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REVIEW

Urinary risk factors for urolithiasis in children: A systematic review and meta-analysis

Derryl Rasad Texaga [1], Saskia Ratna Desita [1], Nadira Muthi Tsania [1], Junjungan Nismasratu Rahmatsani [1], Kevin Yuwono [1], I Gede Yogi Prema Ananda [2], Radika Naufal Hadi Surya [2], Dimas Panca Andhika [2, 3, 4]

[1] Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
[2] Department of Urology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
[3] Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
[4] Universitas Airlangga Hospital, Surabaya, Indonesia.

Summary

Introduction: Urolithiasis in children has become a clinical concern because of its long-term impact on kidney function and quality of life. In previous studies, the role of urinary biomarkers in predicting the risk of urolithiasis in children was still unclear due to inconsistent findings. This meta-analysis aimed to evaluate the diagnostic potential of various urinary risk factors in children with urolithiasis.
Methods: A systematic review and meta-analysis was performed based on PRISMA 2020 guidelines, registered in PROSPERO (CRD42025644893). A total of six studies (1 cohort and 5 case-control) involving 2,060 pediatric patients (817 with urolithiasis; 1,243 controls) were analyzed. Urinary risk factors - including citrate/creatinine (Cit/Cr), oxalate/creatinine (Ox/Cr), calcium/creatinine (Ca/Cr), phosphorus/creatinine (P/Cr), magnesium/creatinine (Mg/Cr), and urea/creatinine (Ur/Cr) - were examined. Standard Mean Differences (SMD) were calculated, and heterogeneity was assessed using the I^2 statistic.
Results: Significant differences were obtained in the Cit/Cr, Ca/Cr, Ox/Cr, and Mg/Cr ratios between children with urolithiasis and controls. Hypocitraturia (Cit/Cr SMD: -0.60, 95% CI: -0.90 to -0.30, p = 0.0001), hyperoxaluria (Ox/Cr SMD: 0.76, 95% CI: 0.37-1.16, p = 0.0001), hypercalciuria (Ca/Cr SMD: 0.55, 95% CI: 0.10-1.01, p = 0.02), and hypomagnesuria (SMD -0.13 (95% CI: -0.24 to -0.01), p = 0.03) were significantly associated with the formation of stones in the urinary tract. On the contrary, there were no significant relationships for P/Cr and Ur/Cr ratios.
Conclusions: This meta-analysis highlights Cit/Cr, Ox/Cr, and Ca/Cr ratios as potential urinary biomarkers to identify the risk of urolithiasis in pediatric patients. Hypocitraturia, hyperoxaluria, and hypercalciuria are the main metabolic abnormalities that contribute to urinary tract stone formation. Future studies with standardized methodology are essential to confirm these findings and guide clinical management strategies.

KEY WORDS: *Urolithiasis; Urinary risk factor; Pediatric kidney stones.*

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INTRODUCTION

Urolithiasis, the formation of calculi in the urinary tract, is a significant clinical condition that can affect children of all ages. The global prevalence of urolithiasis in children under 20 years of age was estimated at 0.01% in 2021, with approximately 123,436 cases worldwide. In Indonesia, there were 1,829 reported cases, highlighting the growing concern for pediatric kidney stone disease (1). Urolithiasis in children warrants great attention, particularly considering the potential long-term impacts on renal function and quality of life for affected children.

Pediatric stone formers differ from adults. For instance, *calcium oxalate* (CaOx) stones, which are more prevalent in adults, are less commonly seen in children, who more frequently present with uric acid or ammonium acid stones, particularly in regions such as *Southeast Asia* and the *Middle East* (2). The proportion of calcium oxalate stones will increase with age as that of carbapatite stones will decrease. In contrast with adult urolithiasis formation, which is more often idiopathic or diet-induced, pediatric urolithiasis necessitates a more nuanced understanding of the factors that influence biomarker profiles in this population (3).

The pathogenesis of urolithiasis in children is complex, involving both genetic and environmental factors. Over time, the primary causes of stone formation have shifted from being predominantly infectious to metabolic (4). In particular, kidney stone formation is closely associated with metabolic abnormalities, including calcium, oxalate, and urate dysregulation (5).

Urine sampling is a widely used clinical tool for diagnosing diseases due to its non-invasive nature, cost-effectiveness, and reliability (6). Urinary risk factors such as calcium, creatinine, and uric acid, detectable through urine sampling, have been implicated in the pathogenesis of kidney stones and offer potential diagnostic and prognostic value in clinical practice (7).

