IJKD KIDNEY DISEASES

The Related Factors of Hyperuricemia in IgA Nephropathy

Feng Yi, Lei Lan, Jun Jiang, Li Peng, Yan Jin, Xiaowan Zhou

Department of Nephrology, the First Affiliated Hospital of University of Science and Technology of China, China

Original Paper

Keywords. IgA nephropathy, hyperuricemia, prognosis

Introduction. Many factors, such as increased serum creatinine, increased blood pressure and abnormal urine protein, may lead to poor prognosis of IgA nephropathy (IgAN). The features of IgAN are also affected by uric acid, but its effect on the prognosis is less reported. We therefore systematically investigated the possible correlation of IgAN with hyperuricemia (HUA) and their prognosis.
Methods. Two groups (HUA group and uric acid normal group) were included of 178 IgAN patients. The indexes in the clinic and pathology were compared; logistic regression and renal survival were used to speculate the correlated factors of HUA in IgAN and their prognosis.
Results. HUA group had higher serum urea nitrogen, serum creatinine, total cholesterol, 24-hour urinary protein quantity, percentage of CKD3-5, the thickness of arteriole, glomerular mesangial hyperplasia, tubular atrophy, glomerulosclerosis, interstitial fibrosis and the area of infiltration of inflammatory cells (ICI), lower eGFR and serum albumin-to-creatinine ratios ($P < .05$). Total cholesterol and ICI in X2 were independent related factors of HUA given by the analysis of logistic regression ($P < .05$). No correlation was found in HUA and normal group used by Kaplan–Meier ($P > .05$).
Conclusion. Severer renal pathological injures (glomeruli, tubules or interstitium) were found in IgAN. Besides, total cholesterol and the area of infiltration of inflammatory cells were independent related factors of hyperuricemia in IgAN.

IJKD 2021;15:256-62
www.ijkd.org

INTRODUCTION

IgA nephropathy (IgAN) is the group with the highest incidence of primary glomerular disease,[1] more prominent on the north side of the earth to the left, accounting for 30 ~ 40% in China.[2] It is generally believed that IgAN is associated with autoimmunity, and deposits of IgA or other immunoglobulin immune complexes mainly in the mesangial area.[3] IgAN is primarily characterized by hematuria and proteinuria, with or without hypertension and hyperlipidemia.[4] It has been reported that increased serum creatinine and blood pressure, decreased plasma miR-29a and plasma IgG, and abnormal urine protein may lead to poor prognosis of IgAN.[5-7] The features of IgAN is also affected by uric acid,[8] but its effect on the prognosis is less reported. This study intends to retrospectively analyze the features of clinical and renal pathology of 178 patients with or without hyperuricemia (HUA) of IgAN in our hospital through statistical analysis, explored correlated risk indexes of hyperuricemia, to provide a certain reference for early clinical intervention.

MATERIALS AND METHODS

Patients

Two groups (HUA group, n = 73; and uric acid normal group, n = 105) involved 178 IgAN

patients confirmed by kidney biopsy in the Department of Nephrology, the First Affiliated Hospital of University of Science and Technology of China from January 2016 to December 2019. The average age of them (82 men and 96 women) was 36.63 ± 11.10. Followings were excluded: 1) secondary nephritis; 2) under 18 years old. The Research Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China approved this study design (Approval Number: 2019-p-036).

Definitions

Hyperuricemia was defined as serum uric acid ≥ 7.0 mg/dL (men) and ≥ 6.0 mg/dL (women).[9] Redefine pathological indicators referred to internationally recognized Oxford pathological classification:[10] the degree of renal tubular atrophy (T2: tubular atrophy > 25%, T1: 0% < tubular atrophy < 25%, T0: no tubular atrophy), glomerulosclerosis (Y2: glomerulosclerosis > 25%, Y1: 0% < glomerulosclerosis < 25%, Y0: no glomerulosclerosis), inflammatory cells infiltration (R3: Multifocal inflammatory cell infiltration, R2: focal inflammatory cell infiltration, R1: small focal Inflammatory cells), crescent (X2: with crescent, X1: no crescent), the degree of glomerular mesangial hyperplasia (G5: heavy, G4: medium to heavy, G3: median, G2: light to median, G1: light, G0: no mesangial hyperplasia). The estimated Glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD), $eGFR = 186*creatinine^{-1.154}*age^{0.203}$ (*0.742, female).[11] The stage of chronic kidney disease (CKD) was classified referred to the Kidney Disease Improving Global Outcomes (KDIGO) guideline.[12] The end events were defined as 100% increase in creatinine, 100% increase in urine protein, end-stage renal disease (ESRD, $eGFR < 15mL*min^{-1}*(1.73m^2)^{-1}$), or death.

