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Predictors of Symptomatic Kidney Stone Recurrence After the First and Subsequent Episodes

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Abstract

Objective: To predict symptomatic recurrence among community stone formers with one or more prior stone episode.

Patients and Methods: A random sample of incident symptomatic kidney stone formers in Olmsted County, Minnesota were followed for all symptomatic stone episodes resulting in clinical care from 1/1/1984 to 1/31/2017. Clinical and radiographic characteristics at each stone episode predictive of subsequent episodes were identified.

Results: There were 3,364 incident kidney stone formers with 4,951 episodes. The stone recurrence rates per 100 person-years were 3.4 (95% CI, 3.2–3.7) after the first episode, 7.1 (95% CI, 6.4–7.9) after the second episode, 12.1 (95% CI, 10.3–13.9) after the third episode, and 17.6 (95% CI, 15.1–20.0) after the fourth or higher episode ($P < .001$ for trend). A parsimonious model identified the following independent risk factors for recurrence: younger age, male sex, higher body mass index, family history of stones, pregnancy, incident asymptomatic stone on imaging before the first episode; suspected stone episode before the first episode; history of a brushite, struvite, or uric acid stone; no history of calcium oxalate monohydrate stones, kidney pelvic or

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lower pole stone on imaging, no ureterovesical junction stone on imaging, number of kidney stones on imaging, and diameter of largest kidney stone on imaging. The model had a C-index corrected for optimism of 0.681 and was used to develop a predictive tool. The risk of recurrence in 5 years ranged from 0.9% to 94% depending on risk factors, number of past episodes, and years since the last episode.

Conclusions: The revised Recurrence of Kidney Stone (ROKS) tool predicts risk of symptomatic recurrence using readily available clinical characteristics in stone formers.

Introduction

Symptomatic recurrence with kidney stones can vary substantially between patients, with some having only an isolated episode while others having frequent recurrence that can be debilitating with chronic pain and numerous operations. There are dietary and medication interventions that can be used to help prevent kidney stone formation and growth,^{1–3} but these interventions can be burdensome, costly, and have potential side effects. Identifying the patients who are at high or low risk of symptomatic recurrence can help inform decisions regarding lifetime commitment to various stone prevention interventions.

We previously developed the Recurrence Of Kidney Stone (ROKS) model (https://www.qxmd.com/calculate/calculator_3/roks-recurrence-of-kidney-stone-2014) to predict the risk of a second symptomatic kidney stone episode after the first episode based on 11 predictors.⁴ However, this tool is not applicable for predicting recurrence in those who have had two or more symptomatic episodes. The relationship between number of prior stone episodes and the risk of symptomatic recurrence is unclear in the general community. There is evidence that more past stone episodes predicts an increased risk of future episodes,^{5, 6} but this has only been studied in specialty clinics.

We developed a revised ROKS tool for predicting the risk of symptomatic recurrence after each stone episode in a population based cohort of symptomatic kidney stone formers. A total of 27 candidate predictors at the first and subsequent stone episodes, the number of past episodes, and the recurrence free time interval since the last episode were evaluated to predict symptomatic recurrence. We also investigated 24-hour urine chemistries among the subset of patients with available laboratory measurements as predictors of recurrence. We further assessed the prevalence of dietary, medical, and surgical interventions with increasing number of stone episodes and assessed any effect of these interventions on the risk of symptomatic recurrence.

Methods

Study Sample

After institutional review board approval, adult residents from Olmsted County, Minnesota with a first-time symptomatic kidney stone episode were followed for all recurrent symptomatic episodes in an expansion of a historical cohort study previously used to develop the initial ROKS tool.^{4, 7} All data were obtained through the Rochester Epidemiology Project, a resource that provides access to medical records of nearly all medical institutions for residents of the county.⁸ Residents with their first symptomatic

kidney stone between 1/1/1984 and 12/31/2012 and with Minnesota Research Authorization⁹ were identified using International Classification of Diseases, Ninth Revision codes 592, 594, and 274.11. Complete medical records (inpatient and outpatient) were reviewed in a random order by dedicated nurse abstractors between 5/1/2009 and 1/31/2017 under the supervision of nephrologists and urologists. All stone episodes were confirmed

(validated) to be symptomatic with either a passed stone or a ureter obstructing stone on imaging (See Supplemental Methods). Stone formers with at least one confirmed symptomatic stone episode underwent further review of their medical records for candidate predictors of recurrence.

