

Assessment of pancreatic ductal stone density on non-contrast computed tomography for predicting the outcome of extracorporeal shock wave lithotripsy



Authors

Ankit Dalal¹, Nagesh Kamat¹, Amit Maydeo¹, Gaurav Patil¹, Amol Vadgaonkar¹, Sanil Parekh¹, Sehajad Vora¹

Institutions

1 Institute of Gastrosciences, Sir HN Reliance Foundation Hospital and Research Centre, Mumbai, India

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Georg Thieme Verlag KG, Rüdigerstraße 14,

70469 Stuttgart, Germany

Corresponding author

Dr. Amit Maydeo, MD, Sir HN Reliance Foundation Hospital and Research Centre, Institute of Gastrosciences, Mumbai, India

amitmaydeo@gmail.com

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ABSTRACT

Background and study aims The utility of stone density at non-contrast computed tomography (NCCT) for predicting the effectiveness of extracorporeal shock wave lithotripsy (ESWL) in chronic calcific pancreatitis (CCP) is relatively unexplored.

Patients and methods This was a prospective observational study of patients with CCP. Hounsfield units (HU) were determined for the largest pancreatic ductal stone during pretreatment NCCT. All patients underwent ESWL until the largest stone was fragmented to <3 mm, followed by endoscopic retrograde cholangiopancreatography (ERCP) for stone extraction. The predictive factors following ESWL for successful stone extraction were studied and the receiver operating characteristic (ROC) curve determined the HU optimal cut-point.

Results Eighty-two patients with a median (interquartile range) age of 36 years (range, 29–55); majority male 45 (54.9%), were included. Idiopathic CCP was noted in 78 patients (95.1%). The median stone density (SD) was 1095 HU (range, 860.7–1260.7) and the number of ESWL sessions was 2 (range, 2–3). Complete stone removal at index ERCP was achieved in 55 patients (67.1%). Those with partial clearance (n=27) needed a repeat ERCP, which was successful in 26 (96.3%); one patient (3.7%) underwent surgery. There was a significant, positive correlation between number of ESWL sessions and SD ($r=0.797$; $P<0.001$). On bivariate analysis, SD and the number of ESWL sessions revealed a significant association with complete ductal clearance. The optimal cut-point for complete stone removal by the ROC curve was 1106.5 HU (Youden index 0.726), with a sensitivity of 93% and a specificity of 80%.

Introduction

Chronic pancreatitis (CP) leads to recurrent hospitalization and significant morbidity, resulting in financial burden and poorer quality of life (QOL) [1,2]. Pancreatic duct stones (PDS) are found in approximately 22% to 60% of patients with CP [3,4]. The calcifications seen in CP can be present in up to 50% of pa-

tients and various conditions [5,6]. Although abdominal pain is the most disabling symptom, about 10% of patients with CP can have a primary painless disease [7]. Recurrent episodes can lead to progressive damage in the functioning of the pancreas. PDS can obstruct pancreatic secretion outflow, raising the intraductal pressure, inducing tissue hypertension and ischemia, and contributing to pain [8,9]. These patients are initially treated

with analgesics and lifestyle modifications, endoscopy, and eventually surgical treatment for pancreatic duct clearance/de-compression in a step-up approach [10, 11].

Endotherapy aims to alleviate pain by removing the obstructing PDS and leading to effective pancreatic ductal drainage [12, 13]. The size, density, and location of the stones and associated strictures can hamper endoscopic PDS extraction and ductal clearance. Radiopaque small stones can be removed with endoscopic retrograde cholangiopancreatography (ERCP), but the larger and more dense ones that can be seen easily on a plain x-ray usually need extracorporeal shock wave lithotripsy (ESWL) for fragmentation before ERCP [14]. ESWL is preferred before ERCP for dense PDS >5 mm but shows varied responses [15]. We hypothesized that the true pancreatic stone density (Hounsfield Units [HU]) measured on a non-contrast computed tomography (NCCT) can determine the success of ESWL [16, 17, 18]. Because most of the studies related to the quantification of stone density before therapy have been in the field of urology [19], its use in planning therapy for pancreatic stones has yet to be well established. So, this study aimed to quantify stone density at NCCT to predict the success of ESWL and endotherapy in Chronic calcific pancreatitis (CCP).

