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Etiological Analysis of 256 Hypouricemia Cases

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Abstract: *Objective:* To analyze the serum uric acid results of patients with hypouricemia hospitalized in the Affiliated Hospital of Hebei University, thereby providing new insights for the prevention and treatment of hypouricemia. *Method:* This study employed a retrospective case analysis, dividing patients into two groups: 16 cases with uric acid levels less than 50 μmol/L (group Level 1), and 240 cases with uric acid levels between 50 μmol/L and 119 μmol/L (group Level 2). Basic data such as age, gender, department, and clinical diagnosis were collected for each patient. Renal indices, including creatinine, urea, β2-microglobulin, and cystatin C, were analyzed and compared. *Results:* The highest percentage of patients with uremia was found in Level 1, with a rate of 31.25%. In Level 2, the highest percentage of patients had malignant tumors, with a rate of 15.41%. Tumor sites included the liver, lungs, endometrium, ovaries, breasts, stomach, pancreas, colon, hypopharynx, and others. The second highest percentage was 13.75% for patients with lung diseases, followed by 10% for patients with cranio-cerebral diseases. Other prevalent conditions included renal diseases, hematological diseases, multiple injuries, orthopedic diseases, rheumatological-immunological diseases, and cardiac diseases. There were significant differences between the two uric acid level groups in terms of prevalent diseases ($P < 0.05$). Additionally, gender differences were significant between the two groups ($P < 0.05$). However, for renal disease indicators, no significant differences were found between the two levels ($P > 0.05$). *Conclusion:* The types of diseases presented by patients were related to different low uric acid levels. Most patients' renal function indices were within normal reference ranges at different low uric acid levels. The prevalence of different low uric acid levels was related to gender.

Keywords: Uric acid; Hypouricemia; Disease composition ratio

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1. Introduction

Serum uric acid (SUA) is a type of organic matter and a weak acid composed of four elements: carbon, hydrogen, oxygen, and nitrogen. It belongs to the class of heterocyclic carbon-based compounds. When transported through the bloodstream in the form of ions, it maintains a pH value of 7.40. SUA has been identified as one of the most abundant water-soluble antioxidants in the body, aiding in the clearance of free radicals and the reduction of inflammation. However, the poor solubility of uric acid can easily lead to crystal formation, causing urinary calculi (stones in the urinary tract). The specific metabolic process of uric acid

consists of four aspects: the catabolism of exogenous purines, the release of endogenous purines from cellular catabolism and death, the breakdown of purine nucleotides, and the excretion of uric acid. Changes in uric acid levels can adequately reflect the metabolic level of the body [1].

The level of uric acid in the body remains constant and is regulated by the rate of uric acid formation, renal excretory function, and intestinal tract secretion. Uric acid (UA) is the final substance produced by cells through the enzymatic hydrolysis of purine nucleotides, deamination, and other metabolic processes [2]. Accumulation of high uric acid levels in the kidneys and joints can lead to stone formation and the development of various cardiovascular diseases. Atherosclerosis research has demonstrated a positive correlation between increased serum uric acid levels and the incidence of chronic kidney disease (CKD). Gout, caused by high uric acid levels, has been extensively researched by scholars and clinicians worldwide [3]. In contrast, hypouricemia is less understood in clinical practice. As a rare genotype of serum uric acid abnormality, hypouricemia has not received significant attention from scholars at home and abroad. However, recent findings indicate an increasing number of diseases associated with hypouricemia, often occurring in patients with renal dysfunction.

Hypouricemia is diagnosed when the body's serum uric acid falls below 119 μmol/L [4,5]. The prevalence of this disease is increasing in the population and accounts for less than 2% [5]. Low uric acid levels have been reported in patients with hereditary renal diseases, cardiovascular diseases, and hypertensive cerebral hemorrhage. A more typical form of renal hypouricemia is low uric acid due to a genetic mutation that impairs the tubular reabsorption of uric acid and increases uric acid excretion [6]. It is also reported in patients with acute renal failure. Uric acid excretion fraction in patients with acute renal failure has been reported to reach 46.6%, exceeding the reference limit.

