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# Does the Urinary Calcium/Citrate Ratio Add to the Diagnostic Workup of Children at Risk of Kidney Stones? A Cross-Sectional Study

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## Abstract

The purpose of the study was to evaluate urinary citrate/creatinine ( $U_{Ci}/U_{Cr}$ ) and urinary calcium/citrate ( $U_{Ca}/U_{Ci}$ ) ratios for distinguishing stone formers (SF) from non-stone formers (NSF) in an at-risk population. This was a retrospective study that included all pediatric patients who underwent urinary citrate testing from April 2017 to March 2018. The urinary levels of citrate, calcium, sodium, potassium, creatinine, oxalate, urate, pH, and specific gravity (SG) were measured in our clinical laboratory. Diagnosis of kidney stones was obtained through chart review.

A total of 97 patients were included (46 NSF and 51 SF). The  $U_{Ci}/U_{Cr}$  ratio was not significantly different between NSF and SF. Median  $U_{Ca}/U_{Cr}$  ratio was higher in SF (0.67) compared with NSF (0.21,  $p < 0.0001$ ). The median ratio of  $U_{Ca}/U_{Ci}$  was also higher in SF (1.30) than in NSF (0.65,  $p = 0.001$ ). Oxalate, urate, pH, SG, and urinary sodium/potassium ratio did not differentiate between the SF and NSF. Positive correlation was seen between  $U_{Ca}/U_{Cr}$  and urinary sodium/creatinine  $U_{Na}/U_{Cr}$  ( $p < 0.0001$ ), as well as between  $U_{Ca}/U_{Cr}$  and  $U_{Ci}/U_{Cr}$  ( $p < 0.0001$ ).

The study has demonstrated significantly higher  $U_{Ca}/U_{Ci}$  and  $U_{Ca}/U_{Cr}$  in SF compared with NSF, while the use of urinary oxalate, urate, pH, and SG did not differentiate between SF from NSF. We also confirmed a positive correlation between  $U_{Na}/U_{Cr}$  and  $U_{Ca}/U_{Cr}$ . While the utility of  $U_{Ca}/U_{Cr}$  is well established, our data suggest that  $U_{Ca}/U_{Ci}$  rather than  $U_{Ci}/U_{Cr}$  may be more predictive in the clinical setting when evaluating for nephrolithiasis.

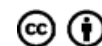
## Keywords

- ▶ urinary calcium
- ▶ urinary citrate
- ▶ urinary creatinine
- ▶ urinary oxalate
- ▶ urolithiasis

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## Introduction

The prevalence of urolithiasis is increasing around the world, especially among children.<sup>1</sup> Citrate can inhibit stone formation by forming a chelate complex with calcium in the urine, thereby inhibiting spontaneous nucleation and preventing the growth of crystals.<sup>2</sup> Hypocitraturia is a well-recognized risk factor for the development of kidney stones,<sup>2</sup> and it is identified as a metabolic abnormality in 20 to 60% of adult stone formers (SF).<sup>2,3</sup> In children, the demographics of nephrolithiasis have been changing<sup>1</sup> and hypocitraturia has now emerged as the most prevalent reason for nephrolithiasis in children.<sup>4,5</sup> Contributing to the development of hypocitraturia are distal renal tubular acidosis, hypokalemia, bowel dysfunction, and a high-protein and low-alkali diet.<sup>2</sup>

The gold standard for the diagnosis of hypocitraturia is a 24-hour urine collection and it is defined as urinary citrate excretion < 320 mg (1.67 mmol) per 24 hours for adults.<sup>6</sup> In children, 24-hour urine collections are notoriously unreliable.<sup>7</sup> Although age-dependent reference intervals for urinary citrate to creatinine ratios ( $U_{Ci}/U_{Cr}$ ) have been established,<sup>8</sup> our own experience of the diagnostic yield of hypocitraturia to differentiate SF from non-SF (NSF) has been low. Höbarth and Hofbauer also suggested a limited value for  $U_{Ci}/U_{Cr}$ .<sup>9</sup>

