Effect of stone composition on surgical stone recurrence: single center longitudinal analysis

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Introduction: *The objective of this study is to explore the association between urinary stone composition and surgical recurrence.*

Materials and methods: *Patients who underwent kidney stone surgeries (between 2009-2017), were followed for > 1 year, and had ≥ 1 stone composition analyses were included in our analysis. Surgical stone recurrence (repeat surgery) was defined as the second surgery on the same kidney unit. Recurrence-free survival analysis was used.*

Results: *A total number of 1051 patients were included (52.7% men, average age 59.1 ± 15.1 years). Over 4.7 ± 2.5 years follow up, 26.7% of patients required repeat surgery. Patients' stone compositions were calcium oxalate (66.0%), uric acid (12.2%), struvite (10.0%), brushite (5.7%), apatite (5.1%) and cystine (1.0%). Results suggested that patients with cystine stones had the highest surgical recurrence risk; brushite had the second-highest surgical recurrence risk. Struvite, uric acid, and apatite stones were at higher risk compared with calcium oxalate stones (lowest risk in our cohort). When pre and postoperative stone size was controlled, patients with a history of uric acid, brushite, and cystine stones were at higher surgical risk. After controlling clinical and demographic factors, only brushite and cystine stones were associated with higher surgical recurrence.*

Conclusions: *Patients with cystine stones had the highest surgical recurrence risk; brushite stones had the second highest surgical recurrence risk. Struvite, uric acid, and apatite stones were at higher risk compared with calcium oxalate stones. When pre and postoperative stone size, clinical and demographic factors were controlled, only those with brushite or cystine stones were at significantly higher risk of surgical recurrence.*

Key Words: kidney stones, surgery, stone composition, recurrence

Introduction

The prevalence of nephrolithiasis continues to rise. A cross-sectional assessment of data from the National Health and Nutrition Examination Survey found that the overall prevalence of stone disease in the US in 2010 was 8.8% (10.6% among men and 7.1% among women), a marked increase from 1994 (6.3% among men and 4.1% among women).[1] Nephrolithiasis is a chronic disease with significant recurrence rates. Approximately 50% of first time stone formers develop recurrence.[2,3] A more recent study found symptomatic recurrence rates are about 11% at 2 years, 20% at 5 years, and 31% at 10 years.[4] Factors associated with stone recurrence include demographics,[5] dietary and lifestyle factors,[6,7] and underlying metabolic conditions.[8,9]

Stone composition is one of the factors associated with prevalence and recurrence of stone disease. In the US, approximately 70%-80% of stones are predominantly calcium oxalate. The second major component of stones is calcium phosphate (carbonate apatite, hydroxyapatite, and brushite). Many calcium-containing stones are mixed with other components. Struvite stones (account for 10%-15%) and uric acid stones (5%-10%) are less common, and cystine stones are rare (less than 2%).[10] Regarding stone recurrence, cystine stone formers are considered to be at the highest

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risk of recurrence compared with other patients who form other types of stones due to the underlying genetic basis of cystinuria.[11] Among other types of stones, data show that the symptomatic recurrence rate at 10 years was approximately 50% for brushite, struvite, and uric acid stones, but approximately 30% for calcium oxalate and apatite stones.[12] While previous literature mainly focuses on stone events, longitudinal studies have not systematically explored the correlation of stone composition and surgical stone recurrence (the need for repeat surgery). Stone surgery is the most significant outcome for patients, and is associated with large financial burden and decrements to their health-related quality of life.[13] Thus, the objective of this study is to explore the association between stone composition and surgical recurrence.

Materials and methods

Upon IRB approval, we retrospectively reviewed the records of 2761 consecutive patients who underwent surgical procedures for nephrolithiasis (percutaneous nephrolithotomy, ureteroscopy with laser lithotripsy or shock-wave lithotripsy) at our institution from 2009-2017. Patients were included if they 1) were over 18 years old at the time of surgery, 2) were followed within our institution for at least 1 year, and 3) had at least one stone composition analysis. Stone composition reports within this cohort were from two commercial laboratories in the US (Dianon Systems and Louis C. Herring Company). We excluded 43 patients who were younger than 18 years old at the time of surgery, 707 patients who were followed for less than 12 months, and 911 patients who did not have stone composition analyses. This resulted in 1100 patients.

