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ORIGINAL ARTICLE

Spontaneous ureteral stone passage: a novel and comprehensive nomogram

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ABSTRACT

BACKGROUND: Ureteral stones pose a high economic and medical burden among Emergency Department (ED) admissions. Management strategies vary from expectant therapy to surgical interventions. Since predictors of ureteral spontaneous stone passage (SSP) are still not well understood, we sought to create a novel nomogram to guide management decisions.

METHODS: Charts were retrospectively reviewed for patients who presented to our institution's ED with non-febrile renal colic and received a radiological diagnosis of ureteral stone ≤10 mm. Demographic, clinical, laboratory, and non-contrast CT data were collected. This novel nomogram incorporates the serum neutrophil-to-lymphocyte ratio (NLR) as a potential predictor of SSP. The model was derived from a multivariate logistic regression and was validated on a different cohort. A receiver operator characteristic (ROC) curve was constructed and the area under the curve (AUC) was computed.

RESULTS: A total of 1186 patients presented to our ED between January 2010 and October 2018. We randomly divided our population into a derivation and validation cohort in one to five ratio. A stone size ≥7 mm was the strongest predictor of SSP failure; OR=9.47; 95% CI: 6.03-14.88. Similarly, a NLR≥3.14 had 2.17; (1.58-2.98) the odds of retained stone. SSP failure was also correlated with proximal position, severe hydronephrosis, and leukocyte esterase ≥75, P=0.02, P=0.05, and P=0.006, respectively. The model had an AUC of 0.804 (0.776-0.832). The nomogram was also used to compute the risk of SSP failure (AUC 0.769 [0.709-0.829]).

CONCLUSIONS: Our novel nomogram can be used as a predictor for SSP and can be used clinically in decision making.

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KEY WORDS: Ureteral calculi; Nomograms; Lithotripsy; Ureteroscopy.

Nephrolithiasis is one of the most common urologic complaints in the Emergency Department (ED). In the USA, around 1.3 million ED admissions yearly are attributed to renal colic from nephrolithiasis.[1] With the rise in worldwide incidence and prevalence of nephrolithiasis,[2] added to the technological advancements in minimally invasive surgery,[3] the financial burden on healthcare is expected to majorly increase. Effectively, in the USA alone, expenditure on nephrolithiasis management is expected to reach $ 4.1 billion by the year 2030.[4]

The rising economic burden and growing incidence of nephrolithiasis encourages proper patient stratification for management decisions. These decisions fall basically into two categories: medical expulsive therapy/watchful waiting or surgical intervention. On one hand, most stones under 10 mm pass spontaneously, so surgical intervention could be unnecessary with added cost.

On the other hand, delaying needed intervention could lead to renal failure and serious urinary infections.[5] The current international guidelines on urolithiasis management base the discussion on spontaneous management of ureteral stones on outdated studies with small sample size.[6, 7]

Previous studies attempted to determine the clinical parameters that influence stone passage. The main determinants of spontaneous ureteral stone passage are stone size and location. The influence of serum inflammatory markers has been studied as potential surrogate markers for SSP.[8-11] However, there are no available holistic predictive nomograms that would influence the rate of ureteral stone passage in the clinical setting. Through this study we sought to derive then internally validate a nomogram that compiles demographic, radiographic, and laboratory markers into a comprehensive novel nomogram incorporating the neutrophil-to-lymphocyte ratio (NLR) inflammatory marker.

Materials and methods

After institutional review board approval, the electronic health records at the American University of Beirut Medical Center, Beirut, Lebanon, was queried for patients presenting to the emergency department between January 2010 and October 2018 for renal colic. Only non-febrile patients with a diagnosis of a single ureteral stone ≤10 mm on non-contrast computer tomography (NCCT) scan performed at our facility were included. The 10mm cut-off was chosen as a clinical parameter of upper limit of size and this is in concordance with contemporary series.[12-14] Patients with concurrent kidney stones and the following comorbidities: leukemia, cancer, chronic inflammatory diseases, acute or chronic steroid intake, positive urine cultures, and concomitant infections were excluded. The primary outcome was spontaneous stone passage (SSP) of the ureteral stone defined as absence of the previously diagnosed stone at four-week follow up NCCT scans. All patients were given tamsulosin and pain medications at diagnosis in the ED. Patients without follow up at four weeks were also excluded from the analysis.

