

# Association between metabolic syndrome and calcium oxalate stone risk in Chinese individuals: a nomogram prediction model

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## Abstract

**Objective:** This retrospective study explored the association between calcium oxalate (CaOx) stones and metabolic syndrome. It also developed and validated a nomogram to aid in the prediction of CaOx stones.

**Methods:** This case-control study enrolled 150 patients with CaOx stones and 635 individuals without urolithiasis from October 2016 to October 2018. Student's t-test, the chi-squared test, and logistic univariate and multivariate regression analyses were used. A nomogram for prediction of CaOx stones was established based on independent associated factors. The concordance index and calibration curves were plotted to determine nomogram accuracy.

**Results:** Female sex, age  $\geq 66$  years, blood pressure (systolic pressure  $\geq 130$  mmHg and/or diastolic pressure  $\geq 85$  mmHg), and blood uric acid level independently influenced the risk of CaOx stones, according to multivariate logistic regression analysis; these factors were included in the nomogram. The concordance index was 0.701 (95% confidence interval: 0.658–0.737). The standard curve showed a robust fit with the calibrated predictive curve.

**Conclusions:** Female sex, age  $\geq 66$  years, elevated blood pressure, and blood uric acid level independently influenced the risk of CaOx stones. Our nomogram for the prediction of CaOx stones may provide a clinical basis for the assessment of CaOx stone and facilitate early prevention efforts.

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## Keywords

Calcium oxalate stone, metabolic syndrome, nomogram, uric acid, case-control study, blood pressure, urolithiasis, sex, age

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## Background

Urolithiasis is a common urological disease that substantially influences health and quality of life for affected individuals worldwide. The incidence of urolithiasis is increasing, such that the lifetime risk of urolithiasis disease currently exceeds 6% to 12% in the United States.<sup>1,2</sup> However, the disease differs with respect to sex, ethnicity, and environment.<sup>2,3</sup> In China, the prevalence of urolithiasis has increased from 4% to 6.4%. Its prevalence is greater in southern China (5.5% to 11.6%) than in northern China (2.6% to 7.2%), presumably because of higher average temperatures in southern China.<sup>4,5</sup> Furthermore, the recurrence rate of urolithiasis approaches 50% within 5 years after the first episode.<sup>6</sup> Because urolithiasis causes severe pain and discomfort to patients, as well as high medical costs, there is a need to identify factors that contribute to its onset. Calcium oxalate (CaOx) is the primary constituent of stones in patients with urolithiasis; factors presumed to influence the formation of these stones include age, sex, ethnicity, medication use, genetics, dietary intake, environmental aspects, insulin resistance, and drinking water content.<sup>7-9</sup> Moreover, CaOx stone formation is associated with features of metabolic syndrome (MS), including elevated blood pressure, dyslipidemia, obesity, and blood glucose intolerance.<sup>10,11</sup>

MS is a growing global concern associated with economic development.<sup>12</sup> In China, the prevalence of MS is reportedly

14.39% in adults >18 years of age.<sup>13</sup> Furthermore, urolithiasis has been associated with aspects of MS in many developed countries.<sup>10,14</sup> Sakhaee et al.<sup>15</sup> found that the supersaturation ratio of urinary calcium and calcium oxalate significantly increased with as the number of MS features increased (from zero to four) in individuals without urolithiasis. In a case-control study of 540 patients with kidney stones and 656 patients without stones, Ding et al.<sup>16</sup> showed that the prevalence of CaOx stones was significantly elevated in patients with MS. However, in developing areas, including most cities in China, there may be differences in these associations.

The lack of a nomogram to aid in the prediction of CaOx stones in the Chinese population, especially among individuals with MS, prompted us to investigate the association between CaOx stones and MS in Chinese individuals. We also aimed to provide an easily accessible clinical tool for the early prediction of CaOx stone risk that could be used for screening of patients with MS.

## Methods

### Participants

This matched case-control study design with 1:4 mapping enrolled patients with CaOx stones (i.e., cases) and control participants without urolithiasis (i.e., non-urolithiasis controls). The inclusion criteria for cases were as follows: presence of CaOx

stones, determined by infrared spectroscopy; age >18 years; and hospitalization in the Department of Urology of the No. 83 Central Hospital of Xinxiang Medical College between October 2016 and October 2018. Exclusion criteria were renal failure, fever, urinary tract infection, urinary tract malformation, obstructive urinary disease, neoplastic disease, or hyperparathyroidism. The controls comprised individuals who visited the Health Check-up Center of our hospital during the same period. This retrospective study was approved by the Ethics Committee of the Xinxiang Medical College in October 2018 and all participants provided written informed consent prior to inclusion in the study.

