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RESEARCH ARTICLE

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A high value of fibrinogen in immunoglobulin A nephropathy patients is associated with a worse renal tubular atrophy/interstitial fibrosis score

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Abstract

Purpose: The purpose of our study was to investigate the relationship between serum fibrinogen value and renal tubular atrophy/interstitial fibrosis in immunoglobulin A nephropathy patients with eGFR ≥90 ml/min/1.73 m^2.

Patients and Methods: Of 359 patients diagnosed with immunoglobulin A nephropathy after renal biopsy were enrolled in this retrospective study. Demographic, histopathological features, and clinical data were collected. The relationships among these factors were analyzed by using Student's t test, Mann-Whitney U test, Kruskal-Wallis test, Chi-square test, or Fisher's exact test, where appropriate. The logistic regression analysis was performed to examine the independent risk factors.

Results: Of 176 immunoglobulin A nephropathy patients with eGFR ≥90 ml/min/1.73 m^2 were included in this study, and patients were classified into low fibrinogen (fibrinogen <304.6 mg/dl) and high fibrinogen (fibrinogen ≥304.6 mg/dl) groups, respectively. High fibrinogen groups had advanced age, a higher classification of renal tubular atrophy/interstitial fibrosis, and higher levels of systolic pressure, D-dimer, 24 h urine protein quantitation, nag enzyme. Multivariate logistic analysis showed that fibrinogen (OR = 1.018) was significantly associated with tubular atrophy/interstitial fibrosis.

Conclusion: Among patients with immunoglobulin A nephropathy, the higher levels of fibrinogen and uric acid may mean a higher score of tubular atrophy/interstitial fibrosis, which suggests the renal biopsy should be performed for these patients as early as possible to defined pathological classification, even though there is no obvious abnormal change in the test of renal function.

KEYWORDS
fibrinogen, immunoglobulin A nephropathy, tubular atrophy/interstitial fibrosis, uric acid

The first two authors contributed to this work equally.

1 | INTRODUCTION

Immunoglobulin A nephropathy (IgAN), which was first diagnosed by Berger in 1968, is the most prevalent morphological pattern of chronic glomerulonephritis in the world.[1,2] A systematic review of biopsy-based studies across multiple countries suggests an incidence of at least 2.5 per 100,000 population in the total population.[3] The clinical manifestations of IgAN are broad, ranging from asymptomatic microscopic hematuria with/without proteinuria to rapidly progressive glomerulonephritis.[4] While IgAN has an indolent course, approximately 20% to 40% of patients with IgAN will reach end-stage renal disease (ESRD) within 20 years, especially in those who present with diabetes, hypertension, or renal insufficiency.[5,6] Kidney biopsy, an invasive detection, is the most common method of obtaining renal pathological tissue to validate the diagnosis of IgAN. The Oxford classification of IgAN, based on pathological characteristics in renal biopsies, was published in 2009 and widely used in clinical practice.[7] The Oxford classification is deemed as the strongest early predictive pathological risk factor for IgAN patients with following parameters: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis or adhesions (S), tubular atrophy and interstitial fibrosis (T).[8] Among them, T-score is widely accepted as a parameter with high prognostic significance, patients with higher T-score mean poorer renal outcomes.[9,10] However, some patients suspected of IgAN often refused to accept renal biopsy due to its bleeding or infection complication, especially those with normal kidney function. That delay in diagnosis may lead to delayed therapy and then cause worse health.

Recently, a small number of studies have shown that fibrinogen is associated with IgAN patient prognosis, and Zhang J et al reported that elevated serum fibrinogen level is associated with poor renal outcomes in IgAN patients.[11] Yu Wang et al found that urinary fibrinogen and renal interstitial fibrinogen deposition is elevated in primary focal segmental glomerulosclerosis.[12] Perhaps, there will be a non-invasive examination based on serum fibrinogen will build to predict the severity of pathological characteristics of IgAN before renal biopsy, and that is going to be beneficial for clinicians to estimate the patient's disease. But so far, the study about the relationship between the fibrinogen and the pathological features of IgAN patients is still few. Consequently, the purpose of our study was to explore the relationship between serum fibrinogen value and renal tubular atrophy/interstitial fibrosis of the Oxford classification in IgA nephropathy patients with eGFR ≥90 ml/min/1.73 m^2.