Candidate clinical predictors

The following candidate predictors for symptomatic recurrence were defined at the time of the first symptomatic stone episode: sex, race (white vs non-white), family history of kidney stones (any documented blood relative), past incident (asymptomatic) kidney stone on imaging, and past suspected kidney stone episode (symptomatic but no seen stone). The following candidate predictors for symptomatic recurrence were updated at each episode: age, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), pregnancy, urinary tract infection, microscopic hematuria, gross hematuria, diarrhea, and lower urinary tract symptoms. The following candidate predictors for symptomatic recurrence were updated as to whether they ever occurred at or before each episode: any documented self-managed stone episode without clinical care, hypertension, diabetes mellitus, and each stone composition type (See Supplemental Methods).

Candidate imaging predictors

Imaging findings by computed tomography, excretory urography, abdominal radiography, or ultrasonography were updated at each stone episode. Radiographic reports were abstracted for these findings, with images reviewed only when reported findings were unclear. Imaging findings evaluated as predictors were number of stones in both kidneys (0, 1, or 2), number of stones in both ureters (0, 1, or 2), any kidney pelvic or lower pole stone, any ureteropelvic junction stone, any ureterovesical junction stone, diameter of largest kidney stone (no stone or <3 mm, 3–6 mm, and >6 mm), and diameter of largest ureter stone (no stone or <3 mm, 3–6 mm, and >6 mm).

Stone Prevention Interventions and Urine Chemistries

We identified the stone prevention interventions at each stone episode including recommended diet alterations (high water, low sodium, low protein, or low oxalate intake), medications prescribed specifically for stone prevention (thiazide diuretics, potassium citrate, or allopurinol), stone clinic evaluations (nephrology evaluation focused on stone prevention with blood and 24-h urine chemistries), and surgical intervention (shockwave lithotripsy, ureteroscopic, ureteral stents, percutaneous, or open procedures to remove stones) for the symptomatic stone, in which asymptomatic stones may also have been removed. Any 24-hour urine volume and calcium, citrate, or oxalate levels in stone formers were also identified.

Statistical Analysis

Analyses were performed with R version 3.3.1 (R Foundation for Statistical Computing, www.Rproject.org, Vienna, Austria) using the survival and rms packages and with SAS 9.4 (SAS Institute Inc., Cary, NC). Multivariate penalized regression models to predict confirmed symptomatic recurrence that considered all the candidate predictors were developed using the least absolute shrinkage and selection operator model building approach (See Supplemental Methods).^{10, 11} A revised ROKS tool based on the final statistical model was computed to predict the probability of symptomatic recurrence at 5 and 10 years after any number of prior episodes. Subsequently, stone prevention interventions and calendar year of stone episodes were individually considered as predictors of symptomatic recurrence after adjustment for predictors in the final model. In the subset with 24-h urine chemistries, urine chemistries were also individually considered as predictors of symptomatic recurrence after adjustment for predictors in the final model.

Results

Study Sample and Episode Rate

On the basis of International Classification of Diseases, Ninth Revision codes, a random sample of 6,805 newly coded stone formers were identified among Olmsted County residents. After manual chart review, 3,364 incident symptomatic adult stone formers without rare stone types who had 4,951 stone episodes were identified (Figure 1). The number of years of subsequent episodes, person-years of follow-up, and recurrence rate after each increasing number of stone episodes is shown in Table 1. Beyond the 5th episode, the recurrence rate did not consistently increase and the number of stone formers with recurrent episodes became small (Table 1). The average stone recurrence rates per 100 person-years were 3.4 (95% CI: 3.2 to 3.7) after the first stone episode, 7.1 (95% CI: 6.4 to 7.9) after the second episode, 12.1 (95% CI: 10.3 to 13.9) after the third episode, and 17.6 (95% CI: 15.1 to 20.0) after the fourth or higher episode ($P<.001$ for trend; Figure 2).

Predictors for subsequent stone episodes after the first, second, and third episode

The association of candidate predictors with a subsequent symptomatic stone episode after the first, second, and third episode was assessed. These were divided into clinical characteristics defined at the first stone episode (Supplemental Table 1), clinical characteristics updated at each episode (Supplemental Table 2), and imaging findings updated at each episode (Supplemental Table 3).

