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Factors and Cut-Off Predicting Stone Passage under Medical Expulsive Therapy (MET)

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Abstract

Background: Ureteral stones are the most common leading cause of acute flank pain. This study aimed to identify sociodemographic and clinical variables predicting spontaneous ureteral stone passage and determine the optimal size cut-off for predicting such passage. **Method:** We conducted a retrospective evaluation of patients presenting with acute renal colic at a urology outpatient clinic. Patients with ureteral stones ≤ 10 mm and no surgical intervention post-initial diagnosis, who attended follow-up visits, were included. Exclusion criteria comprised stone size > 1 cm, fever due to obstructive pyelonephritis, acute kidney injury, single kidney status, or bilateral ureteral obstruction. **Results**: Of 124 included patients, the spontaneous stone passage rate was 57.3%, with a mean passage time of 11.1 (SD 6.25) days. Bivariate analysis revealed that factors predicting spontaneous passage were stone size ($p < 0.001$), stone size below 7 mm ($p < 0.0001$), and stone location, particularly at the ureterovesical junction (UVJ) ($p < 0.001$). However, only stones with size < 7 mm had a significantly shorter passage time. Multivariate logistic regression confirmed these three factors as significantly associated with spontaneous passage, with stones at the UVJ showing an eightfold likelihood of passage (OR = 8.62, $p = 0.009$). ROC curve analysis suggested a stone size cutoff < 6.85mm was more likely to pass with MET with maximum sensitivity (78.9%) and specificity (71.1%) and area under the curve (AUC) of 0.832. **Conclusions**: Stone size < 7 mm, UVJ or distal ureter location, emerged as key predictors of stone passage in nephrolithiasis, and stone size below 6.85 mm is a reasonable cut off to initiate MET rather than 10 mm.

Keywords

Ureteral Stones, Nephrolithiasis, *Spontaneous Stone Passage*

1. Introduction

Ureteral stones represent one of the most prevalent causes of acute flank pain worldwide [1]. The stones originate as crystalline formations within the kidneys and traverse the ureters, inducing obstructive symptoms [2]. Nephrolithiasis, a frequently encountered urological ailment, demonstrates a prevalence of 11% in men and 7% in women [3], with incidence rates varying geographically. Notably, Arab nations exhibit elevated prevalence rates of nephrolithiasis, with Saudi Arabia reporting the highest incidence at 20.1% [4].

Renal colic, characterized by abrupt and intense pain radiating from the flank to the groin, primarily stems from the passage of calculi through the urinary tract [5], often accompanied by hematuria, urinary urgency, and potential complications such as fever [6]. Previous studies have shown that 75 - 90% of stones pass spontaneously [7] [8]. The initial approach when a stone is likely to pass on its own is often watchful waiting, with or without medical expulsive therapy (MET) [9]. Medical expulsive therapy (MET) serves as the initial approach to facilitate the spontaneous passage of ureteral stones, aiming to reduce the need for invasive procedures such as surgery or lithotripsy [10]. However, stones that are unlikely to pass spontaneously are treated with extracorporeal shock wave lithotripsy (ESWL), laser lithotripsy, or percutaneous stone extraction via the renal pelvis.

The dilemma between active management and waiting until spontaneous passage, versus intervention choice represents a primary challenge for urologists in the management of patients with ureteric stones [11]. The principal objectives of MET include pain relief, acceleration of stone expulsion, and prevention of complications such as urinary tract infections and renal impairment [12]. Alpha-blockers stand out as a pivotal component of MET, endorsed by guidelines from both the European Association of Urology (EAU) and the American Urological Association (AUA) [13]. Their ability to relax ureteral smooth muscle helps in the passage of stones [14]. However, there is currently no conclusive recommendation regarding the concurrent use of phosphodiesterase-5 inhibitors or corticosteroids alongside alpha-blockers in MET [15]. MET is typically indicated for patients with uncomplicated ureteral stones, particularly those measuring less than 10 mm in size and situated in specific locations [16]. Nevertheless, for patients presenting with larger stones, signs of infection, solitary kidneys, acute kidney injury, or intolerance to prescribed medications, MET may not be the appropriate course of action [17].

A strong association is widely acknowledged between stone size, location, and the probability of spontaneous stone passage [18] [19]. Consequently, the guidelines state that watchful waiting represents an optional initial approach for ureteral stones measuring less than 10 mm. Notably, these recommendations have remained unchanged in the latest guidelines issued by the European Association of Urology (EAU) [20]. Therefore, identifying specific predictive factors that can help to predict the spontaneous passage can help urologists determine the suitability of conservative management versus interventional approaches for each patient.