MATERIALS AND METHODS

The indicators, including gender, age, blood pressure (systolic and diastolic pressure), serum creatinine, blood urea nitrogen, blood uric acid, triglyceride, cholesterol, 24-hour urine protein, and renal pathology; were collected before and after renal biopsy. The features of clinical and renal pathology of two groups (HUA group and normal group) involved 178 patients with or without hyperuricemia of IgAN were analyzed through statistical analysis.

Statistical Analysis

Data were analyzed by SPSS 23. Continuous variables that conform to a normal distribution apply to the T-test, or suitable for, Mann-Whitney U-test or Kruskal-Wallis H-test presented as means ± standard deviation or medians with the 25th and 75th percentiles. Qualitative variables were performed with the $\chi 2$ test. Logistic regression and renal survival were used to speculate the correlated factors of HU in IgAN and their prognosis, $P < .05$ was deemed significant.

RESUILTS

Clinical and Pathological Characteristics of IgAN in Normal Group and HU Group

178 IgAN patients in two groups (HU group, n = 73; and normal group, n = 105) confirmed by kidney biopsy were involved, whose mean age was 36.63 ± 11.10, and the morbidity of HUA was 41.01%. General clinical and pathological comparations between two groups were displayed in Table 1. HUA group had higher serum creatinine, serum urea nitrogen, total cholesterol, 24-hour urinary protein quantity and CKD stages but lower eGFR and serum albumin-to-creatinine ratio ($P < .05$).

In pathology, the patients with hyperuricemia also presented with thicker arteriole wall, and higher degree of G1 and G3 in glomerular mesangial hyperplasia ($P < .05$). Moreover, also HUA group presented with higher-level of incidence of interstitial fibrosis, degree of T1 and T2 in tubular atrophy, the proportion of Y2 in glomerulosclerosis and infiltration area of R1 and R3 in glomerular inflammatory cells (ICI) ($P < .01$). However, no differences were discovered in age, blood pressure, total triglyceride, or segmental sclerosis ($P > .05$).

Univariate and Multivariate Logistics Regression Analysis Identified the Independent Clinical and Histological Predictors of IgAN with Hyperuricemia

Univariate logistics regression analysis presented that the serum creatinine, blood urea nitrogen, serum albumin-to-creatinine ratio, eGFR, total cholesterol, stage of CKD, interstitial fibrosis, tubular atrophy, the thickness of arteriole wall, the proportion of glomerular sclerosis and infiltration area of

Table 1. Clinical and Pathological Characteristics of IgAN in Normal Uric Acid Group and Hyperuricemia Group