2 | METHODS

2.1 | Patients

This study was a single-center cross-sectional study. Clinical records of 359 IgAN diagnosed by renal biopsy in the department of nephrology, Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University from January 2017 to December 2017 were analyzed. Exclusion criteria were as follows: (1) Patients aged <18 years; (2) Patients with eGFR <90 ml/min/1.73 m^2; (3) Missing data on laboratory variables; (4) Pathological results showed that the patient had secondary renal diseases, including lupus nephritis, diabetic nephropathy, Henoch-Schonlein purpura nephritis, and hepatitis-associated nephritis; (5) patients with a history of infection in the two weeks before renal biopsy. According to the exclusion criteria, 176 cases were selected. Figure 1 shows the flowchart for selecting cases for this study.

2.2 | Data collection and Diagnosis criteria

The baseline demographic and laboratory variables were gathered at the time of renal biopsy from database, including age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fibrinogen, D-dimer, 24 h urine protein quantitation

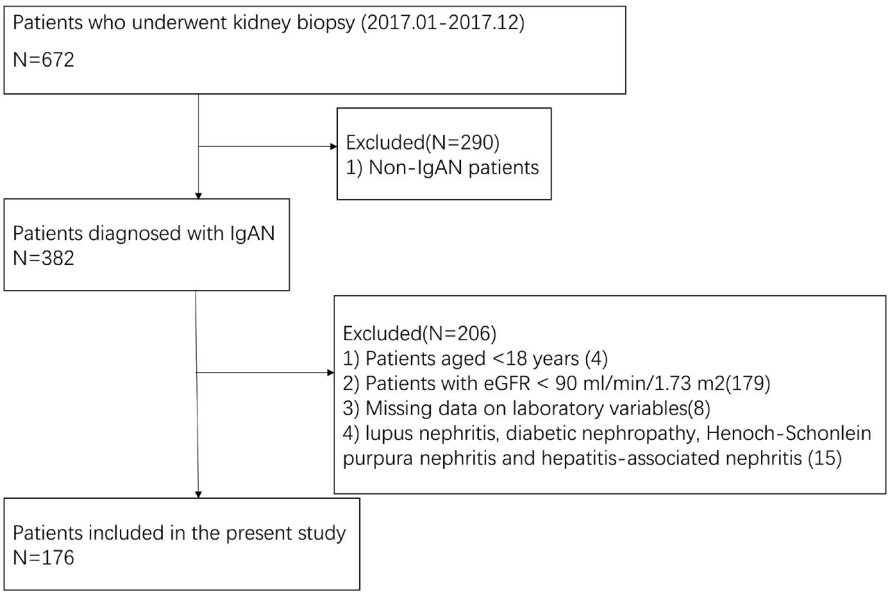

FIGURE 1 Flow diagram for patient's enrollment

(24 h-u-pro), uric acid (UA), serum creatinine (Scr), albumin (Alb), cystatin C (Cys-C), estimated glomerular filtration rate (eGFR), homocysteine (HCY), urea, and nag enzyme (NAG). Fibrinogen and D-dimer were measured by Sysmex CS-5100 analyzer. UA, Scr, Alb, Cys-C, eGFR, HCY, and NAG were detected by Beckman AU-5800 analyzer. BMI was calculated as weight (kg)/height $(m)^2$. eGFR was calculated using the CKD-MDRD (the Modification of Diet in Renal Disease) formula. Renal pathological diagnosis was reviewed independently by two nephropathologists according to the Oxford classification of IgAN using the MEST-C criteria.[7]

2.3 | Statistical analysis

Continuous variables were expressed as mean ±standard deviation (normally distributed) or median with inter-quartile range (non-normally distributed), and categorical values were expressed by absolute and relative frequencies. Variables with a normal distribution were compared in unpaired Student's t test. Variables with a non-normal distribution were compared using the Mann-Whitney U test or Kruskal-Wallis test. The chi-square test or Fisher's exact test was used for categorical data, where appropriate. Variables with $p < 0.05$ in the univariate analysis were progressed to a multivariate logistic regression analysis using backward stepwise selection. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The receiver operating characteristics (ROC) curve was calculated to measure the discriminatory power of fibrinogen, and the Youden index is commonly used to determine an optimal cut-off point. The area under ROC curve (AUC) and Hosmer-Lemeshow test was counted to verify the discrimination degree and calibration degree of the logit model.

