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ORIGINAL ARTICLE

Advanced non-contrasted computed tomography post-processing by CT-Calculometry (CT-CM) outperforms established predictors for the outcome of shock wave lithotripsy

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Abstract

Objectives To evaluate the predictive value of advanced non-contrasted computed tomography (NCCT) post-processing using novel CT-calculometry (CT-CM) parameters compared to established predictors of success of shock wave lithotripsy (SWL) for urinary calculi.

Materials and Methods NCCT post-processing was retrospectively performed in 312 patients suffering from upper tract urinary calculi who were treated by SWL. Established predictors such as skin to stone distance, body mass index, stone diameter or mean stone attenuation values were assessed. Precise stone size and shape metrics, 3-D greyscale measurements and homogeneity parameters such as skewness and kurtosis, were analysed using CT-CM. Predictive values for SWL outcome were analysed using logistic regression and receiver operating characteristics (ROC) statistics.

Results Overall success rate (stone disintegration and no re-intervention needed) of SWL was 59% (184 patients). CT-CM metrics mainly outperformed established predictors. According to ROC analyses, stone volume and surface area performed better than established stone diameter, mean 3D attenuation value was a stronger predictor than established mean attenuation value, and parameters skewness and kurtosis performed better than recently emerged variation coefficient of stone density. Moreover, prediction of SWL outcome with 80% probability to be correct would be possible in a clearly higher number of patients (up to fivefold) using CT-CM-derived parameters.

Conclusions Advanced NCCT post-processing by CT-CM provides novel parameters that seem to outperform established predictors of SWL response. Implementation of these parameters into clinical routine might reduce SWL failure rates.

Keywords CT-Calculometry (CT-CM) · Urinary calculi · Homogeneity · 3-D · SWL · Predictor

Introduction

Non-contrasted computed tomography (NCCT) represents the gold standard examination for diagnosis and further treatment of urinary calculi [1]. Shockwave lithotripsy (SWL) is still recommended as first-line treatment for the most stone scenarios [1, 2]. SWL is safer and less invasive compared to other established techniques such as ureterorenoscopy (URS) or percutaneous nephrolithotomy (PCNL) but associated with lower stone free rates [2]. Therefore, many attempts to reduce SWL failure rates by identification of appropriate SWL outcome predictors have been made.

Several parameters, such as skin-to-stone distance (SSD), body mass index (BMI), and established mean attenuation values (in Hounsfield units; HU) have been shown to be

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significantly associated with SWL outcome and are, therefore, considered by leading urological guidelines [1, 2].

Recent studies found that exact volumetric measurements might predict SWL outcome more precisely than widely used planar stone diameter [3]. However, this fact is not yet part of the leading urological guidelines, probably due to its technically demanding application in daily clinical routine.

Moreover, stone homogeneity and microstructure have been recently introduced as promising predictors of SWL success in vitro [4–6]. So far, clinical studies assessing the impact of 3D-greyscale measurements and homogeneity parameters in vivo are lacking.

CT-Calculometry (CT-CM) was lately introduced as an advanced NCCT post-processing method in a proof-of-concept study and facilitates precise 3D-analyses of size and shape of urinary calculi as well as analyses of internal structural homogeneity with a small effort [7].

Therefore, the aim of this study was to investigate the predictive value of novel 3D greyscale measurements, homogeneity parameters such as skewness and kurtosis, stone size and shape metrics, assessed by CT-CM, and to compare it to established predictors of SWL success.

Materials and methods

Study design

Totally 312 consecutive patients suffering from urolithiasis, who were treated by SWL between March 2012 and October 2017, were retrospectively assessed. Patients were included in this study if preoperative NCCT was available and if SWL had been performed for a single renal or ureteral stone of ≥ 0.4 cm (largest diameter in NCCT). The study was approved by the local ethics committee (EKOS 17/051).

