Clinical Research

Clinical risk factors of recurrent kidney stone disease: a cohort retrospective study in a tertiary referral hospital

Widi Atmoko[1], Febriyani[1], Ary Indriana Savitri[2], Cuno Uiterwaal[2], Siti Setiati[3], Agus Rizal Ardy Hariandy Hamid[1], Ponco Birowo[1], Nur Rasyid[1]

pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.oa.247166
Med J Indones. 2023;32:224–9

Received: September 18, 2023
Accepted: January 09, 2024
Published online: February 02, 2024

Authors' affiliations:
[1]Department of Urology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [2]Department of Clinical Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands, [3]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Widi Atmoko
Department of Urology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Salemba Raya No. 6, Central Jakarta 10430, DKI Jakarta, Indonesia
Tel/Fax: +62-21-3912477
E-mail: dr.widiatmoko@yahoo.com

ABSTRACT

BACKGROUND Nephrolithiasis or kidney stone disease (KSD) is common worldwide. Despite various effective treatment strategies, KSD recurrence remains a problem. This study aimed to investigate the risk factors of KSD recurrence.

METHODS This retrospective cohort study used medical records of all patients who came to the Department of Urology, Cipto Mangunkusumo Hospital, Jakarta, from January 2014 to December 2019, with asymptomatic and symptomatic KSD. Demographic information, clinical data, exposure to risk factors, and recurrent KSD diagnosis were collected. Univariate and multivariate analyses using logistic regression were performed to determine the significant risk factors.

RESULTS We reported 325 patients with a median age of 52 years. More than half of the patients were males and from Java. Staghorn stone dominated the KSD types found in 181 patients (55.7%). After undergoing percutaneous nephrolithotomy, 214 patients (65.8%) became stone-free. However, about 40.6% of them later developed recurrent KSD. The adjusted odds ratio in recurrent KSD were 1.46 (95% confidence interval [CI] 1.33–1.59) for younger age, 1.86 (95% CI 1.61–2.07) for overweight–obese, 2.13 (95% CI 1.89–2.31) for less fluid intake, 1.81 (95% CI 0.97–2.12) for routine tea consumption, 1.24 (95% CI 1.06–1.84) for routine vegetables consumption, 2.27 (95% CI 1.83–2.84) for a family history of KSD, and 2.08 (95% CI 1.77–2.39) for diabetes mellitus (DM).

CONCLUSIONS Most patients with recurrent KSD were younger, overweight/obese, had less fluid intake, a family history of KSD, and DM. Modifying a healthy lifestyle and a balanced diet is important to prevent KSD recurrence.

KEYWORDS kidney calculi, nephrolithiasis, urolithiasis

Kidney stone disease (KSD) and nephrolithiasis are among the most common urological diseases, affecting approximately 5–9% of Europeans, 7–13% of North Americans, and 1–19.1% of Asians.[1–3] Decreased kidney function, which can result in chronic kidney disease and end-stage renal failure, is one of the main negative consequences of KSD. Furthermore, it is associated with an increased risk of other comorbidities such as malignancy and cardiovascular disease events, thus leading to a financial burden resulting from increased healthcare costs.[4,5] Due to lifestyle, dietary habits, and climate change, the incidence of KSD is increasing.[6]

The main goal of treatment is to maintain a stone-free condition, leaving no residual fragments.[7,8] There are various established treatment options for KSD, including conservative management, open surgery, percutaneous nephrolithotomy (PCNL), ureterorenoscopy, and extracorporeal shock wave lithotripsy (ESWL). Despite the satisfactory outcome

after treatment, the recurrence of KSD remains high.[9,10] Studies have reported that the recurrence rate is 6–7% after 1 year and 21–53% after 3–5 years, and the lifetime risk of recurrence is estimated to be 60–80%.[11,12]

The high recurrence rate remains a challenge for clinicians treating patients with KSD. Identifying high-risk stone patients and preventing KSD are important for reducing further complications. However, data on the risk factors for recurrent KSD are still lacking, especially in Indonesia, despite the high prevalence of patients. This study is among the first to explore whether demographics, dietary habits, and lifestyle play a role as significant risk factors for recurrent KSD. The results of this study contribute to the existing knowledge regarding KSD as benchmark data for further studies and serve as clinician guidelines for preventing recurrent KSD.

