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Research Article

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Analysis of Clinical Factors for Hyperoxaluria in Patients with Calcium Oxalate Stones: A Single-Center Retrospective Cross-Sectional Study

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Abstract

Background: Hyperoxaluria is associated with calcium oxalate (CaOx) stone disease and is

assessed using quantitative urinary oxalate excretion. We aimed to identify routinely available clinical factors associated with concurrent hyperoxaluria among adults with CaOx stones.

Methods: This single-center retrospective cross-sectional study included 385 adults with infrared-spectroscopy-confirmed CaOx stones who underwent stone surgery and completed at least one valid 24-hour urine collection between January 1 and December 1, 2024. Demographic, clinical, serum, urinalysis, and stone-related variables were compared between patients with and without hyperoxaluria. Univariable and multivariable binary logistic regression analyses were used as exploratory analyses of associated factors.

Results: Hyperoxaluria was present in 132 of 385 patients (34.3%). In the multivariable model, hyperlipidemia (odds ratio [OR] 1.591, 95% confidence interval [CI] 1.031–2.457; P=0.036), a positive urine nitrite test (OR 2.356, 95% CI 1.114–4.986; P=0.025), diabetes mellitus (OR 1.811, 95% CI 1.055–3.109; P=0.031), and at least two previous stone operations (OR 1.632, 95% CI 1.048–2.541; P=0.030) were associated with hyperoxaluria in the multivariable model.

Conclusions: Routinely available indicators may help prioritize patients with CaOx stones for confirmatory 24-hour urine testing and metabolic counseling. Because the findings are cross-sectional and exploratory, prospective multicenter validation is needed.

Keywords: Hyperoxaluria; Calcium oxalate stones; Associated factors; Urolithiasis

Background

Urolithiasis is a common urological disease, and population studies have documented a substantial burden of kidney stone disease in China [1,2]. Calcium oxalate (CaOx) stones are the predominant stone type, constituting 70% to 80% of all urinary calculi [3]. While

minimally invasive techniques such as percutaneous nephrolithotomy and retrograde intrarenal surgery have progressed considerably, allowing safe and efficient management of most stones [4], recurrence prevention still requires attention to the underlying metabolic profile.

Stone formation is an extremely complex physicochemical and biological cascade process, the core pathological mechanism of which is the supersaturation and precipitation of lithogenic solutes in urine[5]. The concentrations of oxalate and calcium ions in urine are key determinants of calcium oxalate stone formation, with the pro-crystallization effect of urinary oxalate being significantly greater than that of urinary calcium[6]. Consequently, hyperoxaluria is considered a major independent risk factor for the formation and recurrence of calcium oxalate stones[7-9]. Specific metabolic evaluation therefore relies on quantitative 24-hour urine testing. The EAU recommends two consecutive collections and states that oxalate excretion above 0.40 mmol/day in adults confirms hyperoxaluria [10,11]. In clinical practice, however, the application of this test is limited by the cumbersome 24-hour urine collection procedure, stringent specimen preservation requirements, and generally poor patient compliance. It is therefore not routinely performed in many primary and secondary healthcare institutions. This limitation results in many patients with hyperoxaluria being diagnosed only after experiencing recurrent, multiple stone episodes or even renal impairment, thereby missing the optimal window for early dietary modification and pharmacological intervention.

This study retrospectively analyzed cross-sectional clinical and laboratory data from patients with calcium oxalate stones to investigate associations between routinely available parameters and concurrent hyperoxaluria. This approach may facilitate early identification of patients who should be prioritized for confirmatory testing in resource-limited settings.

Methods

Ethical approval

The Ethics Committee of the First Affiliated Hospital of Guangdong Medical University approved this study (Approval No. ES-2026-K227-01), and all procedures complied with the Declaration of Helsinki. Owing to the retrospective nature and use of deidentified data without additional interventions, the committee exempted the need for written informed consent.

