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Original Research Article

Neutrophil-to-Lymphocyte Ratio: is it an Indicator of Spontaneous Passage of Ureteral Stones.

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Abstract

Objective: Conservative management of ureteral stones is affected by many factors of which Location and the size of stones are most important. Inflammation around the stone has been identifies as an important variable related to spontaneous passage of stone (SPS). Our aim was to investigate the role of neutrophil-to-lymphocyte ratio (NLR) for SPS.

Methods: A prospective study was performed on 74 patients who attended urology outpatient clinic and emergency department between January 2018 and December 2018. Non-contrast-enhanced computed tomography (NCCT) was done in all patients for confirmation of ureteral stones. History, physical examinations and needed blood investigations, plain x-rays were done in all patients. SPS was confirmed by either patient noticing stone passing during urination or by NCCT done 3 weeks after the first stone episode. XLSTAT was used to analyze the data.

Results: SPS was observed in 56 (75.6%) of patients out of 74 enrolled in the study. SPS rates within 3 weeks according to stone size were 61% (5-10 mm) and 86% (≤5 mm). NLR (<2.4) (odds ratio (OR), 8.96; p: 0.002), smaller stone size (≤5 mm) (OR: 9.28; p: 0.001) and lower stone location (OR: 10.86; p: 0.001) were independent predictors of SPS.

Conclusion: A low NLR (< 2.4) may be a predictor of SPS for ureteral stones <1.0 cm size and ureteral inflammation is independent factor in SPS. So, early intervention may be considered in patients with high NLR (≥2.4).

Key Words: Ureteral calculi, NLR, spontaneous passage, inflammation, stone.

Introduction

Ureteric stone is the most common urological emergencies encountered in day to day clinical practice. Along with the agonizing pain and dysuria it can also lead to complications like renal obstruction, urinary tract infection (UTI) [1-2]. The treating urologist is always in dilemma to choose between conservative management and surgical intervention. Patients also demand some basis for the treatment offered to them. There are many factors associated with Spontaneous Passage of Ureteric Stone (SPS). Stone size and location are the most important of all factors, still they are inadequate alone [3-4].

Different inflammatory markers are available today to assess the inflammatory state which is related to the SPS. C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) are used in studies as an adjunct to predict SPS. Other factors predicting inflammation like pyuria, hydronephrosis (HDN), and non-contrast computed tomography (NCCT) findings of perinephric fat stranding and the tissue-rim sign are also used [5-6].

The ratio of absolute counts of neutrophils and lymphocytes defined as the Neutrophil-to-Lymphocyte Ratio (NLR) is being used recently to predict the inflammatory changes. It is a simple to asses and is a effective marker [7-11]. Only few studies have been done to predict the SPS using NLR. In this study we aim to study the predictive ability of NLR for SPS.

Materials and Methods:

A prospective study comprising of 74 patients was conducted in Osmania General Hospital on patients of ureteric stone who attended urology outpatient clinic and emergency department. The study was conducted for one year between January 2018 and December 2018. NCCT was done in all patients for

confirmation of ureteric stones. Detailed History, Physical examination, Urinalysis, complete blood count, serum chemistry, ESR, CRP, Plain x-rays and Ultrasonography Kidney-Ureter-Bladder (USG KUB) was done for all the patients. Stone size was determined from the greatest diameter of stone measured in NCCT and was stratified in two groups: up to 5 mm and 5-10 mm. Location of stone was also determined from NCCT and classified into upper and lower. Plain X-ray was used to determine the radio-opaque or radiolucent stone and Hounsfield Unit (HU) of stone was used for determining the stone density.

All patients were prescribed analgesics, advised to drink >2.5 liters of water and given urine alkalysers and tamsulosin 0.4mg was given. In follow up visits, patients were asked for pain severity, complications, whether they observed any sensation or stone passing during urination. Plain radiography, urinalysis and USG KUB were done in the follow up visits. If patients did not report SPS or USG showed HDN, NCCT was done at 3 weeks from the first stone episode for confirmation of SPS. After 3 weeks, option of continuing the conservative management further for two weeks or to go for surgical intervention was given to the patients who did not had SPS. Following patients were excluded from our study, who were not willing to participate in the study, who were not willing for conservative treatment, who did not complete follow up till SPS or surgical intervention and those with complications (renal failure, severe UTI).

