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Original Article

Serum fibronectin combined with urine α1-MG in the diagnosis, treatment outcomes prediction and prognosis of chronic glomerulonephritis

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Abstract: Purpose: To investigate the predictive value of serum fibronectin (FN) and urine α1-microglobulin (α1-MG) in the diagnosis of chronic glomerulonephritis (CG). Methods: A total of 119 CG patients in our hospital were selected for our study cohort. 80 healthy people receiving a physical examination in our hospital during the same period were selected for the control group. ELISA and immunoturbidimetric assays were used to detect the serum FN and α1-MG levels. The clinical efficacy of each patient was recorded. Results: When the cut-off value was 0.541, the sensitivity of the CG diagnosis detected by FN combined with α1-MG was 92.16%, and the specificity was 88.00%. After treatment, the FN of the study group was higher than it was before the treatment (P< 0.001), and the urine α1-MG of the study group was lower than it was before treatment (P<0.001). After examining an ROC analysis curve, when the cut-off value was 0.701, the sensitivity of predicting the efficacy determined by FN and α1-MG was 88.00%, and the specificity was 88.00%. Conclusion: Due to the significant difference between CG patients and healthy people in terms of their serum and urine levels of FN and α1-MG, the combined diagnosis of FN and α1-MG is very valuable in diagnosing CG and predicting the treatment efficacy of CG.

Keywords: Serum fibronectin, urine α1-microglobulin, chronic glomerulonephritis, diagnosis

Introduction

Chronic glomerulonephritis (CG) is an allergic reaction which mainly manifests as glomerular damage. It is one of the most common chronic diseases in clinical practice [1]. Data from Wetmore et al. [2] also show that the current CG rate is increased year by year. As there are no obvious symptoms in early CG, most CG patients are diagnosed when the disease reaches an advanced stage, even chronic renal failure, making successful treatment even more difficult [3, 4]. At present, in clinical practice, the main diagnostic method for CG is to evaluate the glomerular filtration rate and the renal injury indicator [5]. Although there are many tools that can be used to reflect renal injury, and the tools are convenient, they usually do not have sufficient sensitivity or detection ability in early renal injury [6]. Because of the growing threat of CG, it has been treated as a key serious disease in clinical practice. In recent years, scholars at home and abroad have been researching how to treat CG more effectively [7-9].

Serum fibronectin (FN) is a complex protein with a polysaccharide binding to proteins. The exiting research has shown that FN is important in the diagnosis and disease course of liver and kidney diseases [10-12]. Urine α1-microglobulin (α1-MG) is a glycoprotein, which is synthesized in the liver and the lymphoid tissues. The pathological increase can be seen in renal tubular damage, which is widely used as an early sensitive indicator for evaluating renal injury [13]. However, no studies have confirmed that FN combined with urine α1-MG has a good diagnostic effect on CG. We speculate that that FN combined with urine α1-MG can have a good predictive value for the diagnosis, treatment, and prognosis of CG and performed this study.

Materials and methods

General information

A total of 119 CG patients in our hospital were selected as the study subjects of our study cohort, including 108 males and 11 females, and ranging in age from 26 to 64 years. The mean age was (34.68 ± 15.33) years, and the mean course of disease was (6.22 ± 3.27) months. 80 healthy subjects receiving a physical examination were placed into the control group, including 73 males and 7 females, and ranging in age from 25 to 65 years. The mean age was (35.16 ± 16.52) years old. This study was approved by the Ethics Committee of our hospital, and the above subjects signed informed consents.

Inclusion and exclusion criteria

Inclusion criteria: all patients in the study group met the clinical manifestations of CG [14]; patients diagnosed with CG in our hospital; after the diagnosis, the patients received regular follow-up and routine treatment in our hospital; patients with complete medical records; patients who participated in the investigation work of our hospital; patients ranging in age from 20 to 70 years old. Exclusion criteria: patients with tumors; patients with other cardiovascular diseases; patients with organ failure; patients with other diseases of the liver and kidneys; patients who had other chronic diseases or who had urinary system diseases; patients who received other drugs before admission; patients with a mental illness; patients transferred halfway.