Study design

This single-center retrospective cross-sectional study enrolled patients diagnosed with urinary tract stones by noncontrast computed tomography who subsequently underwent surgical stone removal in our hospital's Department of Urology. This study strictly followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Additional file 1). All patients had infrared spectroscopy confirming calcium oxalate as the stone composition and completed at least one valid 24-hour urine collection meeting the prespecified quality-control standards (urine volume >600 mL, with urinary creatinine >600 mg/24 h [5.3 mmol/24 h] for females and >800 mg/24 h [7.1 mmol/24 h] for males) between January 1 and December 1, 2024. Patients with inflammatory bowel disease, chronic diarrhea, intestinal resection, long-term medications affecting oxalate metabolism, primary or secondary hyperparathyroidism, pregnancy or lactation, or incomplete clinical or laboratory records were excluded. A clean polyethylene urine container, preserved with toluene, was provided to each patient. Starting at 7:00 AM on the first day, 24-hour urine was collected continuously until 7:00 AM the following morning. The collected urine was measured and recorded (at 4°C). During the collection period, all participants maintained their usual diet and

fluid intake. Urinary oxalate was measured using ion exchange chromatography (Metrohm, Switzerland). Urinary sodium, potassium, chlorine, calcium, and creatinine were determined using the Unicel DxC 600 synchronous biochemical detection system. Urinary uric acid and magnesium were measured using the Beckman Coulter AU680 automated biochemical analyzer. Data obtained from the urinalysis included calculations of the supersaturation of relevant stone components. All 24-hour urine analyses were conducted at the First Affiliated Hospital of Guangzhou Medical University following a standardized protocol, with samples stored at 4°C and processed within 72 hours of collection. Each patient completed at least one 24-hour urine collection, and the data from the collection closest to the surgery date were included for analysis.

All eligible patients during the prespecified study period were included; therefore, no a priori sample-size calculation was performed, and the available sample comprised 385 patients. Patient selection and analytic grouping are summarized in Figure 1. Patients were classified using the prespecified laboratory cutoff as hyperoxaluria (urinary oxalate ≥40 mg/24 h) or normoxaluria (urinary oxalate <40 mg/24 h). Clinical data included age, sex, BMI, hypertension, diabetes mellitus, total number of stone-removal procedures, duration of stone disease, urinalysis, blood lipid profiles, blood biochemistry, 24-hour urine composition (creatinine, calcium, magnesium, sodium, potassium, chloride, and oxalate), and urine culture results. Hyperlipidemia was defined by at least one abnormal lipid parameter according to the 2007 Chinese guidelines for the management of dyslipidemia: total cholesterol (TC) ≥6.22 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥4.14 mmol/L, or triglyceride (TG) ≥2.26 mmol/L.

Statistical analysis

All statistical analyses and figures were performed using SPSS version 25. Continuous variables were compared using Student's t test or the Mann–Whitney U test, as appropriate, and categorical variables were compared using the chi-square test or Fisher's exact test. Variables with $P<0.05$ in univariable analyses were included in a multivariable binary logistic regression model using forward likelihood-ratio selection. This exploratory, data-driven selection strategy may produce unstable estimates and does not replace prespecification of clinically important confounders; therefore, the reported associations are interpreted as hypothesis-generating. Effect estimates are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Baseline characteristics

Using the prespecified cutoff for 24-hour urinary oxalate excretion (≥40 mg/24 h), 132 of 385 patients (34.3%) were classified into the hyperoxaluria group, and the remaining 253 patients were classified into the normoxaluria group.

Table 1 summarizes baseline demographics and clinical features for the two groups. The age distribution was similar between the hyperoxaluria and normoxaluria groups (mean age: 54.7 ± 11.4 years vs. 54.9 ± 11.9 years, independent t test, P=0.865). Although male patients outnumbered female patients in both groups, the sex composition was not significantly different (male proportion: 67.4% vs. 59.7%, chi-square test, P=0.137).

Significant between-group differences were observed for several metabolic and medical-history variables. Hyperlipidemia was present in more than half of the patients in the

hyperoxaluria group (56.1%), whereas it was present in 44.3% of those in the control group (P=0.028). This metabolic pattern was further reflected in the prevalence of diabetes mellitus, which was greater in the hyperoxaluria group (24.2%) than in the control group (15.0%, P=0.026). The proportion of positive urinary nitrite tests, suggestive of gram-negative bacterial activity, was also significantly greater in the hyperoxaluria group (12.9%) than in the normoxaluria group (5.9%, P=0.019). With respect to disease history, patients with hyperoxaluria presented features of more recurrent and refractory stone disease. A greater proportion of patients had been diagnosed with urolithiasis more than 10 years prior (23.5% vs. 14.2%, P=0.023), and a history of ≥2 previous surgical interventions was more common (44.7% vs. 31.6%, P=0.011).