Information on patient's demographics, basic metabolic profile, complete blood count with differential, urine analysis and culture, stone location, and size were collected. Stone size was divided into three groups:<5 mm, >5-7 mm, and ≥7 mm as previous studies demonstrated significantly variable SSP rates among these categories.[15] The NCCT scan was used to report on stone location, stone size, and presence of hydronephrosis or fat streaking. Based on the Onen Classification, hydronrephosis grades 0 and 1 were categorized as no to mild hydronephrosis, a score of 2 was deemed as moderate hydronephrosis, and a score of 3 or 4 was considered as severe hydronephrosis. The primary objective of the study was to determine the predictors of SSP and evaluate the role of the neutrophil-to-lymphocyte ratio (NLR) in anticipating single ureteral stone passage. The secondary objective of the study was to internally validate the model and construct a Kattan nomogram that could be used as a clinical tool. Thereby, by sharing the model's formula, external validation could be achieved by other medical centers.

Statistical analysis

The software randomly assigned the population into either a derivation or a validation cohort in a 5:1 ratio. Then, baseline demographics of the two cohorts were compared to confirm the random assignment. Then, patient demographic, basic metabolic profile, serum NLR, urine analysis as well as radiological parameters were evaluated as potential predictors of SSP at the univariate level using independent *t*-test and χ^2 test for continuous and categorical variables respectively. To account for covariates, a backward conditional logistic regression model was constructed adjusting for age, sex, hypertension, diabetes, creatinine level, NLR, white blood count (WBC) in urine, leukocyte esterase level, presence of hydronephrosis, stone position, and its size. Then, using the derived logistic regression's formula, each patient's risk (%) was computed to estimate SSP failure by replacing the variables in the following equation:

$$2.87+(0.947\times a)+(0.234\times b)+(0.931\times c)+(0.511\times d)+(1.226\times e)+(2.249\times f)+(0.729\times g)+(0.773\times h)+(0.353\times i)+(0.587\times j)$$

In particular, *a* was the creatinine level. The

variables *b*, *c*, *d*, *e*, *f*, *g*, *h*, *i*, *j*, represent the following conditions moderate hydronephrosis, severe hydronephrosis, female sex, stone size ≥5-7 mm, stone size ≥7 mm, female sex, leukocyte esterase ≥75, NLR≥3.14, mid-ureteral stone, and proximal stone, respectively. The variables are subsequently replaced by either a 0, if not applicable to the patient; or 1 if the condition applies. Subsequently, the individual risks for SSP failure were plotted into a receiver operating characteristic (ROC) curve and the area under the curve (AUC) was calculated.

The same equation was also used to compute the individual risks of SSP failure among the validation cohort. These risks were also plotted into a ROC curve and the AUC compared to the AUC retrieved from the derivation cohort. Furthermore, different cut-offs for SSP failure were chosen and the sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated to assess the model's reliability. Statistical tests were performed with a two-sided P>0.05 set for significance using the Statistical Package for the Social Sciences statistical package IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) and R statistical package (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) was used for plotting the Kattan nomogram.

Results

For the designated period, 1186 patients presented to the emergency department where a radiological diagnosis of ureteral stone was given. The median age was 46 (34-56) and 868 (73.2%) of the patients were male. The average stone size was 5 (4-6) mm and 25.4%, 11.8%, and 62.8% of the ureteral stones were proximal, mid-ureteral, and distal, respectively. Around half of the patients (52.7%) of the patients had SSP.

The derivation and validation cohorts were compared for demographics and ureteral stone parameters to ensure that the selection process was random (Table I). There was no difference in rates of hypertension (P=0.282), diabetes (P=0.554) admission (P=0.288) or SSP (P=0.720). Similarly, there was no difference in the average stone size (P=0.353).