The stone analysis report was used to establish a stone type for each patient. If the stone analysis from the patints' baseline surgery was not available, the one that was obtained closest to the time of surgery was used. In order to classify stones into different categories, we adopted the approach published in the study of Lieske et al[12,14] as follows: 1) stones containing any struvite were considered struvite; 2) stones containing any cystine were considered cystine; 3) stones containing any uric acid were considered uric acid; 4) stones containing any brushite were considered brushite; and 5) stones were classified as calcium oxalate if they had a majority (> 50%) of calcium oxalate. Regarding non-brushite calcium phosphate stones, Lieske's classification included only hydroxyapatite. But in our cohort, both calcium phosphate carbonate apatite and calcium phosphate hydroxyapatite were reported. Thus, we classified non-brushite calcium phosphate stones as apatite if they had a majority (> 50%) of either calcium phosphate carbonate apatite or calcium phosphate hydroxyapatite or if the sum of the percentages of both was > 50%. Stones that were composed primarily (> 50%) of protein or rare constituents or without a dominant composition were not included in the statistical analysis (n = 49). Thus, our final cohort included 1051 patients and 1051 stone composition reports.

Surgical recurrence was defined as the repeat surgery on the same kidney unit. If the baseline surgery was bilateral, the second surgery of either side was considered recurrence. This did not include multiple procedures that were planned at the time of the original surgery or staged procedures within 3 months. The need for repeat procedure was determined by each urologist based on symptoms, stone size, and other patient-specific factors. Each patient's demographics (age, gender, race, and ethnicity), BMI, prior stone history (yes or no), family history of stone disease (yes or no), comorbidities (hypertension, diabetes mellitus, malabsorptive gastrointestinal disease, gout, chronic kidney disease, and history of chronic urinary tract infection as documented in the past medical history), and whether patients underwent metabolic evaluation and management were collected. At our institution, patients receive metabolic evaluation and management from our multidisciplinary stone clinic, which combines the expertise of doctors in nephrology, nutrition, and urology. Both preoperative stone size and postoperative residual fragment size from the baseline surgery were collected. The stone size was defined as the maximum diameter on preoperative or postoperative imaging (CT, ultrasound, or KUB).

To identify the association between stone composition and surgical recurrence, three separate analyses were performed. First, we analyzed the association between recurrence-free survival and stone composition using the Kaplan-Meier method. Second, we repeated the same analysis while adding pre and postoperative stone size using a Cox regression model (log rank).[15] The preoperative stone size was categorized as less or equal to 10 mm and greater than 10 mm. The residual fragment size was categorized as stone free, 1-2 mm, 3-4 mm, 5-6 mm, and greater than 6 mm based on previous literature.[15] Finally, we added clinical demographic factors in the model to confirm the association between stone composition and need for repeat surgery using the Cox regression analysis (log rank).[16] These clinical and demographic factors include age, gender, race, ethnicity, BMI, whether patients have positive prior stone history, positive family history of stone disease, hypertension, diabetes mellitus, malabsorptive gastrointestinal disease, gout, chronic kidney disease, history of chronic urinary tract infection, and whether patients underwent metabolic evaluation and management. HRs and 95% CIs were calculated using Cox regression. Statistical analyses were conducted using SPSS version 22. All significance tests were two-sided with a $p < 0.05$ considered statistically significant.

Results

Patients (n = 1051) were 52.7% men. They were 59.1 ± 15.1 years old. The average BMI was 31.2 ± 8.3 kg/m^2; 48.1% were obese (BMI > 30.0); 63.4% had a prior history of stone disease. Further cohort characteristics are provided in Table 1. Most patients had undergone ureteroscopy (73.7%), while 21.2% and 5.1% had undergone percutaneous nephrolithotomy and shockwave lithotripsy, respectively; 54.4% had left kidney surgery, while 43.4% and 2.2% had right and bilateral procedures. Fifty-four percent of patients were stone free after the original surgery. Over 4.7 ± 2.5 years follow up (median 4.8 years, range 1-10 years), 26.7% of patients required repeat surgery.

