Serum uric acid level is correlated with the clinical, pathological progression and prognosis of IgA nephropathy: an observational retrospective pilot-study

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Objectives. This study was aimed to assess the relationship between serum uric acid (SUA) level and the clinical, pathological phenotype of IgA nephropathy (IgAN), and to determine the role of SUA level in the progression and prognosis of IgAN.

Methods. A total of 208 patients with IgAN were included in this study, which was classified into the normo-uricemia group and hyperuricemia group according to the SUA level. The clinical data at baseline, IgA Oxford classification scores (MEST-C scoring system), and other pathological features were collected and further analyzed. All patients were followed up and the prognosis was assessed using Kaplan-Meier survival curves. GraphPad Prism 7.0 and SPSS 23.0 were used for statistical analyses.

Results. In clinical indicators, patients with hyperuricemia had the significantly higher proportion of males to females, mean arterial pressure, the levels of total cholesterol, triglyceride, Scr, BUN, 24 hour-urine protein, C3, and C4, the lower levels of high-density lipoprotein cholesterol and eGFR than those without(p<0.05). In terms of pathological characteristics, the tubular atrophy/interstitial fibrosis scores, vascular injury scores, and glomerular sclerosis percentage were significantly higher in patients with hyperuricemia compared with those without(p<0.01). There was no significant difference in the scores of mesangial hypercellularity, endocapillary hypercellularity, focal segmental glomerulosclerosis, as well as crescents between the two groups(p>0.05). As for the depositions of immune complexes deposition in IgAN, the hyperuricemia group had less deposition of immunoglobulin G and FRA than the normo-uricemia group (p<0.05), while the deposition of immunoglobulin A, immunoglobulin M, and complement C3 in the two groups showed no statistical difference. The survival curve suggested that patients in the hyperuricemia group have significantly poorer renal outcome than those in the normo-uricemia group (p= 0.0147). Results also revealed that the SUA level is a valuable predictor of renal outcome in patients with IgAN. The optimal cutoff value was 361.1μmol/L (AUC=0.76±0.08167) and 614 μmol/L (AUC=0.5728±0.2029) for female and male, respectively.

Conclusions. The level of SUA is associated with renal function level and pathological severity of IgAN, and maybe a prognostic indicator of IgAN.

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Abstract

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Methods. A total of 208 patients with IgAN were included in this study, which was classified into the normo-uricemia group and hyperuricemia group according to the SUA level. The clinical data at baseline, IgA Oxford classification scores (MEST-C scoring system), and other pathological features were collected and further analyzed. All patients were followed up and the prognosis was assessed using Kaplan-Meier survival curves. GraphPad Prism 7.0 and SPSS 23.0 were used for statistical analyses.

Results. In clinical indicators, patients with hyperuricemia had the significantly higher proportion of males to females, mean arterial pressure, the levels of total cholesterol, triglyceride, Scr, BUN, 24 hour-urine protein, C3, and C4, the lower levels of high-density lipoprotein cholesterol, and eGFR than those without ($p < 0.05$). In terms of pathological characteristics, the

29   tubular atrophy/interstitial fibrosis scores, vascular injury scores, and glomerular sclerosis

30   percentage were significantly higher in patients with hyperuricemia compared with those without

31   (p < 0.01). There was no significant difference in the scores of mesangial hypercellularity,

32   endocapillary hypercellularity, focal segmental glomerulosclerosis, as well as crescents between

33   the two groups (p > 0.05). As for the depositions of immune complexes deposition in IgAN, the

34   hyperuricemia group had less deposition of immunoglobulin G and FRA than the normo-

35   uricemia group (p < 0.05), while the deposition of immunoglobulin A, immunoglobulin M, and

36   complement C3 in the two groups showed no statistical difference. The survival curve suggested

37   that patients in the hyperuricemia group have significantly poorer renal outcome than those in the

38   normo-uricemia group (p = 0.0147). Results also revealed that the SUA level is a valuable

39   predictor of renal outcome in patients with IgAN. The optimal cutoff value was 361.1μmol/L

40   (AUC = 0.76 ± 0.08167) and 614 μmol/L (AUC = 0.5728 ± 0.2029) for female and male,

41   respectively.

42   **Conclusions.** The level of SUA is associated with renal function level and pathological severity

43   of IgAN, and maybe a prognostic indicator of IgAN.

Introduction

44

45   IgA Nephropathy (IgAN), whose feature is the deposition of IgA-dominant in the mesangial area,

46   is the most prevalent primary glomerular disease in the world. Approximately 40% of patients

47   almost completely lose their renal function within 30 years after diagnosis (Coppo & D'Amico,

48   2005; D'Amico, 2004). Previous studies have demonstrated that clinical features, including

49   severe proteinuria, poor renal function, and hypertension at the initial diagnosis are the predictors

50   of poor outcomes in IgAN (Le et al., 2012; Barbour & Reich, 2018; Mariani et al., 2018; Barbour

51   & Reich, 2012). Histological features were also identified as crucial predictors of IgAN patients.