This study aims to determine the sociodemographic and clinical variables, including stone size and location, that can predict the likelihood of spontaneous ureteral stone passage, alongside identifying the optimal size cutoff for predicting spontaneous stone passage.

2. Materials and Methods

Patients who presented to the urology outpatient clinic with acute renal colic, were retrospectively evaluated through medical records. Patients with negative surgical intervention after the first diagnosis and attended follow-up visits, with ureteral stones equal or less than 10 mm on unenhanced CT using thin slice (1 mm) were included in the study. Patients with Stone size higher than 10 mm, fever due to obstructive pyelonephritis, acute kidney injury, single kidney patient, or bilateral ureteral obstruction were excluded from the study.

The CT images were taken without the injection of oral or intravenous contrast material with the patients holding their breath in the supine position. All CT examinations were performed with a HiSpeed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI). Axial images were obtained from the top of the kidneys to the base of the bladder using a 5 mm slice thickness, a pitch of 1, and a reconstruction interval of 5 mm. According to CT-scan results, the maximum length was measured in the coronal section, measurements were performed by the radiologist.

The CT images were interpreted together by an experienced radiologist. Stone size was measured at the maximal diameter within the plane of the coronal CT image using standard soft-tissue window and level settings. Stone location was defined as proximal (above the sacroiliac joints), mid (overlying the sacroiliac joints), distal (below the sacroiliac joints), and at the ureterovesical junction. Stone location was categorized based on anatomical landmarks: stones located cranial to the sacroiliac joint were classified as proximal, those overlying the sacroiliac joint as mid-ureter (mid), and those distal to the sacroiliac joint as distal. Stones positioned at the ureterovesical junction (UVJ) constituted a separate category. The presence of hydronephrosis was assessed and divided into 3 grades, 1 representing mild hydronephrosis, 2 indicating moderate hydronephrosis, 3 denoting severe hydronephrosis.

Medical expulsive therapy was considered as oral tamsulosin 0/4 mg once daily, and patients were advised to do exercise. At the follow up visit, a follow up ct scan showing no stone, or absence of patient complaints and the patients reporting to have stone in the urine, were accepted as spontaneous passage, the time that patients reporting to have witnessed stone expulsion was accepted as the spontaneous passage time.

This study was conducted in accordance with the Declaration of Helsinki, the Institutional Review Board (IRB) of Al Sahel Hospital approved the study with a reference number (6/2024). Participants were provided with a clear and explicit explanation of the purpose and procedures of the study before giving their consent to participate. Informed consent was obtained from all participants, and only individuals who read, understood, and consented to fill out the online questionnaire were permitted to participate in the study. To safeguard participants' anonymity and ensure the confidentiality of their information, no personally identifying data were collected during the study. Participants were explicitly informed that their involvement was voluntary, and they retained the right to withdraw from the study at any point without facing any consequences.

Statistical analyses were conducted using SPSS software (version 23, Statistical Procedures for Social Sciences; Chicago, Illinois, USA). Socio-demographic and clinical data are presented as means or medians, accompanied by standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. Differences in variables between spontaneous stone passage and non-passage were assessed using independent sample t-tests, ANOVA tests, or Mann-Whitney U tests for quantitative variables, and Chi-squared tests or Fisher's exact tests for categorical data. A p-value of less than 0.05 was considered statistically significant. Multivariate logistic regression analyses were performed to identify factors influencing the spontaneous passage of ureteric stones. The results of the regression analysis are expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). In all statistical tests, a $p\text{-value} < 0.05$ was considered indicative of statistical significance. Stone size was evaluated via ROC curve analysis to determine a threshold above which spontaneous passage is recommended. The cut-off point was determined by identifying the maximum value of the Youden's index ($J = \text{sensitivity} + \text{specificity} - 1$).

3. Results

A total of 124 patients were included in the study, with 4 patients excluded due to refusing to continue medical therapy, and 9 patients lost to follow-up. The demographic composition comprised 95 males (76.6%) and 29 females (23.4%), with a mean (SD) age of 38.5 (13.1) years. The mean stone size for the entire data set was 6.01 (2) mm, with 71 (57.3%) patients having stones below 7 mm and 53 (42.7%) patients exhibiting stones equal to or greater than 7 mm. The predominant stone location was observed at the uretero-vesical junction (41.9%), followed by the distal ureter (21.8%), proximal ureter (19.4%), and the mid-ureter (16.9%). Hydronephrosis was prevalent in the majority of patients (91.1%), predominantly categorized as mild (87.6%). Spontaneous stone passage occurred in 57.3% of patients, with a mean (SD) passage time of 11.1 (6.35) days. A significant proportion of patients (78.2%) had no previous comorbidities, while 13.7% had a history of urolithiasis or previous stone surgery (**Table 1**).