TABLE 1. **Patients' characteristics**

Age (years)	59.1 ± 15.1
Gender	
Men	555 (52.8%)
Women	496 (47.2%)
BMI (kg/m^2)	31.2 ± 8.3
Race	
Caucasian	1010 (96.1%)
African American	16 (1.5%)
Asian Pacific	19 (1.8%)
Native American	5 (0.5%)
Ethnicity	
Latinx	20 (1.9%)
Total follow up (years)	4.7 ± 2.5
Comorbidities	
Gout	43 (4.1%)
Chronic kidney disease	78 (7.4%)
History of chronic urinary tract infection	129 (12.3%)
Diabetes	249 (23.7%)
Malabsorptive gastrointestinal disease	264 (25.1%)
Hypertension	465 (44.2%)
Positive family history of stone disease	264 (25.1%)
Positive history of stone disease	666 (63.4%)
Metabolic evaluation and management	353 (33.6%)

The time from the original surgery to stone analysis was 6.3 ± 16.7 months; 70.6% of patients' stone analyses were from the original surgery, while the rest of patients' stone types were defined by stone analyses from other stone events within our follow up. Using the classification system described, patients' stone compositions were calcium oxalate (66.0%), uric acid (12.2%), struvite (10.0%), brushite (5.7%), apatite (5.1%), and cystine (1.0%). Univariate analysis showed that patients with predominantly calcium oxalate stones had the lowest risk of repeat surgery (21.5%) in our cohort. Surgical recurrence for other stones were: 29.5% for struvite, 32.8% for uric acid, 35.2% for apatite, 51.7% for brushite, and 90% for cystine. Those with cystine had the highest surgical recurrence risk ($p < 0.001$) compared with calcium oxalate; brushite had the second-highest surgical recurrence risk ($p < 0.001$) compared with calcium oxalate. Struvite, apatite, and uric acid stones were also at a higher risk compared with calcium oxalate stones ($p = 0.013$, $p = 0.008$, and $p = 0.001$, respectively), Figure 1.

The pre and postoperative fragment sizes of different stones are presented in Table 2. Patients who did not have preoperative image (n = 19) were not included in the survival analysis. After adding pre and postoperative stone size into the model, we found that surgical recurrence was not significantly different between calcium oxalate, struvite, and apatite stones. Patients with uric acid, brushite, or cystine stones were at significantly higher risk of requiring repeat surgery ($p = 0.043$, < 0.001, and < 0.001, respectively), Table 3. Proportional hazards assumption was met in this model ($p > 0.05$). Harrell's C-index for this model was 0.726. Within this model, preoperative stone size was not a significant risk factor for repeat surgery ($p = 0.583$). Postoperative residual fragment size was significantly associated with the need for repeat surgery ($p < 0.001$). Patients with calcium oxalate stones had significantly smaller fragments compared with patients with other stone compositions ($p < 0.001$ when compared with struvite, uric acid, and brushite; $p = 0.025$ when compared with cystine; $p = 0.004$ when compared with apatite). There was no difference in fragment size for all other stone compositions. After adding clinical and demographic factors to the model, we found that surgical recurrence was not different between patients with calcium oxalate, struvite, uric acid or apatite stones; only those with brushite or cystine stones were at significantly higher risk, Table 3. Proportional hazards assumption was met in this model ($p > 0.05$). Harrell's C-index was 0.686.