Recent studies have suggested that urinary calcium to citrate ratio ( $U_{Ca}/U_{Ci}$ ) would be a superior marker to identify those at risk of urolithiasis.<sup>10–13</sup> Sikora et al.<sup>14</sup> compared the yield of  $U_{Ca}/U_{Ci}$  as compared with hypercalciuria and hypocitraturia for the identification of SF in children and found  $U_{Ci}/U_{Cr}$  to be superior; however, no precise cutoffs were determined. As the topic is understudied, we performed a retrospective study to evaluate the utility of  $U_{Ca}/U_{Ci}$  to identify stone formation in a pediatric population. We also wanted to determine the diagnostic cutoff values including state-of-the-art Youden's index calculation for  $U_{Ci}/U_{Cr}$ , to determine the best reporting of risk factors for children with nephrolithiasis. We hypothesized that the  $U_{Ca}/U_{Ci}$  in a spot urine would differentiate between SF and NSF patients.

## Materials and Methods

### Study Design

This retrospective cohort study adhered to the Declaration of Helsinki and was approved without the need to obtain written informed consents by the Research Ethics Board of the University of Western Ontario (REB no.109434). The study was conducted at the Children's Hospital of London Health Sciences Centre (LHSC); a teaching hospital for the University of Western Ontario.

The LHSC is a tertiary referral center with a catchment area of 629,000 children and youths in Southern and North-western Ontario in Canada. The population is predominantly Caucasian, with a 15% Middle Eastern minority, < 5% indigenous population, and a very small African-American population. All patients from the pediatric nephrology clinic who had at least one urinary citrate ordered from April 2017 to March 2018 were eligible for the study. Patients were classified as either having confirmed nephro- or urolithiasis (SF) or

not (NSF) based on the presence of urolithiasis on ultrasound or other imaging modalities (computed tomography and X-ray studies); and stone analysis for those who spontaneously passed stones prior to imaging. If more than one measurement was available per patient, we only used the earliest measurement within the study period to reduce the impact of any intervention such as changes in lifestyle.

### Experimental Methods

Patients were identified through the Laboratory Information System at LHSC. The spot urinary levels of citrate, calcium, sodium, potassium, creatinine, oxalate, urate, pH, specific gravity, diagnoses of stone formation, and ultrasound findings were obtained through review of physical charts and electronic medical records. Methods for the urinary biomarkers have been previously published.<sup>15</sup> Values were reported in standard international units. Urinary citrate was measured enzymatically using a BEN-Biochemical Enterprise (Milano, Italy) diagnostic kit.

### Statistical Methods

Data analysis was performed using GraphPad Prism 5 for Mac OS X (GraphPad Inc., San Diego, California, United States, version 5.0f). Normal distribution was tested using the D'Agostino & Pearson omnibus normality test. Normally distributed parameters were analyzed using parametric tools; otherwise, nonparametric tools were used to report median, and 25th and 75th percentiles. For correlation analysis, we used the Pearson correlation coefficient. The diagnostic performance of all urinary parameters and urinary ratios was assessed using receiver-operated-characteristics (ROC) plots. To compare ROC curves, we used the method proposed by Hanley.<sup>16</sup> Youden's index was used to calculate the optimal cutoff value for the identification of stone formation ( $U_{Ca}/U_{Ci}$ ).<sup>17</sup> No adjustments were made for the missing values. The missing data values were predominantly  $U_{Na}$ ,  $U_{K}$ , and  $U_{Oxalate}$ .

### Theory/Calculation

Youden's statistic, Gini index, chi-square statistic, relative risk, and kappa statistic all theoretically recover a true threshold.<sup>18</sup> While chi-square statistic and Gini index may have the smallest bias, Youden's statistics are deemed best when the probability is larger.<sup>18</sup> Therefore, Youden's index was used in this study.