Patients and methods

This was a prospective observational study of CCP patients who underwent ESWL followed by ERCP from June 2019 to May 2022. The first and last patients were enrolled in June 2019 and December 2021, respectively, and the follow-up (6 months) of the last patient was in May 2022. The clinical symptom was abdominal pain for undergoing ESWL. NCCT examination was performed before treatment. All chronic comorbidities were managed as per appropriate guidelines. This study was conducted by following Good Clinical Practice and in a manner to conform to the Helsinki Declaration of 1975, as revised in 2013, concerning human rights. The study protocol and all procedures performed in this study were reviewed and ethically approved by the Institutional Ethics Committee (IEC/OA-40/19). Written informed consent was obtained from each subject before enrollment. The first and third authors vouch for the accuracy of the data given and the study's adherence to the protocol. The trial was prospectively registered in a publicly accessible database before recruiting the first subject at the Clinical Trials Registry of India – URL: <http://ctri.nic.in> (Unique identifier: CTRI/2019/06/019750). All authors accessed the study data, reviewed it, and approved the final manuscript.

Symptom evaluation

All patients had been evaluated clinically and with relevant blood investigations. Fluoroscopy was performed at the initial presentation. The number and distribution of radiopaque stones seen on fluoroscopy were documented. Subsequently, the presence of pancreatic calculi was determined with an NCCT of the abdomen and magnetic resonance cholangiopancreatography (MRCP) [20]. On the pre-treatment NCCT, stone size, location, attenuation value, and HU were determined.

Study eligibility

Inclusion criteria included patients with CCP (diagnosed on MRCP/NCCT) aged >18 years with PDS radiopaque calculi (size >5 mm). The exclusion criteria included patients with ongoing or recent pancreatitis <4 weeks, pancreatic malignancy, pancreatic fluid collections, presence of ascites and/or coagulopathy, patients with renal or liver disease, pregnancy, and refusal of consent.

Stone characteristics assessed by NCCT

A GE Discovery CT750 HD 64 Slice CT Scanner (General Electric Healthcare, Milwaukee, Wisconsin, United States) was used to conduct the NCCT examination. Each patient remained supine and was given instructions during scanning to hold their breath at the end of inspiration. The scanning area extended from the superior border of the liver to the anterior superior iliac spine, and all images were rebuilt within the bone window using a common algorithm. The same radiologist assessed CT scans. The software Philips IntelliSpace Portal version 6.0.4 (Netherlands) was used to import all thin-slice NCCT images. This program automatically detected all PD stones and produced indexes like preoperative stone volume and the mean value of CT attenuation (MSD) (► Fig. 1a–f). The largest stone with the longest transverse length (a) and smallest diameter (b) was identified. $MST = (a + b)/2$ was used to determine the mean stone length (MST). By measuring the diameter of the dilated point distally to the pancreatic head along the obstructed pancreatic duct, the pancreatic duct diameter was calculated. By computing the ratio of MSD and MTL, attenuation density (AD; density of HU) was calculated.

Anesthesia for ESWL

A higher degree of sedation was achieved with total intravenous anesthesia (TIVA) in the form of benzodiazepines (midazolam), corticosteroid/antiallergic (dexamethasone), opiates (nalbuphine), sedative (dexmedetomidine), anticholinergics (glycopyrrolate), antispasmodics (hyoscine butylbromide), and antiemetics (ondansetron). Sedation was maintained with continuous/intermittent injections of propofol administered by an anesthesiologist. Supplemental nasal oxygen was administered at 3 L/min. Vital signs were continuously monitored by a multiparameter patient monitor.

Extracorporeal shock wave lithotripsy

ESWL sessions were conducted using an electromagnetic lithotripter (Compact Delta II; Dornier MedTech, Germany) for accurate stone targeting. The system has an integrated C-arm (FS 2000 UIIMS; Dornier MedTech, Germany). For easy positioning, the Dornier Relax Imaging Table was used and the patient was in the right anterior oblique position. Each ESWL session lasted for 120 to 150 minutes with a maximum of 8,000 shocks per sitting with an intensity of 70 kV at a frequency of 60 shocks per minute on the desired site. Fluoroscopy was performed prior to each session to assess stone fragmentation. The procedure was carried out on successive/alternate days on an outpatient basis until the largest stone was fragmented to <3 mm or

