International Urology and Nephrology (2019) 51:1797–1804
https://doi.org/10.1007/s11255-019-02254-7

NEPHROLOGY - ORIGINAL PAPER

Serum uric acid is an independent predictor of renal outcomes in patients with idiopathic membranous nephropathy

Ji Zhang[1,3] · Min Pan[2] · JianNa Zhang[1,3] · XiaoHan You[1,3] · Dou Li[3] · Fan Lin[3] · GuoYuan Lu[1]

Received: 31 January 2019 / Accepted: 5 August 2019 / Published online: 28 August 2019

Abstract

Purpose Accumulating evidence suggests that a relationship exists between serum uric acid (UA) and the progression of chronic kidney disease (CKD), but information regarding idiopathic membranous nephropathy (IMN) is limited.

Methods Patients with renal biopsy-confirmed diagnosis of IMN between 2009 and 2017 were identified. The demographic and clinical data recorded at the time of renal biopsy were considered the baseline values. The included cases were separated into three groups based on tertiles of the baseline serum UA level, and the relationship between serum UA and poor renal outcome was investigated by receiver operating characteristic (ROC) and time-event analyses. The primary endpoint was poor renal outcome, which was defined as a decrease in the estimated glomerular filtration rate to 50% of the baseline level or progression to end-stage renal disease during the follow-up.

Results Of 989 cases, 572 eligible patients were included. During a median of 18 months of follow-up, 45 (7.9%) patients progressed to the primary endpoint. Both baseline serum UA and time-averaged UA levels could be used for discrimination of renal outcomes, but the difference was not significant (p value = 0.6). Our Cox regression analysis further demonstrated that baseline serum UA was an independent predictor of poor renal outcome in IMN patients, and subgroup analysis revealed a gender difference in the predictive effect of serum UA.

Conclusions Our study demonstrated that baseline serum UA was an independent predictor of poor renal outcome in patients with IMN, and a gender difference in the predictive effect was observed in our cohort.

Keywords Uric acid · Idiopathic membranous nephropathy · Renal outcomes · Chronic kidney disease

Abbreviations

UA	Uric acid
CI	Confidence interval
HR	Hazard ratio
MN	Membranous nephropathy
ESRD	End-stage renal disease
CKD	Chronic kidney disease
BP	Blood pressure
eGFR	Estimated glomerular filtration rate
SD	Standard deviation
Scr	Serum creatinine
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Introduction

Idiopathic membranous nephropathy (IMN) is an organ-specific autoimmune disease that is a common cause of nephrotic syndrome in adults [1]. The deposition of autoimmune complexes on the glomerular basement membrane (GBM) is an apparent characteristic of IMN, and the M-type phospholipase A_2 receptor (PLA_2R) and thrombospondin type 1 domain-containing 7A (THSD7A) have been confirmed as the target antigens on the GBM [2, 3]. Thus, the inflammatory pathways that are activated in the glomerulus might cause renal injury and result in disease progression [4].

✉ GuoYuan Lu
lu_guoyuan@hotmail.com

1 Department of Nephrology, The First Affiliated Hospital of Soochow University, 88 Shizi St., Suzhou 215006, Jiangsu, People's Republic of China

2 Department of Nephrology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

3 Department of Nephrology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

Although IMN is considered a "benign disease", 30–40% of patients with IMN, particularly patients with persistent proteinuria and/or impaired renal function, are likely to progress to end-stage renal disease (ESRD) within 5–15 years [5–7]. An increased serum creatinine level and severe 24-h proteinuria at the time of renal biopsy have been considered independent risk factors for poor renal outcomes in patients with IMN [8]. Furthermore, gender, blood pressure, and age are also associated with renal outcomes [9, 10]. However, few studies have investigated the role of serum uric acid (UA) levels in the progression of renal disease in IMN.

Based on accumulating evidence, serum UA is closely associated with inflammation [11, 12]. Recent studies have reported a relationship between high serum UA concentrations and increased risks of cardiovascular events and mortality, which may be attributed to UA-induced inflammation [13, 14]. Furthermore, a high serum UA level is an independent risk factor for renal progression in patients with chronic kidney disease (CKD) [15]. Therefore, our study was designed to investigate the relationships between serum UA and renal outcomes in patients with IMN.

