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Original research article

Correlation of the Standard Deviation of Urinary Stone Density by Non-Contrast Computed Tomography and the Shock Wave Lithotripsy Outcomes

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ABSTRACT

The extracorporeal shock wave lithotripsy (ESWL) is the first line treatment for stone smaller than 20 mm. Many parameters which are measured from medical images have been widely studied as a predictor of ESWL outcomes. This study aims to determine the utility of standard deviation (SD) of stone density or stone heterogeneity index (SHI) from Non-Contrast Computed Tomography (NCCT) for predicting the outcomes of ESWL. This retrospective study included 61 patients with 71 stones smaller than 20 mm, who had preoperative NCCT and ESWL session at Thammasat University Hospital between January 2010 and November 2017. The stone size, mean and SD of stone density were recorded. All stones were assigned to two groups, low and high SHI, using mean value of measured SD. The success rate of ESWL outcomes of these two groups were compared. The success ESWL outcome in the stone with high SHI was significantly higher than in stones with low SHI. The univariate logistic regression model showed that stone size and SHI were associated with successful outcome (OR=0.939, 95% CI 0.847 to 1.041, p-value=0.23 and OR=2.940, 95% CI 1.113 to 7.771, p-value=0.03 respectively). The multivariate logistic regression model revealed that they have no independent impact on the successful outcome. In conclusions, stone with high SHI may suggested higher success rate of ESWL especially in a small stone size (smaller than 10 mm) and regardless of the mean stone density.

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Keywords: ESWL; NCCT; Standard deviation; Stone density; Urinary tract stone

1. Introduction

Urinary tract stone is a common health problem in Thailand and worldwide. Improper management can cause chronicity of the disease, unwanted complication, prolonged hospitalization and further expense to patient. Recently, the non-contrast computed tomography (NCCT) becomes popular for stone detection. ACR Appropriateness Criteria® for acute onset flank pain with suspicious of stone disease also suggested low dose NCCT to be an initial imaging modalities of choice [1]. In point of fact, it has higher reliability of stone localization and size determination than KUB radiograph or ultrasonography. It also provides additional information such as stone density and complication related to stone.

Extracorporeal shock wave lithotripsy (ESWL) has been proved to be an effective non-invasive treatment for urinary tract stone since 1980s [2]. It revolutionized the stone treatment and became the first line treatment for small stone (smaller than 20 mm). The advantages of ESWL includes no need of hospitalization, low risk of complication without ureteric stenting [3]. However, some stones can be resistant to ESWL. The failure of ESWL will necessitates multiple sessions or alternative intervention which leads to increased undesirable complications such as acute renal injury and hemorrhage as well as additional medical expense to patient. Several clinical factors have been proposed to predict ESWL outcomes. Patient with favorable factors for ESWL will lead to successful outcomes and can prevent unwanted complication. Some of these clinical factors can be sorted out form readily provide medical imaging. Stone size is the most influent factor to predict ESWL outcomes [4]. It can be easily retrieved from any images in picture archiving and communication system (PACS). Mean stone density is another potential independent predictor of ESWL outcomes from many studies [5-12]. It is an average value of the density of all pixels of the targeted stone and can be easily measured from images of NCCT on the PACS. Unfortunately, mean stone density cannot represent the diversity of each pixel density within the targeted stone. Other than mean value, the PACS also provides other statistic values which are minimum,

