



# Ureteral wall thickness as a significant factor in predicting spontaneous passage of ureteral stones of $\leq 10$ mm: a preliminary report

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## Abstract

**Purpose** To evaluate the clinical significance of ureteral wall thickness (UWT) for predicting spontaneous passage (SP) of uncomplicated ureteral stones of  $\leq 10$  mm.

**Methods** We retrospectively reviewed 418 patients with a diagnosis of uncomplicated ureteral stones who presented to Kori Hospital from 2011 to 2018. The maximum stone diameter and UWT at the stone site were measured from axial computed tomography images. Clinical predictors of 4-week SP were assessed using univariate and multivariate analyses. Receiver operating characteristic (ROC) curve analysis was applied to evaluate the accuracy of factors in predicting SP of ureteral stones.

**Results** Of the 418 patients, 202 (48.3%) spontaneously passed their stones within 4 weeks of their initial visit. Multivariate analysis showed that stone location, stone size, and UWT (odds ratio, 0.40;  $P < 0.001$ ) were independent predictors of 4-week SP. ROC analysis showed that 2.71 mm was the optimal cut-off value for UWT, with a predictive accuracy of 0.83. Low UWT had a significantly higher 4-week SP rate than high UWT (76.4% vs. 14.7%, respectively;  $P < 0.001$ ). In addition, high UWT was associated with a higher risk of stone-related complications within 4 weeks compared with low UWT (16.4% vs. 7.2%, respectively;  $P = 0.0044$ ).

**Conclusions** UWT can serve as a potential predictive factor for 4-week SP and may help physicians to select patients who require immediate interventions among those with  $\leq 10$ -mm ureteral stones.

**Keywords** Predictive factor · Spontaneous stone passage · Ureteral stone · Ureteral wall thickness

## Abbreviations

ESWL	Extracorporeal shock wave lithotripsy
MET	Medical expulsive therapy
NCCT	Non-contrast computed tomography
ROC	Receiver operating characteristic
SP	Spontaneous passage
SRC	Stone-related complication
URS	Ureteroscopy

UTI	Urinary tract infection
UWT	Ureteral wall thickness

## Introduction

Ureteral stones are very common, and 10–15% of the general population is diagnosed once or more in their lifetime [1, 2]. According to guidelines, patients with uncomplicated ureteral stones of  $\leq 10$  mm should be offered conservative treatment including observation or medical expulsive therapy (MET) for 4–6 weeks [3]. However, proper selection of patients with ureteral stones who would most likely benefit from conservative treatment or immediate interventions such as extracorporeal shock wave lithotripsy (ESWL) or ureteroscopy (URS) remains controversial. Therefore, there is an urgent need to identify significant factors with which to accurately predict spontaneous passage (SP) of ureteral

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stones as well as stone-related complications (SRCs) during conservative treatment [3, 4].

Stone size and location are traditionally important clinical factors for predicting SP of ureteral stones during expectant management [5]. The likelihood of SP is greater when the stone is smaller and located more distally in the ureter [5]. However, these factors do not consider stone impaction. Impacted ureteral stones are those that remain unchanged at the same location for a prolonged time period, causing local inflammation, and they do not undergo SP even if small in size [6, 7].

Recent studies showed that ureteral wall thickness (UWT), measured at the stone site by preoperative non-contrast computed tomography (NCCT) could predict the failure of ESWL and the presence of impacted stones during URS [8, 9]. Thus, we hypothesize that the UWT will improve the accuracy of predicting SP and need for immediate intervention for ureteral stones. In the present study, we evaluated the potential ability of UWT to predict SP in patients with ureteral stones of  $\leq 10$  mm. In addition, we investigated the association between the degree of UWT and the incidence rate of SRC.