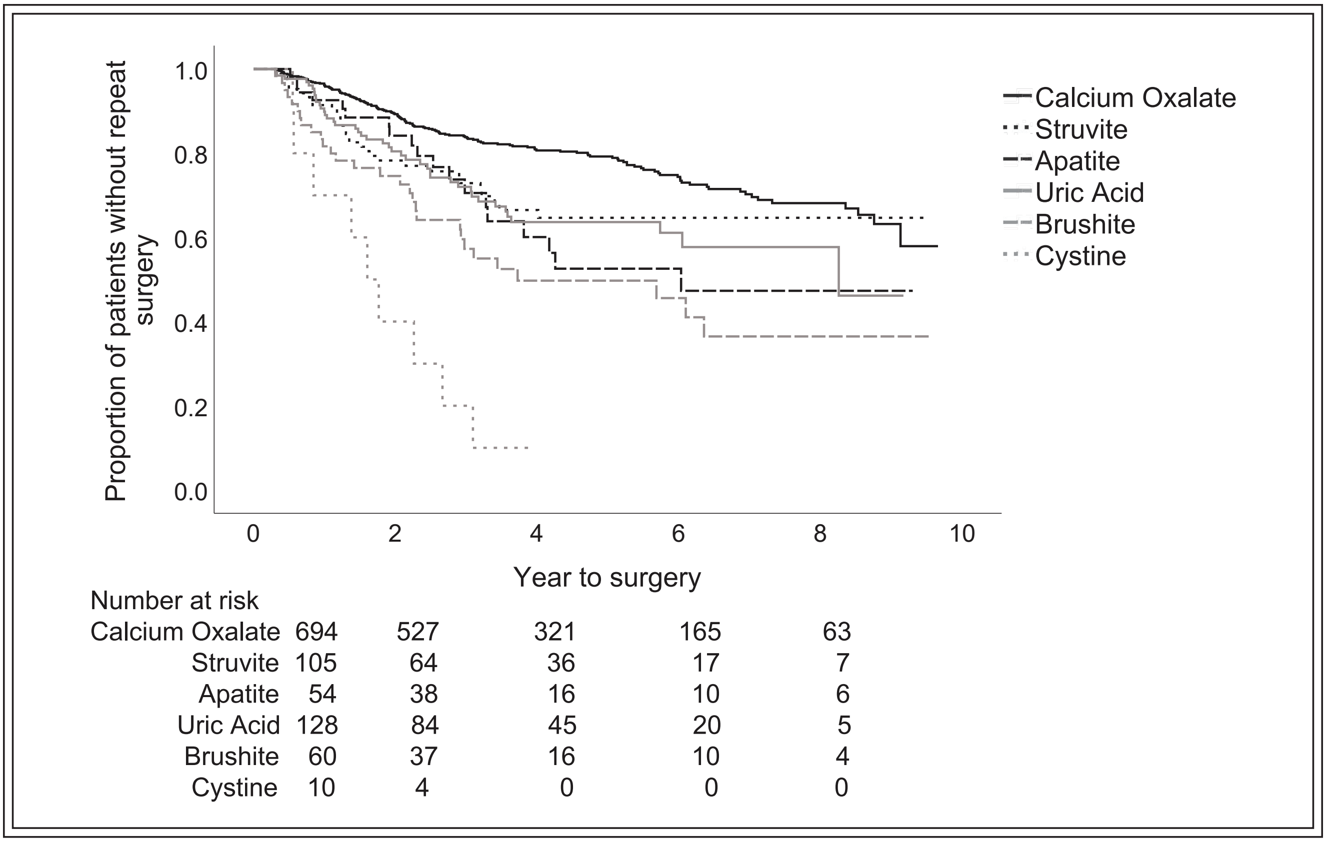

Figure 1. Surgical recurrence-free survival curves among patients stratified by stone composition.

