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Role of inflammatory markers in predicting spontaneous passage of ureteral stones less than 10 mm

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Summary

Introduction: In ureterolithiasis, the prediction of spontaneous passage poses a challenge for urologists. Moreover, there is controversy surrounding the preferred management approach, whether medical or surgical, as each approach has its disadvantages. Procalcitonin and other inflammatory markers were studied for predicting stone passage spontaneously, but their significance remains controversial. This study aims to assess the association between these markers, especially procalcitonin, and spontaneous ureteral stone passage.

Materials and methods: In this multicenter prospective cohort study from March 2022 to October 2023, consecutive patients with a single unilateral distal ureteric stone less than 10 mm were enrolled. Exclusion criteria were specified. Patients underwent medical expulsive therapy (MET) and were monitored for stone passage. The significance level was set at $p < 0.05$.

Results: Out of 94 patients enrolled, 72.3% were male and 27.7% were female, with a mean age of 38.84 ± 10.41 years. Stone sizes varied, with the most common range being 4 mm-5.9 mm. Participants were categorized based on spontaneous stone passage as spontaneous stone passage (SSP) and non-SSP. No significant differences were observed in most demographic and laboratory variables. However, serum procalcitonin and C-reactive protein showed significant differences between the SSP and non-SSP groups.

Conclusions: Although several inflammatory markers were studied to predict the spontaneous passage of the ureteral stone, the current study concluded that only elevated procalcitonin, C-reactive protein, and large stone diameter decrease the chance of spontaneous ureteral stone passage.

KEY WORDS: Nephrolithiasis; Spontaneous stone passage; Inflammatory marker; Procalcitonin level; Renal stone surgery.

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INTRODUCTION

Nephrolithiasis is a common urinary tract disease, ranking third in terms of prevalence after urinary tract infection and benign prostate obstruction. It affects around

5% to 10% of the population, leading many individuals to seek medical care for stone-related problems in emergency and general outpatient departments. The lifetime possibility of experiencing urolithiasis is estimated to be around 13% for males and 7% for females.

The incidence of urolithiasis is highest for males between the ages of 40 and 60, whereas for females, it peaks in the late 20s (1-3). A ureteric stone accounts for 20% of stones in the urinary tract, with 70% of these stones typically situated in the distal part of the ureter (3).

Major complaints such as urinary tract infection, vomiting, renal obstruction, nausea, hematuria (bloody urine), and abdominal or back pain in ureteral calculi can be noticed (4). A non-contrast computed tomography (NCCT) scan is the most preferred imaging technique for urolithiasis diagnosis in symptomatic patients. The sensitivity and specificity of this diagnostic method were found to be approximately 100%, making it an extremely reliable diagnostic tool (4).

Regarding the management of stone passage, a considerable number of ureteral stones have the potential to pass on their own (5). Per the European Urological Association's and American Urological Association's recommendations, medical expulsive therapy (MET) is considered the primary treatment for ureteral stones measuring less than 10 mm (6). Not all patients taking MET can achieve spontaneous stone passage. The key factors influencing predictability include the stone's size and its location. As indicated by the American Urological Association, 68% of stones measuring less than 5 mm and 47% of stones exceeding 5 mm in size were noted to pass spontaneously (7). In cases where the stone cannot pass naturally, treatment alternatives such as extracorporeal shockwave lithotripsy (ESWL), ureteroscopy, and open surgery may be considered (4). Inflammatory markers are indicators of an inflammatory response in the human body. The level of inflammation can be detected by various markers, such as serum procalcitonin, C-reactive protein (CRP), and others (8). Elevated levels of these markers are observed in various conditions, including COVID-19, cancer, and inflamma-

tory bowel disease (9). Newly conducted research has been released, demonstrating that biochemical indicators of inflammation can function as predictors for the spontaneous passage of stones (10). The relevance of inflammatory markers in the spontaneous passage of ureteral stones is a subject of debate among various studies (11). The current study aims to assess the association between serum procalcitonin, CRP, and other inflammatory markers with the possibility of passing stones spontaneously.

MATERIALS AND METHODS

Study design and setting

This prospective observational cohort study was conducted from March 2022 to October 2023. Ethical approval was secured by the ethics committee with a degree No. 53. and both written and informed consent were obtained from each participant.

Inclusion and exclusion criteria

The study focused on patients aged between 18 and 64 years, including both genders. It only included patients diagnosed through a non-contrast-enhanced CT scan with single unilateral stones less than 10mm in size and located in the distal ureter below the lower border of the sacroiliac joint.

Individuals with a single functioning kidney, more than 1 stone in the same ureter, bilateral ureteric and/or concurrent renal stones, severe hydronephrosis [defined as Grade 4 hydronephrosis based on the Onen classification system-which characterizes severe hydronephrosis as greater than 50% loss of renal parenchyma or a cyst-like kidney with no significant visible renal parenchyma (12)], impaired renal function, congenital or acquired anatomical anomaly of the urinary tract, pregnant patients, history of ureteral stenosis or reconstructive ureteral surgery, previous intervention for a stone or any other operation (within 2 months of inclusion in the study), or individuals who had ESWL and stent or nephrostomy insertion for a stone in the same ureter were not included.