Materials and methods

Patients with a biopsy-proven diagnosis of membranous nephropathy (MN) between January 2009 and June 2017 who were followed up at the outpatient service of the First Affiliated Hospital of Wenzhou Medical University were identified and retrospectively reviewed. The inclusion criteria were as follows: (1) renal biopsy-confirmed diagnosis of IMN; (2) CKD stage 1–3 at the time of renal biopsy; and (3) follow-up of at least 6 months. The exclusion criteria were as follows: (1) secondary causes of MN, such as systemic lupus erythematosus or hepatitis B-related MN; (2) malignant tumors at the time of renal biopsy or during follow-up; (3) donor kidney biopsy specimens; and (4) missing important data, including age, gender, serum UA and serum creatinine at the time of renal biopsy.

Collection and conversion of clinical data

All clinical data were collected from the hospital information system of the First Affiliated Hospital of Wenzhou Medical University, and the protocol for data collection and masking patient-identifiable information was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Demographic data (age and gender) and systolic and diastolic blood pressure (SBP and DBP, respectively) were collected at the time of renal biopsy. Laboratory data, such as the serum creatinine, serum albumin, serum UA, and 24-h proteinuria levels, were collected at the time of renal biopsy and during follow-up. Mean arterial pressure (MAP) was calculated as one-third of the SBP plus two-thirds of the DBP. Time-averaged UA levels were calculated from the area under the curve of follow-up measurements divided by the length of the follow-up time. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation [16]. The missing values for laboratory data at the time of follow-up were imputed using linear imputation.

The use of diuretic and UA-lowering agents at the beginning of the follow-up period was recorded, and the immunosuppressant treatment strategies were recorded during the follow-up. Patients receiving different immunosuppressant treatments other than glucocorticoids were divided into the following four groups: (1) no, defined as no treatment with immunosuppressants; (2) CTX, defined as treatment with cyclophosphamide; (3) CNI, defined as treatment with tacrolimus or cyclosporine; (4) others, defined as treatment with other immunosuppressants, including leflunomide, mycophenolate mofetil, and tripterygium glycosides, or a switch in the immunosuppressant therapeutic strategy during follow-up.

The included cases were divided into three groups according to the tertiles of the baseline serum UA levels to investigate the relationship between baseline serum UA levels and other characteristics of IMN patients.

Definitions

Hypertension is defined as an SBP higher than 140 mmHg or a DBP higher than 90 mmHg. CKD was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [17]: Stage 1 is defined by kidney damage (proteinuria or hematuria) with a normal eGFR (eGFR $\geq$ 90 ml/min/1.73 m^2); stage 2 is defined as kidney damage and a slightly decreased eGFR (eGFR 60–89 ml/min/1.73 m^2); stage 3 as an eGFR of 30–59 ml/min/1.73 m^2; stage 4 as an eGFR of 15–29 ml/min/1.73 m^2; and stage 5 as an eGFR < 15 ml/min/1.73 m^2 (or dialysis). Nephrotic syndrome is defined as a serum albumin level < 30 g/l and 24-h proteinuria $\geq$ 3.5 g or a urine protein/creatinine ratio $\geq$ 3.5 g/g. The primary endpoint is poor renal outcome, which is defined as a decrease in the eGFR to 50% of the baseline level or progression to ESRD during follow-up. Renal survival is defined as the absence of the primary endpoint event during follow-up.

Statistical analysis

The numerical data were presented as the means (standard deviations (SD)) for normally distributed data or the medians [interquartile ranges (IQRs)] for skewed data, and differences between the groups were examined using one-way analysis of variance (ANOVA) for normally distributed

data or the Kruskal–Wallis rank test for skewed data. The Shapiro–Wilk test was used to examine the distribution of the numerical data. The categorical data were presented as counts with percentages (%), and differences between the groups were examined using Pearson's Chi square test. Receiver operating characteristic (ROC) analysis was performed to assess the roles of baseline serum UA, time-averaged UA, and their gender subgroups in discriminating renal outcomes, and the areas under the ROC curves (AUC) were calculated and examined using DeLong's test [18]. A Kaplan–Meier survival analysis was performed to calculate the cumulative renal survival rate in the three groups, which was examined using the log-rank test. Univariate and multivariate Cox regression analyses and a subgroup analysis stratified by gender were performed to further investigate the relationships between baseline serum UA and poor renal outcome. All reported p values are two-tailed, and p values less than 0.05 were considered to indicate a statistically significant difference. R (version 3.5.2, R Core Team) was used to perform the analyses and create the figures [19–21].

Results

In total, 989 cases with renal biopsy-proven MN were enrolled in the study. One case of missing age and serum UA information at the time of renal biopsy and 268 (17.1%) cases with follow-up durations less than 6 months were removed. Then, the histories of the selected cases were reviewed, and one case that did not meet the inclusion criteria and 147 (14.9%) cases that met the exclusion criteria were removed. Finally, 572 (57.8%) eligible patients were included in the study (Fig. 1). In our cohort, the ratio of males to females was 1.2:1; 412 (72%) patients presented nephrotic syndrome, and 241 (42.1%) patients presented hypertension at the time of the renal biopsy. The median age at the time of renal biopsy was 51.3 years (IQR 41–61 years).

