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Original Article

Evaluating blood and urinary markers for prediction of spontaneous ureteral stone passage

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Abstract: Objectives: The predictive value of blood and serum markers for spontaneous ureteral stone passage (SSP) has been investigated, with no substantial conclusion about their reliability. Therefore, we aim to evaluate the predictive potential of blood and urine laboratory tests for ureteral stone passage. Methods: This prospective, single-center observational study included patients with a solitary obstructing ureteral stone <10 mm diagnosed via non-contrast computerized tomography (NCCT). Definition for SSP was strict including physical evidence of stone passage, follow-up NCCT, or ureteroscopy, and patients were followed until stone passage or urologic intervention occurred. Blood and urine markers, including white blood cells count (WBC), neutrophil-to-lymphocyte ratio (NLR), creatinine, calculated glomerular filtration rates, urine leukocyte esterase and nitrates were collected. Univariate analysis, multivariate analysis, and receiver operating characteristic curves were performed to assess the association between markers and SSP. Results: Cohort consisted of 165 participants who met the inclusion and exclusion criteria with adequate data collection and follow-up. Median age was 54 years with a male to female ratio of 11:5. Most stones were in the mid-distal ureter (56%) and median stone size was 3.5 mm. SSP was observed in 87 patients (53%). None of the blood or urine markers demonstrated a significant association with SSP, and areas under the curves were poor and insignificant. Smaller stone size and distal location significantly predicted SSP. Conclusions: Routine blood and urine markers are not associated with SSP, and their contribution to SSP nomograms might be negligible. These negative results may redirect providers' focus to other factors when predicting SSP.

Keywords: Ureteral stone, spontaneous stone passage, white blood cell count, creatinine, urinalysis

Introduction

The American Urological Association (AUA) guidelines for ureteral stone management recommend observation and a trial for spontaneous stone passage (SSP) in cases of uncomplicated ureteral stones smaller than 10 mm [1]. However, the decision to pursue active management of small ureteral stones when observation is likely to be unsuccessful remains at the discretion of the urologist. Stone characteristics and patient preferences are factors in determining who may benefit from active intervention [2, 3]. While most small ureteral stones pass spontaneously, a significant portion still require intervention [4, 5]. Failure of SSP trial increases the risk of urosepsis, severe pain, and reduced renal function [4]. Procedures like ureteroscopy and shock wave lithotripsy provide immediate management of ureteral stones but are invasive and carry the risk of side effects and complications [6].

Stone size and location have been established as important factors in predicting SSP in patients with ureteral stones, with smaller distal ureteral stones more likely to pass spontaneously [7]. Blood and urine markers have also been investigated as potential predictors, with less consistent results. While some studies have demonstrated that white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and creatinine are predictive of ureteral obstruction and SSP failure, others have not supported these markers' reliability in predicting SSP [3-8]. Several studies have found higher levels of NLR (3.84±0.41) and WBC to be associated with SSP [3, 6].

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Additionally, Özcan et al. identified an association between CRP and SSP, with a cutoff value of 0.506 mg/L predicting failure [5]. Leukocyturia has also been reported as a predictor of SSP failure [4]. However, systematic review and multicenter study found no significant correlation between most inflammatory markers and SSP (P>0.05) [7, 8]. Procalcitonin, a more unique marker, also yielded inconsistent results: while some studies showed that higher levels (above 160 pg/mL) were associated with SSP [3, 4], others reported the opposite [8].

More studies are needed to elucidate the association between blood and urine markers and SSP. This study aims to determine whether common blood and urine markers can predict SSP in patients with ureteral stones.

Patients and methods

Protocol

This is an IRB-approved, prospective, single-center study of patients with acute renal colic diagnosed with an obstructing ureteral stone at our large urban tertiary referral center (IRB # 14-00879). Enrolled patients were adults over the age of 18 with a solitary ureteral stone ≤10 mm in maximal dimension, diagnosed by non-contrast computed tomography (NCCT). Exclusion criteria included functional or anatomical solitary kidney, clinical indications to skip the trial of SSP (such as intractable nausea/emesis, significantly elevated serum creatinine, pain not controlled by oral analgesics, fever, or evidence of infection), and anatomical anomalies. As per study protocol, all patients provided informed consent prior to participation and were followed until spontaneous passage of their ureteral stone or until a urological intervention was required. Based on a previous study by Jain et al., we set the expected SSP rate to be 25% with an acceptable deviation of 10%, and the estimated minimal sample size at a 5% level of significance and 80% power was 132 [9].