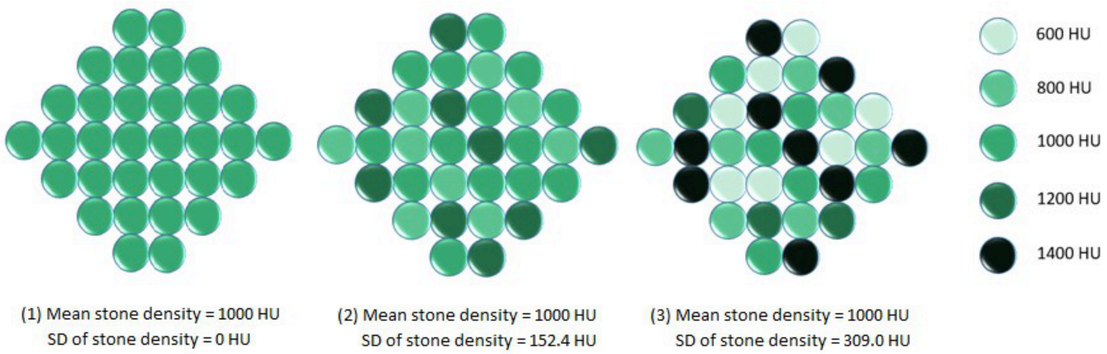

Fig. 1. Illustration of the heterogeneity of the stone density. Each stone density heterogeneity can be different from others even if they have a same mean stone density. Adapted from "Stone heterogeneity index as the standard deviation of Hounsfield units: A novel predictor for shock-wave lithotripsy outcomes in ureter calculi" by Lee et al. [14].

maximum, and standard deviation (SD) of the density. Statistically, the SD represent spreading of values within the certain set of data. So a higher SD indicates that the measured data have wider range of values distribution. In the same way, a higher SD of measured stone density may suggest more heterogeneity of density within the stone. The SD of stone density stone or herterogeniety index (SHI) can predict the heterogeneity of stone composition [13, 14]. So that it may be a potential imaging parameter for stone fragility. The heterogeneity of urinary stones can differ even if they have an equal mean stone density as demonstrated in Fig. 1. The more heterogeneous stone, the more fragile it is. There by the SD of stone density or SHI may play an important role for prediction of ESWL outcomes besides stone size and mean density. Objective of our study is to determine the utility of SHI from NCCT for predicting the outcomes of ESWL.

2. Materials and Methods

2.1 Data collection

This study is a retrospective study conducted at Thammasat University Hospital, Pathum Thani, Thailand. The ethics board committee approved the study protocol (Approval No. MTU-EC-RA-0-131/60) before embarking on this study. Patients who had pre-treatment NCCT for urinary stones and underwent ESWL between January 1, 2010 and November 30, 2017 at Thammasat University Hospital were collected.

Inclusion Criteria

Age more than 15 years old, patients with a pretreatment NCCT imaging, renal/ureteric stones size 4-20 mm in maximal diameter and patients with post-treatment imaging.

Exclusion Criteria

Patients with staghorn stones, anatomical anomalies of the kidneys or renal transplantation, and patients who lost to follow up.

A total of 61 patients with 71 CT-opaque stones were included to the study. Stone size, mean stone density and SHI were measured on pre-operative NCCT images on PACS (Synapse, Fuji Medical Systems). All stones were assigned to two groups, low and high SHI of stone density by using mean value of SD of measured stone density as cut point.

2.2 ESWL

All patient underwent ESWL session with an electroconductive lithotripter (Dornier Compact Sigma lithotripter, Dornier MedTech GmbH, Wessling, Germany) under fluoroscopic guidance. The number of shock waves per ESWL session are about 5000 shock waves per session at a rate of less than 90 shock waves per minute.

2.3 CT techniques and stone characteristics

All NCCTs were performed with institutional single-energy low-dose protocol in one of our two CT machines (256-slice Brilliance iCT, Philips healthcare, and SOMATOM Definition AS, Siemens healthineers). The tube voltage was set at 100 kVp. The tube current was adjusted depending on patient's body mass, using machine's automatic tube current modulation.

Stone characteristics, consisting of location, size, mean stone density, and SHI, were recorded. The longest stone diameter was recorded as stone size. It was measured on any imaging plane, either axial coronal or sagittal planes, which stone has its maximum diameter. Measurement of stone density was made by using free-hand region of interest (ROI) on the same image that was for measuring stone size. All ROIs were drawn on by tracing the external contour of the stone, avoiding the surrounding soft tissue, as shown in Fig. 2. Mean and SD of stone density of each stone were retrieved from the same ROI. All measurements were done by one radiologist

(P.K.) and performed on bone-windowed images (window level of 400 and window width of 2000) with proper magnification.

