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ABDOMINAL IMAGING

ORIGINAL ARTICLE

The usefulness of the Hounsfield unit and stone heterogeneity variation in predicting the shockwave lithotripsy outcome

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PURPOSE

This study aimed to evaluate the use of stone density variation coefficient (SDVC) as an indicator of stone heterogeneity and previously reported parameters for predicting extracorporeal shock wave lithotripsy (ESWL) outcome in urinary calculi. Moreover, a new formula that could be used to predict ESWL success was suggested.

METHODS

A total of 850 patients, who underwent the first session of ESWL for urinary stones between 2015 and 2020, were examined, and 220 eligible patients were included in the study. Stone density variation coefficient and other parameters associated with stone attenuation values and stone size parameters were studied as potential predictors based on noncontrast computed tomography (NCCT). Extracorporeal shock wave lithotripsy success was considered after 3 months by radiography or NCCT. Logistic regression analysis was performed to determine the factors contributing to treatment success.

RESULTS

For the 220 patients, ESWL success rate was 39.5%. The receiver operating characteristic analysis showed that SDVC (AUC=0.82; 95% confidence interval [CI]: 0.76–0.87; $P < .001$), mean stone density (AUC=0.81; 95% CI:0.75–0.87; $P < .001$), maximum stone density (AUC=0.70; 95% CI: 0.63–0.78; $P < .001$), stone volume (AUC=0.70; 95% CI: 0.62–0.77; $P < .001$), and major diameter (AUC=0.67; 95% CI: 0.59–0.74; $P < .001$) had significant prediction accuracy from high to low. Additionally, SDVC was found to be successful in predicting ESWL success, especially for patients with high mean stone density (OR=10; 95% CI: 3.55–28.57; $P < .001$). The logistic regression model, in which the "stone disintegration probability" (SDP) formula was found, correctly predicted ESWL success with a single session by 79.1%.

CONCLUSION

In conclusion, size and attenuation values were predictors of treatment success, and the best predictor was SDVC. Evaluation of SDP formula prior to ESWL could predict treatment outcomes and facilitate the decisions regarding treatment strategies.

Extracorporeal shockwave lithotripsy (ESWL) remains as one of the effective and safe treatment strategies for urinary stones because of its noninvasiveness and simplicity.[1,2] Despite many advantages of ESWL, it has a lower stone-free rate compared with ureteroscopy or percutaneous nephrolithotomy.[3] Some calculi are found to be completely or partially resistant, and the failure of the first ESWL may cause the continuation of symptoms and prolonged ureteral obstruction, thus requiring ancillary therapy procedures that increase medical costs.[4] Therefore, it is important to identify the predictive factors of ESWL outcomes and patients with maximum benefit prior to treatment to provide an appropriate treatment plan for patients with urolithiasis.

Radiomics is a field of medical study that aims to use quantitative data from medical images for predicting clinical outcomes. Several parameters, such as stone location, stone size, and multiplicity, were reported as the predictors of ESWL success.[5] In addition, an increasing number of studies explored the parameters measured from noncontrast computed tomography (NCCT), such as mean stone density (MSD), maximum stone density

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(MXSD), standard deviation of stone density (SDSD), and skin–stone distance, as indicators to predict ESWL success.[6-11]

Previous studies showed that ESWL success was also affected by stone heterogeneity.[6,12,13] An *in vitro* study showed that the internal structure of calcium oxalate monohydrate stones in computed tomography (CT) images predicted lithotripsy fragility.[12] Defining a CT parameter that represents stone heterogeneity is required due to the lack of accepted parameters in NCCT that demonstrate stone heterogeneity. The standard deviation (SD) is a statistical parameter that measures the dispersion of a dataset relative to its mean. A high SD indicates that the values tend to be far from the mean, which may reflect heterogeneity in stone composition. As shown in Figure 1, the stone composition may differ even if they have a similar SD or mean. Therefore, SD cannot be considered independently of the mean. Therefore, it was postulated that the variation coefficient of stone density (SDVC) calculated using MSD and SDSD could be more accurate to show stone heterogeneity, and heterogeneous stones might be more fragile than homogeneous ones.

This study aimed to evaluate SDVC as one of the predictors of ESWL success after a single session, as well as previously reported parameters including MSD, MXSD, SDSD, skin-stone distance, and stone volume.