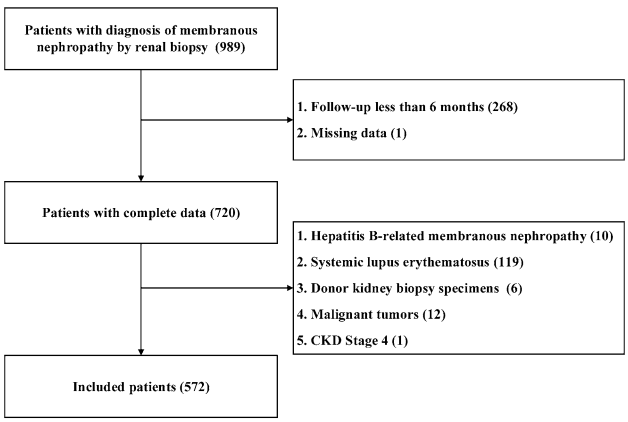

Fig. 1 Flow chart of the patients included in the study

At the beginning of the follow-up period, approximately 223 (40.0%) patients received diuretic therapy, and 25 (4.4%) patients received UA-lowering agents, including benzbromarone, febuxostat or allopurinol. During a median follow-up of 18 months (IQR 9–33 months), 45 (7.9%) patients progressed to the primary endpoint, and 16 (2.8%) patients progressed to CKD stages 4–5.

Comparison of the clinical characteristics of the included patients stratified according to the tertiles of the baseline serum UA

The included patients were divided into the following three groups according to the tertiles of the baseline serum UA at the time of the renal biopsy: the low, median, and high groups, with values ranging from 166 to 335 μmol/l, 335 to 405 μmol/l, and 405 to 710 μmol/l, respectively. The range in the low group was similar to the normal range of serum UA levels in women (range from 137 to 362 at our hospital). However, the range of the merged low and median group was still less than the normal range in men (range from 214 to 488 at our hospital).

The results of the comparison of the differences in the clinical characteristics among the three groups are presented in Table 1. Significantly lower serum UA levels were observed in the women compared to those observed in the men (p value < 0.001). A significant association was observed between the serum UA level and renal function at the time of renal biopsy (relationships with the serum creatinine and eGFR levels and CKD stage, all p-values were less than 0.001). The proportions of patients with hypertension were significantly higher in the median and high groups than in the low group (p value = 0.003). In particular, significant differences in the means of SBP (p value < 0.001) and MAP (p value = 0.009) were observed between the three groups. Furthermore, patients with a high serum UA level at the time of the renal biopsy exhibited significantly decreased serum albumin levels and increased proteinuria. The proportions of patients receiving diuretic therapy were slightly higher in the median and high groups than in low group at the time of renal biopsy, but the differences between the three group were not significant (p value = 0.08).

No significant differences in the follow-up time were observed (p value = 0.56). The proportions of patients receiving glucocorticoids were higher in the median and high groups than in the low group, but a significant difference was not observed in the proportions of patients receiving the immunosuppressive agents other than glucocorticoids between the three groups. However, significantly higher proportions of patients achieved the primary endpoint in the group with a higher serum UA level (2.6% in the low group, 8.4% in the median group, and 12.6% in the high group, p value = 0.001). Furthermore, two

Table 1 Clinical characteristics of included patients at the time of renal biopsy and during follow-up