52   The Oxford classification of IgAN, also known as MEST score, including mesangial

53   hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S),

54   tubular atrophy/interstitial fibrosis (T) has been shown to be of significant value in predicting the

55   prognosis IgAN (Barbour et al., 2016; Maixnerova et al., 2016; Herzenberg et al., 2011a;

56   Katafuchi et al., 2011; Coppo et al., 2014a; Lv et al., 2013). Recently, crescents (C) have been

57   proposed to add to the Oxford classification of IgAN to form an updated MEST-C score system,

58   which can provide a more comprehensive pathological prediction for the prognosis of IgAN

59   (Trimarchi et al., 2017).

60   Numerous studies have shown that the level of uric acid can predict the incidence of

61   atherosclerosis (Feig 2014; Gustafsson & Unwin 2013; Li et al. 2014), hypertension (Wang et al.

62   2014), and coronary heart disease (Kim et al. 2010). Moreover, some studies have emphasized

63   that high levels of serum uric acid (SUA) would form urates crystals that deposit in renal tubules

64   and interstitial, leading to kidney fibrosis and failure (Su et al. 2020; Viggiano et al. 2018).

65   Recently, some studies have found that there is a correlation between the SUA level and the

66   progression of IgAN. A cohort study has shown that hyperuricemia is associated with the

67   progression of IgAN, however, the effect of hyperuricemia on renal pathology was not evaluated

68   (Bakan et al. 2015) in this study. The study conducted by Nagasawa et al. has shown that the

69   SUA level is a predictor of IgAN in females but not in males (Nagasawa et al. 2016). Similarly,

70   the evaluation of renal pathological changes was not included. Moriyama et al. have reported that

71   hyperuricemia is a risk factor for the progression of IgAN with CKD stage G3a but not for stage

72   G1, G2, or G3b-4. This study also has shown that, except for glomerulosclerosis percentage,

73   there is no significant difference in the 2009 Oxford classification, crescentic percentage, and

74   focal segmental sclerosis between the hyperuricemia group and the normo-uricemia group

75   (Moriyama et al. 2015). Another study suggested that the relationship between hyperuricemia

76   and IgAN progression was not very significant in patients with older age, lower eGFR, or

77   interstitial

78   lesion (Zhu et al. 2018). Similarly, this study did not use the updated Oxford classification of

79   IgAN. These studies are partially inconsistent even contradictory and not comprehensive, cannot

80   clarify the role of the SUA level in the progression and prognosis of IgAN. Therefore, it is

81   imperative to conduct further research.

82   In this retrospective study, we first used the updated Oxford classification criteria (MEST-

83   C), vascular injury, glomerulosclerosis, immunofluorescence score, clinical indicators, and

84   prognosis analysis to comprehensively evaluate the relationship between the SUA level and the

85   clinical, pathological characteristics of IgAN, to determine the impact of hyperuricemia on the

86   development and prognosis of IgAN.

Methods

88   Patients screening and Clinical Data Collection

89   From January 2015 to May 2016, a total of 240 patients diagnosed with IgAN according to

90   diagnostic criteria at Tongji Hospital were included in the study. The exclusion criteria of this

91   study were listed as below: (1) the secondary IgAN caused by systemic diseases such as

92   autoimmune disorders, chronic hepatitis, tumor, (2) incomplete clinical and pathologic data, or (3)

93   the number of glomeruli in renal biopsy specimen less than eight. According to the above criteria,

94   32 patients were excluded and 208 patients were eventually involved in our research. The

95   clinical data were collected at IgAN diagnosis. Blood samples were collected in the morning

96   from fasting participants who had been directed to avoid eating any food that might affect the

97   test result. The SUA levels > 420 μmol/L in men and > 360 μmol/L in women was defined as

98   hyperuricemia. Based on the levels of SUA, there were 138 cases with hyperuricemia and 70

99   cases with normo-uricemia.

100   This study was approved by the Ethical Committee of Tongji Hospital (No.TJ-IRB20180608),

101   and the Ethics Committee waived the need for informed consent from participants of this study.

Histologic Evaluation

103   Every renal biopsy specimen was scored by two pathologists who did not know the patient's

104   clinical data. All of the renal specimens were classified and graded by five key pathological

105   features: M, E, S, T, and C according to the MEST-C score of Oxford Classification(Trimarchi et

106 al., 2017). Other pathological features, including glomerular global/ ischemic sclerosis,

107 arteriosclerosis, arteriolar hyalinosis, and immune complex deposition were also described in all

108 specimens. The histopathological grading schema we used was presented in Table 1. When the

109 two pathologists differed in their assessments, the biopsy specimen must be reviewed again until

110 an agreement was reached.

Statistical Analyses

111

112 GraphPad Prism 7.0 and SPSS 23.0 were used for statistical analyses. Continuous and

113 categorical data were presented as mean ± SD and number (%), respectively. The comparison

114 between the normo-uricemia group and the hyperuricemia group using the parametric t-test or

115 Mann-Whitney. The overall renal survival rate of IgAN was presented using the Kaplan-Meier

116 curve and the difference between the two groups was compared using the log-rank test. The p <

117 0.05 was regarded as statistical significance in all tests.

Results

118

Demographic and clinical data

119

120 The demographic and clinical data of 208 participants in this study were shown in Table 2. The

121 ages of all patients ranged from 15 to 63 years old, with an average of 33.8 ± 10.7 years old.