Among the derivation cohort, SSP rates were 41% (99/240) for proximal stones, 41% (48/117) for mid-ureteral stones, and 60% (349/582) for distal stones (Table II). Patients who failed to spontaneously pass the calculus were older (48 (36-58) for retained stone *versus* 43 (33-54) for SSP), more likely to be males (29.9% *versus* 23.6%), hypertensive (29.7% *versus* 19.3%), and diabetic (15.5% *versus* 9.6%); P<0.0001, P=0.028, P<0.0001, and P=0.006, respectively

TABLE I.—*Comparison of baseline demographics between the derivation and validation cohort using Student's* t*-test and* χ^2.

Variable	Derivation cohort N.=946	Validation cohort N.=240	P value
	N. (%)/Median (IQR)	N. (%)/Median (IQR)	
Age	46 (34-56)	45 (34-57)	0.586
Male	695 (73.5%)	173 (72.1%)	0.666
Hypertension	227 (24.2%)	50 (20.9%)	0.282
Diabetes	116 (12.4%)	33 (13.8%)	0.554
SSP	501 (53.0%)	124 (51.7%)	0.720
Admission	477 (50.7%)	131 (54.6%)	0.288
Admitted			0.652
SSP	97 (20.3%)	29 (22.1%)	
Failed SSP	380 (79.7%)	102 (77.9%)	
Discharged			0.789
SSP	399 (86.2%)	95 (87.2%)	
Failed SSP	64 (13.8%)	14 (12.8%)	
Stone size	5 (4-6)	5 (4-6)	0.353
Ureteral stone position			0.327
Proximal	240 (25.6%)	60 (25.0%)	
Mid-ureteral	117 (12.5%)	22 (9.2%)	
Distal	582 (62.0%)	158 (65.8%)	

SSP: Spontaneous stone passage.

TABLE II.—*Comparing the demographics, comorbidities, and laboratory serum markers among those who passed and failed to pass the ureteral stone using Student's* t*-test and* χ^2.

Variable	Failed SSP (N.=445)	SSP (N.=501)	P value
	N. (%)/Median (IQR)	N. (%)/Median (IQR)	
Age	48 (36-58)	43 (33-54)	<0.0001
Female	133 (29.9%)	118 (23.6%)	0.03
Hypertension	132 (29.7%)	95 (19.3%)	<0.0001
Diabetes	69 (15.5%)	47 (9.6%)	0.006
Creatinine	1.2±1.0	1.0±0.4	<0.0001
NLR≥3.14	279 (62.7%)	194 (39.0)	<0.0001
Hematuria			0.1
0-rare	40 (9.1%)	43 (8.6%)	
2-4 RBC/HPF	46 (10.5%)	29 (5.8%)	
4-6 RBC/HPF	35 (8.0%)	48 (9.6%)	
8-10 RBC/HPF	54 (12.3%)	71 (14.2%)	
Numerous RBC	265 (60.2%)	308 (61.7%)	
Urine WBC			
0-rare	173 (39.3%)	245 (49.1%)	<0.0001
2-4 WBC/HPF	102 (23.2%)	144 (28.9%)	
4-6 WBC/HPF	64 (14.5%)	50 (10.0%)	
8-10 WBC/HPF	41 (9.3%)	28 (5.6%)	
Numerous WBC	60 (13.6%)	32 (6.4%)	
Leukocyte esterase ≥75	77 (17.5%)	32 (6.5%)	<0.0001
Stone Position			<0.0001
Proximal	141 (31.8%)	99 (20.0%)	
Mid-ureteral	69 (15.6%)	48 (9.7%)	
Distal	233 (52.6%)	349 (70.4%)	
Fat streaking			0.001
None	109 (24.7%)	149 (29.9%)	
Mild	245 (55.6%)	296 (59.3%)	
Moderate	67 (15.2%)	45 (9.0%)	
Severe	20 (4.5%)	9 (1.8%)	
Hydronephrosis			<0.0001
None	22 (5.0%)	51 (10.2%)	
Mild	227 (51.5%)	329 (65.9%)	
Moderate	157 (35.6%)	112 (22.4%)	
Severe	35 (7.9%)	7 (1.4%)	
Stone size (mm)	6 (5-7)	4 (3-5)	<0.0001

HPF: High power field; NLR: neutrophil to lymphocyte ratio; RBC: red blood cell count: SSP: spontaneous stone passage; WBC: white blood cell count.

