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Clinical Features and Outcomes of Symptomatic Urinary Stone Disease: An Analysis According to Stone Compositions

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ABSTRACT

Background: The incidence of urinary stone disease is increasing, and these patients are at greater risk for various kidney complications. Given its heterogeneity and potential clinical implications, we investigated the baseline characteristics and clinical outcomes of symptomatic stone disease according to stone compositions.

Methods: This was a single-center, retrospective study that analysed symptomatic urinary stone disease patients with known stone compositions from 2002 to 2020. Patients were grouped into three categories: calcium-containing, urate, and struvite stones. Baseline characteristics, prevalence of diverse comorbidities, concurrent acute kidney injury (AKI) events, long-term kidney function deterioration, and mortality were analysed.

Results: Calcium-containing stones were the most common type. Patients with urate stones were significantly older, predominantly male, and more likely to have various comorbidities and low urinary pH. Calcium excretion was significantly higher in patients with calcium-containing stones, while the excretion of other components was comparable across all stone compositions. The incidence of AKI in symptomatic urinary stone disease patients was 35.3%. Of note, urate and struvite stones were independently associated with concurrent AKI. An eGFR decline of more than 30% was observed in 5.7% of the patients, with the highest rates among patients with urate stones. Older age, female sex, higher baseline serum creatinine level, and concurrent AKI episodes, but not stone composition, were independently associated with subsequent kidney function deterioration.

Conclusion: In symptomatic urinary stone disease, concurrent AKI episodes, older age, female sex, and lower baseline kidney function were independently associated with progressive kidney function deterioration, regardless of stone composition.

Keywords: Urinary stone disease; Stone composition; Risk factors; Acute kidney injury; Kidney function deterioration

Abbreviations: Acute Kidney Injury (AKI); Chronic Kidney Disease (CKD); Chronic Obstructive Pulmonary Disease (COPD); C-Reactive Protein (CRP); estimated Glomerular Filtration Rate (eGFR); End-Stage Kidney Disease (ESKD); Erythrocyte Sedimentation Rate (ESR); Extracorporeal Shock Wave Lithotripsy (ESWL); Hazard Ratio (HR); Institutional Review Board (IRB); National Health Insurance Service (NHIS); National Kidney Foundation and the U.S. Food and Drug Administration (NKF-FDA); Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Odds Ratio (OR)

INTRODUCTION

Several epidemiological studies have shown that the incidence of urinary stone diseases is increasing. Although its incidence varies depending on the geological, clinical, and social characteristics, it is undeniable that it is emerging as a global concern. In the United States, one in 11 individuals experience kidney stone

disease during their lifetime [1]. A study conducted on 1,543 adults in Florence, Italy, reported a prevalence of 7.5%, and a recurrence rate of more than 50% [2]. In Asian countries, the reported incidence is somewhat lower, but an increasing trend in urinary stone disease with its associated social burden is also noted. Zeng et al. reported that the prevalence of kidney stones in China was 6.4% [3]. A recent study from South Korea that analysed the National Health Insurance Service (NHIS) sample cohort dataset showed that the annual incidence of urinary stone disease is 3.27 per 1,000 person-years [4]. Despite limitations in direct comparison due to differences in patient populations and methods used for analysis, it is evident that urinary stone disease is emerging as an increasingly important global medical issue.

Traditionally, urinary stone disease is considered a urologic disorder, requiring pain management and stone removal. However, recent nephrological perspectives reported that it is more chronic medical conditions that are associated with acute kidney injury (AKI), chronic kidney disease (CKD), end-stage kidney disease (ESKD) and other metabolic diseases, contributing to an increase in morbidity and mortality [5-10].

Until recently, most studies have been population-based historical cohort studies that used diagnostic codes without considering the stone types. Considering that urinary stone disease is a highly heterogeneous condition with different risk factors and concurrent comorbidities that are potentially linked to different clinical outcomes according to stone composition [11], we analysed symptomatic patients with stones of known composition. Baseline characteristics, including comorbid conditions, urinalysis, and 24-hour urine chemistry, as well as risk factors for concurrent AKI, subsequent kidney function deterioration, and mortality were analysed [12].

MATERIALS AND METHODS

Study population and data selection

This single-center, retrospective observational study analysed data from patients admitted to the Department of Nephrology or Urology, Korea University Anam Hospital, due to symptomatic urinary stone disease, between January 2002 and December 2020. All included patients had baseline serum creatinine measurements. This study was approved by the Institutional Review Board (IRB) of the Korea University Anam Hospital (IRB approval No. 2022AN0310). We included all patients whose stone composition was analysed using ureteroscopic removal or ESWL (extracorporeal shock wave lithotripsy) during the study. Demographic and laboratory data, including blood biochemistry, urinalysis, and 24-hour urine chemistry, were collected. Concurrent AKI and long-term outcome data regarding kidney function deterioration and mortality were analysed. Moreover, 24-hour urine chemistry, from 233 patients were also analysed.

