the performance of urinary cofilin-1 to predict renal prognosis in IgAN patients was influenced by proteinuria.

The tubular damage caused by cofilin-1 has also been suggested as a mechanism of renal progression in addition to the mechanism of its effects on podocytes [21]. Cofilin-1 and the expression of monocyte chemotactic protein 1 (MCP1), interleukin-1β (IL1β) and NF-κB, all types of inflammatory mediators, were also observed to be increased in PTECs of the Hypertensive rats, and cofilin-1 was found to be involved in the development of hypertensive nephropathy by regulating the expression of NF-kB nuclear translocation and its downstream inflammatory factors in PTECs [16]. The above findings suggested that tubular cell injury caused by cofilin-1 may also be an important factor in the progression of IgAN kidney.

There were still some limitations of this study. First, this study was a single-center study with a small sample size. Second, the patients of our study was followed up for a relative short period (at least 6 months), but we compared the real ability of cofilin-1 in evaluating actual event occurrence with the prediction ability of International IgAN prediction tool in predicting event occurrence, which could confirm the predictive efficiency of cofilin-1. Third, this study did not include other glomerular diseases related to podocyte lesions such as membranous nephropathy and FSGS, so the clinical value of cofilin-1 as a biomarker of podocyte to predict the renal adverse prognosis of IgAN needs to be further validated. Therefore, future studies with other renal diseases associated with podocyte lesions, large samples, prospective multicenter cohort studies, and analysis of dynamic monitoring of cofilin-1 values are still necessary to confirm our findings in future.

Conclusion
The urinary cofilin-1 levels, actin-blinding protein of podocyte, was increased in IgAN patients compared with the normal controls, and the level of urinary cofilin-1 is closely related to the baseline renal function decline in IgAN patients. Cofilin-1 has certain clinical value in predicting the risk of renal prognosis in IgAN, and podocyte lesions affected the progression of renal function in IgAN patients.

Abbreviations

IgAN	IgA nephropathy
ESRD	End-stage renal disease
ELISA	Enzyme-linked immunosorbent assay
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
Hb	Hemoglobin
ALB	Albumin
UA	Uric acid
TC	Blood cholesterol
TG	Blood triglycerides
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
eGFR	Estimated glomerular filtration rate
24h-UTP	24-hour urine protein
M	Mesangial hypercellularity
E	Endocapillary hypercellularity
S	Segmental glomerulosclerosis
T	Tubular atrophy/interstitial fibrosis
C	Crescents
NGAL	Neutrophil gelatinase-associated lipocalin
RhoA	Ras homology family member A
AEP	Asparagine endopeptidase
PA	Puromycin aminonucleoside
MCP1	Monocyte chemotactic protein 1
IL1β	Interleukin-1β

Supplementary Information
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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Zhao *et al. BMC Nephrology*   (2024) 25:289

Page 9 of 9

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Declarations

Ethical approval
This study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University (approval number:2016 (036)) and was conducted in accordance with the Declaration of Helsinki Compliance with ethical standards.

Informed consent
All subjects signed an informed consent before enrolment in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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