

## Original Article

# High excretion of urinary beta-2-microglobulin and IgG predicts progressive renal function in idiopathic membranous nephropathy

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**Abstract:** Background: The treatment of idiopathic membranous nephropathy with nephrotic syndrome is contradictory. Although several biological markers have been used as predictors of prognosis, little is known about the clinical use of biomarkers which can explain contradictory results. We compared the accuracy of urinary beta-2-microglobulin (U $\beta$ 2m), UlgG, N-acetyl-beta-glucosaminidase (U $\beta$ -NAG) and  $\alpha$ -1-microglobulin (U $\alpha$ 1m) in predicting renal insufficiency and analyzed the risk factors. Methods: We studied U $\beta$ 2m, UlgG, U $\beta$ -NAG and U $\alpha$ 1m in urinary samples from patients with idiopathic membranous nephropathy according to the kidney disease progression or not. Kaplan-Meier curve was used to present renal survival rates, and Cox regression analysis was employed to analyze the risk factors. Progression was defined as serum creatinine rise >50%, or serum creatinine rise to an absolute value of >135 mmol/L. Remission was defined as proteinuria <2.0 g/day with stable renal function. Results: Sixty patients were included (41 males and 19 females; age, 33  $\pm$  15 years). So far, 20 (33.3%) patients progressed to the preset end point of renal failure and remission affected 27 patients (45%). The area under the receiver operating characteristic curve for U $\beta$ 2m and UlgG was 0.786 and 0.769, respectively. Sensitivity and specificity for U $\beta$ 2m (threshold value 1.17 mg/l) were 82% and 70%, respectively, and those for UlgG (threshold value 24.98 mg/l) were 80% and 62%, respectively, higher than those for U $\beta$ -NAG and U $\alpha$ 1m. Multivariable COX model analysis revealed that the relative risk of UlgG and U $\beta$ 2m was 1.045 and 1.126, respectively, with the 95% confidence interval of 1.015-1.076 and 1.105-1.137, respectively. Conclusions: Although U $\beta$ 2m, UlgG, U $\beta$ -NAG and U $\alpha$ 1m all can predict progression in iMN, U $\beta$ 2m and UlgG have a higher specificity and sensitivity, which are independent risk factors for progressive renal function and provide a better guidance for clinical physicians.

**Keywords:** Idiopathic membranous nephropathy, kidney survival rate, beta-2-microglobulin, IgG

## Introduction

Idiopathic membranous nephropathy (iMN) is a kind of autoimmune glomerular disease with unknown etiology, which is a leading cause of nephrotic syndrome (NS) in adults [1]. NS is associated with an increased risk of kidney failure and death from cardiovascular and cerebrovascular diseases. Approximately half of the patients with nephrotic iMN eventually develop renal insufficiency, and they even have to accept a replacement therapy [2]. But it is possible that the patients who will develop spontaneous remission do not unnecessarily receive toxic therapy. There is no specific treatment for iMN and there are certain differences on the use of immunosuppressant, which should be

initiated at an early stage or only in patients who will otherwise have some complications. This requires an ideal prognostic biomarker to identify highly risky patients.

The severity of kidney disease is usually staged according to the kidney function based on estimated glomerular filtration rate (eGFR) [3]. However, eGFR is not an early predictive marker for progression and treatment decisions. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have been mainly studied in acute kidney injury. Although studies have further confirmed that they can also predict outcomes of the patients with iMN [4], there is lack of more evidence. Researchers have previously validated that

**Table 1.** Baseline characteristics of the patients with iMN (n = 60)

Item	Data
Gender (M/F)	41/19
Age (year)	33 ± 15
MAP (mmHg)	98 ± 16
eGFR (ml/min/1.73 m <sup>2</sup> )	72 ± 23
Serum Creatinin (μmol/l)	64.33 ± 26.42
Serum albumin (g/l)	28.06 ± 9.11
Follow-up (months)	21 ± 9
Urine Sample	
Proteinuria (g/24 h)	3.63 ± 2.34
β2m excretion (mg/l)	1.25 ± 1.19
IgG excretion (mg/l)	27.24 ± 20.29
α1m excretion (mg/l)	51.32 ± 41.42
NAG excretion (U/L)	57.46 ± 32.69

high urinary concentrations of proteins that reflect tubular or glomerular damage precede a decline in eGFR. Urinary β-2m and IgG excretion rates have been reported to be used to predict disease progression and preserved renal function in patients with iMN [5-7]. However, most of these studies are carried out on Caucasian population. The purpose of this study was to evaluate the prognostic value of urinary β-2m and IgG excretion in patients with iMN.

