Prediction of Uric Acid Component in Nephrolithiasis Using Simple Clinical Information: A Machine Learning-Based model

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Abstract

There is a great need for a diagnostic tool using simple clinical information collected from patients to diagnose uric acid (UA) stones in nephrolithiasis. We built a predictive model making use of machine learning (ML) methodologies entering simple parameters easily obtained at the initial clinical visit. Socio-demographic, health, and clinical data from two cohorts (A and B), both diagnosed with nephrolithiasis, one between 2012 and 2016 and the other between June and December 2020, were collected before nephrolithiasis treatment. A ML-based model for predicting UA stones in nephrolithiasis was developed using eight simple parameters - sex, age, gout, diabetes mellitus, body mass index, estimated glomerular filtration rate, bacteriuria, and urine pH. Data from Cohort A were used for model training and validation (ratio 3:2), while data from Cohort B were used only for validation. One hundred forty-six (13.3%) of 1098 patients Cohort A and three (4.23%) of 71 patients in Cohort B had pure UA stones. For Cohort A, our model achieved validation AUC (area under ROC curve) of 0.842, with 0.8475 sensitivity and 0.748 specificity. For Cohort B, our model achieved 0.936 AUC, with 1.0 sensitivity, and 0.912 specificity. This ML-based model provides a convenient and reliable method for diagnosing urolithiasis. Using only eight readily available clinical parameters, it distinguished pure uric acid stones from other stones before treatment.

Introduction

Urolithiasis is a common disease worldwide. The prevalence and incidence of these urinary stones are increasing¹. This rise global prevalence is a major contributing factor to increases healthcare costs associated with nephrolithiasis². Moreover, recurrence rates range between 50% and 80%, depending on type of stone³.

In urolithiasis, uric acid (UA) stones account for 10–15% of all stones⁴. Unlike other component type stones, uric acid stones have been associated with several features of metabolic syndrome including diabetes mellitus^{5–7}. In addition, unlike other stones which require surgery, most uric acid stones can be treated conservatively⁸. Thus, it is important to be able to tell the difference in components uric acid and non-uric acid stone diseases prior to surgery. Uric acid stones are usually diagnosed by analysis of stones after they have been retrieved via surgery or medical expulsive therapy. Although recent studies have reported that dual-energy computed tomography (CT) can be an accurate test for distinguishing uric acid from non-uric acid stone diseases prior to treatment⁹, these studies have used different cutoffs and CT machine types^{10, 11}, making replication difficult. In addition, dual-energy CT produces a relatively high radiation dose and the equipment is prohibitively expensive for most clinics around the world.

Previously, we used structural equation modeling to construct a model for pathway analysis of UA nephrolithiasis identifying several simple clinical factors affecting UA stone disease⁶. Among these clinical factors, we found eight variables, which were sex, age, gout, diabetes mellitus (DM), body mass index (BMI), estimated glomerular filtration rate (eGFR), bacteriuria, and urine pH, that could have indirect and direct effects on the formation of uric acid stones^{6, 7}. The aim of this study was to build a reliable diagnostic model making use of machine learning using these variables to predict the uric acid component in nephrolithiasis

and test it. The eight variables chosen were simple clinical factors easily obtained during the patients first clinical visit.

Results

Characteristics of Study Samples

Cohort A consisted of 1098 patients, 146 (13.3%) pure uric acid stones and 952 (86.7%) non-uric acid stones (Tables 1 and 2). Cohort B consisted of 71 patients, three male patients with pure uric acid stones (Table 3 and 4). Statistical similarity between patients with non-uric acid nephrolithiasis in Cohort A and those in B was observed.