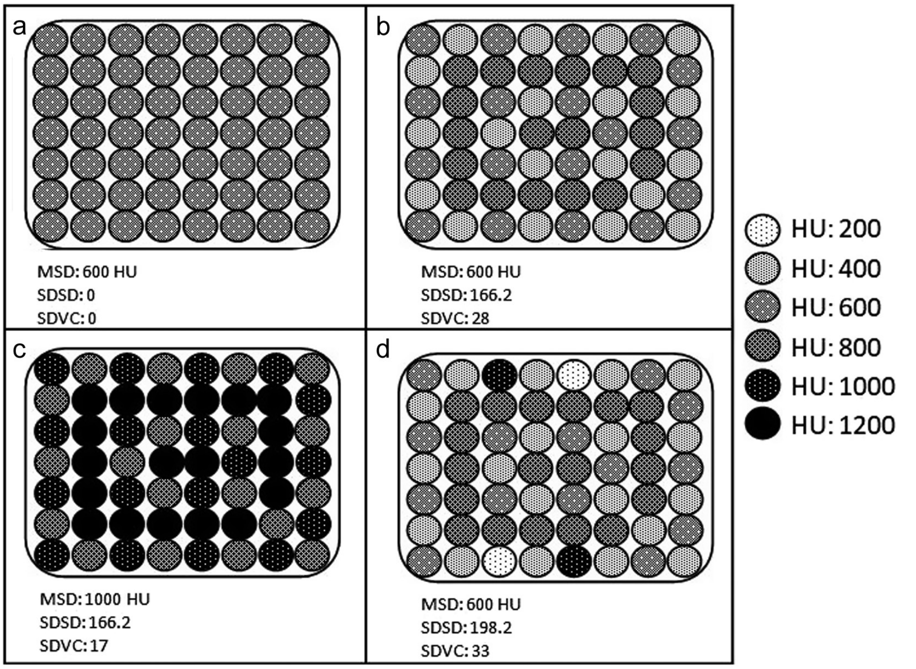

Figure 1. a-d. The compositional heterogeneity of a stone is shown in the schematic diagram. When stones with the same mean stone density (MSD) values are evaluated **(a, b, d)**, increases in the standard deviation of stone density (SDSD) and variation coefficient of stone density (SDVC) values are observed in parallel with stone heterogeneity. The SDSD value alone may be sufficient to predict the heterogeneity and fragility of stones with the same MSD value. However, considering the varying MSD values **(c, b)**, SDSD alone may be misleading in assessing the heterogeneity and fragility of the stone, while SDVC provides a more accurate assessment.

Methods

The database of patients who had undergone the first session of ESWL at our institution between January 2015 and March 2020 was retrospectively searched. A total of 850 patients were found during this time interval. The inclusion criterion for this study was adults (>18 years) who had undergone NCCT prior to ESWL with solitary renal and ureteral radiopaque stones and stones with a diameter between 4.0 and 30.0 mm. The exclusion criteria were patients whose outcomes after treatment were unknown, patients for which NCCT was not obtained before the first ESWL session, patients who had a history of prior treatment and residual calculus, and patients whose treatment success could not be demonstrated radiologically after the ESWL procedure using x-ray or NCCT. Thus, 220 patients (69 women and 151 men) with ureteral and renal stones were found to be suitable for the present analysis (Figure 2).

Main points

- The variation coefficient of stone density value accurately reflected the heterogeneity of the stone composition and predicted the success of shockwave lithotripsy (ESWL) in the best way compared with other noncontrast CT parameters.
- Stone density variation coefficient was the best predictor of ESWL success, especially for stones with low success rates due to high mean stone density values.
- The newly defined stone disintegration probability formula directly calculated the probability of treatment success.
- ESWL success could be predicted by radiomics obtained from noncontrast CT.

ESWL and imaging

The ESWL procedure was performed on an outpatient basis using a Modularis Vario lithotripter (Siemens AG Healthcare). The total shock wave energy and the number of shock waves for all patients were obtained from the procedure records. The Toshiba Aquilion scanner (64-slice, Toshiba Medical Systems) was used for NCCT with the following scan parameters: 120 kV, 150-200 mAs, pitch factor 0.6 mm, collimation width 0.6 mm, and slice thickness 2-3 mm. All images were examined with a free-hand trace tool on the workstation using Sectra (IDS 7, 21.2.9.6220, Linkoping) imaging program to determine Hounsfield unit (HU) values. This study was approved by the Institutional Clinical Research Ethics Committee (Approval No. 2020/7-28). However, informed consent was not obtained from the patients due to the retrospective nature of the study.