Statistical analysis was done using Xlstat 2018 software. Student's t-test, $\chi 2$ test were used for comparison, univariate and multivariate analysis was done in order to adjust any confounding factors and Area Under Receiver operating Characteristic curve (roc) was used to derive the cut-off values for the parameters under the study. p value of <0.05 was considered as statistically significant.

Results:

Out of 80 patients enrolled in our study, 6 were lost during follow up and 74 were available for analysis of the data. 56 (75.6%) patients had SPS within 3 weeks, 15 (20.3%) patient underwent URSL and rest 3 (4.1%) patients has SPS within 4 weeks (Figure 1).

Figure 1: Flowchart of patient selection, treatment and follow up.
SPS: spontaneous passage of ureteric stone, URSL: ureterscopic lithotripsy

Patient characteristics and rates of SPS with statistical significance of the data are shown in table 1.

Table 1: Patient characteristics and comparison between SPS and non SPS groups

Patient Characteristics		Total	SPS	No SPS	P value
No of patients		74 (100%)	56 (75.6%)	15 (20.3%)	
Age (years)		42.9 (19-67)	43.4 (21-67)	42.7 (19-64)	0.865
Sex (Male)		51 (68.9%)	40 (71.4%)	11 (73.3%)	0.624
Previous history of ureteric stone		13 (17.5%)	8 (14.2%)	5 (21.7%)	0.032
Previous history of ureteric stone treatment		5 (6.7%)	2 (3.5%)	3 (16.6 %)	**0.009**
Previous history of SPS		8 (10.8%)	5(8.9%)	3(16.6%)	**0.021**
Serum TLC		8.8 (6.7-12.4)	8.6 (6.1-11.4)	9.1 (6.3-12.6)	0.852
Neutrophil percentage		62.1 (46.2-79.3)	61.4 (49.2-78.2)	72.6 (49.2-79.3)	0.031
Lymphocyte percentage		26.3(15.4-39.5)	19.2 (18.5-39.5)	27.6 (5.4-37.8)	0.084
Neutrophil to Lymphocyte ratio		2.21 (1.32-5.43)	2.03 (1.62-3.84)	3.8 (1.8-5.43)	**0.002**
ESR (ml/hr)		8.2 (4-22)	6.4 (4-19)	8.8 (5-22)	0.757
CRP (mg/L)		1.1 (0.3-2.1)	1.0 (0.3-2.0)	1.2 (0.4-2.1)	0.683
Urine WBC		1.3 (0-5)	1.2 (0-4)	1.4 (0-5)	0.982
Urine RBC		7.8 (0-15)	5.9 (0-12)	8.2 (0-15)	0.648
Size of stone		4.9 (3.8-9.1)	4.4 (3.8-8.2)	6.1 (4.5-9.1)	**0.001**
Presence of hydronephrosis		74 (100%)	56 (100%)	18 (100%)	0.846
Radiopacity		38 (51.3 %)	18 (47.4%)	20 (52.6%)	0.632
Housefield Units		392 (167-732)	383 (172-735)	388 (169-741)	0.861
Level of stone	Upper	22 (29.7%)	10 (17.8%)	13(72.2%)	**0.012**
	Lower	52 (70.2%)	46 (82.1%)	5 (27.7%)	

SPS: spontaneous passage of ureteric stones, TLC: total leucocyte count, ESR: erythrocyte sedimentation rate, CRP: C - reactive protein, WBC: white blood cells, RBC: Red blood cells
Data as median (and interquartile ranges)

Previous stone treatment history, previous history of SPS, NLR, size and level of stones were showing significance in this analysis.