Model Performance

The model we developed exhibited good discriminatory power in predicting who would have pure uric acid nephrolithiasis which it achieved using only a small amount of information that can be or is often collected at the initial patient clinical visit. The model achieved a validation AUC of 0.842 (95% CI, 0.800-0.885) when applied to the Cohort A validation dataset. Optimal cut-off value, which was determined by Youden's index for pure uric acid nephrolithiasis, was 0.470. Using this cut-off value, the model had a sensitivity of 0.848 (95% CI, 0.756-0.939) and a specificity of 0.748 (95% CI, 0.704-0.792). The positive predictive value (PPV) was 0.343 (95% CI, 0.266-0.419) and the negative predictive value (NPV) was 0.969 (95% CI, 0.950-0.989). The overall correction ratio was 76.13%.

The model was also applied to patients in Cohort B. The AUC of the ROC curve was found to be 0.936 (95% CI, 0.854-1.0). Optimal cut-off value for this ROC curve was 0.688. Using this cut-off value, the model had a sensitivity of 1.0 (95% CI, 1.0-1.0) and a specificity of 0.912 (95% CI, 0.844-0.979), The PPV was 0.333 (95% CI, 0.025-0.641) and the NPV 1.0 (95% CI, 1.0–1.0). The overall correction ratio was 91.55%. Even when cut-off value 0.470 obtained from Cohort A was applied, the model was able to correctly predict all three pure uric acid nephrolithiasis patients in Cohort B, achieving a 1.0 sensitivity, though specificity was reduced to 0.647 and the overall correction ratio reduced to 66.2%.

The validation ROC curves of the model are shown in Figure 1.

Discussion

In urolithiasis disease, uric acid stones account for 10–15% of all urinary stones⁴. Because the chemical properties of uric acid stones are very different from those of other stones (particularly calcium-containing stones), treatment and prevention of uric acid stones could be improved with a diagnostic approach that can exclude non-uric acid stones⁸. This study showed that eight simple clinical variables can be used to build a diagnostic model to distinguish pure uric acid stones from non-uric acid ones with very good accuracy. These variables, including age, sex, past medical history, routine urine analysis, and eGFR, can be easily obtained during the first visit to an emergency room or clinic. These findings can help first-line medical staff distinguish uric acid stones from non-uric acid stones when patients are diagnosed as having

nephrolithiasis. This knowledge could make possible the timely oral administration of chemolysis agents to dissolve the uric acid stones.

A meta-analysis of studies investigating the prediction of uric acid stones using dual-energy CT recently showed that this approach had a highly accurate prediction rate⁹. However, the studies reviewed used different methods and machines. For example, in an early retrospective study on CT image prediction for uric acid stones, Ascenti et al. used 120 Kv dual-energy CT and post-processing software (Syngo Kidney Stone, Siemens Healthcare) to predict uric acid stones¹². Zhang et al. performed a prospective study in 2016 using dual-source dual-energy computed tomography to predict the stone components¹³. There are some problems with the use of CT machines. First, the CT machines used in previous studies were different with some not commonly used in clinical practice. Second, radiation exposure should be kept to a minimum. In low-dose non-contrast abdominal CT for ureter stone diagnosis, some studies limited the radiation dose to be no more than 3 mSv, while others have limited it to only 1–1.5 mSv¹⁴. A relatively high radiation dose (8–10 mSv) has been used by Zhang et al. to analyze stone components¹³. Third, dual-energy CT machines are more expensive than single-energy CT machines. Most abdominal CT scans are single energy. Although single-energy CT scans were used to predict uric acid stones in 2021, many sophisticated post-CT image processing methods, such as Laplacian filtering, were required¹⁵. Thus, image-based diagnostic tools may be impractical in clinical use. We believe our model and methodology, which use only simple clinical variables, is easier to perform and avoids subjecting patients to radiation. The model can also be easily applied in clinics or even in areas where health professionals and medical resources, including CT machines, are not widely available.