This paper aims to investigate the levels of low uric acid in patients of different ages and genders, along with assessing the status of renal function indexes in patients with hypouricemia. Additionally, it aims to analyze the etiology of hypouricemia, providing accurate and reliable results for clinical use. This will enable clinicians to swiftly diagnose and devise treatment plans for patients, thus alleviating the burden on families and mitigating the suffering caused by the disease. Ultimately, the goal is to achieve early detection, diagnosis, and treatment of hypouricemia.

2. Materials and methods

2.1. Study population

This study employed a retrospective case collection for analysis, focusing on inpatients with hypouricemia treated at the Affiliated Hospital of Hebei University. Following the 2019 Japanese Clinical Practice Guidelines for Renal Hypouricemia (first edition), hypouricemia is defined as a condition where the uric acid level in the blood falls below the lower limit of the reference value. According to the Clinical Practice Guidelines for Renal Hypouricemia, a serum uric acid level lower than 119 μmol/L or 2 mg/dL is indicative of hypouricemia. The study data did not specify age or gender requirements, and individuals meeting the diagnostic criteria, along with their corresponding test results, were eligible for inclusion in the study.

2.2. Inclusion and exclusion criteria

(1) Inclusion criteria: Participants must adhere to the 2019 Japanese Clinical Practice Guidelines for Renal Hypouricemia (first edition), with serum uric acid levels below 119 μmol/L or 2 mg/dL.

(2) Exclusion criteria: (a) Infants and young children in specific physiological stages of growth and development, as well as pregnant women experiencing early temporary pregnancy reactions; (b) Individuals adhering to a long-term vegetarian diet; (c) Temporary low uric acid levels resulting from

consuming large quantities of cherries, grapes, watermelon, etc., during the summer season; (d) Female patients currently menstruating; (e) Patients with slow metabolic function.

2.3. Research methodology

The primary disease type, age, gender composition, and renal function indicators of patients with hypouricemia were retrieved through the information system of the Department of Laboratory Medicine at the Affiliated Hospital of Hebei University. These indicators mainly included urea, creatinine (Cr), cystatin C (Cyc), and β2-microglobulin (BMG) levels.

Basic clinical data included age, gender, medical history, department of consultation, clinician's diagnosis, presence of hereditary diseases, and medication history. Laboratory biochemical qualification indexes were obtained from 5 mL of venous blood drawn from patients in the early morning after fasting for 8 to 12 hours or more than 12 hours (meaning they did not eat anything after midnight to avoid influencing test results due to food, hormones, drugs, etc.). These samples were sent to the Hospital's Laboratory Department for examination. Renal function was tested using the uric acid-peroxidase coupled method of the double reagent two-point method on a fully automated biochemical analyzer. Levels of indicators (urea, creatinine, cystatin C, β2-microglobulin, and uric acid) were measured by a fully automated biochemical analyzer using a dual reagent two-site method with a uricase-peroxidase coupling method. Additionally, results of hematological analysis, biochemical analysis, and routine urinalysis were examined, with special attention given to urokinase protein (PRO) results in urine dry chemistry assays to exclude erroneous results caused by interfering factors.

2.4. Statistical analysis

All data in this study were processed using the statistical analysis software SPSS 20.0. The serum uric acid concentration of the experimental group was subjected to a *t*-test. Specifically, the type of Independent-Samples *t*-test applied in this case aimed to represent the two-sample equal variance hypothesis, determining whether the samples are likely to come from the whole population with the same mean. The results were presented by providing the mean ± standard deviation (SD). The number of sample cases in the count data was expressed as a percentage (%) to compare whether there was a difference between the two experimental groups. A *P*-value less than 0.05 indicated a significant difference between the data of the experimental groups, signifying statistical significance. Conversely, if the *P*-value was greater than 0.05, it indicated no significant difference in the data between the groups, rendering it statistically insignificant.

3. Results

3.1. Disease types and composition ratios of patients with hypouricemia

Although the number of diseases in patients with uric acid values < 50 μmol/L (group Level 1) was low, the various diseases were not scattered but concentrated. Uremia was the most prevalent disease with a prevalence of 31.25%, followed by lung disease with a slightly higher prevalence of 18.75%, and other diseases such as subarachnoid hemorrhage (SAH), rheumatic diseases, and pancytopenia, as shown in **Table 1**.

