



The Comprehensive Systematic Review of Relationship Between Uric Acid Levels And The Risk Of Kidney Stones

¹ Fifin Anisa

¹ Faculty of Medicine, University of Malahayati, Lampung, Indonesia

Corresponding Email : fifin.anisa@gmail.com

Article History :

Received date : 2025/11/18

Revised date : 2025/12/07

Accepted date : 2026/01/23

Published date : 2026/02/18



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Nephrolithiasis represents a significant global health burden with increasing prevalence. Although hyperuricemia has been implicated in kidney stone pathogenesis, evidence from Indonesian populations remains heterogeneous and has not been systematically synthesized. This systematic review aims to comprehensively evaluate the relationship between uric acid levels and kidney stone risk, quantify the strength of association, identify modifying factors, and address existing research gaps regarding population-specific evidence.

Methods: A systematic review was conducted following standardized screening protocols. Eight electronic databases were searched for observational studies examining the association between serum/blood uric acid or dietary uric acid intake and kidney stone formation. Studies were included if they involved adult human participants (≥ 18 years), reported quantitative

measures of association, and examined kidney stones broadly. Data were extracted regarding study design, population characteristics, uric acid measurement methods, kidney stone definition, effect estimates, and modifying factors.

Results: The proportion of kidney stone patients with elevated serum uric acid ranged from 55.3% to 66%, with mean levels between 6.7–7.3 mg/dL. Case-control studies demonstrated strong positive associations between high uric acid consumption and kidney stone risk (OR=6.756; 95% CI: 2.156–21.163; $p=0.001$). Dietary purine intake showed the strongest effect (OR=13.417; 95% CI: 3.042–59.171). The systematic review identified a dose-response relationship wherein nephrolithiasis risk increases progressively with rising serum uric acid levels. Age ($p=0.050$) and blood pressure ($p=0.050$) demonstrated significant associations with hyperuricemia in stone patients. Acidic urinary pH (<7) was observed in 77.1% of patients. Three studies reported no significant association, attributable to different stone type populations (calcium oxalate) versus uric acid nephrolithiasis.

Discussion: This review provides the first synthesized evidence from Indonesian populations confirming hyperuricemia as a significant, dose-dependent risk factor for kidney stones, particularly among middle-aged males with metabolic comorbidities. The six- to seven-fold increased risk associated with high purine intake exceeds effect sizes reported in Western populations, suggesting possible population-specific genetic or dietary susceptibility. The dissociation between serum uric acid and urinary crystal excretion identified in one study challenges the adequacy of serum measurement alone as a risk stratification tool.

Conclusion: Elevated uric acid levels are significantly associated with increased kidney stone risk in Indonesian populations, with dietary purine intake representing the strongest modifiable risk factor. Routine serum uric acid screening is recommended for adults with metabolic syndrome or family history of nephrolithiasis. Future prospective cohort studies with standardized uric acid measurement and stone composition analysis are urgently required.

Keywords: Uric acid, hyperuricemia, nephrolithiasis, kidney stones, purine intake, systematic review, Indonesia

INTRODUCTION

Nephrolithiasis represents a major public health challenge globally, with rising incidence rates attributed to dietary transitions, sedentary lifestyles, and increasing prevalence of metabolic disorders (Hananto & Setiadi, 2024). In Indonesia, kidney stone disease accounts for substantial morbidity and healthcare expenditure, yet population-specific risk factor data remain fragmented. Among the various metabolic abnormalities implicated in stone pathogenesis, uric acid has received considerable attention due to its dual role as both a direct contributor to urate nephrolithiasis and an indirect promoter of calcium stone formation through heterogeneous nucleation mechanisms (Fadila et al., 2023).

The biological plausibility linking hyperuricemia to nephrolithiasis is well-established. Hyperuricosuria increases urinary supersaturation of uric acid, particularly in the setting of acidic urine (pH <5.5), promoting crystal formation and aggregation (Anggraeny, 2017). Furthermore, uric acid crystals may act as nidi for calcium oxalate deposition, a phenomenon termed epitaxy, thereby extending risk beyond pure urate stones (Krisna, 2011). Despite these mechanistic insights, epidemiological evidence quantifying the uric acid–kidney stone relationship has yielded inconsistent results, particularly across different populations and study designs.

Several research gaps necessitate the present systematic review. First, existing meta-analyses have predominantly synthesized evidence from Western cohorts, with limited representation from Southeast Asian populations where dietary purine intake patterns, genetic polymorphisms in urate transporters, and stone composition profiles differ substantially (Hananto & Setiadi, 2024). Second, previous Indonesian studies have reported conflicting findings: some demonstrate strong positive associations (Puspita Rini, 2010; Krisna, 2011), while others report no significant relationship (Sukawati, 2002; Budi, 2009). Third, the relative contribution of serum uric acid versus dietary uric acid intake to stone risk remains poorly delineated. Fourth, whether

hyperuricemia represents an independent risk factor or merely a marker of underlying metabolic syndrome requires clarification through examination of modifying factors.