### **Data collection**

The participants' demographic characteristics were recorded, including age, sex, comorbidities (e.g., hypertension, diabetes, dyslipidemia, and cerebrovascular and cardiopulmonary diseases), medications, and family history of urolithiasis. All participants underwent physical examination (including height, weight, and blood pressure), laboratory tests (including analyses of blood and urine biochemistry, as well stone chemical composition), and imaging diagnosis (including ultrasonography and computed tomography). Blood pressure was assessed by standard sphygmomanometry. Laboratory tests were conducted on early-morning fasting blood and urine samples after an overnight fast.

Analysis of demographic data among Chinese individuals has shown that, for a body mass index of 25 kg/m<sup>2</sup>, the corresponding waist circumference is approximately 90 cm for men and 80 cm for women.<sup>12</sup> Therefore, body mass index data were used in this study as the standard for central obesity.

### **Statistical analyses**

All data were analyzed using IBM SPSS Statistics, version 21 (IBM Corp. Armonk, NY, USA) and R version 3.5.3 (The R Project for Statistical Computing, Vienna, Austria; <http://www.r-project.org>). The normalities of the distributions of continuous variables were determined by one-sample Kolmogorov–Smirnov tests; all continuous variables exhibited normal distributions in this study. Continuous variables with normal distributions were presented as mean ± standard deviation and categorical variables were presented as number (percentage). The means of two continuous normally distributed variables were compared by independent sample Student's t-test, while the means of categorical variables were compared using Pearson's  $\chi^2$  test. Univariate and multivariate logistic regression models were used to explore the associations of MS and its features with CaOx stones; the results were displayed as odds ratios (ORs) and 95% confidence intervals (CIs). All P-values were two-tailed and P < 0.05 was considered statistically significant. A nomogram for predicting CaOx stones was established on the basis of the independently associated factors. The concordance index (c-index) and calibration curves were plotted to determine the predictive performance of the nomogram models. The theoretical value of the c-index was between 0 and 1; a c-index >0.5 was considered to indicate prediction performance better than random guessing. The validations for risk models were performed by 1000-fold bootstrapping.

## **Results**

### **Demographic characteristics of study participants**

This study included 785 participants, of which 635 (80.9%) were considered non-

urolithiasis cases and 150 (19.1%) were considered CaOx stone cases. The demographic characteristics of study participants with and without urolithiasis are shown in Table 1. The median participant age was 48 years (range, 18–75 years).

### Association of CaOx stones with MS and its features

Univariate regression analysis indicated that sex, age, blood pressure (systolic pressure  $\geq 130$  mmHg and/or diastolic pressure  $\geq 85$  mmHg), body mass index ( $\geq 25$  kg/m<sup>2</sup>),