Stone classification

Stone composition was analysed using Fourier transform infrared spectroscopy. The stone analysis test items were structured to list the presence or absence of individual components, such as calcium, oxalate, and urate. The stone composition groups were redefined based on, the classification established by the Mayo Clinic [13]. Stones were classified as follows: 1) stones containing phosphate, ammonium, or magnesium were classified as struvite stones; 2) stones containing urate were classified

as urate stones; 3) stones containing calcium or oxalate were classified as calcium-containing stones. Patients with mixed stones of more than two main component types (e.g. stones containing both calcium and urate) and those with unclassified stones were excluded from the analysis. Subsequently, 725 patients were classified into three groups based on stone composition as follows: 1) calcium-containing stones; 2) urate stones; and, 3) struvite stones. Patients with brushite and cystine stones were not identified in the study population.

Definition

The baseline serum creatinine level was defined as the average of all serum creatinine values measured in the year immediately preceding the year of admission for stone removal. AKI was defined as a rise of serum creatinine ≥ 0.3mg/dL compared with baseline serum creatinine, or the need for temporary dialysis treatment, at the time of treatment for urinary stone disease. The estimated glomerular filtration rate (eGFR) was obtained from serum creatinine levels using the 2021 version of the CKD-EPI (chronic kidney disease epidemiology collaboration) equation. CKD was defined as baseline eGFR <60 ml/min/1.73m^2, based on the baseline creatinine level. Patients were defined as having ESKD progression if they required maintenance hemodialysis, peritoneal dialysis, or kidney transplantation. Kidney function deterioration was defined as a comprehensive concept, indicating a decline of more than 30% in eGFR calculated by comparing the baseline eGFR and eGFR estimated from the last serum creatinine measurement during the study period or progression to ESKD. This threshold was supported as a surrogate endpoint for progressive CKD in large-scale meta-analysis and expert consensus, including the NKF-FDA (National Kidney Foundation and the U.S. Food and Drug Administration) workshop report and subsequent validation in clinical outcome studies [14,15].

The data collected from the patient charts included demographics, comorbidities, stone analysis, blood tests, and urine extractions. The baseline patient characteristics were collected at the time of first admission. Data regarding progression to ESKD and mortality were collected from the registry of the Korean Society of Nephrology and the National Database of Statistics, Korea, and electronic medical records, respectively.

Statistical Analysis

Categorical variables were reported as frequencies and percentages, and continuous variables were reported as means and standard deviations. The stone composition groups were compared using one-way analysis of variance with Tukey's post-hoc analysis. A subgroup analysis was performed for patients who completed 24-hour urine collection, and a complete case analysis was applied by excluding those with missing data.

Multivariate logistic regression analysis was performed to identify and assess risk factors for AKI. Results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals. Cox proportional hazards model was used for risk factors for mortality and kidney function deterioration. Results were reported as hazard ratios (HRs) with 95% confidence intervals. For logistic regression and Cox analyses, variables were chosen using p<0.05 in univariate analysis, along with age and sex. Statistical significance was set at p<0.05 was considered significant. All analyses were performed using the SPSS software (SPSS version 23.0, Chicago, IL, USA).

RESULTS

Study participants

Among the 758 patients admitted for symptomatic urinary stone disease who underwent stone removal procedures during the study period, a total of 33 patients were excluded: 30 with mixed or unclassified stones and 3 with a history of ESKD. Finally, 725 patients were included. The mean age of the participants was 58.7 years, with 64.3% being male (N=466). Twenty-four urine samples were collected from the 233 patients.

Baseline demographics and laboratory data according to stone subtypes

Table 1 shows the baseline demographic and laboratory data. Calcium-containing stones were the most common subtype (N=510, 70.3%), followed by struvite (N=117, 16.1%) and urate stones (N=98, 13.5%). Patients with urate stones were significantly older, were predominantly male, and had a higher prevalence of comorbidities including diabetes, hypertension, heart failure, dementia, chronic obstructive pulmonary disease (COPD), cancer, and CKD. The differences in baseline laboratory data according to the stone subtype were also remarkable. Those with urate stones had significantly lower hemoglobin and total cholesterol levels, higher uric acid levels, and lower eGFR than those with the other stone subtypes. Patients with struvite stones were characterized by lower total CO_2, phosphate, and albumin levels, while inflammatory markers such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were significantly elevated, suggesting the presence of concurrent urinary tract infections.