METHODS

Study design and participants

This retrospective cohort study used medical records from January 2014 to December 2019 from the Urology Outpatient Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The inclusion criteria were patients with asymptomatic or symptomatic KSD who visited the hospital and aged 18–80 years. The diagnosis of KSD was made by a urologist based on clinical and radiological examinations, which included ultrasonography, plain abdominal photography, and computed tomography, referring to the Indonesian Urological Association guidelines for KSD. Patients with incomplete medical records were also excluded. The sample size was calculated using the formula for the cohort study, which resulted in a minimum sample size of 273. The patient's demographic and dietary information, clinical symptoms, and stone-free status were collected and assessed. Data were obtained from medical records, interviews, and online questionnaires. Patients with KSD recurrence after treatment for the first stone episode were identified.

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital, Jakarta, Indonesia (No: KET-199/UN2.F1/ETIK/PPM.00.02/2022). Written informed consent was obtained from all participants prior to their participation. If a participant was illiterate, a written informed consent was obtained from a legal representative.

Assessment of the variables

Based on their stone-free status after PCNL, the participants were classified into stone-free or residual stone groups. Stone-free status was defined as the absence of residual stone fragments or fragments ≤4 mm in diameter. Stone recurrence was diagnosed when patients with symptomatic stones presented to the emergency department or urology clinic and asymptomatic patients with radiological recurrence after stone intervention with a stone-free status. A radiological recurrence was defined as new stones reported from imaging studies after surgery.[13] The recurrent and non-recurrent KSD groups were then compared to the following variables: age, sex, ethnicity, family history of KSD, fluid intake, tea consumption, vegetable consumption, diabetes mellitus (DM), hypertension, hypercholesterolemia, physical activity, and body mass index (BMI).[14–16]

The mean/median age of the participants was first evaluated and became the cut-off value for categorizing the age group. Subjective variable data, such as dietary habits, were collected using either online or direct questionnaire forms filled out by the participants. Fluid intake was evaluated using the approximate fluid intake within 24 hours. After determining the mean/median value, the participants were categorized into two groups based on the cut-off value. The tea and lean/fatty meat consumption variables were categorized into routine, defined by ≥3 times/week, and non-routine, defined by <3 times/week. A nonstop and minimum of 30 min of physical exercise can be defined as physical activity. They were then categorized into routine (≥3 times/week) or non-routine (<3 times/week). Vegetable consumption included any vegetable intake, defined as routine (≥7 times/week) or non-routine (not daily or <7x/week).

Statistical analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as mean (standard deviation) and were tested using Student's *t*-test. Medians and ranges were used to represent non-normally distributed data. Categorical variables are presented as numbers (percentages) and were tested using the chi-square test. Univariate analysis using logistic regression was performed to evaluate the crude association between each factor and the occurrence of recurrent KSD. Variables with $p<0.25$ were then included in the multivariate analysis using

logistic regression. The results are expressed as odds ratios (ORs) with 95% confidence intervals and corresponding *p*-values. Statistical significance was a 2-sided *p*-value of <0.05. All analyses were performed using SPSS software version 25 (IBM Corp., USA).