Further univariate analysis (Table 2) of these and other probable factors of SPS were done. Multivariate analysis (Table 3) was done for factors showing significant results on univariate analysis and odds ratio (OR) was calculated for each factor. A NLR of < 2.4 was found to have highest sensitivity and specificity for predicting SPS on a Receiver Operating Characteristic (ROC) Curve.

Table 2: Univariate analysis of factors affecting spontaneous passage of ureteric stones

Factors	OR	95% CI	P value
Age	1.00	0.903-1.012	0.728
Sex	0.65	0.223-1.921	0.496
Previous history of ureteric stone	0.20	0.768-0.681	0.231
Previous history of ureteric stone treatment	0.16	0.015-0.639	**0.012**
Previous history of SPS	0.41	0.116-1.723	0.204
Neutrophil percentage (<65%)	4.12	1.412-11.625	**0.009**
Neutrophil to Lymphocyte ratio (2.4)	4.00	1.373-12.153	**0.010**
Erethrocyte Sedimentation rate	1.02	0.968-1.032	0.767
c-reactive protein	0.86	0.936-1.107	0.405
Urine WBC	1.23	0.824-1.735	0.694
Location of stone (Lower)	4.50	1.711-11.523	**0.003**
Size of Stone (<5mm)	4.62	1.689-11.792	**0.002**
Radiopaque stone (yes)	1.38	0.501-3.221	0.561
House field Unit (CT)	1.32	0.627-1.850	0.658

OR: Odds Ratio, CI: Confidence interval, CT: Computed Tomography.

Table 3: Multivariate analysis of factors affecting spontaneous passage of ureteric stones

Factors	OR	95% CI	P value
Previous history of ureteric stone	0.86	0.158-5.921	0.986
Previous history of ureteric stone treatment	0.25	0.026-2.574	**0.263**
Neutrophil percentage (<65%)	2.40	0.179-21.105	0.594
Neutrophil to Lymphocyte ratio (<2.4)	8.96	2.152-38.263	**0.002**
Location of stone (Lower)	10.86	2.872-46.052	**<0.001**
Size of Stone (<5mm)	9.28	2.266-29.186	**<0.001**

OR: Odds Ratio, CI: Confidence interval

In univariate analysis following were found to affect the SPS rates: Previous history of ureteric stone treatment (p = 0.012), neutrophil percentage <65% (p= 0.009), NLR < 2.4 (p= 0.010), location of stone in lower ureter (p= 0.003) and stones less than 5mm (p= 0.002). Upon multivariate analysis, previous history of ureteric stone and neutrophil percentage were found not to affect SPS. Location of stone in lower ureter (OR: 10.86, p <0.001), Size of stone lower than 5 mm (OR: 9.28, p< 0.001) and NLR<2.4 (OR: 8.96, p= 0.002) were found to be associated with SPS in multivariate analysis. Variance inflation factors were analyzed to exclude any multicollinearity between Neutrophil percentage and NLR and none were found. Pyuria, Hydronephrosis and previous stone history traditionally considered as factors for SPS were not significantly associated in our study. Other inflammatory factors like ESR, CRP were also not found to be associated with SPS.

Discussion:

Almost always the question will arise "Will the stone pass?", "What will be the complications if there is just observation?" Observation of stone until SPS is associated with some undesirable complications like Urinary tract infections and recurrent bouts of renal coliky pain. It is important to categorize those patients who must be observed and the others whom should be intervened. So this study was done to evaluate the predictors of the SPS for the ureteral stones <10mm size at 3 weeks. The small < 5mm size of the stone, the lower ureteric location of stone, and the NLR<2.4 were found to predict the SPS for the ureteric stone significantly.