Table 1: *Baseline demographics, clinical characteristics, and laboratory findings according to stone subtypes.*

Characteristics	Ca containing stone (n=510, 70.3%)	Urate stone (n=98, 13.5%)	Struvite stone (n=117, 16.1%)	p-value
Sex, male, n (%)	322 (63.1%)	75 (76.5%)*	69 (59.0%)‰	0.017
Age (years)	57.44 ± 13.41	67.95 ± 12.94*	56.38 ± 15.89‰	<0.001
BMI (kg/m^2)	24.94 ± 3.74	25.25 ± 3.60	26.54 ± 26.96	0.388
Comorbidities				
DM, n (%)	140 (27.5%)	47 (48.0%)*	22 (18.8%)‰	<0.001
HTN, n (%)	230 (45.1%)	71 (72.4%)*	53 (45.3%)‰$	<0.001
Chronic liver disease,n (%)	69 (13.5%)	12 (12.2%)	14 (12.0%)	0.870
IHD, n (%)	37 (7.3%)	14 (14.3%)	11 (9.4%)	0.070
PAOD, n (%)	23 (4.5%)	9 (9.2%)	4 (3.4%)	0.105
HF, n (%)	6 (1.2%)	6 (6.1%)*	4 (3.4%)	0.006
Dementia, n (%)	5 (1.0%)	4 (4.1%)*	1 (0.9%)	0.047
Hemiparesis, n (%)	6 (1.2%)	1 (1.0%)	2 (1.7%)	0.876
COPD, n (%)	8 (1.6%)	9 (9.2%)*	4 (3.4%)‰	<0.001
Cancer, n (%)	71 (13.9%)	24 (24.5%)*	22 (18.8%)	0.023
CKD, n (%)	25 (4.9%)	42 (42.9%)*	8 (6.8%)‰	<0.001
Laboratory test				
Hb (g/dL)	14.11 ± 1.68	13.52 ± 2.11*	13.74 ± 2.12	0.004
WBC (× 10^3/μL)	8.17 ± 3.47	8.80 ± 4.51	8.34 ± 3.72	0.299
Na (mmol/L)	139.54 ± 2.81	138.99 ± 3.14	139.44 ± 3.18	0.234
K (mmol/L)	4.16 ± 0.39	4.27 ± 0.46*	4.12 ± 0.43‰	0.019
Cl (mmol/L)	104.11 ± 2.91	103.68 ± 3.38	104.25 ± 3.35	0.359
Total CO_2 (mmol/L)	25.27 ± 3.26	24.44 ± 3.62	24.11 ± 3.59$	0.012
BUN (mg/dL)	16.06 ± 7.69	21.59 ± 11.89*	16.99 ± 10.00‰	<0.001
Baseline Cr (mg/dL)	0.87 ± 0.31	1.15 ± 0.31*	0.88 ± 0.45‰	<0.001
Baseline eGFR (mL/min/1.73m^2)	89.67 ± 16.91	65.93 ± 19.61*	90.66 ± 20.95‰	<0.001
Total Ca (mg/dL)	9.21 ± 0.68	9.15 ± 0.70	9.30 ± 0.93	0.380
Phosphate (mg/dL)	3.52 ± 0.63	3.42 ± 0.66	3.23 ± 0.87$	0.002
Magnesium (mmol/L)	0.85 ± 0.09	0.85 ± 0.11	0.85 ± 0.11	0.960
Uric acid (mg/dL)	5.55 ± 1.65	6.19 ± 1.69*	5.66 ± 2.02	0.012
Protein (g/dL)	7.16 ± 0.57	7.12 ± 0.58	7.07 ± 0.68	0.304
Albumin (g/dL)	4.32 ± 0.44	4.22 ± 0.44	4.20 ± 0.57$	0.011
CRP (mg/L)	20.29 ± 50.35	27.22 ± 65.54	41.11 ± 75.61$	0.008
ESR (mm/hr)	19.06 ± 19.97	28.59 ± 30.38*	28.75 ± 31.07$	<0.001
Glucose (mg/dL)	125.62 ± 47.32	131.72 ± 43.84	117.85 ± 51.78	0.098
Total cholesterol (mg/dL)	185.17 ± 43.08	169.60 ± 38.86*	182.29 ± 46.43	0.005
LDL cholesterol (mg/dL)	111.38 ± 35.68	105.91 ± 36.36	116.79 ± 35.03	0.217
HDL cholesterol (mg/dL)	45.52 ± 11.95	43.81 ± 12.16	46.53 ± 12.01	0.428
Triglyceride (mg/dL)	153.49 ± 88.20	155.33 ± 101.97	145.72 ± 96.59	0.781

Urinary parameters according to stone subtypes

Urine pH was significantly low in patients with urate stones, while those with struvite stones had a higher urine pH (Table 2). Urine biochemistry using 24-hour urine collection data was available only in 233 patients (32.1%). The analysis showed that calcium excretion was significantly elevated in patients with calcium-containing stones. However, the excretion of sodium, uric acid, citrate, oxalate, and protein did not vary according to different stone compositions (Table 2). However, the high missing rate of the 24-hour urine study might affect the results of the analysis.