## Results

A total of 97 patients were reviewed with 46 NSF and 51 SF patients. Patient characteristics are provided in ► **Table 1**. The indications for spot urine testing in our study population were as follows: all patients in the SF group had nephrolithiasis, 11 (25%) of the NSF group had microscopic hematuria, 8 (17%) had glomerulonephritis, 7(15%) had a tubulopathy, 7(15%) had congenital anomalies of the kidneys and urinary tract (CAKUT), 5(11%) had urinary tract infections, 2(4%) had metabolic syndrome, and 6(13%) had miscellaneous diagnoses (dysfunctional voiding, primary enuresis, cystic fibrosis, neuroblastoma, chromium intoxication, and failure to thrive). The reasons for

**Table 1** Patients' characteristics and comparison of parameters

Group	SF	NSF	Comparison	Test
Number of patients	51	46		
Age (y) (median, IQR)	8 (3,15)	10 (6.8, 15)	0.1755	Mann–Whitney <i>U</i> test
Female (%)	19 (37.3%)	22 (47.8%)	0.3074	Fisher's exact test
Urinary citrate (mmol/L) (median, IQR)	1.55 (0.95, 2.32)	1.675 (0.79, 3.13)	0.7743	Mann–Whitney <i>U</i> test
Urinary calcium (mmol/L) (median, IQR)	1.87 (1.21, 4.29)	1.0 (0.26, 2.3)	0.0021	Mann–Whitney <i>U</i> test
Urinary sodium (mmol/L) (median, IQR)	77 (30, 121)	107 (48, 154)	0.0963	Mann–Whitney <i>U</i> test
Urinary potassium (mmol/L), (median, IQWR)	42 (28, 101)	48 (19, 80)	0.9895	Mann–Whitney <i>U</i> test
Urinary creatinine ( $\mu$ mol/L), (median, IQR)	3.4 (1.5, 6.8)	4.6 (1.9, 9.0)	0.3878	Mann–Whitney <i>U</i> test
Urinary oxalate ( $\mu$ mol/L), (median, IQR)	189 (111, 291)	134 (38, 290)	0.1438	Mann–Whitney <i>U</i> test
Urinary urate ( $\mu$ mol/L), (median, IQR)	1.9 (1, 5.7)	2.3 (1, 12)	0.2544	Mann–Whitney <i>U</i> test
Urinary pH (mean $\pm$ SD)	6.6 $\pm$ 0.91	6.5 $\pm$ 0.98	0.7366	Student's <i>t</i> -test
Urinary-specific gravity (median and IQR)	1.010 (1.005, 1.020)	1.015 (1.005, 1.020)	0.1842	Mann–Whitney <i>U</i> test
Urinary citrate/creatinine (mmol/mmol) (median, IQR)	0.48 (0.21, 0.90)	0.38 (0.21, 0.86)	0.8784	Mann–Whitney <i>U</i> test
Urinary calcium/creatinine (mmol/mmol) (median, IQR)	0.67 (0.31, 1.37)	0.24 (0.11, 0.73)	0.0029	Mann–Whitney <i>U</i> test
Urinary calcium/citrate (mmol/mmol) (median, IQR)	1.30 (0.73, 2.78)	0.68 (0.29, 1.83)	0.0114	Mann–Whitney <i>U</i> test
Urinary sodium/potassium (mmol/mmol) (mean $\pm$ SD)	2.08 $\pm$ 1.92	2.50 $\pm$ 1.36	0.3185	Student's <i>t</i> -test

Abbreviations: IQR, interquartile range; NSF, non-stone former; SD, standard deviation.

Glossary for Table 1: IQR (25th and 75th percentiles).