## Materials and methods

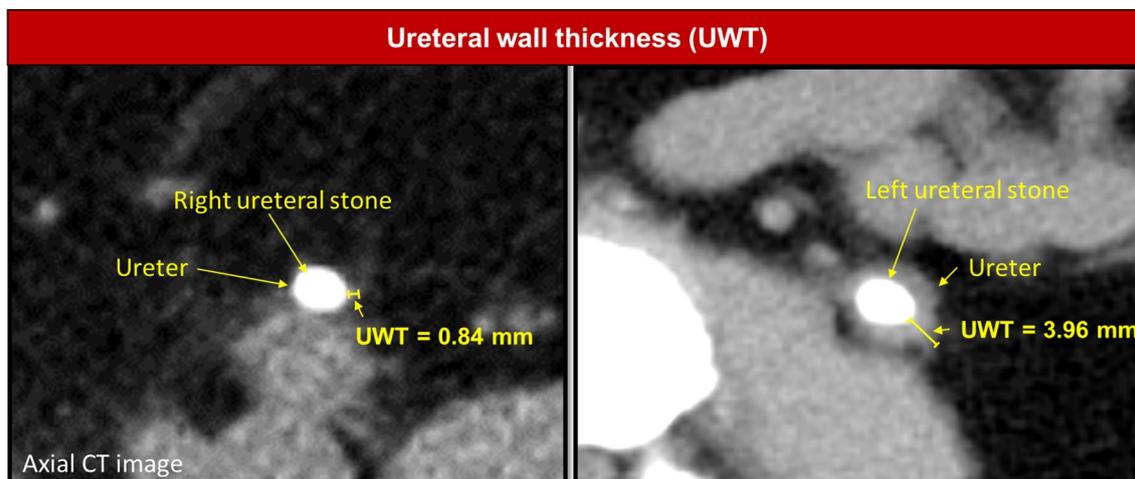
### Patients

After obtaining institutional review board approval, we reviewed the medical records of 752 consecutive patients who presented to Kori Hospital from January 2011 to August 2017 with a diagnosis of urinary stones based on NCCT. We excluded patients with only renal stones,  $> 10$ -mm ureteral stones, multiple ureteral stones, acute renal failure, congenital urinary anomalies, requirement

for immediate insertion of a ureteral stent or percutaneous nephrostomy tube because of a severe urinary tract infection (UTI) at the initial visit, and insufficient clinical data. The remaining 418 patients had complete clinical variables.

### Data collection

All clinical data were collected from the patients' medical records and the hospital's imaging system. These data comprised age, sex (male/female), body mass index, stone side (right/left), history of urinary stones (no/yes), use of MET (no/yes), hydronephrosis (grade 0/1/2/3/4) [10], stone location (proximal/middle/distal), stone size, UWT (Fig. 1), and SRCs secondary to ureteral obstruction by stones. SRCs were defined as persistent renal colic (uncontrolled pain even with the use of adequate analgesics), deteriorated renal function (significant decline in the estimated glomerular filtration rate from baseline), and febrile UTI (fever of  $\geq 38$  °C) [4]. MET was performed using alpha-1 blockers such as tamsulosin at 0.2 mg once daily (Japanese dose), naftopidil at 50–75 mg once daily, or silodosin at 4 mg twice daily at the physicians' discretion [11–13]. The stone and its surrounding tissue were assessed based on axial NCCT images with soft-tissue radiodensity (width, 350; level, 50). The stone diameter was measured as the longest diameter of the stone. The UWT was measured as the point of greatest soft-tissue thickness (ureteral wall  $\pm$  peri-ureteral edema) around the circumference of the stone; this evaluation ranged from the top to the bottom of the stone [8, 9]. All NCCT images were evaluated manually and independently by a radiologist (N.O.) without knowledge of clinical outcomes.



**Fig. 1** Non-contrast computed tomography images of ureteral wall thickness

## Follow-up protocol

Our practice protocol is as follows: patients with uncomplicated ureteral stones of  $\leq 10$  mm are observed by follow-up imaging studies for 4 weeks after the initial visit. SP and SRCs were checked at regular intervals or at emergency visits due to stone-related symptoms. If the patients have not passed their stones by 4 weeks based on follow-up imaging studies, they are offered ESWL or URS, as appropriate. In the present study, SP was defined as the absence of stones on NCCT ( $n = 281$ , 67.2%) or kidney–ureter–bladder radiographs with ultrasound if the stones were radiopaque ( $n = 137$ , 32.8%). Non-SP was defined as the presence of stones on imaging studies after 4 weeks or the need for urgent interventions (drainage/ESWL/URS) due to SRCs within 4 weeks.

## Statistical analysis

All continuous variables are reported as median and range. Clinical variables were compared by the Chi-square test or Mann–Whitney  $U$  test. Univariate and multivariate analyses were performed using a logistic regression model. The

predictive accuracy was analyzed using the area under the receiver operating characteristic curve. The best cut-off point for UWT was determined using receiver operating characteristic (ROC) analysis. The estimated incidence rate was evaluated with the Kaplan–Meier method and log-rank test. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 21.0 (IBM Corporation, Armonk, NY). A two-sided  $P$  value of  $< 0.05$  was considered statistically significant.