Table 2: *Random urine findings and 24-hour urinary excretory parameters according to stone subtypes.*

Urinary excretory variables, Mean ± SD	Ca containing stone (n=513, 70.5%)	Urate stone (n=98, 13.5%)	Struvite stone (n=117, 16.1%)	p-value
Urine SG	1.01 ± 0.006	1.01 ± 0.006	1.01 ± 0.006	0.772
Urine pH	6.09 ± 0.89	5.59 ± 0.84*	6.40 ± 0.98$%	<0.001
24-hr urine variable,Mean ± SD	**Ca containing stone (n=139, 59.7%)**	**Urate stone (n=53, 22.7%)**	**Struvite stone (n=117, 17.6%)**	**p-value**
Sodium (mmol/d)	178.43 ± 89.40	186.13 ± 115.96	150.93 ± 109.56	0.350
Potassium (mmol/d)	54.10 ± 25.08	55.02 ± 38.33	44.81 ± 24.04	0.290
Chloride (mmol/d)	192.39 ± 94.72	194.14 ± 116.91	162.93 ± 108.38	0.391
Total calcium (mg/d)	193.22 ± 139.25	74.84 ± 60.81*	163.59 ± 136.96%	0.000
Phosphate (mg/d)	594.66 ± 340.89	573.62 ± 302.88	426.48 ± 244.57	0.121
Magnesium (mmol/d)	3.77 ± 1.83	4.60 ± 2.61	3.34 ± 2.08	0.154
Uric acid (mg/d)	560.73 ± 269.95	594.04 ± 341.70	493.38 ± 272.26	0.395
Protein (mg/d)	438.40 ± 1493.28	531.87 ± 1264.74	528.80 ± 990.02	0.905
Citrate (mg/d)	218.49 ± 235.44	119.29 ± 134.11	182.41 ± 187.34	0.165
Oxalate (mg/d)	27.88 ± 13.33	30.77 ± 13.28	25.87 ± 13.30	0.476

AKI according to stone composition

Among the 725 patients, 256 (35.3%) had concurrent AKI. The incidence of AKI was highest in those with urate stones (63.3%), followed by those with struvite (39.3%) and calcium (29%) stones (Table 3).

Table 3: *Incidence of acute kidney injury according to stone subtypes.*

Subtypes	Ca containing stone	Urate stone	Struvite stone	p-value
Acute kidney injury	148 (29.0%)	62 (63.3%)*	46 (39.3%)%	<0.001
Stage 1	122 (23.9%)	40 (40.8%)	36 (30.8%)	
Stage 2	19 (3.7%)	10 (10.2%)	4 (3.4%)	
Stage 3	7 (1.4%)	12 (12.2%)	6 (5.1%)	

Patients with AKI were more likely to be older and to have other comorbidities, such as diabetes, hypertension, chronic liver disease, hemiparesis, COPD, cancer, and CKD than those without AKI. Patients with concurrent AKI showed significantly lower hemoglobin, serum total CO_2, total calcium, protein, and albumin levels than those without AKI. Concurrent AKI was also associated with higher leukocyte counts and higher CRP, ESR, and uric acid levels (Table 4).

In the multivariate logistic regression analysis, patients with urate stones had a 98.4% higher risk of developing AKI event (OR 1.984, 95% Confidence Interval [CI] 1.047-3.761, p=0.036) than those with calcium-containing stones. Patients with struvite stones also showed a 92.7% higher risk of AKI events (OR 1.927, 95% CI 1.119-3.317, p=0.018) than those with calcium-containing stones, indicating that stone composition was an independent risk factor for AKI. Additionally, hypertension

Table 4: *Baseline demographics, clinical characteristics, laboratory findings, and random urinary findings by acute kidney injury status.*

