

[ORIGINAL ARTICLE]

The Visceral-to-subcutaneous Adipose Tissue Area Ratio Is Associated with Retreatment in Chronic Pancreatitis Patients with Pancreatolithiasis after Extracorporeal Shock Wave Lithotripsy

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Abstract:

Objective Extracorporeal shock wave lithotripsy (ESWL) has been used to treat pancreatolithiasis in patients with chronic pancreatitis (CP), but the high recurrence rate remains challenging. We therefore evaluated the association between body composition parameters and the prediction of retreatment after ESWL.

Methods This study retrospectively evaluated 42 patients with CP who had been treated with ESWL between 2008 and 2019 in a single center. Body composition parameters were measured on pretreatment computed tomography images. Patients who underwent repeat ESWL were classified as the retreatment group.

Results There were 13 (31.0%) and 29 (69.0%) patients in the retreatment and non-retreatment groups, respectively. The visceral-to-subcutaneous adipose tissue area ratio (VSR) of the retreatment group was significantly lower than that of the non-retreatment group ($p=0.016$). When divided by the median VSR, 10 of the 20 patients with a VSR of <0.85 underwent retreatment, whereas 3 of the 22 patients with a VSR of ≥ 0.85 underwent retreatment ($p=0.019$). According to a multivariate analysis, the VSR ($p=0.010$) and age ($p=0.037$) were independent factors associated with retreatment after ESWL.

Conclusion This study showed that the VSR can predict the retreatment of patients with CP after ESWL.

Key words: body composition, chronic pancreatitis, pancreatolithiasis, extracorporeal shock wave lithotripsy, skeletal muscle

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Introduction

Chronic pancreatitis (CP) describes a wide range of progressive fibroinflammatory diseases of the exocrine pancreas that eventually lead to damage of the gland. If widespread, this damage causes failure of the exocrine and endocrine functions of the pancreas (1). A recent population-based study from the Mayo Clinic revealed that the age-adjusted and sex-adjusted incidence of CP was 4.05 per 100,000 person-years [95% confidence interval (CI) 3.27-4.83] and that the prevalence of CP was 41.76 per 100,000 population

(95% CI 30.21-53.32) (2). Pancreatolithiasis develops during the natural course of CP and is observed in 90% of CP patients (3).

Endoscopic therapy and surgery are both conventional treatments that allow the restoration of pancreatic duct flow and decompression of intraductal pressure. Extracorporeal shock wave lithotripsy (ESWL) for pancreatolithiasis was first reported by Sauerbruch et al. in 1987 (4), and since then, it has been clinically applied to the treatment of pancreatolithiasis. ESWL is reported to be less invasive and with higher efficacy and lower complication rates than surgery (5, 6). However, the high recurrence rate of pancreato-

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lithiasis (up to 40%) after ESWL remains an important clinical problem (7, 8). Little is known about the predictive factors of recurrence after ESWL.

The body mass index is a widely used anthropometric index for assessing the degree of obesity and is associated with clinical outcomes of malignancies (9). In addition, recent studies have revealed that the quantification of several body composition parameters, such as skeletal muscle mass and visceral adipose tissue (VAT) volumes, is also useful for determining the prognosis of patients with hepatocellular carcinoma (10, 11). We previously reported that a high subcutaneous adipose tissue (SAT) volume is associated with improved survival outcomes in patients with hepatocellular carcinoma treated with transarterial chemoembolization (12). To our knowledge, no reports have examined the clinical significance of body composition parameters in patients with CP and pancreatolithiasis treated with ESWL.

We therefore investigated the relationship between body composition factors (subcutaneous fat, visceral fat, and skeletal muscle) and recurrence in patients with pancreatolithiasis who underwent ESWL.

Materials and Methods

Patients

We retrospectively analyzed 42 consecutive CP patients who underwent ESWL for pancreatolithiasis as an initial treatment at Niigata Prefectural Yoshida Hospital between November 2008 and October 2019. The diagnosis of pancreatolithiasis was confirmed based on computed tomography (CT). The day of treatment completion was defined as the first day of follow-up. After treatment completion, patients were followed up regularly in outpatient clinics every 3 to 12 months, with a median follow-up period of 1,142 (range, 70-3,969) days. Imaging surveillance of post-treatment recurrence of pancreatolithiasis was conducted with CT every 12 months. Patients with a suspected recurrence of pancreatolithiasis underwent CT at the time. Four patients were followed at another outpatient clinic, with no evidence of pancreatolithiasis recurrence. Five patients died during the observation period and causes of death were lung cancer in two, aspiration pneumonia in one, and unknown in two. There were no cases of pancreatolithiasis recurrence during the observation period in these patients.