Furthermore, exclusion criteria were patients with diabetes, thyroid or hepatic disease, active malignancy, active inflammatory bowel disease, active infectious disease, immunological diseases, active chronic inflammatory disease, or patients who used antibiotic, steroid, NSAIDs, or immune suppressant medicines (within 2 weeks of inclusion in the study) or patients with documented infection clinically (fever > 38) or via investigations (positive urine culture) or patients who were also unable to comply with MET or had contraindications to MET therapy or side effects of the medications or patients who preferred immediate active treatment of stones, or who were lost follow-up during the study.

Sample and data collection

Upon admission and throughout the acute phase, demographic information such as age, gender, body weight, and height were obtained from all patients. This information was obtained as part of the initial assessment to characterize the study population. *Body mass index* (BMI) was computed as the ratio of height in meter square to weight in

kilogram and expressed as kg/m^2 . A medical history and thorough physical examination were conducted on each participant to assess their overall health and identify any clinical signs. As part of the initial assessment, inflammatory markers were measured, including complete blood count (*white blood cells* (WBCs), *neutrophils* (NCs), *lymphocytes*, *neutrophil-to-lymphocyte ratio* (NLR), *platelet-to-lymphocyte ratio* (PLR), serum procalcitonin, C-reactive protein, and serum creatinine to evaluate disease severity. All patients underwent NCCT scans of the kidney, ureter, and bladder. Axial NCCT images with a slice thickness of 5 mm were obtained, utilizing specific imaging parameters such as a soft-tissue window with a width of 360, a pitch of 1.5, a tube voltage of 120 kV, and a tube current ranging from 70 to 90 mAs. Radiological findings included a detailed analysis of stone characteristics, determining stone side (right versus left), site (proximal, mid, and distal), size (defined by the stone's greatest diameter), and density measured in Hounsfield units. In terms of hydronephrosis grading, the study utilized the Onen classification system. This system categorized grades 0 and 1 as indicating no-to-mild hydronephrosis. Conversely, grades 2, 3, and 4 were grouped to represent moderate-to-severe hydronephrosis. This classification allowed for a concise and clinically relevant assessment of the degree of hydronephrosis in the study population, providing a more detailed analysis of renal conditions and their implications (12). Concerning the anatomical position, the distal ureter was specified as the segment extending from the lower boundary of the sacroiliac joint to the bladder. Stone size calculations were performed using both coronal and axial images obtained through cross-sectional imaging. Finally, all the obtained data were recorded for further analysis.

Follow-up

Patients without indications for interventional treatment underwent observation and MET, which involved a prescription of diclofenac sodium (75 mg/day) and tamsulosin (0.4 mg/day) for four weeks, along with a recommended daily fluid intake of 2-3 liters. Those on MET attended weekly outpatient controls, excluding emergencies. During these visits, patients were asked about the stone passage and any renal colic incidents. For those unable to pass the stone, confirmation was sought through ultrasound/plain kidney-ureter-bladder at weeks one, two, and three, and at the fourth week using non-contrast abdominal CT. Individuals failing to pass the stone were categorized as passage negative (NO SSP), while those successful were grouped as *passage positive* (SSP). Failure of passage was defined as the stone's presence on NCCT after four weeks or urgent intervention within the period due to stone-related complications, such as drainage, shockwave lithotripsy, or *ureteroscopy* (URS). Inflammatory markers were not reassessed during the follow-up period; instead, the follow-up focused on monitoring stone passage and patient progress.

Statistical analysis

The acquired data were analyzed via Statistical Package for the Social Sciences software 25.0. Quantitative variables were analyzed by using an independent sample t-test and

chi-square; additionally, these data were presented in the form of means and standard deviations. Qualitative data were presented as proportions and percentages. In this study, a p-value of < 0.05 was considered significant.

RESULTS

Demographic characteristics

Of the total patients enrolled in this study (n = 94), 68 (72.3%) were male and 26 (27.7%) were female. They had a mean age of 38.84 ± 10.41 years (19-64 years), with the majority of the patients (33%) being between 29 and 38 years old. The mean BMI of the participants was 26.3 ± 4.638, with the majority of participants falling within the normal range (18.5-24.9). Stone sizes were further classified into different classes; the most common stone size falls within the 4 mm-5.9 mm range, comprising the largest percentage of the sample (39.36%). Further characteristics of the enrolled participants are given in Table 1.

Clinical characteristics and statistical analysis

The individuals enrolled in this study were divided into two main groups depending on whether they experienced spontaneous passage of stones or non-spontaneous passage of stones, with a mean age of 39.4 ± 10.8 and 37.78 ± 9.73, respectively. The mean stone size ± SD in SSP was 5.41 ± 1.6, while the size of the stone in non-SSP was 6.37 ± 1.76.