122 Among them, 82 (39.42%) were males, and 126 (68.68%) were females. The mean arterial

123 pressure of patients was 94.0 ± 11.7 mm Hg, among which 23 patients had hypertension

124 previously, 16 (7.69%) had poor blood pressure control, and 22 (10.58%) were taking

125 antihypertensive medication. In this study, 14.42% of the patients had previously received ACEI

126 and/or ARB treatment, and 4.81% underwent tonsillectomy previously. For all patients, the mean

127 levels of serum albumin, 24-h urine protein, SUA, serum creatinine (Scr), and eGFR were 39.48

128 ± 5.77 g/l, 1.35 ± 1.58 g/d, 348.00 ± 109.10 μmol/l, 89.89 ± 41.49 μmol/l and 82.23 ± 30.22

129 ml/min/1.73 m^2, respectively.

The comparison of clinical characteristics between the normo-uricemia group and the

hyperuricemia group

The comparison of baseline characteristics between the normo-uricemia group and the
hyperuricemia group was presented in Table 3. There were 70 patients (33.65%) with
hyperuricemia, including 36 males (51.43%). These results were similar to the previous study
conducted by Shi-Y (Shi et al., 2012). Results showed that the mean arterial pressure of patients
with hyperuricemia was significantly higher than those without (91.8 ± 10.7 mm Hg vs 98.2 ±
12.5 mm Hg, p = 0.0004). In terms of coagulation indicators, although the FDP level was higher
in the hyperuricemia group (3.23 ± 0.74 mg/l vs 3.86 ± 1.38 mg/l, p = 0.0006), the APTT level
was similar in both groups (p = 0.7833). As for blood lipids, hyperuricemia patients had an
elevated level of total cholesterol, triglyceride, and decreased level of HDL-C (p = 0.026, p =
0.0005, p = 0.0056, respectively). However, the LDL-C levels of the two groups were similar (p >
0.05). This study also revealed the blood urea nitrogen (5.12 ± 1.52 mmol/l vs 6.49 ± 1.95
mmol/l), Scr (80.40 ± 40.58 μmol/l vs 109.00 ± 36.54 μmol/l) and 24-h urine protein (1.05 ±
1.27 g/d vs 1.81 ± 1.67 g/d) in hyperuricemia patients were higher, while the eGFR (98.98 ±
25.12ml/min/1.73m^2 vs 74.50 ± 29.52 ml/min/1.73m^2) was lower than those in normo-uricemia
patients (all p < 0.05). When comparing immunological indexes of patients between the two
groups, no significant difference was found in the levels of IgA, IgG, IgM, and C3 (all p > 0.05).
However, the level of C4 was significantly decreased in the normo-uricemia group (p = 0.003).

The comparisons of Oxford classification for IgAN between two groups

Histological features were evaluated using the MEST-C score of the 2016 updated Oxford
Classification as Hernan et al. have reported (Trimarchi et al., 2017). The comparisons in
histological manifestations between the hyperuricemia group and normo-uricemia group were
shown in Figure 1. The M, E, and S scores in the two groups were similar(p > 0.05). However,
hyperuricemia patients had higher T scores than normo-uricemia patients (1.00 ± 0.87 vs 0.64 ±
0.76, p = 0.0023). In the previous Oxford study, crescent formation was not listed as an
independent predictor of renal outcomes. However, Hernan Trimarchi and his working group

157   supported crescents as a predictor of renal outcome and suggested that crescent (C) should be

158   added to the MEST score. Therefore, we compared the crescent scores in two groups; no

159   significant differences were found (p = 0.4650). When comparing arterial lesions of patients in

160   the two groups, hyperuricemia patients had higher scores of arteriosclerosis (0.99 ± 0.79 vs 0.48

161   ± 0.71, p < 0.0001) and hyalinosis (1.21 ± 0.87 vs 0.63 ± 0.76, p < 0.0001) than those without.

162   The glomerular sclerosis percentage in hyperuricemia patients was higher than that in normo-

163   uricemia patients (0.22 ± 0.20 vs 0.12 ± 0.15, p = 0.0007).

164   **The comparison of different types of crescent lesions between the normo-uricemia group**

165   **and the hyperuricemia group**

166   In the current investigation, results did not show any significant difference between the normo-

167   uricemia group and hyperuricemia group in crescent (C) scores. Crescents could be divided into

168   large and small crescents according to size and can be divided into cellular, fibrocellular and

169   fibrous crescents according to crescent component (Jennette, 2003). Then we tried to explore

170   whether SUA affected the formation of different types of crescents. As shown in Figure 2,

171   patients with hyperuricemia had slightly higher percentages of total crescents, large crescents,

172   and small crescents than normo-uricemia, however, there was no statistical difference (0.10 ±

173   0.14 vs 0.08 ± 0.10, 0.06 ± 0.09 vs 0.05 ± 0.08, 0.04 ± 0.09 vs 0.03 ± 0.05, respectively; all p >

174   0.05). Our data also showed that participants with hyperuricemia had a slightly higher percentage

175   of fibrocellular (0.05 ± 0.09 vs 0.04 ± 0.07, p = 0.1916) and fibrous crescent (0.04 ± 0.08 vs 0.02

176   ± 0.05, p = 0.0837), while a significantly lower percentage of cellular (0.005 ± 0.02 vs 0.020 ±

177   0.05, p = 0.0024) compared to participants without hyperuricemia.