Outcome parameters

The patient age, sex, stone side, stone location (stones in calyces and renal pelvis location were evaluated as renal stones, and stones in proximal and middle ureter location were evaluated as ureteral stones), stone size (long diameter [x] and short diameter [y] on axial images and longitudinal diameter [z] on coronal images, maximum stone length in any dimension and volume), skin-stone distance, waist circumference, MSD, MXSD, SDSD, and SDVC were evaluated. As described previously, skin-stone distance was calculated as the mean distance by measuring three distances (0°, 45°, and 90°) from the center of the stone to the skin.[14] Waist circumference was measured by taking the belly button line as a reference point from NCCT images. The

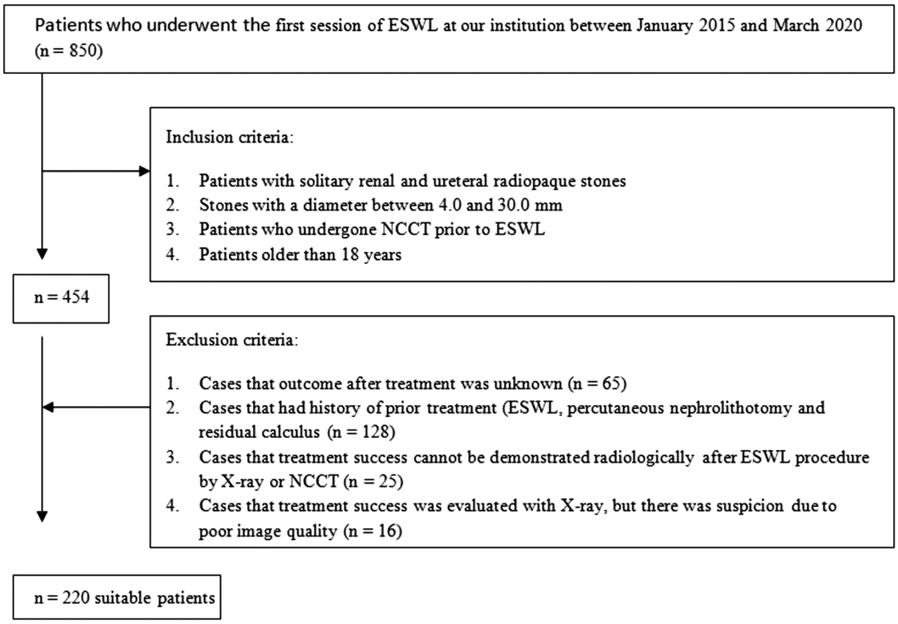

Figure 2. Flow diagram of the study population (n = 220) ESWL, extracorporeal shockwave lithotripsy; NCCT, noncontrast computed tomography.

stone volume was calculated by dividing the stone's three-axis diameter multiplied by two ($x \times y \times z/2$). Hounsfield unit was measured using bone windows (window width 2500/window level 500) on the magnified axial NCCT image from the point of the largest stone diameter by a free-hand trace of the stone edge without including adjacent soft tissue (Figure 3). Mean, SD, and maximum HU in the region of interest were defined as MSD, MXSD, and SDSD, respectively, and SDVC was calculated as SDSD/MSD) ×100.

The success of the procedure was determined using NCCT or good-quality abdominal x-ray examination within 3 months after the first ESWL treatment. While evaluating the treatment response with x-ray, suspicious cases were excluded from the study. Patients who were stone-free or had residual stone fragments <4 mm (clinically insignificant residual fragments) with a single ESWL session formed the success group. Patients who had residual fragments ≥4 mm and required multiple ESWL formed the failure group.

Statistical analysis

Statistical analysis was carried out for comparing ESWL failure and success groups. The normal distribution of the results was checked using the Kolmogorov–Smirnov test. Continuous variables were summarized as median and minimum–maximum (min–max) for nonparametric data or as mean and SD for parametric data. According to the normality test, the results were analyzed using the independent samples t test or Mann-Whitney U test. Categorical variables were compared using Pearson's chi-squared test. Among significant values, receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values. Before the logistic regression analysis, the Pearson's correlation coefficient between stone density and size variables was calculated internally, and only one of the correlated parameters was included in the analysis. Binomial logistic regression analysis was performed for the significant factors of success in the first session. The omnibus test was performed to determine the compatibility of the logistic regression test model and its value in predicting the analysis. Statistical analyses were carried out using SPSS version 23.0, and $P < .05$ indicated a statistically significant difference.