## Materials and methods

### Study population

In this study, urine and blood samples were collected from patients who had proven iMN by biopsy. The patients were diagnosed between January 2010 and March 2015 in the Division of Nephrology, Nephrology Department of People's Hospital of Xinjiang Uyghur Autonomous Region. It was shown that a lower glomerular density was associated with progression based on a 50% reduction in eGFR or reaching end-stage renal disease (ESRD) [8]. Thus the morphological diagnosis of all cases was established by light microscopy and immunofluorescence staining of representative kidney biopsy specimens containing at least six glomeruli. The inclusion criteria: nephrotic proteinuria (24-hour proteinuria ≥3.5 g, or urinary albumin/creatinine ratio ≥2.0 g/g); serum albumin ≤35 g/l; baseline sCr ≤135 μmol/l and eGFR ≥24 ml/min/1.73 m<sup>2</sup>). All subjects were followed up for

6 months or more. Some secondary factors of iMN were eliminated, such as systemic lupus erythematosus, thyroid disease, cancer, or medication with gold or penicillamine. A total of 60 cases were enrolled, and informed consent was obtained from all patients. The baseline data of the subjects are shown in **Table 1**.

### Clinical data, laboratory measurements and definitions

Patient gender, age, blood pressure, serum albumin, serum creatinine, proteinuria, UNAG, Uβ2m, Uα1m and UIgG were evaluated. All of the above indicators were recorded within 1 week of biopsy and during the follow-up. Although several studies have confirmed that for assessment of the potential independent risk factors of kidney outcomes, time-average proteinuria is better than a single time-point value of proteinuria [9-12], this particular parameter could not be easily obtained in our cohort. Thus, the baseline proteinuria was used in the present study.

Mean arterial pressure (MAP) was diastolic blood pressure plus 1/3 pulse pressure difference. In our institution the level of renal insufficiency was used to indicate immunosuppressive therapy. If the patient's serum creatinine exceeded 135 μmol/l or increased by >50% from the baseline, it was defined as progression. Survival was calculated using the date of the baseline measurements as  $t = 0$ . Complete remission (CR) was defined as proteinuria <0.2 g/day with a stable serum creatinine concentration, normal serum albumin and negative urine protein. Partial remission (PR) was defined as proteinuria <2.0 g/day with stable renal function (compared with baseline serum creatinine, less than 20%) or decline of 24-hour urinary protein baseline by more than 50%. No remission (NR) described that proteinuria was in nephrotic range, not achieving CR or PR after 6-month treatment and falling to less than 50% of the baseline level.

### Calculations

In order to understand the kidney function better, a modified three-variable equation was applied to estimate GFR of the subjects, which was Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [3]. Continuous variables were expressed as mean ± SD. Fre-

## Decreased those protein can improve prognosis of iMN

**Table 2.** Sensitivity, specificity, PPV and NPV of the most discriminative thresholds of urinary proteins for the prediction of renal failure in patients with iMN

Parameter	AUC	Threshold	Sensitivity	Specificity	PPV	NPV
U $\beta$ 2m excretion	0.786	1.17 mg/l	82%	70%	74%	75%
UIgG excretion	0.769	24.98 mg/l	80%	62%	71%	70%
U $\beta$ -NAG excretion	0.659	40.34 U/L	80%	60%	68%	71%
U $\alpha$ 1m excretion	0.647	40.35 mg/l	75%	63%	65%	72%

**Table 3.** Prognostic factors of IMN patients revealed by univariate COX model analysis

Parameter	B	SE	Wald	P	RR	95% CI
U $\alpha$ 1m	0.003	0.007	0.205	0.651	1.003	0.990~1.017
U $\beta$ -NAG	-0.024	0.010	6.094	0.014*	0.976	0.957~0.995
U $\beta$ 2m	0.450	0.177	6.444	0.011*	1.568	1.108~2.219
UIgG	0.040	0.020	3.869	0.049*	1.041	1.000~1.083

\*The difference was statistically significant,  $P < 0.05$ .