Characteristics	No AKI (n=469, 64.7%)	AKI (n=256, 35.3%)	Total (n=725)	p-value
Sex, male, n (%)	301 (64.2%)	165 (64.5%)	466 (64.3%)	1.000
Age (years)	57.07 ± 14.17	61.64 ± 13.94	58.69 ± 14.25	<0.001
BMI	24.79 ± 3.65	26.01 ± 17.84	25.22 ± 10.98	0.285
Comorbidities				
DM, n (%)	109 (23.2%)	100 (39.1%)	209 (28.8%)	<0.001
HTN, n (%)	196 (41.8%)	158 (61.7%)	354 (48.8%)	<0.001
Chronic liver disease,n (%)	52 (11.1%)	43 (16.8%)	95 (13.1%)	0.038
IHD, n (%)	35 (7.5%)	27 (10.5%)	62 (8.6%)	0.166
PAOD, n (%)	21 (4.5%)	15 (5.9%)	36 (5.0%)	0.475
HF, n (%)	7 (1.5%)	9 (3.5%)	16 (2.2%)	0.110
Dementia, n (%)	6 (1.3%)	4 (1.6%)	10 (1.4%)	0.748
Hemiparesis, n (%)	2 (0.4%)	7 (2.7%)	9 (1.2%)	0.011
COPD, n (%)	8 (1.7%)	13 (5.1%)	21 (2.9%)	0.018
Cancer, n (%)	61 (13.0%)	56 (21.9%)	117 (16.1%)	0.003
CKD, n (%)	18 (3.8%)	57 (22.3%)	75 (10.3%)	<0.001
Laboratory test				
Hb (g/dL)	14.25 ± 1.63	13.46 ± 2.05	13.97 ± 1.83	<0.001
WBC (× 10^3 /μL)	7.95 ± 3.16	8.89 ± 4.40	8.28 ± 3.67	0.003
Na (mmol/L)	139.58 ± 2.53	139.20 ± 3.52	139.45 ± 2.92	0.123
K (mmol/L)	4.17 ± 0.38	4.17 ± 0.46	4.17 ± 0.41	0.989
Cl (mmol/L)	104.12 ± 2.74	103.98 ± 3.56	104.07 ± 3.05	0.592
Total CO_2 (mmol/L)	25.50 ± 3.07	24.12 ± 3.68	24.89 ± 3.42	<0.001
BUN (mg/dL)	15.29 ± 4.89	20.01 ± 13.00	16.96 ± 8.95	<0.001
Baseline Cr (mg/dL)	0.84 ± 0.19	1.05 ± 0.50	0.91 ± 0.35	<0.001
Baseline eGFR (mL/min/1.73m²)	91.80 ± 15.40	77.13 ± 23.07	86.62 ± 19.75	<0.001
Total Ca (mg/dL)	9.27 ± 0.62	9.13 ± 0.87	9.22 ± 0.73	0.040
Phosphate (mg/dL)	3.49 ± 0.65	3.42 ± 0.74	3.46 ± 0.69	0.289
Magnesium (mmol/L)	0.85 ± 0.08	0.85 ± 0.10	0.85 ± 0.09	0.357
Uric acid (mg/dL)	5.42 ± 1.48	6.04 ± 2.01	5.67 ± 1.73	<0.001
Protein (g/dL)	7.19 ± 0.51	7.04 ± 0.70	7.14 ± 0.59	0.002
Albumin (g/dL)	4.36 ± 0.39	4.14 ± 0.55	4.29 ± 0.47	<0.001
CRP (mg/L)	17.23 ± 43.66	36.15 ± 73.25	24.69 ± 57.88	0.001
ESR (mm/hr)	16.89 ± 18.13	30.17 ± 29.93	22.37 ± 24.58	<0.001
Glucose (mg/dL)	122.45 ± 42.46	130.21 ± 55.81	125.19 ± 47.71	0.053
Total cholesterol (mg/dL)	186.95 ± 41.58	174.58 ± 45.45	182.59 ± 43.36	<0.001
LDL cholesterol (mg/dL)	114.39 ± 33.91	106.29 ± 38.18	111.37 ± 35.73	0.031
HDL cholesterol (mg/dL)	46.04 ± 11.86	44.30 ± 12.17	45.41 ± 11.99	0.159
Triglyceride (mg/dL)	146.73 ± 94.21	162.39 ± 86.58	152.53 ± 91.67	0.075
Urine test				
Urine SG	1.02 ± 0.01	1.01 ± 0.01	1.01 ± 0.01	0.159
Urine pH	6.10 ± 0.92	6.02 ± 0.94	6.07 ± 0.93	0.290

Note: Data are presented as numbers (percentage) or mean ± standard deviation. AKI: Acute Kidney Injury; BMI: Body Mass Index; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; PAOD: Peripheral Arterial Disease; HF: Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; Hb: Hemoglobin; WBC: White Blood Cell; Na: Sodium; K: Potassium; Cl: Chloride; BUN: Blood Urea Nitrogen; Cr: Creatinine; eGFR: estimated Glomerular Filtration Rate; Total Ca: Total Calcium; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein. Comparison between AKI *vs.* non-AKI groups were done using Student's t-test (continuous variables) or Chi-square test (categorical variables). A p value ≤ 0.05 was considered as statistically significant.

