

# Time Averaged Uric Acid Is Associated With the Prognosis of IgAN in Females

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## Research Article

**Keywords:** IgA Nephropathy (IgAN), Time averaged, uric acid, prognosis, females

**Posted Date:** June 4th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-562936/v1>

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# Abstract

**Background** IgA Nephropathy (IgAN) is one of the most common glomerular diseases. However, the effect of uric acid on the prognosis of IgAN is still unclear, especially between males and females. Therefore, the present study aimed to explore the role of hyperuricemia in IgAN patients and the differences in gender. Consequently, the study conducted a retrospective analysis of the prognosis of IgAN in patients from the General Hospital of Tianjin Medical University.

**Methods:** A total of 1,022 patients with primary IgAN, diagnosed through renal biopsy were enrolled from the Department of Nephrology, General Hospital of Tianjin Medical University. However, after applying the exclusion criteria, only 463 patients remained and were regularly followed up in the hospital. In addition, the relationship between Time Average Uric Acid (TA-UA) and prognosis of IgAN was analyzed.

**Results:** The findings showed that TA-UA was an independent risk factor for the prognosis of IgAN in the 463 patients studied (OR=1.752, 95%CI=1.348-2.277, p<0.001). Additionally, higher TA-UA values were associated with a faster progression of disease and worse prognosis (p < 0.05). Elevated TA-UA was also shown to be an independent risk factor for the progression of disease in female patients but not in their male counterparts (women: HR=1.998, 95%CI=1.398-2.854, p<0.001; men: HR=1.405, 95%CI=0.869-2.274, p=0.166).

**Conclusion:** Increased TA-UA is an independent risk factor for the progression of IgAN, especially in women.

## Introduction

IgA Nephropathy (IgAN) is currently the most common type of primary glomerulonephritis in the world (McGrogan et al. 2011; Yu et al. 2011), accounting for 58.2% of primary glomerulonephritis in China (Zhou et al. 2009). According to a previous report, patients with End-stage Renal Disease (ESRD) had a 10-year survival rate of only 50% (Moriyama et al. 2014). Hyperuricemia is also closely associated with the progression of IgAN, in addition to hypertension, proteinuria, decreased renal function and other classic features of the disease (Syrjanen et al. 2000).

Additional studies reported that hyperuricemia was an independent risk factor for the poor prognosis of IgAN (Bakan et al. 2015; Caliskan et al. 2016; Goto et al. 2009; Shi et al. 2012). Notably, the risk of poor prognosis in IgAN patients with hyperuricemia was reported to be 2.4 times higher than that in patients with normal serum uric acid (Fan et al. 2019). Moreover, Masukuma et al. (Masukuma et al. 2017) reported that serum uric acid was associated with the progression of IgAN, especially in women. However, the findings from recent studies have been inconsistent. For instance, Nagasawa et al. (Nagasawa et al. 2016) suggested that hyperuricemia was an independent risk factor for the progression to ESRD in female IgAN patients but not in their male counterparts. On the other hand, Moriyama et al. (Moriyama et al. 2015) showed that hyperuricemia was only a risk factor for the progression of IgAN in stage 3a Chronic Kidney Disease (CKD).

It is therefore clear that the role of serum uric acid in IgAN is still controversial. Nonetheless, a large number of previous studies rarely included the analysis of pathological data and the baseline value of serum uric acid at renal biopsy was used as the research index (Ghani et al. 2011; Le et al. 2012; Liu et al. 2018; Matsukuma et al. 2017; Moriyama et al. 2015; Nagasawa et al. 2016). However, the baseline value of serum uric acid may not accurately reflect the dynamic level of serum uric acid during the follow-up period because the level of blood uric acid fluctuates greatly and is easily affected by specific food and eating habits (Roddy et al. 2018). Changes in the circadian rhythm should also be taken into account. Therefore, the present study chose the Average Time Uric Acid (TA-UA) of patients to evaluate the relationship between changes in serum uric acid and the prognosis of IgAN. This would be useful in guiding the treatment of IgAN.