Inclusion criteria for the control group: people aged from 20 to 70 years, people who underwent a physical examination in our hospital and were confirmed to be healthy. Exclusion criteria for the control group: people who refused to participate in this experiment.

Methods

In the study group, the patients were given the conventional treatment for CG in our hospital. The therapeutic schedule was as follows: anticoagulant therapy was conducted, infection was prevented, and strenuous exercise was avoided. 10 mg benazepril was taken orally before meals, with 1 d/time (Beijing Novartis Pharmaceutical Co., Ltd., GYZZ H20030514). A 2.4 g nephritis rehabilitation tablet was also taken, with 3 d/time (Tianjin Tongrentang Group Co., Ltd., GYZZ Z10940034). The course of treatment was one month. 4 mL of fasting venous blood and 10 mL of morning urine were collected before and after the treatment. They were placed at room temperature for 30 min, and centrifuged (4000 rpm/min) for 10 min to obtain upper serum and supernatant. Serum FN concentration (Human Fibronectin ELISA Kit Abcam, USA, ab219046) of the blood samples was determined using ELISA. The α1-MG concentration of the urine samples was measured using immunoturbidimetry (α1-microglobulin Assay Kit, Shanghai Xinfan Biotechnology Co., Ltd., XFSW251B). The evaluation of the CG patients by Kou [15] was referred. The treatment efficacy was evaluated and rated. A prognosis follow-up was conducted on the patients for 3 years. The patients come back to the hospital once every quarter for follow-up and any CG recurrence was recorded.

Outcome measures

The concentrations of FN and α1-MG in the study group before and after the treatment were compared with those in the control group. We wanted to determine the diagnostic value of the combination of FN and α1-MG to detect CG before the treatment, the predictive value of the combination of FN and α1-MG in the treatment outcome after the treatment, and the predictive value of FN and α1-MG in the recurrence of CG.

Statistical method

All the experimental results were statistically calculated using SPSS 24.0 statistical software (Beijing Strong Vinda Information Technology Co., Ltd.). All the graphs were drawn using Graphpad 8 software (Shenzhen Tianruiqi Software Technology Co., Ltd.), and the results were confirmed by a secondary proof. The enumeration data such as patient gender, place of residence, etc. were expressed in the form of a rate, and a chi-square test was used for comparisons between groups. The measurement data such as FN and α1-MG were expressed in the form of mean ± standard deviation (mean ± SD). An independent-samples *t* test was used for comparisons between groups, and a paired *t* test was used for comparisons within a group, and an ROC curve was used for the predictive analysis. An SPSS binary logistic regression

Table 1. Comparison of the clinical data between the study and control groups [n (%)]

	Study group (n=119)	Control group (n=80)	t or X^2	*P*
Age	34.68 ± 15.33	35.16 ± 16.52	0.210	0.834
BMI (KG/cm^2)	22.16±5.69	22.76 ± 5.27	0.739	0.461
White blood cells (×10^9/L)	5.05±1.27	5.28 ± 1.05	1.341	0.182
Red blood cells (×10^{12}/L)	4.16±0.64	4.22 ± 0.73	1633	0.104
Platelet count (×10^9/L)	227.31 ± 42.63	235.16 ± 46.83	1.224	0.222
Gender			0.014	0.905
Male	108 (90.76)	73 (91.25)		
Female	11 (9.24)	7 (8.75)		
Marital status			1.164	0.281
Married	112 (94.12)	72 (90.00)		
Unmarried	7 (5.88)	8 (10.00)		
Education level			0.246	0.620
<High school	42 (35.29)	31 (38.75)		
≥High school	77 (64.71)	49 (61.25)		
Smoking habits			0.538	0.463
Yes	98 (82.35)	69 (86.25)		
No	21 (17.65)	11 (13.75)		
Exercise habits			0.821	0.365
Yes	14 (11.76)	13 (16.25)		
No	105 (88.24)	67 (83.75)		
Place of residence			0.687	0.407
Town	86 (72.27)	62 (77.50)		
Rural	33 (27.73)	18 (22.50)		
Ethnicity			0.134	0.715
Han	113 (94.96)	75 (93.75)		
Minority	6 (5.04)	5 (6.25)		

