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Original Research Article

Investigating the predictive effect of neutrophil to lymphocyte ratio as an inflammatory marker in the spontaneous excretion of ureteral stones

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ABSTRACT

Background: The size and location of the stone have been suggested as the most important predictors of the possibility of spontaneous passage of the stone. The aim of this study was to investigate the predictive effect of neutrophil to lymphocyte ratio as an inflammatory marker in the spontaneous excretion of ureteral stones.
Methods: This descriptive-analytical study was done on 95 patients with ureteral stone during 2020-21. Required data include sex, age, BMI, previous history of stone, previous history of spontaneous passage of stone, side, location and size of stones, spontaneous passage of stone, and neutrophil and lymphocyte ratio were extracted from file of patients. The presence of the stone and its characteristics were confirmed by ultrasound. Patients were followed up for 2 weeks to determine whether or not the stone passed spontaneously.
Results: There was a significant relationship between spontaneous passage of ureteral stone with stone size, location, and neutrophil to lymphocyte ratio. The cut-off points of neutrophil to lymphocyte ratio for predicting spontaneous passage of ureteral stone was 2.52, so that patients with higher values were faced with a 4.2-fold increase in the risk of no spontaneous passage of stones (OR=4.202, 95% CI: 1.563-11.298, Sig.=0.004).
Conclusions: The results of the study showed that the ratio of neutrophils to lymphocytes is a significant predictor of spontaneous passage of ureteral stones, so that if used in addition to the size and location of the stone, the accuracy of predicting patients who benefit from conservative management, increase significantly.

Keywords: Neutrophil to lymphocyte ratio, Ureter stone, Spontaneous passage

INTRODUCTION

Urinary stone disease (USD) is a general term that refers to the presence of stones in any part of the urinary system, including the kidney, ureter, bladder, and urinary tract. USD is a common complication with an annual incidence of approximately 7 to 12 cases per 10,000. The prevalence of this disease has increased continuously in recent decades, so that, for example, in the United States alone, more than 8% of the population is affected by it. Based on the acute nature of symptoms, USD accounts for a large volume of emergency department visits and hospital admissions.[1] The lifetime risk of urinary stone formation is more than 12-14% in men and 6% in women. The probability of stone recurrence is very high, so that within 5 years, 50% of patients will have a recurrence. The prevalence of this disease has doubled over the past 15 years, and the rate of infection in low-risk groups such as women and children has grown faster. The frequency of urolithiasis in people with a low medical history has increased by approximately 4 to 6% per year due to several factors, including increased obesity and changes in diet such as decreased calcium and increased fructose in the diet, especially in the adult age group. According to recent evidence, the incidence of ureteral stones in developed countries is reported to be about 58-1116 per 100,000 people, while its incidence in

developing countries or in less developed countries is not precisely known.[2] However, it is stated that ureteral stones constitute 20% of all urinary tract stones.[3] Patients with ureteral stones usually present with complaints such as flank pain, nausea, vomiting, and lower urinary tract symptoms.[4] Urgent intervention is often necessary in patients with ureteral stones with uncontrollable pain, blood infection (sepsis), or renal impairment, but in patients who present with acute ureteral colic, are clinically stable, and have no indication for immediate intervention. , is there uncertainty about whether a patient may need active treatment for stones or not.[5,6] Medical Expulsive Therapy (MET), is a non-invasive treatment method that is specifically recommended in this category of patients and consists of high fluid intake and pharmacological agents such as anti-inflammatory drugs, alpha-blockers, calcium channel, corticosteroids, or phosphodiesterase inhibitors. It has been shown that the probability and speed of spontaneous expulsion of ureteric stones increases with this approach.[7] Additionally, this approach reduces the number of hospital visits, costs, and the need for invasive interventional treatments.[8]

Clinical trials that have evaluated the effect of expulsive therapy on spontaneous stone passage have shown that three-quarters of stones (mostly stones less than 10 mm in size) can be passed without the need for any surgical intervention.[5] Therefore, active intervention for ureteral stones can be considered as an additional and unnecessary treatment that adds to costs. On the other hand, waiting for stone removal can cause unwanted side effects such as kidney failure and urosepsis.[9,10] Therefore, it is necessary to select the right patient for proper management of ureteric stones. A biomarker that can predict which group of patients with ureteral stones will pass their stone spontaneously and which group is likely to require intervention, to guide the management of patients who are clinically stable at presentation, it is beneficial.[11] In this regard, some studies have used serum inflammatory markers such as white blood cell count, neutrophil count, and C-reactive protein to predict spontaneous passage of ureteric stones.[12,13] Some recent studies have also shown that the ratio of neutrophils to lymphocytes, as a serum inflammatory marker with the possibility of simple and low-cost measurement, works much better than other markers in predicting the spontaneous excretion of ureteral stones but the studies conducted in this field are few in the world and no study has been conducted in this field in Iran.[14,15] Therefore, the present study was conducted with the aim of investigating the predictive effect of the neutrophil to lymphocyte ratio as an inflammatory marker in the spontaneous excretion of ureteral stones in patients referred to Ardabil city hospital in 2020-2021.