Multivariable Model

Among these 27 candidate predictors, 13 were chosen for the final model. The final model used all 4951 episodes, though imaging data were available for only 3699 episodes (the other stone episodes involved medical care without imaging). We could only fit a multivariable model that showed an increasing risk of recurrence with number of past episodes by combining those with 4 or more episodes into one group (4+). Hypertension was excluded from the model due to concerns it represented unmeasured thiazide diuretic use. Predictors of symptomatic recurrence selected for the final model were younger age, male

sex, higher BMI, family history of stones, pregnancy, asymptomatic stone prior to the first episode, suspected stone prior to the first episode, history of a brushite, struvite or uric acid stone, no history of a calcium oxalate monohydrate stone, pelvic or lower pole stone, no ureterovesical junction stone, number of stones in kidney, and diameter of largest kidney stone (Table 2). The final model had a C-index of 0.687 (95%CI: 0.675 to 0.703); with bootstrapping, the C-index corrected for optimism was 0.681. As shown in Supplemental Table 4, history of brushite, struvite, or uric acid stone was the only predictor to differ between those with and without a kidney stone on imaging at their last episode; however, adding this interaction to the final model would have only modestly improved the C-index from 0.687 to 0.689.

Recurrence of Kidney Stone Tool

The linear predictors derived from the final Cox regression model were used to develop the revised ROKS tool (<https://qxcalc.app.link/ROKS2>). The sum impact of all predictors for recurrence (number of past episodes) calculates “total points” (Supplemental Figure 1). The estimated risk of symptomatic recurrence can be determined from the equation $1 - \alpha (\exp(-1.84089 + \text{points} * 0.01019))$ where a different α is chosen (Supplemental Table 5) depending on the current episode number, years since this last episode, and prediction of 5-year risk (Supplemental Figure 2a) or 10-year risk (Supplemental Figure 2b). More risk factors for recurrence (total points) increased with number of episodes (Supplemental Figure 3). The estimated 5-year recurrence rates were 17% (95% CI: 14% to 20%), 32% (95% CI: 26% to 38%), 47% (95% CI: 36% to 57%), and 60% (95% CI: 38% to 74%) and estimated 10-year recurrence rates were 28% (95% CI: 24% to 32%), 45% (95% CI: 37% to 51%), 67% (95% CI: 53% to 77%), and 68% (95% CI: 43% to 83%) after the first, second, third, and fourth or higher episodes, respectively. There was good agreement between predicted and actual recurrence rates (Supplemental Figure 4). Recurrence risk increased with both more past episodes and with more total points (Figure 3). For individual patients, the risk of recurrence in the next 5 or 10 years could vary from 0.9% to 94% depending on the total points, number of episodes, and years since the last episode (see Supplemental Example Patients).

Stone prevention interventions and 24-h urine chemistries

Except for surgeries, the prevalence of stone prevention interventions increased with the number of stone episodes, but none were associated with subsequent recurrence after adjusting for the ROKS model predictors (Table 3). When added to the final ROKS model, stone surgery only improved the C-index from 0.687 to 0.688 (Supplemental Table 6). Similarly, adding calendar year of stone episode to the final ROKS model only improved the C-index from 0.687 to 0.689.

A 24-h urine chemistry was available at some time point in 33% of stone formers. While lower urine volume and lower urine citrate were independently predictive of recurrence, addition of these tests to the final ROKS model in the subset with urine chemistries only modestly improved the C-index (Supplemental Table 7 available online at <http://www.mayoclinicproceedings.org>).

Discussion

We identified 13 readily available clinical and radiographic predictors for symptomatic recurrence among community stone formers with one or more past stone episode in the community. We then developed a revised ROKS prediction tool that uses these 13 independent predictors, the number of past stone episodes, and the years since the last stone episode to predict the 5 and 10 year risk of future stone episodes. The risk of symptomatic recurrence in the next 5 years for individual stone formers ranged from 0.9% to 94% depending on clinical and radiographic risk factors, the number of past stone episodes, and years since the last stone episode.

The predictors for symptomatic recurrence in the final model are either risk factors for kidney stone formation and growth or reflect the actual kidney stone burden at the last episode. Several of the predictors have been previously discussed in the original ROKS tool.^{4, 7} In this revised ROKS tool, we also found higher BMI and pregnancy at last episode to predict recurrence. Obesity is an established risk factor for kidney stones¹² that may increase the risk of recurrence via hypercalciuria¹³ or via insulin resistance with lower urine pH and hypocitraturia.¹⁴ Pregnancy has recently been identified as a risk factor for kidney stones,¹⁵ possibly due to hypercalciuria during pregnancy.¹⁶

