Patients treated for uric acid stones reoccur more often and within a shorter interval in comparison to patients treated for calcium stones

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Abstract

Introduction: We aimed to investigate the association between stone composition and recurrence rate in a well-characterized group of patients.
Methods: From our prospectively assembled database of 1328 patients undergoing ureteroscopy and percutaneous nephrolithotomy (PCNL) between 2010 and 2015, we identified 457 patients who met the inclusion criteria: a minimum of two years' followup, stone-free status following surgery, normal anatomy, and FT-IR stone analysis results. Stone recurrence was identified by kidney-ureter-bladder (KUB) or an ultrasound (US). All symptomatic events were recorded. Kaplan-Meier and Cox proportional hazard regression methods were used to assess the differences in recurrence rates and associated risk factors.
Results: Calcium oxalate (CaOx), uric acid (UA), and struvite stones were found in 298 (65.2%), 99 (21.7%), and 28 (6.1%) patients, respectively. During a median followup of 38 months (interquartile range [IQR] 31–48), stone recurred in 111 (24%) patients. One-year stone-free rates stratified by composition were: CaOx 98%, UA 91.9%, calcium phosphate 90%, struvite 88%, and, cystine 83%; the two-years stone-free rates were 92.6%, 82.7%, 80%, 73%, and 75%, respectively. On multivariate Cox regression analysis, UA composition, the absence of medical preventive therapy, and preoperative stone burden were associated with a shorter time to recurrence. Secondary intervention for recurrent, symptomatic stones was required in 11 (11.1%) and 22 (7.4%) of patients with UA and CaOx stones, respectively (p=0.02).
Conclusions: UA stone-formers are more likely to have a recurrence and to undergo surgical intervention in comparison to CaOx stone-formers, regardless of MPT. These differences are more prominent during the first year of followup and should be incorporated into the patient's followup protocol.

Introduction

Nephrolithiasis is a common, recurrent disease. The lifetime risk of stone formation in an individual is estimated at 5–10%, and the risk for recurrence is reported to be as high as 50% at five years and 80–90% at ten years. [1, 2]. Routine Follow-up and medical prevention have been shown to decrease stone recurrence.[3] To balance between the medical yield and the economic burden of metabolic workup and treatment, Major urological associations recommend that first-time stone formers who have Uric acid (UA), Brushite, and infection stones, or certain medical conditions, should undergo extensive evaluation. However, follow up protocols after surgical stone removal are uniform despite the substantial differences in the pathogenesis, risk factors, and medical management of the various stone types.[4, 5]

UA stones are the second most common stone composition in Israel following calcium oxalate stones, found in 21.4% in patients 60 years and older, and reaching 29% in specific populations.[6, 7] This unique distribution of stone compositions allowed us to study the impact of stone type, particularly uric acid, on stone recurrence, in order to evaluate whether a uniform follow-up protocol is appropriate for all stones types.

Methods

After obtaining approval from the institutional ethic committee, we reviewed our retrospective database of patients who underwent percutaneous nephrolithotomy (PCNL) or ureteroscopy (URS) for the treatment of kidney stones at our center, between January 2010 and January 2015. We included patients aged 18 years and older who were found to be stone free bilaterally at the first post-operative visit, with two-years or longer follow-up, and had stone analysis results available. Stone free status was defined as no residual stones

Patients with anatomical abnormalities, urinary diversion, medullary sponge kidney, Hyperparathyroidism, renal tubular acidosis, and enteric hyperoxaluria, were excluded from the study. Initial postoperative assessment of residual stones was performed in the first postoperative clinic visit, usually one month after the procedure, and comprised a combination of KUB and an ultrasound for Radio-opaque stones, and NCCT for radio-lucent stones. Follow-up Imaging studies using KUB and ultrasound for radio-opaque and radiolucent stones, respectively, were done at six months and yearly thereafter. Imaging studies were also performed following any symptomatic event. Stones were analyzed using infra-red spectrometry (FT-IR; Bruker Alpha-T Spectrometer), and the composition was determined by the predominant component comprising >50% of the stone. The study's primary outcome was radiologic stone recurrence, defined as any new identifiable stone in a patient who was stone free. The study's secondary outcomes were symptomatic events and the need for surgical re-intervention. To identify predictors for recurrence, we collected data on age, gender,

preoperative cumulative stone size, type of surgery (PCNL/URS), and data on medical preventive treatment (MPT), obtained from an outpatient electronic system, which is automatically populated upon medication purchase. This system is very reliable in recording purchased medications as the same health management organization (HMO) operates our hospitals, clinics, and pharmacies. All patient data, including drugs prescribed and dispensed, are entered into the HMO's centralized database. Preparations used in Israel for urine alkalization include Uralyt-U and Alkasolve, both contain Potassium Sodium Citrate. Allopurinol is used for hyperuricosuria and hydrochlorothiazide or Chlorthalidone for hypercalciuria.

