# Assessment of factors affecting the spontaneous passage of lower ureteric calculus on the basis of lower ureteric calculus diameter, density, and plasma C- reactive protein level

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Abstract Introduction: The study aimed to evaluate the factors which affect the spontaneous passage of lower ureteric calculus on the basis of noncontrast computed tomography kidneys, ureters, and bladder (NCCT KUB) stone diameter, stone density, and plasma C-reactive protein (CRP) level.

**Materials and Methods:** We conducted a prospective study of 200 patients with lower ureteric calculus 5–10 mm in size, from October 2015 to December 2016. All patients underwent NCCT KUB region with a 5 mm axial and reformatted coronal section. Edema just above the calculus and rim sign at the level of calculus and density of calculus is evaluated. Only scan with isolated, unilateral, solitary ureteric calculus was included in the final analysis and monitored up to 4 weeks, and plasma CRP is estimated in all patients to determine the clinical outcome.

**Results:** A total of 200 patients (145 males, 55 females; mean age  $\pm$  standard deviation, 34.73  $\pm$  10.29) were included in the study. Lower ureteric calculus between 5–7 mm passed in 70% and 7–10 mm passed in 40%. There was 18% underestimation of maximum stone diameter in axial plane as compared to coronal plane. For spontaneous passage of calculus, craniocaudal (CC) diameter is more reliable then axial in NCCT. Rim sign and edema is absent in 64% of those passed spontaneous calculus. CRP level more than 2.45 mg/dl has low spontaneous expulsion rate. The stone with different HU passes through the ureter with same rate. **Conclusion:** Plasma CRP level and CC diameter and absence of rim sign on NCCT KUB are more reliable factors then density for spontaneous passage of ureteric calculus.

Keywords: Axial and craniocaudal diameter, C-reactive protein, Lower ureteric calculus

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#### **INTRODUCTION**

Urolithiasis is a common disorder of the urinary tract affecting about 5%–10% of population, visiting to the emergency and general outpatient department (OPD) for

Access this article online				
Quick Response Code:	Website:			
	www.urologyannals.com			
	<b>DOI:</b> 10.4103/UA.UA_89_17			

stone problem. The prevalence and incidence of ureteric calculus is increasing and is related to the improvement in quality of life.<sup>[1]</sup>

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**How to cite this article:** Hada A, Yadav SS, Tomar V, Priyadarshi S, Agarwal N, Gulani A. Assessment of factors affecting the spontaneous passage of lower ureteric calculus on the basis of lower ureteric calculus diameter, density, and plasma C- reactive protein level. Urol Ann 2018;10:302-7.

The incidence of calculus disease varies with geography and food habit variation; ureteric stones are more common between 20 and 40 years of age.<sup>[2]</sup> About 22% of all urinary tract stones are found in the ureter, and out of all ureteric calculi, 68% are seen in the distal ureter.

Noncontrast computed tomography (NCCT) scan is the imaging of choice for the diagnosis of urolithiasis in symptomatic patients with reported sensitivity and specificity close to 100%.<sup>[3,4]</sup> Ureteric calculi can be managed either by conservative treatment or by extracorporeal shock wave lithotripsy, ureterorenoscopy, retrograde intrarenal surgery, percutaneous nephrolithotripsy, and laparoscopic or open surgery.<sup>[5,6]</sup>

Although there are many factors which need to be considered in the decision of the management of ureteric calculi, most patients with small ureteric calculus are recommended to wait until spontaneous passage of calculus. However, during conservative management, patients may experience undesirable symptoms of recurrent colic and urinary tract infection.<sup>[7,8]</sup> Understanding of the natural history of ureteric calculus disease is important for patient management.<sup>[9]</sup> Morse and Resnick reported that 60% of ureteric calculus passed spontaneously particularly a calculus in the lower one-third of ureter (71%).<sup>[10]</sup> Another study shows that majority (two-thirds) of calculi pass out within 4 weeks after the onset of symptoms.<sup>[9]</sup> There is a reverse linear relationship between calculus size and spontaneous passage; therefore, determination of maximum calculus diameter is very crucial for the management of lower ureteric stones. Lee et al. recently noted that calculus longitudinal diameter was a significant predictor of calculus expulsion.<sup>[11]</sup> The coronal reconstruction of NCCT scan not only helps for better ureteric calculus detection but also in accurately assessing the calculus diameter oriented in the vertical plane.<sup>[12]</sup> Many modifications have been suggested to improve the calculus diameter estimation. The most commonly used is estimation of coronal and reconstructed images, but no method is accepted as standard technique.<sup>[13]</sup>