## Results

The patients' characteristics are shown in Table 1. Among all 418 patients, a younger age, no history of urinary stones, grade  $< 3$  hydronephrosis, stones at a distal location, smaller stone size, and lower UWT were strongly associated with 4-week SP ( $P < 0.05$  for all). SRCs occurred in 47 patients (11.2%) during 4 weeks of conservative treatment and comprised persistent renal colic ( $n = 14$ , 3.3%), renal function deterioration ( $n = 12$ , 2.9%), and febrile UTI ( $n = 21$ , 5.0%). Immediate interventions then were performed, including the placement of a ureteral stent or percutaneous nephrostomy

**Table 1** Clinical characteristics of 418 patients with ureteral stones of  $\leq 10$  mm

Variable	Total ( $n = 418$ )	Spontaneous passage ( $n = 202$ )	Non-spontaneous passage ( $n = 216$ )	$P$ value
Age, years	56 (13–86)	53 (13–86)	59 (19–89)	$< 0.001$
Sex				0.167
Female	123 (29.4)	53 (26.2)	70 (32.4)	
Male	295 (70.6)	149 (73.8)	146 (67.6)	
Body mass index ( $\text{kg}/\text{m}^2$ )	23.6 (12.8–38.3)	23.6 (16.8–35.5)	23.7 (12.8–38.3)	0.835
Side				0.793
Left	229 (54.8)	112 (55.4)	117 (54.2)	
Right	189 (45.2)	90 (44.6)	99 (45.8)	
History of urinary stones				0.039
No	299 (71.5)	154 (76.2)	145 (67.1)	
Yes	119 (28.5)	48 (23.8)	71 (32.9)	
Medical expulsive therapy				0.094
No	358 (85.6)	167 (82.7)	191 (88.4)	
Yes	60 (14.4)	35 (17.3)	25 (11.6)	
Hydronephrosis				$< 0.001$
Grade 0/1/2	295 (70.6)	176 (87.1)	119 (55.1)	
Grade $\frac{3}{4}$	123 (29.4)	26 (12.9)	97 (44.9)	
Stone location				$< 0.001$
Proximal ureter	184 (44.0)	54 (26.7)	130 (60.2)	
Middle ureter	76 (18.2)	29 (14.4)	47 (21.8)	
Distal ureter	158 (37.8)	119 (58.9)	39 (18.1)	
Stone size (mm)	3.7 (1.0–10.0)	2.7 (0.4–9.2)	4.9 (1.0–10.0)	$< 0.001$
Ureteral wall thickness (mm)	1.9 (0.2–6.7)	1.2 (0.1–4.5)	3.1 (0.2–6.7)	$< 0.001$

Values are presented as median (range) or number (%)

tube ( $n=25$ , 6.0%), ESWL ( $n=3$ , 0.7%), and URS ( $n=19$ , 4.5%). After 4 weeks of conservative management, patients without expelled stones underwent ESWL ( $n=25$ , 6.0%), URS ( $n=124$ , 29.7%) or continuation of conservative management based on the patients' preference ( $n=12$ , 2.9%), while 55 patients (13.2%) experienced SP.

The univariate analysis showed that patients who successfully passed a stone were more likely to be younger ( $P<0.001$ ) have no history of urinary stones ( $P=0.04$ ), have grade  $<3$  hydronephrosis ( $P<0.001$ ), have a stone located in the distal ureter ( $P<0.001$ ), have a smaller stone size ( $P<0.001$ ), and have a lower UWT ( $P<0.001$ ) (Table 2).