Results

Patient characteristics are summarized in Table 1. The patients were divided into two groups: ESWL success group (n = 87; 39.5%) and ESWL failure group (n = 133; 60.5%). The results of the univariate analysis of factors that predicted one-session ESWL success and the characteristics of 2 groups are summarized in Table 2. While comparing these two groups, no significant differences were observed in terms of age, sex, stone side, number of shocks, total energy of shock wave, waist circumference, and skin-stone distance.

The univariate analysis revealed that the success group had lower MSD and MXSD HU values and higher SDVC values compared with the failure group (Table 2). On the contrary, no statistically significant difference in SDSD was observed between the two groups ($P = .07$). Other factors predicting ESWL outcome were stone volume and maximum stone length in any dimension (MXSL); both of them were significantly ($P < .001$) lower in the success group (Table 2). In addition, as a categorical variable, the univariate analysis of stone location revealed that ureteral location [OR 1.85, 95% confidence interval (CI): 1.08–3.22, $P = .026$] was an independent predictor of ESWL success.

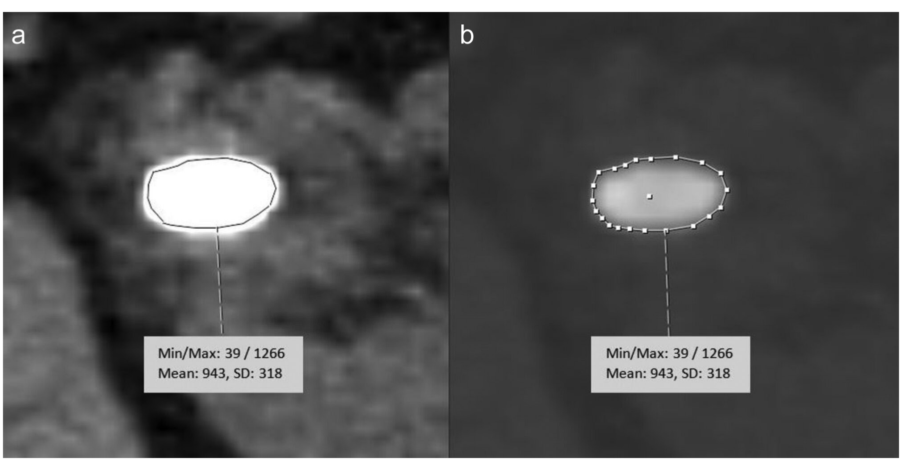

Figure 3. a, b. Images of the stone in the soft tissue (**a**) and bone tissue (**b**) window. Hounsfield unit was measured using the bone window on the magnified axial noncontrast computed tomography images from the point of the largest stone diameter by the free-hand trace of the stone edge without including adjacent soft tissue.

Table 1. Patient characteristics

n (%)	220 (100)
Age (year), mean (SD)	42 (14)
n (%)	
• Sex	
∘ Male	151 (68.6)
∘ Female	69 (31.4)
• Side	
∘ Right	99 (45)
∘ Left	121 (55)
• Stone location	
∘ Calyces	35 (15.9)
∘ Renal pelvis	79 (35.9)
∘ Proximal ureter	93 (42.3)
∘ Middle ureter	13 (5.9)
Mean (SD)	
• Number of shocks	2438 (698)
• Total energy of shock wave (J)	67 (27.1)
• Mean stone density (HU)	827 (244)
• Maximum stone density (HU)	1310 (307)
• Standard deviation of stone density (HU)	332 (96)
• Variation coefficient of stone density (%)	41 (10)
• Skin to stone distance (mm)	109 (22)
• Waist circumference (cm)	96 (13)
• Stone volume (mm^3)	502 (788)

SD, standard deviation; HU, Hounsfield units.

