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Original Research Article

Relationship between spontaneous excretion of lower ureter stones with stone size and serum level of C-reactive protein

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ABSTRACT

Background: According to the recent studies on patients with stones in the urinary system, the CRP serum levels can be useful in predicting the possibility of success in expectant treatment and spontaneous excretion of stone and thus, selecting the appropriate patient for this treatment approach; however the studies conducted in this field are inadequate and the results obtained are slightly contradictory. The aim of this study was to investigate the relationship between spontaneous excretion of lower ureter stones with stone size and serum level of C-reactive protein.
Methods: This cross-sectional study has been done on 95 patients with lower ureter stone during 2020-2021. Information including gender, age, body mass index, stone size, spontaneous excretion of stone, and CRP serum level were extracted from the files of patients. The existence of stone and its characteristics have been confirmed using ultrasound.
Results: The mean CRP serum level was 8.74±5.06 mg/l and the frequency of spontaneous stone excretion was 72.6% (n=69). CRP serum level was significantly lower in patients with spontaneous stone excretion (7.42 vs. 12.23 mg/l and p=0.001). The cut-off point of CRP serum level was 13.5 mg/l for patients with ureter stone size of 4-7 (with 84% sensitivity and 58% specificity) and for patients with ureter stone size of 7-10, it was 12.5 mg/l (with 83% sensitivity and 56% specificity).
Conclusions: The results showed that there is a significant relationship between the CRP serum levels, along with stone size with spontaneous excretion of lower ureter stones.

Keywords: C-reactive protein, Lower ureter stone, Spontaneous excretion

INTRODUCTION

Urinary system stones, including kidney, ureter, bladder, and urinary tract stones, are the third most common urinary tract disease and with the reported prevalence of 1-15% in different communities.[1-2] Meanwhile, ureter stones are more important than other stones in terms of the severity of symptoms and the rate of destruction in kidney function, due to the narrow diameter of the ureter.[3] Of all urinary system stones, 20% are ureter stones, about 70% of which are located in the lower ureter. Ureter stones are usually associated with lateral pain spread to the groin, obstruction, nausea, hematuria, and rarely life-threatening infection.[4] Currently, there are several options, including conservative (expectant) management, medication, or surgery to manage patients with urinary tract stones. Choosing patient management depends on a variety of factors, including disease manifestation, clinical evaluation, and the stone characteristics.[5] Both expectant and aggressive approaches carry risks. The main risk of the expectant approach is the possibility of

failure in spontaneous excretion of the stone and as a result, the patient will have to endure the symptoms without any advantage in treatment. On the other hand, the main risk of surgical intervention is that the intervention may be unnecessary and therefore expose the patient to potential risks such as anesthesia, urinary tract infection and urethral injury. Therefore, accurate prediction of the probability of spontaneous excretion of a stone is very important in choosing the appropriate treatment strategy, so that the choice between "waiting in care until spontaneous excretion" or "early invasive intervention" is the main challenge for urologists when managing patients with urinary tract stones.[6-8]

Urinary system stones, including kidney, ureter, bladder, and urinary tract stones, are the third most common urinary tract disease and with the reported prevalence of 1-15% in different communities. There are four main types of urinary stones, the majority of which (75-90%) consists of calcium oxalate and uric acid (5-20%), calcium phosphate (6-13%), struvite (2-15%) and cysteine (0.5-1%) are in the next ranks. C-reactive protein (CRP) is an acute phase inflammatory marker that is synthesized in the liver and its level is increased in various diseases such as renal tubular injury, pyelonephritis and vesicoureteral reflux. The parameters effecting the spontaneous stone excretion, including the size and location of the stone, which are among the most accepted parameters in clinical medicine, have been more or less studied in the sources.[9] However, there may be other parameters in addition to these parameters that can play a more precise role in predetermining the success rate of spontaneous stone excretion and guiding urologists in selecting the right patient. Among these latent factors, we can mention the inflammatory reactions caused by the stones.[10]

Meanwhile, C-reactive protein (CRP) is an acute phase inflammatory marker that is synthesized in the liver and its level is increased in various diseases such as renal tubular injury, pyelonephritis and vesicoureteral reflux and recent studies conducted on patients with urinary tract stones have shown that CRP serum levels can be useful in predicting the success of expectant treatment and spontaneous excretion of stone and thus, selecting the appropriate patient, but the studies conducted in this field are inadequate, and the results obtained are slightly contradictory.[11-15] In order to investigate this issue, this study was done to investigate the relationship between spontaneous excretion of lower ureter stone with stone size and serum level of C-reactive protein in patients referring to Ardabil city hospital.