For stone imaging and physical parameters, no significant intergroup differences were found in the median CT stone density (1100 HU vs. 1150 HU, P=0.099), the proportion of multiple or staghorn calculi (84.8% vs. 84.2%, P=0.866), the intrastone composition ratio of calcium oxalate monohydrate to dihydrate (P=0.268), or the final surgical modality chosen (URL, RIRS, PCNL, and their combinations, P=0.995). These findings indicate that hyperoxaluria, as a biochemical metabolic abnormality, is associated with stone formation and recurrence but does not significantly alter the CT density or the compositional ratio of the resulting calcium oxalate stones.

Figure 1. Patient selection flowchart.

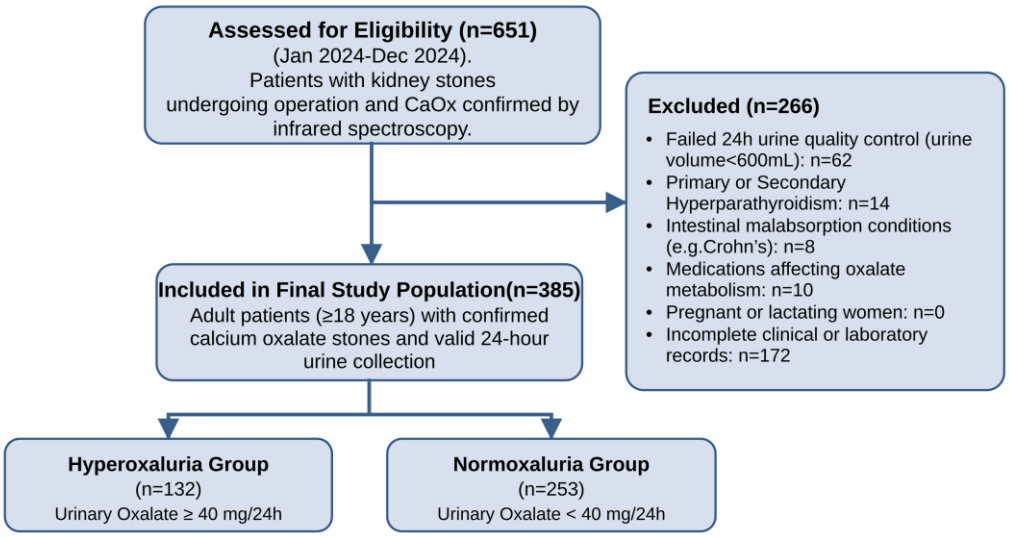


Table 1. Patient characteristics at baseline.

Variables	Hyperoxaluria group n=132	Normoxaluria group n=253	p value
Age (yr)	54.7 ± 11.4	54.9 ± 11.9	0.865
Gender, n (%)			0.137
Male	89 (67.4)	151 (59.7)	
Female	43 (32.6)	102 (40.3)	
BMI (kg/m2)			0.204
<20	8 (6.1)	18 (7.1)	
≥20 to <25	63 (47.7)	146 (57.7)	
≥25 to <30	50 (37.9)	75 (29.6)	
≥30	11 (8.3)	14 (5.5)	

Variables	Hyperoxaluria group n=132	Normoxaluria group n=253	p value
Hypertension, n (%)	50 (37.9)	88 (34.8)	0.548
Diabetes, n (%)	32 (24.2)	38 (15.0)	0.026*
Preoperative ureteral stenting, n (%)	11 (8.3)	12 (4.7)	0.158
Elevated serum creatinine(>73 μmol/L),n (%)	78 (59.1)	148 (58.5)	0.911
Elevated urea nitrogen (>7.5 mmol/L), n (%)	17 (12.8)	34 (13.4)	0.878
Hyperlipidemia, n (%)	74 (56.1)	112 (44.3)	0.028*
Hypercalcemia (>2.58 mmol/L), n (%)	12 (9.1)	13 (5.1)	0.135
Urine pH	6.0 (6.0,6.5)	6.0 (5.5,6.5)	0.062
Positive urine culture, n (%)	27 (20.5)	41 (16.2)	0.299
Positive urine protein, n (%)	48 (36.4)	89 (35.2)	0.818
Positive nitrite test, n (%)	17 (12.9)	15 (5.9)	0.019*
Stone composition, n(%)			0.268
Pure whewellite	31 (23.5)	49 (19.4)	
Whewellite predominantly	69 (52.3)	154 (60.9)	
Weddellite predominantly	32 (24.2)	50 (19.8)	
Operative time (min)	80.0 (49.0,120.0)	70.0 (53.0,102.0)	0.616
NCCT value of stone (HU)	1100.0 (900.0,1200.0)	1150 (1000.0,1300)	0.099
Surgical modality, n (%)			0.995
URL	13 (9.8)	24(9.5)	
RIRS	61 (46.2)	117 (46.2)	
PCNL	50 (37.9)	95 (37.5)	
Combination	8 (6.1)	17 (6.7)	
Laterality, n (%)			0.335
Unilateral	71 (53.8)	123 (48.6)	
Bilateral	61 (46.2)	130 (51.4)	
Stone type, n (%)			0.866
Single	20 (15.2)	40 (15.8)	
Multiple or staghorn	112 (84.8)	213 (84.2)	
History of calculi >10 years, n (%)	31 (23.5)	36 (14.2)	0.023*
Number of operations, n (%)			0.011*
≥2	59 (44.7)	80 (31.6)	
<2	73 (55.3)	173 (68.4)	