Table 1. Disease types and composition ratios of Level 1 patients

Disease type	Number of examples	Component ratio (%)
Lung disease	3	18.75
Uremia (medicine)	5	31.28
Non-uremic kidney disease	2	12.50
Trauma and orthopaedic diseases	2	12.50
Other diseases	4	25.00

The types of diseases presented in patients with uric acid values between > 50 μmol/L and < 119 μmol/L (group Level 2) are complex and varied. Among them, malignant neoplasms are the most frequent, accounting for 15.41% of all cases. These include liver malignancies, lung malignancies, gynecological malignant neoplasms, mammary gland malignant neoplasms, and others. Following closely are lung diseases, constituting 13.75% of the cases, which can be compared with malignant tumors. Additionally, other diseases encompass various inflammatory conditions such as acute pharyngitis, fever, and abdominal pain, among others. Specific disease types and their composition are outlined in **Table 2**.

Table 2. Disease types and composition ratios of Level 2 patients

Disease type	Number of examples	Component ratio (%)
Lung cancer	10	4.16
Other lung diseases	33	13.75
Diseases of the liver	7	2.91
Diseases of the gallbladder	7	2.91
Trauma and orthopaedic diseases	15	6.25
Heart disease	2	0.83
Leukemia	12	5.00
Other blood diseases	5	2.08
Cranial diseases	24	10.00
Non-uremic kidney disease	12	5.00
Uremia (medicine)	5	2.08
Diabetes	8	3.33
Hypertensive	2	0.83
Rheumatological and immunological diseases	14	5.83
Diseases of the digestive tract	7	2.91
Gastrointestinal diseases	9	3.75
Gynecological malignancy	11	4.58
Other malignant tumours	16	6.66
Respiratory diseases	4	1.66
Gynecological disease	6	2.50
Other diseases	31	12.91

There were both overlaps and differences in disease types between the two levels of patients with low uric acid. Patients with a uric acid value of less than 50 μmol/L presented with relatively fewer disease types, whereas there was a significant increase in the number of disease cases among those with a uric acid value of more than 50 μmol/L and less than 119 μmol/L. This included the presence of conditions such as leukemia, cranial and brain diseases, gynecological tumors, and respiratory diseases, among others. A *t*-test yielded a *P*-value of 0.006, which is less than the threshold value of 0.05, indicating a statistically significant difference in the types of diseases between these two levels of patients with low uric acid.

3.2. Distribution of renal indicator concentrations in different types of disease in patients with low uric acid

Based on the results in **Tables 3–5**, most of the concentrations of renal function indices in the two groups of patients with different uric acid levels fell within the normal reference ranges. The reference ranges in the laboratory were as follows: urea, 3.60–9.50 mmol/L; creatinine, 57–111 μmol/L; β2-microglobulin, 1.0–3.0 mg/L; cystatin C, 0.60–1.55 mg/L. It is worth noting that the levels of renal indicators in patients with hypouricemia and patients with renal diseases in both groups of results were significantly elevated beyond the normal reference intervals, indicating that patients with uremia and severe renal diseases were at the end stage of renal failure. Statistical analysis using SPSS 20.0 software was conducted through a *t*-test on the two groups of data, resulting in a *P*-value of 0.64. Since the *P*-value is greater than 0.05, it was concluded that there is no statistically significant difference between the two groups of data.