**Table 1.** Demographic characteristics of study participants with and without calcium oxalate stones.

Variables	All participants	CaOx stone cases	Non-urolithiasis controls
Sex			
Male	534 (68)	130 (86.7)	404 (63.6)
Female	251 (32)	20 (13.3)	231 (36.4)
Age (years)			
18–40	178 (22.7)	27 (18)	151 (23.8)
41–65	564 (71.8)	106 (70.7)	458 (72.1)
$\geq 66$	43 (5.5)	17 (11.3)	26 (4.1)
MS			
No	451 (57.5)	69 (46)	382 (60.2)
Yes	334 (42.5)	81 (54)	253 (39.8)
BMI (kg/m <sup>2</sup> )			
$< 25$	451 (57.5)	68 (45.3)	383 (60.3)
$\geq 25$	334 (42.5)	82 (54.7)	252 (39.7)
Blood pressure (mmHg)			
SP $< 130$ and/or DP $< 85$	332 (42.3)	42 (28)	290 (45.7)
SP $\geq 130$ and/or DP $\geq 85$	453 (57.7)	108 (72)	345 (54.3)
HDL-C (mmol/L)			
Male $< 1.04$ ; female $< 1.3$	308 (39.2)	49 (32.7)	259 (40.8)
Male $\geq 1.04$ ; female $\geq 1.3$	477 (60.8)	101 (67.3)	376 (59.2)
Triglyceride (mmol/L)			
$< 1.7$	452 (57.6)	70 (46.7)	382 (60.2)
$\geq 1.7$	333 (42.4)	80 (53.3)	253 (39.8)
FBG (mmol/L)			
$< 5.56$	440 (56.1)	71 (47.3)	369 (58.1)
$\geq 5.56$	345 (43.9)	79 (52.7)	266 (41.9)
MS features			
0	68 (8.7)	5 (3.3)	63 (9.9)
1	183 (23.3)	28 (18.7)	155 (24.4)
2	200 (25.5)	36 (24)	164 (25.8)
3	192 (24.5)	41 (27.3)	151 (23.8)
4	97 (12.4)	25 (16.7)	72 (11.3)
5	45 (5.7)	15 (10)	30 (4.7)
Total cholesterol	4.91 $\pm$ 0.92	5.01 $\pm$ 0.98	4.89 $\pm$ 0.91
LDL-C	2.86 $\pm$ 0.71	2.87 $\pm$ 0.75	2.85 $\pm$ 0.70
Blood uric acid	341.58 $\pm$ 94.23	378.48 $\pm$ 99.87	332.87 $\pm$ 90.77
Urine pH	5.6 $\pm$ 0.72	5.54 $\pm$ 0.69	5.60 $\pm$ 0.73

Data are shown as mean  $\pm$  standard deviation or n (%).

BMI, body mass index; SP, systolic pressure; DP, diastolic pressure; FBG, fasting blood glucose; MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

fasting blood glucose ( $\geq 5.56$  mmol/L), triglyceride ( $\geq 1.7$  mmol/L), and MS were independently associated with the risk of CaOx stones (Table 2). The risk of CaOx stones significantly increased as the number

of MS features increased ( $P = 0.007$ ). Notably, the incidence of CaOx stones in the group with five features of MS reached 33.3%, which was 7.4-fold higher than that of the group with no features of MS. When

**Table 2.** Univariate and multivariate logistic regression analysis of the features of metabolic syndrome for calcium oxalate stones.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex		<0.001		0.002
Male	1		1	
Female	0.269 (0.164–0.443)		0.423 (0.245–0.733)	
Age (years)		0.002		0.011
18–40	1		1	
41–65	1.294 (0.816–2.052)	0.272	1.230 (0.757–2.000)	0.403
$\geq 66$	3.657 (1.752–7.632)	0.001	3.126 (1.451–6.735)	0.004
BMI (kg/m <sup>2</sup> )		0.001		0.181
<25	1		1	
$\geq 25$	1.833 (1.280–2.623)		1.366 (0.865–2.158)	
Blood pressure (mmHg)		<0.001		0.032
SP <130 and/or DP <85	1		1	
SP $\geq 130$ and/or DP $\geq 85$	2.161 (1.465–3.190)		1.638 (1.024–2.574)	
HDL-C (mmol/L)		0.067		
Male <1.04; female <1.3	0.704 (0.484–1.026)			
Male $\geq 1.04$ ; female $\geq 1.3$	1			
Triglyceride mmol/L		0.003		0.403
<1.7	1		1	
$\geq 1.7$	1.726 (1.206–2.468)		1.221 (0.764–1.951)	
FBG (mmol/L)		0.017		0.492
<5.56	1		1	
$\geq 5.56$	1.544 (1.080–2.206)		1.165 (0.754–1.798)	
MS		0.002		0.529
No	1		1	
Yes	1.772 (1.239–2.536)		0.817 (0.436–1.533)	
MS features		0.007		
0	1			
1	2.276 (0.841–6.160)	0.105		
2	2.766 (1.039–7.366)	0.042		
3	3.421 (1.292–9.060)	0.013		
4	4.375 (1.581–12.108)	0.004		
5	6.300 (2.094–18.956)	0.001		
	Student's t-test			
Total cholesterol		0.151		
LDL-C		0.806		
Blood uric acid		<0.001	1.003 (1.000–1.005)	0.021
Urine pH		0.300		

OR, odds ratio; CI, confidence interval; BMI, body mass index; SP, systolic pressure; DP, diastolic pressure; FBG, fasting blood glucose; MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

the number of MS features increased from two to five, the OR of CaOx stones increased from 2.766 to 6.300.