RESULTS

Within 5 years, 479 patients with kidney stones visited the Urology Outpatient Clinic, Cipto Mangunkusumo Hospital. However, owing to incomplete medical record data for 154 patients, 325 patients were included in the analysis. The baseline characteristics of the study participants are shown in Table 1. Normality test results for some variables, such as age, were not normally distributed; therefore, a nonparametric test was used. The median patient age was 52 years (ranged from 18–80 years). Most of the patients were males and from Java. Approximately 32.6% of the patients were office workers. Staghorn stones were more common than non-staghorn stones. The mean stone size before the intervention was 24.3 mm. None of the patients had undergone any prior surgical intervention. PCNL was the treatment of choice for all patients. After PCNL, 214 (65.8%) patients became stone-free; the remaining patients still had residual stones. Among patients with a stone-free status, follow-up visits or monitoring were performed for a mean duration of 30.7 (3.2) months, and 40.6% of them later developed recurrence from the prior KSD.

Table 1. Baseline characteristics of study participants

Characteristics	N = 325
Age (years), median (min–max)	52 (18–80)
Follow-up (months), mean (SD)	30.7 (3.2)
Male sex, n (%)	176 (54.1)
Origin, n (%)	
Sumatra	74 (22.8)
Java	174 (53.5)
Borneo	27 (8.3)
Sulawesi	25 (7.7)
Bali and Nusa Tenggara	14 (4.3)
Maluku and Papua	11 (3.4)
Occupation, n (%)	
Student	38 (11.7)
Office worker	106 (32.6)
Industrial worker	55 (16.9)
Entrepreneur or freelance	77 (23.7)
Unemployed	49 (15.1)
Status after PCNL, n (%)	
Stone-free	214 (65.8)
Residual stone	111 (34.2)
Stone type, n (%)	
Staghorn	181 (55.7)
Non-staghorn	144 (44.3)
Recurrence, n (%)	
Recurrent	87 (40.6)
Non-recurrent	127 (59.4)

PCNL=percutaneous nephrolithotomy; SD=standard deviation

The associations between the evaluated factors and KSD recurrence are shown in Table 2. Younger age, less fluid intake, routine vegetable consumption, a family history of KSD, and DM were associated with recurrent KSD. The risk of recurrent KSD increased more than 2-fold with less fluid intake, routine vegetable consumption, and a family history of KSD. Male sex, overweight/obesity, tea consumption, fatty meat consumption, hypercholesterolemia, hypertension, and lack of routine physical activity tended to increase the odds of recurrent KSD, although the difference was not statistically significant. Multivariate analysis was performed with age, BMI, fluid intake, vegetable consumption, tea consumption, family history of KSD, and DM as independent variables. The adjusted OR for BMI was higher than the crude OR, and patients who were overweight and obese had a recurrent KSD 1.86 times higher compared to the underweight and normal BMI groups.

DISCUSSION

In this study, patients with kidney stone ranged from 18 to 80 years old. In line with previous studies,[14–17] 52 years old was the median age of patients, and younger patients (18–51 years) had a higher risk of KSD. All patients in this study underwent PCNL as the first method for active stone removal and as the treatment of choice for kidney stones >20 mm based on the guidelines, with no history of surgical intervention. Some patients had undergone prior ESWL and a trial with oral medication. This study reported the successful stone-free rate following PCNL. Only the stone-free status group after the intervention was included in the risk factor analysis to minimize the confounding effect of stone history. However, almost half of the patients experienced recurrence.