All analyses were performed by the software statistical package for social sciences version 22.0 (SPSS). All figures were plotted by R version 4.1.0 (http://www.r project.org/). All statistical tests were two-sided, and p values of less than 0.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Patients

Of 176 patients who met the inclusion criteria were enrolled in the study. The median age of the included patients was 32.85 years (range 18.23–74.64 years), and 107 (60.8%) were female. According to the Oxford classification, 152 (86.4%) patients were T0, 21 (11.9%) were T1, and 3 (1.7%) were T2. As shown in Figure 2, serum levels of fibrinogen in various T scores were significant difference ($p < 0.001$).

3.2 | Prediction values of fibrinogen

The ROC curve showed that fibrinogen had better discrimination between IgAN patients with T0 and T1/T2 (Figure 3). The optimal cut-off value was 304.6 mg/dl with a specificity of 76.3% and a sensitivity of 75.0%.

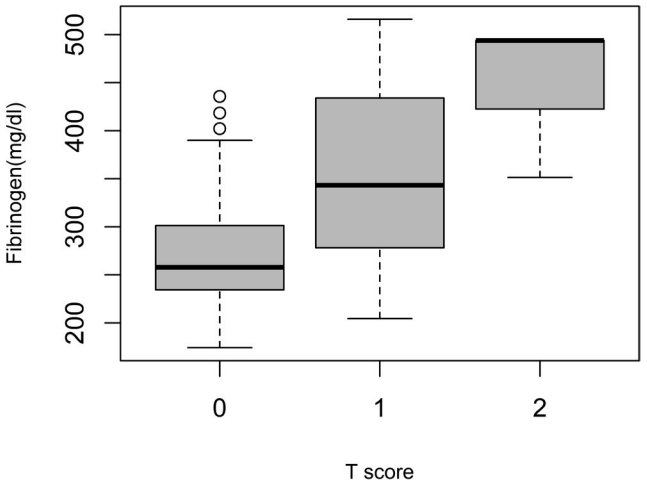

FIGURE 2 Box plot of the relationship between T-score and serum fibrinogen levels

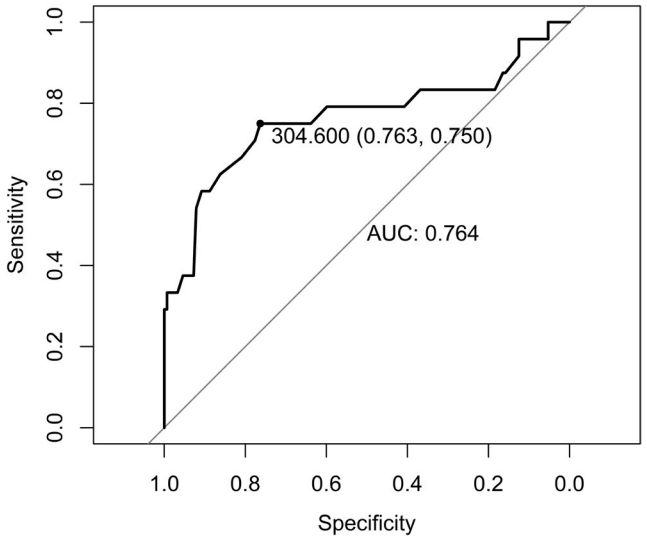

FIGURE 3 ROC analysis of renal tubular atrophy/interstitial fibrosis by fibrinogen

3.3 | Comparison of clinical and pathological features between groups

According to the optimal cut-off value, IgAN patients were divided into two groups: 122 patients (69.3%) with fibrinogen <304.6 mg/dl were regarded as low fibrinogen group, whereas the remaining 54 (30.7%) patients with fibrinogen ≥304.6 mg/dl were considered as high fibrinogen group. Compared with the low fibrinogen group, the high fibrinogen groups had advanced age, a higher proportion of T1/T2, higher levels of SBP, D-dimer, 24h-u-pro, NAG, and lower levels of Alb, Scr ($p < 0.05$). However, the levels of BMI, sex ratio, DBP, Cys-C, UA, Urea, HCY, and eGFR did not differ between the groups. Moreover, no obvious differences in the occurrence of mesangial