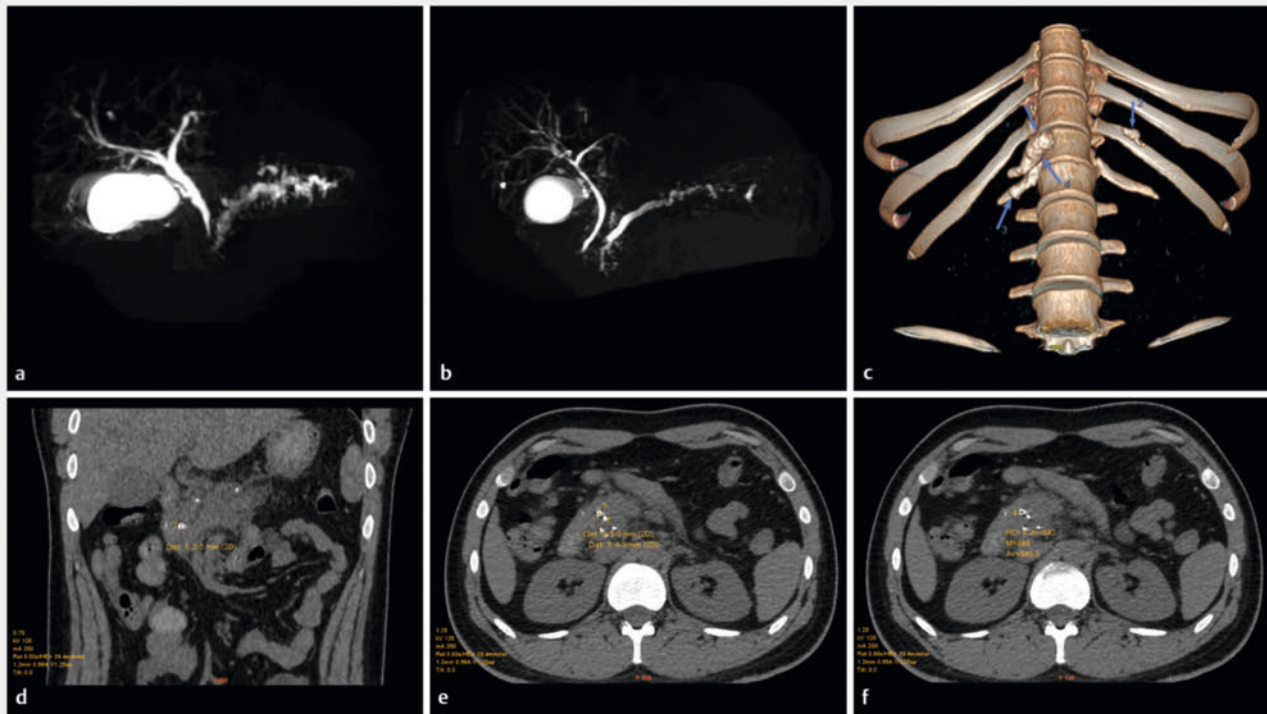


Fig. 1 **a** MRCP showing pancreatic stones. **b** MRCP showing pancreatic stricture. **c** 3D reconstruction of a CT scan of the abdomen showing pancreatic calculi. **d** Sagittal view of CT abdomen showing stone density measurement. **e, f** Axial view of CT abdomen showing stone density measurement.

as per desired fragmentation on fluoroscopy. Once satisfactory fragmentation was noted by a visible loss of stone density and the fragments spreading along the duct (Steinstrasse sign), an ERCP was carried out to extract the stone fragments and clear the duct.

A diclofenac suppository 100 mg was given to all patients rectally 30 minutes before ERCP unless contraindicated. The procedure was performed supine under TIVA using propofol with continuous hemodynamic monitoring. All ERCPs were conducted using a duodenoscope (TJF-160 R Olympus, Japan) with a large (4.2-mm) accessory channel under fluoroscopic guidance. A pancreatic sphincterotomy was performed (TRUEtome Sphincterotome, Boston Scientific, United States), and a pancreatogram was obtained to examine the anatomy of the main pancreatic duct. The pulverized stones were removed by Tetra-Catch V Wire-Guided stone extraction basket (FG-V432P; Olympus Japan) or trawled with an extraction balloon (Multi-3V Plus; Olympus Japan) to confirm a clear duct. A temporary pancreatic duct stent (5F single pigtail/7F straight) was placed to ensure drainage and reduce the risk of pancreatitis before the next session of ERCP. At 3 months, the pancreatic stent was removed. If a pancreatic stricture was encountered, therapeutic stenting was done (10F), ERCP was attempted after 3 months, and the same steps were followed as discussed. Success was defined as adequate stone fragmentation allowing for extraction of stones and ductal clearance at ERCP.