# Materials & Methods

## 2.1 Data sources and study population

The study assessed 4,365 patients who had received renal puncture biopsy between January 1, 2010 and December 31, 2019, in the Department of Nephrology, General Hospital of Tianjin Medical University. The dataset included 1,022 patients who had been diagnosed with IgAN. The pathological criteria for the diagnosis of IgAN were as follows: fluorescent immunoassay showing that the IgA based immune complex was deposited in the mesangial region of the glomerulus, with or without deposition of complement C3, IgG and IgM. However, the study excluded 8 patients with a glomerular count  $\leq 8$  and aged  $\leq 16$  years as well as 27 individuals with secondary IgAN, such as Henoch Schonlein purpura, autoimmune diseases, liver cirrhosis, psoriasis and ankylosing spondylitis. The study also excluded 366 patients with unclear renal outcomes and 158 individuals with incomplete clinical follow-up data. Finally, data from 463 patients was retrospectively analyzed.

## 2.2 Study endpoint, definition and data measurement:

The clinical indices (serum uric acid, serum creatinine, serum albumin, hemoglobin and 24-hour urinary protein) and the MEST-C scores following renal biopsy were recorded. The study also recorded the clinical indices and the time of detection in the subsequent review. All the data was then time averaged according to the trapezoidal rule. In other words, the area under the curve formed by repeated measurements at each visit was divided by the elapsed time before the end of the follow-up period. Moreover, hyperuricemia was defined as TA-UA  $> 7$  mg / dL in males and  $> 6$  mg / dL in females. The estimated glomerular filtration rate was then calculated using the CKD-EPI formula.

The primary endpoint of the study was a major adverse renal event, IgAN progression, defined as a 30% decrease in the Estimated Glomerular Filtration Rate (EGFR), a 50% increase in serum creatinine or initiation of dialysis.

## 2.3 Statistical methods

Normally distributed continuous variables were presented as the mean  $\pm$  SD. On the other hand, continuous variables that did not conform to normal distribution were presented as medians and interquartile ranges (25th percentile; 75th percentile) while categorical variables with skewed distribution were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of the data. In addition, the Student's t-test was used to compare the clinical characteristics and identify differences between groups of normally distributed data while the Mann-Whitney U test was utilized to analyze the skewed data. Moreover, the chi-square test was employed to analyze the categorical variables. Additionally, Kaplan-Meier survival curves with log-rank tests and a univariate Cox proportional hazards model were used to examine the effect of serum TA-UA levels on the progression of IgAN. A multivariate Cox proportional hazards model was also applied to adjust the variables that may have affected the progression of IgAN. Furthermore, the Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) were calculated to compare the risks of IgAN progression. Restricted cubic splines were also used to demonstrate the non-linear relationships between the serum UA level and IgAN progression. All the data was analyzed and plotted using SPSS version 26 (SPSS Inc.) and R version 4.0.3 (The R Foundation for Statistical Computing, <https://www.R-project.org/>). In addition, all the statistical tests were two-tailed and a p value  $< 0.05$  was considered to be statistically significant.

# Results

## 3.1 Clinical characteristics of the study population

The present study analyzed data from 463 patients and the median follow-up period was 3 years (0.5-10.5 years). The average age of the study population was  $37.95 \pm 12.42$  years and 43.4% of the patients were male. In addition, 168 patients were found to have hyperuricemia, during the follow-up period. Table 1 summarizes the clinical features of individuals in the control and hyperuricemia groups. Compared to the control group, there were more men and older people in the hyperuricemia category. The results also showed that patients in the hyperuricemia group had higher levels of serum creatinine and urinary protein, compared to individuals in the control category. Moreover, the pathological manifestations of M, S, T and C were more severe in patients in the hyperuricemia group.

### 3.2 Relationship between TA-UA and prognosis of IgAN

In this study, 47 patients (10.2%) developed IgAN during the follow-up period. Additionally, Cox regression analysis showed that TA-UA was significantly different from IgAN patients in terms of prognosis (HR = 1.537, 95% CI = 1.258-1.877,  $P < 0.001$ ), as well as in men (HR = 1.706, 95% CI = 1.175-2.486,  $P = 0.005$ ) and women (HR = 2.077, 95% CI = 1.526-2.829,  $P < 0.001$ ).

The adjusted Cox model also showed that the risk of IgAN progression was significantly higher in patients with hyperuricemia (HR = 1.752, 95% CI = 1.348-2.277,  $p < 0.001$ ), after adding the general data (age, gender and model 1), pathological data (MEST-C and model 2) and clinical indicators (hemoglobin, creatinine, urinary protein and model 3), respectively. In other words, the results showed that hyperuricemia was an independent risk factor for the progression of IgAN.