METHODS

Study design and participant

This cross-sectional descriptive study has been done on 95 patients with lower ureter stones who selected randomly from all patients referring to Ardabil city hospital in 2020-2021. The necessary sample was calculated and estimated based on Cochran formula in 95% confidence interval and power 80%. Necessary data were extracted from the records of patients. Inclusion criteria included records of patients over 18 years old and with lower ureter stones. Patients with urinary tract infections, severe hydronephrosis, pregnant women, patients with one kidney, and patients with a history of urinary tract surgery were excluded from the study. Due to the outbreak of Covid-19, in addition to taking a history and physical examination, CRP test was performed and evaluated for patients with renal colic who referred to the hospital in 2020-2021 with symptoms associated with fatigue, loss of appetite and fever and its documentation was available in the files of the studied patients. The existence of stone and its characteristics were confirmed by ultrasound or CT scan and was attached to the patients' files. Patients who referred with renal colic symptoms were followed up for about 15 days and then evaluated with the same primary diagnostic tool (ultrasound and KUB or contrast-free spiral CT scan) in order to determine whether or the spontaneous stone excretion and documents were attached to the files. Patients were divided into two groups based on spontaneous stone excretion or non-spontaneous stone excretion and the relationship between CRP serum level and stone size with spontaneous stone excretion or non-spontaneous stone excretion was determined by comparing the two groups. Statistical analysis was performed in SPSS software version 25 with a significance level of 0.05. A checklist was completed for each patient. Collected data were statistically analyzed based on descriptive and analytical statistical methods. In descriptive statistics, mean and standard deviation were used for quantitative variables and frequency index and frequency percentage were used for qualitative variables. In analytical statistics, t-test was used to compare quantitative variables between two groups, chi-square test was used to compare qualitative variables between the two groups, and ROC curve analysis test and binary logistic regression test was used to determine the cut-off point and risk rate.

RESULTS

There was no statistically significant relationship between spontaneous stone excretion with gender, age, BMI, history of having stone and the side of the stone. There was a statistically significant relationship between spontaneous stone excretion and stone size so that the frequency of spontaneous excretion in patients with stone size of 4-7 mm was significantly higher than patients with stone size of 7-10 mm (81.8% vs. 51.7%) (Table 1).

The mean of CRP in all patients was 8.8±5.1 mg/l. There was a statistically significant relationship between spontaneous stone excretion rate and CRP serum level (p=0.001) so that its serum level was significantly lower in patients who had spontaneous excretion (7.42 vs. 12.23 mg/l) (Table 2). ROC curve analysis and logistic

regression analysis were used to determine the cut-off point of CRP serum level to predict spontaneous excretion of ureter stone. The ROC curve for patients with 4-7 mm stone ureter, with a surface area below the curve of 0.785 is a good value (AUC=0.785, 95%CI: 0.668-0.883, p=0.001). Moreover, the cut-off point of CRP serum level was obtained to be 13.5 mg/l (with 84% sensitivity and 58% specificity) using the Yuden index, so that patients with 4-7 mm ureter stone whose CRP serum level was more than 13.5 mg/l, were 7.3 times more likely to have a spontaneous stone excretion compared with patients with lower CRP serum level (OR=7.305, 95% CI: 2.784-19.172, Sig.<0.001) (Figure 1).

Table 1: The relationship between spontaneous excretion of ureter stone and studied variables.

Variables		Spontaneous excretion of ureter stone		Total (%)	P value
		Yes (%)	No (%)		
Sex	Male	42 (71.2)	17 (28.8)	59 (100)	0.686
	Female	27 (75)	9 (25)	36 (100)	
Age (year)		43.2±10.2	41.1±8.8	42.9±9.8	0.624
BMI	Normal	36 (78.38)	10 (21.7)	46 (100)	0.31
	Overweight	21 (72.4)	8 (27.6)	29 (100)	
	Obese	12 (60)	8 (40)	20 (100)	
History of urinary stone	With	19 (76)	6 (24)	25 (100)	0.66
	Without	50 (71.4)	20 (28.6)	70 (100)	
Stone side	Right	32 (69.3)	12 (30.4)	46 (100)	0.516
	Left	37 (75.5)	12 (24.5)	49 (100)	
Stone size	mm 4-7	54 (81.8)	12 (18.2)	66 (100)	0.002
	mm 7-9	15 (51.7)	14 (48.3)	29 (100)	

Table 2: The relationship between spontaneous excretion of ureter stone and CRP serum level.