Inflammatory markers are regarded as predictive factors for the evaluation of spontaneous stone passage. In this study, several demographics, laboratory, and radiological variables were analyzed to investigate their association with spontaneous stone passage. No statistically significant differences among several variables between the NO SSP and SSP groups were found, including age, BMI, side (right or left) of the kidney stone, serum creatinine, PLR, white blood cells, granulocytes, and platelets.

Regarding the association between inflammatory markers and the possibility of stone passage spontaneously, a high statistically significant difference in serum procalcitonin levels was found between the NO SSP and SSP groups (p < 0.001), with the mean of procalcitonin being higher (0.14 ± 0.089) among the NO SSP groups compared to the SSP group (0.05 ± 0.027). CRP, as another inflammatory marker, was found to have statistical significance between the NO SSP and SSP groups (p < 0.001), with the mean of CRP being lower among the SSP group (5.55 ± 5.06) compared to the NO SSP group (12.63 ± 11.03). Additionally, NLR and lymphocytes were found to have statistical significance difference between the NO SSP and SSP groups with a p-value of (0.032, and 0.032), respectively (Table 2).

Accordingly, the size of the stone also showed a statistically significant difference between the NO SSP and SSP groups (p-value =

0.009), with the mean stone size being higher among the NO SSP group (6.37 ± 1.76) compared to the SSP group (5.41 ± 1.6). Which indicated that larger stone sizes have less possibility of passing spontaneously. Additionally, stone sizes were grouped into 2 major groups and analyzed

Table 1.
Baseline characteristics.

Variables	Frequency	Percentage (%)
Gender		
Male	68	72.3
Female	26	27.7
Age		
19-28	17	18.1
29-38	31	33
38-47	27	28.7
Above 47	19	20.2
Stone Size (Longest Diameter)		
2 mm-3.9 mm	13	13.82
4 mm-5.9 mm	37	39.36
6 mm-7.9 mm	28	29.8
8 mm-9.9 mm	16	17.02
Side		
Right	48	51.06
Left	46	48.94
BMI		
< 18.5	3	3.2
18.5-24.9	33	35.1
25-29.9	41	43.6
> 30	17	18.1
Hydronephrosis grade		
Mild	68	72.3
Moderate	26	27.7

Table 2.
Analyzing demographic, laboratory, and radiological variables for predicting passage of stones spontaneously.

Variable	Total	NO SSP	SSP	P-value
Age (Mean ± SD)	38.84 ± 10.41	37.78 ± 9.73	39.4 ± 10.8	0.474
Gender				0.018
Male (n, %)	68 (72.3%)	19 (61.2%)	49 (77.8%)	
Female (n, %)	26 (27.7%)	12 (38.7%)	14 (22.2%)	
BMI (Mean ± SD)	26.3 ± 4.638	26.05 ± 4.38	26.44 ± 4.8	0.695
Side				0.717
Right (n, %)	48 (51.06%)	16 (48.48%)	32 (52.46%)	
Left (n, %)	46 (48.94%)	17 (51.52%)	29 (47.54%)	
Size (Mean ± SD)	5.7 ± 1.7	6.37 ± 1.76	5.41 ± 1.6	0.009
Serum procalcitonin (Mean ± SD)	0.083 ± 0.072	0.14 ± 0.089	0.05 ± 0.027	< 0.001
CRP (Mean ± SD)	8.04 ± 8.36	12.63 ± 11.03	5.55 ± 5.06	< 0.001
Serum creatinine (Mean ± SD)	0.88 ± 0.22	0.92 ± 0.21	0.86 ± 0.22	0.197
NLR (Mean ± SD)	3.39 ± 2.186	2.74 ± 1.61	3.75 ± 2.37	0.032
PLR (Mean ± SD)	126.62 ± 86.66	112.78 ± 86.78	134.1 ± 86.38	0.257
White blood cells (Mean ± SD)	9.73 ± 2.9	9.01 ± 2.77	10.12 ± 2.92	0.078
Hydronephrosis grade				0.018
Mild (n, %)	68 (72.3%)	19 (57.6%)	49 (80.3%)	
Moderate (n, %)	26 (27.7%)	14 (42.4%)	12 (19.7%)	
Size group (n, %)				0.022
< 6 mm	62 (65.96%)	17 (51.5%)	45 (73.77%)	
> 6 mm	32 (34.04%)	16 (48.5%)	16 (26.23%)	
Granulocyte (Mean ± SD)	7.68 ± 2.51	7.26 ± 2.45	7.91 ± 2.53	0.233
Lymphocyte (Mean ± SD)	3.16 ± 3.38	4.17 ± 5.38	2.61 ± 1.20	0.032
Platelets (Mean ± SD)	276.21 ± 73.12	275.5 ± 71.3	276.59 ± 74.67	0.946

Table 3.
Association between procalcitonin level at admission and weeks of stone passage and Hydronephrosis grade.