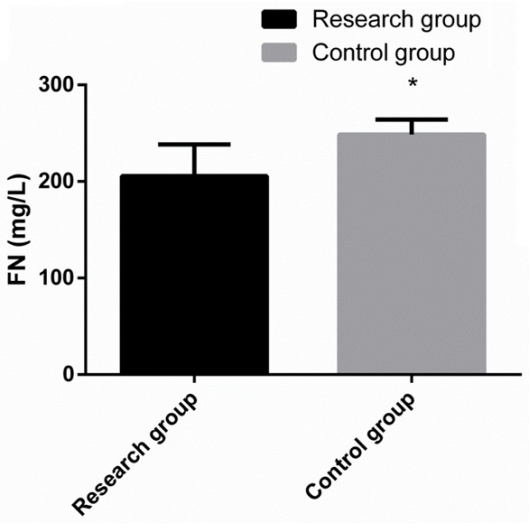

Figure 1. The serum FN concentration of the study group before treatment was compared with the concentration in the control group. *represented that it was compared with the serum FN concentration of the study group before treatment, and P < 0.001.

analysis was performed for the prediction of the combined detection, and then the ROC curve analysis followed. *P*<0.05 was considered statistically significant.

Results

General data comparison

There were no differences in age, BMI, white blood cells, red blood cells, platelet count, gender, marital status, education level, smoking habits, exercise habits, living environment, or ethnicity between the study and control groups (P>0.050). This meant that the two groups of patients were comparable (**Table 1**).

Comparison of FN and α1-MG concentrations

The serum FN of the study group before treatment was 205.62 ± 32.83 mg/L, which was lower than the level of 248.63 ± 15.59 mg/L in the control group, and P<0.001. The urine α1-MG of the study group before treatment was 14.83 ± 4.86 mg/L, which was higher than the level of 8.53 ± 2.08 mg/L in the control group, and P<0.001 (**Figures 1**, **2**).

Diagnostic value of combined detection of FN and α1-MG for CG

The combined predictive probability values of FN and α1MG in the two groups were obtained using an SPSS binary logistic regression analysis. After the ROC curve analysis, when the cut-off value was 0.541, the sensitivity of the CG diagnosis determined by FN and α1-MG was 92.16%, and the specificity was 88.00% (**Figure 3**, **Table 2**).

Comparison of FN and α1-MG concentrations before and after treatment

The FN of the study group after treatment was (238.17 ± 12.97) mg/L, which was higher than

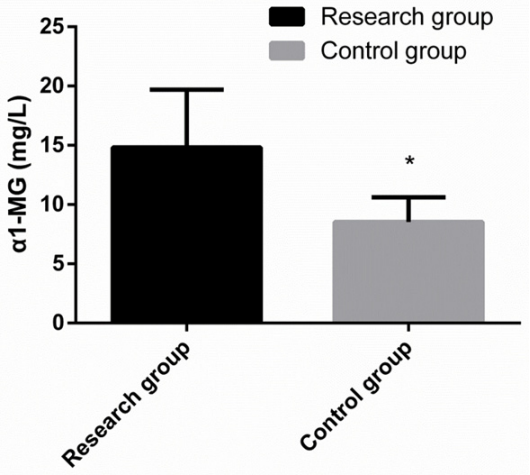

Figure 2. The urine α1-MG concentration of the study group before treatment was compared with the concentration of the control group. *represented that it was compared with the urine α1-MG concentration of the study group before treatment, and P < 0.001.