Stone may lead to local inflammatory reactions which can be detected by NCCT as edematous area (rim sign).<sup>[14,15]</sup>

NCCT can also assess the level of density of ureteric calculi that corresponds to the amount of X-ray that passes through the structure and can be measured in the Hounsfield unit.<sup>[16]</sup> The plasma C-reactive protein (CRP) is an acute phase protein whose serum level increases in response to inflammation as in ureteric inflammation which can be induced by an impacted ureteral calculus.<sup>[17]</sup>

#### Urology Annals | Volume 10 | Issue 3 | July-September 2018

#### Aim of study

- 1. Radiological features predicting spontaneous passage of lower ureteric calculus width and length, rim sign, and density
- 2. Whether CRP can help predicting spontaneous passage of lower ureteric calculi
- 3. Whether body mass index (BMI) has some relation to stone expulsion.

### MATERIALS AND METHODS

The present study was undertaken from October 2015 to December 2016 in a tertiary care institute in Western India after clearance from the Institutional Review Board. Adult patients (age >18 years), found to have 5–10 mm lower ureteric calculus, situated below the lower SI joint on NCCT KUB were included in this study.

#### **Inclusion criteria**

All patients above 18 years who were diagnosed with lower ureteric calculus by NCCT KUB in urology OPD/emergency room and willing for expectant management were included in this study. None other than antispasmodic medicine were used for pain relief in these patients.

### **Exclusion criteria**

Patients with renal insufficiency, multiple calculi, solitary kidney, bilateral ureteric calculus, positive urine culture and sensitivity, severe hydronephrosis, and previous stone surgery were excluded from this study. Patients already on  $\alpha$ -blockers, suffering from other comorbidities, pregnant and lactating mother, and patients those shifted to surgical treatment and those lost to follow-up were excluded from this study.

We have examined NCCT KUB scans of all eligible patients; our protocol for computed tomography (CT) KUB scan was scanning from xiphisternum to the lower border of symphysis pubis. All scans were obtained from 164-slice MDCT without the use of contrast; 5 mm of axial and reformed coronal section was taken. In the current study, diameter of ureteric calculus was defined as longest diameter on axial as well as coronal reformed section. Craniocaudal (CC) and transverse width (axial) of calculus, site of stone, periureteric edema, rim sign, degree of proximal dilatation, and density of stone were observed on NCCT scan.

Rim sign is defined as a 1to 2 mm rim of soft-tissue attenuation 20–40 HU surrounding the intraureteral calculus. Tissue rim sign could be determined only when

serve a clear fat plane around a calculus<sup>[14]</sup> or because of the edematous wall of ureter.<sup>[15]</sup> CRP (quantitative) level was also measured at the time of diagnosis of ureteric calculus. Thirty-eight patients out of a total of 238 were excluded from this study during follow-up because of their being shifted to surgical treatment or medical expulsive therapy (MET).

All patients were followed for 4 weeks after the diagnosis of ureteric stone; these patients were followed and investigated by USG KUB for the movement of calculus. Patients were advised to use mesh net during voiding to procure passed out stone. In case, the patient did not passed stone or was not sure about passage of stone; then, it was confirmed by NCCT KUB.

Diameter (both axial and CC) of the passed stone was also measured by Vernier caliper to see the exact size of stone. Patients were categorized into two groups, Group A those who were not able to pass stone and Group B who passed stone spontaneously.

## Statistical analysis

Statistical analysis was performed with the SPSS, Trial version 20 for Windows statistical software package (SPSS Inc., Chicago, IL, USA) and PRIMER. The categorical data were presented as numbers (percent) and were compared among groups using Chi-square test. Demographic data were presented as mean and standard deviation and were compared using by ANOVA test. Logistic regression was used to identify independent risk factors for nonexpulsion of stone. Probability P < 0.05 was considered statistically significant.