Statistical analysis

Continuous variables are described as the median and IQR. Categorical variables are described as the number and percent. T-test or Mann Whitney U test and Chi-Square or Fisher's exact tests were used to comparing continues and nominal variables, respectively. Recurrence probability was calculated by the Kaplan-Meier method with statistical differences evaluated by the log-rank test. Univariate cox proportional hazard model was used to correlate time to stone recurrence with potential prognostic indicators. For all analyses stratified by stone composition, CaOx was used as a reference. All statistical analyses were 2-sided. Data were analyzed with SPSS® Statistics, Version 21.0, with $p<0.05$ considered statistically significant.

Outcome measures and results

From A total of 1328 patients who were operated during the study period, 457 (34.4%) patients met the inclusion criteria. The median age of the study cohort was 53 years (Q1=37, Q3=64), and 317 (69.4%) patients were male. PCNL and URS were performed in 112 (24.5%) and 345 (75.5%) patients for a median stone size of 25 mm (Q1=18, Q3=35) and 10 mm (Q1=7, Q3=17), respectively. Stone composition was CaOx, UA, Calcium Phosphate (CP), Struvite, and Cystine in 298 (65.2%), 99 (21.7%), 20 (4.4%), 28 (6.1%), and 12 (2.6%) patients, respectively. MPT was used by 149 (32.6%) patients, including 20% of CaOx stones formers, and 58% of UA stones formers. Clinical characteristics of patients stratified by stone composition are depicted in table 1.

During a median follow-up of 38 months (Q1=31, Q3=48), 111 (24.2%) patients developed stone recurrence, with a median time of 25 months. The median time to stone recurrence was reached only in patients with Cystine stones (14 months). One-year stone-free rates stratified by composition were: CaOx 98%, UA 91.9%, CP 90%, Struvite 88%, and, Cystine 83%, and the 2-years stone-free rates were 92.6%, 82.7%, 80%, 73%, and 75%, respectively.

On univariate Cox regression analysis, UA (HR 2.1, 95% CI, 1.41-3.2, p=0.001), Struvite (HR 2.1, 95% CI 1-4.4, p=0.05), and Cystine (HR 3.07, 95% CI 1.23-7. 7, p=0.016) stones, as well as preoperative stone size (HR 1.02, 95% CI 1.01-1.03, p=0.001), and MPT (HR 0.53, 95% CI 0.37-0.77, p=0.001) were associated with stone recurrence, while age (HR 1, 95% CI 0.99-1.02, p=0.48), gender (HR 0.92, 95%

CI 0.76-1.12, p=0.44), BMI (HR 1.1, 95% CI 0.62-1.33, p=0.6) and the type of surgery (HR 1.33, 95% CI 0.89-2, p=0.17) were not. On multivariate cox regression analysis adjusted for stone composition, MPT, and stone size, UA composition (HR 1.61, 95% CI 1.02-2.53, p=0.04), and MPT (HR 0.81, 95% CI 0.61-0.91, p=0.048), remained independent predictors for stone recurrence, while stone size (HR=1.013, 95% CI 1-1.03, p=0.055) was marginally associated with stone recurrence. Table 2 presents univariate and multivariate cox regression analysis of different variables. Figures 1a and 1b shows the Kaplan Meier curves for stone recurrence stratified by stone composition and MPT status.

Symptomatic recurrence occurred in 69 (15.1%) patients, including 3 (25%) patients with Cystine stones, 20 (20.2%) patients with UA stones, 3 (15%) patients with CP stones, 40 (13.4%) patients with CaOx stones, and 3 (10.7%) patients with Struvite stones (p=0.001) . Surgical intervention was required in 43 (9.4%) patients: 4 patients (33.3%) had Cystine stones, 3 patients (15%) had CP stones, 3 patients (10.7%) had Struvite stones, 11 (11.1%) patients had UA stones, and, 22 patients (7.4%) had CaOx stones (p between UA and CaOx = 0.02). Median sizes of the recurrent stones were 5mm (q1=6, q3=8), 8mm (q1=6, q3=9), 8mm (q1=6, q3=9), 9mm (q1=6, q3=10), and, 15 mm (q1=5, q3=18), for CaOx, UA, CP, Struvite, and cysteine stones, respectively. Recurrent Struvite stones were significantly larger than CaOx stones (p=0.02).