TABLE 1 Clinical characteristics of the study population

Variable	Group		
	Low Fibrinogen (<304.6 mg/dl)	High Fibrinogen (≥304.6 mg/dl)	*p*-value
Gender			
Male	52 (42.6)	17 (31.5)	0.163
Female	70 (57.4)	37 (68.5)	
M			
M0	2 (1.6)	0 (0)	1.000
M1	120 (98.4)	54 (100)	
E			
E0	93 (76.2)	43 (79.6)	0.620
E1	29 (23.8)	11 (20.4)	
S			
S0	16 (13.1)	11 (20.4)	0.218
S1	106 (86.9)	43 (79.6)	
T			
T0	116 (95.1)	36 (66.7)	<0.001
T1+T2	6 (4.9)	18 (33.3)	
Age (median [IQR], years)	32.61 (11.32)	40.1 (14.32)	0.047
SBP (mean [SD], mmHg)	119.61 (16.81)	127.96 (19.23)	0.028
DBP (mean [SD], mmHg)	73.80 (13.32)	74.83 (11.60)	0.719
BMI (median [IQR], kg/m^2)	22.30 (3.99)	23.54 (6.50)	0.133
D-dimer (median [IQR], μg/L)	220 (235.0)	400 (617.5)	<0.001
UA (median [IQR], μmol/L)	310 (126.5)	364.5 (100.3)	0.773
24 h-U-P (median [IQR], g/24 h)	0.63 (0.67)	1.01 (1.02)	<0.001
Alb (median [IQR], g/L)	39.3(4.4)	38.9(7.9)	0.015
Cys-C (mean [SD], mg/L)	0.68 (0.15)	0.72 (0.22)	0.303
NAG (median [IQR], U)	9.4 (8.8)	12.2 (17.5)	0.003
Urea (median [IQR], mmol/L)	4.6 (1.7)	4.00 (1.9)	0.076
HCY (median [IQR], μmol/L)	12.6 (2.6)	12.5 (4.4)	0.311
eGFR (median [IQR], ml/min/1.73 m ^{2})	109.6 (23.2)	112.95 (18.1)	0.287
Scr (median [IQR], mmol/l)	61 (19.3)	56.5 (20.3)	0.019

Abbreviations: M: Mesangial hypercellularity; E: Endocapillary proliferation; S: Segmental glomerulosclerosis or adhesions; T: Tubular atrophy/interstitial fibrosis; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; 24 h-u-pro: 24 h urine protein quantitation; UA: Uric acid; Scr: Serum creatinine; Alb: Albumin; Cys-C: Cystatin C; eGFR: Estimated glomerular filtration rate; HCY: Homocysteine; NAG: Urea and nag enzyme; SD: Standard Deviation; IQR: Inter-Quartile Range.

hypercellularity, endocapillary cellularity, and segmental sclerosis were observed in the different groups (Table 1).

3.4 | Risk factors in patients with tubular atrophy/interstitial fibrosis

Logistic regression analysis was performed according to whether renal tubular atrophy/interstitial fibrosis occurred. Univariate logistic regression analysis showed that the gender (OR, 1.047, 95% CI, 1.008–1.086, $p = 0.017$), age (OR, 1.027, 95% CI, 1.002–1.052, $p = 0.031$), SBP (OR, 1.027, 95% CI, 1.003–1.052, $p = 0.027$), BMI (OR, 1.130, 95% CI, 1.007–1.269, $p = 0.038$), fibrinogen (OR, 1.017, 95% CI, 1.010–1.024, $p < 0.001$), D-dimer (OR, 1.002, 95% CI, 1.001–1.003, $p = 0.003$), 24h-u-pro (OR, 1.670, 95% CI, 1.075–2.594, $p = 0.022$), and NAG (OR, 1.041, 95% CI, 1.008–1.075, $p = 0.013$) were significantly associated with tubular atrophy/interstitial fibrosis (Table 2). Multivariate analysis showed that fibrinogen (OR, 1.018, 95% CI, 1.010–1.025, $p < 0.001$) was confirmed to be an independent risk factor for tubular atrophy/interstitial fibrosis (Table 3).

3.5 | The model's performance

The logit model was constructed based on fibrinogen and UA. The chi-square, degree of freedom, and *p*-value for the Hosmer-Lemeshow

test of the model were 13.8, 8, and 0.088, respectively. The calibration plot of the model was shown in Figure 4, which pointed that the logit model was well calibrated. To further validate the discrimination of the model, we plotted the ROC curve for the model, fibrinogen, uric acid, and eGFR. The model achieved an AUC of 0.781 (95% CI, 0.659–0.903), while fibrinogen, uric acid, and eGFR were 0.764 (95% CI, 0.634–0.894), 0.624 (95% CI, 0.510–0.739) and 0.573 (95% CI, 0.459–0.687), indicating a good discrimination degree of the model (Figure 5).