Characteristics	Tertiles of UA			*p* value
	Low	Median	High	
At the time of renal biopsy				
Number of patients (*n*)	191	191	190	
Age (years, median [IQR])	50.0 [41.0, 58.1]	51.0 [41.0, 61.0]	53.0 [42.2, 63.0]	0.2
Female (*n*, %)	139 (72.8)	81 (42.4)	39 (20.5)	< 0.001
Serum albumin (g/l, median [IQR])	26.7 [21.4, 31.3]	24.3 [20.2, 28.7]	25.5 [21.0, 29.8]	0.02
Serum fibrinogen (g/l, median [IQR])	4.4 [3.8, 5.2]	4.8 [4.0, 5.8]	4.8 [4.1, 5.5]	0.02
Serum creatinine (μmol/l, median [IQR])	54.1 [48.5, 64.6]	65.7 [55.4, 76.0]	73.2 [62.8, 82.6]	< 0.001
eGFR (ml/min/1.73 m^2, median [IQR])	110.7 [101.4, 119.7]	106.8 [95.0, 117.5]	101.7 [87.7, 114.3]	< 0.001
CKD stage (*n*, %)				< 0.001
Stage 1	167 (88.4)	152 (80.4)	127 (67.9)	
Stage 2	19 (10.1)	31 (16.4)	53 (28.3)	
Stage 3	3 (1.6)	6 (3.2)	7 (3.7)	
Proteinuria (g/24-h, median [IQR])	3.7 [1.9, 6.1]	4.9 [2.8, 7.7]	4.8 [2.7, 7.3]	0.002
Hypertension (*n*, %)	70 (36.6)	72 (37.7)	99 (52.1)	0.003
SBP (mmHg, mean (SD))	128.9 (20.5)	133.0 (19.8)	137.7 (19.9)	< 0.001
DBP (mmHg, mean (SD))	79.0 (12.9)	78.2 (11.7)	80.6 (12.2)	0.2
MAP (mmHg, mean (SD))	143.4 (20.9)	144.7 (19.4)	149.5 (20.0)	0.009
Nephrotic syndrome (*n*, %)	126 (66.0)	141 (73.8)	145 (76.3)	0.06
Diuretic use (*n*, %)	62 (32.5)	81 (42.4)	80 (42.1)	0.08
UA-lowering agent use (*n*, %)	2 (1.0)	6 (3.1)	17 (8.9)	< 0.001
During follow-up				
Follow-up (months, median [IQR])	21.0 [12.0, 36.0]	18.0 [10.5, 33.0]	18.0 [9.0, 33.0]	0.6
Primary endpoint (*n*, %)	5 (2.6)	16 (8.4)	24 (12.6)	0.001
eGFR (ml/min/1.73 m^2, median [IQR])	103.8 (22.5)	92.3 (27.2)	88.6 (31.0)	< 0.001
CKD stage (*n*, %)				< 0.001
Stage 1	159 (83.2)	128 (67.0)	110 (57.9)	
Stage 2	23 (12.0)	34 (17.8)	41 (21.6)	
Stage 3	7 (3.7)	22 (11.5)	31 (16.3)	
Stage 4	1 (0.5)	7 (3.7)	3 (1.6)	
Stage 5	1 (0.5)	0 (0.0)	5 (2.6)	
Time-averaged UA (μmol/l, mean (SD))	320.4 (58.9)	380.7 (58.4)	438.6 (68.9)	< 0.001
Glucocorticoids (*n*, %)	107 (56.0)	121 (63.4)	133 (70.0)	0.02
Immunosuppressant use (*n*, %)				0.3
No	83 (43.5)	77 (40.3)	70 (36.8)	
CTX	17 (8.9)	25 (13.1)	25 (13.2)	
CNI	37 (19.4)	46 (24.1)	52 (27.4)	
Others	54 (28.3)	43 (22.5)	43 (22.6)	

patients in the low group, but seven and eight patients in the median and high group, progressed to CKD stage 4-5 during follow-up. Although the patients in our cohort may have received different treatment regimens during follow-up, the correlation between the time-averaged UA and baseline serum UA levels was consistently significant (p value < 0.001).

The role of baseline serum UA and time-averaged UA in discriminating renal outcomes

The results of our ROC analyses are shown in Fig. 2. The AUC values of the baseline serum UA (0.66, 95% confidence interval (CI) 0.58–0.74) and time-averaged UA (0.69, 95% CI 0.60–0.77) for discriminating renal outcomes were

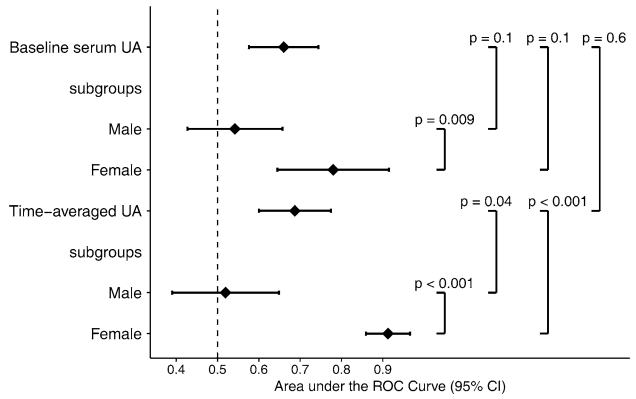

Fig. 2 The AUC of the baseline serum UA and time-averaged UA for identification of poor renal outcome and the subgroup analysis stratified by gender. The diamond shapes and short horizontal bars represent AUC values and 95% CIs, respectively. The vertical short bars with p-values indicate comparisons between two AUC values. Patients were separated into men and women for the subgroup analysis