178   **The comparison of deposition of immune complexes and complements in renal biopsy**

179   **between the two groups**

180   The pathogenesis of IgAN was considered to be associated with immunological and or genetic

181   mechanisms. Therefore, we evaluated the deposition of immune complexes and complements in

182 the two groups. We classified the immune complex deposition according to the fluorescence

183 intensity (FI) in this study. As shown in Figure 3, the deposition of IgG and FRA in

184 hyperuricemia group was less than those in normo-uricemia group (0.16 ± 0.44 vs 0.33 ± 0.63, p

185 $= 0.0239; 0.27 \pm 0.51$ vs 0.45 ± 0.55, p $= 0.0258$, respectively). No significant difference was

186 detected in IgA, IgM, and C3 deposition between the two groups (all p > 0.05).

187 **The value of the SUA level in predicting renal prognosis**

188 Finally, after an average of 25 months of follow-up, follow-up data were obtained from 193

189 patients. The endpoint of follow-up was defined as when patients needed dialysis treatment or

190 when creatinine levels doubled. In this study, bout 70% of patients with HUA received uric acid-

191 lowering drugs during the follow-up. The renal survival curves according to the uric acid level

192 suggested that patients with hyperuricemia have poorer renal outcome than patients without (p =

193 0.0147, Figure 4A). And then, we plotted a ROC curve to estimate the value of SUA in

194 predicting the prognosis of IgAN. For females, the optimal cutoff value was 361.1 μmol/L, with

195 sensitivity, specificity, and area under curve (AUC) of 0.7143, 0.7589, and 0.7679 ± 0.08167,

196 respectively (Figure 4B). However, for males, the optimal cutoff value was 614 μmol/L, with the

197 sensitivity and specificity of 0.3333 and 0.9718. The AUC for male patients was 0.5728 ± 0.2029

198 (Figure 4C). Our results revealed that the SUA level was a valuable indicator in predicting the

199 prognosis of IgAN patients, especially in female patients, which is consistent with the research of

200 Oh et al. (Oh et al. 2020).

Discussion

202 IgAN has a high incidence and a variety of clinical manifestations, from asymptomatic hematuria

203 to progress to renal failure rapidly with a few months. Consequently, it is imperative to ascertain

204 its influencing indicator, delay its progression, and prevent ESRD. A few studies have

205 demonstrated that the SUA level is closely related to the progression of IgAN (Shi et al., 2012;

206 Bakan et al., 2015; Cheng et al., 2013). However, there are still inconsistencies and even

207 contradictions in some studies. Therefore, predicting the prognosis of IgAN remains difficult due

208 to its diverse clinical features. In this retrospective study of 208 IgAN patients, we

209 comprehensively evaluated the correlation between SUA levels and clinical and

210 histopathological features. Our results revealed that the SUA level can be considered as a

211 predictor for the prognosis of IgAN.

212   Results showed that patients with hyperuricemia have a poorer renal function and higher blood

213 pressure, which is consistent with Cui et al. researched on 148 patients with IgAN (Cui et al.,

214 2011). The results also revealed significant increases in blood pressure, lipid, C3, and C4 levels

215 in patients with hyperuricemia. Previous studies have found that hyperuricemia is closely related

216 to metabolic syndrome. Elevated SUA level has been confirmed to be an independent predictor

217 of the development of diabetes, hypertension, hypertriglyceridemia, and nonalcoholic fatty liver

218 disease (Lv et al., 2013; Grayson et al., 2011; Kuwabara et al., 2018; Yamada et al., 2010). Some

219 studies also showed a significant improvement in homeostasis assessment for the IR index after

220 lowering the level of SUA (Liu et al. 2015; Takir et al. 2015). Previous researches revealed that

221 the levels of serum C3 and C4 positively correlated with the development of the metabolic

222 syndrome and had been identified as important markers relevant to this disease (Meng et al.,

223 2017; Meng et al., 2018; Xin et al., 2018). The increased activation products of C3 can accelerate

224 the uptake of free fatty acids, the synthesis of triacylglycerol, and inhibit hormone-sensitive

225 lipase in several adipocytes, thus contribute to the development of the metabolic syndrome

226 (Phieler et al., 2013; Barbu et al., 2015). However, the mechanism of C4 in metabolic syndrome

227 remains unclear.

228   To evaluate pathological changes, we classified patients using the 2016 update Oxford

229 classification of IgAN as described above. We found that among patients with hyperuricemia,

230 32.86% had M, 28.57% had S, and 35.71% had E, which was higher than those in normo-

231 uricemia patients, data were 29.71%, 27.54%, 30.43% respectively. However, no significant

232 difference was discovered in M, E, and S scores between the hyperuricemia group and normo-

233 uricemia group. As for the tubular atrophy/interstitial fibrosis, this study revealed that the T score

234   of hyperuricemia patients was statistically higher than that of normo-uricemia patients. This

235   result demonstrated that the level of SUA was related to tubular atrophy/interstitial fibrosis, and

236   hyperuricemia can be used as a clinical marker for T, which was consistent with the founding of