(Table II). The median NLR was 3.14; where most of those who had retained stones (62.7% *versus* 39.0%) had a NLR≥3.14 at their presentation. A higher RBC number/HPF, higher WBC count in urine, and leukocyte esterase were associated with failure of stone passage (P<0.0001 for all variables). Retained stones were more likely to be proximal (31.8% *versus* 20.0%) and to have moderate to severe fat streaking and hydronephrosis. Additionally, SSP was associated with smaller stones (4 (3-5) mm *versus* 6 (5-7) mm); P<0.0001.

At the multivariate level, every one-unit increase in serum creatinine and serum NLR≥3.14 had OR=2.58 95% CI: 1.50-4.43 and 2.17 (1.58-2.98) the odds respectively of SSP failure (Table III). Stone size was the most significant predictor of retained stones where size between >5 and <7 mm and a size of ≥7 mm had an Odds Ratio of 3.41 (2.42-4.80) and 9.47 (6.03-14.88), respectively. Similarly, proximal stones 1.80 (1.11-2.93) and evidence of collecting system dilation 2.54 (1.01-6.39) predicted a need for intervention. Moreover, female gender (P=0.01) and leukocyte esterase ≥75 (P=0.006) were other significant predictors of SSP failure. The model was used to calculate the individual risk for SSP failure among the derivation cohort. According

TABLE III.—*Multivariate backward logistic regression predicting stone passage.*

Variables	SSP Failure (N.=902)	
	Odds Ratio (95% CI)	P value
Female	1.67 (1.13-2.46)	0.01
Creatinine	2.58 (1.50-4.43)	0.001
NLR≥3.14	2.17 (1.58-2.98)	<0.0001
stone size >5-7	3.41 (2.42-4.80)	<0.0001
Stone size ≥7	9.47 (6.03-14.88)	<0.0001
Mid-ureteral stone	1.42 (0.99-2.05)	0.06
Proximal stone	1.80 (1.11-2.93)	0.02
Moderate hydronephrosis	1.56 (1.01-2.40)	0.05
Severe hydronephrosis	2.54 (1.01-6.39)	0.05
Leukocyte esterase >75	2.07 (1.24-3.47)	0.006

95.3% of the patients were included in the multivariate analysis. Variables entered into the model: age, gender, hypertension, diabetes, creatinine, neutrophil-to-lymphocyte ratio, white blood cell count in urine, leukocyte esterase, hydronephrosis, stone position, and stone size.
NLR: Neutrophil to lymphocyte ratio.

to the ROC curve, the model explained 80.4% (c-statistic=0.804; 0.776-0.832) of the variability in the outcome (SSP) (P<0.0001) (Figure 1).

The model was also used to estimate the risk of SSP failure among the validation cohort. Figure 2 depicts the internal validation's ROC curve which revealed an overlapping c-statistic=0.769 and confidence interval (0.709-0.829). Different cut-offs were tested and the sensitivity of the model was computed. Table IV illustrates

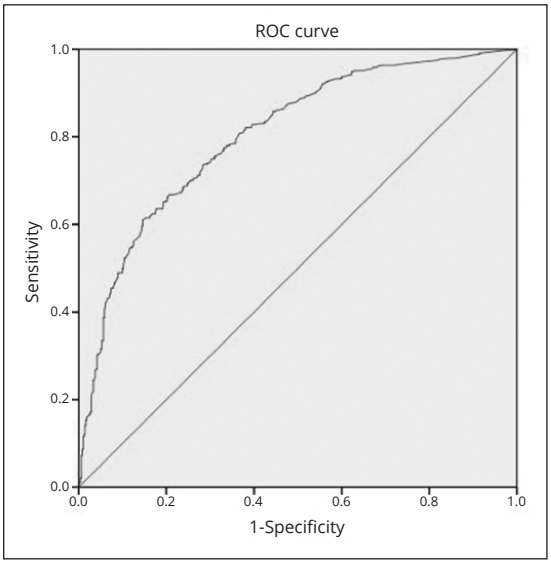

Figure 1.—Receiver operating characteristic curve for the derivation cohort.
AUC ROC c-statistic =0.804 (0.776-0.832) P<0.0001