Table 2. Univariate analysis of factors that predict extracorporeal shockwave lithotripsy success

Variable	Success	Failure	*P*
• n	87	133	
• Age (years), mean (SD)	40 (13.4)	41 (14.5)	.218
• Sex, n (%)			
∘ Male	61 (40.4%)	90 (59.6%)	.702
∘ Female	26 (37.7%)	43 (62.3%)	
• Side, n (%)			
∘ Right	34 (34.3%)	65 (65.7%)	.153
∘ Left	53 (43.8%)	68 (56.2%)	
• Stone location, n (%)			
∘ Renal stones	37 (32.5%)	77 (67.5%)	.026
∘ Ureteral stones	50 (47.2%)	56 (52.8%)	
Variable, mean (SD)			
• Mean stone density (HU)	669 (226)	930 (195)	<.001
• Maximum stone density (HU)	1167 (343)	1404 (238)	<.001
• Standard deviation of stone density (HU)	317 (107.5)	341.8 (87)	.070
• Variation coefficient of stone density (%)	48 (9.4)	37.2 (8.1)	<.001
• Skin to stone distance (mm)	112 (20)	108 (22)	.228
• Waist circumference (cm)	95 (12)	96 (14)	.523
• Number of shocks	2405 (695)	2459 (701)	.572
• Total energy of shock wave (J)	65.8 (28)	67.7 (26)	.607
Variable, median (min–max)			
• Maximum stone length in any dimension (mm)	9.5 (5.3-27.4)	12.3 (5.2-29.6)	<.001
• Stone volume (mm^3)	181 (41-8283)	390 (47-4895)	<.001

SD, standard deviation; HU, Hounsfield units.

Among these quantitative factors demonstrating significant differences in the univariate analysis, a strong positive correlation existed between MXSD HU and MSD HU ($r=0.88$, $P < .001$), but no correlation was found between SDVC and any other parameter related to CT attenuation (SDVC and MXSD: $r=-0.69$, $P=.31$; SDVC and MSD: $r=-0.46$, $P=.12$). Also, a positive correlation was observed between stone volume and MXSL ($r=0.67$, $P<.001$).

Before multivariate analysis, ROC analyses were performed to determine the factors that should be chosen as explanatory variables. The AUCs, 95% CI, cutoff levels, sensitivity, and specificity of these five parameters are summarized in Table 3, and ROC curves are shown in Figure 4. Among these parameters, SDVC has the highest prediction accuracy, followed by MSD (SDVC: AUC=0.82, 95% CI 0.76–0.87, $P<.001$; MSD: AUC=0.81, 95% CI 0.75–0.87, $P < 0.001$). In addition, when the patients were evaluated according to the cutoff values determined for MSD and SDVC, 90.9% (n=80) of the patients with a high MSD value in the failure group had low SDVC values. For patients with an MSD value 824 or higher, the OR for patients with SDVC less than 43.2 compared with patients with SDVC 43.2 or higher on the ESWL failure rate was 10 (95% CI 3.55–28.57; $P<.001$).

According to ROC analysis and correlation analysis results, MSD, SDVC, stone volume, and stone location were included in the logistic regression model (Table 4). Before the analysis, all variables were regrouped into dichotomous variables based on the cutoff levels of ROC curves, and the multivariate analysis of these factors was performed to test their power in predicting the ESWL outcome. The multivariate analysis showed that predicting factors in the univariate analysis remained statistically significant, except stone location. Using the logistics model, the probability of success

Table 3. Cutoff values obtained from ROC curves

Variable	Cutoff value	Sensitivity	Specificity	*P*	AUC (95% CI)
Maximum stone length in any dimension (mm)	10.8	0.67	0.61	<.001	0.667 (0.593-0.741)
Stone volume (mm^3)	293	0.62	0.74	<.001	0.696 (0.624- 0.768)
Mean stone density (HU)	824	0.71	0.75	<.001	0.808 (0.748- 0.867)
Maximum stone density (HU)	1371	0.60	0.69	<.001	0.703 (0.629- 0.776)
Variation coefficient of stone density (%)	43.2	0.71	0.79	<.001	0.815 (0.759- 0.871)

AUC, area under the curve; CI, confidence Interval; HU, Hounsfield units.