## RESULTS

Table 1 shows demographic parameters of patients. Out of a total of 200 patients, 98 patients were able to pass stone (Group B) and the remaining 102 cannot pass who were not

Table	1: Demographic info	rmation of	f distribution o	of groups
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Parameter	Group A (not passed) (n=102)	Group (passed) ( <i>n</i> =98)	Р	
Mean age±SD (year)	34.55±10.29	34.73±11.55	0.9 (NS)	
Male/female $(n)$	72/30	73/25	0.64 (NS)	
Number of persons with stone size 5-7 mm (60)	18 (30)	42 (70)	<0.001 (S)	
Number of persons with stone size 7-10 mm (140)	84 (60)	56 (40)		
BMI (mean±SD) <25 kg/m <sup>2</sup> (n) >25 kg/m <sup>2</sup> (n)	23.59±4.04 69 33	23.97±4.20 63 35	0.52 (NS) 0.72 (NS)	

Values are presented as mean $\pm$ SD. SD: Standard deviation, BMI: Body mass index, S: Significant, NS: Not significant

placed in Group A. Both groups were age and sex matched. BMI of both groups was statistically nonsignificant. Majority of stone passed were smaller (5–7 mm) while the incidence of passage of bigger stone (7–10 mm) was comparatively less.

Thirty percent of patients with stone size <5-7 mm were in Group A while 70% of them were in Group B. On the other hand, 60% of patients with stone size >7-10 mm were in Group A and 40% in Group B.

Table 2 shows various parameters of stone in reference to self-stone expulsion; axial diameter of calculus (mm) was also higher in Group A as compared to Group B ( $7.22 \pm 0.85$  vs.  $6.28 \pm 0.93$ ) (P < 0.001 significant [S]). The CC was also more in Group A as compared to Group B ( $8.97 \pm 1.08$  vs.  $7.62 \pm 1.01$ ), P (<0.001S). CRP (mg/dl) was more in Group A as compared to Group B ( $4.00 \pm 0.74$  vs.  $1.71 \pm 0.28$ ), P value <0.001S. Statistically significant differences were noted in terms of the CRP (mg/dl), axial, and CC diameter of calculus (mm).

In Table 3, rim sign shows local edema of ureter secondary to inflammation which occurs in response to stone. There was a statistically significant rim sign and edema in Group A as compared with Group B (80.39% vs. 26.53%; P < 0.05 [S]) [Table 4].

Patients with spontaneous stone expulsion had significantly lower serum CRP levels  $(1.71 \pm 0.28)$  than those who failed to pass the stone spontaneously  $(4.00 \pm 0.74)$ . Receiver operating characteristic (ROC) curve is used to determine CRP cutoff point for prediction of spontaneous ureteric stone expulsion. In the present study, a cutoff point of 2.45 mg/dl for CRP yielded appeared optimal for prediction of spontaneous ureteric stone expulsion with sensitivity and specificity of 100% and 98%, respectively, with area under curve 0.998.

The mean CC diameter was  $18.63\% \pm 2.94\%$  higher than axial as whole, and also, the mean difference in both the diameters was significantly higher in not passed  $17.77\% \pm 1.63\%$  group as compared to passed group  $19.44\% \pm 1.92\%$  (P < 0.001S).

On univariate analysis, predictors of spontaneous passage of lower ureteric calculus were the axial and CC diameter, low CRP level, and absence of tissue rim sign. However, in multivariate analysis, only CRP level was significant.

## DISCUSSION

The management of patients with ureteral stone has changed dramatically in the current era with conservative Hada, et al.: Assessment of factors affecting the spontaneous passage of lower ureteric calculus on the basis of diameter, density and plasma CRP level

Group	CC diameter (mm)	Axial diameter (mm)	Density (HU)	CRP (mg/dl
Stone not passed A				
n	102	102	102	102
Mean±SD	8.97±1.08	7.22±0.85	620.85±271.43	4.00±0.74
Stone passed B				
n	98	98	98	98
Mean±SD	7.62±1.01	6.28±0.93	569.95±86.14	1.71±0.28
P value LS	<0.001 (S)	<0.001 (S)	<0.078 (NS)	<0.001 (S)

Values are presented as mean ± SD. CRP: C-reactive protein, SD: Standard deviation, S: Significant, NS: Not significant, LS: Less Significant, CC: Craniocaudal

Table 3: Association	ı of	rim	sign	with	stone	size
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Stone size (mm)	Group A (not passed) ( <i>n</i> =102)			Group B (passed) (n=98)			P value LS
	Absent, <i>n</i> (%)	Present, n (%)	Total (n)	Absent, <i>n</i> (%)	Present, <i>n</i> (%)	Total (n)	
5-7	3 (16.67)	15 (83.33)	18	27 (64.29)	15 (35.71)	42	0.002 (S)
>7-10	17 (20.24)	67 (79.76)	84	45 (80.36)	11 (19.64)	56	<0.001 (S)
Total	20 (19.61)	82 (80.39)	102	72 (73.47)	26 (26.53́)	98	( )