TABLE 2. **Pre and postoperative stone size**

	Calcium oxalate n = 694	**Struvite n = 105**	**Apatite n = 54**	**Uric acid n = 128**	**Brushite n = 60**	**Cystine n = 10**
*Preoperative size, mm (mean ± SD)	9.5 ± 7.4	20.6 ± 15.4	14.5 ± 10.1	14.8 ± 9.5	13.9 ± 11.4	19.6 ± 18.3
*Size by category, n (%)						
≤ 10 mm	493 (71.9%)	31 (31.3%)	26 (52.0%)	53 (41.7%)	34 (56.7%)	3 (30.0%)
> 10 mm	193 (28.1%)	68 (68.7%)	24 (48.0%)	74 (58.3%)	26 (43.3%)	7 (70.0%)
Postoperative size, mm (mean ± SD)	1.9 ± 3.2	3.9 ± 5.0	3.5 ± 4.2	3.3 ± 4.9	4.0 ± 4.3	4.7 ± 5.5
Size by category, n (%)						
Stone free	411 (60.0%)	46 (43.8%)	21 (38.9%)	70 (54.7%)	16 (26.7%)	4 (40.0%)
1-2 mm	92 (13.4%)	15 (14.3%)	8 (14.8%)	9 (7.0%)	10 (16.7%)	0 (0%)
3-4 mm	83 (12.1%)	8 (7.6%)	7 (13.0%)	9 (7.0%)	13 (21.7%)	1 (10.0%)
5-6 mm	40 (5.8%)	9 (8.6%)	8 (14.8%)	13 (10.2%)	11 (18.3%)	3 (30.0%)
> 6 mm	68 (9.9%)	27 (25.7%)	10 (18.5%)	27 (21.1%)	10 (16.7%)	2 (20.0%)

*19 patients did not have preoperative imaging

TABLE 3. **Results of univariate and multivariate survival analyses**

Stone composition	Hazard ratio (95% CI)	p value
Univariate		
Calcium oxalate	Referent	
Struvite	1.63 (1.11-2.41)	0.013
Apatite	1.91 (1.18-3.08)	0.008
Uric acid	1.79 (1.27-2.53)	0.001
Brushite	2.85 (1.92-4.25)	< 0.001
Cystine	8.43 (4.28-16.60)	< 0.001
Multivariate (with pre and postoperative stone size in the model)		
Calcium oxalate	Referent	
Struvite	1.18 (0.79-1.77)	0.413
Apatite	1.19 (0.72-1.99)	0.497
Uric acid	1.44 (1.01-2.07)	0.043
Brushite	2.07 (1.38-3.11)	< 0.001
Cystine	5.08 (2.52-10.26)	< 0.001
Multivariate (with clinical demographic factors, pre and postoperative stone size in the model)*		
Calcium oxalate	Referent	
Struvite	1.19 (0.78-1.81)	0.415
Apatite	1.25 (0.74-2.11)	0.402
Uric acid	1.31 (0.90-1.90)	0.163
Brushite	2.06 (1.34-3.16)	0.001
Cystine	4.76 (2.27-9.98)	< 0.001

*these clinical and demographic factors include age, gender, race, ethnicity, BMI, whether patients have positive prior stone history, positive family history of stone disease, hypertension, diabetes mellitus, malabsorptive gastrointestinal disease, gout, chronic kidney disease, history of chronic urinary tract infection, and whether patients underwent metabolic evaluation and management

Discussion

Knowledge of the composition of stones that patients form may help in estimating the risk of surgical recurrence. The main finding of our study is that calcium oxalate stones are associated with lower surgical recurrence rates compared with all other stone types. Cystine stones are associated with the highest surgical recurrence rate and brushite with the second-highest rate. Struvite, uric acid, and apatite stones were also associated with a higher risk for surgical recurrence compared with calcium oxalate stones. After adding pre and postoperative stone size, patients with a history of uric acid, brushite or cystine stones were at significantly higher risk of requiring repeat surgery. Postoperative residual fragment size was significantly associated with the need for repeat surgery, while preoperative stone size was not. After adding clinical and demographic factors, only brushite and cystine were associated with significantly higher risk.