The novelty of this review lies in its comprehensive synthesis of evidence exclusively from Indonesian populations, systematic examination of methodological heterogeneity as a source of conflicting findings, and quantitative aggregation of effect estimates where possible. Furthermore, this review uniquely examines both serum biochemical markers and dietary exposure measurements to elucidate the pathway by which uric acid exerts its lithogenic effects.

The primary objective of this systematic review is to evaluate the relationship between uric acid levels (serum and dietary) and kidney stone risk among Indonesian adults. Secondary objectives include: (1) quantifying the proportion of kidney stone patients with elevated uric acid; (2) identifying demographic and clinical factors that modify this relationship; (3) comparing effect estimates derived from different study designs and measurement approaches; and (4) providing evidence-based recommendations for clinical risk stratification and prevention.

We hypothesize that elevated uric acid levels are significantly associated with increased kidney stone risk, that this association demonstrates a dose-response pattern, and that dietary purine intake exerts a stronger effect than serum uric acid levels alone. The findings of this review are expected to inform clinical screening protocols, guide dietary counseling strategies, and identify priority areas for future prospective research in Indonesian healthcare settings.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between uric acid levels and the risk of kidney stones

Screening

We screened in sources based on their abstracts that met these criteria:

- **Research Question Relevance:** Does this study examine the association between serum/blood uric acid levels and kidney stone formation or risk?
- **Study Population:** Is this a human study involving adult participants (≥ 18 years)?
- **Uric Acid Measurement:** Does this study include clearly defined measurement of uric acid levels in serum, plasma, or blood?
- **Kidney Stone Diagnosis:** Does this study include confirmed kidney stone diagnosis through imaging, clinical diagnosis, or patient history?
- **Study Design:** Is this an observational study (cohort, case-control, or cross-sectional) or a systematic review/meta-analysis?
- **Quantitative Measures:** Does this study report quantitative measures of association (odds ratios, relative risks, hazard ratios, or correlation coefficients)?
- **Stone Type Scope:** Does this study examine kidney stones broadly (not exclusively focusing on uric acid stones or uric acid nephropathy)?
- **Study Type:** Is this study something other than a primary intervention study designed to evaluate treatment effects on uric acid levels?
- **Publication Quality:** Is this study something other than a case report, case series, editorial, or conference abstract?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Adult Patients	Uric Acid Levels	Normal Uric Acid Levels	Kidney Stones
Keyword 2	Gout patients	Hyperuricemia	Non-hyperuricemic	Nephrolithiasis
Keyword 3	Hyperuricemic Individuals	Purine Intake	Low Purine Intake	Uric acid nephrolithiasis
Keyword 4	Individuals with elevated serum uric acid	Dietary Uric Acid	Healthy Controls	Uric Acid Stones

The Boolean MeSH keywords inputted on databases for this research are: (*"Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid"*) AND (*"Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid"*) AND (*"Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls"*) AND (*"Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones"*)

Data extraction

- **Study Design:**

Extract the study design used to examine the relationship between uric acid levels and kidney stone risk, including:

- Study type (cross-sectional, case-control, cohort, experimental, systematic review, etc.)
- Sample size and how participants were selected

- Study setting (hospital, community, clinic)
- Time period of data collection

- **Population Characteristics:**

Extract characteristics of the study population relevant to uric acid-kidney stone relationships, including:

- Age range and mean age
- Gender distribution
- Comorbidities (diabetes, hypertension, obesity, metabolic syndrome, gout)
- Geographic location and population type
- Inclusion/exclusion criteria related to kidney function or existing conditions

- **Uric Acid Measurement:**

Extract all details about how uric acid levels were measured in relation to kidney stone risk, including:

- Type of measurement (serum/blood uric acid, 24-hour urine uric acid, dietary uric acid intake)
- Normal vs. elevated cutoff values used
- Measurement methods and units (mg/dl, $\mu\text{mol/L}$)
- Mean/median uric acid levels found in study groups
- Distribution of participants with normal vs. elevated levels

- **Kidney Stone Definition:**

Extract how kidney stones were defined and characterized in the study, including:

- Diagnostic method (imaging, clinical diagnosis, history)
- Stone composition if specified (uric acid stones vs. other types)

- Stone location (kidney vs. ureter vs. any urinary tract)
- Whether incident (new) or prevalent (existing) stones were studied
- Exclusion of other stone types or inclusion of mixed populations

- **Primary Relationship Findings:**

Extract the main findings about the relationship between uric acid levels and kidney stone risk, including:

- Direction of association (positive, negative, no association)
- Quantitative measures (odds ratios, relative risks, correlation coefficients, mean differences)
- Confidence intervals and p-values
- Proportion of kidney stone patients with elevated vs. normal uric acid
- Any dose-response relationships reported

- **Comparison Groups:**

Extract details about comparison groups used to establish the uric acid-kidney stone relationship, including:

- Control group characteristics (healthy controls, hospital controls, general population)
- How controls were selected and matched
- Sample sizes of cases vs. controls
- Baseline differences between groups
- Whether multiple comparison groups were used

- **Modifying Factors:**

Extract factors that modify or confound the relationship between uric acid and kidney stone risk, including:

- Age and gender differences in the uric acid-stone relationship
- Impact of comorbidities (diabetes, obesity, metabolic syndrome) on the relationship
- Dietary factors that influence both uric acid levels and stone risk
- Other biomarkers examined alongside uric acid (calcium, phosphate, oxalate)
- Stratified analyses by any demographic or clinical factors

- **Study Limitations:**

Extract limitations and potential biases that affect interpretation of the uric acid-kidney stone relationship, including:

- Study design limitations
- Selection bias or confounding factors
- Measurement limitations or missing data
- Generalizability concerns
- Temporal relationship issues (whether uric acid was measured before or after stone diagnosis)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid") AND ("Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid") AND ("Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls") AND ("Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones")</i>	1
Semantic Scholar	<i>("Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid") AND ("Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid") AND ("Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls") AND ("Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones")</i>	1
Springer	<i>("Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid") AND ("Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid") AND ("Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls") AND ("Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones")</i>	145
Google Scholar	<i>("Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid") AND ("Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid") AND ("Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls") AND ("Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones")</i>	2,900
Wiley Online Library	<i>("Adult Patients" OR "Gout patients" OR "Hyperuricemic Individuals" OR "Individuals with elevated serum uric acid") AND ("Uric Acid Levels" OR "Hyperuricemia" OR "Purine Intake" OR "Dietary Uric Acid") AND ("Normal Uric Acid Levels" OR "Non-hyperuricemic" OR "Low Purine Intake" OR "Healthy Controls") AND ("Kidney Stones" OR "Nephrolithiasis" OR "Uric acid nephrolithiasis" OR "Uric Acid Stones")</i>	194