Note: Statistically significant differences were bolded. The comparison column represents the *p*-value, and in the test column, the test that was used is listed (based on the distribution and data type).

ordering urinary citrate in the 35 patients who did not have microscopic hematuria were not stated. SF did not differ from NSF regarding age, gender, urinary citrate, urinary sodium, urinary potassium, urinary creatinine, urinary oxalate, urinary urate, urinary pH, urinary specific gravity,  $U_{Ci}/U_{Cr}$ , and urinary sodium/potassium ratio ( $U_{Na}/U_{Pa}$ ) (**Table 1**). Statistically significant differences only existed for the  $U_{Ca}/U_{Cr}$ , urinary  $U_{Ca}/U_{Ci}$ , and urinary calcium concentration.

In our population, a diagnosis of hypocitraturia was not predictive of stone formation (4 of the NSF vs. 7 of the SF had hypocitraturia,  $p = 0.5283$ ). We then examined correlations previously tested in the literature. There was a statistically significant positive correlation between the  $U_{Ca}/U_{Cr}$  and urinary sodium/creatinine ratio ( $U_{Na}/U_{Cr}$ ) (Pearson  $r^2 = 0.5099$ ,  $p < 0.0001$ ). In contrast to the expected negative correlation between the  $U_{Ca}/U_{Cr}$  and the urinary potassium/creatinine ratio ( $U_{Pa}/U_{Ci}$ ), a weak positive correlation (Pearson  $r^2 = 0.126$ ,  $p = 0.0036$ ) was demonstrated.  $U_{Ca}/U_{Cr}$  also correlated positively but weakly with  $U_{Ci}/U_{Cr}$  (Pearson  $r^2 = 0.1180$ ,  $p = 0.0007$ ). In addition,  $U_{Ca}/U_{Cr}$  correlated positively with  $U_{Ca}/U_{Ci}$  (Pearson  $r^2 = 0.5511$ ,  $p < 0.0001$ ).

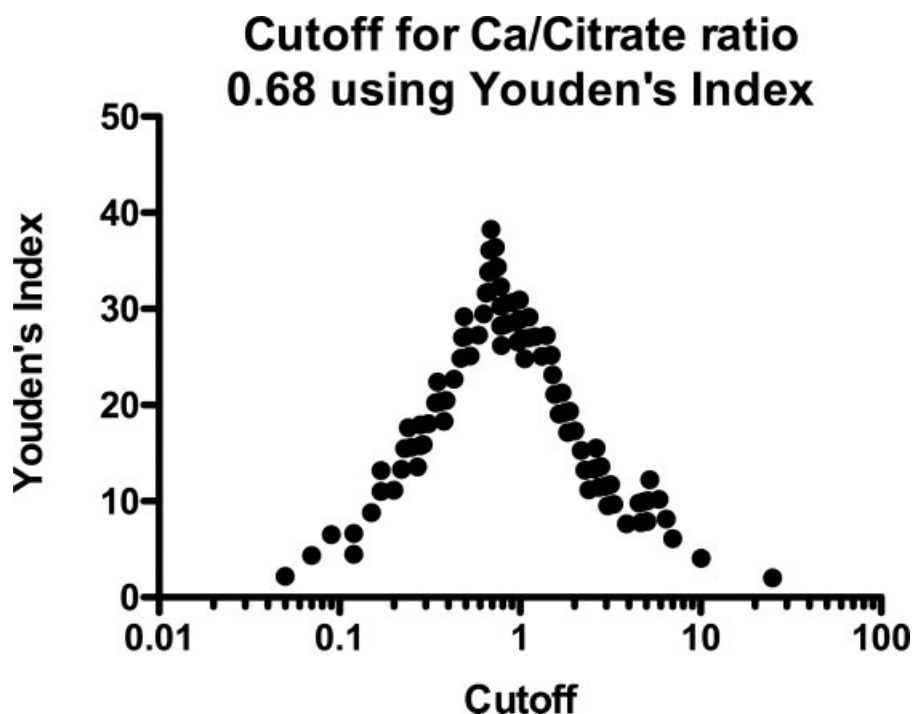
Furthermore, we determined the ROC area of the SF versus NSF group. Useful discrimination between SF and NSF existed for  $U_{Ca}/U_{Cr}$  (ROC area  $0.7361 \pm 0.05109$  with a 95% confidence interval between 0.636 and 0.836,  $p < 0.0001$ ) and for  $U_{Ca}/U_{Ci}$  (ROC area  $0.6965 \pm 0.05418$  with a 95% confidence interval

