# Diagnostic Accuracy of Single Spot Urine for Detecting Renal Uric Acid Underexcretion in Men

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## Abstract

**Background:** The uric acid (UA) clearance test to evaluate the hyperuricemia phenotype requires a great deal of time. However, the utility of single spot urine is scarce. The study aimed to determine the diagnostic accuracy of single spot urine for predicting renal UA underexcretion (the decreased UA excretion) in men.

**Methods:** A total of 73 male participants aged 20 - 74 years with a UA level of 6.0 - 7.9 mg/dL were enrolled in the study. Renal UA underexcretion was defined as < 7.3 mL/min using the 60-min method. Urinary UA to creatinine ratio (UACR), fractional clearance of urate (FCU), and the Simkin index were calculated. A receiver operating characteristic (ROC) analysis was performed to compare the diagnostic utility of these parameters for predicting UA underexcretion.

**Results:** In the ROC analysis, the area under the curve values of the UACR, FCU, and the Simkin index for predicting UA underexcretion were 0.903 (95% confidence interval (CI): 0.830 - 0.976), 0.841 (95% CI: 0.749 - 0.933), and 0.779 (95% CI: 0.673 - 0.885), respectively. An optimal UACR cutoff of 0.460 (sensitivity 89.2%, specificity 80.6%, overall diagnostic accuracy 84.9%, positive predictive value 82.5%, and negative predictive value 87.9%) was identified.

**Conclusions:** These results suggest that the UACR is a simple and efficient test with high sensitivity and specificity levels for predicting renal UA underexcretion in men.

**Keywords:** Uric acid to creatinine ratio; Fractional clearance of urate; Simkin index; Diagnostic accuracy

## Introduction

Hyperuricemia is a major risk factor for gout and is also independently associated with cardiovascular disease [1]. Moreover, hyperuricemia is a common disease that can be treated by general and family physicians, with a wide range of diagnoses and treatment options [2]. The hyperuricemia pathogenesis consists of overproduction and underexcretion, which can be estimated using the uric acid (UA) clearance (Cua) test. As a result, hyperuricemia was classified into four types: overproduction, underexcretion, combined, and normal type [3]. However, the Cua test is a time-consuming method as urine volume should be measured on time in primary care settings. Therefore, the Simkin index [4, 5] and fractional clearance of urate (FCU) [6, 7] have been used in physiological studies but usually employ 60-min or 24-h urine collections. The urinary UA to creatinine ratio (UACR) was used as a screening test for congenital purine metabolism disorders [8, 9]. However, research evidence between the UACR and renal UA underexcretion has been scarce. This study aimed to determine the diagnostic accuracy of single spot urine for predicting renal UA underexcretion in men.

## Materials and Methods

### Participants

This study was performed using baseline data from a randomized controlled trial according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) reporting guidelines [10]. The participants were recruited through flyers and word of mouth in Matsumoto City, Nagano Prefecture, Japan. The inclusion criteria were: 1) Male subjects aged 20 - 74 years old; and 2) Subjects who showed a serum UA (SUA) level of 6.0 - 7.9 mg/dL. The exclusion criteria included: 1) Subjects who regularly consume food or supplement improving the UA level; 2) Subjects who are currently receiving treatment for hyperuricemia or gout; 3) Subjects who are under treatment

or have a medical history of disease for gout, urinary stone, kidney stone, and rheumatoid arthritis; 4) Subjects who have serious disease or medical history in the brain, liver, kidney, heart, lung, gastrointestinal tract, or blood; 5) Subjects who excessively drink alcohol (alcohol conversion over 60 g/day); 6) Subjects who had a medical history of serious allergy to medicine or food; 7) Participants in other clinical trials; and 8) Subjects who were judged unsuitable for participating in this study based on subject background, physical finding, and interview by physician. The study was approved by the Matsumoto Junior College Ethics Committee, Japan. This trial was registered with the University Hospital Medical Information Network (UMIN000039465). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