The exploration of urinary biomarkers as predictors of urolithiasis in children demonstrates significant variability of research findings. A study identified increased urinary levels of Cystatin C and NGAL as potential indicators of early kidney tubular dysfunction in children with urolithiasis, even when serum creatinine remained normal (8). In contrast, another study stated that these biomarkers were less reliable for assessing renal injury due to urinary stone in pediatric populations (9). The inconsistent results highlight the complexity of using urinary biomarkers in pediatric urolithiasis, indicating a critical need for larger, standardized research to establish their clinical utility.

METHODS

This meta-analysis was performed according to the 2020 *Preferred Reporting Items for Systematic Review and meta-analysis* (PRISMA) guideline and has been registered to PROSPERO database (https://www.crd.york.ac.uk/prospero/) with a registration number CRD42025644893.

Eligibility criteria

Inclusion criteria for this study were: (1) Patients under 18 years old with urolithiasis; (2) Study that examines urinary risk factor of stone formation; (3) Written full-text in English. The exclusion criteria were: (1) The type of studies being review, case-report, meeting report, comments and other unrelated studies; (2) Non-human studies; (3) Studies that focus only on healthy children. Selection of the study was demonstrated on the PRISMA diagram (Figure 1).

Data selection, search strategy, and selection of studies

A comprehensive literature research was conducted in several databases including MEDLINE, Science Direct, Springer, and PLOS One from the initial period of the study until January 2025. The following keywords were used as follows [(“*Nephrolithiasis*”) OR (“*Urolithiasis*”)] AND [(“*Pediatric*”) OR (“*Infant*”) OR (“*Children*”)] AND [(“*Risk factor*”) OR (“*Dietary*”)]. Studies retrieved were exported into Rayyan.ai–Intelligent Systematic review for article screening and duplication removal.

Two authors (D.R.T and S.R.D) screened the literature and extracted the data independently.

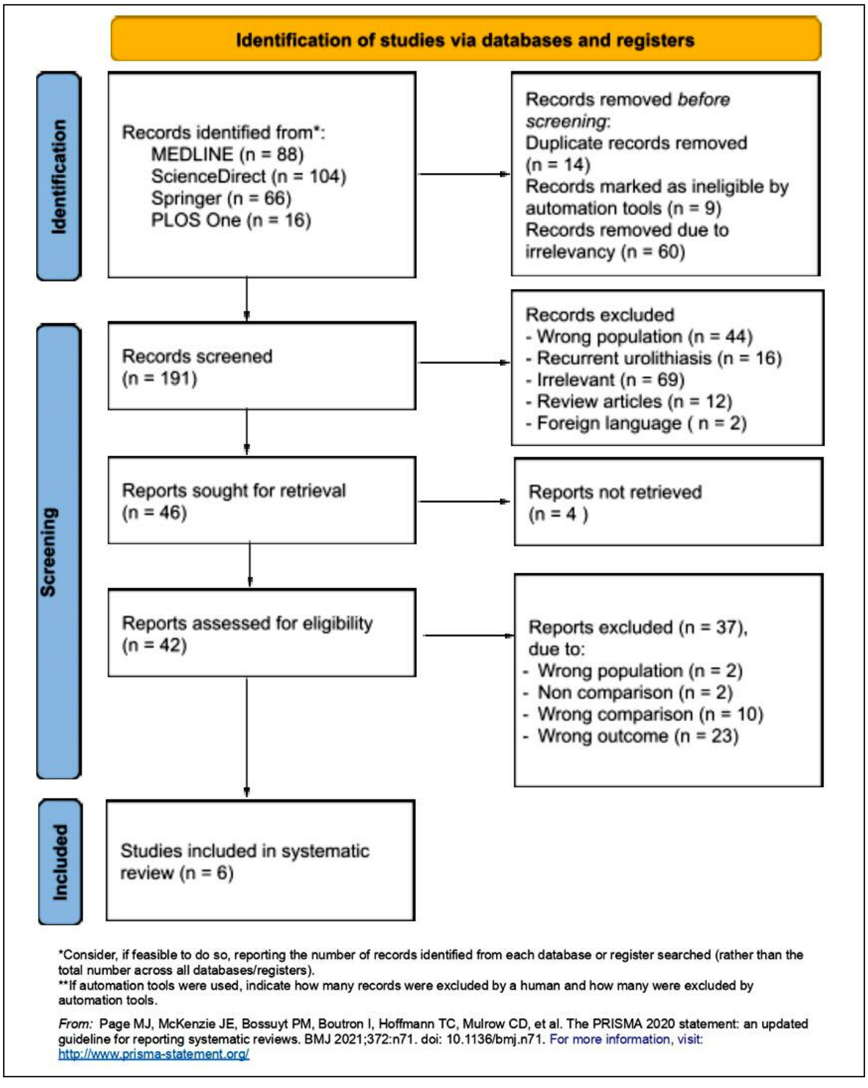
Disagreements between two authors were discussed until agreement was established. The following data were collected: (1) Information of the study: first author, publication year, country; (2) Basic study characteristics: sample size, patient’s age of enrollment; (3) Study findings including key risk factors of urolithiasis, methods of diagnosis, and biochemical measurement.