Parameter	Hyperuricemia (n = 73)	Normal Uric Acid (n = 105)	Statistic	*P*
Uric Acid, mmol/L	456.28 ± 69.64	314.87 ± 59.13	-14.581	< .001
Male, mmol/L	491.85 ± 63.27	364.98 ± 48.94	-11.649	< .001
Female, mmol/L	428.52 ± 61.85	285.68 ± 52.33	-12.236	< .001
Age, y	36.10 ± 10.55	37.01 ± 11.49	0.433	> .05
SBP, mmHg	130.51 ± 17.43	128.65 ± 15.27	-0.754	> .05
DBP, mmHg	85.73 ± 11.87	82.79 ± 10.50	-1.739	> .05
ACR, mg/mg	336.37 ± 138.38	446.50 ± 174.57	4.496	< .001
Cr, mmol/L	107.66 ± 37.56	84.09 ± 30.34	-4.620	< .001
BUN, mmol/L	6.75 ± 2.59	5.46 ± 1.76	-3.718	< .001
eGFR, mL*min-1* $(1.73m^2)^{-1}$	71.55 ± 29.82	93.84 ± 34.61	4.470	< .001
Total Cholesterol, mmol/L	5.08 ± 1.23	4.71 ± 0.99	-2.096	< .05
Total Triglyceride, mmol/L	1.94 ± 1.02	1.74 ± 0.99	-1.351	> .05
TPU, mg	2090 (1073 to 2832)	1747 (839 to 2151)	-1.992	< .05
FCR	0.10 (0.00 to 0.13)	0.07 (0.00 to 0.09)	-1.745	> .05
CKD			21.692	< .001
Stage 1	16 (21.92)	54 (51.43)	15.717	< .001
Stage 2	26 (35.62)	35 (33.33)	0.100	> .05
≥ Stage 3	31 (42.47)	16 (15.24)	16.428	< .001
Interstitial Fibrosis	54 (73.97)	49 (46.67)	13.169	< .001
AWT	67 (91.78)	85 (80.95)	4.048	< .05
GMH			9.766	< .05
G0	0 (0.00)	2 (1.90)	1.406	> .05
G1	3 (4.11)	15 (14.29)	4.906	< .05
G2	48 (65.75)	71 (67.62)	0.068	> .05
G3	19 (26.03)	14 (13.33)	4.595	< .05
G4	3 (4.11)	3 (2.86)	0.207	> .05
Glomerulosclerosis			15.660	< .001
Y0	7 (9.59)	22 (20.95)	4.077	< .05
Y1	28 (38.36)	58 (55.24)	4.915	< .05
Y2	38 (52.05)	25 (23.81)	15.024	< .001
SS	29 (39.73)	38 (36.19)	0.229	> .05
Tubular Atrophy			14.272	< .05
T0	4 (5.48)	12 (11.43)	1.863	> .05
T1	38 (52.05)	75 (71.43)	6.972	< .05
T2	31 (42.47)	18 (17.14)	13.841	< .001
ICI			27.276	< .001
R1	4 (5.48)	37 (35.24)	21.511	< .001
R2	34 (46.58)	47 (44.76)	0.057	> .05
R3	35 (47.95)	21 (20.00)	15.595	< .001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ACR, serum albumin-to-creatinine ratios; Cr, blood creatinine; BUN, blood urea nitrogen; TPU, 24-hour urine protein; FCR, fibrous crescent/glomeruli; AWT, arteriole wall thicken; GMH, glomerular mesangial hyperplasia; SS, segmental sclerosis; ICI, inflammatory cells infiltration.

glomerular inflammatory cells were correlated with HUA as shown in Table 2 ($P < .05$). Furthermore, multivariate logistics regression analysis showed that total cholesterol and ICI were independent risk factors of HUA in IgAN ($P < .05$, Table 2).

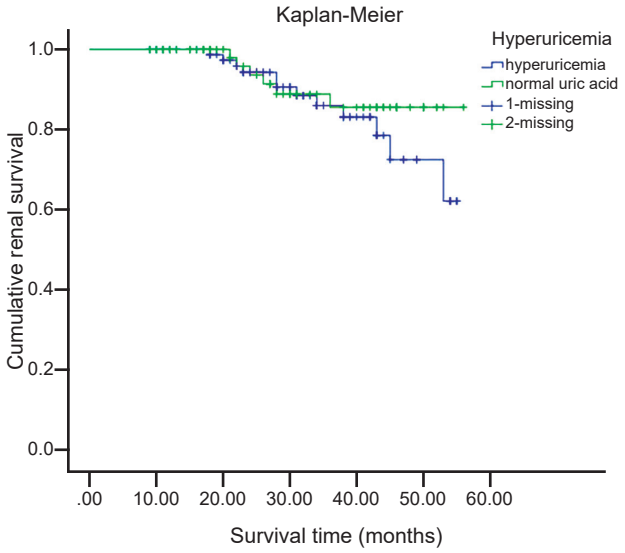
Comparison of Cumulative Renal Survival Rate Between the Two Groups (Kaplan-Meier)

Figure showed 178 patients were visited until August 2020, the median follow-up time was 28 months, 10 cases were lost, and 18 cases reached the end event. In hyperuricemia group, 1 case reached ESRD, and 5 case achieved 100% increase in urine protein; In the normal uric acid group, 1 case died, 1 case achieved 100% increase in creatinine, and 10 cases achieved 100% increase in urine protein. No correlation was found in UH and normal group used by Kaplan–Meier ($\chi 2 = 0.666$, $P > .05$).