Table 2. Univariate and multivariate analyses of risk factors for recurrent KSD

Characteristics	Recurrent, n (%)	Non-recurrent, n (%)	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (years)				**0.049**		**<0.001**
18–51	44 (50.6)	47 (37.0)	1.38 (1.01–1.90)		1.46 (1.33–1.59)	
52–80	43 (49.4)	80 (63.0)	1.00		1.00	
Male sex	49 (56.3)	68 (53.5)	1.12 (0.64–1.93)	0.688	-	-
BMI*				0.115		**0.003**
Overweight–obese	52 (59.8)	62 (48.8)	1.55 (0.89–2.71)		1.86 (1.61–2.07)	
Underweight–normal	35 (40.2)	65 (51.2)	1.00		1.00	
Fluid intake (l/day)				**0.008**		**0.008**
<1.8	51 (58.6)	51 (40.2)	2.11 (1.21–3.67)		2.13 (1.89–2.31)	
≥1.8	36 (41.4)	76 (59.8)	1.00		1.00	
Tea consumption†				0.082		0.083
Routine	44 (50.6)	49 (38.6)	1.33 (0.96–1.83)		1.81 (0.97–2.12)	
Non-routine	43 (49.4)	78 (61.4)	1.00		1.00	
Vegetable consumption‡				**0.001**		**0.034**
Routine	52 (59.8)	37 (29.1)	1.85 (1.49–2.14)		1.24 (1.06–1.84)	
Non-routine	35 (40.2)	90 (70.9)	1.00		1.00	
Lean/fatty meat consumption†				0.35		-
Routine	45 (51.7)	51 (40.2)	1.31 (0.95–1.81)		-	
Non-routine	42 (48.3)	76 (59.8)	1.00			
Family history of KSD	36 (41.4)	18 (14.2)	2.09 (1.55–2.80)	**0.001**	2.27 (1.83–2.84)	**<0.001**
DM	35 (40.2)	31 (24.4)	1.51 (1.10–2.06)	**0.014**	2.08 (1.77–2.39)	**0.015**
Hypercholesterolemia	31 (35.6)	39 (30.7)	1.24 (0.70–2.22)	0.45	-	-
Hypertension	33 (37.9)	44 (34.6)	1.15 (0.65–2.03)	0.623	-	-
Physical activity†				0.82		-
Routine	48 (55.2)	72 (56.7)	1.02 (0.81–1.28)		-	
Non-routine	39 (44.8)	55 (43.3)	1.00			

BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; KSD=kidney stone disease; OR=odds ratio
*Overweight–obese: BMI ≥23 kg/m^2 and underweight–normal: BMI <23 kg/m^2; †routine: ≥3 times/week, non-routine: <3 times/week; ‡routine: ≥7 times/week, non-routine: not daily or <7 times/week

Varying KSD recurrence rates have been reported. In a retrospective study, Rule et al[14] presented that KSD recurrence rates at 2, 5, 10, and 15 years were 11%, 20%, 31%, and 39%, respectively. Compared to the present study, the recurrence rate was higher (40.6%) after >2 years of follow-up. The present study found a strong positive association between KSD recurrence and age, BMI, fluid intake, vegetable consumption, a family history of KSD, and DM.

In the present study, patients with a family history of KSD had 2.09 times higher odds of recurrence than those without a family history of KSD. This finding was consistent with a previous study reporting a higher prevalence of stone disease in patients with a family history of KSD (hazard ratio 1.64, p<0.001).[14] This is probably because of genetic factors contributing to the recurrence of KSD.[14] Metabolic disease has been associated with KSD. Chronic inflammation and insulin resistance lead to complex metabolic derangements that contribute to the pathogenesis of various diseases. Recent studies have shown that the early processes of kidney stone formation involve inflammatory responses, including the expression of inflammatory molecules such as monocyte chemoattractant protein-1 and osteopontin and macrophage infiltration.[18]

DM was a significant risk factor for recurrent KSD. Insulin resistance, which plays a role in type 2 DM, has been linked to the formation of uric acid stones. It results in a deficit in ammonium production in the kidney, which lowers urinary pH, thus generating a milieu for the stone formation.[18] However, it is not a surprising fact that the prevalence of patients with diabetes is increasing globally, including Indonesia. Unfortunately, Indonesia has low public health.[19] This should attract the attention of all clinicians, especially those in primary healthcare. Prevention and management of diabetes are needed to avoid KSD and its recurrence.

In a previous study of 146 patients with KSD recurrence, 100 (68.5%) were males;[20] this aligns with the finding that KSD occured more frequently in men than in women. However, sex was not a significant risk factor in this study. This suggests that well-known lifestyle factors for KSD in male patients explain only a fraction of the observed risk, indicating that other factors, such as genetics or hormones, might also play a role.