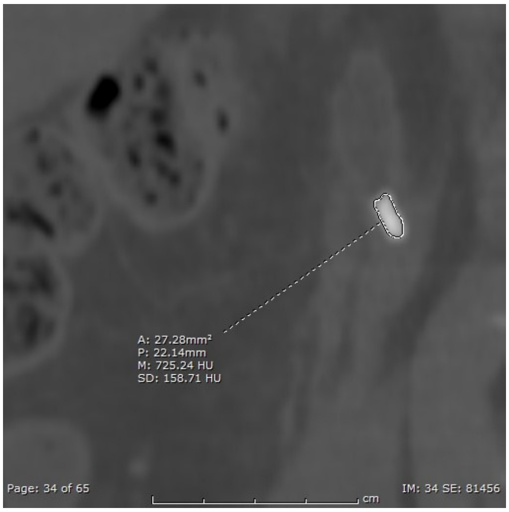

Fig. 2. Measurement of stone density. Free-hand ROI for measurement of stone density was drawn along the external contour of the stone on the magnified bone-windowed image of the longest stone diameter, excluding the surrounding soft tissue. M is mean stone density and SD is standard deviation of stone density.

2.4 ESWL outcomes

The outcomes of ESWL were classified as success or failure. The success outcome was called when patient has stone-free period or residual fragments less than 4 mm without symptoms at least 3 months after ESWL, as shown in Fig. 3. The failure outcome was defined when patient has residual stone fragments greater than or equal to 4 mm as confirmed by a follow up plain film, ultrasonography or CT, as shown in Figs. 4 and 5.

2.5 Statistical analysis

The categorical values (location of stone and ESWL outcome) were presented in number (%). While, the continuous values (stone size, mean stone density and SHI) were presented as mean ± SD. Student's *t*-test was used for comparing stone size, mean stone density and SHI between low and high SHI groups. Fisher's Exact test was used for comparing success ESWL rate between low and high SHI groups. Univariate and multivariate logistic

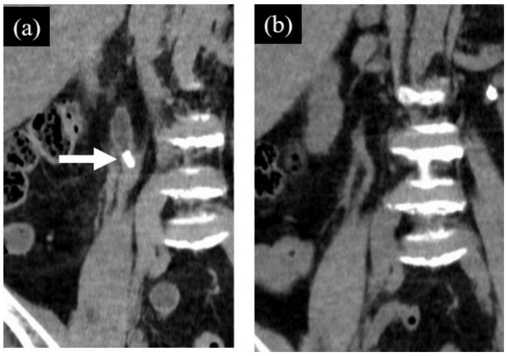

Fig. 3. CT imaging of a 61-year-old woman with successful ESWL outcome. A pre-operative imaging (a) showed a 10.4-mm right proximal ureteric stone (arrow). A follow-up imaging after ESWL treatment (b) showed disappearance of the aforementioned stone.

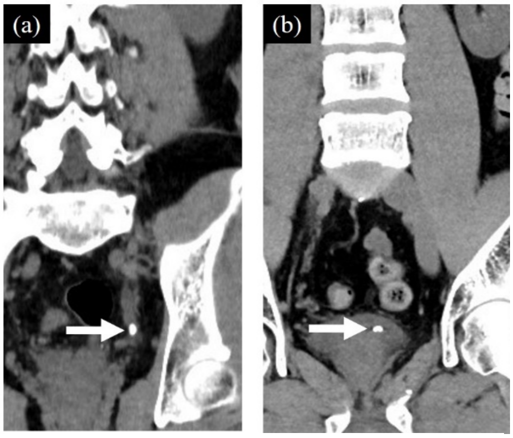

Fig. 4. CT imaging of a 34-year-old man with failure ESWL outcome. A pre-operative imaging (a) showed a 5.9-mm left distal ureteric stone (arrow). A post-operative imaging (b) showed inferior migration of the aforementioned stone to the left ureterovesical junction (arrow).