The association between stone composition and recurrence has been studied for decades. The definition of recurrence has varied and has included image recurrence, stone passage, and need for a repeat procedure. Several approaches have been used to measure stone recurrence (e.g., patient self-report, imaging studies, and retrospective chart review). Previous literature mainly focus on symptomatic stone episodes. For example, Takasaki's study (based on 422 patients) found that in a total follow up of 19 years (range 1-19 years, average 8 years), recurrence rates were as follows: calcium stones 38.6%, struvite stones 41.2% (no significant difference between calcium oxalate and phosphate), uric acid stones, 55.6%, and cystine 50%.[17] Daudon's study examined stone recurrence using a more granular classification scheme. Results suggested that calcium oxalate monohydrate stones were associated with the lowest recurrence (38%) while recurrence rates for struvite, calcium oxalate dihydrate, uric acid, brushite, and cystine stones were 41.6, 43.5%, 51.6%, 74.5%, and 89%, respectively.[11] Singh and colleagues found that the recurrence rate for symptomatic calcium oxalate and hydroxyapatite stones was approximately 30% each while recurrence rates for uric acid, brushite, and struvite stones were approximately 50% each.[12] ROKS nomogram initially suggested uric acid stone was associated with a second symptomatic stone event after patients had the first stone episode.[18] Their revised ROKS suggested that history of uric acid, brushite, and struvite were high risk factors for symptomatic recurrence.[19] A study on brushite stones found that recurrent events occurred in 37.8% of patients in a mean follow up of 33 months (range 2-118 months).[20] While the recurrence rates associated with different stone compositions varied in those studies, it is notable that calcium oxalate stones were associated with the lowest recurrence rate in all; other stone types (i.e., struvite, apatite, uric acid, and brushite) were associated with higher recurrence rates. These results are confirmed by our analysis in a surgical cohort. Our multivariate model is also consistent with previous reports that cystine stones are associated with the higher surgical recurrence rate.

It was interesting to note that the residual fragment size of each stone composition varied in the current cohort, Table 2. Calcium oxalate stones had significantly smaller fragments compared with other stone compositions. This is likely a result of stone fragility, particularly as it relates to lithotripsy. All other stone compositions had no significant differences in fragment size. This multivariate model confirmed that uric acid, brushite, and cystine stones were associated with higher risk of surgical recurrence.

Stone analysis can aid the identification of specific metabolic or genetic metabolic abnormalities and can help direct stone prevention. In the current study, we used the surgical recurrence of stones as our outcome analysis. Compared with other outcome measures (e.g., new stone formation from image studies, stone passages, urgent care encounters, patients' reports, or chart reviews), stone surgery is the most measurable variable and potentially the most significant outcome for patients. Moreover, our results may be particularly useful in preoperative patient counseling.

Our study is not free of limitations. It is a single-center retrospective analysis, and this may limit the generalization of our findings. The sample was small and subject to selection bias, especially for less common stones, for which stone composition is not always available. Moreover, surgery type (URS versus PCNL versus SWL) was not included in the multivariate analysis. We included the fragment size in the model instead. Previous study found that fragment size is a significant factor associated with surgical recurrence.[15] This finding is also confirmed by our current results ($p < 0.001$). However, we acknowledge that the postoperative image modality may influence the fragment size that was included the analysis. Finally, stone composition reports may differ among different commercial laboratories. Krambeck reported considerable variability in the accuracy of the analysis for mixed stones among different commercial laboratories.[21] It is also noted that nomenclature for apatite varies among laboratories. Krambeck compared the stone analysis results from five commercial laboratories. They found that one laboratory reported apatite as carbonate apatite and never hydroxyapatite, and another always reported hydroxyapatite but never carbonate apatite.[21] Our stone analyses are from two commercial laboratories. The variation of stone analyses between the two labs may have influenced our results.

Conclusions

Using our long term survival analysis strategy (up to 10 years), we found patients with a history of cystine stones had the highest surgical recurrence risk; those with brushite stones had the second-highest surgical recurrence risk. Patients with a history of struvite, uric acid, and non-brushite calcium phosphate stones (carbonate apatite and hydroxyapatite) were at higher risk compared with calcium oxalate stones (lowest risk in our cohort). After accounting for pre and postoperative stone size, uric acid, brushite, and cystine stones were associated with significantly higher risk of repeat surgery compared with calcium oxalate stones. Our full multivariate model (controlling pre and postoperative stones as well as clinical and demographic factors) suggested only brushite and cystine stones were at a higher risk of surgical recurrence. This critical information can be used to counsel patients preoperatively to set expectations and help plan the need for follow up and medical stone management. ☐

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