(OR 1.968, 95% CI 1.233-3.142, p=0.005), high baseline serum creatinine levels (OR 19.255, 95% CI 4.225-87.765, p<0.001), high uric acid levels (OR 1.224, 95% CI 1.062-1.410, p=0.005), low hemoglobin (OR 0.827, 95% CI 0.715-0.957, p=0.011), and low serum albumin levels (OR 0.436, 95% CI 0.273-0.696, p=0.001) were also found to be independent risk factors of concurrent AKI in symptomatic urinary stone disease patients (Table 5).

Table 5: *Logistic regression analysis of factors associated with acute kidney injury.*

For AKI	Odds ratio	95% CI	p-value
Sex (Female to male)	1.604	0.912-2.823	0.101
Age, years	0.999	0.982-1.016	0.881
DM	1.369	0.871-2.152	0.173
HTN	2.005	1.258-3.196	0.003
Baseline Cr (mg/dL)	12.532	4.006-39.204	<0.001
Hb (g/dL)	0.828	0.715-0.958	0.011
Uric acid (mg/dL)	1.224	1.063-1.411	0.005
Albumin (g/dL)	0.442	0.277-0.706	0.001
Stone composition (based on calcium containing stone)	-	-	0.017
Urate stone	1.911	1.014-3.600	0.045
Struvite stone	1.889	1.101-3.241	0.021
Note: CI: confidence interval; DM: diabetes mellitus; HTN: hypertension; Cr: creatinine; Hb: hemoglobin.			

Mortality and kidney function deterioration according to stone composition

During the mean follow-up of 852.2 days, 33 patients (4.6%) died and 42 patients (5.8%) showed kidney function deterioration defined as an eGFR decrease of more than 30% from baseline or ESKD progression. Patients with urate stones had significantly higher rates of both mortality and kidney function deterioration (Table 6).

Table 6: *Incidence of mortality and kidney function deterioration according to stone subtypes.*

	Ca containing stone (n=510, 70.3%)	Urate stone (n=98, 13.5%)	Struvite stone (n=117, 16.1%)	p-value
Mortality	14 (2.7%)	11 (11.2%)[*]	8 (6.8%)	0.001
Kidney function deterioration	22 (4.3%)	12 (12.2%)[*]	8 (6.8%)	0.008
Note: Stone composition groups were compared using one-way analysis of variance with Tukey post-hoc analysis. A p value ≤ 0.050 was considered as statistically significant. [*]Ca Containing stone *vs.* Urate stone, [$]Ca Containing stone *vs.* Struvite stone, [%]Urate stone *vs.* Struvite stone (post-hoc analysis)				

No independent risk factors for mortality were identified in the Cox proportional hazards model analysis (Table 7). In contrast, concurrent AKI episodes (HR 7.887, 95% CI 2.719-22.880, p<0.001), older age (HR=1.047, 95% CI 1.016-1.078, p=0.002), female sex (HR 1.992, 95% CI 1.032-3.845, p=0.040), and high baseline serum creatinine (HR 2.103, 95% CI 1.477-2.995, p<0.001) were independent predictors of kidney function deterioration (Table 8, Figure 1). Notably, stone composition was not an independent factor for subsequent kidney function deterioration.

Table 7: *Cox regression analysis of factors associated with mortality.*

For mortality	Hazard ratio	95% CI	p-value
Sex (Female to male)	1.965	0.657-5.878	0.227
Age, years	1.021	0.977-1.066	0.350
DM	0.955	0.402-2.274	0.918
HTN	0.378	0.130-1.095	0.073
AKI	1.751	0.749-4.092	0.196
Baseline Cr (mg/dL)	2.057	0.893-4.738	0.090
Stone composition (based on calcium containing stone)	-	-	0.309
Urate stone	1.640	0.536-5.017	0.386
Struvite stone	2.632	0.762-9.088	0.126
Note: CI: Confidence Interval; DM: Diabetes Mellitus; HTN: Hypertension; AKI: Acute Kidney Injury; Cr: Creatinine. Multivariate cox regression was performed to adjust for sex, age, diabetes mellitus, hypertension, baseline serum creatinine, stone composition, and acute kidney injury.			