### Cua test

The Cua test was performed according to the Japanese guidelines for the hyperuricemia and gout management [11, 12]. Cua was measured using the 60-min method. Briefly, patients ate low purine diets for 3 days before the start of the test, fasted on the day of the test, and voided at 30 min after drinking 300 mL of water. Urine was collected during a 60-min period, and a blood sample was obtained at the midpoint of urine collection. Renal UA underexcretion was defined as < 7.3 mL/min of Cua. Urine uric acid (UUA) per urine creatinine (UCr) rates were calculated using the formula: UUA/UCr. FCU was calculated using the formula: FCU = (UUA × serum creatinine (SCr))/(SUA × UCr). In contrast, the Simkin index does not include plasma UA concentrations: Simkin index = UUA × SCr/UCr.

### Measures

Height, body weight, body mass index (BMI), alcohol consumption, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), SCr, SUA, UCr, and UUA were measured. The formula for BMI is weight in kilograms divided by height in meters squared. Estimated glomerular filtration rate (eGFR) was calculated using an equation designed for the Japanese subjects, as previously described [13].

### Sample size

Sample size was estimated using the easy ROC: a web tool for ROC curve analysis (version 1.3) (http://www.biosoft.hacettepe.edu.tr/easyROC/). We estimated that a sample size of 66 participants would allow us to estimate areas under the curve (AUCs) of 0.7, 80% power, and allocation ratio of 1:1.

### Statistical analysis

Receiver operating characteristic (ROC) curve analysis was

used to determine the optimal cutoff points of the parameters for detecting renal UA underexcretion. The AUC with confidence intervals (CIs) was also presented. The AUC values of ≥ 0.90 are considered excellent, values between 0.80 - 0.89 are deemed good, values 0.70 - 0.79 are fair, and those < 0.70 are considered poor [14, 15]. The Youden index was used to identify the optimal cutoff value for detecting renal UA underexcretion [16]. The AUC values were adjusted for age, BMI, and logarithm of alcohol consumption. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated. The distribution of the different variables was examined for normality using the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation or percentage. All normally distributed data were analyzed using the Student's $t$-test to evaluate differences in mean and Chi-square test and evaluate differences in proportions. Data found to be non-normally distributed were analyzed using the Mann-Whitney U test for independent subgroups and the Wilcoxon test for dependent subgroups. In order to identify significant differences between groups after $\chi^2$ tests, we consecutively carried out a residual error analysis. A P value of less than 0.05 was deemed statistically significant.

## Results

### Clinical characteristics of patients with renal UA underexcretion

The UA underexcretion prevalence was 54.8%. The participants with renal UA underexcretion had a higher age than those without, although they had lower eGFR, UACR, FCU, and Simkin index (Table 1). There was no difference in alcohol consumption and medication between groups.

### Diagnostic performance of the parameters in predicting renal UA underexcretion

In the ROC analysis, the AUC values of the UACR, FCU, and Simkin index for predicting renal UA underexcretion were 0.903 (95% CI: 0.830 - 0.976), 0.841 (95% CI: 0.749 - 0.933), and 0.779 (95% CI: 0.673 - 0.885), respectively (Fig. 1). An optimal UACR cutoff was 0.460 (sensitivity 89.2%, specificity 80.6%, overall diagnostic accuracy 84.9%, positive predictive value 82.5%, and negative predictive value 87.9%). The UACR and FCU were superior to the Simkin index for predicting renal UA underexcretion (P = 0.004 and P = 0.013, respectively) (Table 2). After adjusting for age, BMI, and logarithm of alcohol consumption, the AUC values of the UACR, FCU, and Simkin index for predicting renal UA underexcretion were 0.936 (95% CI: 0.875 - 0.997), 0.911 (95% CI: 0.842 - 0.981) , and 0.874 (95% CI: 0.790 - 0.959), respectively.