In a subgroup analysis of patients with recurrent stones, re-retreatment was associated with younger age (44 years vs 55 years, p<0.01), larger recurrent stone size (9.5 mm vs 7.5 mm, p=0.05), and symptomatic recurrence (49.2% vs 17.3%, p<0..01), but not with gender (p=0.9), or stone composition (p=0.24), in comparison to patients that were not treated for recurrent stones.

Discussion

In the present study, we evaluated the impact of stone composition on recurrence rates. The time to recurrence of UA stones was shorter than that of CaOx stones, and patients with recurrent UA stones were more likely to undergo surgical intervention. Additionally, larger preoperative stone size and the absence of preventive medical treatment were also associated with stone recurrence.

Several studies evaluated risk factors for stone recurrence after surgical treatment. Ying-Huei et al. developed a stone recurrence predictive score, comprising eight clinical variables. Family history, Number of stones, and gouty arthritis were all associated with stone recurrence.[8] Kamihira et al. found that stone burden and postoperative pyuria are associated with earlier recurrence among 903 patients undergoing ESWL, while Strauss et al. identified hypercalciuria and shorter interval between previous stone episodes as a risk factors for recurrence among 522 patients receiving MPT. [9, 10] These studies and others focused on CaOx stone formers, comprising the majority of stone formers In the western world, while UA stones, found in up to 40% of the patients in other areas, have hardly been studied.[11] The high

prevalence of UA stones in our area, reaching 29% in some populations, allowed us to investigate the impact of stone composition on stone recurrence.[7] Median recurrence time was shorter for UA stones compared with CaOx stones (23 vs. 28 months), and, SFR was substantially lower after the first year of follow-up, during which, UA stones were 4 times likelier to in comparison to CaOx stones (SFR 98% vs. 92%). Likewise, the SFRs at 2-year follow-up were 92.6% for CaOx stones, 82.7% for UA stones, and 80%, 73%, and 75% for CP, Struvite, and Cystine stones, respectively. Median recurrence time and the Kaplan Meier curves of CP, Struvite, and Cystine stones suggest that their recurrence rates are even higher. However, the limited number of patients in the last three stone compositions precluded any definite conclusion regarding their recurrence rates.

Clues to the impact of stone composition on stone recurrence are scarce. Takashima et al. performed a retrospective study of the recurrence pattern in 145 patients who underwent endourological intervention. UA and calcium stones recurred in 33% and 17% of the patients, respectively. However, their cohort was composed of a mixed population of patients who underwent extracorporeal shockwave lithotripsy, URS, and PCNL, and only three patients in this cohort had UA stones.[12] Rule et al. utilized a large database of 2239 first time stone formers from the Olmsted County, Minnesota, to design the ROKS nomogram for the prediction of stone recurrence. Ten-year recurrence varied from 12% to 56%. They found that UA composition, as well as younger age, male sex, white race, family history of nephrolithiasis, and the presence of non-obstructing stones, were all associated with increased risk for recurrence. Their study, however, was designed to predict symptomatic rather than radiographic stone recurrence. As such, imaging surveillance was not available. Additionally, stone composition was available for only 50% of the patients, and only 4% of the cohort had UA stone composition. Lastly, 30.4% of the patients had another non-obstructing kidney stone, which was found to be the most predominant predictor for symptomatic recurrence.[13] More recently, Daudon et al. studied the association between stone composition and recurrence rate by identifying recurrent stones in a database of 38,274 stones. 51% of the patients with UA stones and 38-43 percent of patients with CaOx stones had recurrent stone episodes. Clinical data, however, was not available for this study.[14] As we aimed to study the impact of stone composition on stone recurrence, we included only patients who were stone-free after PCNL or URS, had stone composition analysis and had at least 2-years of imaging follow-up. Using these strict criteria, we provide the largest data to date to address this issue.