Parameters		Procalcitonin level	P value
Week of stone passage (Mean ± SD)	Week 0	0.021 ± 0.002	< 0.001
	Week 1	0.038 ± 0.016	
	Week 2	0.049 ± 0.022	
	Week 3	0.077 ± 0.013	
	Week 4	0.084 ± 0.059	
Hydronephrosis grade (Mean ± SD)	Mild	0.075 ± 0.07	0.093
	Moderate	0.103 ± 0.077	

statistically to demonstrate their association with stone passage; a statistically significant difference was also found (p -value = 0.022). Hydronephrosis grade was determined for all the patients and further classified into mild and moderate to determine its association with the spontaneous passage of stones. This variable was also found statistically significant (p -value = 0.018). Another factor that should be taken into account in this study is the significant difference in gender distribution between the NO SSP and SSP groups (p = 0.018). The SSP group had a higher percentage of males (77.8%) (Table 2).

Figure 1.

Receiver operator curve analysis for Association between serum procalcitonin and stone passage.

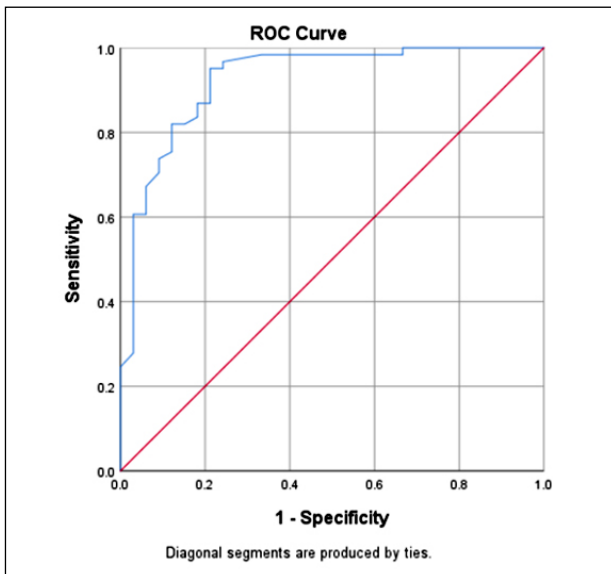


Table 4.
Receiver operating characteristic (ROC) for the association between procalcitonin and stone passage.

Parameters	Area under curve	95% confidence interval	Cut off value	P-value
Procalcitonin	0.925	0.866-0.984	0.076	< 0.001
ROC		Sensitivity		82%
		Specificity		87.9%

Regarding the association between procalcitonin level at admission with the weeks of stone passage and hydronephrosis grade, it was found that procalcitonin levels vary significantly across different weeks of stone passage (p < 0.001). Procalcitonin levels were lowest at Week 0 (0.021 ± 0.002) and increased progressively in subsequent weeks: Week 1 (0.038 ± 0.016), Week 2 (0.049 ± 0.022), Week 3 (0.077 ± 0.013), and Week 4 (0.084 ± 0.059). However, no significant difference in procalcitonin levels between different hydronephrosis grades was found (p = 0.093) (Table 3).

Receiver operating characteristic (ROC) for the association between procalcitonin and stone passage showed an area of 0.925 (95% C.I. 0.866-0.984) with a cut-off value of 0.076, a sensitivity of 82%, a specificity of 88%, and a p -value < 0.001 (Figure 1) (Table 4).

DISCUSSION

Nephrolithiasis is a commonly occurring urinary tract condition, which is the third most prevalent disease after infections in the urinary tract and benign obstruction in the prostate (1). Various therapeutic approaches and treatment methods exist for the management of stones in the ureter, depending on factors such as the size of the stone, location, composition, and clinical aspects (11). These treatment options range from conservative treatment or non-surgical treatment (with analgesics with or without MET to assist spontaneous stone passage) to invasive treatments such as ESWL and ureteroscopy (URS-L) (flexible or semi-rigid) (6, 13, 14). Medical treatment is considered cost-effective, alleviating the need for surgical procedures and leading to minimal complications. Potential disadvantages of MET may include recurring colic and urinary tract infections (11). Conversely, invasive procedures lead to a safer and more efficient stone removal rate, with a higher cost compared to medical treatment. Furthermore, potential complications in the urinary system, such as the formation of hematomas, urinary infections, and urinary extravasation, should be taken into account as adverse effects of this treatment approach (15).

The success of ESWL and URS-L treatments depends on the stone's location and size, with reported success rates ranging from 68% to 90% for ESWL and 80% to 97% for URS-L (6). Likewise, delaying surgical intervention until medical therapy fails can be stressful for the patient and increase treatment costs compared to the immediate surgical removal of a stone (11). These controversies about choosing the management method have led many researchers to study inflammatory markers. These markers can help clinicians decide on the most effective treatment method for patients.