It is estimated that around 95% of stones up to 4 mm will pass within 40 days according to European Association of Urology (EUA) [12] and around 98% of stones < 5mm can pass spontaneously according to American Urology Association (AUA) with conservative treatment [13]. And the exact cutoff size for the stones which are likely to pass spontaneously cannot be provided but <10 mm may be considered as the best estimate [12]. EAU mentions that SPS decreases with increasing size of the stone and there are differences between the individual. There have been several other studies which show that SPS depends on the size of the

stone [12-14]. A meta-analysis consisting of 224 patients showed SPS rates of 68% and 47% for patients with stone < 5mm and 5-10mm respectively [14]. In our study SPS rates of 86% and 61% were noted for patients with stone < 5mm and 5-10mm respectively which was consistent with the other studies.

Several studies have stated that SPS rates are affected by the location of the stone within the ureter, lower being favored for SPS [15]. Both EAU and AUA guidelines also state the rates of SPS depend on the location of the stone. In a study done in 378 patients Morse et al reported SPS rates of 22%, 46% and 71% from proximal, middle and distal ureter [15]. Lee et al [16] reported SPS rates of 62.2% and 88.2% from upper and lower ureter. Our study had SPS rates of 45.5% and 88.4% from upper and lower stones respectively which also showed favorable SPS rates for lower ureteric stones.

NLR has emerged as a new parameter that denotes the inflammatory state of the patient. It is being used in several other conditions that have inflammation associated with the disease process. NLR has been proven as a prognostic factor in various cancers, major cardiovascular events, post operative complications and many infectious diseases [17-22]. Our study showed that NLR can be used as a predictive marker for the SPS. The normal value of NLR was reported to be between 0.78 and 3.53 in healthy non geriatric population by Forget et al [23]. Azab et al [24] studied a sample of 9426 persons in United States and found a average NLR of 2.15 in general population. The mean NLR of our study population of 74 patients was 2.21. NLR in patients having SPS and no SPS were 2.03 and 3.8 respectively which was very similar to results of Lee et al [16] 2.04 and 3.67 in SPS and no SPS groups respectively. These results and the related studies prove the role of inflammation in SPS and the role of NLR in its prediction.

The other inflammatory factors analyzed in our study like ESR, Neutrophil percentage, CRP and urine WBC or pyuria, presence of hydronephrosis and NCCT signs of perinephric fat stranding and tissue rim sign were not significantly associated with the SPS rates in univariate and multivariate analysis as reported in other studies [3-6]. There is risk of stone recurrence in the patients and many will have recurrence within 5 years [25-26]. Contrary to belief that the previous SPS will leave ureter scarred and the further chances of SPS will decrease many studies have shown that previous SPS favors the SPS at next stone event [27]. So the previous ureteral stone history, treatment history and SPS history may play a role in predicting SPS at current stone event but when these factors were analyzed it was found to be non significant in our study.

Stone in ureter provokes inflammatory changes around it and as it increases the SPS rates will decrease. During the conservative treatment patients were prescribed NSAIDS to relieve the pain and decrease the inflammation which will promote SPS. All patients were prescribed alpha blockers (tamsulosin 0.4mg), urinary alkalysers and water intake of >2.5 liters daily as part of their medical expulsive therapy (MET). Other than alpha blockers other drugs of drug combinations like low dose steroids, calcium channel blockers, phosphodiesterase-5 inhibitors were not used as per EAU guidelines [12].

Our study is probably the first study in Indian population and is done prospectively and very few studies of NLR in SPS of ureteric stones have been done. Calculation a NLR can be done very easily and patients can be stratified for conservative management or intervention. It will help to avoid the complications of waiting for the stones that are unlikely to pass and complications of interventions for the stones which will pass off. Our study is limited by the small sample size; the selection of patients who were willing for the conservative treatment was not randomized, so some selection bias may be there. The adherence of the patients to the conservative treatment protocol at home and the compliance also cannot be ensured completely. Still this study has highlighted the role of NLR in prediction of SPS for ureteral stones and large multicentre randomized prospective studies are needed to validate its routine use worldwide.

Our study showed that NLR < 2.4 was independent predictor of the SPS in ureteral stone of less than 10 mm. NLR is very easy to obtain and can be done in every patient presenting with ureteric stones. If NLR < 2.4 patients can be considered for conservative treatment and if >2.4 early intervention may be considered.

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