Shock wave lithotripsy

SWL was performed with a SLX-F2 (Storz Medical, Tägerwilen, Switzerland) under X-ray monitoring [8]. Each session consisted of a maximum of up to 4000 shocks applied to the stone according to best practices in SWL [8]. All interventions were conducted by three experienced technicians and supervised by an urologist. Treatment was performed until complete stone fragmentation occurred, including a maximum of three subsequent applications during one in-patient stay. If after three SWL sessions, stones showed no disintegration or disintegration was insufficient (i.e. fragments ≥ 0.4 cm present) and/or there was a need for a re-intervention (URS, PCNL or SWL), the patient was considered as treatment failure. Disintegration was assessed by kidney, ureter and bladder X-ray (KUB) and ultrasound after each SWL session and 6 weeks postoperatively.

NCCT and established parameters

For all patients, diagnosis and planning of treatment was based on a pre-interventional NCCT, performed by a multidetector row helical CT scanner (Siemens, Sensation 64; Somatom Definition; Definition Flash; Definition Force; Forchheim, Germany). Standard dose non-contrast CT was performed at a reference setting of 120 kV and 100 quality reference mAs using automated attenuation-based tube current modulation (CAREDose4D; Siemens Healthcare) with a slice collimation of 0.6-mm CT images were reconstructed using a slice thickness of 2 mm with an increment of 1.5 mm.

SSD was calculated by measuring the distance from the stone to the skin in three angles (0°, 45° and 90°) and determining the mean distance as described elsewhere [9]. Body mass index was assessed by dividing the patient's weight (kg) by the square of the height (m^2). Conventional stone size was measured by taking the largest diameter of the stone in NCCT in coronal and axial planes. Established mean attenuation values (in HU) were measured in axial NCCT scans using a region of interest radiographic calliper slightly smaller than the stone to be measured [7, 10]. As described previously [11], the variation coefficient of stone density (VCSD) is calculated by [(Standard deviation of mean attenuation value)/(mean attenuation value)]. For practical reasons and to improve accuracy, this parameter was calculated using the software mentioned below. Stone location was classified in five groups including upper, middle and lower calices and proximal and distal ureter.

CT-Calculometry (CT-CM)

CT-CM was performed by advanced NCCT post-processing using the software 3D Slicer Version 4.6.2 (http://www.slicer.org) as recently described [7]. 3D Slicer is a free open-source application similar to a radiology workstation. It supports versatile visualizations, but also provides advanced functionality such as automated segmentation and reconstruction [12]. The data were imported from Digital Imaging and Communications in Medicine (DICOM), afterwards the stone was isolated from the neighbouring soft tissue by HU threshold adaption [13]. A 3D model of each stone resulted, which was the basis for further analyses using the extension OpenCAD for Slicer 4.6.2.

Established parameters and CT-CM parameters that were analysed are described in Table 1.

Table 1 Established parameters and parameters generated by CT-CM. Adopted from Aerts et al. [21]