Sample size calculation

An area under the receiver operating characteristic (ROC) curve of 0.85 was used [17] for correctly predicting the complete or incomplete removal of PD stones using a mean stone density. With a 1% level of significance, 95% power and a proportion of complete to incomplete removal (1:1), the sample size was found to be 38 [21]. After correcting 25% for missing data and dropout, the minimum sample size required was 52.

Changes to methods after trial commencement

For study inclusion, patients had to screen negative for COVID-19 pneumonia. The study duration was initially planned for 12 months (including 6 months follow-up) and extended by another 24 months.

Statistical analysis

The patient details were coded and anonymized. The database was imported from Microsoft Excel (Office 2016 Professional for Windows, Microsoft, United States) into IBM Statistical Package for the Social Sciences (SPSS) for Windows [version 26.0, Professional] (IBM Corp, United States). The normality of the data was analyzed through the Shapiro-Wilk test. For continuous variables, descriptive statistics were used. Categorical variables were reported as frequency and percentage. The Chi-square test was applied for nonparametric data and an unpaired t-test for intergroup comparison. The Kruskal-Wallis test compared two or more independent groups of different

► **Table 1** Baseline patient characteristics.

Variable	n=82
Age, median (IQR), y Range	36 (29–55) 20–75
Gender, male, n (%) Male: female	45 (54.9) 1.2:1
Etiology Idiopathic Alcoholic	78 (95.1) 4 (4.9)
Non-contrast CT findings, median (IQR) Maximal transverse length, mm Stone density, HU Stone volume before ERCP, mm ³	9.05 (7.1–14.2) 1095 (860.7–1260.7) 470.7 (209.9–1059.7)
Number of stones, n (%) Single Multiple Median (IQR)	19 (23.2) 63 (76.8) 6 (2.7–7)
Pancreatic duct diameter, median (IQR), mm Dilated pancreatic duct, n (%)	7.5 (6.2–10.7) 79 (96.3)
Stone location, n (%) [*] Head Body Tail Head/body/tail	10 (12.2) 8 (9.8) 1 (1.2) 63 (76.8)
MPD stricture, n (%)	20 (24.4)

^{*}Some patients may have pancreatic duct stones in more than one location. IQR, interquartile range; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MPD, main pancreatic duct.

sample sizes. The nonparametric Mann–Whitney U test (between groups) was used to compare the distribution in the two groups. Bivariate logistic regression analyses were conducted to define predicting factors for stone fragmentation following ESWL, and significant factors were further analyzed. The ROC curve was plotted. Youden index was used to find the HU optimal cut-off value with maximal sensitivity and specificity, and the area under the curve (AUC) was calculated. $P < .05$ was considered statistically significant.

Results

Patient demographics and NCCT characteristics

Eighty-two patients with a median (IQR) age of 36 years (range, 29–55) were included. The majority were male, 45 (54.9%), and the most common etiology was idiopathic CCP in 78 patients (95.1%). The PD was dilated in 79 patients (96.3%). The median pancreatic duct size was 7.5 mm (IQR 6.2–10.7). On NCCT, the median stone density was 1095 (860.7–1260.7) HU (**Supplementary Fig. 1**). Most patients had multiple stones (63; 76.8%). PD stricture was noted in 20 patients (24.4%) (**Table 1**).

► **Table 2** Outcomes of ESWL and ERCP.