## Discussion

This study demonstrated that the UACR was an excellent pre-

**Table 1.** Clinical Characteristic of the Participants With or Without Renal UA Underexcretion

| Variables | Renal UA clearance (mL/min) | | P value |
|---|---|---|---|
| | ≥ 7.3 (n = 33) | < 7.3 (n = 40) | |
| Age, years | 46.4 (12.0) | 56.1 (10.4) | < 0.001 |
| BMI, kg/m$^2$ | 24.4 (3.3) | 24.4 (2.8) | 0.982 |
| AST, IU/L | 25.8 (8.2) | 21.7 (10.1) | 0.067 |
| ALT, IU/L | 30.5 (19.1) | 24.9 (19.3) | 0.221 |
| GGT, IU/L | 43.7 (31.1) | 38.3 (29.2) | 0.451 |
| Serum UA, mg/dL | 6.7 (0.5) | 6.9 (0.6) | 0.174 |
| SCr, mg/dL | 0.91 (0.13) | 0.97 (0.12) | 0.026 |
| eGFR, mL/min/1.73 m$^2$ | 74.29 (12.78) | 64.34 (9.01) | < 0.001 |
| UACR | 0.52 (0.07) | 0.40 (0.08) | < 0.001 |
| FCU | 0.07 (0.01) | 0.06 (0.01) | < 0.001 |
| Simkin index | 0.47 (0.08) | 0.39 (0.08) | < 0.001 |
| Alcohol consumption, g/week | 56.0 (0, 134.4) | 14.0 (0, 128.2) | 0.416 |
| Medication, % | | | |
| Hypertension | 6.1 | 7.5 | > 0.999 |
| Diabetes | 6.1 | 0 | 0.201 |

Mean (standard deviation), median (25%, 75%), or %. BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine transferase; GGT: γ-glutamyl transferase; UA: uric acid; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; UACR: urinary uric acid to creatinine ratio; FCU: fraction clearance of urate.

dictor of renal UA underexcretion. Thus, the UACR was found to be a simple, rapid, low-cost, and reliable test for UA underexcretion screening. The UA underexcretion prevalence was 58.9% in this study. The value was lower than the previous study (85%) [17]. These differences might account for the hyperuricemia or gout severity.

FCU showed good accuracy, although the Simkin index was fairly accurate in detecting renal UA underexcretion.
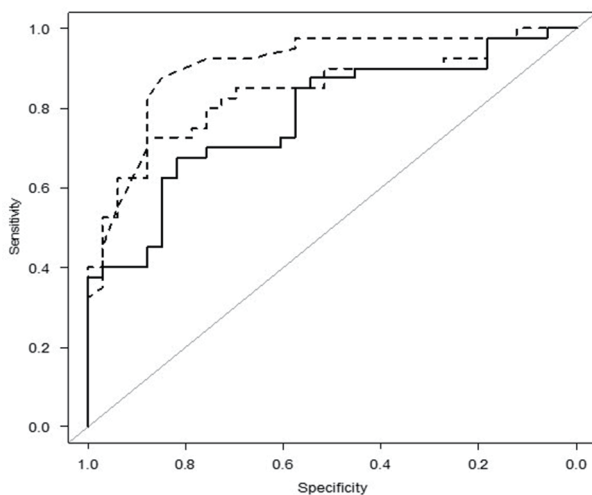


**Figure 1.** The ROC curve of the UACR, FCU, and the Simkin index for predicting renal UA underexcretion. ROC: receiver operating characteristic; UACR: urinary uric acid to creatinine ratio; FCU: fractional clearance of urate.

Measurement of urine volume is not required, which is a significant practical advantage. Graessler et al used 0.06 as the lower limit of normal [18]. In this study, we also identified an optimal cutoff point of 0.06 for FCU, which is consistent with a previous study [18]. Further examination is required to confirm these issues in different populations.

