

## **A study on the risk factors for acute kidney injury in acute gouty arthritis.**

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### **Abstract**

**Purpose:** To study clinical characteristics of Acute Kidney Injury (AKI) in gouty arthritis.

**Methods:** A total of 199 individuals, who were diagnosed gouty arthritis cases at Tongde Hospital of Zhejiang Province. They were divided into two groups according to dynamics and serum creatinine changes. Their clinical manifestations, demographic data, complications, drugs usage and laboratory data were studied.

**Results:** Incidence of AKI was 11.1%. Compared with the non-AKI group, the AKI group had significantly higher basic serum creatinine levels  $155.29 \pm 44.39$  vs.  $107.25 \pm 91.98$ ,  $p < 0.001$  and higher level of urine N-acetyl-beta-D-glucosamidase (NAG)  $27.44 \pm 18.77$  vs.  $14.87 \pm 10.42$ ,  $p < 0.001$ . There were significantly higher proportion of patients with Chronic Kidney Disease (CKD) in the AKI group (50% vs. 12.99%,  $p < 0.001$ ), higher proportion of patients with Ischemic Cardio-Cerebrovascular Disease (ICVD) (40.91% vs. 14.12%,  $p = 0.002$ ) and higher proportion of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) users (72.73% vs. 48.59%,  $p = 0.033$ ). High urine NAG level (OR: 1.113,  $p < 0.001$ ) can independently reflect the occurrence of AKI. Logistic regression analysis showed that use of NSAIDs (OR: 6.054,  $p = 0.031$ ) and lower urine pH(acidity) (OR: 0.283,  $P = 0.049$ ) were high risk factors for AKI in gouty arthritis.

**Conclusion:** Low urine pH and the use of NSAIDs are major risk factors for AKI in gouty arthritis. These findings underscore the need to cause clinical attention and early prevention.

**Keywords:** Gouty arthritis, Hyperuricemia, Acute kidney injury (AKI), Non-steroidal anti-inflammatory drugs (NSAIDs).

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### **Introduction**

Gouty Arthritis (GA) is a kind of crystal-induced arthritis, which is due to increased uric acid production and decreased uric acid excretion caused by disorders in purine metabolism. The biochemical basis of GA is hyperuricosuria and the clinical manifestations are acute and chronic arthritis caused by deposition of sodium urate crystals [1]. Incidence of hyperuricosuria and gout are on the increase, due to rising incidence of hypertension, obesity, CKD, metabolic syndrome and type II diabetes, as well as dietary changes, and the use of thiazide and loop diuretics [2]. Gout affects not only the joints but also the viscera, especially the kidneys. Multiple acute and chronic renal diseases may occur, which in severe cases may lead to renal failure. Hyperuricosuria can lead to urate-induced kidney stones, as well as acute and chronic urate nephropathy. Indeed the population of patients with acute kidney injury may be higher than the number actually seen in clinics. Clinical study data on the relationship between AKI and gouty arthritis are limited. AKI is kidney injury of short-term, which manifests mainly in impairment of kidney structure and function. If diagnosis and treatment are not carried out in time,

AKI may cause irreversible kidney injury that may necessitate kidney replacement therapy. This imposes a serious financial and emotional burden on the patient.

This study was designed as a retrospective investigation on the incidence of AKI in GA and the associated risk factors, through analyses of general clinical and experimental data of 199 patients with acute GA.

### **Methods**

#### ***Clinical data***

A total of 199 patients diagnosed with primary GA at Tongde Hospital of Zhejiang Province from September 2009 to August 2014, were enrolled in this retrospective study. Diagnosis of gout met the ACR classification standard for acute gout arthritis in 1977 [3]. The following conditions were excluded: secondary gout, usage of contra-indicated agents, acute infection, and pathological conditions of dehydration and obstruction of urinary system. General data and experimental data were collected from the patients, who were divided into AKI and non-AKI groups according to dynamic conditions and

changes in serum creatinine profiles. Records of demographic data, complications, medication and relevant experimental data of patients in the two groups were obtained.