Quality assessment

Three authors (J.N.R., R.N.H.S, and I.Y.P.A) independently assessed the *Risks of Bias* (RoB) from selected studies using *Newcastle Ottawa Scale* (NOS) assessment tool for cohort and case-control studies.

Figure 1.

Flow of literature search and selection based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Statistical analysis

The study was analyzed using Review Manager 5.4 (*Cochrane Collaboration*). The *Standard Mean Differences* (SMDs) were calculated as effect sizes using inverse variance methods for continuous outcomes. For dichotomous outcomes, pooled *risk ratios* (RRs) were computed using Mantel-Haenszel methods. Heterogeneity across the included studies was assessed using the I^2 statistic. A random-effects model was applied if the I^2 value was greater than 50%, indicating moderate-to-high heterogeneity. Conversely, a fixed-effects model was used if the I^2 value was less than 50%. Statistical significance was determined with a p-value of less than 0.05. Begg’s funnel plots were employed to evaluate potential publication bias, and the trim-and-fill method was applied if any publication bias was detected.

RESULTS

Study selection

From four databases, a total of 274 studies were retrieved. After the removal of duplicates and irrelevant studies, 191 studies remained for screening. Following the inclusion and exclusion criteria, 42 studies were assessed eligible. Upon full-text review, 6 studies were included in this study. The study selection process is summarized in the PRISMA flowchart.

The six studies included in this study included 5 case-control studies, and 1 cohort study. Quality assessment for case-control and cohort study using the NOS assessment tool revealed that 2 studies were classified as very good, while 4 were assessed as good quality.

Study characteristics

In our review, we analyzed a total cohort of 2,060 pediatric patients, consisting of 817 subjects with urolithiasis, and 1243 controls. Out of the six studies included, five were case-control studies and one is cohort studies. Two of the studies were conducted in Poland, one in Turkey, while the remaining three were done in Hungary, Germany, and Spain respectively. We examined multiple urinary biomarkers and their relationship to the incidence of urolithiasis. To diagnose urolithiasis, the studies used a range of methods, including standard ultrasound, intravenous urography, plain X-rays, infrared spectroscopy, and surgical intervention. Detailed biochemical urinary measurements and additional study details are presented in Table 1.

Urinary risk factors

Cit/Cr

Citrate/Creatinine ratios were evaluated using 24-hour urinary samples and urine spot samples. Four studies examined a total of 1769 subjects (717 with urolithiasis, 1052 controls). The meta-analysis demonstrated there was a sig-

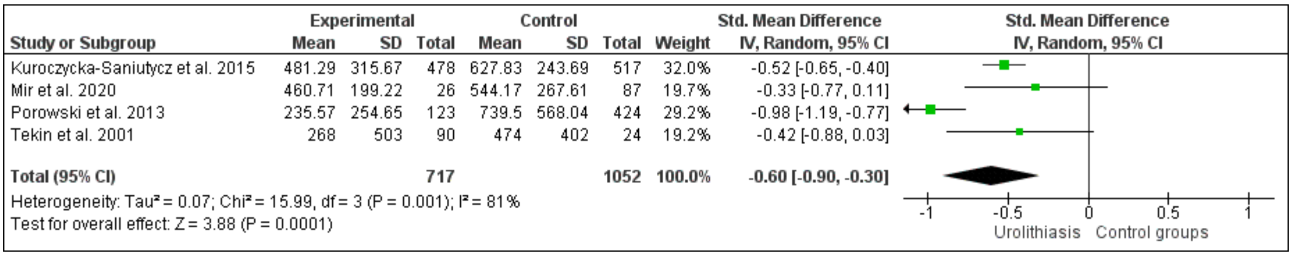
Table 1.
Characteristics of the study.