quency or percentage was used to express frequency data. Unpaired t-test was used for intergroup comparison, and chi-square analysis was used as appropriate. Renal survival rates were calculated using Kaplan-Meier curve. Predictive accuracy was assessed by receiver operating characteristics (ROC) curve. The area under the curve (AUC) was determined, and the sensitivity and specificity were calculated by using the most discriminative cut-off points for both parameters. The sensitivity and specificity of these cut-off points were used to calculate the positive likelihood ratio (Table 2). Using the data of the present patient cohort, we also studied the effect of other parameters in predicting renal outcomes. Statistically significant indicators would be selected and used as covariates in the Cox regression analysis. On the basis of the cut-off, the patients were divided into two groups, high risk group and low risk group.

All statistics were performed using SPSS 21.0 software.  $P < 0.05$  indicated significant difference.

### Results

The complete data of 60 cases (41 males and 19 females; age,  $33 \pm 15$  years) with iMN were collected. The baseline characteristics of these patients are listed in Table 1.

About treatment, 97% of patients were treated with hormone and immunosuppressive thera-

py. The average follow-up was  $21 \pm 9$  months (range, 6-29 months). In the process, 20 (33.3%) patients progressed to the pre-set end point of renal failure. The reason for renal death was serum creatinine  $>135 \mu\text{mol/l}$  in 14 patients and serum creatinine rise  $>50\%$  in 6 patients. Overall renal survival was 90% at 6 months, 81% at 1 year, and 63% at 2 years. Thus in most patients, the kidney disease progressed within 2 years after diagnosis. It was known that a fixed serum creatinine as end point was controversial [5]. As a matter of fact, it was possible to make a patient fulfill the renal failure criteria even when a

small increase of serum creatinine concentration was detected. Thus the rate of renal function deterioration was also assessed. In the 20 patients who reached the predefined end point of renal failure, serum creatinine was increased by an average of 41%, from  $74.3 \pm 10.4$  to  $131.8 \pm 17.1 \mu\text{mol/l}$ . The eGFR was  $73.7 \pm 14.3 \text{ ml/min/1.73 m}^2$  at the baseline and  $43.6 \pm 8.3 \text{ ml/min/1.73 m}^2$  at the end point. The absolute decrease of eGFR was  $43 \text{ ml/min/1.73 m}^2/\text{year}$  on average. The serum creatinine was  $44.7 \pm 12.5 \mu\text{mol/l}$  at the baseline and  $52.8 \pm 14.7 \mu\text{mol/l}$  at the end of follow-up compared with the non-failure group.

ROC curve was used to evaluate the predictive accuracy of U $\beta$ 2m, UIgG, U $\beta$ -NAG and U $\alpha$ 1m. From the coordinate points of the ROC curve, sensitivity and specificity for all parameters were calculated using the best discriminative threshold (Table 2).

In univariate COX model analysis, the following parameters were significantly related to renal outcomes: urinary excretion of  $\beta$ 2m, U $\beta$ -NAG, UIgG ( $P < 0.05$ ). Multivariable COX model analysis revealed that UIgG and U $\beta$ 2m were the independent predictive factors, and the relative risk was 1.045 and 1.126, respectively, with the 95% confidence interval of 1.015 to 1.076 and 1.105 to 1.137, respectively (Tables 3, 4).

Renal survival curves using the risk stratification for U $\beta$ 2m, UIgG and U $\beta$ -NAG are depicted

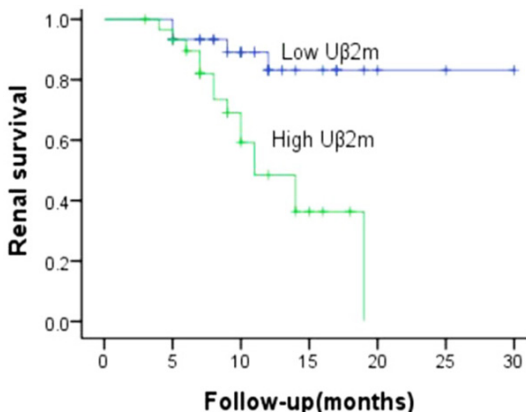
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**Table 4.** Prognostic factors of IMN patients revealed by multivariable COX model analysis