Parameters	Formula	Description
Patient habitus		
BMI (kg/m^2)		Body mass index of the patient
Mean SSD (mm)		The mean of the distance from the stone to the skin measured in three angles (0°, 45°, 90°)
Stone size and shape	A = surface area; V = volume; N = total number of triangles covering the surface; a, b, c = edge vectors of the triangles	
(Established) max. diameter (mm)	Measured as the largest distance between pixels on the surface of the stone in one plane	The maximum diameter of the stone measured in one plane
Max. 3D diameter (mm)[a]	Measured as the largest distance between voxels on the surface of the stone	The maximum 3D diameter of the stone
Volume (mm^3)[a]	Determined by counting the number of voxels and multiplying this value by the voxel size	The volume of the stone
Surface area (mm^2)[a]	$A = \sum_{i=1}^{N} \frac{1}{2} \lvert \boldsymbol{a}_i\boldsymbol{b}_i \times \boldsymbol{a}_i\boldsymbol{c}_i \rvert$	The surface area of the stone
Shape compactness[a]	$\text{Compactness} = 36\pi \frac{V^2}{A^3}$	A measure for compactness/shape regularity of the stone
Stone density	X denotes the vector of grey levels of all voxels of the stone's 3D image with N voxels. Index i denotes the individual voxel	
(Established) mean attenuation value (HU)		The mean grey level of the image in a region of interest
Mean 3D attenuation value (HU)[a]	$\text{Mean} = \frac{1}{N} \sum_{i=1}^{N} \boldsymbol{X}(i)$	The mean grey level of the stone's 3D image
Stone homogeneity	X denotes the vector of grey levels of all voxels of the stone's 3D image with N voxels. Index i denotes the individual voxel	
VCSD	VCSD = (SD attenuation value)/(mean attenuation value)	Measures the variation coefficient value based on the mean attenuation value and standard deviation of attenuation value as a measure of stone's homogeneity
Skewness[a]	$\text{Skewness} = \frac{\frac{1}{N}\sum_{i=1}^{N}\left(\boldsymbol{X}(i)-\bar{X}\right)^3}{\left(\sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\boldsymbol{X}(i)-\bar{X}\right)^2}\right)^2}$	Measures the asymmetry of the distribution of grey values of the stone's 3D image around the mean of the values
Kurtosis[a]	$\text{Kurtosis} = \frac{\frac{1}{N}\sum_{i=1}^{N}\left(\boldsymbol{X}(i)-\bar{X}\right)^4}{\left(\sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\boldsymbol{X}(i)-\bar{X}\right)^2}\right)^2}$	A measure of the peakedness of the distribution of values in the stone's 3D image. A higher kurtosis implies that extreme values deviate more from "normal values"
Total squared 3D-intensity (energy)[a]	$\text{Energy} = \sum_{i}^{N} \boldsymbol{X}(i)^2$	Combines information about stone size, mean intensity and variation

[a]CT-CM parameters

Statistical analysis

Our sample size (312 patients) was chosen such as to include the full range of variation in each of the predictors to properly compare their importance, and to observe at least 10 successes and failures per predictor.

The predictive impact of established parameters such as SSD, BMI, mean attenuation or stone diameter on SWL success was compared to that of novel parameters generated by CT-CM in three ways. First, logistic regression was used to determine whether and how each parameter was related to the probability of treatment success (no re-intervention needed). The slope coefficient b of the regression model indicated whether high values ($b > 0$) or low values ($b < 0$) of the parameter predict treatment success. The significance of the relationship was tested by likelihood-ratio tests, and

p-values < 0.05 were considered significant. The X^2-test statistic additionally measured the strength of the association.

Second, the predictive values of the different parameters were further evaluated with receiver operating characteristic (ROC) curve statistics. The area under the curve (AUC) was determined as a second overall measure of association between predictors and SWL success. An optimal cutpoint for the distinction between patients with high and low probability of SWL success was determined as the value maximising the sum of sensitivity and specificity. Sensitivity and specificity, positive predictive and negative predictive values and percentage of patients for whom success is predicted were calculated for these cutpoints.

Finally, because the ROC analysis showed that a single cutpoint would not allow for prediction with high accuracy with any of these parameters, we additionally determined for how many patients either SWL success or SWL failure could be predicted reliably using two cutpoints. We sorted parameter values in increasing order and identified two cutpoints such that values above and below these were associated with ≥ 80% probability of success or failure, respectively, depending on the slope of the logistic regression. We then counted the number of patients with such values.

Results

Overall success (disintegration and no re-intervention needed) of SWL was 59% (184 patients). At least slight stone disintegration in KUB after the last SWL session was reported in 90% of the patients ($n = 279$). CT-CM analysis

Table 2 Patient characteristics, established predictors and novel parameters obtained by CT-CM in relation to SWL success