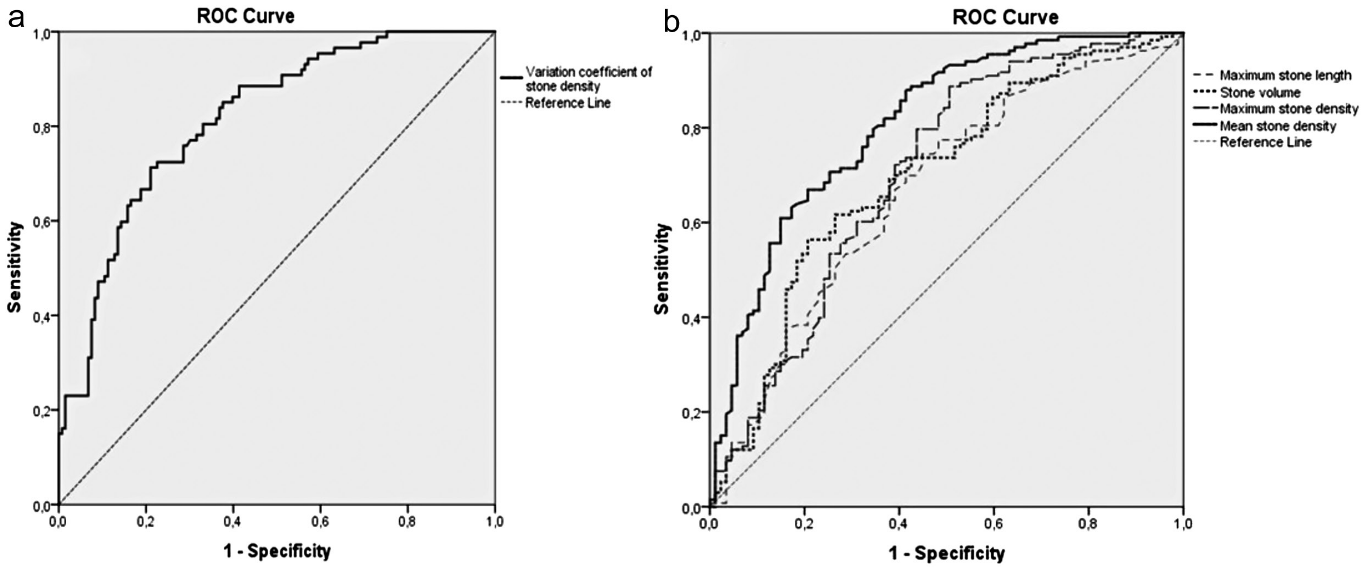

Figure 4. a, b. ROC curve of variation coefficient of stone density (**a**) and ROC curves of mean stone density, maximum stone density, stone volume, and maximum stone length in any dimension (**b**). ROC, receiver operating characteristic.

with a single ESWL was directly calculated using the following formula:

SDP (%) = (SDVC, 0 or 1) × 1.835 + (MSD, 0 or 1) × 1.394 + (stone volume, 0 or 1) × 0.932 + (stone location, 0 or 1) × 0.160–2.604

This formula was termed the "SDP formula."

The logistic regression model, in which the SDP formula was found, correctly predicted ESWL success with a single session by 79.1% ($h^2 = 87.05$, $df = 4$, $P < .001$). Among the values obtained from NCCT, the adjusted OR for SDVC 43.2 or higher values compared with SDVC lower than 43.2 values, for MSD lower than 824 HU values compared with MSD 824 HU or higher values, and for stone volume lower than 293 mm^3 values compared with stone volume 293 mm^3 or higher values on the ESWL success rate was 6.27 (95% CI 3.2-12.4; $P < .001$), 4.03 (95% CI 2-8; $P < .001$), and 2.54 (95% CI 1.2-5.4; $P = .015$), respectively (Table 4).

Discussion

NCCT is currently the most sensitive and essential diagnostic tool for identifying urinary stones. This study found that easily measurable NCCT parameters of urinary stones could be used to predict ESWL success accurately. In addition, a new indicator of SDP was identified as a reliable predictor of treatment success.

Many studies evaluated the relationship between CT attenuation value and prediction of ESWL success; most of these studies used mean HU. In these studies, the mean HU values of stones were significantly lower in patients benefiting from ESWL. Nakasato et al.[14] revealed an 815 HU threshold for predicting the ESWL outcome, Park et al.[15] suggested the cutoff value of a stone density of 863 HU for predicting ESWL failure. Ouzaid et al.[16] found a 970 HU threshold for predicting ESWL success; according to the American Urological Association guideline, patients with MSD value higher than 900-1000 HU showed less successful ESWL results.[17] In the present study, the cutoff value was found to be 824. The differences between studies were caused by the use of different CT states, inclusion criteria, or measurement techniques.