The above factors independently associated with CaOx stones (Table 2) were included in multivariate regression analysis. The results showed that four factors independently influenced the risk of CaOx stones: female sex (OR: 0.423; 95% CI: 0.245–0.733;  $P=0.002$ ), age  $\geq 66$  years (OR: 3.126; 95% CI: 1.451–6.735;  $P=0.004$ ), blood pressure (systolic pressure  $\geq 130$  mmHg and/or diastolic pressure  $\geq 85$  mmHg; OR: 1.638; 95% CI: 1.042–2.574;  $P=0.032$ ), and blood uric acid level (OR: 1.003; 95% CI: 1.000–1.005;  $P=0.021$ ) (Table 2 and Figure 1).

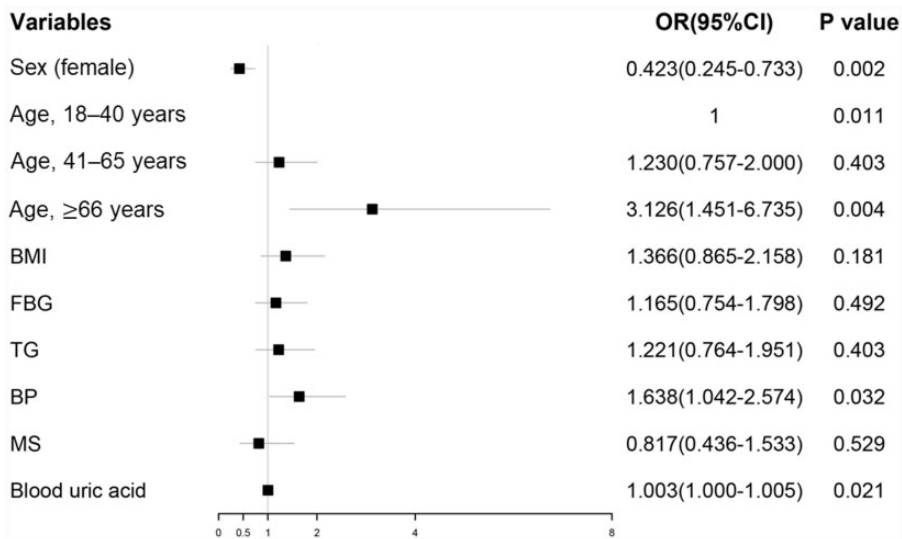
### Establishment and validation of the nomogram model

A nomogram model was successfully established (Figure 2) using the multivariate

logistic regression results; this model was intended to predict the risk of CaOx stones in patients with MS. The c-index of the nomogram was 0.701 (95% CI: 0.658–0.737), indicating that the accuracy of the nomogram for predicting CaOx stones was  $>70\%$ . Figure 3 shows the calibration curves of the predicted CaOx stone risk compared with actual incidence of CaOx stones, based on bootstrap resampling and validation data; the model demonstrated good consistency.