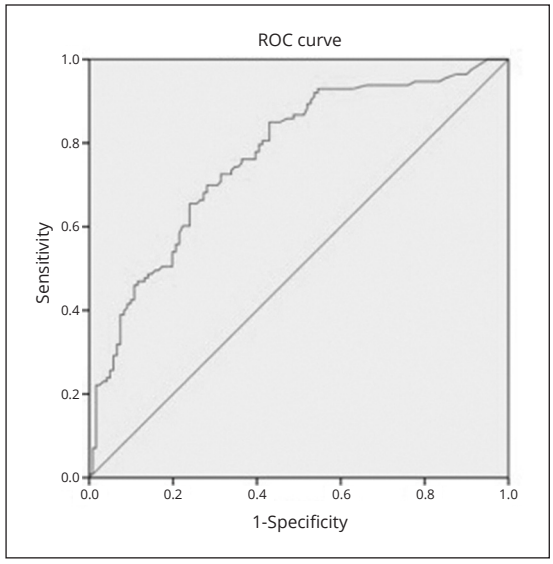

Figure 2.—Receiver operating characteristic curve for the validation cohort.
AUC ROC c-statistic =0.769 (0.709-0.829) P<0.0001

the different cut-off levels and their respective sensitivities. For instance, at a cut-off of 2.5%, the model has a 92.6% sensitivity and a 81.3% NPV. Similarly, a 3.0% yields a 98.3% sensitivity and a 92.3% NPV. While a lower cut-off compromised the sensitivity and NPV, a range of cut-off between 2.5% and 3.0% guaranteed a nomogram-missed SSP failure cases (false negative) between 0.9% and 3.8% among patients with ureteral stones.

Discussion

Currently, the American Urologic Association[7] and European Association of Urology[6] Guidelines on managements of urolithiasis do not dwell on the role of predictive models for management of ureteral stones. Actually, the guidelines are based on outdated studies with relatively small sample size and do not "dissect" the role of radiological findings on decision-making.[16, 17] In this study, using a large dataset from a single tertiary referral center, we derived a comprehensive model that will be helpful for decision-making.

Similar to most studies, we found that stone size and location are main factors associated with SSP.[15, 18, 19] Although the proximal stones were only about twice as likely to pass than mid

TABLE IV.—*Sensitivity and specificity of the predictive tool at different cutoff values.*

Nomogram	Nomogram-missed SSP –failure cases (false negative)	Avoided admission or intervention (true negative)	Sensitivity	Specificity	PPV	NPV
	N. (%)	N. (%)	%	%	%	%
≥1.00%	48 (20.5%)	86 (36.8%)	60.3%	76.1%	73%	64.2%
≥2.00%	16 (7.2%)	54 (23.2%)	86.7%	47.8%	63.8%	77.1%
≥2.5%	9 (3.8%)	39 (16.7%)	92.6%	34.5%	60.2%	81.3%
≥3.00%	2 (0.9%)	24 (10.3%)	98.3%	21.2%	57.2%	92.3%

and proximal ureteral stones, significance might have been diluted due to a low frequency of mid-ureteral stones (12.5%) in our cohort. Coll *et al.* report higher rates of SSP: 48% for proximal stones, 60% for mid-ureteral stones, and 75% for distal ones *versus* 41%, 41%, and 60%, respectively in our cohort).[15] This could be attributed to impacted stones at the ureterovesical junction (UVJ). SSP rates at the UVJ were variable (33-92%) depending on the stone size.[15]