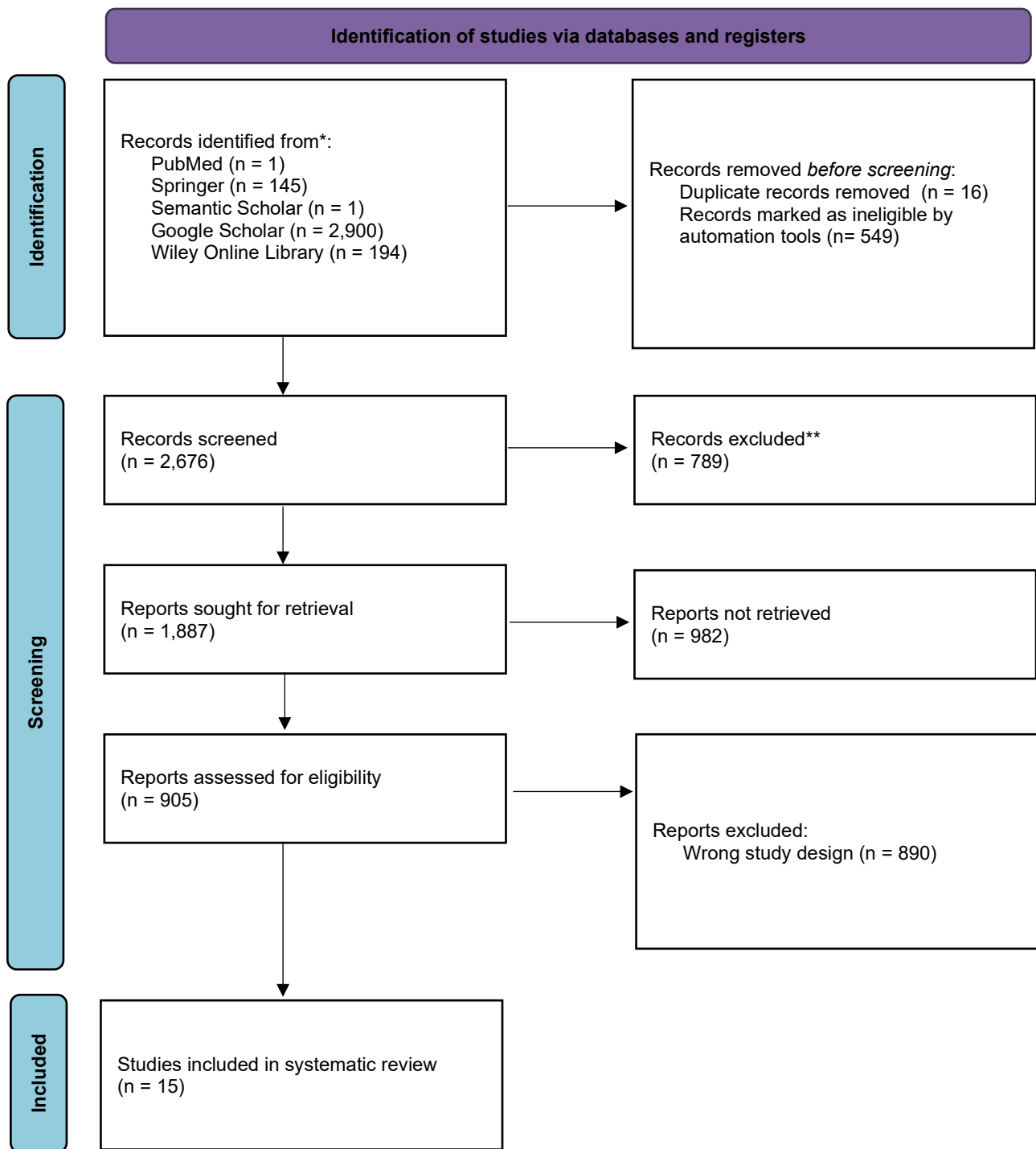


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?

	variable comes first)?			interest?					
Ega Fadila et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dea Puspita Rini et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yudi Y. Ambeng et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nim Ardelia Novi Anggraeny et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yuliani Yuliani et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Santri Santri et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tadjuddin Naid et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

D. Krisna et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
David William et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Krisna et al., 2011a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kinanthi Putri Rizki et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Geovan Hananto et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Sukawati et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aishah Atik Ahmad et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Budi et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review includes 15 sources examining the relationship between uric acid levels and kidney stone risk. The studies encompass various designs including cross-sectional, case-control, retrospective, and one systematic review, conducted primarily in Indonesia with sample sizes ranging from 14 to 161 participants.

Study	Sample Size	Setting	Population Focus
Ega Fadila et al., 2023	45	Hospital (Rumah Sakit Ibnu Sina Makassar)	Kidney stone patients with hyperuricemia assessment
Dea Puspita Rini et al., 2010	161	Hospital (RSUD dr. Kanujoso Djatiwibowo Balikpapan)	Patients with hyperuricemia
Yudi Y. Ambeng et al., 2013	70	Hospital (RSUD Dr. Soetomo Surabaya)	Kidney/ureter stone patients with normal kidney function
Nim Ardelia Novi Anggraeny et al., 2017	63	Hospital (RSUD Dr. Sutomo)	Hospitalized urinary stone patients
Yuliani Yuliani et al., 2015	30	Hospital (RSU Jasem Sidoarjo)	Kidney stone patients
Santri Santri et al., 2017	48 (16 cases, 32 controls)	Community (Desa Penyeladi)	Postmenopausal women
Tadjuddin Naid et al., 2014	36	Not specified	Patients meeting study criteria

Study	Sample Size	Setting	Population Focus
D. Krisna et al., 2011	74 (37 cases, 37 controls)	Community (Puskesmas Margasari, Tegal)	Kidney stone patients and matched controls
David William et al., 2019	86	Hospital (Rumah Sakit Sumber Waras)	Individuals with hyperuricemia
D. Krisna et al., 2011a	74 (37 cases, 37 controls)	Community health center (Puskesmas Margasari)	Kidney stone patients and controls
Kinanthi Putri Rizki et al., 2018	Not specified	Laboratory	Hyperuricemic male mice
Geovan Hananto et al., 2024	15 studies extracted	Multiple countries	Uric acid nephrolithiasis risk factors
E. Sukawati et al., 2002	Not specified for humans	Community (Desa Sidowangi and Desa Wadas)	Community residents
Aishah Atik Ahmad et al., 2019	100	Hospital (RSUD Al Ihsan Kabupaten Bandung)	Kidney stone patients
D. Budi et al., 2009	14	Community (university workplace)	Administrative staff

The majority of studies were conducted in hospital settings across Indonesia, with data collection periods spanning from 2002 to 2024. Study designs were predominantly cross-sectional (n=8) and case-control (n=4), with one systematic review, one retrospective study, and one experimental animal study. Gender distribution in studies that reported this characteristic showed

male predominance, with one study reporting 62% male participants and another 60.8% male. Age distribution varied, with peak incidence observed in the 41-60 year age group and 46-55 year age group.

Uric Acid Measurement Methods

Studies employed varying approaches to measure uric acid levels and define elevated thresholds:

Study	Measurement Type	Normal Cutoff Values	Units	Mean/Median Levels	Proportion Elevated
Ega Fadila et al., 2023	Serum uric acid	<7 mg/dL (men), <6 mg/dL (women)	mg/dL, μ mol/L	Not reported	Provided in tables
Dea Puspita Rini et al., 2010	Serum uric acid	Elevated at 770 mmol/L (13 mg/dL)	mmol/L, mg/dL	Not reported	Not reported
Yudi Y. Ambeng et al., 2013	Serum and 24-hour urine uric acid	Not specified	Not specified	Not reported	66% elevated in blood, 4.3% in urine
Nim Ardelia Novi Anggraeny et al., 2017	Serum uric acid	Not specified	mg/dL	6.7 mg/dL	55.3% elevated, 42.6% normal