regression models were used for evaluating significant factors of the successful outcome. All variables with *p-value* <0.25 on the univariate analysis were entered into the multivariate analysis to evaluated independent factors (*p-value* < 0.05). Student's *t*-test (two-tailed, independent) was used for comparison of SHI in ESWL outcome according to the stone size and mean stone density. Pearson's Chi-squared test was used for comparison of stone size, mean stone density, SHI and successful outcome in stone with low and high SHI groups. *p-value* < 0.05 was used to determine statistical significance. IBM SPSS (version 24) were used for all statistical analyses.

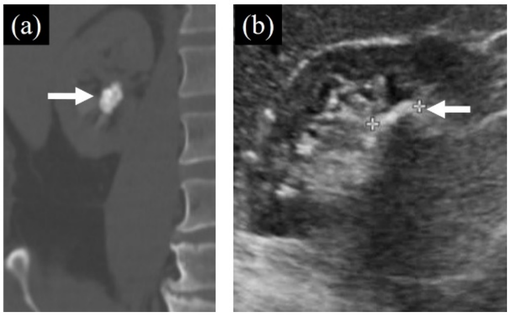

Fig. 5. A 54-year-old man with failure ESWL outcome. A pre-operative imaging (a) showed an 18.8-mm right lower calyceal stone (arrow). A post-operative follow-up KUB ultrasound (b) showed a 13.5-mm stone at right lower calyx (arrow).

3. Results and Discussion

3.1 Demographic analysis

The distribution of urinary stone locations, as shown in Table 1, are consisted of 18 cases of proximal ureteric stones (25.3%), 2 cases of mid ureteric stones (2.8%), 5 cases of distal ureteric stones (7.0%), 9 cases of upper calyceal stones (12.7%), 7 cases of intercalyceal stones (9.9%), 22 cases of lower calyceal stones (31.0%), 6 cases of renal pelvic stones (8.5%) and 2 cases of ureteropelvic stones (2.8%).

3.2 Stone characteristic

The Table 2 demonstrates stone characteristics. The mean stone size is 9.62±4.72mm. The mean stone density is 591.94±265.79 HU and the mean SD of stone density is 155.05±88.68 HU.

Table 1. Location of stones in two study groups.

Location	Total (%)	Stone with low SHI group (%)	Stone with high SHI group (%)
Proximal ureter	18 (25.3)	4 (10.0)	14 (45.2)
Mid ureter	2 (2.8)	2 (5.0)	-
Distal ureter	5 (7.0)	3 (7.5)	2 (6.5)
Upper calyx	9 (12.7)	5 (12.5)	4 (12.9)
Interpolar calyx	7 (9.9)	6 (15.0)	1 (3.2)
Lower calyx	22 (31.0)	14(35.0)	8 (25.8)
Renal pelvis	6 (8.5)	5 (12.5)	1 (3.2)
UPJ	2 (2.8)	1 (2.5)	1 (3.2)

The total success rate is 46.5%. All stones were assigned to low and high SHI groups, using the mean SD of stone density as a cut point. There is no significant difference of stone size and mean stone density between the two groups. The success rate in the high SHI group is significantly higher than in the low SHI group (61.3% vs. 35.0%, *p-value* = 0.03).

Results of univariate and multivariate logistic regression models on successful outcome in patients with urinary tract stone are demonstrated in Table 3. For the univariate logistic regression model, the result showed that stone size and SHI were associated with successful outcome (OR= 0.939, 95% CI 0.85 to 1.04, *p*-value=0.23 and OR=2.94, 95% CI 1.11 to 7.77, *p-value*= 0.03, respectively). Nonetheless, they had no independent impact on the success outcome after entry these factors into the multivariate logistic regression model.