LS: Less Significant, S: Significant

## Table 4: Predictors for not passing stone using multiple logistic regression (multivariate analysis)

Variables	Significance	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Step 1ª				
CC	0.966	0.656	0.000	191,194,114.436
Rim (1)	0.845	0.532	0.001	301.028
CRP	0.035	26,907.277	2.081	347,862,304.046
Axial	0.868	6.375	0.000	18,100,849,443.797
Constant	0.085	0.000		

<sup>a</sup>Variable (s) entered on Step 1: CC, rim, CRP, axial diameter. On univariate analysis predictors of spontaneous passage of lower ureteric calculus were the axial and CC diameter, low CRP level, and absence of tissue rim sign. However, in multivariate analysis, only CRP level was significant. CC: Craniocaudal, CRP: C-reactive protein, CI: Confidence interval

approach being the primary focus as it is associated with minimum morbidity. The success of active stone monitoring is largely dependent on the stone size, location, as well as the time after the diagnosis. Medical therapy is a useful adjunct to observation.

NCCT KUB is the gold standard for diagnosis of ureteric calculus; it not only diagnoses ureteric stone but also provides information regarding presence, location, density, size of ureteric calculus, hydroureteronephrosis, local edema, and perinephric stranding that can help in the management.<sup>[18]</sup> CT scan can display the urinary tract in its longitudinal axis, thus improving the orientation of stone without increasing the evaluation times. Various methods have been described to measure the stone size in radiographs, but there is no accepted standard technique for stone measurement using CT scan.<sup>[15,19-22]</sup>

Tchey *et al.* investigated that the stone's size and location are the most important clinical predictor for spontaneous passage of ureter stones during expectant management. According to this study, 5–10 mm lower ureteric stones had 88% spontaneous passage rate in 4 weeks and majority of stone passed within 4 weeks.<sup>[22]</sup>

Although measurement of maximum transverse diameter from axial images traditionally has been reported as the most commonly used method. The ureteric calculus can be rounded or elongated. Most of the stones are oriented vertically along the long axis of ureter with maximum diameter in coronal plane as CC diameter. We observed that maximum diameter in axial plane was 18% less than the coronal plane.

Nadler *et al.*<sup>[20]</sup> in their studies evaluated that the axial images consistently underestimated the stone size compared with coronal reconstruction.

It is an unanswered question as to which image gives nearly accurate measurement of stone size whether coronal view or axial view. Paulson *et al.* confirmed that the advantage of coronal image is that it enables visualization of the kidney, ureter, and bladder simultaneously in a plane that it is more familiar and intuitive to urologist because it is analogous to projection of an abdominal X-ray or excretory urogram.<sup>[23]</sup>

In our study, both width (axial diameter) and length (CC diameter) of passed stone were measured on Vernier caliper and CT scan; for the passed stone, CC diameter was equal, but axial diameter was 13% less in CT scan as compared and measured by Vernier caliper. Similarly, a significant proportion of calculi were underestimated in size on axial image measurement.

Metser *et al.*<sup>[12]</sup> compared axial and coronal plane for ureteric calculus size measurement and showed that the average underestimation of calculus size was approximately 13% in axial planes and less than 3% in coronal plane.

In 1977, Ueno *et al.* found that the degree of obstruction was more directly related to the width rather than the length of the stone and concluded that width was the critical measurement<sup>[24]</sup> to decide the mode of treatment.

Lee *et al.*<sup>[11]</sup> found that the longitudinal diameter is more significant predictor of stone expulsion of ureteral calculus and concludes that this measurement in coronal reconstruction can help to better select patients who are suitable for calculus expulsion. Our study shows that CC diameter is almost equally measured in CT SCAN those passed, so our finding is compatible with Lee *et al.* 

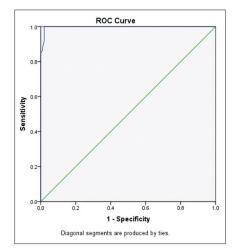
The chance for spontaneous passage of ureteric calculus was reported to be 60% and 39% for stone between 5–7 mm and more than 7–10 mm in diameter, respectively.<sup>[5]</sup> In our study, spontaneous passage rate was 70% for 5-7 mm size stone whereas it was 40% for >7–10 mm size stone within 4-week expectancy period. Our study correlated with the finding of the existing ones that the difference between the calculus diameters that were passed spontaneously versus which could not was significant. In case where axial diameter was same, but CC diameter was different, a CC diameter more than 7–10 mm was associated with a lesser ureteric stone passage rate. Thus, we can conclude that the best predictor of spontaneous passage of calculus is CC diameter in coronal view.