Variable	Spontaneous excretion of stone		P-value
	Yes	No	
CRP serum level (mg/l)	7.42±4.02	12.23±5.91	0.001

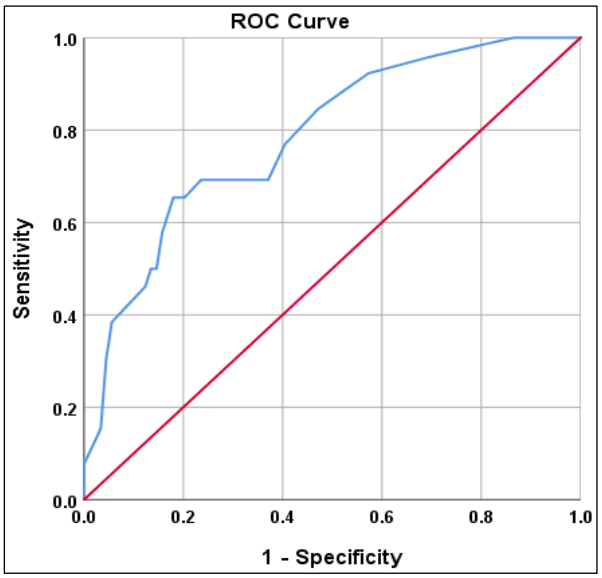

Figure 1: ROC curve for determining the cut-off point of CRP serum level in patients with 4-7 mm stone.

The ROC curve analysis for patients with 7-10 mm stone ureter, with a surface area below the curve of 0.752 is a good value (AUC=0.752, 95%CI: 0.618-0.886, p=0.002). Moreover, using the Yuden index, the cut-off point of CRP serum level was 12.5 mg/l (with a sensitivity of 83% and a specificity of 56%) so that patients with 10-7 mm ureter stone whose CRP serum level was more than 12.5 mg/l were 5.9 times more likely to face non-spontaneous stone excretion, compared with patients with lower CRP serum level (OR=5.937, 95% CI: 1.588-22.196, p=0.008) (Figure 2).

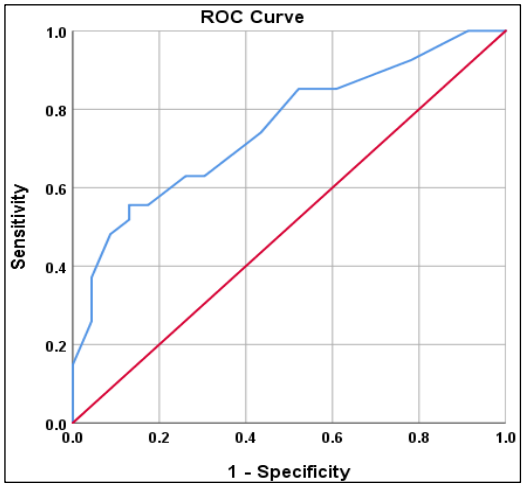

Figure 2: ROC curve for determining the cut-off point of CRP serum level in patients with 7-10 mm stone.

DISCUSSION

The spontaneous excretion rate of lower ureter stones in the present study was 72.6%, which is consistent with the study of Shah et al., conducted in the United Kingdom., which was reported to be 74%.[12] This rate has been reported to be 79.6% and 77.9% in studies conducted in Sweden and Egypt respectively, which are higher than the present study.[14-15] The spontaneous excretion rate of lower ureter stone was reported to be 65.9% and 55% in two studies in India, which are lower than our study.[11,13] The main reason for this difference in studies may be related to the differences in the size of the lower ureter stone.