Study	Study type	Enrollment	Participants		Mean Age at enrollment		Male (n)		Key risks factor	Outcomes	Methods of diagnosis	Biochemical measurement
			Intervention	Control	Intervention	Control	Intervention	Control				
Tekin et al., 2001	Retrospective cohort	Turkey	90 children with normal anatomy and urolithiasis	24 healthy children	7.70 ± 10.45 years	7.8 ± 6.3 years	NA	NA	Hypocitraturia Hyperoxaluria	Incidence of nephrolithiasis in children with upper tract anatomy anomalies	Intravenous urography and ultrasonography	24-hour-urine excretion Serum biochemistry
Reustz et al., 1995	Case-control study	Hungary	27 with renal stones	156 healthy children	6-16 years	1-14.5 years	NA	NA	Hyperoxaluria Hypercalciuria	Calcium, oxalate excretion, activity product (measurement of Ca/Cr and Ox/Cr in first-morning urine samples is suitable for screening for hypercalciuria and hyperoxaluria)	Intravenous urography and sonography	Urine samples
Kuroczycka-Saniutycz et al., 2015	Case-control study	Poland	478 children with urolithiasis	517 healthy children	14.19 ± 4.16 years	13.9 ± 4.43 years	205	219	Hyperuricemia Obesity	Incidence of urolithiasis	Ultrasonography X-ray	Blood sample Urine sample
Sikora et al, 2008	Case-control study	Germany	60 patients with idiopathic calcium oxalate urolithiasis 13 patients with primary hyperoxaluria	35 healthy children	13.3 ± 4.1 years	11.1 ± 3.6 years	41	23	Intestinal hyperabsorption of oxalate	Incidence of idiopathic calcium oxalate urolithiasis	Infrared spectroscopy	[13C2] oxalate absorption test
Mir et al, 2020	Case-control study	Spain	26 stone-forming children	87 healthy children	12 ± 4 years	12 ± 3 years	15	50	12 hour daytime 12 hour overnight 24 hour	Diagnosis of lithiasis	NA	24-hour-urine excretion 12-hour-day-urine excretion 12-hour-overnight-urine excretion
Porowski et al, 2013	Case-control study	Poland	123 Stone-formers with hypocitraturia	424 healthy children	13.30 ± 8.06 years	12.3 ± 8.67 years	66	212	Hypercalciuria Hypocitraturia Urinary Ph Ca^{2+}/Citrate ratio	Diagnosis of lithiasis	Ultrasonography X-ray	24-hour-urine collection

Table 2.
Quality assessment.

Study	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled	Assessment of outcome	Statistical test	Total score	Result
Tekin et al., 2001	1	0	0	2	2	2	1	8	Good
Reustz et al., 1995	1	1	0	2	2	2	1	9	Very good
Kuroczycka-Saniutycz et al., 2015	1	1	0	2	2	2	1	9	Very good
Mir et al., 2020	1	1	0	1	1	1	1	6	Good
Sikora et al., 2008	1	1	0	1	1	1	1	6	Good
Porrowski et al., 2013	1	1	0	1	1	1	1	6	Good

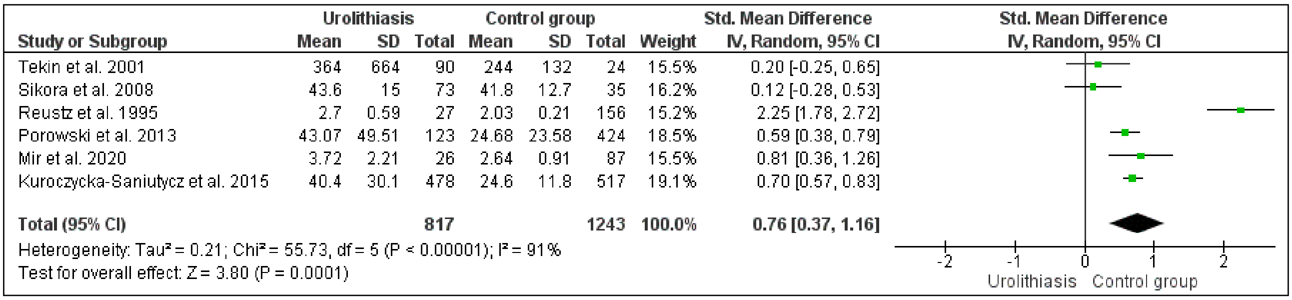
Figure 2.
Forest Plot of Cit/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kuroczycka-Saniutycz et al. 2015	481.29	315.67	478	627.83	243.69	517	32.0%	-0.52 [-0.65, -0.40]
Mir et al. 2020	460.71	199.22	26	544.17	267.61	87	19.7%	-0.33 [-0.77, 0.11]
Porowski et al. 2013	235.57	254.65	123	739.5	568.04	424	29.2%	-0.98 [-1.19, -0.77]
Tekin et al. 2001	268	503	90	474	402	24	19.2%	-0.42 [-0.88, 0.03]
Total (95% CI)			**717**			**1052**	**100.0%**	**-0.60 [-0.90, -0.30]**

Heterogeneity: Tau² = 0.07; Chi² = 15.99, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 3.88 (P = 0.0001)