METHODS

This descriptive and analytical study was conducted on 95 patients with ureteral stones referred to Ardabil city hospital in 2020-2021. Patients over 18 years of age with ureteral stones were included in the study, and patients with urinary tract infections, severe hydronephrosis, pregnant women, patients with a single kidney, and patients with a history of urinary system surgery were excluded from the study. The presence of stone and its characteristics were confirmed by ultrasound or CT scan. Referral patients with symptoms of renal colic were followed up for about 15 days and then evaluated with the same primary diagnostic tool (sonography and KUB or spiral CT scan without contrast) in order to determine whether or not the stone is spontaneously expelled, were assessed. The patients were divided into two groups based on the spontaneous excretion or non-excretion of stones, and the effect of neutrophil-to-lymphocyte ratio on the spontaneous excretion or non-excretion of stones was determined by comparing these two groups.

Statistical analysis

The data extracted from the patients' files were statistically analyzed in SPSS version 25 based on descriptive and analytical statistics methods. In descriptive statistics, mean and standard deviation indices were used for quantitative variables, and frequency indices and frequency, percentage were used for qualitative variables. In analytical statistics, to compare quantitative variables between two groups using the t-test, to compare qualitative variables between two groups using the chi-square test, and to determine the cut-off point and risk ratio was used the ROC curve and the binary logistic regression method.

RESULTS

Out of all patients, 64 patients (67.4%) were men. The average age of the patients was 43.7 years (with a standard deviation of 12.1). In terms of body mass index, 26 patients (27.4%) were overweight. The ureteral stone was located on the right side in 51 patients (53.7%). The stone size in 61 patients (64.2%) was 4 to 7 mm and the ureteral stone position was distal in 66 patients (69.5%). The frequency of spontaneous excretion of ureteral stones in the studied patients was 65.3% (Table 1). The overall average ratio of neutrophils to lymphocytes in patients was 2.62 (with a standard deviation of 0.93), which ranged from 1.34 to 4.54.

There was no statistically significant relationship between spontaneous stone passage with gender, age, body mass index, history of stone, history of spontaneous stone passage and stone side. There was a statistically significant relationship between spontaneous stone passage and stone size (P=0.001), so that the frequency of spontaneous passage in patients with stone size of 4 to 7 mm is significantly higher than in patients with stone size of 7 to 10 mm (77% versus 44.1%). There was also a statistically significant relationship between spontaneous stone passage and stone location (P=0.009), so that the frequency of spontaneous passage was higher in patients

with distal ureteral stones than the middle and it was more than the proximal (74.2%, 58.3%, and 35.3%, respectively). There was a statistically significant relationship between the spontaneous excretion of stones and the ratio of neutrophils to lymphocytes (P<0.001), so that the average of this ratio was significantly lower in patients who had spontaneous excretion (2.33 vs. 3.15) (Table 2).

Table 1: Relation between spontaneous excretions of ureteral stones and demographic information.

Variables	Levels	Spontaneous excretions of ureteral stones				Total		p-value
		Yes		No				
		N	%	N	%	N	%	
Gender	Male	44	68.8	20	31.3	64	100	0.31
	Female	18	58.1	13	41.9	31	100	
Age (year)	Mean±SD	43.4±12.3		44.2±12.1		43.7±12.1		0.77
BMI	Normal	36	70.6	15	29.4	51	100	0.46
	Overweight	16	61.5	10	38.5	26	100	
	Obsess	10	55.6	8	44.4	18	100	

Table 2: Relation between spontaneous excretions of ureteral stones and demographic information.