TABLE 2 Univariate logistic regression analysis for tubular atrophy/interstitial fibrosis

Variable	OR	95% CI	*p*-value
Gender	1.047	1.008–1.086	0.017
Age	1.027	1.002–1.052	0.031
SBP	1.027	1.003–1.052	0.027
DBP	1.006	0.973–1.040	0.717
BMI	1.130	1.007–1.269	0.038
Fibrinogen	1.017	1.010–1.024	<0.001
D-dimer	1.002	1.001–1.003	0.003
24 h-u-pro	1.670	1.075–2.594	0.022
UA	1.004	0.999–1.009	0.093
Alb	0.936	0.853–1.026	0.159
Cys-C	4.116	0.281–60.283	0.302
HCY	0.985	0.919–1.057	0.679
Urea	0.884	0.615–1.270	0.504
NAG	1.041	1.008–1.075	0.013
Scr	0.862	0.597–1.246	0.430

Abbreviations: BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; 24 h-u-pro: 24 h urine protein quantitation; UA: Uric acid; Scr: Serum creatinine; Alb: Albumin; Cys-C: Cystatin C; eGFR: Estimated glomerular filtration rate; HCY: Homocysteine; NAG: Urea and nag enzyme.

TABLE 3 Multivariate logistic regression analysis for tubular atrophy/interstitial fibrosis

Variable	OR	95% CI	*p*-value
Fibrinogen	1.018	1.010–1.025	<0.001
UA	1.005	1.000–1.011	0.065

Abbreviation: UA: Uric acid.

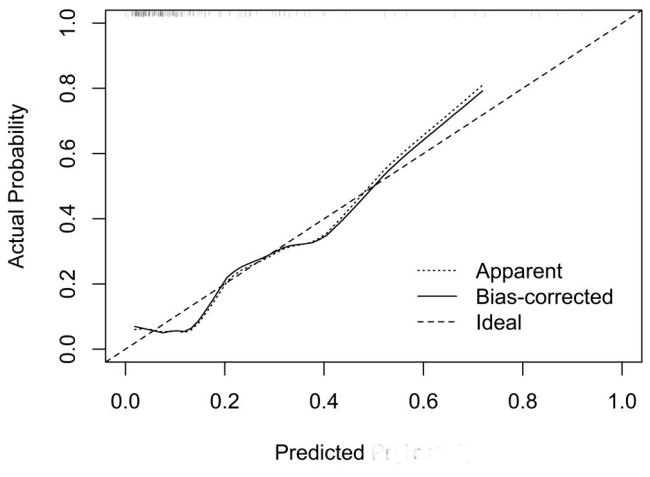

FIGURE 4 Calibration curves for predicting renal tubular atrophy/interstitial fibrosis probability by the model

4 | DISCUSSION

IgAN is a slowly progressive disease, and approximately 20–40% of patients with IgAN progressed to end-stage renal disease (ESRD) within 20 years. The extent of tubulointerstitial fibrosis on renal biopsy is consistently the most powerful predictor of progression to end-stage kidney disease in immunoglobulin A nephropathy (IgAN).[7] Although numerous studies have been conducted on the prognosis of IgAN, few have been focused on renal tubular atrophy/interstitial fibrosis. In this study, we retrospectively analyzed the clinical and pathological data of 176 patients with primary IgAN diagnosed by renal biopsy and found that 86.4% of the patients presented T0 score, and 13.6% presented T1/T2 score. To our knowledge, it is the first report of renal tubular atrophy/interstitial fibrosis's proportion in IgAN patients with eGFR ≥90 ml/min/1.73 m^2. This suggests a stable renal function does not mean a well pathological finding. Then, we evaluated the relationship between serum fibrinogen level and tubular atrophy/interstitial fibrosis in IgAN patients at the time of renal biopsy and found elevated fibrinogen level could be an important risk factor for moderate to severe renal interstitial fibrosis lesions in patients with IgAN.