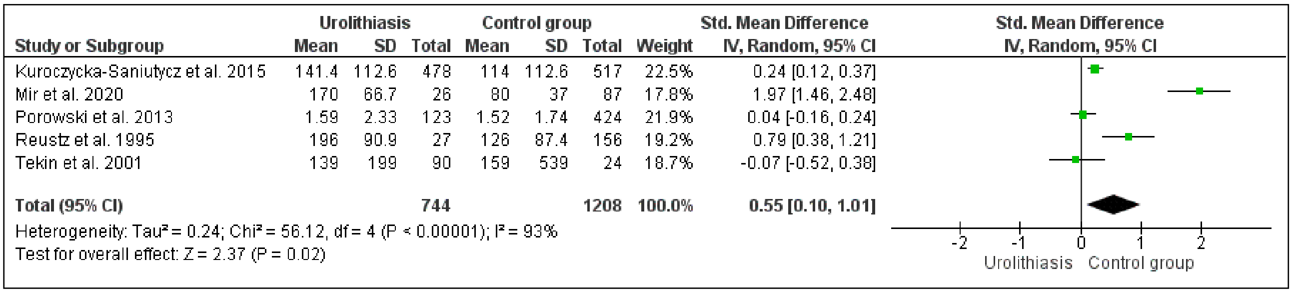
Figure 3.
Forest Plot of Ox/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Urolithiasis Mean	Urolithiasis SD	Urolithiasis Total	Control group Mean	Control group SD	Control group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Tekin et al. 2001	364	664	90	244	132	24	15.5%	0.20 [-0.25, 0.65]
Sikora et al. 2008	43.6	15	73	41.8	12.7	35	16.2%	0.12 [-0.28, 0.53]
Reustz et al. 1995	2.7	0.59	27	2.03	0.21	156	15.2%	2.25 [1.78, 2.72]
Porowski et al. 2013	43.07	49.51	123	24.68	23.58	424	18.5%	0.59 [0.38, 0.79]
Mir et al. 2020	3.72	2.21	26	2.64	0.91	87	15.5%	0.81 [0.36, 1.26]
Kuroczycka-Saniutycz et al. 2015	40.4	30.1	478	24.6	11.8	517	19.1%	0.70 [0.57, 0.83]
Total (95% CI)			**817**			**1243**	**100.0%**	**0.76 [0.37, 1.16]**

Heterogeneity: Tau² = 0.21; Chi² = 55.73, df = 5 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.80 (P = 0.0001)

Figure 4.
Forest Plot of Ca/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Urolithiasis Mean	Urolithiasis SD	Urolithiasis Total	Control group Mean	Control group SD	Control group Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kuroczycka-Saniutycz et al. 2015	141.4	112.6	478	114	112.6	517	22.5%	0.24 [0.12, 0.37]
Mir et al. 2020	170	66.7	26	80	37	87	17.8%	1.97 [1.46, 2.48]
Porowski et al. 2013	1.59	2.33	123	1.52	1.74	424	21.9%	0.04 [-0.16, 0.24]
Reustz et al. 1995	196	90.9	27	126	87.4	156	19.2%	0.79 [0.38, 1.21]
Tekin et al. 2001	139	199	90	159	539	24	18.7%	-0.07 [-0.52, 0.38]
Total (95% CI)			**744**			**1208**	**100.0%**	**0.55 [0.10, 1.01]**

Heterogeneity: Tau² = 0.24; Chi² = 56.12, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.37 (P = 0.02)

nificant decrease of citrate in children with urolithiasis compared to controls (SMD -0.60 (95% CI: -0,90 to -0.30), p = 0.0001) with moderate effects. The heterogeneity test showed a statistically significant high heterogeneity (I^2 = 81%, p = 0.0001) indicating the use of a random-effect model.

Ox/Cr

Six studies with a total of 2060 patients (817 with urolithiasis, 1243 controls) measured Oxalate/Creatinine ratios in 24-hour urinary and urine spot samples. This study found children with urolithiasis have significantly higher Ox/Cr ratios compared to controls (SMD 0.76 (95% CI: 0.37 to 1.16, p = 0.0001), with moderate to large effect. The heterogeneity test showed a statistically significant high heterogeneity (I^2 = 91%, p = 0.0001) indicating the use of a random-effect model.

Ca/Cr

Calcium/Creatinine ratios were measured in 1952 subjects consisting in 744 patients with urolithiasis and 1208 controls using 24-hour urinary and urine spot samples. The meta-analysis revealed children with urolithiasis have a higher Ca/Cr ratios compared to controls (SMD 0.55 (95% CI: 0.10 to 1.01), p = 0.02, I2 = 93%), with a moderate effect. The I^2 tests showed a high heterogeneity test, resulting in random-effect models methods.