Variables	Levels	Spontaneous excretions of ureteral stones				Total		p-value
		Yes		No				
		N	%	N	%	N	%	
History of stone	+	15	71.4	6	28.6	21	100	0.51
	-	47	63.5	27	36.5	74	100	
History of spontaneous excretions of ureteral stones	+	8	72.7	3	27.3	11	100	0.74
	-	54	64.3	30	35.7	84	100	
Side of stone	Right	32	62.7	19	37.3	51	100	0.58
	Left	30	68.2	14	31.8	44	100	
Size of stone	4-7 mm	47	77	14	23	61	100	0.001
	7-10 mm	15	44.1	19	55.9	34	100	
Location of stone	Proximal	6	35.3	11	64.7	17	100	0.009
	Middle	7	58.3	5	41.7	12	100	
	Distal	49	74.2	17	25.8	66	100	
Ratio of neutrophils to lymphocytes		2.33±0.73		3.15±0.96				0.001

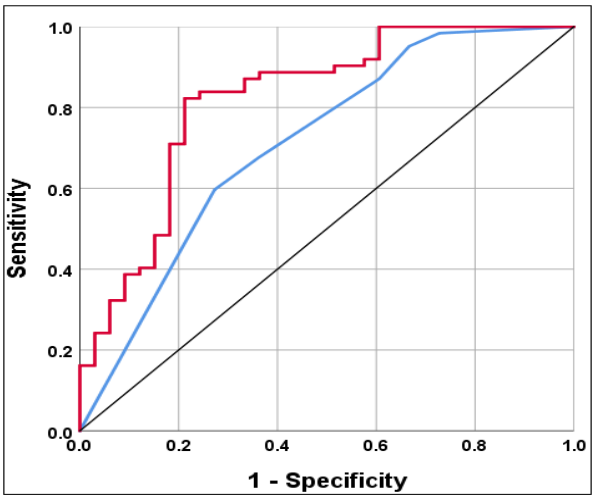

Figure 1: ROC curve.

In order to determine the effect of neutrophil to lymphocyte ratio in predicting the probability of spontaneous ureteral stone passage compared to when only two markers of stone size and location are used, ROC curve was used (Figure 1).

The area under the curve in the case where only the two factors of stone size and location were used was equal to 71.1%, which is a relatively good value in the ROC curve, but when the ratio of neutrophils to lymphocytes was added to the previous two factors, the level Under the curve increased to 82.1%, which is a very good value. In addition, the sensitivity and specificity when only the two factors of stone size and location were used were 60% and 73%, respectively, and with the addition of the ratio of neutrophils to lymphocytes, these two parameters were significantly improved (increase in sensitivity and specificity to 82% and 79%, respectively). In addition,

the cut-off point of the ratio of neutrophils to lymphocytes was found to be 2.52, so that patients with ureteral stones in whom this ratio was more than 2.52 faced a 4.2-fold increase in the risk of not passing stones spontaneously (OR=4.202, 95% CI: 1.563-11.298, sig.=0.004) (Table 3).

Table 3: The sensitivity and Specificity of study based on ROC curve.

Variable	Sensitivity	Specificity	AUC	sig	95% CI
Size and location of stones	60	73	0.71	0.001	0.598-0.825
Size and location of stones and ratio of neutrophils to lymphocytes	82	79	0.82	0.001	0.726-0.915

DISCUSSION

The results of the present study showed that the spontaneous excretion of stone had a significant relationship with its location, so that the rate of spontaneous excretion of proximal, middle, and distal ureteral stones were 35.3%, 58.3%, and 74.2%, respectively. Consistent with our findings, the guidelines published by the American and European Association of Urologists state that the rate of spontaneous ureteral stone passage varies significantly according to the location of the stone in the ureter.[16,17] Several studies have investigated the role of ureteral stone position in spontaneous excretion.[18,19] The results of Morse et al study on 378 patients showed that the rate of spontaneous passage for proximal, middle, and distal ureteral stones was 22%, 46%, and 71%, respectively.[18] In a systematic review consisting of 6 studies and 850 patients, it was found that the spontaneous passage rate for proximal ureteral stones was 48%, middle ureteral stones 60%, and distal ureteral stones was 75%.[19] In the study of Lee et al., this rate was reported as 62.2% for upper ureteral stones and 88.2% for lower ureteral stones.[15] In this respect, our observations were consistent with the results of previous studies.

In the present study, there was a significant relationship between the size of the ureteral stone and its spontaneous excretion rate (77% in 4-7 mm stones and 44.1% in 7-10 mm stones). According to the report of the latest version of the above-mentioned guidelines, the majority of stones smaller than 5 mm pass spontaneously using a conservative approach.[16,17] In a meta-analysis on 224 patients, it was shown that the rate of spontaneous passage of ureteral stones was 68% in patients with a stone size of less than 5 mm and 47% with a stone size of 5-10 mm.[20] This rate was reported in the study of Lee et al., in South Korea for ureter stones less than 5 mm and 5-10 mm, respectively, 88.2% and 62.2%.[15] In terms of the relationship between spontaneous excretion and the size of the ureteral stone, there were also similarities between the studies.