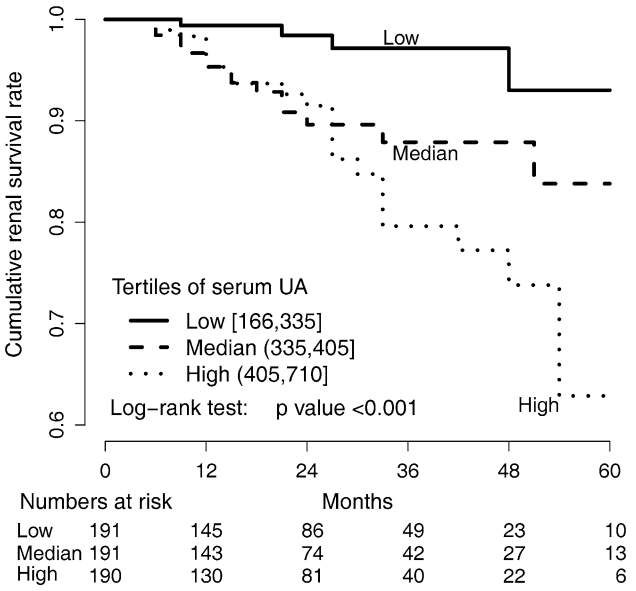

Fig. 3 Kaplan–Meier survival plot of patients stratified by the tertiles of the serum UA levels

significantly higher than 0.5 (both p values < 0.001), but no significant difference was found between baseline serum UA and time-averaged UA (p value = 0.6). In particular, our subgroup analysis showed obviously increased AUC values for the baseline serum UA and time-averaged UA in the women (0.78, 95% CI 0.65–0.92, and 0.91, 95% CI 0.86–0.97, respectively). Furthermore, compared to the men, the AUC values for the baseline serum UA and time-averaged UA were significantly increased in the women (p values = 0.009 and < 0.001, respectively), suggesting that a gender difference exists in serum UA as a predictor of renal outcomes.

Relationship between the baseline serum UA and renal outcomes

The Kaplan–Meier survival analysis of our cohort showed significantly different cumulative renal survival rates between the three groups (log-rank test: p value < 0.001), and the renal survival rate decreased rapidly in the groups with median and high levels of baseline serum UA, suggesting a significant correlation between baseline serum levels and the renal survival rate in IMN patients (Fig. 3). Our Cox regression analysis further demonstrated a significant association between baseline serum UA and poor renal outcome (Table 2). For low serum UA levels, the hazard ratio (HR) was significantly increased in the groups with median (HR 3.39, 95% CI 1.24–9.26, p value = 0.02) and high (HR 5.73, 95% CI 2.17–15.15, p value < 0.001) levels of baseline serum UA in the univariate model. Furthermore, the multivariate Cox regression models adjusted for the traditional risk factors of age, gender, the eGFR, 24-h proteinuria, and hypertension and other confounders of treatments with immunosuppressants and diuretics demonstrated that baseline serum UA was an independent predictor of poor renal outcome in patients with IMN. The subgroup analysis indicated that baseline serum UA was more strongly associated with poor renal outcomes in women than in men, and the women with higher levels of serum UA may be more

Table 2 Univariate and multivariate Cox regression analyses of renal survival in patients stratified by tertiles of serum UA levels

Parameter	Model 1		Model 2	
	HR [95% CI]	p value	HR [95% CI]	p value
Total				
Low	Ref	–	Ref	–
Median	3.39 [1.24, 9.26]	0.02	2.65 [0.91, 7.70]	0.07
High	5.73 [2.17, 15.15]	< 0.001	3.01 [1.00, 9.07]	0.05
Subgroup				
Male				
Low	Ref	–	Ref	–
Median	3.43 [0.75, 15.64]	0.1	2.70 [0.58, 12.66]	0.2
High	3.72 [0.85, 16.31]	0.08	2.01 [0.41, 9.86]	0.4
Female				
Low	Ref	–	Ref	–
Median	2.39 [0.56, 10.18]	0.2	2.13 [0.36, 12.57]	0.4
High	9.69 [2.55, 36.80]	0.001	5.89 [1.26, 27.65]	0.03

Model 1: Univariate model of the tertiles of the serum UA levels. Model 2: Multivariate Cox model of the tertiles of the serum UA levels adjusted for the traditional risk factors of age, gender, eGFR, 24-h proteinuria, and hypertension and other confounders of treatment with immunosuppressants and diuretics in the total dataset; gender was removed in the subgroup analysis

likely to progress to poor renal outcome, which is consistent with the results of the ROC analyses.