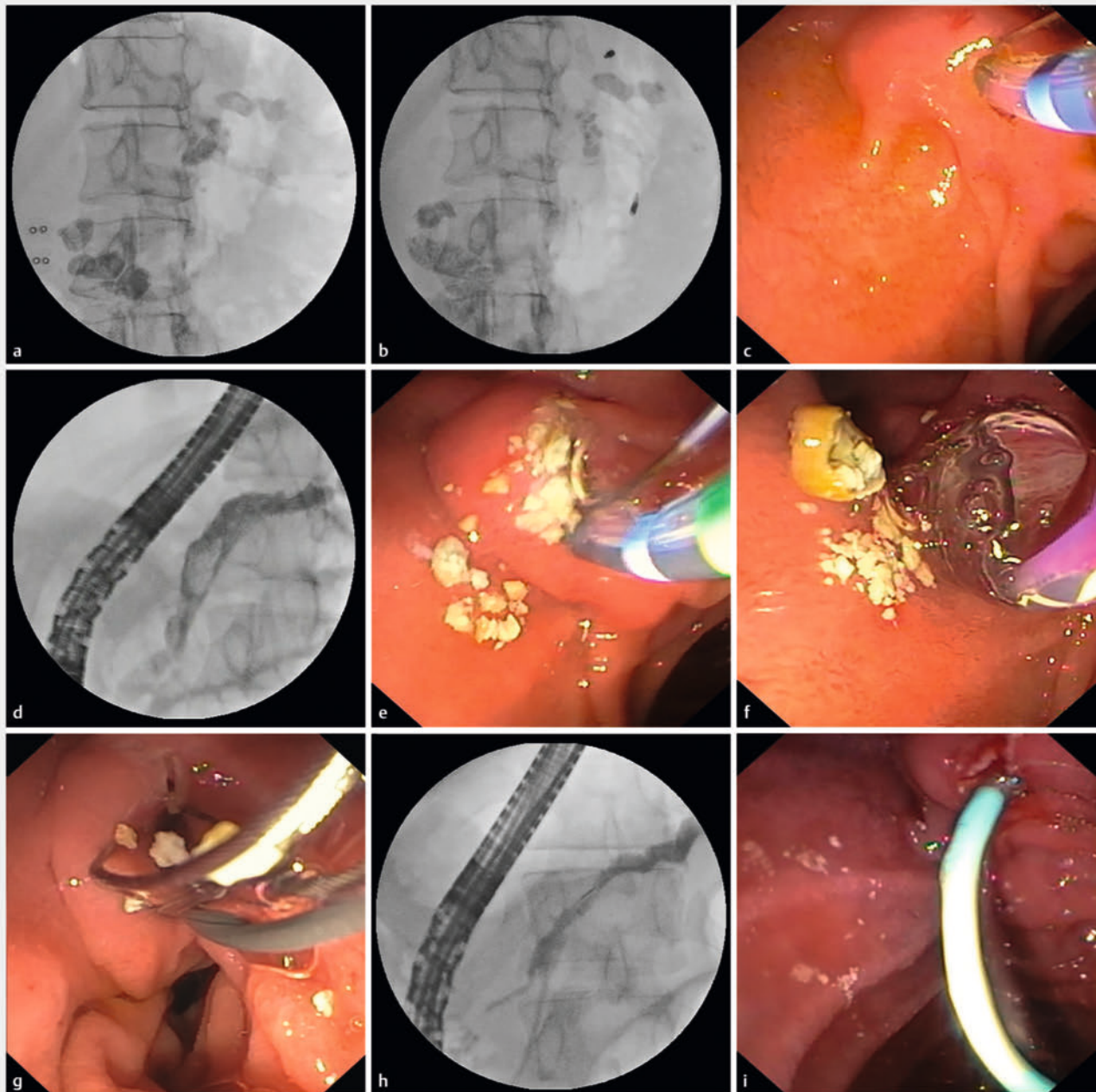
Variable	N=82
No of ESWL sessions, median (IQR)	2 (2–3)
ESWL shockwave number, median (IQR)	16000 (15000–24000)
Pulverization, n (%) Completely pulverized (<5 mm) Incomplete	56 (68.3) 26 (31.7)
Adverse events after ESWL, n (%)	8 (9.8)
No of ERCP sessions, median (IQR)	1 (1–2)
Stone clearance at index ERCP, n (%) Complete Partial	55 (67.1) 27 (32.9)
Partial clearance, n (%) (n = 27) Repeat ESWL Spyglass system laser lithotripsy at ERCP Successful repeat ERCP Patient referred for surgery	4 (14.8) 2 (7.4) 26 (96.3) 1 (3.7)

ESWL, extracorporeal shockwave lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range.