### Relevant definitions

According to Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline, AKI was defined as increase in level of serum creatinine to 0.3 mg/dL (26.5  $\mu$ mol/L) within 48 h, or 1.5-fold increase in serum creatinine over baseline value within 7 d, or urine volume less than 0.5 ml/kg/h for 6 continuous h. Patients with the elevated blood creatinine value (before admission to hospital and within 7 d of visit) which met these standards were deemed to have AKI. Demographic data referred to age and sex. Complications included hypertension, diabetes, chronic kidney diseases, ICCVD and urolithiasis. Medication included whether or not the patient used NSAIDs, colchicine or allopurinol at hospital visit time or before visit. Experimental data referred to serum creatinine, uric acid, plasma albumin, hemoglobin (HGB), blood glucose, blood cholesterol, blood triglycerides, ESR, CRP index, urine pH, microalbuminuria, urine microglobulin and urine NAG at the time of hospital admission. Patients with history of hypertension and who were taking antihypertensive drugs were classified as hypertensive, while those who had a history of diabetes and who were using insulin and taking anti-diabetic drugs were taken as diabetic. The definition of CKD was chronic disorder in kidney structure and function (due to various factors), and decline in Glomerular Filtration Rate (GFR) (<60 ml/min.1.73 m<sup>2</sup>) for more than 3 months without any obvious cause. ICCVD included coronary heart disease and ischemic encephalopathy. The former referred to clear angina and history of Myocardial Infarction (MI) onset and stent implantation after surgery, while the latter referred to Transient Ischemic Attacks (TIA) and cerebral infarction patients. Kidney stone referred to stone in kidney, ureter and urinary bladder as tested by iconography.

### Statistical treatment

IBM SPSS Statistics 17.0 software package was used for statistical analysis. Demographic characteristics and various experimental data were given descriptive statistics. Measurement data of normal distribution were represented by  $\bar{x} \pm s$ . Comparison between groups was done using t-test.

Measurement data of abnormal distribution were represented by  $\bar{M} \pm Q$ . Comparison between groups was done with Mann-Whitney U-test, while enumeration data comparison between groups was performed with Chi-square test. Correlation was analyzed by using Spearman correlation analysis. Risk factor analysis was done with single factor analysis to identify correlation risk factors. Variables with statistical differences were brought into Logistic multiple regression analysis. P values < 0.05 were taken as indicative of statistical differences.

## Results

### General conditions of the admitted patients

The 199 patients were composed of 191 males (96%) and 8 females (4%). The ratio of male to female was 24:1. The mean age was  $57.84 \pm 16.93$  y, while the mean duration was  $8.78 \pm 9.74$  y. Basic complications consisted of 118 cases of hypertension (69.97%), 36 cases of diabetes (18.09%), 34 cases of chronic kidney diseases (17.09%), 34 cases of ICCVD (17.09%), and 53 cases of urinary stones (26.6%). Prior to hospital admission, 102 patients (51.26%) used NSAIDs while 46 patients (23.1%) used colchicine. There were 17 cases (8.5%) of diarrhoea. Allopurinol was used by 79 patients (39.7%) at the time of visit.

### Analysis of general conditions of patients in the two groups

There were 22 (11.1%) cases of AKI in the study population. Table 1 shows the general conditions of the patients. The results of statistical analysis revealed that, relative to the group without AKI, serum creatinine level in AKI group was significantly higher ( $p < 0.001$ ). Hemoglobin level was significantly lower ( $p = 0.001$ ) and 24 h urate excretion was significantly lower ( $p = 0.035$ ). In addition, urine level of NAG was significantly higher in the AKI group ( $p < 0.001$ ). The AKI group had a significantly higher incidence of chronic kidney diseases than patients in the non-AKI group ( $p < 0.001$ ). Cases of ICCVD and number of patients using NSAIDs were higher in the AKI group ( $p = 0.002$  and  $p = 0.033$ , respectively). There were no significant differences between the two groups with respect to number of patients with hypertension, diabetes and urinary stones.