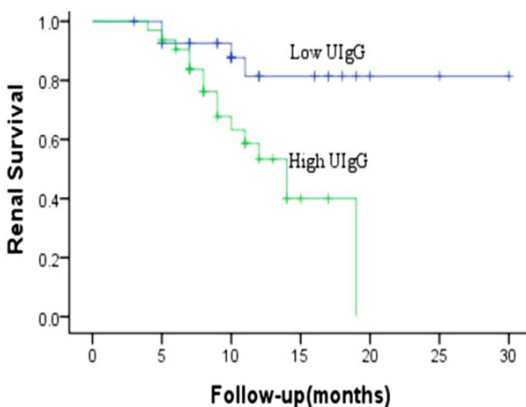
Parameter	B	SE	Wald	P	RR	95% CI
UlgG	0.044	0.015	9.026	0.003*	1.045	1.015~1.076
U $\beta$ 2m	0.132	0.064	4.878	0.046*	1.126	1.105~1.137

\*The difference was statistically significant,  $P < 0.05$ .

( $\leq 40.34$  U/L) were 64% and 76% in the first year, respectively. At the end of follow-up, the renal survival was 38% in patients with high U $\beta$ -NAG and 74% in patients with low U $\beta$ -NAG. All differences in survival rates were highly significant.



**Figure 1.** Renal survival in patients with iMN with  $\beta$ 2m excretion  $\leq 1.17$  mg/l (low U $\beta$ 2m) and  $> 1.17$  mg/l (high U $\beta$ 2m).



**Figure 2.** Renal survival in patients with iMN with IgG excretion  $\leq 24.89$  mg/l (low UlgG) and  $> 24.89$  mg/l (high UlgG).

in **Figures 1-3.** Renal survival was 52% at 1 year in patients with high U $\beta$ 2m ( $> 1.17$  mg/l) and 83% in patients with low U $\beta$ 2m ( $\leq 1.17$  mg/l). At the end of follow-up, the survival rates were 36% and 80%, respectively. The survival rates at 1 year in high UlgG group (threshold  $> 24.98$  mg/l) and low UlgG group ( $\leq 24.98$  mg/l) were 50% and 81%, respectively. At the end of follow-up, the renal survival was 36% in patients with high UlgG and 80% in patients with low UlgG. The survival rates in high NAG group (threshold  $> 40.34$  U/L) and low U $\beta$ -NAG group

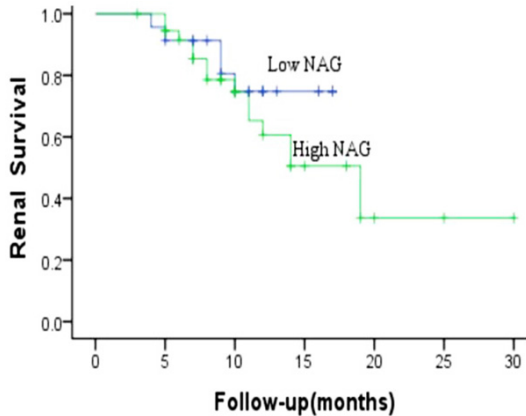
We found that remission occurred in 27 patients (45%) during follow-up, among which complete remission affected 12 patients. There was significant difference between complete remission (CR) and partial remission (PR) group in all the urine and blood samples parameters except the urine protein. Two patients relapsed (one suffered CR, and the other suffered PR).

### Discussion

Our data had predictive value for the prognosis of iMN patients to a certain degree. The performance of U $\beta$ 2m, UlgG and U $\beta$ -NAG as predictors for renal insufficiency has been validated, and the first two parameters were superior in terms of specificity and sensitivity, which were the independent predictive factors.

Our conclusion may be criticized, because a fixed serum creatinine value of  $135 \mu\text{mol/l}$  was used as the end point to define renal failure in our study. We have mentioned that a small increase of serum creatinine concentration may be sufficient to make a patient fulfill the renal failure criteria. Some scholars think that double creatinine is considered as renal replacement end point, but Coresh J [13] have found that no matter whether renal function is poor or better in patients with chronic kidney disease (CKD), the chance of double creatinine within 2 years is very low. However, it has been shown in many studies that moderate renal insufficiency with serum creatinine levels of  $125\text{-}135 \mu\text{mol/l}$  is an accurate predictor of ESRD [14, 15]. Furthermore, it is evident from a perpetual change in serum creatinine and decrease in eGFR that renal function is severely disturbed at the end point. When compared to the non-failure group, decrease of eGFR has a highly significant difference over time, indicating that we are able to identify whether the disease has progressed or not with this end point. Our data suggested that serum albumin did not indicate disease progression and ease. Kaneko K [21] mentioned that biological antioxidant potentials (BAP) had significant correlation with