A positive tissue rim sign is specific for the diagnosis of ureterolithiasis; however, a negative tissue rim sign does not rule out ureteral stones. Its presence or absence correlates with the size of calculus but not with the degree of urinary obstruction.<sup>[15]</sup> In our study, majority of patients having positive rim sign failed to pass spontaneously ureteric stone. Rim sign was absent in 64% of patient which have spontaneously passed calulus of 5-7 mm. Similarly, 83% of Group A patients had positive rim sign and stone was not passed spontaneously. Nevertheless, the tissue rim sign was positive in 20% and negative in 80% of patients who successfully passed more than 7-10 mm diameter sized stone. Hence, as per the present study, evidence of rim sign is predictor of spontaneous passage. Our results are compatible with Erdodru et al.,<sup>[14]</sup> although according to study of Takahashi et al., ureteral tissue rim sign was not predictive for spontaneous passage of ureteral stones.<sup>[18]</sup> In our study, negative rim sign was present more commonly in those who passed stone as compared to those who did not. Hence, negative rim sign is predictor of stone passage.

In our study, the usability of the HU value in predicting spontaneous passage was investigated; our concept before conducting the study was that calculus with higher HU values would be more impacted. We expected that such impacted calculus would advance more slowly and with greater difficulty. On analysis, we found that although HU value of Group A was higher than the HU values of Group B, it was not statically significant; thus, we can conclude that density of stone as measured by CT scan does not have any bearing on spontaneous stone expulsion. In this matter, our study is compatible with Erturhan *et al.*<sup>[25]</sup>

Ureteral stones may lead to increase local inflammation which may interfere in the ability of spontaneous passage of calculus; the degree of local inflammation can be judged by measurement of CRP level. Patients with spontaneous stone expulsion had significantly lower serum CRP levels (1.71  $\pm$  0.28) than those who failed to pass the stone spontaneously (4.00  $\pm$  0.74). It implies more the inflammation less chance of spontaneous stone expulsion. ROC curve can be used to determine CRP cutoff point for prediction of spontaneous ureteric stone expulsion. According to Angulo et al.[26] study, if CRP level is more than 2.8 mg/dL, then one should go for initiate the aggressive treatment. According to Chang et al., aggressive treatment of high CRP levels from the moment of their diagnosis will result in effective treatment outcomes.<sup>[27]</sup> In the present study, a cutoff point of 2.45 mg/dl for CRP appeared optimal for prediction of spontaneous ureteric stone expulsion. Patients with CRP >2.45 mg/dl have low stone expulsion rate and should directly be subjected for an immediate, minimally invasive ureteric stone surgery.

In univariate analysis, [Figure 1] we found that the axial and CC diameter, CRP level, absence of tissue rim sign, and



**Figure 1:** Receiver operating characteristic curve is used to determine C-reactive protein cutoff point for prediction of spontaneous ureteric stone expulsion. In the present study, a cutoff point of 2.45 mg/ dl for C-reactive protein yielded appeared optimal for prediction of spontaneous ureteric stone expulsion with sensitivity and specificity of 100% and 98%, respectively, with area under curve 0.998

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density of calculus are the key predictor of spontaneous stone expulsion; however, on multivariate analysis, only CRP level found to be a significant factor for spontaneous stone passage.

#### CONCLUSION

In patients with lower ureteric calculus, transverse diameter on axial images of NCCT KUB underestimates size compared to measuring the coronal diameter so that we can easily ascertain and better discriminate the possibility of spontaneous passage of calculus on the basis of coronal diameter. Biomarker CRP discriminates between patients with calculus of passable size who will pass and those requiring surgical intervention. There is no significant difference in the measurement of density in HU on spontaneous passage of calculus. Hence, calculus density cannot be used to predict spontaneous passage of calculus.

Financial support and sponsorship Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

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