Table 3. Results of renal function indexes for different types of diseases in Level 1 patients (mean ± SD)

Disease	Urea (mmol/L)	Cr (μmol/L)	BMG (mg/L)	Cyc (mg/L)	Uric acid (μmol/L)
Lung disease	3.5 ± 3.3	47.0 ± 5.3	3.3 ± 1.8	0.9 ± 0.3	44.1 ± 2.5
Uremia (medicine)	5.0 ± 4.7	253.0 ± 163.0	41.1 ± 17.4	7.8 ± 3.1	36.5 ± 11.8
Non-uremic kidney disease	3.7 ± 2.3	139.0 ± 22.0	41.1 ± 37.6	6.5 ± 4.6	33.2 ± 11.1
Traumatic orthopedic diseases	4.3 ± 2.2	62.5 ± 2.5	2.1 ± 0.5	0.8 ± 0.2	44.0 ± 5.7
Other diseases	4.4 ± 1.0	49.5 ± 15.6	1.1 ± 0.3	0.8 ± 0.1	37.5 ± 8.1

Table 4. Results of renal function indexes for different types of diseases in Level 2 patients (mean ± SD)

Disease type	Urea (mmol/L)	Cr (μmol/L)	BMG (mg/L)	Cyc (mg/L)	Uric acid (μmol/L)
Lung cancer	3.6 ± 1.2	45.3 ± 13.4	2.1 ± 0.7	0.8 ± 0.1	101.5 ± 9.2
Other lung diseases	4.1 ± 2.0	49.1 ± 10.9	2.0 ± 0.6	0.9 ± 0.2	96.9 ± 12.7
Diseases of the liver	3.9 ± 0.2	45.4 ± 7.0	1.8 ± 0.9	0.9 ± 0.1	82.1 ± 17.0
Diseases of the gallbladder	3.9 ± 1.7	48.6 ± 14.9	2.2 ± 1.0	0.9 ± 0.4	87.1 ± 15.3
Trauma and orthopaedic diseases	3.9 ± 1.4	43.5 ± 7.9	1.9 ± 0.4	0.8 ± 0.1	88.1 ± 16.1
Heart disease	4.9 ± 2.6	40.5 ± 2.5	1.9 ± 0.3	0.9 ± 0.1	108.1 ± 6.8
Leukemia	4.0 ± 1.2	53.2 ± 13.5	2.2 ± 0.9	0.9 ± 0.2	94.2 ± 14.1
Other blood diseases	6.5 ± 3.2	67.0 ± 30.5	3.2 ± 2.4	0.9 ± 0.4	94.0 ± 16.5
Cranial diseases	3.9 ± 1.4	45.9 ± 10.1	1.7 ± 0.6	0.7 ± 0.1	82.6 ± 17.4
Non-uremic kidney disease	10.2 ± 6.4	301.9 ± 224.1	15.9 ± 16.2	3.7 ± 2.4	91.0 ± 19.7

Table 4. (Continues)

Disease type	Urea (mmol/L)	Cr (μmol/L)	BMG (mg/L)	Cyc (mg/L)	Uric acid (μmol/L)
Uremia (medicine)	8.7 ± 1.9	349.4 ± 46.9	63.1 ± 24.5	9.3 ± 0.8	95.3 ± 13.1
Diabetes	3.7 ± 0.9	49.2 ± 11.8	2.4 ± 0.5	1.1 ± 0.2	98.9 ± 11.0
Hypertensive	3.9 ± 0.8	53.5 ± 6.5	2.5 ± 0.2	0.9 ± 0.1	86.1 ± 11.3
Rheumatological and immunological diseases	4.8 ± 1.9	51.6 ± 14.5	2.0 ± 0.6	1.1 ± 0.3	89.7 ± 15.4
Diseases of the digestive tract	3.4 ± 1.6	40.4 ± 10.9	2.1 ± 0.9	0.9 ± 0.2	90.2 ± 20.4
Gastrointestinal diseases	3.9 ± 0.9	54.4 ± 9.4	2.1 ± 1.4	0.9 ± 0.5	91.1 ± 14.3
Gynecological malignancy	4.2 ± 1.2	48.6 ± 13.7	1.5 ± 0.5	0.8 ± 0.2	106.7 ± 4.5
Other malignant tumours	4.7 ± 1.8	51.9 ± 19.8	2.9 ± 1.8	0.9 ± 0.4	90.3 ± 14.9
Respiratory diseases	2.9 ± 1.0	50.0 ± 11.1	1.7 ± 0.6	0.7 ± 0.1	90.7 ± 19.8
Gynecological disease	4.1 ± 1.5	47.6 ± 14.7	1.8 ± 0.6	0.7 ± 0.1	94.0 ± 12.7
Other diseases	3.9 ± 1.5	51.0 ± 17.6	2.1 ± 1.0	0.8 ± 0.2	92.5 ± 15.8