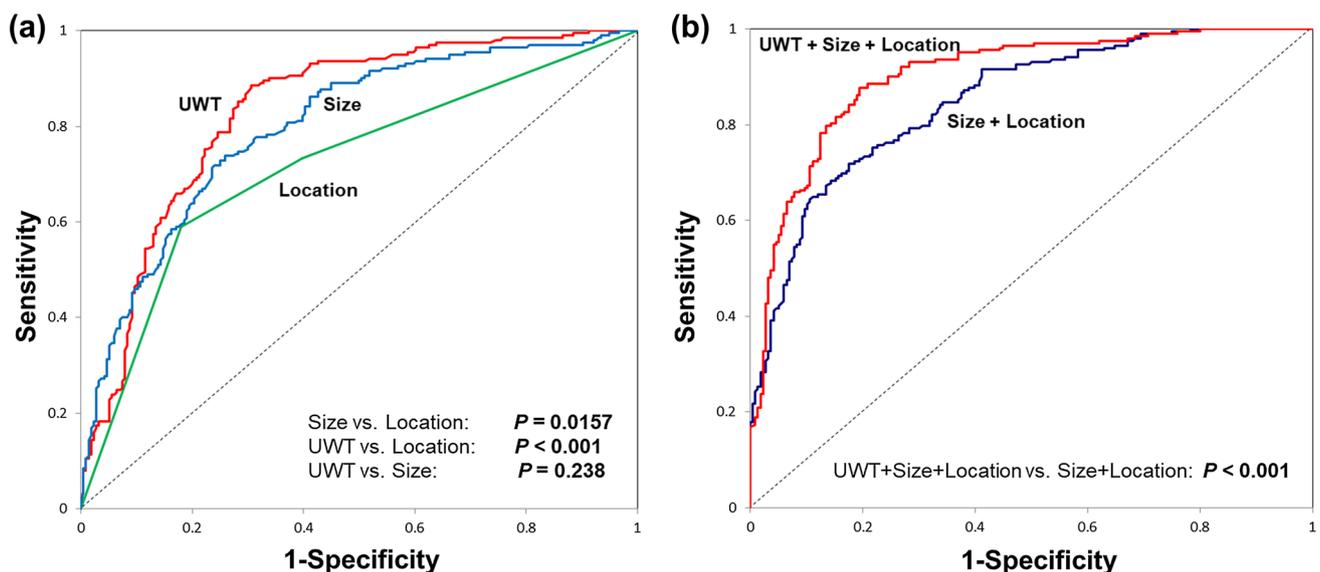
Multivariate analysis showed that the stone location (proximal vs. distal ureter; odds ratio [OR], 5.94;  $P<0.001$ ), stone size (OR, 0.60;  $P<0.001$ ), and UWT (OR, 0.40;  $P<0.001$ ) were independent factors for predicting 4-week SP (Table 2).

ROC analysis was performed to evaluate the superiority of stone size, stone location, or UWT as a 4-week SP predictor. Stone size and UWT showed a significantly higher predictive accuracy than stone location (0.80 vs. 0.72, respectively;  $P=0.0157$  and 0.83 vs. 0.72, respectively;  $P<0.001$ ) (Fig. 2a). Figure 2b shows a significant difference in accuracy between UWT + stone size + stone location and stone size + stone location (0.90 vs. 0.85, respectively;  $P<0.001$ ).

**Table 2** Univariate and multivariate analyses of potential predictive factors for spontaneous stone passage

Variable	Univariate		Multivariate	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age (years)	0.98 (0.96–0.99)	$<0.001$	0.99 (0.97–1.01)	0.39
Sex (female vs. male)	1.35 (0.88–1.91)	0.17	–	–
Body mass index (kg/m <sup>2</sup> )	1.01 (0.96–1.06)	0.65	–	–
Side (right vs. left)	0.79 (0.43–1.45)	0.45	–	–
History of urinary stones (no vs. yes)	0.64 (0.41–0.98)	0.04	0.86 (0.47–1.59)	0.64
Medical expulsive therapy (no vs. yes)	1.60 (0.92–2.79)	0.10	–	–
Hydronephrosis (grade 0/1/2 vs. 3/4)	0.18 (0.11–0.30)	$<0.001$	0.53 (0.27–1.07)	0.08
Stone location				
Proximal ureter	1.00 (reference)		1.00 (reference)	
Middle ureter	1.49 (0.85–2.60)	0.17	1.49 (0.72–3.11)	0.28
Distal ureter	7.35 (4.54–11.88)	$<0.001$	5.94 (3.13–11.26)	$<0.001$
Stone size (mm)	0.53 (0.46–0.61)	$<0.001$	0.60 (0.51–0.72)	$<0.001$
Ureteral wall thickness (mm)	0.28 (0.22–0.37)	$<0.001$	0.40 (0.30–0.52)	$<0.001$

CI confidence interval, OR odds ratio



**Fig. 2** Receiver operating characteristic curve of stone location, stone size, and ureteral wall thickness for predicting 4-week spontaneous stone passage. **a** Each factor. **b** Combined factors

Based on ROC analysis, the best cut-off value of UWT for predicting 4-week SP was 2.71 mm. When using this cut-off value, low UWT had a significantly higher 4-week SP rate than high UWT (71.4% vs. 14.7%, respectively;  $P < 0.001$ ) (Fig. 3a). Regarding the incidence of SRC, the 4-week SRC rate was higher in association with a high than low UWT (16.4% vs. 7.2%, respectively;  $P = 0.0044$ ) (Fig. 3b).