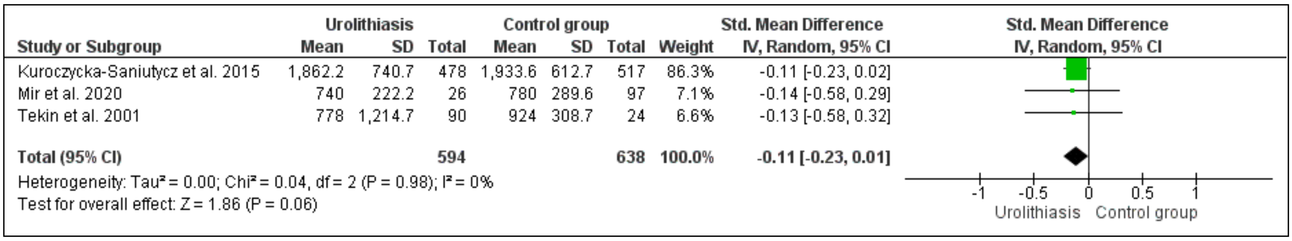
P/Cr

Three studies with a total of 1232 patients examined Phosphorus/Creatinine ratios of 24 hour urinary and urine spotsamples, respectively. The meta-analysis demonstrated there was no significant difference in children with urolithiasis compared to controls (SMD -0.11 (95% CI: -0.23 to 0.01), p = 0.06, I^2 = 0%), with low effect. A fixed-effect model was applied since the low heterogeneity test.

Mg/Cr

Magnesium/Creatinine ratios were evaluated using 24 hour urinary and urine spot samples respectively. Three studies with a total of 1222 patients were examined. The studies

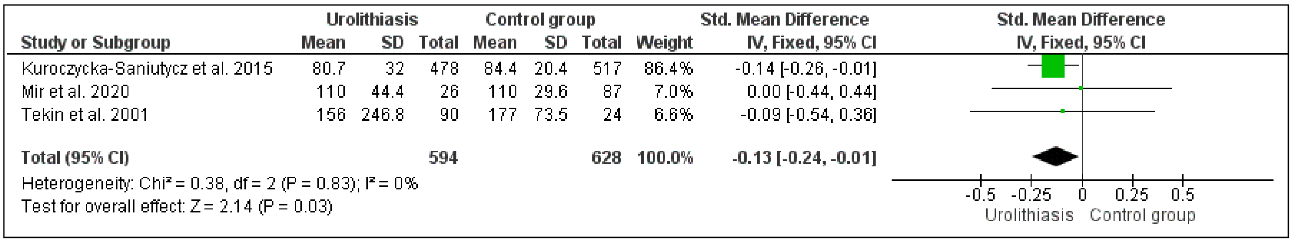
Figure 5.
Forest Plot of P/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Urolithiasis Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kuroczycka-Saniutycz et al. 2015	1,862.2	740.7	478	1,933.6	612.7	517	86.3%	-0.11 [-0.23, 0.02]
Mir et al. 2020	740	222.2	26	780	289.6	97	7.1%	-0.14 [-0.58, 0.29]
Tekin et al. 2001	778	1,214.7	90	924	308.7	24	6.6%	-0.13 [-0.58, 0.32]
Total (95% CI)			**594**			**638**	**100.0%**	**-0.11 [-0.23, 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)

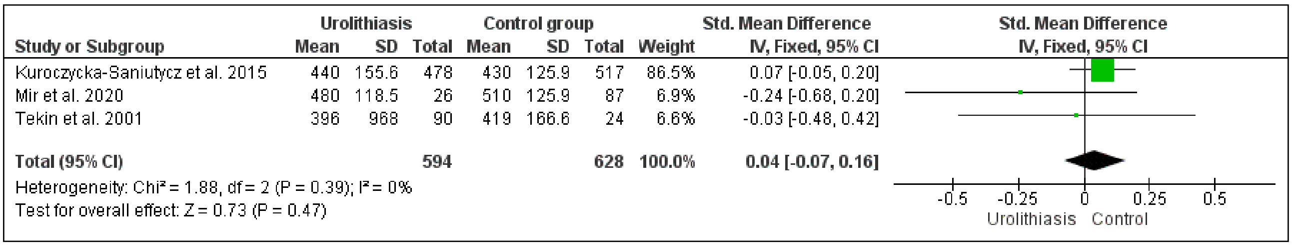
Figure 6.
Forest Plot of Mg/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Urolithiasis Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Kuroczycka-Saniutycz et al. 2015	80.7	32	478	84.4	20.4	517	86.4%	-0.14 [-0.26, -0.01]
Mir et al. 2020	110	44.4	26	110	29.6	87	7.0%	0.00 [-0.44, 0.44]
Tekin et al. 2001	156	246.8	90	177	73.5	24	6.6%	-0.09 [-0.54, 0.36]
Total (95% CI)			**594**			**628**	**100.0%**	**-0.13 [-0.24, -0.01]**

Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Figure 7.
Forest Plot of Ur/Cr biomarker in urolithiasis vs healthy children.