Parameter	Class	No. (%) of patients[a]	
		No SWL success	SWL success
Gender	Male	89 (41.6%)	125 (58.4%)
	Female	39 (39.8%)	59 (60.2%)
Stone location	Upper calyx	15 (44.1%)	19 (55.9%)
	Middle calyx	16 (28.1%)	41 (71.9%)
	Lower calyx	34 (34.3%)	65 (65.7%)
	Proximal ureter	61 (52.6%)	55 (47.4%)
	Distal ureter	02 (33.3%)	04 (66.7%)
Parameter (unit)	**No. (success no/yes)**	**Median (range)**	
		No SWL success	SWL success
Age (year)	128/184	51.5 (21.5–94.7)	49.3 (18.6–85.2)
SSD (mm)			
0°	128/184	105.5 (42–186)	98.5 (52–181)
45°	128/184	108.0 (44–197)	98.0 (47–190)
90°	128/184	112.0 (52–177)	101.0 (45–182)
BMI (kg/m^2)	125/176	27.2 (16.8–44.1)	26.3 (16.9–50.9)
Stone size and shape			
(Established) max. diameter (mm)	128/184	9.0 (4–42)	7.0 (4–20)
Max. 3D-diameter (mm)[a]	128/183	14.2 (7.2–65.4)	11.3 (4.5–36.4)
Volume (mm^3)[a]	128/183	348.3 (65.0–9607.5)	191.3 (16.5–2310.2)
Surface area (mm^2)[a]	128/183	424.9 (134.9–4474.6)	272.4 (39.1–1579.2)
Shape compactness[a]	128/183	0.21 (0.05–0.32)	0.22 (0.04–0.51)
Stone density			
(Established) mean attenuation value (HU)	128/184	1120.0 (319–1886)	964.5 (313–1861)
Mean 3D attenuation Value (HU)[a]	128/183	568.5 (196.6–964.7)	445.0 (195.4–908.1)
Stone homogeneity			
VCSD	128/183	0.69 (0.32–0.83)	0.68 (0.37–0.85)
Skewness[a]	128/183	0.63 (−0.41 to 1.47)	0.77 (−0.23 to 1.77)
Kurtosis[a]	128/183	−0.81 (−1.53 to 1.41)	−0.49 (−1.53 to 2.26)
Energy × 10^{-6} (total sq. 3D-intensity)[a]	128/183	163.1 (1.4–4833.6)	70.4 (1.2–2415.3)

[a]CT-CM parameters

Table 3 Results of logistic regression relating established parameters and parameters acquired by CT-CM to the probability of treatment success (chi-squared test statistic and *p* value), as well as ROC curve statistics

Predictor	*p* value	X^2	AUC	Cutpoint	Sign	Sens.	Spec.	% PP	PPV	NPV
SSD	0.010	6.6	0.58	104.3	Below	0.585	0.584	51.5	0.67	0.5
BMI	0.061	3.5	0.57	28.9	Below	0.74	0.39	68.8	0.63	0.52
Stone size and shape										
(Established) max. diameter	< 0.001	20.7	0.66	8.0	Below	0.67	0.58	56.5	0.69	0.56
Max. 3D-diameter[a]	< 0.001	21.3	0.66	12.8	Below	0.65	0.62	54.2	0.71	0.56
Volume[a]	< 0.001	28.9	0.67	354.8	Below	0.77	0.50	66.1	0.68	0.61
Surface area[a]	< 0.001	29.6	0.68	416.9	Below	0.76	0.51	64,.5	0.69	0.60
Shape compactness[a]	0.004	8.3	0.60	0.228	Above	0.42	0.72	36.2	0.68	0.47
Stone density										
(Established) mean attenuation value	< 0.001	21.5	0.66	1019	Below	0.59	0.70	46.6	0.74	0.54
Mean 3D attenuation value[a]	< 0.001	39.5	0.70	474	Below	0.56	0.77	42.8	0.77	0.55
Stone homogeneity										
VCSD	0.455	0.56	0.53	0.70	Below	0.65	0.45	60.8	0.63	0.48
Skewness[a]	< 0.001	20.4	0.64	0.65	Above	0.68	0.53	59.2	0.67	0.54
Kurtosis[a]	< 0.001	20.3	0.65	− 0.67	Above	0.65	0.59	54.6	0.69	0.54
Energy (total sq. 3D-intensity)[a]	< 0.001	35.5	0.70	109.6	Below	0.68	0.66	54.3	0.74	0.59

The column “sign” indicates whether success is predicted by values above or below the cutpoint (chosen to maximise the sum of sensitivity and specificity), and “%PP” indicates the percentage of cases for which a positive outcome (SWL success) is predicted. PPV = positive predictive value (SWL success rate among patients with success predicted), NPV = negative predictive value (SWL failure rate among patients with no success predicted)

[a]CT-CM parameters

failed in one patient due to DICOM importing problems into the slicer application package. Patient characteristics are reported in Table 2.