In contrast, Sugino et al.[7] measured the maximum HU value to obtain a simpler way and overcome the possible bias problem when measuring the mean HU by the conventional method. This study showed an equivalent prediction accuracy between the maximum and average HU. However, the present study showed that MSD and SDVC prediction accuracies were higher compared with those of MXSD.

Previous studies indicated that heterogeneity of stone composition and internal microstructure were important predictors of ESWL success.[12,13] Maximum stone density and MSD can only represent the stone hardness and do not provide any extra information about stone heterogeneity. Few reports described an index based on the SD value of stones representing stone heterogeneity, which was defined by Lee et al.[6] However, SD can only represent the amount of variation

Table 4. Multivariate analysis of factors that predict extracorporeal shockwave lithotripsy success

Variables	B	Odds ratio (95% CI)	*P*
Variation coefficient of stone density (%)			
• ≥43.2	1.835	6.27 (3.2-12.4)	<.001
• <43.2		1 (reference)	
Mean stone density (HU)			
• <824	1.394	4.03 (2-8)	<.001
• ≥824		1 (reference)	
Stone volume (mm^3)			
• <293	0.932	2.54 (1.2-5.4)	.015
• ≥293		1 (reference)	
Stone location			
• Ureteral	0.160	1.2 (0.6-2.4)	.67
• Renal		1 (reference)	

HU, Hounsfield units; CI, confidence interval.

and cannot be evaluated independently of stone hardness. Therefore, the heterogeneity of stone composition is not reflected by SDSD only. Moreover, in the present study, SDSD was found to be statistically insignificant. In contrast, the variation coefficient is often used to compare the distribution between multiple groups with different mean values and is calculated by dividing the standard deviation by the mean value. Therefore, it was speculated that the SDVC value could reflect the heterogeneity of stone composition accurately and predict ESWL success in the best way. In the present study, compared with other CT attenuation-associated factors, SDVC had stronger predictive power on ESWL success compared with MSD and MXSD. Also, the multivariate analysis showed that higher SDVC was the independent and the most significant predictor of ESWL success ($P < 0.001$) in patients. Some studies used the variation coefficient of CT attenuation value as a predictive parameter for ESWL success, showing different results.[7,18] In addition, this study demonstrated that the SDVC value was a promising parameter in determining the treatment for patients with urinary stones and especially selecting suitable ESWL candidates among patients with a stone of high MSD values. Based on the results of the present study, the development of scoring systems or nomograms including stone heterogeneity by SDVC can help in decision-making for patients. Also, it is possible to directly calculate the probability of success using the newly defined SDP formula. The SDP formula helps in calculating the probability of success with a single ESWL session with dichotomous variables and thus can be easily applied in daily practice.

This study had some limitations. First, this was a retrospective analysis undertaken at a single center. Larger prospective designed studies should be performed to determine the generalization of the results. Second, ESWL success was evaluated only after the first session due to standardization, and stones that could be broken in more than one ESWL session were considered unsuccessful. Third, body mass index (BMI) measurements were not available in all patient files in this retrospective study, but waist circumference and skin-stone distance measurements were made in all patients and no significant difference was found between the two groups. Hence, it was accepted that no bias was caused by the BMI difference. Fourth, the confirmation of the absence of urinary stones using x-ray can be considered as a limitation in evaluating ESWL success in some patients, especially for low-density stones. However, suspicious cases due to poor image quality were excluded to avoid this situation. The ability to free-hand trace a stone and derive HU measurements does not exist across all picture archiving and communication system vendors. This situation can be considered as another limitation of the described technique.

In conclusion, this study evaluated the ability to predict the success of shockwave lithotripsy using the assessment of NCCT imaging features, based on the increasing number of studies on radiomics. This study revealed that the size and attenuation values obtained from NCCT were the predictors of treatment success, and the SDVC value would reflect the heterogeneity of stone composition accurately and predict ESWL success in the best way. Also, this study showed that the SDP formula newly defined using the logistic regression model helped directly calculate the probability of treatment success. The estimated success rate can be easily calculated by sparing a few extra minutes for the NCCT assessment often used in diagnosis. This will facilitate the decision of treatment approach for patients and hopefully minimize unnecessary delay in treatment.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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