Data collection included demographic, clinical, radiological, and laboratory variables, stored in a REDCap database [10]. Blood and urinary markers included WBC, NLR, creatinine, calculated eGFR, urine nitrates, and urine leukocyte esterase, and were retrieved from routinely performed complete blood count (CBC), basic metabolic panel (BMP), and urinalysis. NCCTs were performed using a multi-detector scanner with a reconstructed slice thickness of 2.0 mm and increments of 1.0 mm. The NCCT protocol consisted of scanning from the lung bases to the groin in one breath-hold while patient was placed in a prone position to facilitate the distinction between a stone located at the ureterovesical junction and one located in the bladder. Decisions regarding medical expulsive therapy, pain medications, and imaging for stone surveillance were left to the discretion of the attending urologist.

Outcomes

AUA guidelines were followed, and intervention was offered to patients who failed to achieve SSP within 4-6 weeks of initial symptoms/diagnosis. The final decision regarding intervention was determined using a shared decision-making approach. The study outcome was SSP, defined as physical evidence of stone passage (patient bringing the stone to the office/clinic or providing photographic evidence of stone passage), follow-up NCCT scan confirming the absence of the stone, or ureteroscopy demonstrating that the stone had passed spontaneously. Intervention was defined as either kidney drainage (stents or nephrostomy tubes) or definitive surgery with stone removal. Patients were followed until SSP or surgical intervention were recorded.

Statistical analysis

Categorical variables were described as frequencies and percentages, and continuous variables were expressed as medians and interquartile ranges (IQR) after presenting a non-normal distribution in Q-Q plots and the Shapiro-Wilk test. To evaluate the correlation between blood and urine indicators and SSP, we used univariable and multivariable logistic regression analyses. Receiver operating characteristic (ROC) curves assessed the performance of the blood markers over the range of possible cutoff points for identifying SSP, and the area under the curve (AUC) provided a measure of predictive performance. All statistical analyses were 2-sided, and significance was defined as P<0.05. SPSS software (IBM SPSS Statistics, Version 29, IBM Corp., USA, 2022) was used for all statistical analyses.

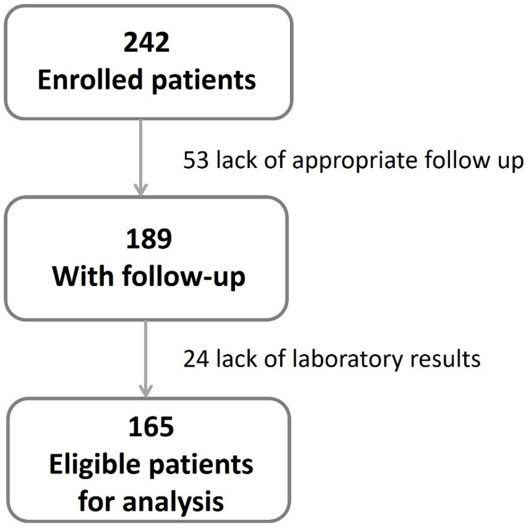

Figure 1. Study flowchart.

Table 1. Baseline and stones characteristics of the study cohort

Variable	Value
Age, years; median (IQR)	54 (41-64)
Male:Female ratio	11:5
Previous stone history, n (%)	79 (48%)
Previous SSP, n (%)	37 (22%)
Previous stone surgery, n (%)	36 (22%)
Stone size, mm; median, (IQR)	3.5 (2.9-4.8)
Stone location, n (%)	
Proximal	73 (44%)
Mid	27 (16%)
Distal	65 (40%)
Laterality	
Right	79 (48%)
Left	86 (52%)

IQR = interquartile range; SSP = spontaneous stone passage.

Results

Patients and participants

The study flowchart is presented in **Figure 1**. Overall, 242 patients met our inclusion and exclusion criteria and were enrolled in the study between April and November 2023. Fifty-three patients were excluded due to a lack of documented SSP by our definitions or noncompliance with follow-up/NCCT. An additional twenty-four patients were excluded due to missing laboratory results (both blood and urine). The study cohort consisted of 165 patients diagnosed with obstructing ureteral stones who were appropriately followed for SSP according to our definitions and had laboratory results that included part or all of the investigated markers. The median age of the cohort was 54 years (IQR 41-64), with a male-to-female ratio of 11:5. A history of previous stones, prior SSP, and previous stone surgery was reported in 48%, 22%, and 22% of the patients, respectively. The stones were located in the proximal, mid, and distal ureter in 44%, 16%, and 40% of the cases, respectively, and the median stone size was 3.5 mm (IQR 2.9-4.8). **Table 1** provides the baseline and stone characteristics of the study cohort.