All assessed parameters except for BMI and VCSD were found to be significantly associated with SWL success in logistic regression analyses. Results of logistic regression and ROC curve statistics for all parameters are reported in Table 3.

Regarding shape metrics, stone volume (AUC 0.67) and surface (0.68) performed slightly better than maximum and 3D diameter (AUC 0.66). CT-CM derived mean 3D attenuation value (AUC 0.70) outperformed established mean attenuation value (AUC 0.66). Skewness (AUC 0.64) and kurtosis (AUC 0.65) were significant predictors whereas VCSD showed an almost random association with SWL outcome (AUC 0.53). ROC curves grouped to “patient characteristics”, “stone size and shape metrics”, “stone density” and “stone homogeneity” are shown in Fig. 1.

Classification of patients into two groups, for which relatively reliable predictions can be made (i.e. either “SWL success” or “SWL failure”, with a probability of at least 80% to be correct) revealed, that such reliable predictions of SWL success can be made in more patients using selected novel, CT-CM-based parameters (e.g., volume, mean 3D attenuation) compared to related established parameters (e.g., stone diameter, mean attenuation) (Table 4).

Discussion

To our knowledge, this work represents the first clinical study evaluating the predictive value of novel 3D-greyscale and homogeneity parameters. Advanced NCCT post-processing techniques, as recently described in ex vivo and model studies [4–7], have been shown to be able to accurately characterise the stones’ geometry, mean attenuation and homogeneity. A recent proof-of-concept study showed that these techniques can be easily implemented into clinical routine [7]. Our study shows that besides stone volume and surface area, mean 3D attenuation and homogeneity parameters skewness and kurtosis are significant predictors of SWL outcome. These novel parameters mainly outperform related established parameters.

Several predictors of SWL outcome have been established in the past to reduce SWL failure rates.

SSD has been shown to be a strong factor predicting failure of SWL [10, 14, 15] and is known to be significantly associated with SWL failure with cut-off values varying between 100 and 119 mm, which is supported by the results of our study.

In strong relation to SSD, BMI is an established predictor as well [9, 10, 14]. In our study BMI performed slightly weaker compared to SSD, which is in line with previously published results [16].