Bivariate analysis summarized in **Table 2** revealed significant associations between spontaneous passage and stone size ($p\text{-value} < 0.001$) and stone location ($p\text{-value} < 0.001$). Patients with stones smaller than 7 mm exhibited a higher rate of spontaneous passage compared to those with stones 7 mm or larger (78.9% vs. 21.1% respectively, $p\text{-value} < 0.001$). Similarly, stones located at the ureterovesical junction demonstrated a significantly higher percentage of spontaneous passage compared to the distal ureter, mid-ureter and proximal ureter (56.3 vs. 25.4 vs. 9.9 vs. 8.5 %respectively, p-value < 0.001)

Table 1. Sociodemographic and clinical data of patients (n = 124).

Characteristics	All (n = 124)
Age (years) Mean (SD)	38.5 (13.1)
Gender n (%)	
Female	29 (23.4)
Male	95 (76.6)
Size (mm) Mean (SD)	6.01 (2.0)
Size n(%)	
<7 mm	71 (57.3)
≥ 7mm	53 (42.7)
Location n(%)	
Proximal ureter	24 (19.4)
Mid ureter	21 (16.9)
Distal ureter	27 (21.8)
UVJ	52 (41.9)
Hydronephrosis n (%)	
Yes	113 (91.1)
Mild	99 (87.6)
Moderate	9 (8)
Severe	5 (4.4)
No	11 (8.9)
MET n (%)	124 (100%)
Spontaneous passage n (%)	
Yes	71 (57.3)
No	53 (42.7)
Time required for passage (days) Mean (SD)	11.1 (6.25)
Comorbidities n (%)	
Yes	27 (21.8)
No	97 (78.2)
History of stone passage or previous surgery for urolithiasis n (%)	
Yes	17 (13.7)
No	107 (86.3)

N: frequency, SD: Standard deviation, %: percentage, mm: millimeter, MET: medical expulsive therapy, UVJ: ureterovesical junction.

Table 2. A comparison of patients with spontaneous stone passage and non-spontaneous passage.

Characteristics	Stone passage		p-value
	Yes (n = 71)	No (n = 53)	
Age (years) Mean (SD)	37.8 (12.8)	39.5 (13.6)	0.488
Gender n (%)			
Female	15 (21.1)	14 (26.4)	0.491
Male	56 (78.9)	39 (73.6)	
Size (mm) Mean (SD)	5.03 (1.72)	7.33 (1.57)	**<0.001***
Size n (%)			
<7 mm	56 (78.9)	15 (28.3)	**<0.001***
≥7 mm	15 (21.1)	38 (71.7)	
Location n (%)			
Proximal ureter	6 (8.5)	18 (34)	**<0.001***
Mid ureter	7 (9.9)	14 (26.4)	
Distal ureter	18 (25.4)	9 (17)	
UVJ	40 (56.3)	12 (22.6)	
Hydronephrosis n (%)			
Yes	62 (87.3)	51 (96.2)	0.085
Mild	57 (91.9)	42 (82.4)	0.208
Moderate	4 (6.5)	5 (9.8)	
Severe	1 (1.6)	4 (7.8)	
No	9 (12.7)	2 (3.8)	
Comorbidities n (%)			
Yes	16 (22.5)	11 (20.8)	0812
No	55 (77.5)	42 (79.2)	
Past urolithiasis history or past stone surgery n (%)			
Yes	10 (14.1)	7 (13.2)	0.888
No	61 (85.9)	46 (86.8)	

*significant p-value, p-value < 0.05; N: frequency, SD: Standard deviation, %: percentage, mm: millimeter, UVJ: ureterovesical junction

The analysis of spontaneous passage time, as summarized in Table 3, revealed stone size as the only significant variable that affects the time required for spontaneous passage. Patients with stones measuring below 7 mm showed a shorter passage time compared to those with stones equal to or larger than 7 mm (mean spontaneous time 9.96 vs. 15.3 days respectively, p-value = 0.003). However, variables such as gender, stone location, presence of hydronephrosis, comorbidities, and past history of urolithiasis or stone surgery did not show a significant correlation with the time needed for stone passage.

Table 3. The spontaneous passage time according to different variables.