Discussion

In our cohort, serum UA levels were significantly increased in male patients and positively associated with increased 24-h proteinuria and blood pressure but inversely associated with decreased serum albumin and eGFR levels. These clinical variables are traditional risk factors for IMN and indicate more severe clinical manifestations in IMN [8–10]. According to the ROC analyses, serum UA can be used to determine the renal prognosis in patients with IMN. Furthermore, our Cox regression analysis suggested that patients with a higher baseline serum UA level had a significantly increased HR for a poor renal outcome. Moreover, our subgroup analysis revealed a strong significant correlation between the serum UA level and poor renal outcome in the women.

UA is a product of purine metabolism generated during the breakdown of adenosine and guanine. The kidney is the main organ responsible for the excretion of serum UA and eliminates approximately two-thirds of serum UA [22]; in addition, a significant relationship exists between renal function and the serum UA level. However, the role of UA in the progression of CKD is unclear. Researchers debate whether hyperuricemia is only a phenomenon resulting from the decreasing renal function or a risk factor for renal progression in patients with CKD [23–25]. However, based on accumulating evidence, hyperuricemia is a risk factor for CKD progression [26–28]. In animal models, an increase in the UA level has been reported to induce oxidative stress and endothelial dysfunction, resulting in the development of hypertension and reduced renal blood flow [29, 30]. Other studies have reported an association between UA levels and activation of the renin-angiotensin system, causing glomerular hypertrophy [31], and UA induces systemic and local inflammation, promoting endothelial dysfunction, cell proliferation, and inflammatory factor release [11, 12]. Our study showed that the serum UA level was significantly associated with the serum fibrinogen level, which is also considered both an inflammatory factor and a risk factor for CKD progression [32]. Moreover, in our cohort, the serum UA level was significantly associated with the traditional risk factors for IMN. The patients with a high serum UA level exhibited severe proteinuria and a low eGFR level commonly in combination with hypertension at the onset of disease.

The ROC and time-event analyses further confirmed the significant relationship between the serum UA and poor renal outcome. Both the baseline serum UA and time-averaged UA levels can be used to determine renal outcomes, and the difference in their predictive abilities was not significant, although a slight increase in the AUC of the time-averaged UA was noted. Considering the significant relationship between baseline serum UA and time-averaged UA, baseline serum UA may be superior to the time-averaged UA level as a predictor because it is an easier and earlier parameter. Furthermore, the Kaplan–Meier survival analysis indicated a significant tendency for patients with an increased baseline serum UA to have a decreased cumulated survival rate. The multivariate Cox regression analyses adjusted for the traditional risk factors and confounders of treatments demonstrated that the baseline serum UA is an independent predictor of a poor renal outcome in IMN.

Our subgroup analysis suggested a gender difference in the predictive effect of the serum UA. Kawabe et al. indicated that an increased level of serum UA was associated with major cardiovascular adverse events more strongly in women than in men with acute coronary syndrome [33]. Other studies, such as the Framingham Heart Study, also demonstrated that serum UA was a predictor of coronary heart disease in women but not in men [34]. These findings are consistent with our findings, which may be attributed to the common risk factors of cardiovascular disease and glomerular disease.

Hyperuricemia is usually defined as a serum UA level > 6.8 mg/dl (404 μmol/l) [35], which is consistent with our high group. However, in our cohort, patients in the median group (ranging from 335 to 405) had an increased HR for a poor renal outcome. Uchida et al. also found that the serum UA target should be less than 6.0 mg/dl (356 μmol/l) to reduce the progressive risk of ESRD [36]. Thus, additional prospective studies are needed to confirm whether a lower serum UA level is a protective factor for renal outcomes in patients with IMN.

A few confounders may affect the serum UA levels during therapies, which could bias the statistics. Diuretics and dehydration can increase the serum UA level. Furthermore, some immunosuppressive agents, such as tacrolimus and cyclosporine, can increase the serum UA levels during therapy by increasing UA re-absorption and/or decreasing UA secretion [35]. In our cohort, although the proportion of patients receiving diuretics in the median and high baseline serum UA groups was slightly higher than that in the low group, the differences were not statistically significant (p value = 0.08), and a significant difference was not observed among our patients receiving different immunosuppressive agents ($p = 0.3$).

Our study has several limitations. First, the observational design of the study identifies associations only and not causal relationships. Although serum UA levels were an independent predictor of renal outcomes in patients with IMN in the present study, further studies are needed to determine the causal association and the effects of UA-lowering therapy on the progression of changes in renal function in patients with IMN. Second, obvious variations in both the

follow-up time and the treatment strategy were observed, which may affect the robustness of our results.