Results of comparison of SHI in ESWL outcome according to the stone size are shown in Table 4. Stones size less than 10 mm with successful ESWL outcome have significant higher SHI than those with failure outcome (156.45±66.88HU vs. 79.55±93.05 HU, *p-value*= 0.008). There is no significant difference of SHI between successful and failure outcome in stones size greater than or equal to 10 mm.

Table 5 shows comparison of SHI in ESWL outcome according to the mean stone density. SHI was significantly higher in stones with successful outcome than in stones with failure outcome regardless of mean stone density.

3.3 Discussion

Multiple factors have an impact on successful ESWL outcomes. Stone fragility is the one of those important factors. Theoretically, stone composition and internal structures have a strong influence on stone fragility [15]. But it is impossible to determine stone composition and internal structures before ESWL session. Mean stone density has been studies as a parameter for prediction of stone composition, internal structures and fragility, as well as a predictive factor on ESWL outcomes. Other CT parameters such as maximum stone density, stone size, stone burden and skin-to-stone distance (SSD) have been also studied. Most studies demonstrated significant association between mean stone density and ESWL success rate. Whereas the role of other CT parameters remains controversial. Study of Deepti et al. showed 100% success rate of ESWL in stone with attenuation less than 500 HU [5]. There are similar results in other studies by Massoud et al. [7], Sultan et al. [9], Williams et al.[16], and Joseph et al. [17]. Gupta et al. studied relationship between mean stone density and ESWL outcomes [18]. They compared the mean density with the number of ESWL sessions and clearance. They found that the worst outcome was in patients with a mean stone density greater than 750 HU and a stone diameter larger than 11mm. They also analyzed that the stone density was a stronger predictor of ESWL outcome than stone size alone. So that mean stone density has been widely used for characterize stones in urinary tract and predict treatment outcomes.

As priorly mentioned above, stone composition and internal structures are strong predictors of treatment outcomes but nearly impossible to determine before intervention. Furthermore, mean stone density cannot establish the heterogeneity of stone density, as illustrated in Fig. 1. Contrarily, SD of stone density or SHI potentially reflect the heterogeneity of the stone density which refer to heterogeneity of stone compositions and internal structures. In prospective study of Zhang et al., they analyzed stone composition by infrared spectroscopy in 625 patients [19]. They found that more than half of the stones (62.6%) in their study had mixed chemical compositions and different internal structures. This result can explain the differences in SD of stone density. Another study of Tailly et al. also found that combining mean and SD of stone density from preoperative CT imaging increased positive predictive value and had higher likelihood ratios for identifying a stone composition [13].

The concept of urinary stone heterogeneity based on measurement of SD of stone density or SHI in NCCT was priorly introduced by Lee et al. [14]. Their study showed higher success outcome in the high SHI group than in the low SHI group (74.3% vs. 63.9%, P = 0.008 in one-session success rate and 70.5% vs. 62.3%, P = 0.043 in one-session stone-free rate). From their univariate and multivariate logistic regression models for success ESWL outcomes, they also found that stone size, mean stone density and SHI were an independent predictive factor. But in this current study, the SHI, mean stone density and stone size are not independent predictors of ESWL outcomes. We thought that because of the very small sample size undermine the internal and external validity of the study. A larger sample size will expand the power of the study, which will allow study's ability to detect a statistically significant difference.

In term of stone size, some studies suggested that the larger stone (i.e. greater than 10mm) will be resistive to ESWL [11, 18]. We found that SHI are significantly higher in stones with success outcome only if it is smaller than 10 mm (Table 4). But in recent study by Cui et al., they developed a statistical model for its ability to predict the likelihood of a successful ESWL outcome, which included size-related and other CT texture analysis variables [20]. They stated that besides size-related variables, other variables did not increase the predictive ability of their model. However, we still believe that the SHI can be the additional factor to stone size to predict the treatment outcomes.