Study or Subgroup	Urolithiasis Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Kuroczycka-Saniutycz et al. 2015	440	155.6	478	430	125.9	517	86.5%	0.07 [-0.05, 0.20]
Mir et al. 2020	480	118.5	26	510	125.9	87	6.9%	-0.24 [-0.68, 0.20]
Tekin et al. 2001	396	968	90	419	166.6	24	6.6%	-0.03 [-0.48, 0.42]
Total (95% CI)			**594**			**628**	**100.0%**	**0.04 [-0.07, 0.16]**

Heterogeneity: Chi² = 1.88, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

have low heterogeneity (I^2 = 0%) and a fixed-effect was applied. Meta-analysis demonstrated there was a statistically significant difference in children with urolithiasis compared to controls (SMD -0.13 (95% CI: -0.24 to -0.01), p = 0.03).

Ur/Cr
Uric acid/Creatinine ratios were evaluated using 24-hour urinary excretions. Four studies with a total of 1222 patients examined 24-hour urinary excretions. The meta-analysis demonstrated there was no significant relationship in children with urolithiasis compared to controls (SMD 0.04 (95% CI: -0.07 to 0.16), p = 0.47, I^2 = 0%). A fixed-effect was applied since the study had low heterogeneity (I^2 = 0%).

DISCUSSION

This study's findings demonstrate significant differences in urinary biomarkers - Cit/Cr, Ca/Cr, Ox/Cr, and Mg/Cr -between pediatric patients with urolithiasis and those without. Among children diagnosed with urolithiasis, the Ca/Cr ratio was markedly elevated in comparison to the controls (SMD 0.55, 95% CI: 0.10-1.01, p = 0.02). Of the five studies that reported Ca/Cr data, four studies identified statistically significant different levels of Ca/Cr between stone-forming children and healthy children.10-13 Hypercalciuria is one of the most prevalent metabolic disorders associated with pediatric urolithiasis, affecting approximately 30% to 50% of patients (2, 14). Idiopathic hypercalciuria is the most frequent etiology of calcium-stone (15).

Several studies shown that hypercalciuria was found in nine of 74 children with recurrent unilateral stones (16). This study was similar to a prior study by *Kamel et al.* (17) that found 22% of children with urolithiasis had hypercalciuria based on their laboratory findings. Similarly, another study by *Kovacevic et al.* (18) found that hypercalciuria was the most common risk factor in pediatric urolithiasis. As most urinary stones are composed of calcium, hypercalciuria is the major risk factor for calcium stone. Kidney stones, particularly those composed of calcium oxalate, often originate from calcium deposits known as Randall's plaques. These plaques form in the renal papilla's interstitial tissue and can serve as a nidus for stone development. When the urothelium's integrity is compromised, regions of the plaque become exposed to urine and crystallization begin (19). Several factors contribute to hypercalciuria and the role of dietary supplementation of calcium or vitamin D had conflicting results towards the risk of urolithiasis. A meta-analysis revealed that patients undergoing long-term vitamin D supplementation experienced an increased risk of hypercalciuria, though the risk of kidney stone disease remained unaffected (20). Other conditions that predispose individuals to hypercalciuria include hyperparathyroidism, metabolic bone diseases, renal calcium leak, and diets that impose a high renal acid load (21).

Hyperoxaluria plays a crucial role in the pathogenesis of crystallization and stone formation (15). Urinary oxalate excretion is an important determinant in the development of *calcium oxalate* (CaOx) urolithiasis, the most common type of kidney stone (22). This meta-analysis revealed that Ox/Cr levels were significantly elevated in stone-forming children compared to controls (SMD 0.76, 95% CI: 0.37-1.16, p = 0.0001). Among the six studies providing Ox/Cr data, five studies demonstrated a significant difference in Ox/Cr levels between the stone-forming and control groups (10-12, 22, 23).

Prior studies found that hyperoxaluria was found in children with multiple and single kidney stones (24). This study align with a previous study by *Issler et al.* (25) that showed as 37 children with renal stone disease had hyperoxaluria as their metabolic abnormality. This study was similar with another study by *Placzynska* (26) that found hyperoxaluria in children with different composition of renal stones, such as weddellite, whewellite, and non-calcium oxalate. Hyperoxaluria is also another major risk factor for stone formation, as calcium oxalate is the most common composition of urinary stones. An in vitro study demonstrated that elevated levels of oxalate boost the ability of renal epithelial cells to adhere to *calcium oxalate monohydrate* (COM) crystals. This increased binding capability is facilitated by a rise in the surface expression of α-enolase, a protein that binds to COM crystals.21

The concentration of urinary oxalate is primarily affected by the intake of dietary oxalate and its precursors, and the absorption rate from the gastrointestinal tract. Therefore, consumption of oxalate-rich foods and increased absorption of oxalate from the intestine (eg. in bypass/bariatric surgery patients) is associated with hyperoxaluria and kidney stones formation (27, 28).