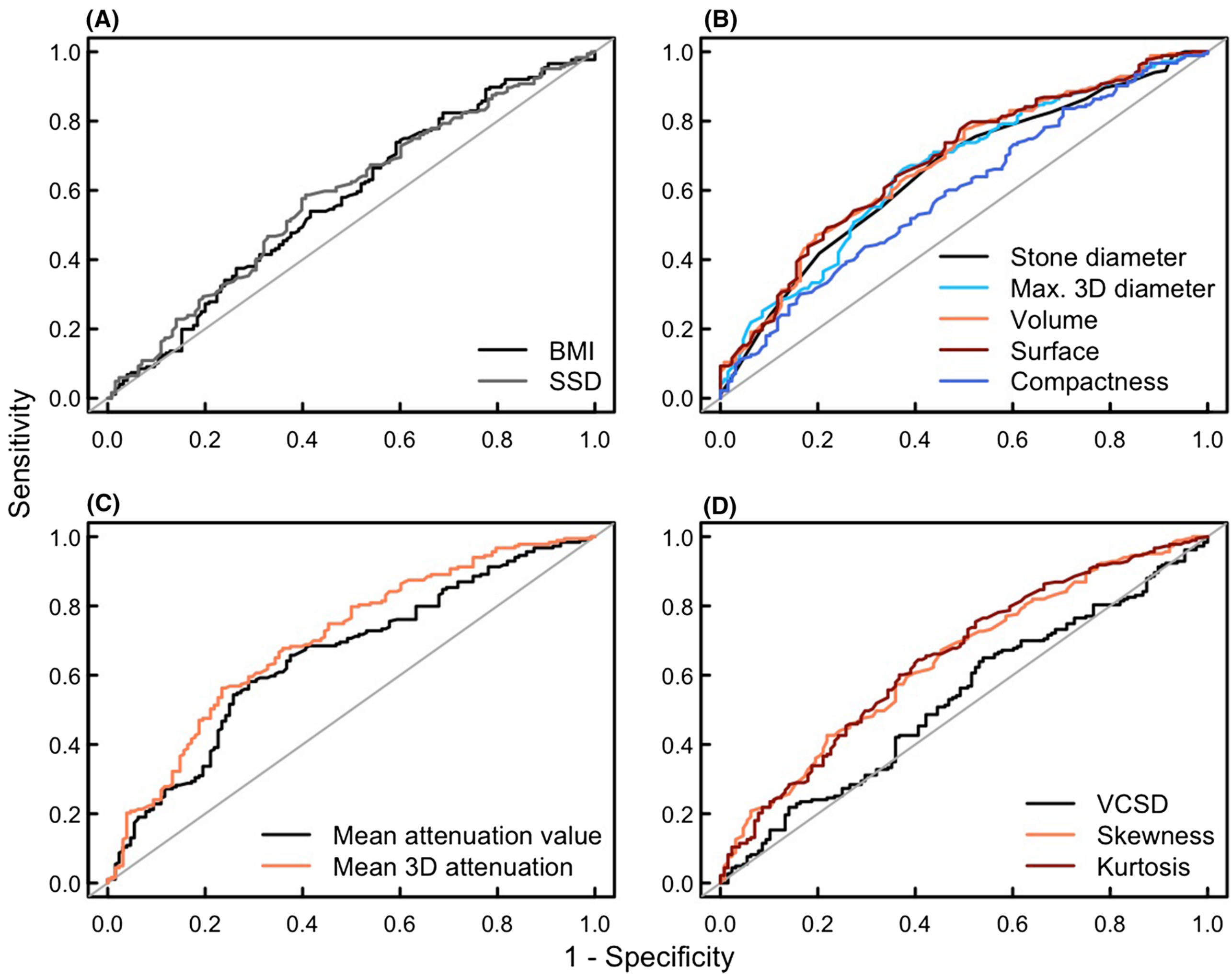

Fig. 1 ROC curves of CT-CM-derived and established parameters. **a** Patient characteristics; **b** stone size and shape metrics; **c** stone density; **d** stone homogeneity. The grey 1:1 lines correspond to the ROC curve expected for a completely unrelated parameter

Table 4 Prediction of SWL success using two different criteria (cutpoints) for the prediction of success and failure, based on selected established and CT-CM-based parameters

Parameter	SWL success predicted			SWL failure predicted			Both
	Crit.1	*n*	*n* success	Crit.2	*n*	*n* failure	*N* total
(Established) max. stone diameter (mm)	$X \le 3$	2	2 (100%)	$X \ge 20$	11	9 (81%)	13 (4%)
Volume (mm^3)[a]	$X \le 95.5$	43	35 (81%)	$X \ge 1445$	18	15 (83%)	61 (20%)
(Established) mean attenuation	$X \le 671$	43	35 (81%)	n.a.	0		43 (14%)
Mean 3D attenuation[a]	$X \le 343$	50	40 (80%)	$X \ge 700$	32	26 (81%)	82 (26%)

[a]CT-CM parameters

n = number of patients fulfilling one criterion, *n* success and *n* failure = number of patients with the predicted outcome; *N* total = number of patients for whom a prediction could be made

Our study confirmed the results of Bandi et al. [3] pointing at superior prediction of exact measurement of stone volume compared to simple stone diameters, which are usually used in clinical practice. In addition, our data show that the exact surface area of a stone might predict the outcome of SWL as well. In contrast, the shape compactness of a stone was not significantly correlated with SWL outcome, which seems to be surprising as shape irregularities seem to be likely to make stones more prone to fragmentation compared to more compact formed stones. The fact that marked shape irregularities are more often found in large stones, in which SWL success as defined in our study is generally lower [3], might be a possible explanation for this finding.