It is generally believed that having a large number of decision variables is necessary to successfully build a predictive model based on machine learning algorithms. However, having many decision variables often makes it difficult to determine possible causality¹⁶. In a recent study, Kazemi et al. used more than 40 variables to build diagnostic tools based on machine learning to predict the stone components¹⁷. Among these variables, some were not confirmed to be related to the formation of stones, such as marital status and smoking. In a previous study, we used a structural equation model to analyze the relationship between uric acid stones and variables that had some evidence for urolithiasis formation^{6,7}. We found eight variables to be related to the development of uric acid nephrolithiasis. In this study, we used these eight variables to build a diagnostic model based on machine learning methodologies. This study found that our model had good predictive power and worked well. Compared with previous methods¹⁷, the model we use here requires fewer computational resources and can be used after the initial clinical visit of the patient to provide a rapid and reliable alternative diagnostic tool for the identification of pure uric acid nephrolithiasis.

Although the AUCs of our diagnostic model for the two groups of patients were relatively high, there were still some false-positive outcomes. Some studies have proposed that uric acid crystals form the nidus for the deposition of other stone components^{18–20}. Additionally, one epidemiological study found patients with hyperuricosuria and gouty diathesis to have a higher incidence of non-uric acid nephrolithiasis²¹. These findings might explain the false positive results. Our model also predicted uric acid stones in some patients who were finally diagnosed with non-uric acid stones. We found that these patients had similar etiologies

and clinical characteristics to patients with uric acid nephrolithiasis, so even when misdiagnosed by our model, these patients would more than likely benefit from the same treatment and nephrolithiasis prevention measures.

This study has some limitations. It did not assess the efficiency of chemolysis medical treatment in patients who were predicted to have uric acid stones and we did not assess the stone recurrence. In the future, a prospective study can be conducted to evaluate efficiency of chemolysis treatment on patients predicted to have uric acid stones by our current model. More advanced models based on machine learning methodologies might be further developed to predict uric acid stone recurrence.

In summary, this ML-based model provides a simple, convenient and reliable method for the diagnosis of uric acid stones. With only eight easily-obtained clinical parameters, this ML-based model can distinguish pure uric acid stones from other stones without advanced equipment before urolithiasis treatment. This diagnostic approach may help optimize timely treatment strategies for urolithiasis.

Method

Selection and Description of Participants

In this retrospective study, we collected data for two cohorts (A and B), patients diagnosed with nephrolithiasis at Kaohsiung Medical University Hospital, Kaohsiung, Taiwan between January 2012 and December 2016 and between June 2020 and December 2020. Cohort A was a group of patients we enrolled in a previous study^{6,7}. The participant selection criteria for Cohort B was the same as that for Cohort A. We included patients diagnosed with nephrolithiasis who had received genitourinary surgery (ureteroscopic lithotripsy, percutaneous nephrolithotomy, or open nephrolithotomy). We excluded any of these patients if they had genitourinary tract tumors, kidney transplants, genitourinary tract anomalies, recurrent nephrolithiasis, mixed stones containing more than one stone component, or renal replacement therapy, such as hemodialysis. Patients younger than 18 years and those without detailed medical records were also excluded.

This study was approved by the Kaohsiung Medical University Chung-Ho Memorial Hospital Institutional Review Board (KMUHIRB-E(I)-20210061) and was conducted according to the principles of the Declaration of Helsinki. The informed consent requirement was waived by Kaohsiung Medical University Chung-Ho Memorial Hospital Institutional Review Board (KMUHIRB-E(I)-20210061) due to the retrospective nature of this study and minimal risk involved.

Data Description and Processing

In addition to the response variable, eight variables were used for data analysis and prediction model building. These included two sociodemographic variables (age and sex), three health-related variables (BMI and the comorbidities DM and gout), and three clinical variables (urine pH and bacteriuria, and eGFR). Socio-demographic, health, and clinical information were collected prior to treatment for nephrolithiasis.

- Response variable

Stones were analyzed using infrared spectroscopy performed by a medical technologist and confirmed by two urologists. They were defined as 1 (uric acid stone) or 0 (other stone).

- Socio-demographic characteristics

Age and gender were recorded. Age was entered as a numeric variable and gender as a binary variable, 1 (male) or 0 (female).

- Health information

Health information items were patient BMIs, and whether or not the patient had a history of DM or gout. BMI was entered as a numeric variable with one decimal fraction. DM was entered as 1 (having a history) or 0 (having no history). Gout was recorded similarly, 1 (have a history) or 0 (having no history).