Table 8: *Cox regression analysis of factors associated with kidney function deterioration.*

For kidney function deterioration	Hazard ratio	95% CI	p-value
Sex (Female to male)	1.992	1.032-3.845	0.040
Age, years	1.047	1.016-1.078	0.002
DM	0.832	0.423-1.634	0.593
HTN	0.880	0.398-1.944	0.752
AKI	7.887	2.719-22.880	<0.001
Baseline Cr (mg/dL)	2.103	1.477-2.995	<0.001

Stone composition (based on calcium containing stone)	-	-	0.263
Urate stone	0.720	0.333-1.556	0.403
Struvite stone	0.454	0.169-1.222	0.118

Note: CI: Confidence Interval; DM: Diabetes Mellitus; HTN: Hypertension; AKI: Acute Kidney Injury; Cr: Creatinine. Multivariate cox regression was performed to adjust for sex, age, diabetes mellitus, hypertension, baseline serum creatinine, stone composition, and acute kidney injury.
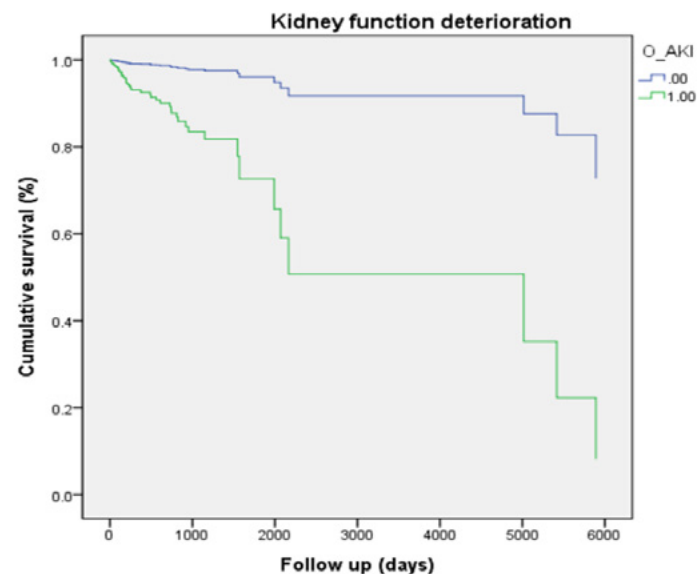

Figure 1: Kaplan-Meier survival curve comparing the AKI and non-AKI groups. Cumulative probability of kidney function deterioration, indicating a significant difference between the groups (HR=7.887, 95% CI 2.719-22.880, p<0.001).

DISCUSSION

Urinary stone disease is increasingly recognized as a chronic medical condition associated with AKI, CKD, ESKD, and other metabolic diseases. Previous studies were largely population-based historical cohort studies that used diagnostic codes without considering stone types, clinical symptoms, or concurrent AKI. Our study included 725 symptomatic patients who underwent stone removal procedures and had known stone composition. Our key findings were as follows: 1) AKI was frequently complicated in symptomatic stone disease (35.3%); 2) higher baseline serum creatinine levels, lower albumin and hemoglobin levels, and urate struvite stone compositions were independent risk factors of AKI; and 3) during the mean follow-up of 852.2 days, 5.8% of patients showed more than a 30% decrease in eGFR, with older age, female gender, high baseline serum creatinine levels, and concurrent AKI episodes identified as risk factors. Conversely, the stone subtypes were not independent predictors of kidney function deterioration.

Urinary stones are formed through mechanisms involving crystal nucleation, supersaturation, crystal growth, and agglomeration [16]. The location and composition of nucleation are heterogeneous and can influence the clinical manifestations of urinary stone disease. Although obstruction might be one of the single most important factors causing AKI, the etiologies of AKI in patients with urinary stone disease are often multifactorial, including a combination of urinary tract infection, volume depletion, and use of nephrotoxic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and contrasts [17,18]. However, due to the retrospective nature of our study, detailed etiological classifications of AKI were not feasible. Thus, our results should be interpreted with caution. We found a significantly higher incidence of AKI in the urate

and struvite stone subgroups. The percentage of stage 3 AKI was also the highest in patients with urate stones, followed by those with struvite stones while patients with calcium-containing stones had the lowest percentage of stage 3 AKI out of the three stone subgroups. Older age, higher CKD prevalence, and comorbidities in patients with urate stones, may have contributed to a higher incidence of AKI in the urate stone subgroup. Similarly, concurrent infections in patients with struvite stones may have contributed to a higher AKI incidence. However, the associations between the stone compositions and the AKI incidence remained independent after adjusting for multiple factors. The lack of information regarding the location or bilaterality of stones, which can also affect AKI, is one of the limitations of our study. In addition to stone subtypes, we also found that higher baseline serum creatinine and uric acid levels, as well as lower albumin and hemoglobin levels, were independently associated with AKI in patients with urinary stone disease.