Blood and urine markers characteristics

Data were partly missing for WBC, NLR, creatinine, and urinalysis in 41, 49, 35, and 9 patients, respectively. The median WBC was 8,800 cells/μL (IQR 7,000-12,400), with a median NLR of 4.48 (IQR 2.96-7.71). The median creatinine level was 0.99 mg/dL (IQR 0.81-1.22), and the median estimated glomerular filtration rate (eGFR) was 74 mL/min/1.73 m^2 (IQR 61-85). The rates of positive urine nitrates and leukocyte esterase were 1% and 20%, respectively (**Table 2**).

SSP prediction

The SSP rate was 53% (87 patients), and univariable analyses demonstrated that none of the blood or urine markers were associated with SSP. Multivariable analysis also confirmed that these markers were not associated with SSP (**Table 3**). Using ROC curves to estimate the diagnostic characteristics of continuous markers and identify cutoffs for predicting SSP, the AUCs for all markers were poor (<0.6) and not statistically significant (**Figure 2**). Combining markers also resulted in low predictive characteristics for SSP, and non-significant results. Among the baseline and stone characteristics, smaller stone size and distal stone location were significant predictors of SSP (OR = 2, P<0.001 and OR = 1.9, P<0.001, respectively), while a history of previous SSP had borderline significance (OR = 1.8, P = 0.1).

Discussion

The role of blood and urine variables in predicting SSP has been investigated before with con-

Table 2. Serum and urine workup results of the study cohort

Variable	Value
Serum	
WBC, count/μL; median (IQR)	8,800 (7,000-12,400)
NLR; median (IQR)	4.48 (2.96-7.71)
Creatinine, mg/dL; median (IQR)	0.99 (0.81-1.22)
eGFR, mL/min/1.73 m^2; median (IQR)	74 (61-85)
Urine	
Positive nitrates, n (%)	2 (1%)
Positive leukocyte esterase, n (%)	31 (20%)

eGFR = estimated glomerular filtration rate; NLR = neutrophils-to-lymphocytes ratio; WBC = white blood count.

Table 3. Univariate and multivariate analyses of blood and urine markers for spontaneous stone passage

Variable	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
WBC	1.07 (0.96-1.19)	0.21	0.98 (0.85-1.13)	0.87
NLR	1.11 (0.99-1.25)	0.06	1.10 (0.95-1.27)	0.18
Creatinine	0.96 (0.84-1.08)	0.48	0.94 (0.72-1.21)	0.62
eGFR	0.99 (0.97-1.01)	0.28	0.99 (0.98-1.01)	0.77
Urine nitrates	10^9 (0-10^{10})	0.99	10^9 (0-10^{10})	1.00
Leukocyte esterase	0.58 (0.26-1.29)	0.18	0.48 (0.18-1.22)	0.12

CI = confidence interval; eGFR = estimated glomerular filtration rate; NLR = neutrophils-to-lymphocytes ratio; OR = odds ratio; WBC = white blood count.

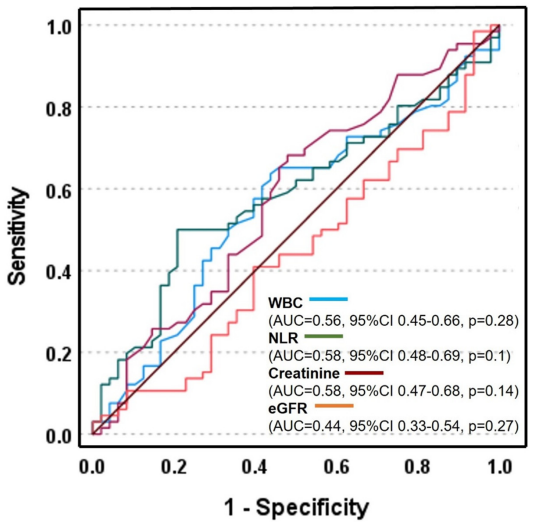

Figure 2. Receiver operating characteristics curves of WBC, NLR, Creatinine and eGFR for predicting SSP. AUC = area under the curve; CI = confidence interval; eGFR = estimated glomerular filtration rate; NLR = neutrophils-to-lymphocytes ratio; SSP = spontaneous stone passage; WBC = white blood cells.