This retrospective study was approved by the ethics committee of Niigata Prefectural Yoshida Hospital and conducted in accordance with the Helsinki Declaration (approval number 147). Because of the anonymous nature of the data, the requirement for informed patient consent was waived.

Treatment procedure

The indications for ESWL were determined according to the clinical practice guidelines for CP of the Japanese Society of Gastroenterology (13). Before ESWL, endoscopic ret-

rograde pancreatography was first performed to evaluate pancreatolithiasis and stenosis, and endoscopic nasopancreatic drainage placement was performed when possible. Stenosis was defined as a main pancreatic duct (MPD) less than 2 mm in diameter with dilatation of the caudal pancreatic duct. In cases with an incarcerated stone, stenosis was determined by endoscopic retrograde pancreatography after the removal of the stones. ESWL was performed with an electrohydraulic spark gap lithotripter (Triptor X-1; Direx, Wiesbaden, Germany) and an electromagnetic lithotripter (Integra; Direx) in 25 and 17 patients, respectively. Diclofenac and pentazocine were used for pain control. ESWL sessions consisted of 3,000 to 4,000 shocks per session and were performed twice per week. The fragmented stones were removed endoscopically with a basket catheter, where possible.

The treatment was deemed a clinical success if pancreatolithiasis disappeared or fragmented into pieces <3 mm in diameter according to abdominal CT, resulting in relief of abdominal pain. This is because, as previously reported, any remaining small stones are expected to be eliminated spontaneously over time (14, 15). A plastic stent (Geenen pancreatic stent; Cook Medical, Tokyo, Japan) was placed if pancreatic stone removal was incomplete at the time of the initial treatment or if the MPD was highly stenotic. Stent placement was performed in 7 patients (16.7%), and its replacement was performed every 3 to 6 months. The median duration of stent placement was 168 (range 69-1,909) days. The indication for retreatment was if pancreatolithiasis recurred and was the cause of abdominal pain. For retreatment, endoscopic treatment was the first step. If the endoscopic treatment failed to remove the stones, ESWL was performed. In this study, patients who underwent ESWL again were defined as the "retreatment group," while the "non-retreatment group" comprised patients without repeat ESWL. No treatment-related deaths occurred.

Body composition quantification

The body composition variables were quantified by acquisition of a plain CT slice image at the umbilical level prior to treatment. The skeletal muscle area, VAT area, and SAT area were measured using the sliceOmatic software program (version 5.0; Tomovision, Montreal, Canada; Fig. 1). The thresholds of tissue Hounsfield units (HU) for the delineation of the regions were as follows: -29 to +150 HU for skeletal muscle, -150 to -50 HU for VAT, and -190 to +30 HU for SAT, as reported previously (16, 17). These cross-sectional areas (cm²) were normalized by the height squared (m²) to determine the skeletal muscle index (SMI), VAT index (VATI), and SAT index (SATI). The VAT-to-SAT ratio (VSR) was calculated. Skeletal muscle attenuation (MA) was also calculated by measuring the average HU of the overall skeletal muscle area at the third lumbar vertebra. All measurements of body composition using CT were performed by K.Y.

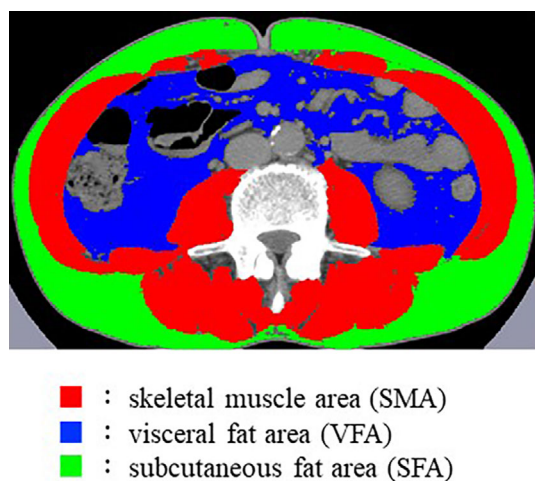


Figure 1. Cross-sectional computed tomography images at the umbilical level to measure body composition areas. Red, blue, and green areas indicate skeletal muscle, visceral fat, and subcutaneous fat area, respectively. SMA: skeletal muscle area, VFA: visceral fat area, SFA: subcutaneous fat area