Medical expulsive therapy (MET) involves the administration of medications to facilitate the expulsion of ureteric stones. Various drugs, including alpha-blockers, calcium channels blockers, corticosteroids, and phosphodiesterase-5 inhibitors, have undergone thorough examination. Recent guidelines recommend alpha-blockers as an effective standalone therapy for the medical removal of stones in the ureter. On the other hand, there isn't enough evidence to consider other drugs mentioned as

standalone therapies (14). According to the recent guidelines from the *European Association of Urology* (EAU), for distal ureteric stones larger than 5 mm, alpha-blockers are recommended as MET (15, 16). Most studies in the literature assess MET outcomes over a four-week duration, and there is no data available to support other time intervals currently. In the present study, patients were given diclofenac sodium (75 mg/day,) as an analgesic to reduce pain and tamsulosin (0.4 mg/day) for four weeks, along with a daily fluid intake of 2-3 liters.

The possibility of passing ureteral stones naturally is highly influenced by two crucial factors, its size and location. The relationship between stone size and *spontaneous stone passage* (SSP) is inversely proportional. Stones measuring less than 5 mm have a 75% chance of passing naturally, with the possibility of passage decreasing as the size increases. For ureteral stones between 5 and 10 mm, the chance of spontaneous passage ranges from 25 to 46%. Additionally, it has been reported that for stones less than 4mm, there is a 95% possibility of spontaneous passage within 40 days (1, 11, 17). The *European Association of Urology* and *American Urological Association* (EAU/AUA) panel examined spontaneous passage rates through a recent meta-analysis, revealing rates of 68% for stones smaller than 5 mm and 48% for stones ranging from 5 to 10 mm (18). One study by *Demehri et al.* classified patients into 3 groups based on stone sizes, groups were less than or equal to 5 mm, between 5 and 10 mm, and greater than 10 mm. A spontaneous passage rate of 92% for stones less than 5 mm and 9.1% for stones larger than 10 mm was observed (19). The current study revealed an overall SSP rate of 67%; additionally, the mean size of the stone was 5.41 ± 1.6 among SSP groups and 6.37 ± 1.76 among NO SSP groups, with a p-value of 0.009, which indicates a statistically significant difference between the two groups in terms of stone size. Likewise, patients in this study were classified into two groups based on stone size, and statistical analysis showed a p-value of 0.022 with the highest rate of SSP (73.77%) for stones less than 6mm.

Several studies have consistently demonstrated that demographic characteristics do not exert a significant influence on the probability of ureteral stones passage spontaneously. A study conducted by *Mohammad et al.* involving 73 patients with distal ureteric stones sized 4-8 mm revealed no significant difference in age, BMI, or gender between the SSP and non-SSP groups statistically (3). In another study, which was conducted on 54 patients with single ureteral stones, no significant difference was found in demographic characteristics between the SSP and NO SSP groups (1). However, according to a study conducted by *Puntub et al.*, which included 139 patients with ureteral stones < 10 mm, demographic characteristics such as age and gender showed statistically significant differences between the SSP and NO SSP groups. The study found that individuals with SSP had a mean age of 44.53 years, while those with NO SSP had an average age of 52.62 years. The study also observed that males had a better chance of SSP than females. The statistical analysis showed a significant relationship between age, gender and stone passage with a p-value of 0.003 and 0.031, respectively (4). In the present study, considering various

demographic characteristics, only gender exhibited a statistically significant difference between the SSP and non-SSP groups. The incidence of SSP was significantly higher among males (77.8%) compared to females (22.2%), and this was found to be statistically significant with a p-value of 0.018.

Regarding the side of the stone, in one study by *Jain et al.* conducted on 185 patients with stones in the ureter, the side of the stone showed no significant difference among the SSP and NO SPP groups (20). In another study in which 156 patients enrolled, the side of the stone showed no statistically significant difference among the SSP and NO SSP groups with a p-value of 0.1 (7). In this study, statistical analysis showed no significant difference in the spontaneous passage of ureteral stones between left- and right-sided stones with a p-value of 0.717.

Regarding the association between inflammatory markers and ureteral stone passage, several inflammatory markers have been studied. In a study involving 156 patients conducted by *Sfoungaristos et al.*, elevated levels of WBCs and NC during the acute phase of renal colic were linked to an elevated possibility of ureteral stones passing spontaneously (7). Likewise, in another study by *Özcan et al.*, which was conducted on 251 renal colic patients, statistical analysis showed a significant difference in WBCs and neutrophils among groups that pass their stones spontaneously and those that do not pass their stones, with the level being higher among NO SSP groups compared to SSP groups (21). In another study, which was performed on 192 patients, WBCs and NCs were decreased among SSP groups compared to NO SSP groups, with a p-value of 0.0005 for both markers (14). Additionally, in a study by *Park et al.*, in which a total of 182 patients were enrolled, it was reported that an elevated level of NC percentage leads to a spontaneous decrease in the rate of ureteral stone passage (22). A possible causation for this finding is that ureteral stone presence leads to swelling of the ureteral mucosa, ultimately resulting in obstruction. These interactions may contribute to increased inflammatory reactions and an elevated percentage of neutrophils and white blood cells (4).