Variable	Passage time (days) Mean (SD)	P-value
Gender n (%)		
Female	10.73 (6.4)	0.801
Male	11.2 (6.2)	
Size n (%)		
<7 mm	9.96 (5.9)	**0.003***
≥7 mm	15.3 (5.6)	
Location n (%)		
Proximal ureter	15.17 (6.4)	0.324
Mid ureter	10.71 (7.5)	
Distal ureter	11.78 (5.7)	
UVJ	10.25 (6.18)	
Hydronephrosis n (%)		
Yes	11.2 (6.2)	0.616
Mild	10.86 (6.12)	0.251
Moderate	15 (8.2)	
Severe	18	
No	10.1 (6.2)	
Comorbidities n (%)		
Yes	9 (5.8)	0.128
No	11.7 (6.2)	
Past urolithiasis history or past stone surgery n (%)		
Yes	11.7 (6.0)	0.746
No	11 (6.3)	

*significant p-value, p-value < 0.05; N: frequency, SD: Standard deviation, %: percentage, mm: millimeter, UVJ: ureterovesical junction

Multivariate logistic regression identified stone size and location as significant predictors of spontaneous stone passage. Stones smaller than 7 mm had a higher likelihood of spontaneous passage (OR = 2.25, p-value < 0.001), as did stones located at the uretero-vesical junction (OR = 6.5, p = 0.009) and distal ureter (OR = 4.6, p = 0.047), as summarized in Table 4.

Receiver Operating Characteristics (ROC) Curve Analysis (Figure 1) and specificity/sensitivity analysis (Table 4) were used to define a threshold for stone size with maximal sensitivity and specificity, as well as Youden's index. our analysis showed, that a stone length greater than 6.85 mm was linked to a very low chance of passing spontaneously, with an AUC of 0.832 (95% CI 0.760 - 0.903, p < 0.001), sensitivity of 78.9%, and specificity of 71.7%.

Table 4. Multivariate logistic regression of the factors predicting the spontaneous passage of stones.

Variable	Multivariate analysis		
	Odds ratio	95% CI	p-value
Age (years) Mean (SD)	0.994	0.949 - 1.042	0.813
Gender n (%) (F vs. M)*	0.817	0.249 -2.679	0.739
Size (mm) Mean (SD)	1.78	1.029 - 3.081	**0.039****
Size n (%) (<7 mm vs. ≥7 mm)*	2.25	1.58 - 3.21	**<0.001****
Location n (%) vs. proximal ureter*			
Mid ureter	1.26	0.345 - 4.630	0.724
Distal ureter	4.69	1.019 - 21.617	**0.047****
UVJ	8.62	1.697 - 43.790	**0.009****
Hydronephrosis n (%) vs. no hydronephrosis*			
Mild	3.2	0.496 - 20.969	0.221
Moderate	9.07	0.806 - 102.08	0.074
Severe		0.391 - 118.412	0.188
Comorbidities n (%) (yes vs. no)*	1.660	0.393 - 7.001	0.490
Past urolithiasis history or past stone surgery n (%) (yes vs. no)*	1.022	0.271 - 3.850	0.974
Constant	0.006		0.029

*Categorical variable; **significant p-value, p-value < 0.05; An OR close to 1 indicates that the variable does not affect the probability of spontaneous stone passage. An OR; >1 indicates that this variable is associated with a higher probability and an OR <1 that this variable is associated; with a lower probability of spontaneous stone passage

Table 5. Sensitivity, specificity, at different cut-off stone sizes.

Passage if less than or equal to (size mm)	Sensitivity	1-Specificity	Youden's index
0	0.000	0.000	0
1.25	0.014	0.000	0.01
1.75	0.028	0.000	0.03
2.25	0.056	0.000	0.06
2.75	0.070	0.000	0.07
3.20	0.169	0.019	0.15
3.45	0.183	0.019	0.16
3.75	0.225	0.019	0.21
4.20	0.380	0.038	0.34
4.45	0.394	0.038	0.36
4.75	0.394	0.094	0.30
5.50	0.620	0.113	0.51
6.25	0.746	0.264	0.48
6.60	0.775	0.283	0.49

Continued

6.85	**0.789**	**0.283**	**0.51***
7.25	0.915	0.491	0.42
7.75	0.915	0.547	0.37
8.25	1	0.717	0.28
8.75	1	0.736	0.26
9.10	1	0.906	0.09
9.35	1	0.925	0.07
9.65	1	0.981	0.02
10.80	1	1	0

*cut-off with maximal sensitivity, specificity, and youden's index.