- Clinical information

Urinalysis results, including bacteriuria and urine pH, were entered. Urine pH was entered as numeric variable with one decimal fraction, bacteriuria was entered as 1 (having bacteriuria) or 0 (having no bacteriuria). eGFR was calculated using the isotope dilution mass spectrometry traceable Modification of Diet in Renal Disease formula, where (eGFR [mL/min/1.73 m²] = 175 × (Scr) – 1.154 × (Age) – 0.203 × [0.742 if female])²².

Model Development, Fitting, and Evaluation

A model for predicting uric acid stones in nephrolithiasis was developed using machine learning methodologies²³. The mathematical representation of this model can be expressed as follows:

$$y = \frac{1}{1 + e^{f(x)}}$$

where x represents the input vector of the eight decision variables, and y the model output, which takes a value between 0 and 1. The model output is expressed as the likelihood that stones were composed of uric acid.

The decision variables $x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8$ carry the values of “gender,” “age,” “eGFR,” “urine pH,” “BMI,” “DM,” “gout,” and “bacteriuria,” respectively. The function $f(x)$ has the following form:

$$f(x) = a_1 f_1(x_1) + \dots + a_5 f_5(x_5) + a_6 f_6(x_6, x_7, x_8) + b,$$

where $a_1, \dots, a_6, b$ are model parameters, and each $f_i(\cdot)$ function is a nonlinear function generated by a fully connected two-layer neural network. Each neural network had an output dimension of 20 for the first layer and 1 for the second layer. In total, the nonlinear function $f(x)$ contained 293 trainable model parameters.

Cohort A data were used for model training and model validation, while Cohort B data were only used for validation. Group A data were randomly divided into training (60%) and validation (40%) sets. We calculated prevalence of patients with pure uric acid and non-uric acid stone in both training and validation datasets. There was very little statistical difference between training and validation sets with regard to sociodemographic characteristics, medical history, and bacteriuria.

The model parameters were trained based on the training dataset (Cohort A) and predictive power was evaluated using the validation datasets (Cohorts A and B), using an area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. The optimal cutoff point on the ROC curve was determined based on Youden's index²⁴, which in turn was used to calculate the sensitivity, specificity, positive predictive value, and negative predictive value for the prediction models applied to the validation data. Finally, the prediction model was applied to data obtained from the Cohort B to determine whether the uric-acid stone patients in Cohort B could be correctly identified by the model.

Declarations

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Contributions

Hao-Wei Chen – study design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical or material support, supervision.

Yu-Chen Chen – study design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis.

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Ting-Yin Chu – study design, statistical analysis, critical revision of the manuscript for important intellectual content.

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Competing Financial Interests Statement

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Tables

Table 1. Descriptive analysis of the Cohort A included in model training and validation sets.

	Training Set (60%)				Validation Set (40%)			
	Pure uric acid (n=87, 13.22%)	Non-uric acid (n=571, 86.78%)	Total patients (n=658)	<i>P</i> -value	Pure uric acid (n=59, 13.41%)	Non-uric acid (n=381, 86.59%)	Total patients (n=440)	<i>P</i> -value
Gender				0.095				0.258
male	66 (75.86%)	382 (66.90%)	448 (68.09%)		44 (74.58%)	256 (67.19%)	300 (68.18%)	
female	21 (24.14%)	189 (33.10%)	210 (31.91%)		15 (25.42%)	125 (32.81%)	140 (31.82%)	
Age				<0.001				<0.001
≤ 45	8 (9.20%)	184 (32.22%)	192 (29.18%)		8 (13.56%)	99 (25.98%)	107 (24.32%)	
45~65	49 (56.32%)	308 (53.94%)	357 (54.25%)		32 (54.24%)	223 (58.53%)	255 (57.95%)	
≥ 65	30 (34.48%)	79 (13.84%)	109 (16.57%)		19 (32.20%)	59 (15.49%)	78 (17.73%)	
DM				<0.001				0.003
with	26 (29.89%)	74 (12.96%)	100 (15.20%)		16 (27.12%)	48 (12.60%)	64 (14.55%)	
without	61 (70.11%)	497 (87.04%)	558 (84.80%)		43 (72.88%)	333 (87.40%)	376 (85.45%)	
Gout				0.046				<0.001
with	5 (5.75%)	12 (2.10%)	17 (2.58%)		9 (15.25%)	9 (2.36%)	18 (4.09%)	
without	82 (94.25%)	559 (97.90%)	641 (97.42%)		50 (84.75%)	372 (97.64%)	422 (95.91%)	
Bacteriuria				0.033				0.155
with	7 (8.05%)	97 (16.99%)	104 (15.81%)		6 (10.17%)	67 (17.59%)	73 (16.59%)	
without	80 (91.95%)	474 (83.01%)	554 (84.19%)		53 (89.83%)	314 (82.41%)	367 (83.41%)	