The *neutrophil-to-lymphocyte ratio* (NLR) and *platelet-to-lymphocyte ratio* (PLR) are other markers that can be used as predictors of ureteral stone passage. Different studies suggested that elevated NLR and PLR are associated with a decreased possibility of spontaneous ureteral stone passage. Statistical analysis showed that there is an inverse relationship between NLR and PLR levels and the spontaneous passage of ureteral stones, as indicated by a p-value of less than 0.005 in various studies (5, 8, 11, 23).

However, in contrast to the above-mentioned studies, according to a study by *Ahmed et al.*, which was performed on 163 patients for spontaneous passage prediction of stones less than 10 mm, it was reported that serum WBCs did not show a significant difference between SSP and non-SSP groups (12). Likewise, in a retrospective study performed on 279 patients, it was found that inflammatory markers, particularly WBCs, NC, and NLR, do not serve as meaningful parameters for passage prediction of ureteral stones as they did not show any difference between both groups significantly (24).

Additionally, in a prospective study that was performed

to find the relationship between stone passage and inflammatory markers, in which 139 patients were enrolled, it was concluded that both WBCs and NCs did not play a role in predicting the passage of stones spontaneously, with a p-value of 0.97 and 0.58, respectively (4). The current study findings are in contrast with these studies. We observed elevated NLR and decreased lymphocyte count among patients who pass their stones spontaneously (SSP), with mean values of 3.75 ± 2.37 and 2.61 ± 1.20 , respectively, compared to NO SSP groups with mean values of 2.74 ± 1.61 and 4.17 ± 5.38 , respectively. The statistical analysis of both variables showed a p-value of 0.032. Additionally, the current study findings did not show any statistically significant differences in WBCs, PLR, NCs, and platelets among the SSP and NO SSP groups.

Another inflammatory parameter that serves as a meaningful parameter for predicting ureteral stone passage is CRP, which is primarily produced by the liver in response to tissue damage and serves as a sensitive indicator of inflammation (25). Previous studies have established associations between CRP and various inflammatory conditions, including diabetic nephropathy (26), subacute thyroiditis (27), and hepatitis (28). In numerous studies, the serum CRP level appeared as a significant predictor for the spontaneous passage of ureteral stones. These studies consistently observed a significant elevation in serum CRP levels among patients who did not experience spontaneous ureteral stone passage (2-4, 20-22). One potential explanation of the mentioned results could be that the rise in these levels reflects the extent of inflammation induced in the ureteral mucosa as a stone passes through. This is supported by the observation that the interaction between the mucosa of the ureter and the stone leads to inflammation at the site where the stone is located (29).

However, in contrast to these findings, a study conducted by Hassan *et al.*, in which 195 patients were enrolled, reported that the spontaneous passage rate of ureteral stones among individuals with high CRP levels was higher, with a statistically significant p-value of less than 0.05 (30). The current study reported that CRP is a strong inflammatory marker to predict spontaneous passage of ureteral stones, with the level being elevated among those who did not pass their stones spontaneously (12.63 ± 11.03), compared to SSP groups (5.55 ± 5.06) with a p-value of < 0.001 .

Apart from stone size, location, WBC indices, and CRP, to our knowledge, there are limited studies in genuine literature that examine the effects of procalcitonin on stone passage (31). Procalcitonin is a peptide composed of 116 amino acids, possessing a molecular weight of approximately 13 kilodaltons. Ghillani *et al.* initially characterized this hormone in 1989 as a precursor to calcitonin, a thyroid gland-produced hormone consisting of 32 amino acids (32). The normal range for procalcitonin in the general population is recognized as being below 0.05 ng/mL. During systemic infections, it may elevate to levels of 2 ng/mL, and in cases of sepsis, it can reach levels higher than 10 ng/mL (33). Likewise, procalcitonin has been identified as useful in establishing a relationship between infections in the urinary tract and obstructed ureteral