However, TA-UA was significantly associated with the progression of IgAN in female patients only (HR = 1.998, 95% CI = 1.398-2.854,  $p < 0.001$ ) and not in their male counterparts (HR = 1.405, 95% CI = 0.869-2.274,  $p = 0.166$ ). Similar results were obtained from the Kaplan-Meier survival curves, as shown in Figure 1. Moreover, the results in Figure 2 show the non-linear relationship between serum uric acid levels and IgAN progression in both genders and in the total study population.

## Discussion

The role of hyperuricemia in the pathogenesis and development of CKD is attracting more attention because of its pathogenic effect on the renal glomeruli and tubules, especially in IgAN. This study analyzed the role of hyperuricemia in the progression and prognosis of IgAN. Consequently, the present study conducted a regular follow up of 463 IgAN patients enrolled from the General Hospital of Tianjin Medical University. In addition, the level of uric acid in patients during treatment was evaluated using TA-UA.

Analysis using the Cox model showed that TA-UA was significantly correlated with the prognosis of IgAN. Notably, TA-UA was still significantly correlated with the prognosis of IgAN after gradually adding age, gender, pathological and time average clinical indicators. It was previously recommended that the level of serum uric acid should be controlled within the normal range based on the age and gender of patients with CKD complicated with hyperuricemia, so as to avoid the possible adverse effects of crystal deposition and extremely low levels of serum uric acid (Roddy et al. 2018). In the present study, survival analysis showed that individuals with hyperuricemia had higher levels of TA-UA than that the normal patients. Additionally, patients with hyperuricemia had worse prognoses than those in which TA-UA was within the normal range. Interestingly, the results differed from those previously reported in that for every 1 mg / dL increase in TA-UA, the increased risk of IgAN progression was higher than that reported before (Matsukuma et al. 2017; Oh et al. 2020). This may be due to the fact that TA-UA was more comprehensive and sensitive to changes in the patient's condition during the follow-up period than the baseline value of serum uric acid (used by previous studies).

Although TA-UA may not fully reflect the actual situation of serum uric acid, it provides a basis of studying the effect of serum uric acid on the progression of IgAN.

Previous studies showed that there are significant gender differences in the impact of serum uric acid on different diseases, especially in cardiovascular and cerebrovascular diseases, chronic kidney disease, diabetes and other ailments(Barbieri et al. 2015; Kohagura et al. 2013; Lou et al. 2020; Sun et al. 2019). However, gender differences in the progression of IgAN are yet to be established since different studies report contradictory results(Ruan et al. 2018; Zhu et al. 2018). For instance, Goto et al.(Goto et al. 2009) showed that men were more likely to progress to ESRD than women. Additionally, Riispere Ž et al.(Riispere et al. 2016) analyzed the factors influencing IgAN and concluded that the disease progressed more rapidly in men than in women. However, a study by Cattran DC et al.(Cattran et al. 2008) showed that there was no significant difference in long-term survival from IgAN, between men and women. Moreover, Matsukuma et al.(Matsukuma et al. 2017) found a correlation between the levels of serum uric acid and IgAN progression in both men and women although the association was more significant in women. According to Yang et al. (Deng et al. 2018), uric acid is an important predictor of IgAN prognosis in both males and females. Furthermore, a study of 935 IgAN patients showed that elevated levels of serum uric acid was an independent risk factor for the progression the disease in women but not in men(Nagasawa et al. 2016). The same results were obtained even after age and serum creatinine matching as well as propensity score matching. The present study similarly found that TA-UA was an independent risk factor for renal outcomes in women with IgAN but not in men.

Additionally, the restricted three sample map revealed that TA-UA and IgAN progression did not show a "U" shape in women and men, which was different from previous reports(Mori et al. 2021). This may be related to the small number of low-level TA-UA in the population analyzed by the present study. Notably, it was easier to increase the level of blood uric acid than to decrease it during the entire follow-up period. In addition, progression to kidney failure and improvement of diet may increase the level of blood uric acid.