1 Data are presented as the mean ± SD (age), median (Q1, Q3), or n (%) as appropriate.

2 BMI, body mass index; URL, ureteroscopic lithotripsy; RIRS, retrograde intrarenal surgery;

3 PCNL, percutaneous nephrolithotomy; HU, Hounsfield units; whewellite, calcium oxalate

monohydrate; weddellite, calcium oxalate dihydrate.

Identification of factors associated with hyperoxaluria

Univariable binary logistic regression identified five variables with P<0.05: a positive urine nitrite test, stone disease duration >10 years, diabetes mellitus, hyperlipidemia, and at least two previous stone operations. All results of univariable and multivariable analyses are presented in Table 2. The final model reported associations for a positive urine nitrite test (OR 2.356, 95% CI 1.114–4.986; P=0.025), hyperlipidemia (OR 1.591, 95% CI 1.031–2.457; P=0.036), diabetes mellitus (OR 1.811, 95% CI 1.055–3.109; P=0.031), and at least two previous operations (OR 1.632, 95% CI 1.048–2.541; P=0.030). The forest plot was estabilshed and presented in Figure 2. To assess multicollinearity among final variables, we calculated variance inflation factor (VIF) and tolerance statistics; all tolerance values exceeded 0.1 (range 0.727–0.992), and all VIF values were well below 5 (range 1.008–1.375), confirming no significant multicollinearity.

Table 2. Univariable and multivariable analyses of factors associated with hyperoxaluria.

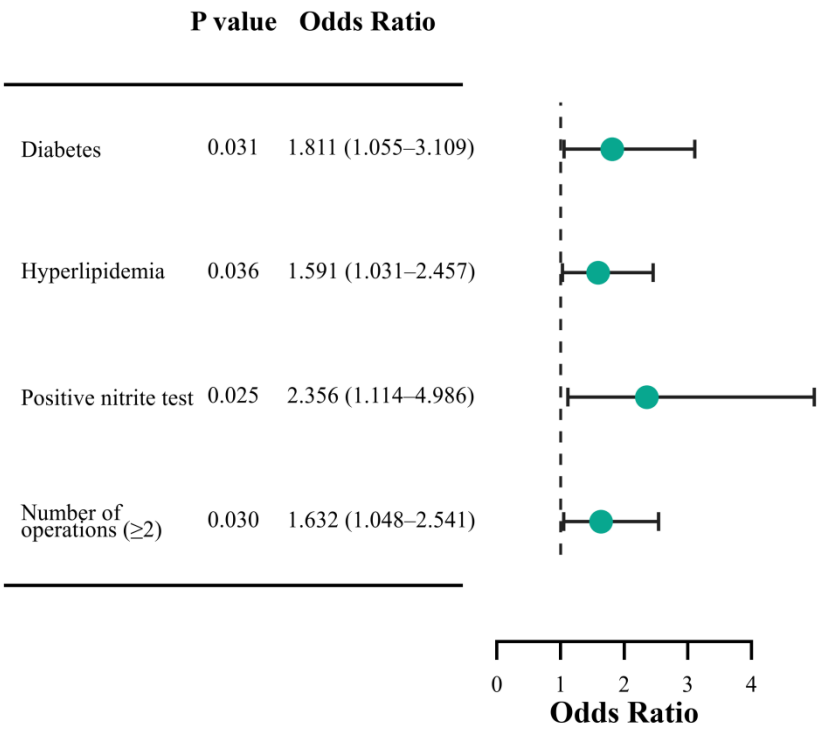
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	0.998(0.981~1.017)	0.865		
Gender (ref: female)	1.398(0.898~2.176)	0.137		
BMI (kg/m2) (ref: <20)				
≥20 to <25	0.971(0.401~2.349)	0.948		
≥25 to <30	1.500(0.606~3.713)	0.381		
≥30	1.768(0.561~5.570)	0.331		