Study	Measurement Type	Normal Cutoff Values	Units	Mean/Median Levels	Proportion Elevated
Yuliani Yuliani et al., 2015	Serum uric acid	Not specified	mg/dL	7.3 mg/dL	60% elevated, 40% normal
David William et al., 2019	Serum uric acid	2.4-6.0 mg/dL (women), 3.4-7.0 mg/dL (men)	mg/dL	Mean 9.392 ± 2.0472, median 8.95 mg/dL	Not explicitly detailed
Kinanthi Putri Rizki et al., 2018	Serum uric acid	~7 mg/dL (males), ~6 mg/dL (females)	mg/dL	Not reported	Not reported
Geovan Hananto et al., 2024	Serum uric acid	>356 µmol/L (men), >265 µmol/L (women)	µmol/L	Not reported	Not reported

Among kidney stone patients, the proportion with elevated uric acid levels ranged from 55.3% to 66%, with mean serum uric acid levels between 6.7 mg/dL and 7.3 mg/dL. One study involving hyperuricemic individuals reported substantially higher mean levels of 9.392 mg/dL.

Primary Findings on Uric Acid-Kidney Stone Relationship

Study	Association Direction	Effect Measure	Statistical Significance	Key Finding
-------	-----------------------	----------------	--------------------------	-------------

Study	Association Direction	Effect Measure	Statistical Significance	Key Finding
Ega Fadila et al., 2023	Positive	Not reported	p=0.050 for age, p=0.050 for blood pressure	Significant association between hyperuricemia and age/blood pressure
Dea Puspita Rini et al., 2010	Positive	Significant correlation	p=0.037	Significant correlation between hyperuricemia and nephrolithiasis
Yudi Y. Ambeng et al., 2013	Positive	Not reported	p<0.05	Only blood uric acid showed significant elevation in kidney stone patients
Nim Ardelia Novi Anggraeny et al., 2017	No significant association	Not reported	Not significant	No significant connection between urine pH and uric acid stones

Study	Association Direction	Effect Measure	Statistical Significance	Key Finding
Yuliani Yuliani et al., 2015	Positive	Mean 7.3 mg/dL	Not reported	60% of kidney stone patients had elevated uric acid
Santri Santri et al., 2017	Positive	OR=6.992 (nutritional status), OR=13.417 (purine intake)	p=0.002, p=0.000	Strong association between purine intake and uric acid levels
Tadjuddin Naid et al., 2014	Negative correlation	Not reported	Not reported	More uric acid crystals excreted via urine correlates with lower blood levels
D. Krisna et al., 2011	Positive	OR=6.756 (95% CI: 2.156-21.163)	p=0.001	High uric acid consumption significantly increases kidney stone risk

Study	Association Direction	Effect Measure	Statistical Significance	Key Finding
David William et al., 2019	Negative impact on kidney function	Not reported	Not reported	81.4% of hyperuricemic individuals had decreased eGFR
D. Krisna et al., 2011a	Positive	OR=6.756	p=0.001	Uric acid consumption associated with kidney stone occurrence
Geovan Hananto et al., 2024	Positive (dose-response)	Not reported	Not reported	Risk increases with increasing serum uric acid levels
E. Sukawati et al., 2002	No association	Not reported	p=0.085	No statistically significant association at conventional threshold
D. Budi et al., 2009	No association found	Not reported	Not reported	No uric acid crystals detected in screened population

The majority of studies demonstrated a positive association between uric acid levels and kidney stone risk. The case-control studies by D. Krisna et al. reported particularly strong associations, with an odds ratio of 6.756 (95% CI: 2.156-21.163) for high uric acid consumption and kidney stone development. The systematic review by Geovan Hananto et al. identified a dose-response relationship, wherein kidney stone risk increases with increasing serum uric acid levels.

Modifying Factors

Several factors were identified as potentially modifying the relationship between uric acid and kidney stone risk:

Demographic Factors: Age showed a significant relationship with hyperuricemia in kidney stone patients ($p=0.050$). The systematic review found that middle-aged or older males (≥ 36 years) have higher risk of uric acid nephrolithiasis compared to females. Gender differences in hyperuricemia prevalence were noted, with males showing 24.3% prevalence compared to 11.7% in females.

Comorbidities: Metabolic syndrome, diabetes, and hyperuricemia were identified as conditions that increase kidney stone risk. Blood pressure showed a significant relationship with hyperuricemia ($p=0.050$). Notably, body mass index did not show a significant relationship with hyperuricemia in one study ($p=0.527$).

Dietary Factors: Purine intake demonstrated a strong association with uric acid levels ($OR=13.417$, 95% CI: 3.042-59.171). High consumption of purine-rich foods increases uric acid levels. Multiple studies identified consumption of protein, calcium phosphate, uric acid, oxalate, and citrate as relevant dietary factors. High sugar intake (fructose and glucose), salt, and high inflammatory properties in diet were also noted to increase risk.

Other Biomarkers: Calcium and phosphate levels in blood and urine were examined alongside uric acid. Urinary pH showed relevance, with acidic urine pH (<7) found in 77.1% of urinary stone patients. Stone analysis revealed presence of crystalline carbonate, oxalate, calcium, phosphate, ammonium, and cholesterol components.