Why would UA stones recurre faster than CaOx stones? The intuitive thinking is that in the absence of an anchoring mechanism on which a stone can gradually accumulate, a substantial lithogenic force is required to promote crystallization during the short transition time of a free-floating particle. However, our understanding of the pathogenesis of UA stone formation is still evolving. The Traditional hypothesis of “simple” crystallization of supersaturated minerals gave its way to a complicated interaction between the crystals and the renal parenchyma in the

form of "Randall's plaques" and, the intramedullary collecting ducts plugging. These extensively studied lesions were considered precursors for calcium stones formation, since they were not found in kidneys of UA stones formers .[15, 16] Recent evidence, however, challenge this concept as well. Evan et al. obtained papillary biopsies from stone formers who have an ileostomy. All seven patients, including four patients with UA stones, had intra-tubular apatite deposits. Interestingly, only in UA stone formers, there was no stone attached to the plaque.[17] Viers et al. compared the endoscopic and histologic appearance of papillary biopsies obtained from UA and CaOx stone formers. Among patients with UA stones, 100% had endoscopic plaques, and 57% had endoscopic plugs, significantly more than CaOx stone formers or controls. They also noted greater interstitial inflammation in biopsies obtained from CaOx stone.[18] These studies suggest that similarly to CaOx stones, tissue factors may play a role in the pathogenesis of UA stones.

This study has several limitations. The electronic computerized system has the advantage of live follow up after medicines that were prescribed for the patients as well as after medicines that were issued. However, there is no reliable way to follow the patient's compliance. Indeed, studies examining patient's adherence to chronic pharmacological therapy found the 1-year adherence of men with LUTS was only 29%.[19] Additionally, we did not account for dietary habits and comorbidities in this study, as it is clear that UA and CaOx stone formers are different in that regard.

This study is novel in providing evidence for the association between stone composition and recurrence rate, an association that is clinically and economically valuable. Because of the tremendous cost of kidney stone treatment and prevention, cost-effective follow-up protocols are desirable. In the present study, the one-year stone recurrence was four times higher in uric acid stone formers. Shorter follow-up intervals in these patients may improve care and decrease the cost of care. Further cost-effectiveness studies are needed to shed light on this question.

Conclusions

UA stones former are more likely to have recurrence and to undergo surgical intervention in comparison to CaOx stones formers, regardless of MPT. These differences are more prominent during the first year of follow-up and should be incorporated into the patient's follow-up protocol.

References

1. Antonelli JA, Maalouf NM, Pearle MS, Lotan Y. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. European urology. 2014 Oct;66(4):724-9. PubMed PMID: 25015037. Pubmed Central PMCID: 4227394.
2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney international. 2003 May;63(5):1817-23. PubMed PMID: 12675858.
3. Uribarri J, Oh MS, Carroll HJ. The first kidney stone. Annals of internal medicine. 1989 Dec 15;111(12):1006-9. PubMed PMID: 2688503.
4. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. The Journal of urology. 2014;192(2):316-24.
5. Skolarikos A, Straub M, Knoll T, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. European urology. 2015;67(4):750-63.
6. Usman KD, Golan S, Abdin T, et al. Urinary stone composition in Israel: current status and variation with age and sex--a bicenter study. Journal of endourology / Endourological Society. 2013 Dec;27(12):1539-42. PubMed PMID: 24266775.
7. Zaidman JL, Pinto N. Studies on urolithiasis in Israel. The Journal of urology. 1976 Jun;115(6):626-7. PubMed PMID: 940190.
8. Lee YH, Huang WC, Lu CM, Tsai JY, Huang JK. Stone recurrence predictive score (SRPS) for patients with calcium oxalate stones. The Journal of urology. 2003 Aug;170(2 Pt 1):404-7. PubMed PMID: 12853786.
9. Kamihira O, Ono Y, Katoh N, Yamada S, Mizutani K, Ohshima S. Long-term stone recurrence rate after extracorporeal shock wave lithotripsy. The Journal of urology. 1996 Oct;156(4):1267-71. PubMed PMID: 8808851.
10. Strauss AL, Coe FL, Deutsch L, Parks JH. Factors that predict relapse of calcium nephrolithiasis during treatment: a prospective study. The American journal of medicine. 1982 Jan;72(1):17-24. PubMed PMID: 7058820.
11. Moran ME, Abrahams HM, Burday DE, Greene TD. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. Urology. 2002 Feb;59(2):206-10. PubMed PMID: 11834386.
12. Nakamoto T, Sagami K, Yamasaki A, et al. Long-term results of endourologic treatment of urinary calculi: investigation of risk factors for recurrence or regrowth. Journal of endourology / Endourological Society. 1993 Aug;7(4):297-301. PubMed PMID: 8252022.
13. Rule AD, Lieske JC, Li X, Melton LJ, 3rd, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. Journal of the American Society of Nephrology : JASN. 2014 Dec;25(12):2878-86. PubMed PMID: 25104803. Pubmed Central PMCID: 4243346.
14. Daudon M, Jungers P, Bazin D, Williams JC, Jr. Recurrence rates of urinary calculi according to stone composition and morphology. Urolithiasis. 2018 Feb 1. PubMed PMID: 29392338.