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Hypertension (ref: no)	1.143(0.739~1.769)	0.548		
Diabetes (ref: no)	1.811(1.069~3.066)	0.027*	1.811(1.055~3.109)	0.031*
Preoperative ureteral stenting (ref: no)	1.826(0.783~4.258)	0.164		
Elevated serum creatinine(>73 μmol/L) (ref: normal)	1.025(0.668~1.572)	0.911		
Elevated urea nitrogen (>7.5 mmol/L) (ref: normal)	0.952(0.510~1.778)	0.878		
Hyperlipidemia (ref: normal)	1.606(1.051~2.454)	0.028*	1.591(1.031~2.457)	0.036*
Hypercalcemia (>2.58 mmol/L), n(ref: normal)	1.846(0.817~4.169)	0.140		
Urine pH	0.766(0.466~1.259)	0.293		
Positive urine culture(ref: negative)	1.330(0.775~2.280)	0.300		
Positive urine protein(ref: negative)	1.053(0.679~1.633)	0.818		
Positive nitrite test(ref: negative)	2.346(1.131~4.863)	0.022*	2.356(1.114~4.986)	0.025*
Stone composition(ref: Pure whewellite)				
Whewellite predominantly	0.708(0.416~1.206)	0.204		
Weddellite predominantly	1.012(0.538~1.903)	0.971		
Operative time (min)	0.997(0.992~1.001)	0.173		
NCCT value of stone (HU)	1.001(1.000~1.001)	0.174		
Surgical modality(ref: URL)				
RIRS	0.963(0.458~2.023)	0.920		
PCNL	0.972(0.456~2.071)	0.941		
Combination	0.869(0.296~2.553)	0.798		
Laterality(ref: Unilateral)	0.813(0.533~1.239)	0.336		
Stone type(ref: single)				
Multiple or staghorn	1.052(0.587~1.885)	0.866		
History of calculi (ref: ≤10 years)	1.850(1.083~3.159)	0.024*		
Number of operations (ref: <2)	1.748(1.133~2.696)	0.012*	1.632(1.048~2.541)	0.030*

Data are presented as the OR(95% CI)

BMI, body mass index; URL, ureteroscopic lithotripsy; RIRS, retrograde intrarenal surgery; PCNL, percutaneous nephrolithotomy; HU, Hounsfield units; whewellite, calcium oxalate monohydrate; weddellite, calcium oxalate dihydrate.

Figure 2. Forest plot of clinical factors associated with hyperoxaluria in patients with calcium oxalate stones.



Discussion

In recent years, the clinical management of urolithiasis has shifted from a narrow focus on achieving high stone-free rates during surgery toward a chronic disease model that emphasizes secondary prevention and recurrence reduction[12, 13]. By conducting a rigorous medical record review and dual binary logistic regression analysis on a single-center cohort of calcium

oxalate stone patients, this study identified hyperlipidemia, a positive urine nitrite test, diabetes mellitus, and at least two previous stone operations were associated with concurrent hyperoxaluria.

A history of at least two stone operations was associated with concurrent hyperoxaluria (OR=1.632). Given that recurrent stone episodes necessitate more frequent clinical interventions, this finding further confirms that the risk of stone recurrence is substantially greater in patients with hyperoxaluria than in those with normal urinary oxalate levels [2].

According to the intestinal free oxalate theory, Hyperlipidemia was associated with concurrent hyperoxaluria (OR=1.591). Under normal physiological conditions, dietary calcium salts bind with oxalate ions in the intestinal lumen to form insoluble calcium oxalate complexes, which are excreted in feces, thereby limiting intestinal oxalate absorption[14-16]. In patients with hyperlipidemia, free fatty acids that are not fully emulsified by bile acids or hydrolyzed by pancreatic lipase preferentially bind with calcium to form insoluble calcium soap[17]. This process increases the concentration of free oxalate within the intestinal lumen. Following intestinal absorption, oxalate enters the portal circulation and is ultimately excreted by the kidneys, inducing the characteristic state of enteric hyperoxaluria. A positive urine nitrite test was also associated with concurrent hyperoxaluria (OR=2.356), which typically indicates a urinary tract infection (UTI) caused by nitrate-reducing gram-negative bacteria such as Escherichia coli [18]. Microbiome studies have demonstrated that patients with recurrent UTIs are frequently exposed to broad-spectrum antibiotics, which can severely disrupt the ecology of the gut–kidney axis [19, 20]. This disruption particularly affects Oxalobacter formigenes, an obligate anaerobic gut bacterium that utilizes oxalate as its sole carbon and energy source. O.