237   Myllymaki et al. (Myllymaki et al., 2005) and Fan et al. (Fan et al. 2019). Recently, a study

238   conducted by Nigro et al. found that the fractal dimension of tubules and the density of tubules

239   negatively correlated the level of SUA and urea. They also suggested that SUA might be a better

240   predictor to identify nephron integrity (Nigro et al. 2018). There were different views on the

241   prognostic value of M, E, and S in different studies (Coppo et al., 2014b; Herzenberg et al.,

242   2011b; Shi et al., 2011; Kang et al., 2012). Nevertheless, T was recognized as a prognostic

243   indicator of IgAN in these studies. Thus, we regard the level of SUA as a valuable factor in

244   predicting IgAN prognosis. The tubular atrophy/interstitial fibrosis caused by SUA might be

245   explained by the following mechanisms. Urate crystals deposit in the renal tubules can directly

246   damage or block the renal tubules, and also form uric acid renal stones to damage the kidney,

247   which results in renal tubular atrophy and interstitial fibrosis, even renal failure (Viggiano et al.

248   2018). HUA could also promote the production of inflammatory factors such as MCP-1 and

249   TNF-β1, which stimulates the inflammatory response and induce renal tubular injury and renal

250   interstitial fibrosis (Romi et al. 2017). Moreover, HUA could decrease E-cadherin expression,

251   increase α-SMA expression, and induced tubular cells epithelial-mesenchymal transition, which

252   results in renal tubulointerstitial injury (Liu et al. 2017).

253   Recently, the updated Oxford classification of IgAN recommends crescents (C) as a

254   pathological predictor of renal outcomes in IgA nephropathy. In this current investigation, no

255   correlation between the SUA level and C score was detected. Then, we compared the

256   percentages of different types of C lesions in patients with hyperuricemia and those with normo-

257   uricemia and found that the percentages of total crescents, large crescents, small crescents,

258   fibrocellular crescents, and fibrous crescents were slightly higher in hyperuricemia patients,

259   while the percentages of cell crescents were significantly lower. It is well known that the

260   formation of the crescent is caused by the deposition of immune complexes, the activation of

261   monocytes, the release of inflammatory cytokines, and the aggregation of fibrocytes. The

262   previous report discovered that uric acid might promote the release of inflammatory cytokines

263   such as TNF-α, IL-1β, IL-6 in IgA patients(Nakagawa et al., 2006). Therefore, we speculate that

264   hyperuricemia may be involved in crescent formation by promoting the release of inflammatory

265   cytokines.

266   As shown in Figure 2, hyperuricemia patients had significantly high percentages of

267   glomerular sclerosis, including global glomerular sclerosis and ischemic glomerular sclerosis.

268   Consequently, the level of SUA might indicate the severity of glomerular sclerosis. As reported

269   in previous studies, many factors were related to glomerular sclerosis, including abnormal

270   cytokine expression, podocyte injury or loss, and the activation of the RAS (Riser et al., 2000;

271   Brown et al., 2000a; Brown et al., 2000b). As mentioned before, SUA could promote the release

272   of inflammatory cytokines, and persistent inflammation may result in glomerular sclerosis.

273   Furthermore, hyperuricemia may activate the renin-angiotensin system, cause glomerular

274   hypertension, and reduce perfusion, which ultimately led to the formation of glomerular sclerosis

275   (Sanchez-Lozada et al., 2005). Besides, the uric acid can induce cellular oxidation through the

276   xanthine oxidase pathway and then result in podocyte damage, which might be another cause of

277   glomerular sclerosis.

278   We also evaluated the effect of elevated uric acid on vascular pathological changes,

279   including arteriosclerosis and arteriolar hyalinosis. We found that the vascular lesions were more

280   severe in hyperuricemia patients, and several mechanisms could explain this difference. Firstly,

281   the elevated uric acid levels could inhibit nitric oxide synthase, induce inflammatory reactions,

282   activate the renin-angiotensin system, cause endothelial cells dysfunction, and eventually lead to

283   the lesions of vascular (Behradmanesh et al., 2013; Corry et al., 2008). Secondly, increased

284   serum lipid levels and oxidation of LDL can promote the progression of atherosclerosis and

285   arteriolar hyalinosis.

286   An early study by Kim SJ et al, which included 343 patients with IgAN found that the

287   decreased serum C3 level and the deposition of C3 in mesangial could independently predict the

288   progression of IgAN, indicating that the activation of complements was closely related to the

289   IgAN pathogenesis (Kim et al., 2012). However, our result showed there was no significant

290   difference in the deposition of IgA, IgM, and C3 between patients with hyperuricemia and those

291   without. This could be due to the small sample size or different races of the study.

292   There are several limitations in this study. On the one hand, the sample size of this pilot

293   study was relatively small. Next, we will conduct a multicenter, large sample size prospective

294   study for further analysis. On the other hand, further studies are required to explore whether

295   lowering uric acid levels could improve the outcome of IgAN.

296   In conclusion, the SUA level affects renal function and pathophysiology of IgAN. The levels

297   of SUA can be considered as a prognostic indicator for IgAN, which is of great significance in

298   guiding treatment decisions and assessing prognosis.

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Competing Interests

304   The authors declare there are no competing interests.

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508

The histopathological grading schema in IgAN.