However, the reason for the difference in the effect of serum uric acid between women and men is still unclear. The secretion and excretion of uric acid are regulated by a variety of uric acid transporters, such as the uric acid transporter 1, ABCG2 and the Glucose Transporter 9 (GLUT9)(Li et al. 2020). Notably, the reabsorption function of the uric acid transporter 1 can be inhibited by estrogen, promoting the excretion of uric acid in urine(Hak & Choi 2008). Additionally, Kao et al.(Kolz et al. 2009; Zhang et al. 2013) reported that mutations in ABCG2 had a stronger effect in increasing the levels of serum uric acid in men than in women. Moreover, the SLC2A9 gene regulates GLUT9 and the rs734553 allele was shown to have a greater effect on the levels of uric acid in women than in men(Dehghan et al. 2008). Another possible explanation is that male IgAN patients are associated with more risk factors for ESRD, including smoking, obesity, hypertension and hyperlipidemia, which were not included in the present study.

Despite the insightful findings, this study had a number of limitations. First, this was a single center retrospective study and the median follow-up time was 36 months (6 months, 126 months). Compared to the development of the disease, the follow-up time used in the present study was not long enough. Therefore, we will continue to follow up these patients. Second, IgAN treatment may have been a confounding factor affecting the prognosis of the disease. However, treatment was not included in the study because of the individualization, flexibility and variability of clinical treatment. Third, given that patient information was obtained from the follow-up records in our hospital, some patients were lost during follow-up. Additionally, there were deviations in the classification and analysis of data. Therefore, further studies that are well-designed, multicenter and with a larger cohort as well as a longer regular follow-up time, are needed to confirm these findings.

## Conclusions

The present study showed that hyperuricemia was an independent risk factor for the progression of IgAN. In addition, TA-UA was identified to be an independent risk factor for IgAN in women but not in men.

## Declarations

### Ethical approval and consent to participate

Not applicable.

This study was conducted in accordance to the principles of the Helsinki declaration. Given that this was a retrospective study and the data used did not include personal identity information, informed consent is not required.

### Consent for publication

Not applicable.

### Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

### Competing interests

Not applicable.

### Funding

Not applicable.

### Authors' contributions

Quan Zhang and Hongling Han wrote the main manuscript text and Luyao Dong prepared figures 1-2 and table 1-2. All authors reviewed the manuscript.

### Acknowledgements

None.

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## Tables

Table 1

Baseline characteristics of 463 IgAN patients according to serum uric acid level and gender.

	All Subjects	Man(n=201)	Woman(n=262)	p-Value	Non-HUA(n=295)	HUA(n=168)	P-Value
M1	392(84.7%)	172(85.6)	220(84.0)	0.635	239(81)	153(91.1)	0.004
S1+S2	294(63.1%)	126(62.7)	168(64.1)	0.246	168(56.9)	126(75.0)	0.001
E1	193(42.7%)	82(40.8)	111(42.4)	0.734	118(40.0)	75(44.6)	0.33
T1	217(46.9%)	100(49.8)	117(44.7)	0.553	134(45.4)	83(49.4)	<0.001
T2	85(18.4%)	35(17.4)	50(19.1)		36(12.2)	49(29.2)	
C1	241(52.1%)	105(52.2)	136(51.9)	0.499	166(56.3)	75(44.6)	<0.001
C2	79(17.1%)	30(14.9)	49(18.7)		34(11.5)	45(26.8)	
Male	201(43.4%)	/	/	/	118(40.0)	83(49.4)	0.62
Age	37.95±12.42	38.74±13.35	37.35±11.64	0.244	37.01±12.26	39.61±12.56	0.03
TA-Hb	129.19±20.14	141.82±18.81	119.66±15.07	<0.001	130.32±18.14	127.47±22.98	0.169
TA-ALB	37.38±5.56	38.59±5.69	36.42±5.34	<0.001	37.66±5.64	36.83±5.48	0.124
TA-SCR	91.16±45.86	106.84±48.48	79.14±39.85	<0.001	78.60±32.37	113.22±56.63	<0.001
TA-UTP	1.2[0.68-2.10]	1.13[0.63-2.09]	1.21(0.73-2.17)	0.715	1.13(0.63-2.09)	1.21(0.73-2.17)	0.001
TA-UA	6.14±1.50	6.88±1.37	5.57±1.33	<0.001	5.30±0.96	7.63±1.05	<0.001
Continuous variables are expressed as mean ± SD or as median (interquartile range). Categorical variables are expressed as frequency (percent). M: mesangial hypercellularity; E: endocapillary hypercellularity; S: segmental glomerulosclerosis; T: tubular atrophy/interstitial fibrosis; C: crescents. TA:time average; Hb: hemoglobin; ALB: albumin; SCR: serum creatinine; UTP: urine total protein; UA: uric acid.							