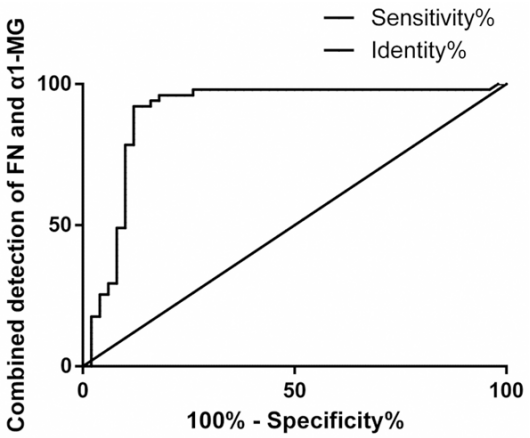

Figure 3. Diagnostic value of the combined detection of FN and α1-MG for CG. After the ROC curve analysis, the sensitivity of the CG diagnosis detected by FN and α1-MG was 92.16%, and the specificity was 88.00%.

the level (205.62 ± 32.83) mg/L of the control group before treatment, and *P*<0.001. The urine α1-MG of the study group after treatment was (10.08 ± 1.73) mg/L, which was lower than the level (14.83 ± 4.86) mg/L of the control group before treatment, and P<0.001 (**Figures 4** and **5**).

Predictive value of the combined detection of FN and α1-MG for CG therapeutic outcomes

After treatment, 13 of the 119 patients in the study group were cured, the treatment in 71

Table 2. The diagnostic value of the combined detection of FN and α1-MG for CG

Indicator	Numerical value
Area under curve	0.899
Std. error	0.037
95% CI	0.826~0.971
Cut-off	0.541
Sensitivity (%)	92.16
Specificity (%)	88.00
P	<0.001

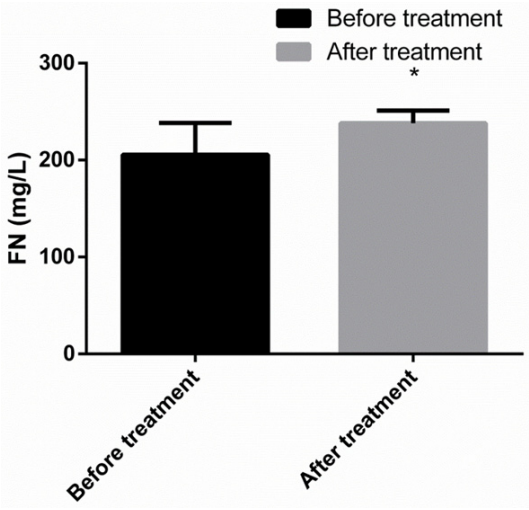

Figure 4. The serum FN concentration in the study group was compared before and after treatment. *represented that it was compared with the serum FN concentration of the study group before treatment, and P < 0.001.

patients was markedly effective, and the treatment in 35 patients was ineffective. The patients who were cured or who had markedly effective outcomes were placed into group A (n=84). The patients with an ineffective outcome were divided into group B (n=35). The serum FN of group A was (242.36 ± 12.57) mg/L, which was higher than the level (215.94 ± 18.54) mg/L of group B, and *P*<0.001. The urine α1-MG of group A was (9.28 ± 1.66) mg/L, which was lower than the level (12.87 ± 2.04) mg/L of group B, and *P*<0.001. The combined predictive probability values of FN and α1-MG in the group A and B were obtained through an SPSS binary logistic regression analysis. After the ROC analysis curve, when the cut-off value was 0.701, the predictive sensitivity of the CG diagnosis detected by FN and α1-MG was 88.00%, and the specificity was 88.00% (**Figures 6**-**8** and **Table 3**).