15. Evan A, Lingeman J, Coe FL, Worcester E. Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. Kidney international. 2006 Apr;69(8):1313-8. PubMed PMID: 16614720.
16. Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. The Journal of clinical investigation. 2003 Mar;111(5):607-16. PubMed PMID: 12618515. Pubmed Central PMCID: 151900.
17. Evan AP, Lingeman JE, Coe FL, et al. Intra-tubular deposits, urine and stone composition are divergent in patients with ileostomy. Kidney international. 2009 Nov;76(10):1081-8. PubMed PMID: 19710630. Pubmed Central PMCID: 3780771.
18. Viers BR, Lieske JC, Vrtiska TJ, et al. Endoscopic and histologic findings in a cohort of uric acid and calcium oxalate stone formers. Urology. 2015 Apr;85(4):771-6. PubMed PMID: 25681832. Pubmed Central PMCID: 4380657.
19. Cindolo L, Pirozzi L, Fanizza C, et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: population-based cohort study. European urology. 2015 Sep;68(3):418-25. PubMed PMID: 25465970.

Figures and Tables

Fig. 1A. Kaplan-Meier curves for stone recurrence stratified by stone composition.

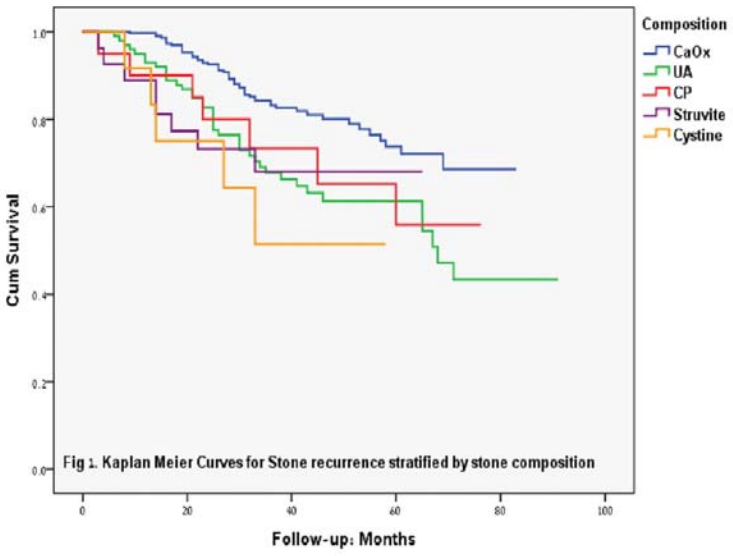

Fig. 1B. Kaplan-Meier curves for stone recurrence stratified by medical preventive treatment status.