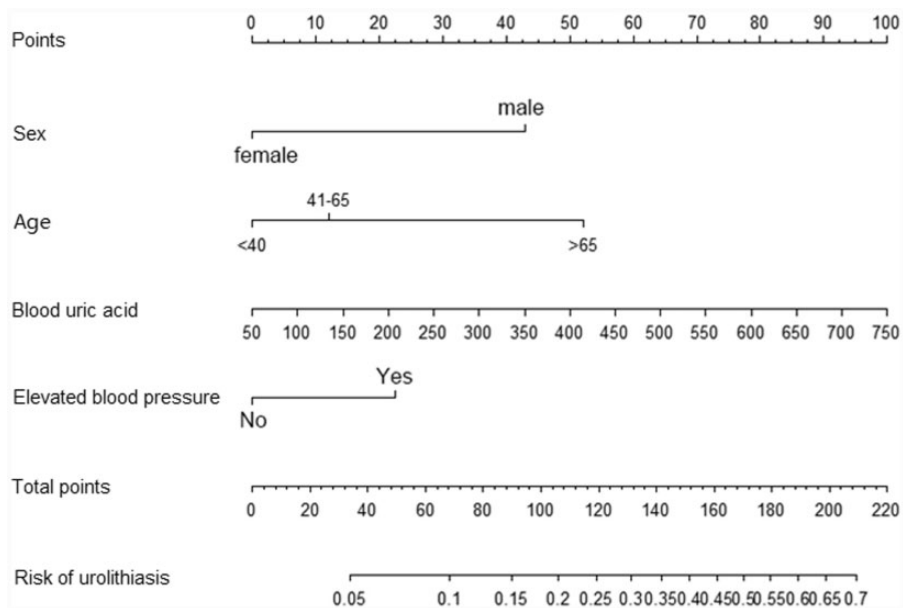
### Discussion

The onset of urolithiasis is a multifactorial result of interactions between environmental and genetic factors.<sup>17</sup> Consistent with previous results,<sup>18–20</sup> the present study showed a significantly elevated risk of CaOx stones among individuals with MS. Here, we established a nomogram containing four independent factors that influenced

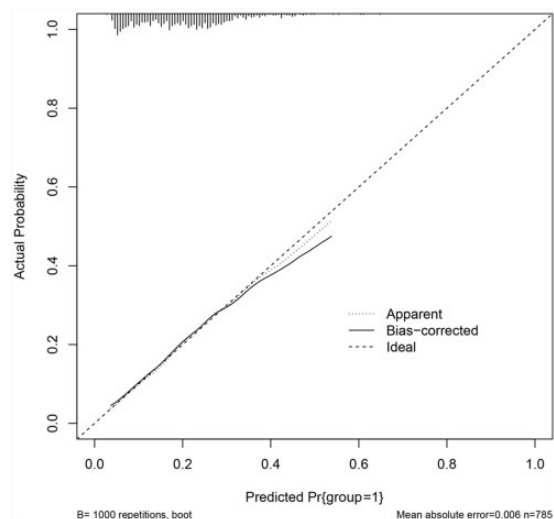


**Figure 1.** Forest plot of multivariate regression results concerning associations of metabolic syndrome features with risk of calcium oxalate stones.

OR, odds ratio; CI, confidence interval; BMI, body mass index  $\geq 25$  kg/m<sup>2</sup>; FBG, fasting blood glucose  $\geq 5.56$  mmol/L; TG, triglyceride  $\geq 1.7$  mmol/L; BP, blood pressure (systolic pressure  $< 130$  mmHg and/or diastolic pressure  $< 85$  mmHg); MS, metabolic syndrome.



**Figure 2.** Nomogram for predicting the risk of calcium oxalate stone formation in patients with metabolic syndrome. The points for all variables are added and the total points value shown on the bottom scale indicates the risk of calcium oxalate stone formation.



**Figure 3.** Calibration curves of the predicted risk of calcium oxalate stone formation compared with actual calcium oxalate stone formation, based on bootstrap resampling and validation data with good consistency.

the risk of CaOx stones. The c-index of the nomogram was 0.701 and calibration curves based on bootstrap resampling and validation data were optimal, indicating that the nomogram had a good predictive value. Our nomogram can be used to screen individuals with MS for the risk of CaOx stones by means of easily accessible metrics; it may aid clinicians in guiding those individuals toward a less “risky” lifestyle.

Previous studies have shown that the incidence of urolithiasis ranges from 2% to 19% in Western countries, with a higher incidence in men.<sup>2</sup> In China, the overall prevalence of urolithiasis is reportedly 4.0%: 4.8% in men and 3.0% in women.<sup>4</sup> In this study, we found that sex and age influenced the prevalence of CaOx stones. Previous studies have shown that men are more likely to develop urolithiasis; the prevalence in men is 1.3 to 5-fold greater than the prevalence in women.<sup>21–23</sup> Consistent with those previous findings, the risk of CaOx stones in women was 0.423-fold lower than the risk in men in our study. Therefore, we concluded that men were more likely to develop CaOx stones because of dietary and activity differences between men and women, including greater meat consumption among Chinese men.<sup>24</sup> Moreover, men are more frequently engaged in heavy physical labor, sweating, and tasks that lead to dehydration, which have been reported as risk factors for the formation of CaOx stones.<sup>25,26</sup> Hormone levels may also contribute to sex-related differences. Estrogen is a protective factor that can promote the secretion of citric acid in urine and regulate the synthesis of 1,25-dihydroxyvitamin D to prevent the formation of stones.<sup>27,28</sup> In contrast, androgen promotes the accumulation of stone-associated factors in the kidney (e.g., oxalic acid, uric acid, and calcium).<sup>29</sup> Furthermore, age is significantly associated with the prevalence of urolithiasis.<sup>4</sup> Wang et al.<sup>30</sup> showed that the prevalence of