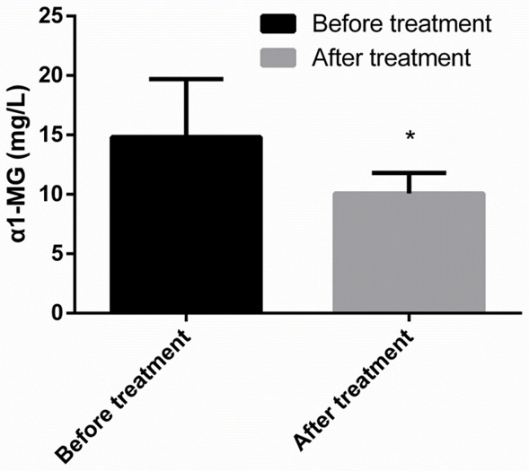

Figure 5. The urine α1-MG concentration in the study group was compared before and after treatment. *represented that it was compared with the urine α1-MG concentration of the study group before treatment, and P < 0.001.

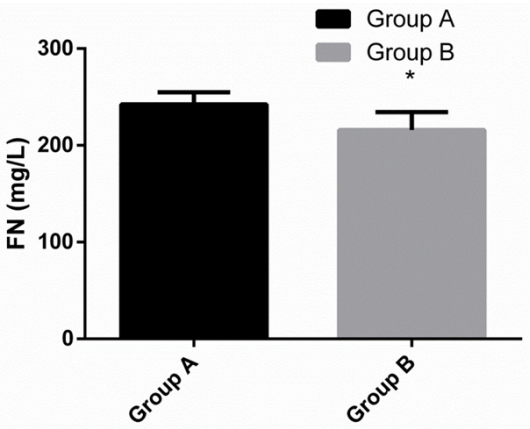

Figure 6. The serum FN concentration was compared between group A and group B. *represented that it was compared with the serum FN concentration of group A, and P < 0.001.

Predictive value of FN and α1-MG in the recurrence of CG

Among the 119 patients, 114 patients were successfully followed up, so the success rate was 95.80%. Among them, 72 cases were stable and no prognosis was reviewed. This cohort was treated as group C. CG recurrence occurred in another 42 patients and that cohort was treated as group D. The serum FN of group C was (240.96 ± 18.93) mg/L, which was higher than the level (209.81 ± 26.87) mg/L of group D, and *P*<0.001. The urine α1-MG of group C was (9.82 ± 2.28) mg/L, which was lower than the level (14.83 ± 5.29) mg/L of group D, and

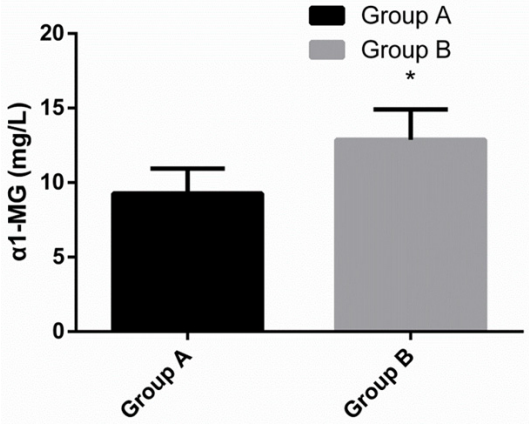

Figure 7. The urine α1-MG concentration was compared between group A and group B. *represented that it was compared with the urine α1-MG concentration of group B, and P < 0.001.

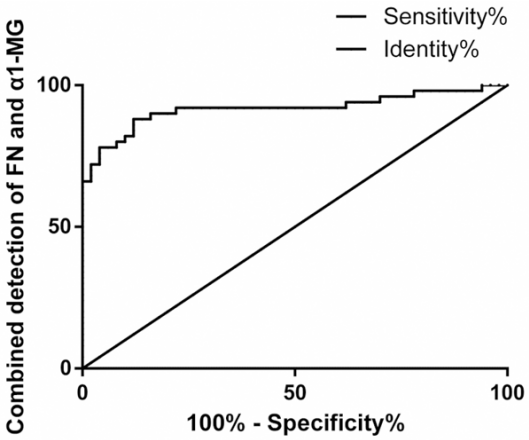

Figure 8. The predictive value of the combined detection of FN and α1-MG for CG therapy outcomes. After the ROC analysis curve, when the cut-off value was 0.701, the predictive sensitivity of the CG diagnosis detected by FN and α1-MG was 88.00%, and the specificity was 88.00%.