stones. According to Papa Giannopoulos *et al.*, they found that procalcitonin levels exceeding 100 pg/ml (0.1 ng/ml) were observed in 18% of patients treated with medical expulsive therapy (MET), 45% of those had undergone procedures such as ureteroscopy with laser lithotripsy (URS-L) or the placement of a ureteral stent (34). In a study conducted by Cilesiz *et al.* to examine the role of procalcitonin in predicting the possibility of spontaneous passage of ureteral stones, in which 54 patients were enrolled, it was reported that the procalcitonin levels were significantly elevated in groups that did not experience spontaneous stone passage (0.207 ± 0.145 ng/ml) compared to those with successful spontaneous stone passage (0.133 ± 0.028 ng/ml) with a p-value of < 0.001 (1). In the current study, in which 94 patients were involved, it was found that procalcitonin levels were significantly higher among groups failing to pass their stones spontaneously (0.14 ± 0.089) compared to those who passed their stones spontaneously (0.05 ± 0.027), with a p-value of < 0.001 . In this study, the determined cutoff value for procalcitonin in predicting stone passage was established at 0.076 ng/ml with an AUC of 0.925, a sensitivity of 82%, and a specificity of 88% (95% CI 0.866-0.984). The possible explanation for elevated procalcitonin among NO SSP groups is linked to an excess of mucosal inflammation. This excess mucosal inflammation might have increased the possibility of stone impaction in the future, making their passage more challenging (1). In this study, the association between procalcitonin levels and weeks of passage among SSP groups was examined at the time. Patients were classified based on weeks of stone passage into five groups. Statistical analysis showed that procalcitonin levels vary significantly across different weeks of stone passage ($p < 0.001$). Procalcitonin levels are lowest at Week 0 (0.021 ± 0.002) and increase progressively in subsequent weeks: Week 1 (0.038 ± 0.016), Week 2 (0.049 ± 0.022), Week 3 (0.077 ± 0.013), and Week 4 (0.084 ± 0.059).

The association between stone passage and hydronephrosis grade is a subject of controversy, yet individuals with no or mild hydronephrosis were more likely to pass their stones spontaneously than those with moderate hydronephrosis, according to a study conducted on 163 patients (13). In contrast, in a study by Jendeberg *et al.*, which was performed on 392 patients retrospectively, it was reported that stones inducing moderate to significant hydronephrosis exhibited a greater likelihood of spontaneous passage compared to stones causing either no hydronephrosis or only mild hydronephrosis, with a p-value of 0.002 (35). In the present study, hydronephrosis grade was significantly different among SSP and NO SSP groups. Statistical analysis showed an increased chance of SSP when dealing with mild hydronephrosis (80.3%) compared to moderate hydronephrosis (19.7%), with a p-value of 0.018.

A notable limitation of this study is that we did not assess the time length from the onset of symptoms to the first admission. Consequently, we did not analyze how this time interval might relate to inflammatory markers. Future research should consider evaluating this aspect to provide further insights into the progression of inflammation and its impact on inflammatory indexes.

CONCLUSIONS

The findings suggest that elevated levels of procalcitonin may be a contributing factor in complicating the stone's passage and lengthening the duration of the stone passage. Likewise, elevated CRP and larger stones were found to decrease the chance of SSP. The validity and confirmation of the current findings require further studies.