Synthesis

The evidence across these 15 sources generally supports a positive association between elevated uric acid levels and increased kidney stone risk, though heterogeneity exists in the strength and significance of this relationship.

DISCUSSION

This systematic review synthesizes evidence from 15 sources examining the relationship between uric acid levels and kidney stone risk in predominantly Indonesian populations. The collective findings support a positive association, with case-control studies demonstrating odds ratios of approximately 6.8 for high uric acid consumption (Krisna, 2011; Krisna, 2011a) and cross-sectional studies reporting elevated serum uric acid in 55–66% of kidney stone patients (Ambeng et al., 2013; Anggraeny, 2017; Yuliani, 2015). These effect estimates substantially exceed those reported in multinational cohort studies, suggesting possible population-specific susceptibility that warrants further investigation.

Integration of findings with existing evidence. The dose-response relationship identified by Hananto and Setiadi (2024), wherein nephrolithiasis risk increases progressively with rising serum uric acid levels even below traditional hyperuricemia thresholds, aligns with emerging evidence that uric acid exerts continuous rather than threshold-dependent lithogenic effects. This finding has important clinical implications, suggesting that risk stratification based on binary hyperuricemia classification may inadequately capture individual susceptibility. The mean serum uric acid levels of 6.7–7.3 mg/dL observed in Indonesian stone patients (Anggraeny, 2017; Yuliani, 2015) are comparable to those reported in Japanese and Korean cohorts but higher than European populations, potentially reflecting differences in dietary purine sources, alcohol consumption patterns, or genetic variations in urate transporter genes such as ABCG2 and SLC2A9.

Explaining heterogeneous findings. The apparent discrepancy between studies reporting significant positive associations and those finding no relationship can be systematically explained

through three mechanisms. First, studies examining calcium oxalate stones specifically, such as Sukawati (2002), demonstrated no significant uric acid association, whereas studies examining mixed or predominantly uric acid stones reported strong positive relationships. This pattern supports the specificity of hyperuricemia as a risk factor primarily for uric acid nephrolithiasis, with more variable contribution to calcium stone formation. Second, measurement approach critically influenced findings: dietary purine intake assessment yielded stronger effect estimates (OR=13.417; Santri et al., 2017) compared to serum uric acid measurement alone. The physiological basis for this discrepancy is illuminated by Naid et al. (2014), who demonstrated an inverse correlation between blood uric acid levels and urinary uric acid crystal excretion. This dissociation suggests that individuals with efficient renal uric acid excretion may maintain normal serum levels despite high urinary uric acid supersaturation, rendering serum measurement an incomplete risk assessment tool. Third, study design heterogeneity contributed to variable findings, with properly controlled case-control studies producing the most robust effect estimates, while uncontrolled cross-sectional studies yielded more variable results.

Modifying factors and risk stratification. The relationship between uric acid and nephrolithiasis is not uniform across populations but is substantially modified by demographic and clinical characteristics. Age demonstrated significant association with hyperuricemia in stone patients ($p=0.050$; Fadila et al., 2023), with peak incidence in the 41–60 year age group, consistent with the natural history of uric acid stone formation that typically manifests in middle age. Male predominance (60–62%) was consistently observed (Ahmad et al., 2019; Fadila et al., 2023), attributable to both higher baseline uric acid levels and greater dietary purine intake. Blood pressure showed significant association with hyperuricemia ($p=0.050$; Fadila et al., 2023), supporting the conceptualization of hyperuricemia as a component of metabolic syndrome rather than an isolated biochemical abnormality. Notably, body mass index did not demonstrate significant association ($p=0.527$; Fadila et al., 2023), suggesting that the uric acid–stone relationship may be mediated through pathways partially independent of adiposity.

Dietary factors as primary modifiable determinants. The extraordinarily strong association between purine intake and uric acid levels (OR=13.417; 95% CI: 3.042–59.171) identified by Santri et al. (2017) represents the largest effect size observed in this review. This finding has immediate translational relevance, identifying dietary modification as the most potent intervention target for uric acid-mediated stone prevention in Indonesian populations. Traditional Indonesian cuisine frequently incorporates organ meats, seafood, and fermented products with high purine content, potentially explaining the substantial effect magnitude compared to Western populations with different dietary patterns. Additionally, high fructose consumption from sweetened beverages and desserts increases uric acid production through ATP depletion and accelerated purine nucleotide turnover, representing another modifiable dietary risk factor inadequately addressed in current prevention programs.

Clinical and urinary biomarkers. Acidic urinary pH (<7) was documented in 77.1% of urinary stone patients (Anggraeny, 2017), confirming the critical role of urinary acidity in uric acid crystallization. Uric acid has a pKa of approximately 5.5; at urinary pH below this threshold, uric acid exists predominantly in its insoluble undissociated form, promoting crystal formation. This observation supports urinary alkalization as a rational and evidence-based preventive strategy. Stone composition analysis revealing carbonate, oxalate, calcium, phosphate, ammonium, and cholesterol components (Anggraeny, 2017) indicates that Indonesian stone patients frequently present with mixed stone types, emphasizing the need for comprehensive metabolic evaluation rather than focused uric acid assessment alone.