P<0.001. The prediction probabilities of FN combined with α1-MG in group A and group B were learned from the SPSS binary logistic regression analysis. According to the ROC curve, when the cut-off value hit 0.487, FN combined with α1-MG had a predictive sensitivity of 95.83% and a specificity of 70.31% in the prognosis recurrence of CG (**Figure 9** and **Tables 4**, **5**).

Discussion

At present, the symptoms of CG mainly are diffuse or focal segmental mesangial proliferation, focal sclerosis, etc., including glomerular

Table 3. The predictive value of the combined detection of FN and α1-MG for CG treatment outcomes

Indicator	Numerical value
Area under curve	0.917
Std. error	0.031
95% CI	0.856~0.978
Cut-off	0.701
Sensitivity (%)	88.00
Specificity (%)	88.00
P	<0.001

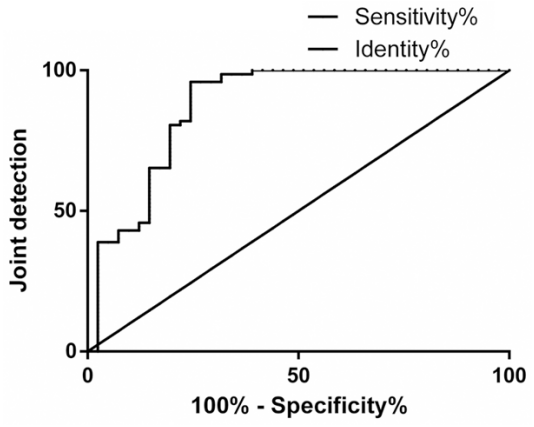

Figure 9. The predictive value of FN and α1-MG in the recurrence of CG. According to the ROC curve, when the cut-off value hit 0.487, FN combined with α1-MG had a predictive sensitivity of 95.83% and a specificity of 70.31% in the prognosis recurrence of CG.

lesions. CG may also have varying degrees of renal tubulointerstitial inflammation and fibrosis, which has a great impact on patients [16]. Moreover, as the kidneys have a strong reserve capacity and compensatory ability, the damage manifestation of early CG to the kidney is not obvious. Therefore, there are still major obstacles to diagnosing early CG in clinical practice [17]. At present, for the current diagnosis of CG, the most common indicators are creatinine (SCr), cystatin C (Cys-C), urea (SUrea), etc. However, these indicators are easily affected in the human environment. They may not accurately respond to the renal injury, or to the occurrence and development of CG [18]. α1-MG in the urine is an excellent laboratory monitoring indicator to reflect the slight functional damage of the proximal renal tubular. It has played a very notable role in the diagnosis and treatment of various renal diseases [19, 20]. As a complex protein widely distributed in human tissues, FN usually plays a role in maintaining homeostasis. Once the concentration changes, it indicates that the disease or inflammation will occur [22]. At present, it has been a long time since the relationship between α1-MG and FN for CG has been confirmed [24, 25]. The exact mechanism of action on CG is not clear. There are few studies on the diagnosis and treatment significance of the combined measurement of α1-MG and FN for CG at home and abroad. This study analyzed the value of FN combined with α1-MG in the diagnosis, treatment outcome, and prognosis of CG, in the hope of providing a more accurate guidance for the future diagnosis and treatment of CG.