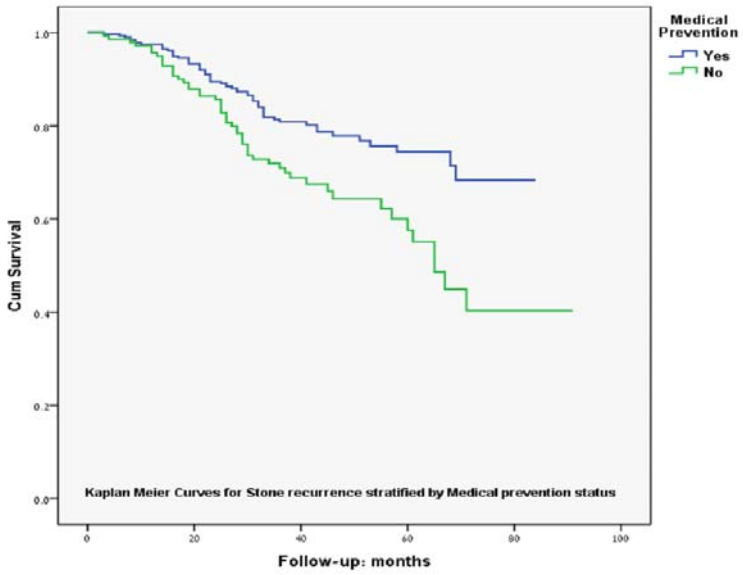

Table 1. Clinical characteristics of patients stratified by stone composition						
	Total (457)	**CaOx (298)**	**UA (99)**	**CP (20)**	**Struvite (28)**	**Cystine (12)**
Median age in years (IQR)	53 (37,64)	51 (38,62)	60 (51,70)	41 (31,50)	59 (40,73)	16 (11,28)
Male gender (%)	317(69.2%)	225 (75%)	65 (65.7%)	9 (45%)	11 (39.337%)	7 (58.3%)
Median BMI (IQR)	26.8 (25.3, 28.6)	26.5 (24.3, 29.2)	29.2 (27.4, 31.2)	26.2 (23.2, 29.1)	27.6 (23.6, 30.1)	24.3 (22.1, 26)
Median preoperative stone size in mm (IQR)	12 (8,20)	10 (7,18)	14 (10,22)	17 (11,30)	20 (16,26)	21 (15,40)
PCNL (%)	104 (22.8%)	50 (16.8%)	30 (30.3%)	8 (40%)	10 (35.7%)	6 (50%)
Medical prevention treatment (%)	140 (36%)	61 (20.5%)	58 (58.6%)	4 (20%)		8 (66.7%)
Alkasole/Uralyt-U (%)	75 (16.4%)	21 (7%)	40 (40%)	4 (20%)	2 (7.1%)	8 (67%)
Hydrochlorothiazide/Chlorthalidone (%)	42 (9.2%)	32 (10.7%)	0	0	5 (17.9%)	0
Allopurinol (%)	29 (6.3%)	12 (4%)	0	0	2 (7.1%)	4 (33%)
Median followup in months (IQR)	37 (20)	37 (32,47)	60 (31,59)	41 (31,63)	59 (31,45)	16 (26,45)
Median recurrence time in months						14
1 year SFR	97.4%	98%	91.9%	90%	88%	83%
2 years SFR	95.2%	92.6%	82.7%	80%	73%	75%
3 years SFR	77.7%	85.1%	72.9%	73%	68%	51%
Symptomatic recurrence (%)	69 (15.1%)	40 (13.4%)	20 (20.2%)	3 (15%)	3 (10.7%)	3 (25%)
Repeat surgical treatment (%)	43 (9.4%)	22 (7.4%)	11 (11.1%)	3 (15%)	3 (10.7%)	4 (33.3%)
Median recurrent stone size (IQR)	7 (5,9)	5 (6,8)	8 (6,9)	8 (6,9)	9 (6,10)	15 (5,18)

BMI: body mass index; CaOx: calcium oxalate; CP: calcium phosphate; IQR: interquartile range; PCNL: percutaneous nephrolithotomy; SFR: stone-free rate; UA: Uric acid.

Table 2. Univariate multivariate analysis of risk factors for stone recurrence				
	Univariate Cox regression analysis		Multivariate Cox regression analysis	
Covariate	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	1 (0.99–1.02)	0.48		
Gender	0.92 (0.76–1.12)	0.44		
BMI	1.1 (0.62–1.33)	0.6		
Type of procedure	1.33 (0.89–2)	0.17		
Stone composition				
Calcium oxalate	1			
Uric acid	2.1 (1.41–3.2)	0.001	1.61 (1.02–2.53)	0.04
Calcium phosphate	1.83 (0.83–4.02)	0.13	1.53 (0.68–3.42)	0.3
Struvite	2.1 (1–4.4)	0.05	1.62 (0.73–3.6)	0.23
Cystine	3.07 (1.23–7.7)	0.016	1.43 (0.47–4.4)	0.53
Preoperative stone size	1.02 (1.01–1.03)	0.001	1.013 (1–1.03)	0.055
Medical prevention	0.53 (0.37–0.77)	0.001	0.81 (0.61–0.91)	0.048

BMI: body mass index; CI: confidence interval; HR: hazard ratio.