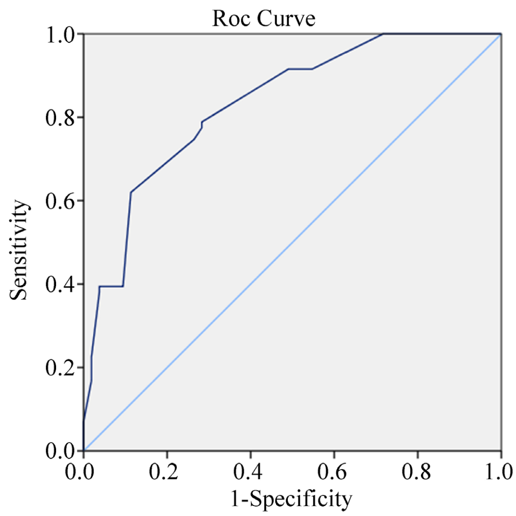

Figure 1. ROC curve for renal stones size (length in mm).

4. Discussion

This study aims to identify the optimal size threshold and other factors that can predict the spontaneous stone passage among patients under Medical Expulsive Therapy (MET) to enhance the management of renal colic patients. In total 124 patients' data were retrospectively included in the study and stones where categorized based on their size (over and under 7 mm) and location (proximal ureter, mid ureter, distal ureter, and UVJ). Our findings evince a strong correlation between stone passage with both stone size and location, with stones smaller than 7 mm and those situated at the ureterovesical junction (UVJ) demonstrating higher rates of passage under MET.

Our analysis showed that a stone length greater than 6.85 mm was linked to a very low chance of passing spontaneously. Consistently, Sandegard *et al.* conducted a study involving 122 renal colic patients, stratifying them into categories of small (< 4 mm), medium (4 - 6 mm), and large (> 6 mm) stones, as well as upper and lower half stones revealing that small and lower half ureteral stones exhibited higher rates of passage [21] [22]. The stratification showed the percentage of passage linked to the size rather than finding a cut-off correlated with the management.

The American Urological Association (AUA) guidelines for ureteral stone management were derived from a meta-analysis indicating an overall spontaneous passage rate of 71 - 98% for stones in the distal ureter measuring 5 mm or smaller, and a spontaneous passage rate of 29 - 98% for stones in the proximal ureter of similar size. However, these results lack a precise definition of stone size [23]. Kinder *et al.* reported a spontaneous passage frequency of 94% for ureterovesical junction stones measuring less than or equal to 5 mm, whereas stones larger than 5 mm exhibited a spontaneous passage frequency of only 45%. [24]

Previous studies have demonstrated spontaneous passage rates of 95% for distal ureteral stones measuring < 5 mm and 47% for those sized 5 - 10 mm. [10] Thus, the likelihood of spontaneous passage of ureteral stones varies with both size and location as determined by CT scans. Our findings corroborate previous research, concluding that stones smaller than 7 mm and those located at the ureterovesical junction and distal ureter have a higher likelihood of spontaneous passage. Additionally, our analysis of the Receiver Operating Characteristic (ROC) curve indicates that stones > 6.85 mm have a low probability of passage.

As for the passage time, Miller *et al.* showed that the interval to stone passage is highly variable and dependent on factors such as stone size, location, and side [25]. Conversely, our study suggests that stone size is the sole variable affecting passage time.

Whereas, Pickar *et al.* demonstrated that Tamsulosin 400 µg and nifedipine 30 mg do not significantly decrease the necessity for further treatment to achieve stone clearance within 4 weeks for patients with expectantly managed ureteric colic. However, there were numerous criticisms regarding the follow-up of patients in this study and the lack of further investigation [26].

On another hand, our study found no significance relating stone passage neither to hydronephrosis nor to the history of stone passage or previous surgery for urolithiasis affecting the current stone.in contrast, Senel *et al.* found that stone size, distal location and hydronephrosis status significantly predicted the stone passage [27]. This gap might be related to the fact that hydronephrosis is not solely related to stone obstruction but might also be related to other anomalies such as ureteropelvic junction obstruction or reflux.

Finally, stones located on the proximal and UVJ showed a higher rate of passage with a significant OR compared to stones located in the mid and proximal ureter, and that can be explained by the fact that MET is highly effective on the distal junction due to the high localization of alpha-receptor on this region compared to mid and proximal part [28].

Limitations of our study include its retrospective nature, single-institution setting, and relatively small sample size. However, the strength of our study lies in being the first conducted in Lebanon on this topic, and notably, stone passage was determined based on CT scans or evidence of passage observed by the patient rather than solely relying on subjective symptoms.

5. Conclusion

In conclusion, stone size and location are identified as the primary variables influencing passage rate, while passage time is primarily influenced by stone size. A stone smaller than 6.85 mm can serve as a suitable cut-off for initiating MET rather than a stone size smaller than 10 mm.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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