between 0.590 and 0.803,  $p = 0.00098$ ). The ROC areas for  $U_{Ca}/U_{Cr}$  and  $U_{Ca}/U_{Ci}$  did not differ ( $p = 0.5029$ ). The  $U_{Ci}/U_{Cr}$  ROC area was  $0.5603 \pm 0.05942$ , with a 95% confidence interval between 0.444 and 0.677,  $p = 0.3112$ .

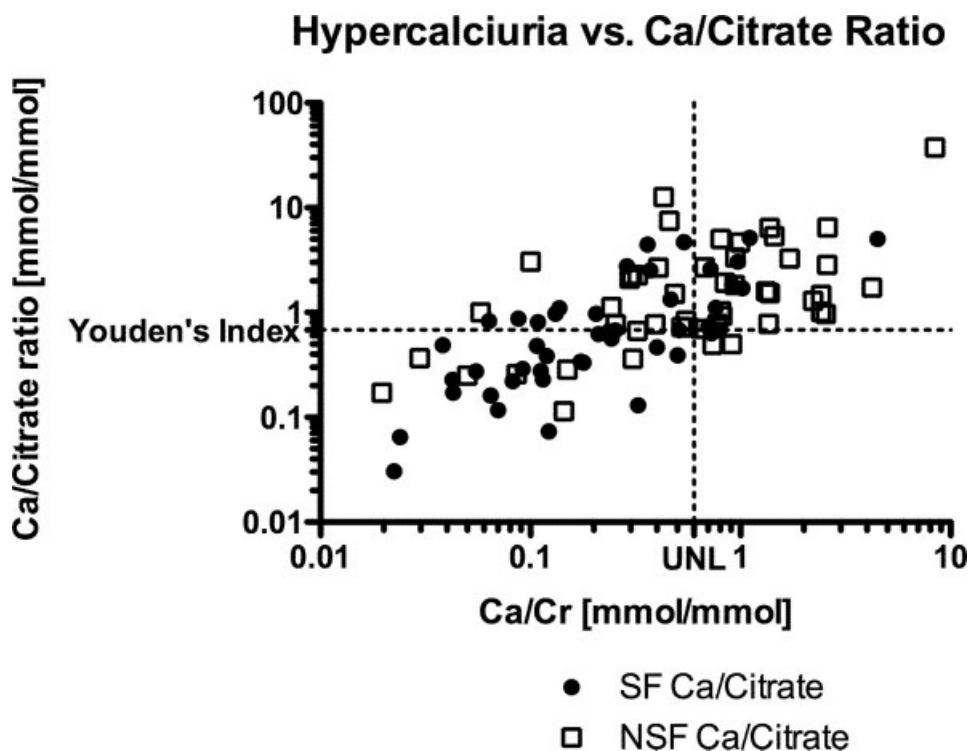
Youden's Index derived from the ROC curves showed that a  $U_{Ca}/U_{Ci}$  ratio  $>0.68$  mmol/mmol was associated with stone formation (**Fig. 1**). When differentiating SF and NSF, 10 (20%) SF patients had an  $U_{Ca}/U_{Ci}$  ratio  $< 0.68$  compared with 27 (58%) NSF, while 39 (80%) SF had  $U_{Ca}/U_{Ci}$  ratio  $> 0.68$  as compared with 19 (42%) NSF patients ( $p < 0.001$ ). The diagnostic sensitivity at this cutoff was 80% and the specificity was 59%. When repeating this analysis for  $U_{Ca}/U_{Cr}$ , 24 (47%) SF patients had an  $U_{Ca}/U_{Cr}$  ratio  $< 0.60$  as compared with 36 (78%) NSF, while 27 (53%) SF had  $U_{Ca}/U_{Cr}$  ratio  $> 0.60$  as compared with 10 (22%) NSF patients ( $p = 0.0018$ ). The patients were not the same. Only 10 patients had both hypercalciuria and unfavorably high  $U_{Ca}/U_{Cr}$  (**Fig. 2**). As can be seen from **Fig. 2**, only 10 patients had both an elevated  $U_{Ca}/U_{Ci}$  and  $U_{Ca}/U_{Cr}$ . Both ratios differentiate between NSF and SF, with  $U_{Ca}/U_{Ci}$  actually providing a stronger discrimination, however, the two ratios identified different populations.