Outcomes of ESWL and ERCP

All patients underwent ESWL with a median (IQR) of two sessions (range, 2–3) (**Table 2**). Patients had up to five sessions with one session in 13 patients (15.9%), two sessions in 31 patients (37.8%), three sessions in 27 patients (32.9%), four sessions in seven patients (8.5%), and five sessions in four patients (4.9%). Nineteen patients (23.2%) had a single stone and 63 patients (76.8%) had multiple stones, but the median ESWL sessions between them was insignificant; $P = 0.481$. When the stone density was < 1100 HU, these patients needed a mean of 2.7 ± 0.9 ESWL sessions versus 3.1 ± 1 when it was ≥ 1100 HU, but the difference was insignificant $P = 0.133$. A Kruskal–Wallis test showed a statistically significant difference in the stone density between the different number of ESWL sessions, $P < 0.001$. ESWL achieved pulverization (< 3 mm) in 56 (68.3%) patients. Adverse events (AEs) after ESWL were seen in eight patients (9.8%) (hematuria [n = 2], abdominal pain [n = 2], skin ecchymosis [n = 1], fever [n = 1], mild bruising [n = 1], and necrotizing pancreatitis [n = 1]). Patients received conservative therapy; no major intervention was required.

Complete stone removal at index ERCP was achieved in 55 patients (67.1%) (**Fig. 2a–i**). All the ERCP procedures were well tolerated. Of those with complete pulverization at ESWL, 55 patients (98.2%) had a favorable index ERCP. Among those with partial clearance (n = 27), four patients (14.8) required repeat ESWL, and two patients (7.4%) needed SpyGlass (Boston Scientific, United States) laser lithotripsy at ERCP. Altogether, repeat ERCP was successful in 26 patients (96.3%). One patient (3.7) had a failed ERCP (tight stricture) on the second attempt and continued to have severe pain; hence, he was referred for surgery (lateral pancreaticojejunostomy). The median follow-up duration was 7 months (range, 6–8).



► **Fig. 2** a Fluoroscopy showing pre-ESWL stones. b Fluoroscopy showing post-ESWL pulverized stones. c Pancreatic sphincterotomy. d Pancreatogram showing pancreatic duct filled with stones. e Pancreatic stones moving out from pancreatic head after sphincterotomy. f Sphincteroplasty with controlled radial expansion balloon. g Pancreatic stones removed by wire-guided stone extraction basket. h Pancreatogram showing pancreatic duct stricture. i Pancreatic duct stenting.

Predictors of a successful outcome

There was a significant, strong positive correlation (Spearman) between the number of ESWL sessions (**Supplementary Table 1**) and stone density ($r=0.797$; $P<0.001$). On bivariate analysis, stone density and the number of ESWL sessions revealed a significant association with complete ductal clearance (► **Table 3**). A logistic regression ascertained the effects of stone density on the likelihood that patients would have stone clearance at ERCP after keeping the number of ESWL sessions constant. The mod-

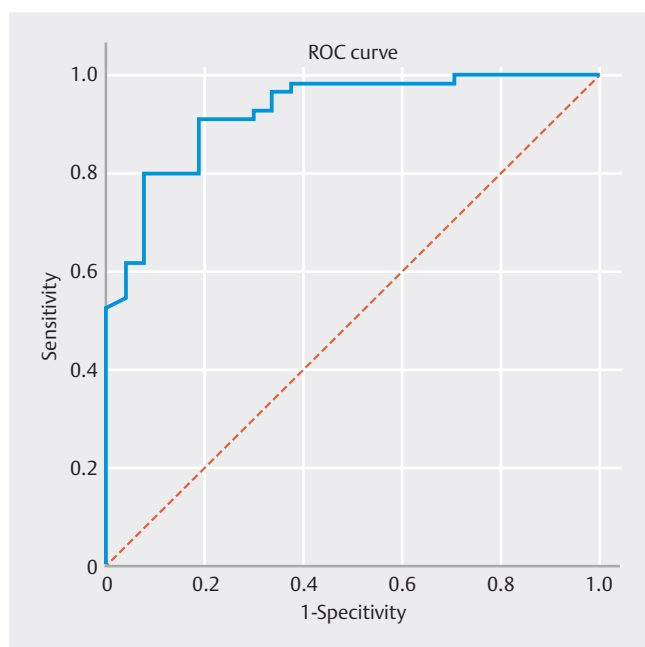
el explained 68.1% (Nagelkerke R^2) of the variance in stone clearance and correctly classified 89% of cases. A stone density >1100 was 91.6% less likely to be associated with stone clearance than a stone density of <1100 after controlling for ESWL sessions (**Supplementary Table 2**).