Table 2

Hazard ratios and 95% CI of primary outcome according to TA-UA among 463 patients with IgA nephropathy

	Total Subjects		Male		Female	
	HR[95%CI]	p-Value	HR[95%CI]	p-Value	HR[95%CI]	p-Value
<b>Crude</b>	1.537[1.258;1.877]	<0.001	1.706[1.175;2.486]	0.005	2.077[1.526;2.829]	<0.001
<b>Model 1</b>	1.925[1.521;2.437]	<0.001	1.709[1.175;2.486]	0.005	2.077[1.526;2.829]	<0.001
<b>Model 2</b>	1.805[1.396;2.335]	<0.001	1.559[1.032;2.354]	0.035	1.998[1.398;2.854]	<0.001
<b>Model 3</b>	1.752[1.348;2.277]	<0.001	1.405[0.869;2.274]	0.166	1.998[1.398;2.854]	<0.001

Model 1, adjusted for age and gender.  
 Model 2, adjusted for age, gender, oxford classification (MEST) score, crescents.  
 Model 3, adjusted for age, gender, oxford classification (MEST) score, crescents, TA-Hb, TA-ALB, TA-SCR, TA-UA, TA-UTP.

## Figures

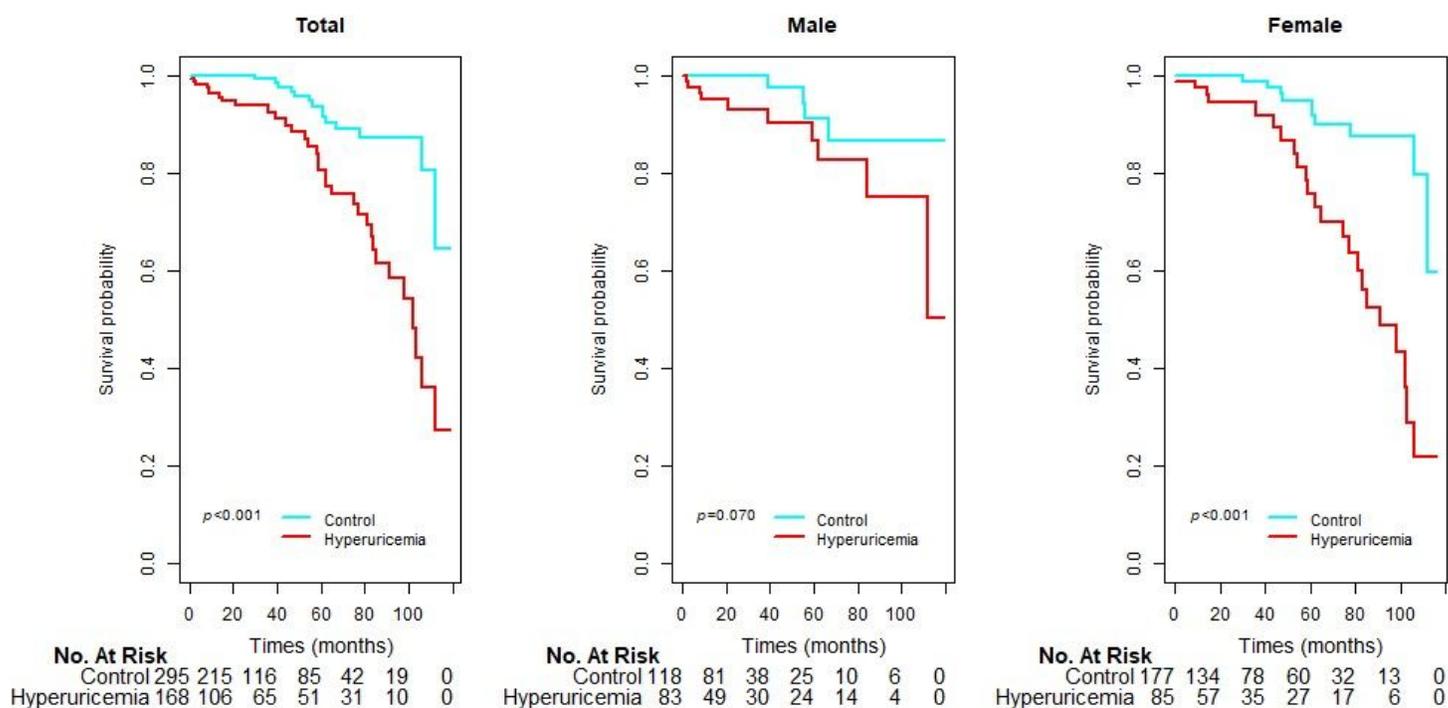
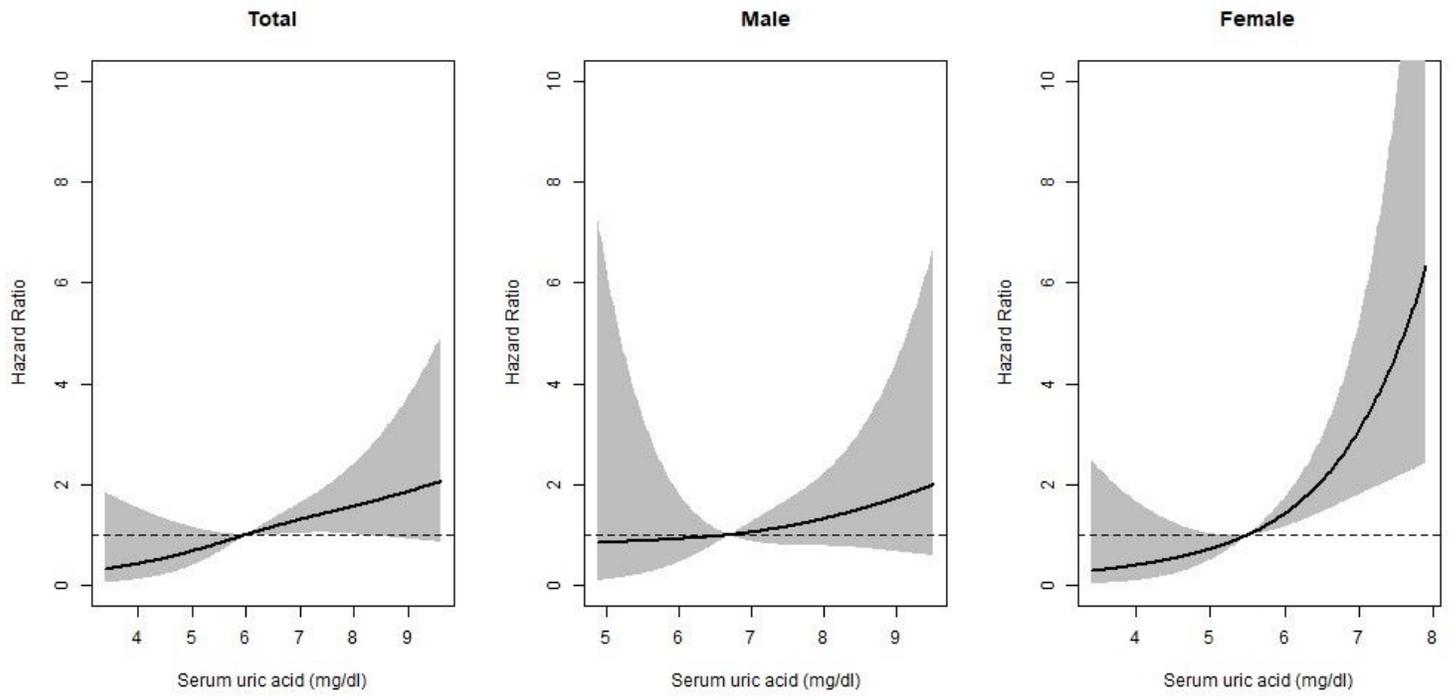


Figure 1

The Kaplan-Meier renal survival curves indicated that the accumulative survival rate for the primary outcome was lower in the hyperuricemia group than that in the control group, whether in total population or in female group, but not in male group.



**Figure 2**

Restricted cubic spline curve of hazard ratio of TA-UA for primary outcome by sex. There is a non-linear relationship between serum uric acid levels and IgAN progression in both genders and in the total study population.