Abbreviations: DM, diabetes mellitus.

Table 2. Age, BMI, urine pH, and eGFR of all study samples in Cohort A.

	Pure uric acid (15.76%) Mean (SD) 95% CI	Non-uric acid (84.24%) Mean (SD) 95% CI	<i>P</i> -value
Age	60.44 (12.52) (58.41 – 62.47)	52.75 (12.69) (51.94 – 53.55)	<0.001
BMI	25.63 (3.80) (25.02 – 26.25)	25.38 (3.53) (25.16 – 25.61)	0.4297
Urine pH	5.51 (0.54) (5.43 – 5.60)	6.09 (0.77) (6.04 – 6.14)	<0.001
eGFR	55.13 (29.45) (50.35 – 59.90)	80.14 (29.37) (78.27 – 82.01)	<0.001

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; CI, confidence interval

Table 3. Patient characteristics in Cohort B.

	Pure uric acid (n=3, 4.23%)	Non-uric acid (n=68, 95.77%)	Total patients (n=71)	<i>P</i> -value
Gender				0.170
male	3 (100.00%)	41 (60.29%)	44 (61.97%)	
female	0 (0.00%)	27 (39.71%)	27 (38.03%)	
Age				0.812
≤ 45	1 (33.33%)	15 (22.06%)	16 (22.54%)	
45~65	1 (33.33%)	37 (54.41%)	38 (53.52%)	
≥ 65	1 (33.33%)	16 (23.53%)	17 (23.94%)	
DM				0.095
with	2 (66.67%)	16 (23.53%)	18 (25.35%)	
without	1 (33.33%)	52 (76.47%)	53 (74.65%)	
Gout				0.034
with	1 (33.33%)	3 (4.41%)	4 (5.63%)	
without	2 (66.67%)	65 (95.59%)	67 (94.37%)	
Bacteriuria				0.632
with	0 (0.00%)	5 (7.35%)	5 (7.04%)	
without	3 (100.00%)	63 (92.65%)	66 (92.96%)	

Abbreviations: DM, diabetes mellitus.

Table 4. Age, BMI, urine pH, and eGFR of all study samples in Cohort B.

	Pure uric acid (4.23%) Mean (SD), 95%CI	Non-uric acid (95.77%) Mean (SD) 95%CI	<i>P</i> -value
Age	56.67 (14.01) (40.72 – 72.52)	54.72 (13.78) (51.44 – 57.99)	0.812
BMI	28.77 (6.11) (21.86 – 35.68)	26.80 (4.75) (25.67 – 27.93)	0.489
Urine pH	5.0 (0) (5.0 – 5.0)	6.24 (0.88) (6.03 – 6.44)	0.019
eGFR	65.20 (18.55) (44.21 – 86.19)	76.91 (32.07) (69.28 – 84.53)	0.534

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; CI, confidence interval

Figures

Figure 1

Validation receiver operating characteristic (ROC) curves of the proposed machine learning (ML) -based model on Cohort A and B patients. (A): ROC curve for Cohort A. (B): ROC curve for Cohort B.