formigenes degrades free intestinal oxalate into carbon dioxide and formate via an efficient enzymatic network containing formyl-CoA transferase (frc) and oxalyl-CoA decarboxylase (oxc), thereby limiting the amount of oxalate available for mucosal absorption [21-23]. However, this bacterial strain is highly fragile and highly sensitive to antibiotics. Antibiotic misuse reduces the colonization abundance of O. formigenes, thereby diminishing intestinal oxalate degradation. Consequently, enteric oxalate absorption increases, promoting hyperoxaluria. Because antibiotic exposure, the gut microbiota composition, and O. formigenes abundance were not measured in this study, this pathway should be regarded as a literature-derived, hypothesis-generating explanation rather than a demonstrated mechanism.

Diabetes mellitus was associated with concurrent hyperoxaluria (OR=1.811). While insulin resistance impairs proximal tubular ammonia genesis to promote urinary acidification and mixed urate-calcium oxalate stone formation[24], recent metabolomic studies revealed a distinct molecular pathway driven by diabetes that results in excessive endogenous oxalate synthesis. The hyperglycemia, lipid peroxidation, and advanced glycation end product (AGE) generation associated with diabetes inevitably results in the production of substantial amounts of highly reactive α-dicarbonyl compounds, most notably glyoxal[25]. Under normal physiological conditions, the intracellular glyoxalase system rapidly converts glyoxal into nontoxic glycolic acid via the use of reduced glutathione (GSH) as a cofactor[26]. In diabetic patients, however, prolonged and severe oxidative stress substantially depletes intracellular GSH, leading to decompensation of the glyoxalase system. The resulting accumulation of undetoxified glyoxal results in aldehyde dehydrogenase (ALDH)-catalyzed oxidation to form glyoxylate, the direct precursor for oxalate synthesis[27, 28]. Lactate dehydrogenase (LDH)

subsequently catalyzes the irreversible oxidation of glyoxylate to oxalate[29]. Serum glyoxal, glyoxylate, glutathione, and related enzyme activities were not measured; therefore, this proposed pathway is also a literature-derived mechanistic hypothesis that requires direct validation.

Several limitations must be acknowledged. The retrospective, single-center, cross-sectional design allows identification of associations but not temporal or causal inference and is susceptible to selection bias. Complete case exclusion may have introduced additional bias, and the stepwise, univariate screening strategy may have omitted clinically relevant covariates. Dietary oxalate intake, antibiotic exposure, the gut microbiota, glyoxal pathway metabolites, and repeated 24-hour urine measurements were not available. Prospective multicenter studies with prespecified models, repeated metabolic assessments, and external validation are needed.

Conclusions

In this single-center retrospective cross-sectional study, hyperlipidemia, a positive urine nitrite test, diabetes mellitus, and at least two previous stone operations were associated with concurrent hyperoxaluria. These routinely available indicators may help prioritize patients for confirmatory 24-hour urine testing, but they should not be used alone to infer causality or direct treatment. Prospective multicenter validation is needed before clinical prediction or intervention strategies are based on these findings.

List of abbreviations

BMI = body mass index

CaOx = calcium oxalate

CI = confidence interval

HU = Hounsfield units

NCCT = noncontrast computed tomography

OR = odds ratio

PCNL = percutaneous nephrolithotomy

RIRS = retrograde intrarenal surgery

SD = standard deviation

URL = ureteroscopic lithotripsy

VIF = variance inflation factor

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Approval No. ES-2026-K227-01) and carried out in compliance with the Declaration of Helsinki. As the study retrospectively analyzed deidentified clinical data and entailed no additional intervention, the Ethics Committee waived the need for written informed consent.

Clinical trial number

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

The deidentified datasets generated and/or analyzed in the current study can be obtained from the corresponding author upon reasonable request, subject to institutional approval and compliance with applicable privacy requirements.

Competing interests

The authors state that they have no competing interests.

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Authors' contributions

YDL supervised the project and contributed to study conception. YPH and LLO contributed equally as co-first authors. YPH, LLO, JHZ, and JPL collected and managed the data. YPH performed the data analysis.YPH, FL, and YL wrote the manuscript. All authors critically reviewed the manuscript, approved its final version, and agreed to be accountable for the work.

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