The results of this experiment showed that the serum FN concentration in the study group was lower than the concentration in the control group, but the α1-MG concentration in the urine was higher than it was in the control group. This suggests that FN and α1-MG may be involved in the occurrence and development of CG, which is consistent with the results of Dabla et al. [26] and Abrass et al. [27]. FN is usually distributed in the human environment in the form of tissue or plasma [28]. After CG occurs, during the process of continuous damage and repair of vascular endothelial cells and mesangial cells, the cell type FN is consumed in a large amount. At this time, the plasma type FN is converted into a cell type and supplemented to the repair process to maintain the homeostasis of the entire body. Therefore, the serum FN concentration of CG patients is greatly reduced. Moreover, α1-MG is mainly produced by hepatocytes and lymphocytes. It needs to pass through the glomerular filtration membrane during its secretion into the urine. It will be reabsorbed and degraded by a large amount of the renal tubules during the filtration process [29]. In this study, the urine α1-MG concentration of the study group before treatment was higher than of the concentration in the control group, which indicated that the proximal kidney tubules had been damaged. Therefore, the reabsorption capacity of the kidney was reduced. During the filtration process, a large amount of α1-MG was not absorbed by the glomerular filtration membrane and released into the urine. The study done by Renke et al. [30] stated that α1-MG can arouse CG through oxidative stress, which serves as evidence for the results of this study. Through the ROC curve analysis, it was found that the combined detection of FN and α1-MG had a good diagnostic efficiency for the occur-

Table 4. Univariate analysis of CG recurrence by FN and α1-MG

	Group C (n=72)	Group D (n=42)	t	P
FN	240.96 ± 18.93	209.81 ± 26.87	7.237	<0.001
α1-MG	9.82 ± 2.28	14.83 ± 5.29	7.013	<0.001

Table 5. The predictive value of FN and α1-MG for CG recurrence

Index	Numerical value
Area under curve	0.875
Std. error	0.039
95% CI	0.798~0.952
Cut-off	0.487
Sensitivity (%)	95.83%
Specificity (%)	70.73%

rence of CG. It was suggested that the combined detection can be used as a screening method for early CG in clinical practice. Donadio et al. [31] revealed the valuable sensitivity of α1-MG for diagnosing CG in their study. But they just found a moderate specificity of α1-MG due to the lack of combined detection with other indexes. Further analysis of the changes of FN and α1-MG before and after treatment, and the predictive value of combined detection for CG therapy, showed that the FN of the study group was higher than it was before treatment. The α1-MG of the study group was lower than it was before the treatment. The ROC curve analysis also showed that the combined detection had a better sensitivity and specificity for the prediction of therapeutic outcomes. It was suggested that the patient's rehabilitation and curing condition can be judged b monitoring the FN and α1-MG concentrations of CG patients. However, in this study, the FN concentration of the study group was lower than Yang et al. found [32]. The differences [32] may be caused by the different therapy methods. The course of nephropathy included in Yang's study was 2 to 3 years, but the course of the subjects in this study was only (6.22 ± 3.27) months. Differences in FN concentrations may be caused by the different development degree of a patient's condition. As the effect of the current course of disease on FN has not been confirmed, we will conduct more in-depth research to verify our results as soon as possible. According to the ROC curve of patients with the prognosis of the recurrence of CG, the combination of FN and α1-MG enjoys a good predictive value, suggesting the feasibility of preventing against CG recurrence via monitoring the FN and α1-MG expressions to improve the prognosis of patients.

The purpose of this experiment was to investigate the diagnosis and treatment significance of the combined detection of FN and α1-MG for CG. However, there are still some shortcomings due to the limited experimental conditions. For example, the influencing mechanism of FN and α1-MG on CG occurrence still needs to be verified by further research. A statistical analysis with big data cannot be performed due to limited experimental subjects and the short course of disease. It is possible that there may be differences in the expression of FN and α1-MG in different races and ethnic groups. We will conduct a longer follow-up study on the subjects of this experiment. In order to obtain more valuable guidance, we will also continue to explore the effects of FN and α1-MG on GG.

In summary, the serum FN of CG patients is lower than that of normal people. The urine α1-MG of CG patients is higher than that of normal people. The combined detection of FN and α1-MG has a good sensitivity and specificity for the diagnosis and treatment of CG. It is expected to be a reliable indicator for clinical CG diagnosis and treatment in the future.

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Disclosure of conflict of interest

None.

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