## Decreased those protein can improve prognosis of iMN



**Figure 3.** Renal survival in patients with iMN with NAG excretion  $\leq 40.34$  U/l (low NAG) and  $>40.34$  U/l (high NAG).

serum albumin in iMN. Roche M [22] found that serum albumin was the most abundant antioxidant in vivo, and hypoalbuminemia reduced the body's ability to repair oxidative stress. Maybe there is a similar mechanism in iMN patients, and hypoalbuminemia promotes the progress of kidney disease. Of course, more studies are needed to confirm this speculation, especially those of different races.

As early as 1995, Reichert [6] had proposed that beta 2-microglobulin in membranous nephropathy could assess renal function, and noted that urine PH should be greater than 6 when testing the beta 2-microglobulin. The validity of  $U\beta 2m$  in predicting renal failure was established in our study, and kidney survival rate significantly reduced within 1 year in patients who excreted high  $U\beta 2m$ . Sensitivity and specificity were 82% and 70%, respectively, a little lower than those in Branten's study [5]. On the one hand, detection method was different, and race may also affect the results. The Research Group on Progressive Renal Diseases in Japan [16] found that the overall renal survival rate was 90% at 10 years and 81% at 15 years after diagnosis. The prognosis seemed considerably better in Japanese patients. In our study,  $U\beta 2m$  was the most significant independent predictive factor. It has been well established that  $U\beta 2m$  reflects the severity of tubulointerstitial injury. But the value of  $U\beta 2m$  in predicting remission was not evaluated in our study.

As in other types of glomerular diseases, the primary lesion of iMN is the glomerular filtra-

tion barrier (GFB) with increased excretion of protein substances of different molecular weight. IgG is a macromolecular substance, which cannot pass through glomerular filtration membrane unless GFB is damaged. Aricim M [17] has explained that urine IgG plays an important role in renal tubule toxicity in the urine protein. Bazzi C [7] reported the predictive value of  $UlgG$  using a cut-off value of 250 mg/24 h, and the sensitivity and specificity were both 88%. In later research, it was confirmed that high fractional excretion of IgG ( $FE-IgG \geq 0.02$ ) predicted an increased risk of renal failure and a lower chance of remission [18]. Our data confirmed the above conclusion. Applying threshold value to our study cohort based on ROC curve, we calculated the sensitivity of 80% and the specificity of 62%, similar to Branten's [5] results. In addition, the specificity was increased when a higher cutoff value was employed.

$\beta$ -NAG belongs to lysosomal enzymes of the proximal tubular cells. Severe tubular cell injury, especially at cell membranes, will lead to loss of cytosolic and lysosomal enzymes in the urine. In our study,  $U\beta$ -NAG was less accurate than  $U\beta 2m$  and  $UlgG$  in predicting progressive disease. The main way for spilling of  $\beta$ -NAG in the urine is exocytosis-endocytosis, not cell injury [19]. Exocytosis of lysosomal content may be responsible for the increased  $U\beta$ -NAG excretion as soon as proteinuria stimulates lysosomal activity. Julia M [20] also explained this phenomenon. In his study, many patients had a normal  $U\beta 2m$ , but  $U\beta$ -NAG was already elevated. Area under the curve (AUC) was smaller, and the differences about renal survival rate between high  $U\beta$ -NAG group and low  $U\beta$ -NAG group were not obvious in the first year. So  $U\beta$ -NAG was a less specific marker of tubular injury.

From what has been discussed above, further studies are needed to confirm the prognostic role of these markers. More importantly, the available data do not specify if these markers are able to identify the patients who respond to an effective therapy or are still valid in patients receiving an adequate therapy. At any rate, if a patient with low excretion of  $UlgG$ ,  $U\beta 2m$  and/or normal albumin responds to the treatment, should he/she be kept in a nephrotic sta-

tus simply because he/she has less possibility of progressing to ESRD?

**Disclosure of conflict of interest**

None.

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## Decreased those protein can improve prognosis of iMN

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