## Discussion

In the present study, we found that UWT was an independent predictive factor for SP of  $\leq 10$ -mm ureteral stones, with a high accuracy of 0.83. When combining UWT with traditional factors such as stone location and size, the predictive accuracy for SP increased from 0.85 to 0.90. Moreover, high UWT was associated with the incidence of SRCs during conservative treatment. These findings suggest that UWT might improve our clinical decision-making at the initial visit regarding whether patients with ureteral stones can be conservatively treated or must undergo immediate interventions. To the best of our knowledge, this is the first report to present the clinical significance of UWT in terms of predicting SP of uncomplicated ureteral stones.

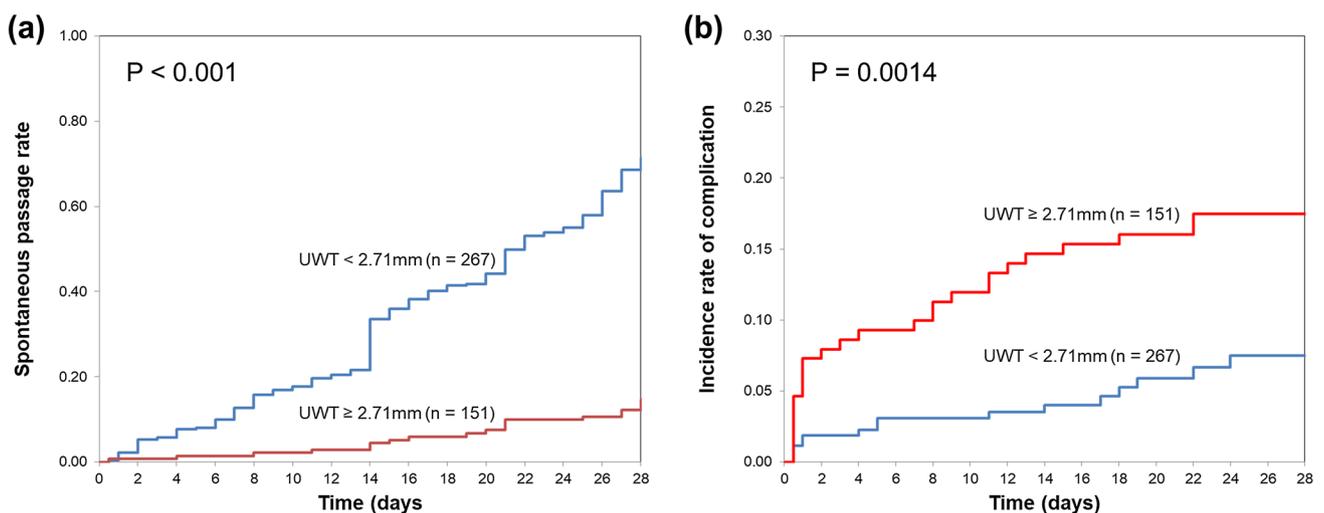
Selection between conservative treatment and immediate surgical intervention is a major issue in the management of ureteral stones. Conservative management is a simpler and more cost-effective treatment than active stone removal [14]; however, it is not free of SRCs such as recurrent pain, urosepsis, deterioration of renal function, and stone impaction [3, 4]. In addition, the optimal duration of conservative management, which has not been clearly elucidated, should be considered according to the individual disease status to

prevent such poor outcomes [3, 4]. Therefore, many efforts have been made to identify predictive factors for estimating SP in the clinical setting.

Stone location is a well-known factor that is associated with SP of ureteral stones. Previously reported SP rates for stones located in the proximal, middle, and distal ureters are 12–48%, 22–60%, and 45–75%, respectively [15]. Moreover, some studies have shown high rates of SP for distal ureteral stones of  $\leq 5$ –6 mm [16]. Similarly, we found that distal ureteral stones were a significant predictor of SP in the multivariate analysis (OR, 5.94;  $P < 0.001$ ), and the possibility of stone passage according to the ureteral location was in the order of the distal, middle, and proximal ureter.