Statistical analyses

All statistical analyses were performed using the SPSS software program, version 25 (IBM Japan, Tokyo, Japan). Continuous and categorical variables are presented as the median (range) and number (percentage), respectively. Differences between the two groups were analyzed with the Mann-Whitney U tests for continuous variables and Fisher's exact tests or chi-squared tests for categorical variables. Spearman's rank correlation test was used to determine correlations between the VSR and other body composition indices, VATI, SATI, MA, and SMI at the third lumbar vertebra (L3-SMI). Independent factors associated with retreatment after ESWL were assessed using a logistic regression analysis. Factors with $p < 0.10$ in the univariate analysis were included in the multivariate analysis. The diagnostic performance of VSR for predicting retreatment after ESWL was evaluated by a receiver operating characteristic (ROC) curve analysis. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient baseline characteristics

A total of 42 consecutive patients (39 men, 3 women) with CP were treated at Niigata Prefectural Yoshida Hospital. The median age was 63 (range, 32-80) years, and the median body mass index was 21.1 (range, 15.0-27.1) kg/m^2 . The cause of CP was alcohol-related in 32 patients (76.2%). The median stone diameter was 10.3 (range, 5.0-23.8) mm. The median SATI and VATI were 28.4 (range, 3.7-70.1) cm^2/m^2 and 25.2 (range, 0.86-75.0) cm^2/m^2 , respectively. Detailed information on patients who underwent ESWL is provided in Table 1. No patients who were followed required

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.

Variable	Total (n=42) Median (range)
Age, years	63 (32-80)
Sex, male/female	39/3
BMI, kg/m^2	21.1 (15.0-27.1)
Etiology, alcohol/non-alcohol	32/10
Diabetes, yes/no	17/25
Stones	
Number, single/multiple	9/33
Distribution, 1 area/ ≥ 2 areas	22/20
Maximum diameter, mm	10.3 (5.0-23.8)
MPD stricture, yes/no	32/10
Complete crushing rate, %	83.3
Partial crushing rate, %	16.7
Stent placement, yes/no	7/35
Laboratory findings	
Serum amylase, U/L	90 (29-1,642)
Serum albumin, g/dL	4.2 (3.2-4.8)
Total cholesterol, mg/dL	162 (95-272)
SATI, cm^2/m^2	28.4 (3.7-70.1)
VATI, cm^2/m^2	25.2 (0.86-75.0)
VSR	0.85 (0.23-1.96)
MA, HU	43.7 (22.3-64.5)
L3-SMI, cm^2/m^2	45.1 (30.9-56.5)

BMI: body mass index, MPD: main pancreatic duct, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, VSR: visceral to subcutaneous adipose tissue area ratio, MA: muscle attenuation, HU: Hounsfield unit, L3-SMI: skeletal muscle index at the third lumbar vertebra

surgery.

Effect of ESWL and differences in clinical characteristics according to the treatment response

Baseline characteristics between the retreatment and non-retreatment groups are shown in Table 2. There were 13 patients (31.0%) in the retreatment group and 29 patients (69.0%) in the non-retreatment group. As in previous reports (7, 18), most of the patients required retreatment within three years. Among those, there were five cases that were retreated early (within one year; Fig. 2). The retreatment group tended to be younger than the non-retreatment group. There were no marked differences in the sex, BMI, alcohol etiology, diabetes, stone characteristics (diameter, number, or distribution), MPD stricture, stenting, or laboratory findings between the two groups. Among the body composition indices, the VATI tended to be lower in the retreatment group than in the non-retreatment group. Of note, the VSR of the retreatment group was significantly lower than that of the non-retreatment group ($p = 0.016$).