**Table 1.** Comparison of general conditions of patients in the two groups (n=199).

Variables	AKI group (n=22)	No AKI group (n=177)	P value
Sex (n, %)	18 (81.82)	173 (97.74)	<0.001
Age (y, $\bar{x} \pm S$ )	62.48 $\pm$ 20.03	57.81 $\pm$ 16.30	0.23
Positive family history of gout (n, %)	2 (9.1)	14 (7.91)	0.84
With hypertension (n, %)	17 (77.27)	101 (57.06)	0.069
With diabetes (n, %)	4 (18.18)	32 (18.08)	0.991

With ICCVD (n, %)	9 (40.91)	25 (14.12)	0.002
With chronic kidney diseases (n, %)	11 (50)	23 (12.99)	<0.001
Use of colchicine (n, %)	5 (22.73)	41 (23.16)	0.963
With diarrhoea (n, %)	1 (4.55)	16 (9.04)	0.477
Use NSAIDs (n, %)	16 (72.73)	86 (48.59)	0.033
Allopurinol (n, %)	11 (50)	68 (38.42)	0.295
Urinary stones (n, %)	4 (18.18)	51 (28.81)	0.293
Serum creatinine level (umol/L, $\bar{x} \pm s$ )	155.29 $\pm$ 44.39	107.25 $\pm$ 91.98	<0.001
Serum uric acid level (umol/L, $\bar{x} \pm s$ )	528.24 $\pm$ 152.32	478.42 $\pm$ 126.54	0.098
Plasma albumin (g/L, $\bar{x} \pm s$ )	40.39 $\pm$ 3.95	43.54 $\pm$ 30.61	0.64
Hemoglobin (g/L, $\bar{x} \pm s$ )	124.9 $\pm$ 15.94	133.85 $\pm$ 19.28	0.043
ESR (mm/h, $\bar{x} \pm s$ )	24.60 $\pm$ 18.43	19.98 $\pm$ 15.70	0.22
CRP (mg/L, $\bar{x} \pm s$ )	60.56 $\pm$ 16.93	46.12 $\pm$ 52.03	0.25
Urine PH value ( $\bar{x} \pm s$ )	5.55 $\pm$ 0.71	5.81 $\pm$ 0.64	0.085
Uric acid excretion (umol/24 h, $\bar{x} \pm s$ )	2108.57 $\pm$ 1280.56	2859.14 $\pm$ 1542.14	0.035
Urine protein quantitation (mg/24 h, $\bar{x} \pm s$ )	314.37 $\pm$ 372.80	249.91 $\pm$ 457.75	0.48
Urine microalbumin (mg/L, $\bar{x} \pm s$ )	32.40 $\pm$ 37.26	29.28 $\pm$ 64.82	0.83
Urine $\alpha$ 1 microglobulin (mg/L, $\bar{x} \pm s$ )	21.68 $\pm$ 24.14	18.82 $\pm$ 33.28	0.66
Urine NAG enzyme (mg/L, $\bar{x} \pm s$ )	27.44 $\pm$ 18.77	14.87 $\pm$ 10.42	<0.001

### Correlation analysis

Results of correlation analysis are shown on Table 2. Serum creatinine level ( $r=0.426$ ,  $p<0.001$ ), urine microalbumin ( $r=0.189$ ,  $p=0.011$ ), urine  $\alpha$ -1 microglobulin ( $r=0.150$ ,  $p=0.034$ ) and urine NAG level ( $r=0.325$ ,  $p<0.001$ ) were

positively correlated with AKI. However, hemoglobin ( $r=0.176$ ,  $p=0.013$ ), urine pH ( $r=0.182$ ,  $p=0.01$ ) and uric acid excretion ( $r=-0.244$ ,  $p=0.001$ ) had negative correlation with AKI.