Mean stone attenuation expressed in HU, a measure for mean stone density, is also known to be significantly linked to SWL success [9, 17, 18]. In our study, this NCCT-derived established parameter performed clearly better compared to SSD and BMI, and prediction could even be improved using CT-CM-based mean 3D attenuation values, which might be explained by a more accurate determination by 3D analysis compared to the use of exemplary regions of interest.

Recent in vitro studies suggested, that the homogeneity and structural integrity of urinary calculi might predict disintegration after SWL [6, 19]. In an attempt to describe the homogeneity of calculi by the variation coefficient of stone density (VCSD, the stone's standard HU deviation divided by the mean HU), a recent work concluded that this parameter might be a novel predictor of SWL success [11]. In contrast, VCSD was not significantly related to SWL success in our study.

Cui et al. tried to characterise the structural homogeneity of urinary calculi more accurately and introduced the parameters skewness and kurtosis in an ex vivo study [4]. Both parameters could be confirmed as statistically significant predictors of SWL outcome in vivo in our study. Nevertheless, it should be kept in mind that these parameters represent a simplified approach to calculate microstructural homogeneity based on the frequency distribution of grey values and that the spatial pattern of grey levels may actually be more relevant for SWL success. For example, the size and the shape of "breaking zones" with reduced density may be relevant for disintegration of generally dense stones, and this aspect is not captured by simple measures of variation. Therefore, further efforts should be directed towards appropriate measures of stone texture in vivo.

In an attempt to combine information of all the above-mentioned categories (stone size, mean intensity and variation) in one single CT-CM parameter, the so-called stone "Energy" was assessed. Though "Energy" represents a further novel significant predictor of SWL outcome, the combination of the three included parameters did not exceed predictive accuracy of the best single CT-CM parameter mainly due to inherent opposing effects of the combined categories.

Reliable predictions (i.e. $\geq 80\%$ accuracy) of SWL success could be made in more patients (up to fivefold) using selected novel, CT-CM-based parameters compared to related established parameters. Nevertheless, the number in whom SWL outcome could be predicted with high accuracy based on a single parameter was still rather low (maximum 26% of the patients met the thresholds allowing for prediction with $\geq 80\%$ accuracy). However, as CT-CM allows for semi-automatic determination of all of the parameters assessed in our study at once with a reasonable expenditure of time (i.e. approximately 4 min per patient), the combination of CT-CM-derived parameters to prognostic models might further improve NCCT-based prediction of SWL outcome, which was beyond the scope of the present study.

The study has some limitations that have to be addressed. In particular, this was a retrospective analysis performed at a single centre. Assessment of disintegration was performed by KUB films supplemented by ultrasound and not by more accurate NCCT. Since it has been shown that KUB-based assessment of disintegration might overestimate the effect of SWL [20], only clinically relevant stone disintegration (i.e., no further treatment necessary) was defined as successful SWL. This approach is supported by an SWL success rate of 59%, which is in line with a recent study assessing SWL success by post-interventional NCCT [11].

Conclusion

Parameters derived by advanced NCCT post-processing are significantly associated with SWL outcome and even outperform some of the established predictors. These novel parameters can be assessed with a small effort and, therefore, can be implemented into daily clinical decision-making.

Author contributions JL and PB data collection, manuscript writing, manuscript editing. LH data collection, manuscript editing. SG project development, statistical analysis, manuscript writing, manuscript editing HPS, DSE, DA project development, manuscript editing. VZ project development, data collection, manuscript writing, manuscript editing.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

Informed consent General consent for data usage was obtained from all individual participants included in the study.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the local research committee and with the 1964 Helsinki declaration and its later amendments.

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