urolithiasis in Chinese people was approximately threefold greater among those who were 60 years of age than among those who were 20 to 30 years of age. Importantly, systemic diseases that are common in older adults (e.g., diabetes, hypertension, and obesity) have been shown to enhance urolithiasis risk.<sup>31</sup> Because the sense of taste is reduced in many older adults, their intakes of sugar, sodium, and animal protein are higher than in younger people, which enhances calcium excretion and increases the risk of stone formation.<sup>32</sup> Moreover, changes in endocrine hormones and frequent urinary tract infections in older adults are associated with the risk of urolithiasis.<sup>33</sup> Notably, the peak age of urolithiasis onset differs among countries and between sexes. In China, men are more likely to develop urolithiasis at  $\geq 70$  years of age, whereas it is more likely to occur in women at  $\geq 50$  years of age.<sup>4</sup> In Japan, the peak age range in women (60–69 years) is significantly older than the peak age range in men (50–59 years).<sup>34</sup> In the current study, we found that with increasing age, the risk of CaOx stones gradually increased, especially in individuals aged  $\geq 66$  years.

In 1965, Tibblin<sup>35</sup> first described the association between blood pressure and urolithiasis. Subsequently, many cross-sectional and prospective cohort studies were performed to explore this relationship.<sup>12</sup> Kohjimoto et al.<sup>19</sup> reported that hypertension was independently associated with multiple or recurrent urolithiasis (OR: 1.14; 95% CI: 1.03–1.26). Similarly, we found that elevated blood pressure was significantly associated with the risk of CaOx stones. However, some studies have demonstrated that hypertension is not significantly associated with urinary calcium excretion, although it has been closely related to low urine pH and urinary citrate excretion. Multivariate analysis of a large cohort of stone formers by Hartman et al.<sup>36</sup> showed that urinary calcium, citrate, and calcium



oxalate levels were significantly lower in patients with hypertension than in patients without hypertension ( $P < 0.05$ ). Inflammatory responses and oxidative stress have been suggested to influence the relationship between CaOx stones and hypertension.<sup>37</sup> Some studies have shown that MS and its features are either positively or negatively correlated with uric acid stones and urine pH, respectively.<sup>38–40</sup> Cho et al.<sup>41</sup> also confirmed that urolithiasis differs between patients with MS and non-MS, primarily in terms of uric acid stones, which are more common in patients with MS. However, in our study, we found that the incidence of CaOx stones was higher among individuals with MS than among individuals without MS; moreover, the risk of CaOx stones was independently associated with blood uric acid level. To the best of our knowledge, there have been few clinical studies concerning the specific relationship between blood uric acid level and CaOx stones. Moe and Xu<sup>42</sup> proposed three physicochemical models of pathogenesis whereby urate enhances the propensity of calcium oxalate precipitation. Moreover, some prospective data analysis and retrospective trials have shown that reduction of the uric acid level leads to fewer stone events in patients with CaOx stones.<sup>42</sup>

Nevertheless, the present study had several limitations. First, the study lacked information concerning other components of stones among patients included in the study, which might have enabled us to avoid potential bias in the data and provide greater insights for clinicians. The interactions between MS and stone composition require further investigation. Second, the sample size was limited primarily by the single-center design of this study. Further prospective studies with larger cohorts of participants are needed to support our findings. Finally, because this was a retrospective study, there was a potential for selection bias and the data may not be

generalizable to other regions of China. Thus, additional data from different cities should be collected to optimize and further validate our nomogram model.

## Conclusions

In this study, female sex, age  $\geq 66$  years, elevated blood pressure, and blood uric acid level were found to independently influence CaOx stone risk. We successfully constructed a nomogram that improved the prediction of the risk of CaOx stone formation based on multivariate regression analysis. Our nomogram may provide a clinical basis for the early prediction of CaOx stone risk and aid in prevention efforts.

## Author contributions

All authors contributed equally to data collection and preparation of this paper.


## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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