REFERENCES

- Çilesiz NC, Arslan B, Balcı MB, et al. The role of procalcitonin and other markers of inflammation in predicting spontaneous passage of ureteral stones. *Journal of Academic Research in Medicine* 2021; 11:179-18.
- Hada A, Yadav SS, Tomar V, et al. 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.
- Mohammad EJ, Abbas KM, Hassan AF, Abdulrazaq AA. Serum c-reactive protein as a predictive factor for spontaneous stone passage in patients with 4 to 8 mm distal ureteral stones. *International Surgery Journal.* 2018; 5:1195-200.
- Puntub A, Lerdpraiwan W. Relationship between the spontaneous passage rates of ureteral stones less than 10 mm and serum C-reactive protein levels, white blood cell counts and neutrophil percentages. *Insight Urology.* 2018; 39:42-9.
- Abou Heidar N, Labban M, Bustros G, Nasr R. Inflammatory serum markers predicting spontaneous ureteral stone passage. *Clin Exp Nephrol.* 2020; 24:277-83.
- Türk C, Petrik A, Sarica K, et al. EAU guidelines on diagnosis and conservative management of urolithiasis. *Eur Urol.* 2016; 69:468-74.
- Sfoungaristos S, Kavouras A, Katafigiotis I, Perimenis P. Role of white blood cell and neutrophil counts in predicting spontaneous stone passage in patients with renal colic. *BJU Int* 2012; 110:E339-45.
- Aldaqadossi HA. Stone expulsion rate of small distal ureteric calculi could be predicted with plasma C-reactive protein. *Urolithiasis.* 2013; 41:235-9.
- Abdullah HO, Braim SA, Rasool MA, et al. Role of Inflammatory Markers in Severity, ICU Admission, and Mortality in COVID-19: A Systematic Review and Meta-analysis of 79,934 Patients. *Barw Med J.* 2024; 2:65-83.
- Kim BH. the authors reply: relationship between spontaneous passage rates of ureteral stones less than 8 mm and serum C-reactive protein levels and neutrophil percentages. *Korean J Urol.* 2013; 54:889-90.
- Aghaways I, Ibrahim R, Bapir R, et al. The role of inflammatory serum markers and ureteral wall thickness on spontaneous passage of ureteral stone < 10 mm: A prospective cohort study. *Ann Med Surg.* 2022; 80:104198.
- Kim SY, Kim MJ, Yoon CS, et al. Comparison of the reliability of two hydronephrosis grading systems: the Society for Foetal Urology grading system vs. the Onen grading system. *Clin Radiol.* 2013; 68:e484-90.
- Ahmed AF, Gabr AH, Emara AA, et al. Factors predicting the spontaneous passage of a ureteric calculus of 10 mm. *Arab J Urol.* 2015; 13:84-90.
- Ramasamy V, Aarthy P, Sharma V, Thakur AP. Role of inflammatory markers and their trends in predicting the outcome of medical expulsive therapy for distal ureteric calculus. *Urol Ann.* 2022; 14:8.
- Bultitude M, Smith D, Thomas K. Contemporary management of stone disease: the new EAU urolithiasis guidelines for 2015. *Eur Urol.* 2016; 69:483-4.
- Türk C, Knoll T, Seitz C, et al. European Association of Urology. Medical expulsive therapy for ureterolithiasis: the EAU recommendations in 2016. *Eur Urol.* 2017; 71:504-7.
- Skolarikos A, Laguna MP, Alivizatos GE, et al. The role for active monitoring in urinary stones: a systematic review. *J Endourol.* 2010; 24:923-30.
- Preminger GM, Tiselius HG, Assimos DG, et al. Guideline for the management of ureteral calculi. *J Urol.* 2007; 178:2418-34.
- Demehri S, Steigner ML, Sodickson AD, et al. CT-based determination of maximum ureteral stone area: a predictor of spontaneous passage. *AJR Am J Roentgenol.* 2012; 198(3):603-8.
- Jain A, Sreenivasan SK, Manikandan R, et al. Association of spontaneous expulsion with C-reactive protein and other clinico-demographic factors in patients with lower ureteric stone. *Urolithiasis.* 2020; 48:117-22.
- Özcan C, Aydogdu O, Senocak C, et al. Predictive factors for spontaneous stone passage and the potential role of serum C-reactive protein in patients with 4 to 10 mm distal ureteral stones: a prospective clinical study. *J Urol.* 2015; 194:1009-13.
- Park CH, Ha JY, Park CH, et al. Relationship between spontaneous passage rates of ureteral stones less than 8 mm and serum C-reactive protein levels and neutrophil percentages. *Korean J Urol.* 2013; 54:615-8.
- Lee KS, Ha JS, Koo KC. Significance of neutrophil-to-lymphocyte ratio as a novel indicator of spontaneous ureter stone passage. *Yonsei Med. J.* 2017; 58:988-993.
- Senel C, Aykanat IC, Asfuroglu A, et al. What is the role of inflammatory markers in predicting spontaneous ureteral stone passage? *Aktuelle Urologie.* 2022; 53:448-53.
- Wang L, Li Y, Wang C, et al. C-Reactive protein, infection, and outcome after acute ischemic stroke: a registry and systematic review. *Curr Neurovasc Res.* 2019; 16:405-15.
- Bilgin S, Kurtkulagi O, Tel BM, et al. Does C-reactive protein to serum Albumin Ratio correlate with diabetic nephropathy in patients with Type 2 diabetes mellitus? The CARE TIME study. *Prim Care Diabetes.* 2021; 15:1071-4.
- Baruah MP, Bhattacharya B, Baruah UM. C-Reactive protein level can be a better indicator than erythrocyte sedimentation rate in assessing the severity of inflammation and guiding glucocorticoid therapy in subacute thyroiditis. *Indian J Endocrinol Metab.* 2022; 26:328.
- Demirkol ME, Aktas G, Bilgin S, et al. C-reactive protein to lymphocyte count ratio is a promising novel marker in hepatitis C infection: the clear hep-c study. *Rev Assoc Med Bras (1992)* 2022; 68:838-841
- Nuss GR, Rackley JD, Assimos DG. Adjunctive therapy to promote stone passage. *Rev Urol.* 2005; 7:67.
- Hassan M, Hayat S, Shahzad M. Frequency of spontaneous expulsion of lower ureteric stones in patients with raised C-protein. *KJMS* 2019; 12:469.
- Abdullah HO, Abdalla BA, Kakamad FH, et al. Predatory Publishing Lists: A Review on the Ongoing Battle Against Fraudulent Actions. *Barw Med J.* 2024; 2:26-30.

32. Ghillani PP, Motté P, Troalen F, et al. Identification and measurement of calcitonin precursors in serum of patients with malignant diseases. *Cancer Res.* 1989; 49:6845-51.

33. Claeys R, Vinken S, Spapen H, et al. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. In *Advances in Critical Care Testing: The 2002 IFCC-Roche Diagnostics Award 2004*, Springer Berlin Heidelberg, pp. 17-31.

34. Papagiannopoulos D, Whelan P, Ahmad W, et al. Procalcitonin is a strong predictor of urine culture results in patients with obstructing ureteral stones: a prospective, pilot study. *Urol Ann.* 2016; 8:277-80.

35. Jendeberg J, Geijer H, Alshamari M, et al. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. *Eur Radiol.* 2017; 27:4775-85.

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