In the present study, there was no statistically significant relationship between spontaneous stone excretion and demographic and baseline variables including gender, age, body mass index, history of urinary stone, and ureter stone position. Similar to our finding, in most previous studies, there was no association between these variables and spontaneous excretion of urinary stones.[11,13,15] Nevertheless, there was a significant relationship between spontaneous excretion of ureter stone and patients' age in a study by Özcan et al, in Turkey, so that the probability of spontaneous excretion of ureter stone was significantly decreased by age which is in contradictory with our findings. However, similar as our results, there was no significant relationship between spontaneous stone excretion and gender and BMI of patients reported in this study.[16]

In the present study, there was a statistically significant inverse relationship between ureter stone size and its spontaneous excretion, so that the frequency of spontaneous excretion in patients with smaller stone size (4-7 mm) was significantly higher than patients with larger stone size (7-10 mm). Consistent with our finding, in the study of Shah et al, conducted in the United Kingdom, there was a statistically significant inverse relationship between the size and spontaneous excretion of ureter stone, so that in their study, the spontaneous excretion rate in stones with a diameter greater than 7 mm had the lowest value (29%) and, the spontaneous excretion rate increased by decrease in the stone size (49% in 7-5 mm stones and 89% in less than 5 mm stones).[12] In a study by Ahmad et al in Egypt on patients with lower ureter stones, it was also found that patients with a stone size up to 65 mm had the highest chance of spontaneous stone excretion, which is similar to our findings.[15] Also, the results of the study of Jain et al, in India showed that the smaller diameter of the ureter stone is an independent and significant predictor of spontaneous excretion.[11] In addition, a study by Jendeberg et al, in Sweden showed that the success rate of spontaneous excretion of ureter stones was significantly inversely related to stone size, as in the present study.[14]

Another finding of the present study was that there is a significant relationship between CRP serum levels and spontaneous excretion of ureter stone, CRP so that serum levels were significantly lower in patients who had spontaneous excretion. Interestingly, different cut-off points were obtained for 4-7 mm and 10-7 mm stones, so that in patients with 4-7 mm lower ureter stone, the CRP serum level being higher than 13.5 mg/l was associated with a significant increase in spontaneous excretion of stone (OR=7.3). Whereas in patients with 7-10 mm lower ureter stone, CRP serum level being higher than 12.5 mg/L was associated with a significant increase in spontaneous excretion of stone (OR=5.9). As we all know, CRP is a non-specific marker of inflammation. Over the last two decades, the use of this marker has been proposed to predict inflammatory conditions such as appendicitis, cystitis, urinary tract infections, and some cardiovascular diseases.[17-18] In recent years, it has been suggested that urinary system stones, including ureter stone, may increase serum levels of this marker by causing inflammatory reactions and changes; therefore, some studies have investigated this relationship.[19] Among which, the results of the study by Hada et al, showed that serum CRP levels in patients who had spontaneous excretion of ureter stone were significantly lower than in patients in whose expectant treatment failed, which is similar to our finding.[13] The cut-off point of CRP serum level for predicting spontaneous excretion of ureter stone in their study was 1/4 mg/l, which is lower than the cut-off point of the present study. The reason for the difference in cut-off point between the two studies could be the differences in populations, differences in laboratory methods of measuring CRP serum levels, and methodological differences. Contrary to our findings and the above studies, in the study by Shah et al., there was no significant relationship between CRP serum levels and spontaneous excretion of ureter stone.[12]

A very important point to note at the end is that in the present study, 16% of patients, even with stone size less than 7 mm and CRP less than 12.5 mg/dl, faced failure of expectant treatment and spontaneous stone excretion. A similar finding was reported in the study by Jain et al., in which 20% of patients with CRP less than the cut-off point were unable to excrete the stone spontaneously.[11] These findings show that the probability of spontaneous excretion of stone cannot be predicted by relying only on these two parameters, i.e. only by relying on the size of the stone and the serum level of CRP, but also there are other effective parameters in this issue that the identification of all these parameters requires further studies in this area. The findings of the present study showed that CRP serum level along with stone size has a statistically significant relationship with spontaneous excretion of lower ureter stones and therefore seems to be an effective marker for a more precise decision making about choosing the expectant or aggressive approach. According to the results of the present study, the expectant approach does not appear to be beneficial and is therefore not recommended for patients with 4-7 mm ureter stones who have CRP greater than 13.5 mg/l, and also for patients with 7-10 mm ureter stones who have

CRP greater than 12.5 mg/l. However, and due to the limited studies conducted in this field, for routine use of this marker in the clinic, it is necessary to conduct further studies with higher sample sizes.

CONCLUSION

The findings of the present study indicated that there is a significant relationship between the CRP serum levels, along with stone size with spontaneous excretion of lower ureter stones and therefore it seems to be an effective marker for more precise decision making about choosing an expectant or aggressive approach.

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