Simkin et al [4] proposed a spot morning urine test of urate excretion normalized to GFR to identify UA overproducers. In this study, we also collected urine samples in the morning. Thus, the timing of urine sample collection is desirable in the morning after overnight fasting and drinking of water.

**Strengths and limitations**

The strengths of the present study include STARD guideline-based research, and sufficient sample size. The limitations of the present study include only male participants and no patients with UA levels of ≥ 8.0 mg/dL or gout. Generalizability was limited because of our findings in men with UA of 6.0 - 7.9 mg/dL. Subjects with SUA levels of ≥ 6.0 mg/dL had a significantly increased risk for kidney impairment [19]. Guideline documents were concordant and recommended a target for SUA < 6.0 mg/dL for long-term control [20]. A simple management recommendation of a 6-7-8 rule was proposed through the consensus of expert physicians [21]. People with these UA ranges were the target for the non-pharmacological approach [22]. We recruited the participants for the study of foods with health claims preventing hyperuricemia and gout. Further researches including patients with UA levels of ≥ 8.0 mg/dL or gout are required. Smoking, alcohol drinking, and

**Table 2.** Comparison of the UACR, FCU and the Simkin Index for Predicting Renal UA Underexcretion

| Variables | Cutoff | Sn, % | Sp, % | PPV, % | NPV, % | DA, % | +LR | -LR | AUC (95% CI) | P value[a] | P value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UACR | 0.460 | 89.2 | 80.6 | 82.5 | 87.9 | 84.9 | 4.59 | 0.13 | 0.903 (0.830 - 0.976) | 0.158 | 0.004 |
| FCU | 0.060 | 67.5 | 87.9 | 87.1 | 69.0 | 76.7 | 5.57 | 0.37 | 0.841 (0.749 - 0.933) | - | 0.013 |
| Simkin index | 0.399 | 81.2 | 65.9 | 65.0 | 81.8 | 72.6 | 2.38 | 0.29 | 0.779 (0.673 - 0.885) | 0.013 | - |

UACR = UUA/UCr; FCU = (UUA × SCr)/(SUA × UCr); Simkin index = UUA × SCr/UCr. [a]vs. FCU; [b]vs. Simkin index. UACR: urinary uric acid to creatinine ratio; FCU: fraction clearance of urate; Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy; +LR: positive likelihood ratio; -LR: negative likelihood ratio; AUC: area under the curve; UUA: urine uric acid; UCr: urine creatinine; SCr: serum creatinine.

other pharmacotherapy affecting insulin sensitivity are informative because these factors can influence the reuptake of UA in renal tubule. After adjusting for age, BMI, and alcohol consumption, the similar results were obtained. But we do not have the data of smoking habits. Careful attention should be paid to interpret the results.

We adopted the 60-min method instead of the 24-h method in this study. We do not know the diagnostic accuracy of UACR for the results using the 24-h method. The measurement of 24-h urinary UA excretion is frequently used to evaluate disease status and select drugs that lower the SUA levels. However, the 24-h urine collection is cumbersome and inconvenient, and sometimes unreliable because of incomplete sampling. Choi et al reported that there was a good correlation between the random urinary UACR and 24-h UUA excretion [23].

Reduced urinary UA excretion was observed in patients with proteinuria or metabolic syndrome [24, 25]. Further examination including proteinuria or metabolic syndrome is required to confirm these issues in the future.

In conclusion, the present study indicates that the UACR is a convenient, valid, and reliable indicator for predicting renal UA underexcretion. The UACR may be applied in primary care settings when they do not perform the 60-min method.

## Acknowledgments

## Financial Disclosure

## Conflict of Interest

None to declare.

## Informed Consent

Informed written consent was obtained from participants.

## Author Contributions

NS, AO, KN, MT, IK, KK, MM, MN, and FA conceived and designed the study. NS analyzed the data. AO, KN, MT, and FA contributed to participants' data collection. IK, KK, and MM contributed to ethical committee approval. NS wrote the paper. All authors read and approved the final version of the manuscript.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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