Another parameter that was related to the rate of spontaneous excretion of ureteral stones in the present study was the ratio of neutrophils to lymphocytes, so that this ratio was significantly lower in patients with spontaneous excretion. In this respect, our results were consistent with the study of Abu Haider et al. in Lebanon and Lee et al., in South Korea.[14,15] The ratio of neutrophils to lymphocytes is a parameter that can be used to evaluate the inflammatory status of patients. The usefulness of this ratio has been proven as a prognostic factor in previous major vascular events, in various types of cancer, in complications after surgery, and also as a marker for inflammatory or infectious conditions.[21-23] In addition to these findings, the results of the present study indicate that the ratio of neutrophils to lymphocytes can also be used as an indicator of spontaneous stone excretion for patients with urinary system stones.

The average ratio of neutrophils to lymphocytes in the patients investigated in the present study was 2.62 and its range was between 1.34 and 4.54. In a population-based study of 9,427 people in the United States, the average neutrophil-to-lymphocyte ratio in the general population was reported to be 2.15.[24] The normal range of neutrophil-to-lymphocyte ratio for non-elderly adults with good health status was reported between 0.78 and 3.53 in the study of Forget et al.[23] As can be seen, the average and range of this ratio in the present study is higher than both of the above studies; considering that this study was conducted on stone patients, but the above studies were conducted on the general population, these differences can be justified. However, our findings are in line with the results of Lee et al.'s study in South Korea, which was also conducted on ureteral stone patients, so that the median ratio of neutrophils to lymphocytes in their study was 2.18 and in the present study it was 2.30, and also like the present study, in their study, this ratio was significantly higher in patients who did not have spontaneous excretion than in patients whose ureteral stones were spontaneously excreted.[15] These findings indicate that inflammation plays an important role in the pathophysiology of spontaneous stone excretion.

A part of patients with a history of ureteral stones have stone recurrence within 5 years of the first episode.[25-28] Clinicians may have difficulty making treatment decisions for patients who have previously experienced

spontaneous ureteral stone passage because such a history may have caused permanent changes in the ureter due to inflammation.[29,30] On the other hand, some studies have shown that a previous history of spontaneous stone passage may be a positive predictive factor for current spontaneous stone passage.[31] In order to evaluate such contradictory reports that existed in the sources, we examined the history of ureteral stones and the history of spontaneous passage of ureteral stones in our patients, and the results showed no significant relationship between these two with the current spontaneous passage of stones. In this respect, our findings are consistent with the study of Lee et al., and Abu Haider et al.[14,15]

The findings of the present study also showed that compared to the situation where the decision for conservative management is made only based on the size and location of the stone, the use of the ratio of neutrophils to lymphocytes along with these two parameters can significantly improve the selection of patients, so that by adding this ratio, the area under the ROC curve increased from 0.71 to 0.82, sensitivity from 60 to 82%, and specificity from 73% to 79%. In this regard, the optimal cut-off point of the ratio of neutrophils to lymphocytes was 2.52, so that this ratio being higher than this number in ureteral stone patients resulted in a 4.2-fold increase in the risk of non-spontaneous excretion. In the study by Lee et al. in South Korea, the optimal cut-off point for the ratio of neutrophils to lymphocytes was 2.3, and the risk of non-spontaneous stone excretion in ureteral stone patients who had a ratio higher than this value was 9 times that in comparison with the present study shows an even stronger correlation between the neutrophil-lymphocyte ratio and the probability of spontaneous ureteral stone passage.[15]

The present study, like all other studies, had limitations: the sample size was relatively small and due to the small number of previous studies, it was not possible to fully compare the results with previous studies. Also considering that in order to control the confounding effect of factors such as infection and inflammation, diabetes, lung and kidney diseases, etc., on the level of neutrophils and lymphocytes, we excluded patients who had such conditions from the study. Therefore, the results of the present study are limited in terms of generalization to patients with such conditions, and this issue requires independent studies.

CONCLUSION

The results of the present study showed that the ratio of neutrophils to lymphocytes is a significant predictive factor for the spontaneous elimination of ureteral stones, so that if it is used in addition to the size and location of the stone, the accuracy of predicting patients who are treated with conservative management method benefit, increases significantly.

It is suggested that early intervention should be considered instead of conservative treatment for ureteral stone patients who have a high neutrophil-to-lymphocyte ratio (more than 2.52).

Also, in order to draw definitive conclusions about the findings of this study and before the routine use of the neutrophil-to-lymphocyte ratio in the clinic, multicenter studies with a larger sample size and long-term follow-up of patients are necessary.

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