## Discussion

The role of the pediatric nephrologist is to identify and diagnose modifiable causes of nephro- or urolithiasis. While



**Fig. 1** Cutoff for urinary calcium/citrate ( $U_{Ca}/U_{Ci}$ ) using Youden's index derived from the  $U_{Ca}/U_{Ci}$  ROC curve. ROC, receiver operated characteristics.



**Fig. 2** Comparison of patients' urinary calcium/citrate ( $U_{Ca}/U_{Ci}$ ) and calcium/creatinine ( $U_{Ca}/U_{Cr}$ ). Stone formers are marked in black circles, whereas non-stone formers are marked in open squares. As can be seen only 10 patients had both an elevated  $U_{Ca}/U_{Ci}$  and  $U_{Ca}/U_{Cr}$ . Both ratios differentiate between NSF and SF, but they identify differing populations. NSF, non-stone formers; SF, stone formers.

many factors contribute to nephro- or urolithiasis, the current recommended approach is the use of  $U_{Ca}/U_{Cr}$  and  $U_{Ci}/U_{Cr}$  for distinguishing SF from NSF. In this study, we found a low diagnostic yield for  $U_{Ci}/U_{Cr}$ , similar to Höbarth and Hofbauer.<sup>9</sup> This low yield could be associated with the

complexities of lithogenesis. The identification of a single metabolic factor may provide insufficient information for diagnosis, therapeutic, and preventive measures.<sup>14</sup> In contrast,  $U_{Ca}/U_{Cr}$  and  $U_{Ca}/U_{Ci}$  had a reasonable diagnostic performance as shown in the ROC areas. However, both ratios

identified different patient cohorts, and only 10 of the SF had both elevated  $U_{Ca}/U_{Cr}$  and  $U_{Ca}/U_{Ci}$ .

The present study suggests that elevated  $U_{Ca}/U_{Ci}$  is an independent risk factor for stone formation, rather than hypocitraturia. In other words, what promotes stone formation may not be the absolute citrate deficiency, but rather insufficient citrate for a given calcium concentration. Parks and Coe<sup>19</sup> found in adults with urolithiasis a higher level of urine calcium for any given level of urine citrate, while Cupisti et al suggested that this relation was higher in recurrent SF.<sup>20</sup>

After establishing Youden's index for the cutoff point and *p*-values,  $U_{Ca}/U_{Ci}$  was more predictive of stone formation than  $U_{Ca}/U_{Cr}$ . However, populations with hypercalciuria and hypocitraturia correspond with different etiologies for lithogenesis, suggesting that both ratios may be useful biomarkers and may both be needed for assessing overall patient risk.

We did not assess whether potassium citrate therapy versus hydrochlorothiazide would be better therapies. However, hydrochlorothiazide treatment tends to reduce serum potassium, increase uric acid levels, and lower urinary citrate excretion.<sup>21</sup> These side effects may actually contravene the urinary calcium-lowering effect, whereas the adverse effects of potassium citrate are limited to abdominal distension, diarrhea, nausea, and abdominal pain.<sup>22</sup> Supplementation of citrate may be safer than the use of hydrochlorothiazide for decreasing the risk of nephrolithiasis in hypercalciuria.