The optimal cut-point by the ROC curve (► **Fig. 3**) was 1106.5 HU (Youden index 0.726), with a sensitivity of 93% and a specificity of 80% with AUROC of 0.860. Patients with stone density <1106.5 HU had a stone clearance rate of 44 of 46

► **Table 3** Bivariate analysis of factors predicting complete stone removal.

Variable	Complete stone removal (n=55)	Partial stone removal (n=27)	P value
Gender, n (%)			
Male	30 (54.5)	15 (55.6)	0.931
Female	25 (45.5)	12 (44.4)	
Age, median (IQR), y	35 (29–55)	38 (30–55)	0.474
Imaging findings			
No. stones, n (%)			
Single	14 (25.5)	5 (18.5)	0.484
Multiple	41 (74.5)	22 (81.5)	
Stone volume, median (IQR), mm ³	389.9 (203.8–870.4)	613.7 (238.5–1568)	0.225
Stone density, median (IQR), HU	931 (786–1100)	1384 (1234–1758)	<0.001
MPD stricture, n (%)			
Presence	12 (21.8)	8 (29.6)	0.439
Absence	43 (78.2)	19 (70.4)	
No of ESWL sessions, median (IQR)	2 (2–2)	3 (3–4)	<0.001
ESWL shock waves, median (IQR)	16000 (13000–16000)	24000 (24000–32000)	<0.001

IQR, interquartile range; MPD, main pancreatic duct; ESWL, extracorporeal shockwave lithotripsy.



► **Fig. 3** Receiver operating characteristic curve for stone density.

(95.6%) compared with 11 of 36 patients (30.5%) with a higher stone density.

Discussion

The common contributory factor to pain in CCP is the presence of PD stones. The standard radiopaque PD stone extraction technique is ESWL followed by complete ductal clearance at ERCP [15]. At some centers, only ESWL is performed; at other centers, only ERCP is preferred. With advances in technique

and experience, ESWL remains the preferred first modality in most centers that routinely perform pancreatic endotherapy. Fragmentation is successful in 74% to 100% of patients [22, 23, 24]. Decompression of the PD is achieved in up to 96% of patients treated with ESWL followed by ERCP [24, 25]. Appropriate patient selection beforehand will help in preventing unnecessary ESWL and ERCP. Patients that have an alcohol etiology, small pancreatic duct, stricture-predominant disease, and complex morphology should ideally undergo surgery upfront. Whereas patients who have a tropical etiology, simpler morphology, pancreatic ductal stones, simple strictures, and dilated ducts are more suitable for endotherapy [13, 26].

Although the mean number of ESWL sessions was slightly lower in those with stone density <1100 HU, the cut-off of 1100 HU did not impact the required number of ESWL sessions. CT attenuation value expressed in HU was initially used to predict outcomes of kidney stones subjected to ESWL. A recent systematic review found that HU <750 was associated with ESWL success, and >1000 HU showed a likelihood of failure [27]. Similarly, studies in pancreatitis showed that a lower stone density was associated with higher rates of complete stone removal [17, 18, 19]. In 2015, Ohyama H et al. in studied 128 patients and found a cut-off of 820.5 HU to be the most sensitive (77.4%) and specific (78.2%) point on the ROC curve (area under the curve 0.854). At this point, complete stone removal was achieved in 52 patients (78.8%). In 2018 in a retrospective study, Liu R et al. included 148 patients with PD stones patients with lower-density stones (cut-off value 1000.45 HU, sensitivity 78.0%, specificity 48.6%) who had a better stone clearance rate [18]. In a 2019 retrospective study, Liu R et al. included 106 patients and used a cut-off value of 375.4 HU. 12 of 106 patients (11.32%) with stone MSD >375.4 HU had an average SCR of 43.96% and 88.68% of patients with MSD <375.4 HU revealed an average SCR up to 67.7% [19]. In our study, the opti-