Fibrinogen is a large hexameric plasma glycoprotein, which plays a key role in some pathophysiologic processes, including inflammation, atherogenesis, and thrombogenesis.[13] Several studies have confirmed that elevated plasma of fibrinogen was associated with a sharp deterioration of kidney function in patients with CKD.[13-15] However, the relationship between fibrinogen and IgAN, especially between fibrinogen and tubular atrophy/interstitial fibrosis, is rarely reported. Only Zhang J et al. reported that elevated serum fibrinogen level is an independent risk factor for IgA nephropathy. The author included patients with every level of eGFR but no subgroup analysis for each level of fibrinogen. The relationship between IgAN and coagulation/fibrinolysis system has been described in several studies.[16-18] In the present study, we first demonstrated that the level of serum fibrinogen was significantly higher in patients with T1/T2 scores as compared to those with T0, and increased with the aggravation of histopathological phenotypes. The mechanism of fibrinogen in renal tubular atrophy/interstitial fibrosis may be complicated. Previous studies have suggested that fibrinogen and its degradation products can promote renal fibrosis by triggering resident fibroblast proliferation through TLR2-, TLR4-, and ICAM-1-dependent signaling pathways.[19] Florin L's research showed that fibrinogen could participate in the development of fibrosis by triggering TGF-β1 expression, the central mediator in fibrosis process, and also by contributing to fibroblast proliferation.[20] Furthermore,

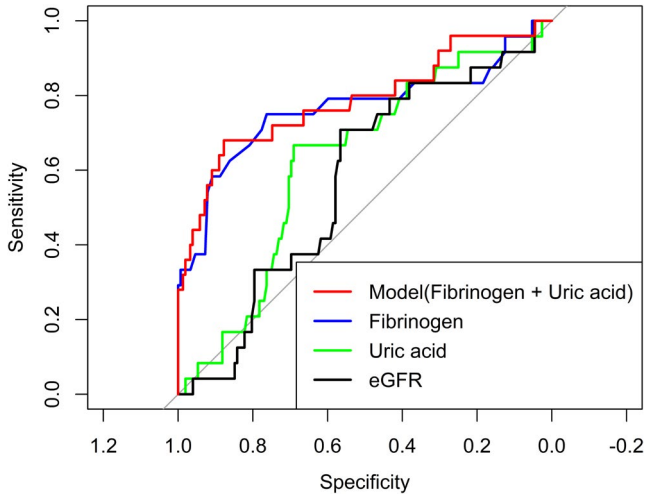

FIGURE 5 The ROC curve of the logit model, fibrinogen, uric acid, and eGFR

as an inflammation factor, fibrinogen activated cell signaling pathways, such as the mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB) signaling pathways. The above inflammatory pathways have also been confirmed to be key mediators of renal inflammation and fibrosis.[20-22]

Besides, our study also showed that uric acid was an important component of the logit model. This is not surprising since hyperuricemia plays an important role in the progression of IgA nephropathy. Hyperuricemia may cause changes in renal structure through different biological mechanisms, such as endothelial dysfunction, glomerulosclerosis, and tubulointerstitial renal damage, which eventually lead to an irreversible decline in kidney function.[23-26] Recent studies also have shown that hyperuricemia patients had higher T scores than normal uricemia patients.[27] The HUA leads to tubular atrophy/interstitial fibrosis might be illuminated by the following mechanisms. Urate crystals sedimentate in the renal tubules can directly block or damage the renal tubules and also form uric acid renal stones to damage the kidney, which makes for renal tubular atrophy and interstitial fibrosis.[28] HUA accelerated the production of inflammatory factors, such as TNF-β1 and MCP-1, which stimulate the inflammatory response and induce renal tubular injury and renal interstitial fibrosis.[29] Moreover, Ryu E reported that UA can induce the phenotypic transformation of renal tubular cells by reducing the synthesis and enhancing the degradation of E-cadherin, thus initiating epithelial-to-mesenchymal transition (EMT) of renal tubules and interstitial fibrosis.[30]

This study has two limitations. Firstly, our sample came from a single center and the size was small, especially in T2. Secondly, the cause-and-effect relationship between fibrinogen and tubular atrophy/interstitial fibrosis was uncertain because this study was retrospective.

In summary, our study has demonstrated that a higher fibrinogen level was found to be a risk factor for tubular atrophy/interstitial fibrosis in IgAN patients with eGFR ≥90 ml/min/1.73 m^2. With higher levels of fibrinogen and UA, patients who are suspicious of IgAN should get a renal biopsy early to defined tubular atrophy/interstitial fibrosis, even though there is no obvious abnormal change in the test of renal function.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University and in accordance with the Declaration of Helsinki. Patient's records were anonymized and de-identified before analysis.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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