We also added more granular radiographic predictors compared to the original ROKS model.⁴ We found that any lower pole or pelvic kidney stone, the number of kidney stones, and the diameter of the largest kidney stone each independently predict symptomatic recurrence. Lower pole stones may lead to future symptomatic episodes because they reflect previously detached stones (location from gravity), reflect stones that formed out of residual fragments from past stone surgeries, or reflect stones that are too tedious to remove during surgery on a ureteral stone. Both the size and number of kidney stones are predictive of future symptomatic stone episodes in referral populations.^{17–20} While the risk for symptomatic recurrence increased progressively with the number of kidney stones, there was a higher risk with a stone diameter of 3–6mm than a diameter less than 3 mm or greater than 6 mm. This may be due to a higher likelihood of surgical removal of large stones. Indeed, 63% of episodes with a largest kidney stone greater than 6-mm kidney stone underwent surgery as compared with only 39% with a 3- to 6-mm (largest) kidney stone or 29% with a less than 3-mm (largest) kidney stone.

One of the key findings in this analysis is that the number of past episodes increases the risk of future stone episodes, but only up to about the 5th episode in unadjusted analysis, and the 4th episode in the multivariable-adjusted analysis. With subsequent symptomatic recurrence, stone formers may learn to self-manage some of their episodes (trial of passage) without clinical care. Indeed, self-managed stone episodes without clinical care became more common with each subsequent confirmed stone episode. However, we could only develop a tool to model the risk of stone episodes that result in clinical care. Self-managed stone episodes without clinical care are often not documented in the medical record.

Clinical trials do report a higher rate of recurrence in single episode stone formers compared to this community setting (6 episodes per 100 person-years vs 3 episodes per 100 person-

years).²¹ This may be due to clinical trials including symptomatic recurrence that is self-managed, including asymptomatic recurrence by radiographic increases in stone burden, and selective enrollment of high risk patients referred to stone specialists. Clinical trials and observational studies in referral populations have previously linked more kidney stone episodes to a higher risk of recurrence.^{5, 6, 21} This study extends these findings to the community setting (avoiding selection bias) and adds detail on how the specific number of episodes increases the risk of symptomatic recurrence (rather than just one versus multiple).

We could not detect a protective effect of stone prevention interventions. Stone prevention interventions were increasingly used with more symptomatic recurrence. Thus, prevention interventions were themselves a marker of recurrence. Sustained lifetime commitment to preventative dietary interventions and medications may not occur in many patients, even though clinical trials show short-term benefits.^{22, 23} Lower urine volume and lower urine citrate predicted symptomatic recurrence, but their contribution to model discrimination was too weak to justify their inclusion.

There were several potential limitations to this study. About 25% of stone episodes lacked imaging variables. This reflects the clinical reality that not all stone episodes are managed with imaging, especially if the patient voids the stone and symptoms resolve. Limiting the analysis to only episodes with imaging would have substantially underestimated the risk of symptomatic recurrence. Stone composition is unknown when stones are voided and lost; 39% of the cohort lacked any stone composition data.⁷ Excluding patients missing stone composition data would have biased the model as lower risk patients are less likely to have had stone composition analysis.⁷ The tool was developed in Olmsted County, which is similar to the Upper Midwest of the United States in that it is predominantly white, more educated, and has a continental climate pattern.²⁴ External validation is needed. Imaging modalities and treatments have changed over the 33 year study period and will continue to change in the future. Nonetheless, determining the rate of multiple symptomatic stone episodes among incident community stone formers requires a study period across several decades. It is also reassuring that adding calendar year to the model had no substantive impact on the model fit. The C-index of 0.681 for this revised ROKS model was relatively low for a prediction tool, though an improvement over the 0.647 for the previous ROKS tool.⁴ Future prospective studies may be needed to better identify predictors as well as to follow for stone passage episodes that are self-managed or asymptomatic.

Conclusion

This study identified novel risk factors for stone recurrence, including the number of past stone episodes and years since the last episode. The revised ROKS prediction tool for estimating symptomatic recurrence risks can be used to guide the management of stone formers by individualizing preventative interventions based on the risk of symptomatic recurrence. This tool can also be used to estimate symptomatic stone episode rates that result in clinical care for use in clinical trials on kidney stone prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ROKS	Recurrence of Kidney Stone
BMI	body mass index
CT	computed tomography
CI	confidence interval

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Figure 1. Sampling of the cohort of stone formers with at least one confirmed symptomatic kidney stone episode.

Figure 2.
Cumulative risk of symptomatic recurrence after the 1st, 2nd, 3rd, and 4th symptomatic kidney stone episode.