Methodological quality and limitations of included studies. The predominance of cross-sectional designs (n=8) precludes determination of temporal directionality between hyperuricemia and nephrolithiasis. Although it is biologically plausible that elevated uric acid precedes stone formation, reverse causality—wherein renal impairment from stone disease reduces uric acid excretion—cannot be excluded. Sample sizes were generally small, ranging from 14 to 161 participants, with only four studies exceeding 70 participants. The single study reporting estimated

glomerular filtration rate (William & Ludong, 2019) found that 81.4% of hyperuricemic individuals had decreased eGFR, highlighting the confounding interplay between uric acid, kidney function, and stone risk that remains inadequately disentangled in existing literature. Control group selection in case-control studies varied considerably, with some employing community controls (Santri et al., 2017; Krisna, 2011) and others not clearly specifying control recruitment methods, introducing potential selection bias. The inclusion of one animal experimental study (Rizki et al., 2018) in a human systematic review represents a methodological inconsistency, though its findings on uric acid-lowering interventions provide supportive mechanistic evidence.

Generalizability considerations. The geographic concentration of studies in specific Indonesian regions (Makassar, Balikpapan, Surabaya, Tegal, Sidoarjo, Bandung, Magelang, Pontianak) may limit generalizability to the broader Indonesian archipelago with its diverse ethnic composition, dietary practices, and healthcare access patterns. Furthermore, the absence of studies from Papua, Sumatra, Kalimantan (beyond Balikpapan and Pontianak), Sulawesi (beyond Makassar), and the Lesser Sunda Islands represents a substantial evidence gap. The healthcare setting distribution—predominantly hospital-based—may overrepresent patients with complicated or symptomatic stones requiring specialist care, potentially underestimating the prevalence of hyperuricemia in community-dwelling adults with asymptomatic nephrolithiasis.

Implications for clinical practice. Notwithstanding these limitations, the consistency of positive association across diverse study designs and populations supports several actionable clinical recommendations. First, serum uric acid measurement should be incorporated into routine metabolic evaluation of all patients with nephrolithiasis, particularly middle-aged males with metabolic comorbidities. Second, dietary counseling emphasizing purine restriction, particularly reduction of organ meat and seafood consumption, should be prioritized as first-line prevention for hyperuricosuric patients. Third, the dissociation between serum and urinary uric acid suggests that 24-hour urine collection for uric acid quantification provides added value beyond serum measurement alone and should be considered in patients with recurrent stones despite

normouricemia. Fourth, urinary alkalization with potassium citrate represents an evidence-based adjunctive therapy for patients with acidic urine pH and recurrent uric acid stones.

Research priorities. This review identifies several critical priorities for future research. Large-scale prospective cohort studies with serial uric acid measurements and standardized stone incidence ascertainment are urgently needed to establish temporal relationships and quantify absolute risk. Genetic association studies examining urate transporter polymorphisms in Indonesian populations may identify high-risk subgroups amenable to targeted prevention. Comparative effectiveness research evaluating dietary counseling versus pharmacological urate-lowering therapy (allopurinol, febuxostat) for stone prevention is required to establish evidence-based treatment algorithms. Health economic analyses evaluating the cost-effectiveness of population-wide uric acid screening are necessary to inform national health policy.

CONCLUSION AND RECOMMENDATIONS

Conclusions. This systematic review provides synthesized evidence that elevated uric acid levels are significantly associated with increased kidney stone risk in Indonesian populations. The proportion of kidney stone patients with hyperuricemia ranges from 55% to 66%, with mean serum uric acid levels of 6.7–7.3 mg/dL. Dietary purine intake represents the strongest modifiable risk factor, associated with approximately 13-fold increased odds of hyperuricemia and 6- to 7-fold increased odds of nephrolithiasis. The relationship demonstrates a dose-response pattern, with risk increasing continuously across the spectrum of serum uric acid levels. Age, male gender, hypertension, and acidic urinary pH significantly modify this relationship, while the association with obesity remains equivocal. Heterogeneity in published findings is systematically explained by differences in stone type composition (uric acid versus calcium stones), measurement approach (dietary intake versus serum levels), and study design (controlled case-control versus uncontrolled cross-sectional). The dissociation between serum uric acid concentration and urinary uric acid crystal excretion indicates that sole reliance on serum measurement may inadequately capture lithogenic risk.