Histopathological features	Definition
Mesangial hypercellularity	
M0	Mesangial score [a] ≤ 0.5
M1	Mesangial score > 0.5
Endocapillary hypercellularity	
E0	absent
E1	present
Segmental glomerulosclerosis	
S0	absent
S1	present
Tubular atrophy/interstitial fibrosis	
T0	$\leq 25\%$
T1	26% - 50%
T2	$> 50\%$
Crescents	
C0	absent
C1	present in ≥ 1 glomerulus
C2	in $> 25\%$ of glomeruli
Arteriosclerosis	
0	no intimal thickening
1	intimal thickened and $<$ thickness of media
2	intimal thickened and $>$ thickness of media
Arteriolar hyalinosis	
0	absent
1	1 - 25% of arterioles present
2	26% - 50% of arterioles present
3	$> 50\%$ of arterioles present

2 **Notes. a. The glomerular mesangial area is the area between the glomerular**

3 **capillary loops and is composed of mesangial cells and mesangial matrix.**

4 **The mesangial hypercellularity score is calculated according to the mesangial cell**

5 **count in per mesangial area: the scores of < 4, 4-5, 6-7, ≥ 8 mesangial cells are 0,**

6 **1, 2, 3, respectively. The mean score of all glomerulus is the mesangial**

7 **hypercellularity score.**

The demographic and clinical data of patients.

Parameters	Results
Age(years; mean ± SD)	33.8 ± 10.7
Gender (male/female)	82/126
mean arterial pressure (mm Hg; mean ± SD)	94.0 ± 11.7
Treated with antihypertensive drugs, n (%)	22 (10.58%)
Taking ACEI and/or ARB, n (%)	30 (14.42%)
Underwent tonsillectomy, n (%)	10 (4.81%)
Hematuria, n (%)	207 (99.52%)
Albumin (g/l; mean ± SD)	39.48 ± 5.77
Uric acid (µmol/l; mean ± SD)	348.00 ± 109.10
Serum creatinine(µmol/l; mean ± SD)	89.89 ± 41.49
eGFR (ml/min per 1.73 m2; mean ± SD)	82.23 ± 30.22
24-h urine protein (g/d; mean ± SD)	1.35 ± 1.58

2 **Notes. eGFR was calculated with the CKD-EPI equation. Data are expressed as mean ± SD**

3 **or number (%).**

The comparison of clinical characteristics between normo-uricemia group and hyperuricemia group.

Parameters	Normo-uricemia	Hyperuricemia	P
Patients(n)	138	70	-
Gender (male/female)	46/92	36/34	**0.012**
Age (years)	33.7 ± 10.5	34.2 ± 11.2	0.7311
Body weight (kg)	59.7 ± 9.3	64.8 ± 12.9	**0.0057**
MAP (mm Hg)	91.8 ± 10.7	98.2 ± 12.5	**0.0002**
White blood cells (*10^9/l)	7.04 ± 1.85	7.55 ± 2.44	0.1248
Hemoglobin (g/l)	129.60 ± 16.75	130.30 ± 23.52	0.8214
Platelet (*10^9/l)	237.50 ± 62.07	239.10 ± 70.38	0.8704
APTT(s)	37.43 ± 3.66	37.57 ± 3.23	0.7833
FDP (mg/l)	3.23 ± 0.74	3.86 ± 1.38	**0.0006**
Total protein(g/l)	68.84 ± 7.08	67.80 ± 8.40	0.3497
Albumin(g/l)	40.03 ± 4.94	38.40 ± 7.05	0.0868
Total cholesterol(mmol/l)	4.53 ± 1.17	5.01 ± 1.55	**0.0260**
Triglyceride(mmol/l)	1.63 ± 1.02	2.54 ± 1.89	**0.0005**
HDL-cholesterol (mmol/l)	1.34 ± 0.49	1.14 ± 0.35	**0.0056**
LDL-cholesterol (mmol/l)	2.73 ± 0.95	3.03 ± 1.41	0.1606
Uric acid (µmol/l)	290.00 ± 66.27	462.40 ± 83.46	**< 0.0001**
Blood urea nitrogen (mmol/l)	5.12 ± 1.52	6.49 ± 1.95	**< 0.0001**
Serum creatinine (µmol/l)	80.40 ± 40.58	109.00 ± 36.54	**< 0.0001**
eGFR (ml/min per 1.73mm2)	98.98 ± 25.12	74.50 ± 29.52	**< 0.0001**
24-hour urine protein (g/d)	1.05 ± 1.27	1.81 ± 1.67	**0.0015**
IgA(g/l)	3.22 ± 1.15	3.11 ± 1.00	0.5328
IgG(g/l)	2.91 ± 0.26	2.95 ± 0.38	0.1506
IgM(g/l)	1.56 ± 1.19	1.42 ± 0.67	0.3222
C3(g/l)	0.90 ± 0.22	1.00 ± 0.24	**0.0055**
C4(g/l)	0.20 ± 0.07	0.25 ± 0.12	**0.0030**

2 **Notes. MAP, mean arterial pressure; APTT, activated partial thromboplastin time; FDP,**

3 **fibrin degradation products. eGFR was calculated with the CKD-EPI equation. Bold P-**

4 **values indicate a statistical significance of P< 0.05.**

Figure 1

Figure 1. The comparisons of Oxford classification and arterial lesions between normo-uricemia and hyperuricemia patients in IgA nephropathy.