In many previous studies, urinary tract stones with higher mean stone density (i.e. more than 1000 HU) have been expected to be resistant to ESWL [5-12, 18]. The results of this current study quite disagree with those. We found that stone with success ESWL outcome has significant higher SHI regardless of their mean stone density (Table 5). So the stones with higher SHI can be aimed for favorable ESWL outcome without consideration of their mean stone density.

Other limitations in this study, other than small sample size, include retrospective design which effect to the significant difference of statistical analysis. We also studied both renal and ureteric stones. The anatomical considerations of renal stone, particularly location stone in calyx or renal pelvis and infundibulopelvic angle, also have an impact on ESWL outcomes.

There is no analysis of chemical composition of the stone in vitro in our center. Consequently, chemical composition cannot be confirmed and correlated. Lastly, patient-related factors that could affect the ESWL outcome such as BMI and SSD were not included.

Further prospective studies with a larger sample size are mandatory to confirm our idea on the relationship between SHI and ESWL outcomes. The cut-off value of SHI for determining suitable candidates for ESWL treatment should be settled. In addition, direct experimental studies of correlation between SD of CT density and chemical compositions and internal structure of the urinary tract stone will be completing the understanding of the clinical significance of the stone heterogeneity index (SHI).

4. Conclusion

The success rate of ESWL in the stone with high SHI was significantly higher than in the low SHI group. The SD of stone density or SHI was a significant predictor for successful outcomes of stone size less than 10 mm and there was a significant difference in SHI between successful and failure treatment groups regardless of mean stone density. However, the SHI did not have independent impact on the successful outcome.

Table 2. Comparison of stone characteristics in two study groups
SHI: stone heterogeneity index. [a]Student T-test. [b]Fisher's Exact test.

	Total	Stone with low SHI	Stone with high SHI	*p-value*
Number of stones	71	40	31	
Stone size (mm)	9.62±4.72	8.68±4.63	10.83±4.63	0.797[a]
Mean stone density (HU)	591.94±265.79	471.56±237.54	747.28±217.32	0.543[a]
SHI (HU)	155.05±88.68	93.02±38.43	235.09±68.41	0.030*[a]
Success rate (%)	33 (46.5%)	14(35.0%)	19 (61.3%)	0.033*[b]

Note: * indicates statistical significance.

Table 3. Univariate and multivariate logistic regression models on successful outcome in patients with urinary tract stone.

Successful outcome	**Univariate**			**Multivariate**[a]		
	OR	**95%CI**	***p-value***	**OR**	**95%CI**	***p-value***
Stone size (mm)	0.939	0.847-1.041	0.233*	0.893	0.792-1.006	0.062
Mean stone density (HU)	1.000	0.999-1.002	0.637			
SD of stone density (HU)	2.940	1.113-7.771	0.030*	1.926	0.369-10.044	0.436

Note: * indicates statistical significance.

Table 4. Comparison of SHI in ESWL outcome according to the stone size.

		N (%)	**SHI (HU)**	***p-value***
stone size < 10 mm		44		
ESWL outcome	Success	24 (54.55%)	156.45±66.88	0.008*
	Failure	20 (45.45%)	79.55±93.05	
stone size ≥ 10 mm		27		
ESWL outcome	Success	18 (66.67%)	193.3±112.85	0.068
	Failure	9 (33.33%)	128.55±75.56	

Note: * indicates statistical significance.

Table 5. Comparison of SHI in ESWL outcome according to the mean stone density.

		N (%)	**SHI (HU)**	***p-value***
Mean stone density< 1000 HU		65		
ESWL outcome	Success	30 (46.2%)	158.85±83.34	0.016*
	Failure	35 (53.8%)	106.60±80.47	
Mean stone density≥ 1000 HU		6		
ESWL outcome	Success	3 (50%)	250.10±73.45	0.016*
	Failure	3 (50%)	175.0±120.05	

Note: * indicates statistical significance.

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