Obesity is a significant risk factor for the development of KSD. Moyano et al[21] revealed that 41.6% of men were overweight, with a BMI ranging from 25 to 30, and 9.6% had a BMI of 30 or greater. In the present study, 59.8% of the patients had an abnormally high BMI, supporting the notion that a high BMI is a risk factor for recurrent KSD. However, the exact mechanism through which obesity increases the risk of incident stone formation remains unclear. However, obesity, which has been suggested to be associated with insulin resistance, can alter urine composition. Insulin resistance may manifest in the kidneys as defects in ammonium production and the ability to excrete acid.[22]

Interestingly, diet was also associated with the recurrence of KSD. Contrary to Zhuo et al,[15] who reported that a high dietary intake of vegetables was a protective factor against urolithiasis (OR 0.856), the present study found that routine vegetable consumption increased the risk of recurrent KSD. This might be caused by high oxalate-rich consumption, as dietary oxalate is mainly derived from plant-based foods. The oxalate-rich vegetables, such as spinach, soybeans, green beans, nuts, and sweet potatoes, are common in Indonesia.[22] However, a certain kind or specific concentration amount of the consumed vegetables was not evaluated, and the retrospective design of study might lead to bias. In addition, these contrary findings might be promoted by combining other imbalanced diets, such as lean/fatty meat consumption and less fluid intake. Further research exploring specific kinds of vegetables and determining the cut-off value for consumption is still needed.

A fluid intake of less than 1.8 liter in 24 hours independently increased the odds of recurrent episodes of KSD by more than 2-fold. Our findings were consistent with those of a previous study, which indicated that high fluid intake decreased the risk of stone formation (OR 0.758). High fluid intake has been shown to increase urine volume and reduce the concentration of calcium oxalate in urine, consequently reducing the risk and recurrence rate of stone formation by 50% and 60–80%, respectively.[15]

In the present study, tea consumption more than 3 times/week also affected urinary stone recurrence. Another study also investigated whether black tea consumption increased the risk of stone formation due to increased oxalate intake.[23] On the contrary, a study in Southern China found that strong tea preference might be a protective factor for urolithiasis (OR 0.793).[18] This contrary finding might be caused by certain kinds of tea from different demographic regions and specific concentrations of tea consumption. The mechanism by which tea exerts protective effects against urolithiasis remains unclear and requires further investigation.

Other risk factors contributing to KSD recurrence, including stone composition, have also been observed. Few studies have examined the risk of recurrence with different stone compositions. The genetic basis of cystine stones reasonably leads to greater stone recurrence than most other stone compositions.[24] Unfortunately, stone analysis is still generally unavailable in all regions of Indonesia and not routinely performed in all patients after PCNL. Therefore, this study did not include these factors in the risk factor analyses.

A limitation of this retrospective study was the possibility of recall bias. Further prospective studies are needed to confirm the causal relationships between these variables. Several variables such as dietary intake may have resulted in high individual subjectivity. The sample size was limited to 325 participants because many other patients who visited over 5 years ago had incomplete medical records, leading to insufficient data. This might have reduced the power of the study and increased the margin of error.

In conclusion, most patients with recurrent KSD were younger, overweight/obese, had less fluid intake, a family history of KSD, and DM. Modifying a healthy lifestyle and maintaining a balanced diet are important in preventing KSD recurrence. Further studies and prospective or clinical trials are needed for a better understanding, and a more specific exploration, such as the role of genetics and hormones, will become an area of interest.

Conflict of Interest

Agus Rizal Ardy Hariandy Hamid is the editor-in-chief of this journal, and Ary Indriana Savitri is the editorial board member but were not involved in the review or decision-making process of the article.

Acknowledgment

The authors would like to thank Center of Evidence-Based Medicine, Cipto Mangunkusumo Hospital, Jakarta.

Funding Sources

None.

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