**Table 2.** Correlation analysis of various variables and AKI.

Basic conditions	Correlation index r	P value
Serum creatinine level at the time of admitted into hospital	0.426	<0.001
Hemoglobin level	-0.176	0.013
Urine pH value	-0.182	0.01
Uric acid excretion level	-0.244	0.001
Urine microalbumin	0.18	0.011
Urine $\alpha$ 1 microglobulin	0.15	0.034
Urine NAG level	0.325	<0.001
With ICCVD	0.223	0.002
With CKD	0.308	<0.001
Use NSAIDs	0.151	0.033

### Analysis of risk factors

Multiple regression analysis was used to find the risk factors for AKI. The results (Table 3) showed that usage of NSAIDs (OR: 6.054,  $p < 0.05$ ) and low urine pH (OR: 0.283,  $p < 0.05$ )

**Table 3.** Analysis of multiple factors for AKI of gouty arthritis.

Variables	OR value	95% CI	P value
Serum creatinine level at the time of admitted into hospital	1.008	1.000-1.005	0.051
Hemoglobin level	1.014	0.961-1.070	0.617
Urine pH	0.283	0.080-0.996	0.049
Uric acid excretion level	0.99	0.999-1.000	0.038
Urine microalbumin	0.998	0.992-1.005	0.601
Urine $\alpha 1$ microglobulin	1.013	0.982-1.045	0.413
Urine NAG level	1.113	1.048-1.181	<0.001
ICCVd	1.208	0.254-5.739	0.812
CKD patients	4.854	0.887-26.56	0.068
NSAIDs usage	6.054	1.18-30.97	0.031

### Prognosis

The patients with AKI (22) were treated by fluid infusion, supportive care, alkalinization of urine and stoppage of NSAID usage. As a result, the serum creatinine of 20 patients returned to basal levels within 7 to 10 d. However the serum creatinine of 2 patients was still higher than basal level after three months of follow-up.

### Discussion

The results obtained in this study showed that the incidence AKI in gouty arthritis was 11.1%. This is higher than AKI incidence reported in previous studies (4.6-9.1%) [4,5]. It may be related the characteristics of the patients studied i.e. old age, high level of complications, high usage of NSAIDs and the new ARF standard for definition of AKI (serum creatinine level of 44-88  $\mu\text{mol/L}$ ).

The results also showed that patients with chronic kidney diseases, ICCVD and patients who used NSAIDs usage were more predisposed to having AKI. Urine pH and decreased urate excretion level may have correlations with AKI. Gout patients with chronic kidney diseases may have kidney injury and decreased kidney function. These patients are more sensitive to drugs such as NSAIDs which can induce kidney injury (renal ischemia). Studies on 328 AKI patients on NSAIDs showed that estimated Glomerular Filtration Rate (eGFR) and kidney hypoperfusion are the main risk factors of AKI [4]. Patients with ICCVD have atherosclerosis, including atherosclerosis of the kidney artery, which can aggravate kidney ischemia, decrease Renal Blood Flow (RBF) regulation function under ischemic state, and easily induce kidney injury. Coronary atherosclerotic heart disease and atherosclerosis of kidney artery usually co-exist. Compared with patients without

may be risk factors for AKI in patients with gouty arthritis. High urine NAG level (OR: 1.113,  $p < 0.001$ ) may induce AKI independently and independently reflect the occurrence of AKI.

kidney atherosclerosis, Patients with kidney atherosclerosis after heart surgical operation are more susceptible to AKI [6]. In the ischemic state, kidney atherosclerosis, sclerosis and stenosis of peripheral vessels are risk factors for AKI. If sclerosis and stenosis of peripheral vessels, carotid artery and multi-vessel coronary artery are detected, there is need to screen for kidney atherosclerosis. In this study, cases of AKI in patients with decreased basic kidney function and ICCVD were high.

In clinics, it is common knowledge that NSAIDs induce AKI. Gout patients with acute arthritis onset have a high rate of usage of NSAIDs. This should attract special clinical attention because NSAIDs can cause kidney injury directly by inducing AIN. The major pathological changes are interstitial inflammatory cell infiltration, kidney tubule metatropy, kidney tubule inflammation, interstitial edema, and different degrees of renal tubular necrosis. NSAIDs can cause indirect renal toxicity by inhibiting Prostaglandin (PG) biosynthesis through disruption of arachidonic acid metabolism and inhibition of cyclooxygenase. In the kidney, PG maintains stable intra-renal environment, water and electrolyte balance, and controls renin release. In kidney ischemia, oxygen free radical production and increased lipid peroxidation have adverse effect on renal cell membranes, leading to reduction in glomerular filtration and increased serum creatinine and urea nitrogen [7]. The risk factors include age more than 60 y, atherosclerotic heart disease, diuretics, renal insufficiency, hypotension, liver cirrhosis, and congestive heart failure. Fortunately, most AKI induced by NSAIDs are reversible after one week of stopping NSAIDs usage. Thus the prognosis is good [8].