Stone size is another traditional significant factor associated with SP of ureteral stones. Guidelines demonstrate that 68% of  $< 5$ -mm stones and 47% of  $\geq 5$ -mm stones undergo SP and state that watchful waiting is an optional initial approach for  $\leq 10$ -mm ureteral stones [3]. However, the method of stone size measurement is still controversial [17]. Some studies have shown a 13–20% rate of underestimation of the stone burden when reviewing axial imaging only, and Metser et al. [17] and Kadihasanoglu et al. [18] reported that the coronal diameter, not the axial diameter, is a significant factor associated with SP. Before conducting the present study, we compared the superiority between the axial and coronal stone diameter to predict 4-week SP. We found that although the two parameters were equivalent to predicting SP (axial, 0.80 vs. coronal, 0.79;  $P = 0.46$ ), the axial diameter was barely a better predictor than the coronal diameter. Therefore, we applied the axial stone diameter as the stone size in the present study.

Apart from the stone location and size, several other factors been examined as potential predictors of SP.



**Fig. 3** Kaplan–Meier curves showing **a** spontaneous passage rate and **b** incidence rate of complications according to ureteral wall thickness with application of a cut-off value of 2.71

Sfoungaristos et al. [19] found that an increased serum white blood cell count and neutrophil count significantly predicted SP of ureteral stones on multivariate analysis ( $P=0.028$  and  $P<0.001$ , respectively). Özcan et al. [20] demonstrated the potential role of serum C-reactive protein for predicting SP in patients with 4–10-mm distal ureteral stones. The concept of these factors is based on the idea that obstruction by an impacted stone, which is more likely not to undergo SP, or ureteral trauma during the passage of stones may potentially cause a systemic inflammatory response, resulting in an increased white blood cell count, neutrophil count, and C-reactive protein level. However, not all patients with ureteral stones need to undergo blood tests for evaluation of these markers in clinical practice [4]. Moreover, as the authors concluded, development of a systemic inflammatory response remains a theory. Therefore, the pathophysiology at the ureteral level should be studied to elucidate these mechanisms [19, 20].

The current study is the first to demonstrate the clinical significance of the UWT based on NCCT for predicting SP. The UWT may increase due to ureteral edema, polyps, and peri-ureteral edema associated with inflammatory changes caused by stone impaction [6]. We previously investigated the association between UWT on NCCT and the actual endoscopic ureteral status at the impacted stone site. We found that an increased UWT was significantly associated with the presence of stone impaction (OR, 5.43;  $P<0.001$ ) and poor endoscopic findings such as ureteral edema, polyps, ischemic mucosa, and stone fixation in the ureter (all  $P<0.01$ ) [9]. Therefore, we believe that UWT measurement can be a surrogate marker for the presence of stone impaction and a significant factor for predicting SP as well as SRCs secondary to stone impaction.

This study had several limitations. First, the study was a single-institution retrospective study with a relatively small cohort. Second, there might be a potential bias with regard to MET use (14.4%) for UWT and SP. However, we additionally confirmed that MET use (yes vs. no) was not correlated with the degree of UWT ( $P=0.678$ ), and MET was not an independent factor for SP even after adjusting for UWT using multivariate logistic regression analysis (MET: OR, 1.68;  $P=0.133$  and UWT: OR, 0.29;  $P<0.001$ ). These findings indicate that MET was not associated with UWT as well as SP in the present study. Third, UWT was measured manually by a radiologist; the development of an automated measurement system of UWT (e.g., software) is required to ensure reproducibility. Finally, external validation with a larger prospective cohort is needed, because this was a preliminary study. Despite these limitations, our study is the first to show a novel aspect of the use of UWT as a prognostic factor for SP and SRCs during a 4-week follow-up in patients with uncomplicated ureteral stones of  $\leq 10$  mm.

## Conclusion

Our study clearly showed that UWT is a significant factor of SP and is associated with the incidence of complications during conservative management in patients with ureteral stones of  $\leq 10$  mm. UWT can be an excellent predictive marker when counseling patients about their clinical course.

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**Author contributions** TY: project development, data collection and analysis, manuscript writing and editing; TI: manuscript review and editing; TM: data collection and manuscript review; NO: data collection and manuscript review; HK: data collection and manuscript review; and TM: manuscript review and editing.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Ethical approval** This quality assurance audit was approved by the Institutional Review Board.

**Informed consent** Informed consent was not obtained as this study is a retrospective audit.

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