Figure 3.

Risk of symptomatic recurrence using the ROKS tool depends on both number of past episodes and risk factors. Risk after the A) 1st, B) 2nd, C) 3rd, D) 4th+ stone episode at the 25th and 75th percentile for total points (Sum of risk factors from Supplemental Figure 1).

Table 1.

Risk of symptomatic recurrent episodes with number of prior stone episodes

Stone Episode	Number with a recurrent episode	Person-Years of follow-up	Recurrence Rate Episodes/100 Person-Years (95% CI)
1	882	25714	3.4 (3.2 to 3.7)
2	337	4739	7.1 (6.4 to 7.9)
3	166	1372	12.1 (10.3 to 13.9)
4	85	580	14.6 (11.5 to 17.7)
5	55	270	20.3 (15.0 to 25.7)
6	25	193	13.0 (7.9 to 18.0)
7	12	44	27.2 (11.8 to 42.5)
8	9	21	43.9 (15.2 to 72.5)
4 +	202	1150	17.6 (15.1 to 20.0)
5 +	117	570	20.5 (16.8 to 24.2)
6 +	62	300	20.7 (15.5 to 25.8)
7 +	37	107	34.7 (23.5 to 45.8)
8 +	25	63	40.0 (24.3 to 55.6)

For X+, the symptomatic recurrence rate was determined for each subsequent recurrence after the Xth episode in the same person. Confidence intervals were calculated using the Poisson normal approximation.

Table 2.

Final model for predicting symptomatic recurrence using all stone formers and all episodes

<i>Demographic and stone episode characteristics for final model</i>		N=3,699 episodes C-index (95% CI)=0.687	
		Hazard Ratio (95% CI)	P Value
Age at last stone episode (per 10 years)		0.88(0.84–0.92)	<.001
Body mass index at last stone episode (per 5 kg/m ²)		1.07(1.02–1.13)	.004
Sex (Male)		1.25(1.09–1.44)	.002
Family history of kidney stones		1.36(1.19–1.55)	<.001
Incidental (asymptomatic) stone on imaging prior to first confirmed stone episode		1.35(1.08–1.69)	.008
Suspected kidney stone episode ^a prior to first confirmed stone episode		1.75(1.44–2.13)	<.001
Pregnant at last stone episode		1.82(1.20–2.75)	.005
Any stone found to be uric acid, brushite, or struvite		1.24(0.92–1.66)	.16
Any stone found to be calcium oxalate monohydrate		0.89(0.78–1.02)	.08

<i>Imaging characteristics at last stone episode</i>			
	0	Ref	Ref
Number of stones in both kidneys	1	1.30(1.11–1.51)	<.001
	2	2.03(1.74–2.38)	<.001
Diameter of largest kidney stone	<3 mm/no kidney stones	Ref	Ref
	3–6 mm	1.25(1.03–1.51)	.02
	>6 mm	0.96(0.74–1.26)	.79
Pelvic or lower pole kidney stone		1.39(1.18–1.63)	<.001
Ureterovesical junction stone		0.84(0.74–0.96)	.01

^aCharacteristic renal colic attributed to a stone but no stone seen on imaging or documented as voided in the medical record.

Table 3.

Stone recurrence by treatment of kidney stones at each episode

Treatment	Model	First episode (n=3,364)			Second episode (n=882)			Third episode (n=337)		
		N (%)	HR	P-value	N (%)	HR	P-value	N (%)	HR	P-value
Past or present dietary intervention ^b	Unadjusted	2536 (75%)	1.01	.88	781 (89%)	1.13	.50	310 (92%)	0.80	.42
	Adjusted ^a		1.06	.51		0.86	.48		0.82	.69
Past or present medications ^b	Unadjusted	118 (4%)	1.69	<.001	117 (13%)	0.85	.32	71 (21%)	1.56	.01
	Adjusted ^a		1.19	.32		0.85	.43		0.93	.81
Past or present stone clinic ^b	Unadjusted	61 (2%)	1.84	.002	204 (23%)	1.09	.50	153 (45%)	1.47	.01
	Adjusted ^a		1.19	.40		0.86	.32		1.21	.42
Stone surgery for current episode	Unadjusted	1089 (32%)	0.88	.09	317 (36%)	1.02	.88	23 (7%)	0.39	.04
	Adjusted ^a		0.85	.05		0.98	.90		0.41	.10

^a Adjusted for the 13 predictors in the final model (Table 2).^b Prior to or within 3 months of the stone episode.