A previous study for the authors with a smaller sample size (N.=520) has found a relationship between increased inflammatory markers and failure to pass ureteral stones.[10] Other studies have also echoed our findings.[8, 20, 21] It is thought that inflammation and edema propagate along the ureteral wall and as a result would decrease ureteral wall compliance and contractile capability.[22, 23] Nevertheless, a large multicenter study has negated the role of inflammatory markers in predicting ureteral stone passage.[18] We postulate that our reliance on NLR instead of leukocyte count might be more pertinent to the inflammatory mechanism. Furthermore, we found that an elevation in serum creatinine and hydronephrosis could indicate an impacted stone thereby lowering SSP rates. Other factors that have been correlated with failure of SSP and increased risk of needing surgical intervention include requiring opioids analgesia, prolonged pain, and history of nephrolithiasis.[24]

There are other factors that have not been taken into account in the authors' analysis. For instance, ureteral wall thickness has been associated with failure of not only SSP[14] but also adverse findings and increased difficulty during ureterscopy.[25] Moreover, Ongun *et al.* found that ureteral jet on Doppler ultrasonography is associated with a higher rate of SSP.[26]

The optimal management of ureteral stone is

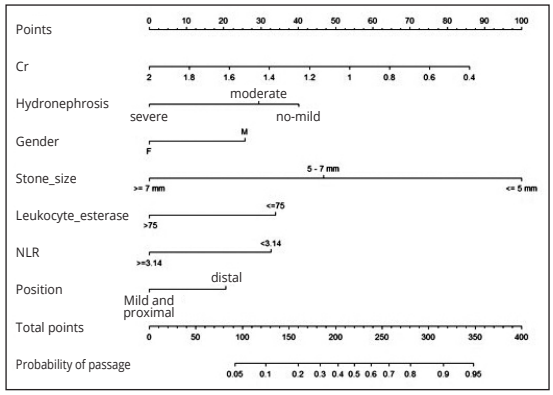

Figure 3.—Novel Predictive nomogram incorporating various clinical factors to predict the probability of spontaneous ureteral stone passage.

elusive if we need to find the adequate balance between conservative management, healthcare cost, and potential complications like infections and kidney injury. Although cheaper, expectant management entails a potential risk for kidney injury and patient discomfort. Additionally, although offered to all patients who presented with ureteral stone<10 mm at our ED, the use of medical expulsive therapy (alpha-blockers) reveals equivocal improvement in SSP outcomes.[27, 28] On the other hand, shock wave therapy (SWL) or ureteroscopy relives patient discomfort, but are more costly and beget procedure-specific complication risk. Therefore, as a first step, physicians need a tool to stratify patients into designated management strategies, such as medical therapy/expectant management, SWL, or ureteroscopy.[6]

We have devised a predictive nomogram incorporating various clinical variables to postulate the probability of SSP (Figure 3). The Kattan nomogram allows the clinician to compute a score that could be converted to a model-specific patient risk. The authors suggest choosing a 2.5% cut-off for SSP failure because it yields

a high sensitivity (92.6%) and a limited number of nomogram-missed cases who eventually need surgical intervention (3.8%). Moreover, unnecessary interventions could be avoided in 16.7% of patients presenting with ureteral colic.

Limitations of the study

This study has several limitations. Although it is retrospective, a prospective randomized interventional trial would be either underpowered or very difficult to conduct.[29] Potential bias could stem from the subjective nature of the management in ureteral stones. Additionally, the reliance on non-contrast NCCT scans is associated with inherent flaws such as artifacts and inter-reader variability. Furthermore, stone composition was not accounted as not all patients had their stones sent for composition analysis. Although external validation was not performed due to lack of access to other databases, we sought to internally validate the model using separate cohorts to further confirm our findings. Nevertheless, this is the largest published study that derives a comprehensive novel nomogram to predict SSP by proving an inflammatory role in stone passage.

Conclusions

The optimal management and decision-making of ureteral stones is complex and multifactorial. Current guidelines are oblivious to patient-centered models. This nomogram has been internally validated and has a 92.6% sensitivity to predict SSP. Nevertheless, we have shared the nomogram's formula to encourage its external validation on a larger and more diverse population.

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