Table 2. Univariate and Multivariable Binary Logistic Regression Analysis in IgAN with Hyperuricemia

Parameter	Univariate			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
BUN	1.343	1.140 to 1.581	< .001	1.168	0.965 to 1.414	> .05
Cr	1.021	1.011 to 1.032	< .001	1.004	0.984 to 1.025	> .05
ACR	0.995	0.993 to 0.998	< .001	0.997	0.991 to 1.002	> .05
eGFR	0.978	0.967 to 0.989	< .001	1.014	0.987 to 1.042	> .05
Total cholesterol	1.354	1.023 to 1.792	< .05	1.391	1.009 to 1.917	< .05
AWT	2.627	0.999 to 6.909	> .05			
Interstitial fibrosis	3.248	1.699 to 6.211	< .001	1.256	0.507 to 3.115	> .05
Tubular atrophy						
T1	1.520	0.459 to 5.031	> .05	0.718	0.172 to 2.993	> .05
T2	5.167	1.448 to 18.433	< .05	0.551	0.069 to 4.382	> .05
ICI						
X2	6.691	2.179 to 20.550	< .05	4.969	1.361 to 18.134	< .05
X3	15.417	4.810 to 49.417	< .001	6.595	0.944 to 46.064	> .05
Glomerulosclerosis						
Y1	1.517	0.579 to 3.973	> .05	0.892	0.289 to 2.753	> .05
Y2	4.777	1.777 to 12.844	< .05	1.800	0.499 to 6.495	> .05
CKD						
Stage 2	2.507	1.179 to 5.330	< .05			
≥ stage 3	6.539	2.875 to 14.873	< .001			

Abbreviations: BUN = serum urea nitrogen, Cr = serum creatinine, ACR = serum albumin-to-creatinine ratios, AWT = Arteriole wall thicken, ICI = inflammatory cells infiltration, OR = odds ratio, CI = confidence interval.



It showed 178 patients were visited until August 2020.

DISCUSSION

The morbidity related to hyperuricemia in IgAN patients was found to be 41.67% in this study while it was 38.8% in a retrospective analysis of 1070 patients.[13] Bakan *et al.* found that 32.5% of IgAN patients are associated with hyperuricemia. Still, the diagnostic cut off for hyperuricemia in women was 6.5 mg/dL, which is slightly higher than ours.[14]

Herein, our study found higher levels of serum urea nitrogen, creatinine and total cholesterol in HUA group, with lower eGFR. We can see that eGFR decreases by 2.39 mL/min as serum uric acid increases by 1 mg/dL in a trial.[15] In Weiner's long-term follow-up study of 13338 patients, they found no renal deterioration in cases without HUA; inversely, HUA accelerated renal function loss, with a 1.01-fold increased risk of renal insufficiency after every 1 mg/dL increase of uric acid.[16] A study finds that after adjusting for baseline levels of eGFR, high uric acid can predict renal survival independently; Regardless of whether eGFR is normal or not initially, renal survival significantly reduces in hyperuricemic group after eGFR stratification.[8] In a Chinese research, for IgAN patients, urine albumin-to-creatinine ratio could predict their prognosis,[17] and we also found the serum albumin-to-creatinine ratio was related to high uric acid. Serum uric acid level is in close connection with visceral fat (omentum majus, perirenal, etc.) accumulation and goes up with the increase of serum total cholesterol and serum triglyceride.[18] However, we found no correlation between hyperuricemia and age or blood pressure, which was inconsistent with

previous literature reports.[19] This might be related to the small sample size or regional and dietary differences in this study.