Although it is difficult to confirm the role of serum UA in the progression of kidney function in IMN, our study demonstrated that the baseline serum UA is an independent predictor of poor renal outcome in patients with IMN. Moreover, a gender difference exists for serum UA as a predictor of renal outcomes, and female patients with higher levels of serum UA are more likely to progress to a poor renal outcome. Therefore, the serum UA levels of patients with IMN warrant more attention.

Acknowledgements The authors would like to thank their colleagues at the Department of Nephrology, the First and Second Affiliated Hospitals of Wenzhou Medical University for their support and assistance during the study period.

Author contributions All authors contributed significant intellectual content to this manuscript as follows: principal investigators, conceived and designed the study: ZJ, PM, and LGY; assessed the study, extracted data, and performed statistical analyses: ZJ, ZJN, YXH, and LD; drafted the manuscript: ZJ; performed a critical review of the manuscript: LF and LGY. All authors have read the manuscript and approved the final version.

Funding This study was supported by the Wenzhou Municipal Science and Technology Bureau under Grant Y20170300 to Min Pan and the Natural Science Foundation of Zhejiang Province under Grant LY14H050006 to Fan Lin.

Compliance with ethical standards

Conflict of interest The authors have no competing interests to declare.

Ethical approval The procedure was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Informed consent This study was performed after obtaining written informed consent from all patients.

References

1. Makker SP, Tramontano A (2011) Idiopathic membranous nephropathy: an autoimmune disease. Semin Nephrol 31(4):333–340. https://doi.org/10.1016/j.semnephrol.2011.06.004
2. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 361(1):11–21. https://doi.org/10.1056/NEJMoa0810457
3. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, Dolla G, Hoxha E, Helmchen U, Dabert-Gay AS, Debayle D, Merchant M, Klein J, Salant DJ, Stahl RA, Lambeau G (2014) Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med 371(24):2277–2287. https://doi.org/10.1056/NEJMoa1409354
4. Wolf G (2006) Renal injury due to renin–angiotensin–aldosterone system activation of the transforming growth factor-β pathway. Kidney Int 70(11):1914–1919
5. Shiiki H, Saito T, Nishitani Y, Mitarai T, Yorioka N, Yoshimura A, Yokoyama H, Nishi S, Tomino Y, Kurokawa K (2004) Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. Kidney Int 65(4):1400–1407
6. Cattran D (2005) Management of membranous nephropathy: when and what for treatment. J Am Soc Nephrol 16(5):1188–1194
7. Schieppati A, Mosconi L, Perna A, Mecca G, Bertani T, Garattini S, Remuzzi G (1993) Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 329(2):85–89
8. Sprangers B, Bomback AS, Cohen SD, Radhakrishnan J, Valeri A, Markowitz GS, D'Agati V, Appel GB (2012) Idiopathic membranous nephropathy: clinical and histologic prognostic features and treatment patterns over time at a tertiary referral center. Am J Nephrol 36(1):78–89
9. Reichert LJ, Koene RA, Wetzels JF (1998) Prognostic factors in idiopathic membranous nephropathy. Am J Kidney Dis 31(1):1–11
10. Segal PE, Choi MJ (2012) Recent advances and prognosis in idiopathic membranous nephropathy. Adv Chronic Kidney Dis 19(2):114–119. https://doi.org/10.1053/j.ackd.2012.01.007
11. Kanellis J, Kang D-H (2005) Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. In: Seminars in nephrology, vol 1, 2005. Elsevier, New York, pp 39–42
12. Meotti FC, Jameson GN, Turner R, Harwood DT, Stockwell S, Rees MD, Thomas SR, Kettle AJ (2011) Urate as a physiological substrate for myeloperoxidase: implications for hyperuricemia and inflammation. J Biol Chem. https://doi.org/10.1074/jbc.M110.172460
13. Pagidipati NJ, Hess CN, Clare RM, Akerblom A, Tricoci P, Wojdyla D, Keenan RT, James S, Held C, Mahaffey KW (2017) An examination of the relationship between serum uric acid level, a clinical history of gout, and cardiovascular outcomes among patients with acute coronary syndrome. Am Heart J 187:53–61
14. Nodera M, Suzuki H, Matsumoto Y, Kamioka M, Kaneshiro T, Yoshihisa A, Ohira T, Takeishi Y (2018) Association between serum uric acid level and ventricular tachyarrhythmia in heart failure patients with implantable cardioverter-defibrillator. Cardiology 140(1):47–51
15. Chang H-Y, Lee P-H, Lei C-C, Hsu Y-C, Chang H-H, Tung C-W, Lin C-L, Yang H-F, Lu L-C, Jong M-C (2010) Hyperuricemia as an independent risk factor of chronic kidney disease in middle-aged and elderly population. Am J Med Sci 339(6):509–515
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604–612
17. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, Zeeuw DD, Hostetter TH, Lameire N, Eknoyan G (2005) Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int 67(6):2089–2100
18. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J-C, Müller M (2011) pROC: an open-source package for R and S+to analyze and compare ROC curves. BMC Bioinform 12(1):77. https://doi.org/10.1186/1471-2105-12-77
19. Wickham H (2009) ggplot2: elegant graphics for data analysis. Springer, New York
20. Team RC (2017) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
21. Yoshida K (2019) tableone: create 'Table 1' to describe baseline characteristics. R package version 0.10.0. https://CRAN.R-project.org/package=tableone
22. Uchida S, Kumagai T, Chang WX, Tamura Y, Shibata S (2018) Time to target uric acid to retard chronic kidney disease progression. In: Treviño-Becerra A, Iseki K (eds) Uric acid in chronic kidney disease, vol 192. Karger Publishers, Basel, pp 56–68