Low urine pH promotes uric acid salt deposit in renal tubule and forms uric acid urinary lithangiuria. Low urine pH and

urate in kidney tubules promote uratic lithangiuria. The present study showed that low urine pH (due to high level of uric acid) is a risk factor for AKI in GA. Compensatory increase kidneys excrete uric acid, and some patients are oral drugs that promote uric acid excretion, which cause renal tubular interstitial local uric acid concentration significantly increased. Acidic environment prompted a lot of urine uric acid crystals form, which may play a significant role in the occurrence of AKI. However, there is little research on the PH value of urine and renal function injury, so the relationship between the two has to be further clarified.

Uric Acid (UA) concentration of patients with gout is usually elevated. Several studies reported that increased serum UA level is an independent risk factor for chronic kidney diseases [9-12]. However, different views have been expressed on whether or not high UA is a risk factor for AKI. Analysis of serum UA level and post-operative AKI of 1056 patients with heart diseases before surgery showed that hyperuricemia may be an independent risk factor for AKI [13]. Results from animal studies show that serum UA may have relationship with contraction of renal vessels, endothelial dysfunction, inflammatory reaction and oxidative stress associated with onset of AKI [14]. Hyperuricemia is activated by oxidative stress, renin and angiotensin, which cause contraction of renal vessels and endothelial dysfunction [15]. It may have potential negative effects for blood hemodynamic stable. UA can influence kidney self-regulation and induce AKI by inhibiting proliferation of endothelial cells and inducing pro-inflammatory reaction. However, in the present study, there was no statistically significant difference between blood UA levels in AKI group and the non-AKI group. In onset of acute gouty arthritis, there is compensatory increase in UA excretion, which can transiently reduce blood UA levels [16,17]. In addition, hemoglobin level had negative correlation with AKI. This is in agreement with the findings of Walsh [18]. It has been reported that low hemoglobin decreases oxygen-carrying capacity, causes anoxia and ischemia of kidney medulla, aggravates the harmful effects of contra-indicated agents, thereby inducing AKI [19]. In this study, hemoglobin level was correlated with AKI, but regression analysis did not show that low hemoglobin level is an independent risk factor for AKI. It means that combination of NSAIDs usage, usage of contra-indicated agents; decreased renal compensatory ability and anaemia constitute the risk factors for AKI.

Several studies have shown that microalbuminuria, urinary  $\alpha$ -1 microglobulin and urine NAG are sensitive indices for detecting early kidney injury. In this study, urine microalbumin, urine  $\alpha$ -1 microglobulin and urine NAG level were positively correlated with AKI. Patients in AKI group had severe kidney injury, except renal tubule injury, and there were varying degrees of glomerular injury. There was abnormally increased urinary NAG level in the AKI group, which increase preceded onset of AKI. Thus urinary NAG can predict onset risk of AKI in these patients.

## **Conclusion**

Patients with gouty arthritis are easily susceptible to AKI. If diagnosed timely, the prognosis is better after symptomatic treatment. NSAIDs usage and low urine pH are high risk factors for AKI in gouty arthritis. Renal function, ICCVD and low hemoglobin level have close correlations with AKI. It is suggested that clinicians assess patients for initial renal conditions and renal conditions at onset of AKI, as well as urine pH in the course of the disease. This will help in identifying populations with high-risk for AKI. Blind use of NSAIDs should be avoided and anaemia should be promptly treated. Allopurinol therapy and alkalinization of urine are essential.

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## **Conflict of Interest**

No conflict of interest is associated with this work.

## **Contribution of Authors**

Xianzheng Zhang and Huaxiang Wu designed the project and drafted the manuscript.

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