The decrease of urinary stone inhibitors increases the risk of urolithiasis, with citrate being a key inhibitory factor (29). This meta-analysis found that Cit/Cr levels were significantly lower in the urolithiasis group compared to the control group (SMD -0.60, 95% CI: -0.90 to -0.30, p = 0.00001). Among the four studies providing Cit/Cr, three studies showed statistically significant results (10, 12, 23). Citrate mitigates stone formation by binding calcium ions in urine, thereby reducing calcium supersaturation and preventing crystallization (30). Another inhibitor, urinary *magnesium* (Mg), also showed a significant negative association with stone formation in this study (SMD = -0.13; 95% CI: -0.24 to -0.01; p = 0.03). Interestingly, none of the three studies that separately analyzed Mg/Cr ratio demonstrated a significant association.

Hypocitraturia was found frequently in pediatric kidney stones (31). *Velasquez et al.* (29) found that hypocitraturia was the main risk factors among children with urolithiasis, which aligns with our meta-analysis. On the contrary, a study by *Lee et al.* (32) reported that hypocitraturia was the less frequent risk factor of urolithiasis in children. Hypocitraturia has long been linked to the development of kidney stones, especially to calcium stone formation. The mechanisms by which citrate inhibits crystal formation are thought to be mediated by its ability to form soluble complexes with calcium, which significantly lowers urinary calcium supersaturation and helps prevent the nucleation of both calcium oxalate and calcium phosphate crystals (33). Additionally, citrate can directly prevent the attachment of calcium oxalate crystals to renal epithelial cells by adsorbing onto the surfaces of the crystals (34). An in vivo study involving genetically hypercalciuric stone-forming rats demonstrated that administering potassium citrate resulted in elevated urinary citrate levels and reduced urinary calcium concentrations in addition to urine alkalinization (35). In children, hypocitraturia has been commonly defined as 24-h citrate excretion of < 400 mg/g creatinine or < 180 mg/g creatinine. However, other proposed definitions exist, and factors such as age and gender also influence them, making interpretation rather difficult (33).

Magnesium also acts as an inhibitor by preventing the crystallization of calcium oxalate and calcium phosphate. It binds to oxalate, which may reduce intestinal absorption of oxalate and lower the supersaturation of calcium oxalate in urine. Some studies have shown that magnesium supplementation may benefit children with secondary hyperoxaluria (2). Urolithiasis in children is predominantly linked to metabolic abnormalities, which are identified in approximately 30% to 84% of cases. Among these, hypomagnesiuria is one of the contributing conditions, although idiopathic hypercalciuria remains the most commonly observed metabolic disorder (36).

In identifying children at high risk of urolithiasis, these findings strengthen the potential use of urinary biomarkers, particularly hypocitraturia and hyperoxaluria. Hypocitraturia in children with urolithiasis can be used as a benchmark for administering potassium citrate that can reduce stone size and recurrence rate (37).

Hyperoxaluria can be managed by eating a diet low in oxalate precursors that can help prevent the formation of

DECLARATIONS

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kidney stones (38). A long-term normal intake of dietary calcium can decrease numbers of stone recurrences due to idiopathic hypercalciuria (39).

CONCLUSIONS

This meta-analysis highlights the important role of urinary biomarkers, especially Cit/Cr, Ox/Cr, and Ca/Cr ratios, in predicting the risk of urolithiasis in children. Hypocitraturia, hyperoxaluria, and hypercalciuria emerged as important risk factors, supporting their clinical relevance in assessing and managing urinary tract stone formation in children. These findings suggest that targeted interventions, such as administration of potassium citrate for hypocitraturia and dietary modification for hyperoxaluria and hypercalciuria, may be effective in preventing recurrence of urinary tract stones. However, the high heterogeneous and limited data on certain biomarkers indicate the need for further standardized and large-scale studies to establish definitive clinical guidelines.

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Correspondence

Dimas Panca Andhika (Corresponding Author)
dimaspanca26@gmail.com

Department of Urology, Faculty of Medicine, Universitas Airlangga;
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Jl. Mayjend. Prof. Dr. Moestopo No. 6-8, Surabaya, East Java, Indonesia, 60286