Most population-based studies have consistently shown a higher risk of CKD in patients with urinary stone disease [19]. We also observed that 5.8% of patients showed a more than 30% decrease in eGFR during the mean follow-up of 852.2 days. Using the data from the National Health Insurance Service (NHIS) of Korea, including 219,570 Korean adults with urinary stone disease and age- and sex-matched controls, Kim et al. recently demonstrated that patients with urinary stone disease have a higher risk of incident CKD than those without stones [20]. Although further studies are needed, they speculate that the progressive scarring of the kidneys from the obstructive uropathy, inflammation caused by the crystal deposition and underlying metabolic disorders prone to CKD may all contribute to the development and progression of CKD in patients with

urinary stone disease. Based on the different baseline clinical and laboratory characteristics and incidence rates of AKI, we hypothesized that the rate of kidney function deterioration may also differ according to stone subtypes. However, our results demonstrated that stone subtypes were not independently associated with the rate of kidney function deterioration. Based on the current analysis, it is not possible to determine whether stone composition is a causal factor of kidney function deterioration or a marker reflecting underlying comorbidities. This represents a limitation of our study and highlights the need for further evaluation to establish a clear causal relationship.

Instead, we found that the female gender, older age, AKI, and higher baseline serum creatinine levels was an independent predictor of kidney function deterioration. Recent studies have reported that female stone formers may be more susceptible to renal impairment, potentially due to a post-menopausal loss of estrogen-mediated renoprotection and sex-specific differences in infection risk and health care utilization [21]. Higher CKD susceptibility in female stone formers was also demonstrated in a population-based study performed in England and Wales and a meta-analysis [22,23]. Interestingly, these findings are contrary to a recently published study that included data from the National Health Insurance Service of Korea database which reported that men had a greater risk of developing CKD when compared to women [24]. Similarly, Ricardo et al. also suggested that men were more susceptible to CKD progression [25]. Further studies are necessary to clarify gender differences and CKD susceptibility in patients with stones.

In contrast to CKD, the association between urinary stone disease and mortality remains unclear. A large population-based study from the United States using data from the National Health and Nutrition Examination Survey [26] demonstrated more than a two-fold increase in the risk of all-cause and cardiovascular mortality in their unadjusted analysis. However, the association was no longer present after adjusting for multiple socioeconomic and comorbid conditions, suggesting that the increased risk of mortality in patients with urinary stones may be attributed to their underlying comorbidities. In our study, we found that all-cause mortality was the highest among patients with urate stones, followed by those with struvite stones, with those with calcium stones having the lowest all-cause mortality. However, after adjusting for other comorbidities, stone subtypes were not independently associated with mortality. These findings may be partly associated with the relatively small number of patients in our study. Further studies with larger number of patients are warranted.

Our study has several strengths. First, we included hospitalized patients with symptomatic kidney stone disease who underwent stone removal procedures which allowed us to perform analyses according to different stone compositions. This approach enabled us to obtain comprehensive demographic and laboratory data both before and after the occurrence of the stone, allowing for the assessment of the impact of the stone composition on various outcomes. Second, we assessed AKI occurring at the time of stone removal and found that a concurrent AKI episode is independently associated with long-term kidney function deterioration. These findings support the concept that kidney stone disease should not be regarded as a one-time condition, but rather as a chronic disease that requires long-term renal function monitoring, imaging follow-up, and appropriate comorbidity management to prevent recurrence, particularly in patients who have experienced urinary stone combined with AKI.

This study also has several limitations. First, as a single-center retrospective study, generalizability of our findings may be limited. Second, kidney function deterioration was defined based on the difference between the baseline eGFR and the eGFR calculated from the last serum creatinine measurement during the study period. Therefore, the outcome may not fully reflect the true CKD progression, as recurrent AKI or early loss to follow-up at the time of the last measurement may have confounded our results. Third, information regarding stone location, bilaterality, stone size, type of intervention, and recurrence was not included in the analysis, which may have limited the comprehensive assessment of disease progression and risk stratification.

CONCLUSION

This study showed different clinical outcomes according to stone compositions. Urate and struvite stone are independent risk factor of concurrent AKI. And this AKI episode, older age, and lower baseline kidney function were independent predictors of progressive kidney function deterioration, regardless of stone composition. These results establish a foundation for future studies and may ultimately guide personalized risk stratification and preventive strategies to mitigate both acute and chronic kidney outcomes in stone formers. Future studies with longer follow-up periods and larger, more diverse study populations will be essential to refine the understanding of kidney function deterioration and to clarify risk factors affecting short and long-term kidney outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization, Investigation: YEC, JY, S-KJ

Data acquisition: YEC, JY, YJ, M-GK

Formal data analysis, interpretation: YEC, SWO, TYK, S-KJ

Supervision: S-KJ

Writing-original draft: YEC, S-KJ

Writing-review & editing: YEC, JY, YJ, TYK, SWO, M-GK, S-KJ

All authors read and approved the final manuscript.

DATA AVAILABILITY

The data presented in this study are available from the authors

upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital, Seoul, Republic of Korea (2022AN0310), and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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