23. Eleftheriadis T, Golphinopoulos S, Pissas G, Stefanidis I (2017) Asymptomatic hyperuricemia and chronic kidney disease: narrative review of a treatment controversial. J Adv Res 8(5):555–560. https://doi.org/10.1016/j.jare.2017.05.001
24. Ramirez-Sandoval JC, Sanchez-Lozada LG, Madero M (2017) Uric acid, vascular stiffness, and chronic kidney disease: is there a link? Blood Purif 43(1–3):189–195. https://doi.org/10.1159/000452726
25. Johnson RJ, Nakagawa T, Jalal D, Sánchez-Lozada LG, Kang D-H, Ritz E (2013) Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant 28(9):2221–2228
26. Mwasongwe SE, Fülöp T, Katz R, Musani SK, Sims M, Correa A, Flessner MF, Young BA (2018) Relation of uric acid level to rapid kidney function decline and development of kidney disease: the Jackson Heart Study. J Clin Hypertens 20(4):775–783
27. Lee JW, Lee KH (2019) Comparison of renoprotective effects of febuxostat and allopurinol in hyperuricemic patients with chronic kidney disease. Int Urol Nephrol. https://doi.org/10.1007/s11255-018-2051-2
28. Sampson AL, Singer RF, Walters GD (2017) Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. Cochrane Database Syst Rev 10:CD009460. https://doi.org/10.1002/14651858.cd009460.pub2
29. Sanchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, Franco M, Rodriguez-Iturbe B, Johnson RJ (2008) Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. Am J Physiol Renal Physiol 295(4):F1134–F1141. https://doi.org/10.1152/ajprenal.00104.2008
30. Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, Rodriguez-Iturbe B, Johnson RJ, Herrera-Acosta J (2005) Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int 67(1):237–247. https://doi.org/10.1111/j.1523-1755.2005.00074.x
31. Nakagawa T, Mazzali M, Kang DH, Kanellis J, Watanabe S, Sanchez-Lozada LG, Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ (2003) Hyperuricemia causes glomerular hypertrophy in the rat. Am J Nephrol 23(1):2–7. https://doi.org/10.1159/000066303
32. Zhang J, Chen C, Zhou Q, Zheng S, Lv Y, Zhang J, You X, Li Z, Zhou Z, Pan M (2017) Elevated serum fibrinogen level is an independent risk factor for IgA nephropathy. Oncotarget 8(58):99125–99135. https://doi.org/10.18632/oncotarget.21702
33. Kawabe M, Sato A, Hoshi T, Sakai S, Hiraya D, Watabe H, Kakefuda Y, Ishibashi M, Abe D, Takeyasu N (2016) Gender differences in the association between serum uric acid and prognosis in patients with acute coronary syndrome. J Cardiol 67(2):170–176
34. Culleton BF, Larson MG, Kannel WB, Levy D (1999) Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 131:7–13
35. Ben Salem C, Slim R, Fathallah N, Hmouda H (2016) Drug-induced hyperuricaemia and gout. Rheumatology 56(5):679–688
36. Uchida S, Chang WX, Ota T, Tamura Y, Shiraishi T, Kumagai T, Shibata S, Fujigaki Y, Hosoyamada M, Kaneko K (2015) Targeting uric acid and the inhibition of progression to end-stage renal disease—a propensity score analysis. PLoS One 10(12):e0145506