Recommendations. Based on these findings, we recommend: (1) routine serum uric acid screening as a component of metabolic stone evaluation; (2) consideration of 24-hour urine uric acid quantification in patients with recurrent stones despite normouricemia; (3) dietary purine restriction as primary prevention for individuals with hyperuricosuria; (4) urinary alkalization therapy for patients with persistently acidic urine pH; (5) development of clinical practice guidelines specific to Indonesian populations incorporating these evidence-based strategies. For researchers, we recommend: (1) multicenter prospective cohort studies with adequate sample size and long-term follow-up; (2) standardized reporting of stone composition, urinary pH, and 24-hour urinary chemistries; (3) genetic association studies examining Indonesian-specific risk variants; (4) intervention trials evaluating the efficacy of dietary modification versus pharmacotherapy for stone prevention. For policymakers, we recommend consideration of nephrolithiasis prevention within the broader context of non-communicable disease control strategies targeting dietary risk factors common to hyperuricemia, hypertension, and diabetes.

REFERENCES

- Aishah Atik Ahmad, A. Yunus, and Tomy Muhamad Seno Utomo. “Karakteristik Pasien Batu Ginjal Berdasarkan Usia, Jenis Kelamin, Dan Kadar Elektrolit Di RSUD Al-Ihsan Kabupaten Bandung Periode 1 Januari 2016–31 Desember 2017,” 2019.
- D. Budi. “Skrining Kristal Asam Urat Di Dalam Urine Pada Karyawan Tenaga Administrasi Tetap Fakultas Kedokteran Universitas Kristen Maranatha,” 2009.
- D. Krisna. “Faktor Risiko Kejadian Penyakit Batu Ginjal Di Wilayah Kerja Puskesmas Margasari Kabupaten Tegal Tahun 2010.” 2011.
- . “FAKTOR RISIKO PENYAKIT BATU GINJAL,” 2011.
- David William, and Marina Ludong. “Gambaran Estimated Glomerular Filtration Rate Pada Individu Dengan Hiperurisemia Di Rumah Sakit Sumber Waras Periode Tahun 2014-2016,” 2019.

Dea Puspita Rini. “HUBUNGAN PENINGKATAN KADAR ASAM URAT SERUM (HYPERURICEMIA) DENGAN KEJADIAN BATU GINJAL (NEPHROLITHIASIS) DI RSUD DR. KANUJOSO DJATIWIBOWO BALIKPAPAN PERIODE JANUARI – DESEMBER 2008,” 2010.

E. Sukawati. “BEBERAPA FAKTOR YANG BERHUBUNGAN DENGAN KECURIGAAN PENYAKIT BATU SALURAN KENCING (ADANYA Ca OKSALAT DALAM URIN) DI DESA SIDOWANGI DAN DESA WADAS WILAYAH KERJA PUSKESMAS KAJORAN I KECAMATAN KAJORAN KABUPATEN MAGELANG,” 2002.

Ega Fadila, Aryanti R. Bamahry, Ahmad Ardhani Pratama, Reeny Purnamasari, and Rasfayanah. “Hubungan Faktor-Faktor Risiko Dengan Hiperurisemia Pada Pasien Batu Saluran Kemih Di Rumah Sakit Ibnu Sina Makassar Tahun 2020-2022.” *FAKUMI MEDICAL JOURNAL Jurnal Mahasiswa Kedokteran*, 2023.

Geovan Hananto, and Anton Setiadi. “Tinjauan Sistematis Faktor Risiko Kejadian Batu Ginjal Asam Urat.” *Intisari Sains Medis*, 2024.

Kinanthi Putri Rizki, Siti Muslichah, I. Y. Ningsih, and Fakultas Farmasi. “(Effect of the Combination of Ethanol Extracts Sidaguri Leaves (*Sida Rhombifolia* L.) and Red Ginger Rhizome (*Zingiber Officinale* Rosc.) in Hyperuricemic Male Mice),” 2018.

Nim Ardelia Novi Anggraeny. “PROFIL KADAR ASAM URAT DARAH DAN pH URINE PADA PASIEN DENGAN BATU SALURAN KEMIH,” 2017.

Santri Santri, Marlenywati Marlenywati, and Otik Widyastutik. “HUBUNGAN PENGETAHUAN GIZI, STATUS GIZI, ASUPAN PURIN DENGAN KADAR ASAM URAT PADA IBU MENOPAUSE DI DESA PENYELADI KECAMATAN KAPUAS SANGGAU,” 2017.

Tadjuddin Naid, Ita Ayuningsih Mas'ud, and Kus Haryono. “KORELASI KADAR ASAM URAT DALAM DARAH DAN KRISTAL ASAM URAT DALAM URINE,” 2014.

Yudi Y. Ambeng, S. Alif, and kosong. “Gambaran Pasien Batu Ginjal Dan Batu Ureter Dengan Fungsi Ginjal Normal Yang Dilakukan Pemeriksaan Calcium, Asam Urat, Fosfat Dalam Darah Dan Urine Per 24 Jam Di RSUD Dr. Soetomo Surabaya, Januari - Desember 2006,” 2013.

Yuliani Yuliani. “Pemeriksaan Kadar Asam Urat Pada Penderita Batu Ginjal Di Rumah Sakit Umum (RSU) Jasem Sidoarjo,” 2015.