troversial results. Abnormal levels of inflammatory markers, including increased WBC and CRP, have been associated with failed SSP for stones ≤10 mm, suggesting their potential use in clinical decisions [4-6, 9, 11]. In addition, more advanced inflammatory markers such as NLR and procalcitonin have also been found to predict failed SSP [4, 11]. However, a large-scale multicenter retrospective study (MIMIC study) with over 2,500 participants found that neither WBC, neutrophil count, nor CRP helped determine the likelihood of SSP [7]. Our study results showed no association between routine blood or urine workup results and SSP, aligning with the suggestion that these factors cannot be used for its prediction.

Our prospective cohort showed an SSP rate of 53%, a median stone size of 3 mm, and 56% of stones located in the mid-distal ureter. These findings are comparable to those of previous large cohort studies which also did not find association between the inflammatory markers and SSP, and reported SSP rates of 53-74%, a median stone size of 4 mm, and stone location predominantly in the distal ureter (>50%) [7, 8]. The blood and urine laboratory results were mostly in the normal range (e.g., only 1% had positive urine nitrates), similar to previous studies exploring predictors for SSP [6-8]. These characteristics suggest that our cohort was appropriately selected and truly composed of uncomplicated cases eligible for conservative management and SSP trial.

Unlike previous studies, our definition for SSP was relatively strict, including only actual or ureteroscopic evidence of a passed stone or NCCT imaging with no ureteral stone. We believe that the study's objective features contribute to its structure, accuracy, and reliability. A previous study found that the combination of WBC ≥10,000/μL and creatinine ≥0.95 mg/dL can predict the presence of ureteral stones in patients presenting to the emergency department with flank pain, improving the utility of NCCT in the acute setting to prevent unneces-

sary scans [12]. This cohort had similar baseline, stone, and laboratory characteristics, with a median stone size of 4 mm, WBC IQR of 7,500-11,300, creatinine IQR of 0.8-1.2, and positive nitrates in 3% of the patients. We assume that elevated WBC and creatinine may assist in identifying ureteral stone patients presenting with acute flank pain due to the combination of kidney obstruction and induced inflammation at the stone site [13]. However, the predictive value of these markers for SSP among uncomplicated patients with relatively normal laboratory results is negligible.

Distinctive laboratory markers may contribute to the prediction of ureteral SSP, as few studies have indicated that high levels of procalcitonin can predict its failure [4, 14, 15]. Procalcitonin is an acute phase reactant that rises in response to a pro-inflammatory stimulus. It is usually used for respiratory infections and critically ill patients [16], and yet its routine use is not established. We decided to explore routine blood and urine markers (WBC, NLR, creatinine, nitrates, leukocyte esterase) to make the study relevant to daily urologic practice. We believe that the prediction of SSP should be easy, fast, and without additional costs.

Radiological stone characteristics, such as size and location, are well established for predicting SSP. Smaller and more distal ureteral stones have a higher probability of passing [2, 7, 17], as found in our study. Other imaging features, such as ureteral width, thickness, and density, have also been explored for SSP prediction, and nomograms have been suggested [7, 18-20]. However, no tool has gained worldwide popularity for clinical practice. Our results suggest that blood and urine markers do not contribute to such nomograms, and that clinical and radiological factors are more significant for SSP prediction.

Although our study is prospective with strict outcome criteria, there are several limitations. First, due to our strict criteria, 22% of our cohort were dropped from the study. This relatively high drop-off rate might subject our study to selection bias of more compliant patients, resulting in relatively low rates of SSP. Second, we lacked some other routinely used blood markers such as CRP and estimated sedimentation rate. Lastly, although meeting our sample size threshold, we are aware that our cohort size might not be large enough for substantial conclusions. Despite these limitations, our study is prospective, with reliable outcomes, and supports existing literature that blood and urine markers have no role in predicting SSP.

Conclusion

Routine blood and urine workup results, including WBC, NLR, creatinine, nitrates and leukocyte esterase, are not associated with ureteral SSP. Thus, they may not serve as valid markers for predicting the success of SSP trial in uncomplicated cases. These negative results may redirect providers' focus to other radiological and clinical factors that should be used for SPP prediction in uncomplicated cases.

Disclosure of conflict of interest

None.

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