(A) mesangial hypercellularity scores; (B) endocapillary hypercellularity scores; (C) segmental sclerosis scores; (D) tubular atrophy / interstitial fibrosis scores; (E) crescent scores; (F) MEST-C total scores; (G) arteriosclerosis score; (H) hyalinosis score; (I) the percent of glomerular sclerosis.
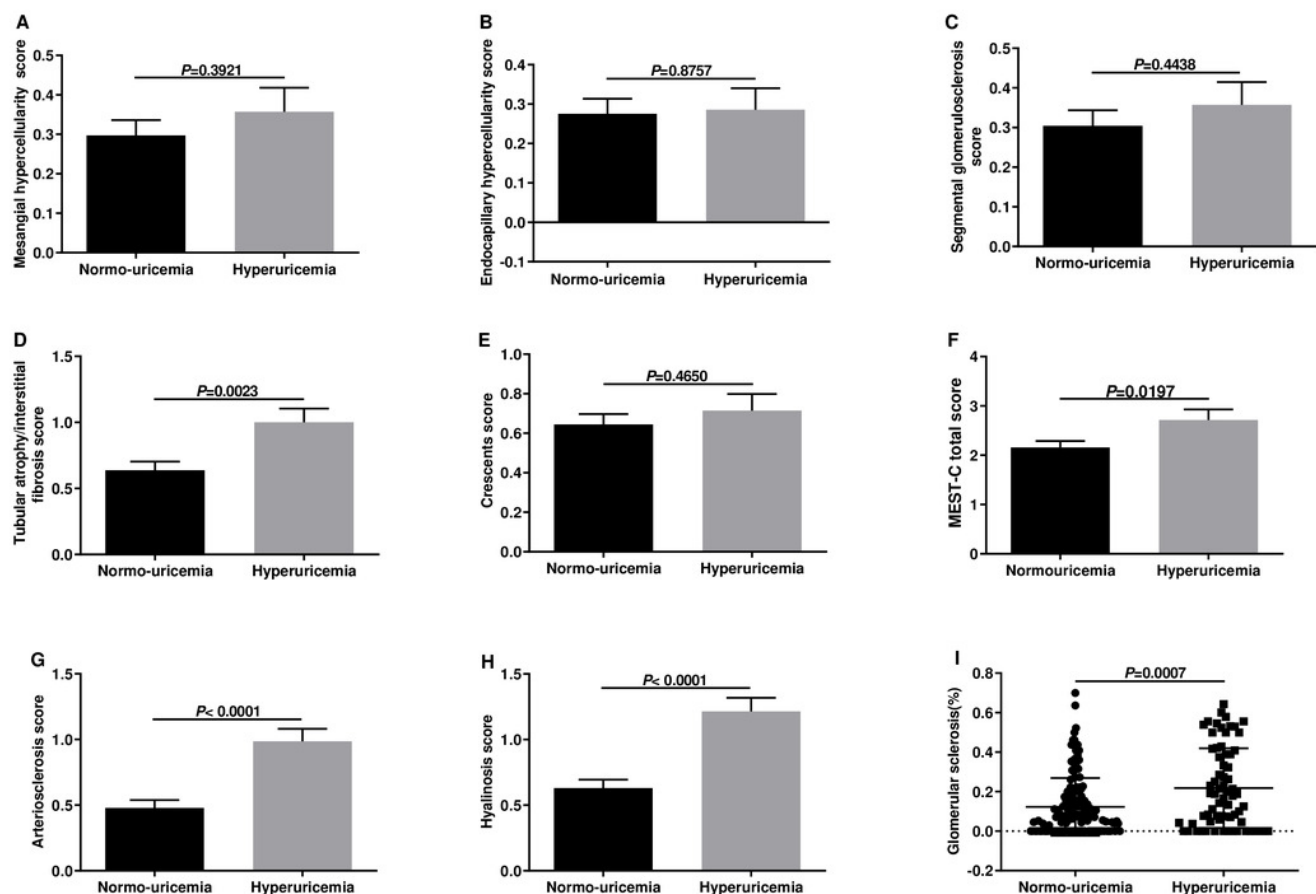
Figure 2

Figure 2. Percentages of different types of crescents among the IgAN patients with normo-uricemia or hyperuricemia.