Currently, the mechanisms of IgAN injuries consist of four steps that are exposure of GD-IgA1 antigen epitome, recognition by GD-IgA1 autoantibody, generation of immune complex deposition in the glomerular mesangial region, induction of various cell proliferation and secretion of inflammatory factors, leading to the kidney damage.[20] Genetics is also involved in this process. The pathogenesis of hyperuricemia is mainly due to uric acid metabolism, which is divided into the excretory type and secretory type. Hyperuricemia changes the structure and function of the kidney through a variety of direct or indirect injuries and eventually progresses to ESRD. It has been found that E-cadherin is the starting link of epithelial-to-mesenchymal transition; In vitro experiments in rats show that high serum uric acid can promote ubiquitination, reduce the expression of E-cadherin in renal tubulointerstitial cells, induce renal tubulointerstitial fibrinolysis and directly damage the kidney.[21] Hyperuricemia induces renal tubulointerstitial inflammation through UA crystals, and results in oxidative stress, renin-angiotensin system activation, and endothelial dysfunction, thus causing indirect renal injury; High serum uric acid can reduce the sensitivity of endothelial cells to nitric oxide, affects the expression and function of adenosine triphosphate binding box transporter G2 (ABCG2) that expresses in renal tubular epithelial cells, affects the transformation of mesenchymal cells, and leads to renal tubular damage, interstitial fibrosis and renal impairment.[22] Calcitonin gene-related peptide-interleukin can repair renal vessels,[23] up-regulates cadherin in vascular endothelial cells and improves interstitial fibrosis.[24] This study also analyzed the differences of pathology between IgAN patients in hyperuricemia group and normal group. Results showed that the incidence of thickening of arteriole wall, proportion of glomerular sclerosis, degree of renal tubular atrophy, area of inflammatory cell infiltration, degree of glomerular mesangial hyperplasia and incidence of renal interstitial fibrosis in HUA group were higher. The more severe damage to the glomerulus, renal tubule and renal interstitial could be seen in IgAN with hyperuricemia. In a multicenter retrospective cohort study, the proportion of crescent formations, whether cellular or fibrous, the risk of composite renal outcomes were parallel to the change in crescent formation ratio.[25] Foreign studies have also shown that the most severe glomeruli, tubular, and interstitial lesions can be observed in IgAN with crescent formation.[26] When the crescents formed, kidney damage was progressively exacerbated, especially interstitial damage. Moriyama *et al.* demonstrated that HUA can induce glomerulosclerosis,[27] but also cause or even worsen interstitial fibrosis and renal tubular atrophy,[28] which is of great significance for the tubular interstitial disease.

This study found that thickening of arteriole wall was related to hyperuricemia, Ben-Dov *et al.* found that hyperuricemia promotes the renal vascular endothelial proliferation, produces the inflammatory response, activates the RAS system, and damages further the kidney.[29] The chronic tubulointerstitial lesions are characteristic changes caused by hyperuricemia, followed by ischemic renal lesions including glomerulosclerosis, tubular atrophy and small artery changes; Glomerular ischemia can lead to decreased downstream renal tubular blood flow and results in interstitial damage, which affects inversely renal vascular function, synergistically deciding the prognosis of IgAN patients.[30] Therefore, we deduce that HUA may cause progressive renal lesions in IgAN.

A cohort study, which assessed the renal survival and relationship between clinical features and prognosis of 1155 IgA nephropathy patients, showed that increased renal creatinine, increased blood pressure, increased uric acid, decreased plasma albumin and abnormal urine protein are independent predictors of the poor renal prognosis.[31] Wuet al. reported that 84% of Chinese IgAN children have a normal renal function after 15 years and found that the incidence of renal insufficiency increases when urine retinol-binding protein is $\geq$ 0.7 **µg/**mL.[32] However, our study did not find the significant relation between HUA and renal outcome in IgAN, perhaps for some reasons as the small number of subjects enrolled and the insufficient follow up time.

Limitations

1. It had involved only one center with a small number of subjects enrolled and was not prospective, so we faced many confounding factors, but future

multi-center studies with larger sample size can help to acquire better data; 2. Some patients' poor compliance led to the unsatisfactory follow-up data, better communication and contact with patients may be needed in future studies.

CONCLUSIONS

More severe renal pathological injures (glomeruli, tubules or interstitium) were found in IgAN. Besides, total cholesterol and the area of infiltration of inflammatory cells were independent related factors of hyperuricemia in IgAN. To some extent, hyperuricemia might affect the prognosis of IgAN.

DISCLOSURE

The authors declare that they have no conflicting of interest.