Table 5. Comparison of index results between the two uric acid level groups at the time of renal disease

Disease type	Uric acid levels	Urea (mmol/L)	Cr (μmol/L)	BMG (mg/L)	Cyc (mg/L)
Non-uremic kidney disease	Level 1	3.7 ± 2.3	139.0 ± 22.0	41.1 ± 37.6	6.5 ± 4.6
	Level 2	10.2 ± 6.4	301.9 ± 224.1	15.9 ± 16.2	3.7 ± 2.4
Uremia (medicine)	Level 1	5.0 ± 4.7	253.0 ± 163.0	41.1 ± 17.4	7.9 ± 3.1
	Level 2	8.7 ± 1.9	349.4 ± 46.9	63.1 ± 24.5	9.3 ± 0.8

3.3. Distribution of patients with hypouricemia in terms of age and gender

The total number of patients with uric acid values below 50 μmol/L was 16, with slightly more males than females. Due to limitations in data collection, there were no patients under 20 years of age or over 90 years of age, and the highest incidence was observed between 51 and 60 years of age. Patients with a uric acid value between 50 and 119 were categorized as having a low uric acid level 2, with more females than males at this level. The prevalence across age groups varied, ranging from minors under 20 years of age to elderly patients over 90 years of age, with the highest prevalence in the age range of 61 to 70 years, as shown in **Tables 6** and **7**.

Table 6. Comparison of the two groups of patients with low uric acid levels in terms of gender

Gender	Level 1	Level 2
Male (persons)	10	110
Female (persons)	6	130

Table 7. Comparison of the two groups of patients with low uric acid levels in terms of age

Age (years)	Level 1 (%)	Level 2 (%)
< 20	0.0	2.08
21–30	6.25	1.67
31–40	25.0	8.30

Table7. (Continues)

Age (years)	Level 1 (%)	Level 2 (%)
41–50	6.25	10.42
51–60	31.25	23.33
61–70	18.75	26.67
71–80	6.25	21.67
81–90	6.25	5.00
> 90	0.0	0.83

The distribution of patients with two levels of low uric acid in terms of age and gender is clearly shown in the table. Male and female patients exhibit different levels of the disease. Using the *t*-test to calculate the *P*-value of 0.008 for gender, suggesting significant differences in the distribution of patients with two levels of low uric acid across genders.

However, the concentration of the disease at different age stages is not the same. Using SPSS 20.0 statistical software, a *t*-test yielded a *P*-value of 0.49, which is greater than the significance level of 0.05. Since $P > 0.05$, there is no significant difference between the two low uric acid levels among patients of different ages, indicating that from a statistical standpoint, the difference is not significant.

4. Discussion

Serum uric acid, an organic compound and weak acid, is the final substance produced by the cells of the body through enzymatic hydrolysis of purine nucleotides, deamination, and other metabolic processes [2]. Most uric acid in the body originates from endogenous purine after cellular catabolism, while a small portion comes from the metabolism of exogenous purines in a nucleoprotein-based diet [7]. Uric acid is processed in the kidneys through four steps: glomerular filtration, tubular reabsorption of uric acid, uric acid excretion, and reabsorption after excretion [8]. In the final stage, less than 10% of the uric acid is excreted in the urine, making changes in uric acid levels a reliable indicator of the organism's metabolic status.

Hypouricemia is a heterogeneous group of rare and uncommon diseases caused by disturbances in purine metabolism, insufficient production of uric acid, abnormalities in renal tubular transport of uric acid, and an abnormally high uric acid excretion fraction [8-10]. While insufficient uric acid production can be managed with drugs and inhibitors, increased uric acid excretion is often seen in familial renal tubular transport impairment.