The proportion of total crescents (A), large crescents (B), small crescents (C), cellular crescents (D), fibrocellular crescents (E), and fibrous crescents (F).
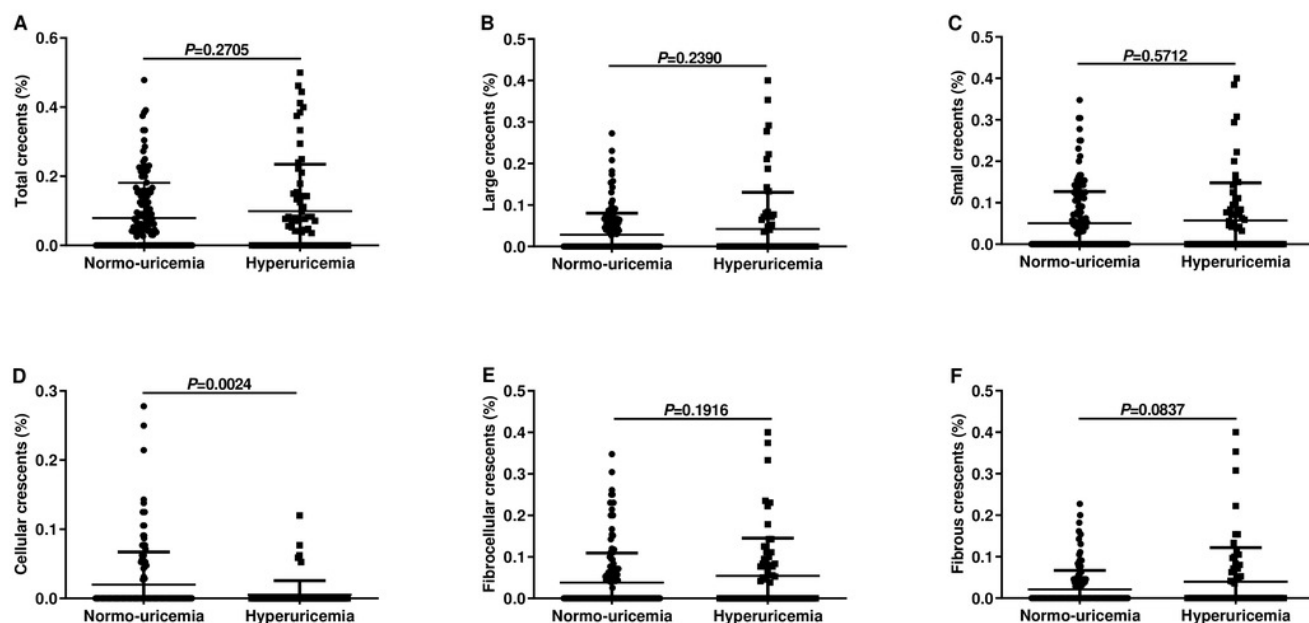
Figure 3

Figure 3. The fluorescence intensity scores of immune complex deposits in renal biopsy.

Fluorescence intensity scores of IgA deposition (A), IgG deposition (B), IgM deposition(C), C3 deposition (D), and FR A deposition(E).
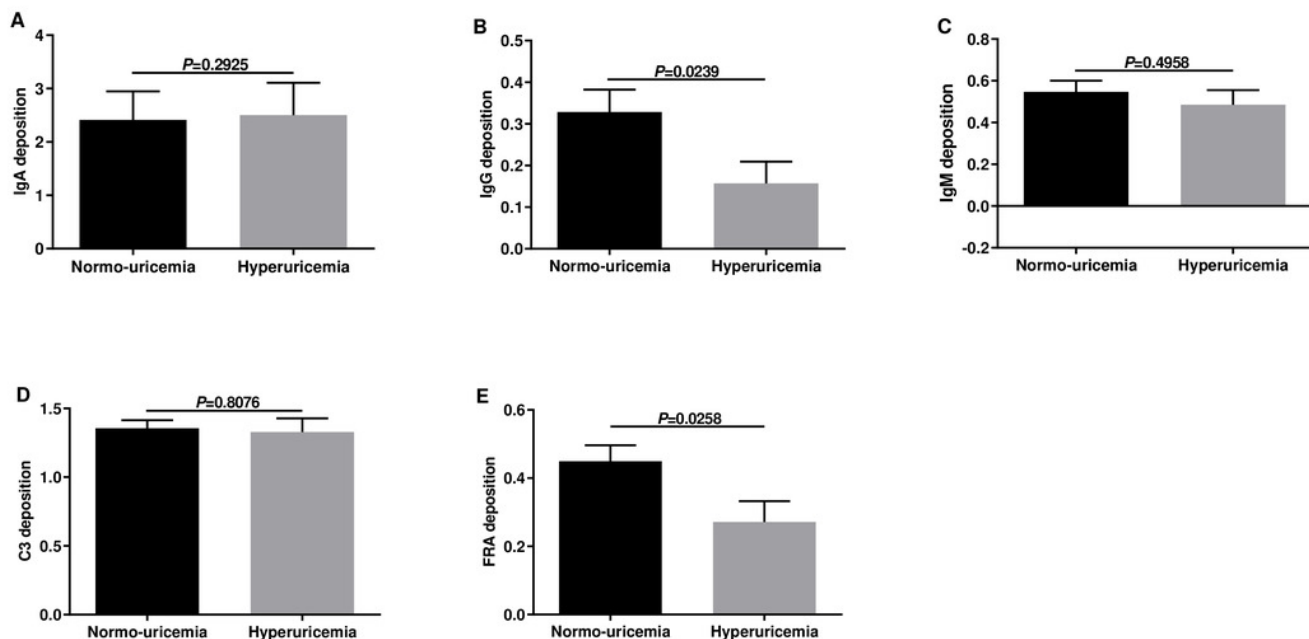
Figure 4

Figure 4. The value of the serum uric acid level in predicting renal prognosis.

The overall renal survival rate of IgAN(A). ROC curve analysis evaluates the predictive value

of uric acid level for the poor renal outcomes in females (B)and in males(C) with IgAN.