In Canada, treatment with hydrochlorothiazide is most commonly prescribed for hypercalciuria because potassium citrate is not covered. Others have used lemon juice as an alternative to potassium citrate. Kang et al<sup>23</sup> found an increase in urinary citrate levels and a decrease in the stone formation rates in 11 adults after 44 months of lemonade therapy consisted of 120 mL concentrated lemon juice (5.9 g citric acid) mixed with 2L of water throughout each day.<sup>23</sup> Penniston et al<sup>24</sup> compared grape, orange, lime, and lemon juice both from fresh fruit and from juice concentrates and found that lime and lemon provide more citric acid per liter than others.<sup>24</sup>

Several papers have identified that  $U_{Ca}/U_{Ci}$  may be preferable for the identification of SF.<sup>10-13,25</sup> Using Youden's index, a cutoff of  $U_{Ca}/U_{Ci}$  ratio > 0.68 mmol/mmol was determined for the identification of SF. Arrabal-Polo et al<sup>12</sup> suggested a cutoff of 0.25 mg/mg (which would be 1.2 mmol/mmol) to identify recurrent SF; however, the authors did not use a standardized method for deriving the cutoff. The only other study on children by Turudic et al suggests that a  $U_{Ca}/U_{Ci}$  ratio below 0.61 mmol/mmol would identify healthy children,<sup>26</sup> but again without any analysis beyond a subjective ROC curve inspection. Our cutoff value of 0.68 mmol/mmol is very similar to that of Turudic et al, albeit determined by more statistically sound methods.

The study has several limitations, including the retrospective nature of the study, the number of patients and a few (maximum 8 per parameter) missing urine electrolytes (mostly potassium and sodium owing to the retrospective nature and lack of a prospective stone workup protocol).

Also, there may have been a selection bias because only pediatric nephrology patients were recruited, rather than the general population. We did not utilize 24-hour urine collections even though these may be more accurate; however, they are notoriously unreliable in children.<sup>27</sup> Additionally in the NSF we did not control for pre-existing conditions that may have an increased risk for kidney stones such as comorbidities like inflammatory bowel disease, need for tube feeds, or cystic fibrosis. One patient in the control group had cystic fibrosis, but no hematuria. Furthermore, while only the earliest measurement in a time period was used, not all patients actually had measurements preintervention. We also realize that kidney stones in low-income countries may be more commonly formed by uric acid or ammonium. This could decrease the utility of  $U_{Ca}/U_{Ci}$  to identify SF in those countries.<sup>28</sup> Nonetheless, the previously proposed cutoffs of around 0.68 mmol/mmol have been solidified. As the sensitivity at this cutoff was 80% and the specificity was 59%, future prospective studies should validate this cutoff.

## Conclusion

This study adds to the growing body of literature supporting both the reporting and use of  $U_{Ca}/U_{Ci}$  instead of  $U_{Ca}/U_{Cr}$  to identify pediatric SF and through an appropriate statistical method propose a cutoff of 0.68 mmol/mmol. Given the results of our analysis, we propose for pediatric patients with nephro- or urolithiasis that an initial urinary workup includes urinary creatinine, urinary calcium, and urinary citrate, in addition to the inexpensive urinary sodium and potassium. The authors further propose the use of  $U_{Ca}/U_{Ci}$  to identify patients at risk of urolithiasis and possibly for initiation of treatment with potassium citrate or even lemon juice. Future prospective studies would be important to validate the findings.

### Authors' Contributions

GF and ML articulated the conceptual framework for this study and obtained ethics approval. VB retrieved the urinary citrate concentrations from the laboratory information system and linked all available data. ML pulled all the charts and performed the data entry. GF developed the analytical approach and GF, ML, CIRC, and RN analyzed the data. GF and CIRC drafted the manuscript. RN, PW, and VB contributed to the interpretation of data, added intellectual content during manuscript preparation, and provided valuable feedback on various aspects of the manuscript. All authors read and approved the final manuscript.

### Conflict of Interest

None declared.

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