At this stage, it is known that changes in serum uric acid levels are strongly associated with pathological conditions and an increase in uric acid concentration has been used as a diagnostic criterion for gout and as an independent risk factor for the development of several metabolism-related pathologies (diabetes mellitus, hypertension, craniocerebral disorders, renal disorders, etc.). In contrast, hypouricemia, caused by an extreme decline in serum uric acid levels, has not attracted much attention. However, many scholars have gradually begun to study hypouricemia from 1996 to the present. The prevalence of hypouricemia in patients admitted to one of the hospitals in Korea was found to be 4.14% [11]. Lehto *et al*. [12] concluded that a decrease in uric acid concentration may be an implied risk factor for liver disease, blood diseases, malignant tumors, uremia, and other renal and lung diseases. Lin *et al.* [7] and Pan [9] have published articles on the analysis of uric acid concentration, concluding that the key causes of hypouricemia are impaired uric acid synthesis and increased uric acid excretion. Zhou and Yao [13] found that the results of hypouricemia disease categories are consistent

with the findings of this paper, showing that liver disease, kidney disease, malignant tumors, craniocerebral disease, and blood disease are common factors causing a decrease in patients' serum uric acid concentration below the reference value.

The site of uric acid operation in the body is in the hepatocytes, which includes the formation of hypoxanthine nucleotides (IMP), adenine ribonucleotides (AMP), and guanine nucleotides (GMP). In the experimental group of this study, seven patients with hypouricemia showed liver damage. When the liver is damaged, enzyme activity is inhibited, resulting in a decrease in the synthesis of xanthine oxidase. Consequently, xanthine cannot be oxidized by xanthine oxidase to form uric acid, leading to a decrease in uric acid levels in the blood and severe hypouricemia [14].

66.7% of the uric acid content is excreted through the kidneys and urinary excretion. Uric acid in the kidneys undergoes four steps: glomerular filtration, tubular reabsorption, secretion, and reabsorption [8]. If glomerular function and tubular function are destroyed, the kidney's ability to manage uric acid is limited, which can cause serum uric acid levels to drop extremely low, resulting in renal hypouricemia. In the experimental group, there are 37 cases of malignant tumor patients and 17 cases of kidney-related disease patients. Malignant tumor patients represent the highest proportion of the disease group. Both malignant tumor and kidney disease patients suffer from renal function damage, glomerular destruction, decreased tubular reabsorption, and malfunctioning uric acid excretion [6].

There were 24 patients with craniocerebral diseases in the experimental group of this investigation, which mainly included cerebral hemorrhage, cerebral infarction, intracranial lesions, cerebral thrombosis, cerebrovascular disease, and subdural hematoma. Cranio-cerebral diseases were also the most prevalent in the relative ranking. Patients with cranio-cerebral diseases usually show cognitive impairment, consciousness disorders, and hemiparesis. The first consideration is that these patients have impaired swallowing function and cannot supplement nutrients in time, resulting in lower exogenous uric acid content. The second consideration is that the application of dehydrating drugs causes increased uric acid excretion through the kidneys. The drugs affecting uric acid mainly include mannitol, vitamin C, aspirin, and adrenal cortical hormones [13,15,16]. Hypouricemia is usually considered one of the most important indicators of renal impairment in patients with craniocerebral diseases who have undergone surgery.

Patients with multiple injuries and orthopedic diseases have low serum uric acid levels. Both Experimental Group I and Experimental Group II included such patients, with 2 cases and 15 cases, respectively. The analysis suggests that this may be related to the excessive use of antimicrobial drugs. Antimicrobial drugs, such as aminoglycosides, can produce side effects, allergic reactions, double infections, and gastrointestinal side effects, which can cause damage to the liver and kidneys [9]. Additionally, the epithelial cells of the proximal tubule may undergo varying degrees of necrosis, leading to increased uric acid excretion, a decrease in serum uric acid levels, and hypouricemia [17].

Excess uric acid deposits in the urine can form salt-containing crystals. As the number of crystals increases, urinary stones may form. Urinary stones are the most common manifestation of patients with hypouricemia [9]. Patients should drink more water daily to dilute the urine effectively. Additionally, using alkaline drugs to promote urine alkalization can be beneficial for disease management and healing [18].

Disclosure statement

The authors declare no conflict of interest.

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