REFERENCES

1. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013; 368(25):2402-2414.
2. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004; 66(3):920-923.
3. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. Kidney Int. 2015; 88(5):974-989.
4. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med. 2002; 347(10):738-748.
5. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol. 2004; 24(3):179-196.
6. Hu H, Wan Q, Li T, et al. Circulating MiR-29a, Possible Use as a Biomarker for Monitoring IgA Nephropathy. Iran J Kidney Dis. 2020; 14(2):107-118.
7. Tang F, Hu H, Xu R, Tao C, Wan Q. Association Between Serum IgG Concentrations and Prognosis in IgA Nephropathy. Iran J Kidney Dis. 2020; 14(6):454-462.
8. Shi Y, Chen W, Jalal D, et al. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. Kidney Blood Press Res. 2012; 35(3):153-160.
9. Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH. Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. Int J Cardiol. 2012; 154(3):316-321.
10. Zeng CH, Le W, Ni Z, et al. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult chinese patients. Am J Kidney Dis. 2012; 60(5):812-820.
11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6):461-470.
12. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39(2 Suppl 1):S1-266.
13. Fan S, Zhang P, Wang AY, et al. Hyperuricemia and its related histopathological features on renal biopsy. BMC Nephrol. 2019; 20(1):95.
14. Bakan A, Oral A, Elcioglu OC, et al. Hyperuricemia is associated with progression of IgA nephropathy. Int Urol Nephrol. 2015; 47(4):673-678.
15. Yang Q, Fu C, Xiao J, Ye Z. Uric acid upregulates the adiponectin-adiponectin receptor 1 pathway in renal proximal tubule epithelial cells. Mol Med Rep. 2018; 17(3):3545-3554.
16. Weiner DE, Tighiouart H, Elsayed EF, et al. Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008; 19(6):1204-1211.
17. Huan L, Yuezhong L, Chao W, HaiTao T. The urine albumin-to-creatinine ratio is a reliable indicator for evaluating complications of chronic kidney disease and progression in IgA nephropathy in China. Clinics (Sao Paulo). 2016; 71(5):243-250.
18. Hikita M, Ohno I, Mori Y, Ichida K, Yokose T, Hosoya T. Relationship between hyperuricemia and body fat distribution. Intern Med. 2007; 46(17):1353-1358.
19. Sánchez-Lozada LG, Tapia E, Santamaría J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int. 2005; 67(1):237-247.
20. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011; 22(10):1795-1803.
21. Ryu ES, Kim MJ, Shin HS, et al. Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. Am J Physiol Renal Physiol. 2013; 304(5):F471-480.
22. Gewin LS, Summers ME, Harral JW, et al. Inactivation of Tsc2 in Abcg2 lineage-derived cells drives the appearance of polycystic lesions and fibrosis in the adult kidney. Am J Physiol Renal Physiol. 2019; 317(5):F1201-F1210.
23. Morimoto R, Satoh F, Murakami O, et al. Expression of adrenomedullin2/intermedin in human brain, heart, and kidney. Peptides. 2007; 28(5):1095-1103.
24. Zhang W, Wang LJ, Xiao F, Wei Y, Ke W, Xin HB. Intermedin: a novel regulator for vascular remodeling and tumor vessel normalization by regulating vascular endothelial-cadherin and extracellular signal-regulated kinase. Arterioscler Thromb Vasc Biol. 2012; 32(11):2721-2732.
25. Park S, Baek CH, Park SK, et al. Clinical Significance of Crescent Formation in IgA Nephropathy - a Multicenter Validation Study. Kidney Blood Press Res. 2019; 44(1):22-32.
26. Rafieian-Kopaei M, Baradaran A, Nasri H. Significance of extracapillary proliferation in IgA-nephropathy patients with regard to clinical and histopathological variables. Hippokratia. 2013; 17(3):258-261.
27. Moriyama T, Itabashi M, Takei T, et al. High uric acid level is a risk factor for progression of IgA nephropathy with chronic kidney disease stage G3a. J Nephrol. 2015; 28(4):451-456.

28. Zhou J, Chen Y, Liu Y, et al. Plasma uric acid level indicates tubular interstitial leisions at early stage of IgA nephropathy. BMC Nephrol. 2014; 15:11.
29. Ben-Dov IZ, Kark JD. Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. Nephrol Dial Transplant. 2011; 26(8):2558-2566.
30. Wu J, Chen X, Xie Y, et al. Characteristics and risk factors of intrarenal arterial lesions in patients with IgA nephropathy. Nephrol Dial Transplant. 2005; 20(4):719-727.
31. Le W, Liang S, Hu Y, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 2012; 27(4):1479-1485.
32. Wu H, Fang X, Xia Z, et al. Long-term renal survival and undetected risk factors of IgA nephropathy in Chinese children-a retrospective 1243 cases analysis from single centre experience. J Nephrol. 2020.

Correspondence to:
Lei Lan, MD
Department of Nephrology, the First Affiliated Hospital of University of Science and Technology of China, Hefei, Anhui Province, China
E-mail: lanlei1976@126.com

Received January 2021
Revised March 2021
Accepted May 2021