mal cut-point by the ROC curve was 1106.5 HU (sensitivity 93%, specificity 80%), with patients with lower stone density having a stone clearance rate of 95.6%. The slight difference in HU in the first two studies is minimal, and the overall notion of 1000 HU stands true. An increase in stone density also requires more ESWL sessions. However, this could be attributed to a different stone composition, and occasionally, patients may have low stone density but may need to be amenable to ESWL therapy. Some of these studies were done more than 5 to 8 years ago [17, 18]. The results of the previous studies could have been due to the type and effectiveness of the lithotripsy machine, the number of shocks delivered, and the definition of complete stone removal. The success of ERCP also depends on the expertise of the endoscopist. Being a high-volume center, the results might have been better with an overall complete ductal clearance in 98.7% of patients.

Optimal anesthesia reduces patient movement, allowing accurate targeting, thereby minimizing exposure of shockwaves to surrounding organs. We used TIVA, which can be more demanding compared with epidural anesthesia. Multiple drugs are used, and their effect depends on the dosage used. With the latter, epidural catheters are inserted in the epidural space, and these patients must be hospitalized. Postdural puncture headache can be encountered, and central neuraxial infection should never be forgotten, which would never have happened otherwise. Often, anesthetic drugs can leak back from a fistulous track, resulting in a need to readjust the epidural catheter. The current recommendation for epidural catheter removal is 48 hours to prevent infection. The cost cannot be compared, but medications with TIVA can be managed at almost half the cost of an epidural catheter, ignoring the added hospitalization expense with the latter modality; the cost-effectiveness may need to be studied. Despite the higher stone density of pancreatic stones, which required more ESWL sittings, TIVA performed satisfactorily in our patients. Thus, most ESWL sessions could be done in the outpatient setting. Pancreatitis contributes to intense visceral pain; hence, a great depth of sedation at ERCP is necessary. A bolus of propofol is preferred, especially in patients with pancreatic strictures, so the peak effect coincides with the dilation of stricture.

We had minimal AEs. One patient developed severe abdominal pain with vomiting. She had elevated pancreatic enzymes (lipase 1000 U/L) and raised C-reactive protein levels (73 mg/L). She received IV analgesics and IV fluids. CT showed multiple ill-defining hypoenhancing areas within the uncinate process, suggestive of early necrosis. She received nasojejunal tube feeding and recovered gradually. AEs in other studies include bleeding, splenic rupture, bruising, bowel perforation, and sepsis [28]. Seven patients (8.5%) complained of mild pain after the ERCP procedure, which was treated with analgesics. There were no major AEs at endoscopy.

This was a single-center prospective observational study with a modest sample size; hence, the findings may not be generalizable. The chemical composition of stones was not studied; cystine, calcium oxalate monohydrate, and brushite are difficult to break with ESWL, contributing to failure. Dual-energy CT is useful for characterizing chemical composition in nephro-

lithiasis and its management [29]. Outcomes could be further improved by conducting a randomized study of dual-energy CT with NCCT in CP. Skin-to-stone distance has been used in previous nephrolithiasis studies, but some found no impact on outcomes [30], so it was not used. NCCT was not performed after ESWL therapy because fluoroscopy provides a clear picture and would unnecessarily contribute to additional cost. Recurrence of pancreatic stones has been seen, but the median follow-up duration was only 7 months. During this time frame, we did not encounter the same. We did not assess pain and QOL before and after therapy, as that was not the study objective. Nevertheless, the optimal cut-off 1106.5 HU does serve as a reference for future studies for successful ESWL therapy before attempting ductal clearance with ERCP or use ESWL as a monotherapy.

Conclusions

To summarize, ESWL effectively pulverizes large radiopaque PD stones in CCP with minimal complications and allows successful extraction during ERCP. A SD of <1106.5 HU is a good indication for successful ESWL therapy and a significant predictor of complete ductal clearance. This is helpful for planning definitive treatment or selecting an alternative therapeutic option. The results may need validation in future well-controlled trials with a larger patient population. Intra-ductal pancreatoscopy-guided laser lithotripsy during endoscopy may be an alternative to ESWL, which requires a prospective randomized trial.

Acknowledgement

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

Trial registry: Clinical Trials Registry India (<http://www.ctri.nic.in/Clinicaltrials>)
Registration number (trial ID): CTRI/2019/06/019750
Type of Study: Prospective observational study

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