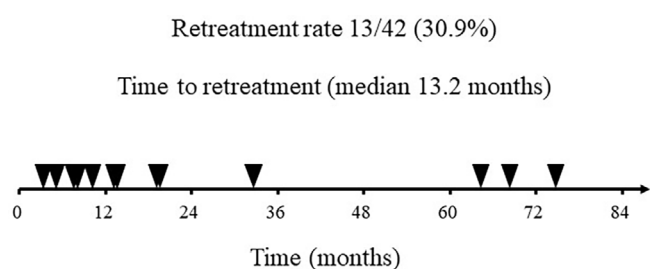
Correlation between the VSR and other body composition indices

We analyzed the correlation between the VSR and other body composition indices (i.e. VATI, SATI, MA, and L3-

Table 2. Comparison of Demographic and Clinical Characteristics between Retreatment and Non-retreatment Groups.

Variable	Retreatment group (n=13) Median (range)	Non-retreatment group (n=29) Median (range)	p value
Age, years	54 (32-77)	64 (40-80)	0.134
Sex, male/female	11/2	28/1	0.222
BMI, kg/m ²	21.3 (15.0-26.3)	21.0 (17.2-27.1)	0.828
Etiology, alcohol/non-alcohol	10/3	22/7	>0.999
Diabetes, yes/no	3/10	14/15	0.179
Stones			
Number, single/multiple	3/10	6/23	>0.999
Distribution, 1 area/≥2 areas	6/7	16/13	0.741
Maximum diameter, mm	11.0 (8.8-13.0)	10.0 (8.3-14.2)	0.683
MPD stricture, yes/no	11/2	21/8	0.466
Stent placement, yes/no	4/9	3/26	0.176
Serum amylase, U/L	93 (29-639)	73 (38-1,642)	0.488
Serum albumin, g/dL	4.1 (3.3-4.8)	4.2 (3.2-4.8)	0.789
Total cholesterol, mg/dL	157 (95-225)	164 (104-272)	0.516
SATI, cm ² /m ²	33.4 (6.3-70.1)	28.0 (3.7-68.3)	0.881
VATI, cm ² /m ²	19.4 (4.7-39.9)	29.3 (0.86-75.0)	0.111
VSR	0.64 (0.25-1.17)	0.91 (0.23-1.96)	0.016
MA, HU	44.8 (28.3-54.6)	42.8 (22.3-64.5)	0.924
L3-SMI, cm ² /m ²	46.9 (35.0-52.1)	42.7 (31.0-56.5)	0.187

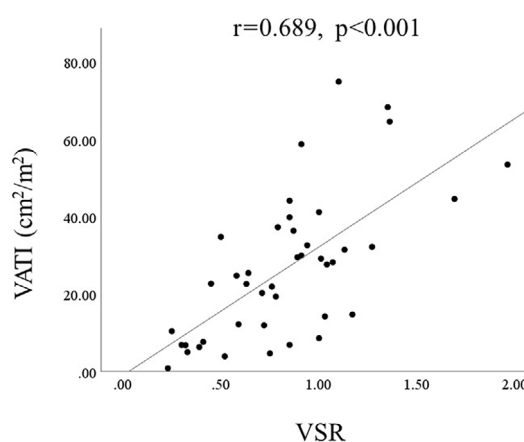
BMI: body mass index, MPD: main pancreatic duct, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, VSR: visceral to subcutaneous adipose tissue area ratio, MA: muscle attenuation, HU: Hounsfield unit, L3-SMI: skeletal muscle index at the third lumbar vertebra

**Figure 2. Time from completion of treatment to retreatment.**

SMI). The VSR was shown to be positively correlated with only the VATI ($r=0.689$, $p<0.001$) (Fig. 3).

Univariate and multivariate analyses for factors associated with retreatment after ESWL

To identify factors associated with retreatment after ESWL, univariate and multivariate logistic regression analyses were performed (Table 3). Each continuous variable denoted in Table 1 was divided by the median. In the univariate analysis, a VSR of <0.85 was found to be a significant factor ($p=0.016$). Subsequently, the VSR and age (univariate significance of $p<0.10$) were included in the multiple logistic regression analysis. An age <63 years old ($p=0.037$, odds ratio 5.732, 95% CI 1.107-29.684) and VSR <0.85 ($p=0.010$, odds ratio 9.122, 95% CI 1.680-49.539) were found to be independent factors associated with retreatment after ESWL.

**Figure 3. Correlation between the VSR and the VATI. VSR: visceral to subcutaneous adipose tissue area ratio, VATI: visceral adipose tissue index**

Prediction of retreatment after ESWL by the VSR

We evaluated the diagnostic performance of the VSR using an ROC curve analysis, which revealed that an area of 0.735 had 84.6% specificity and 58.6% sensitivity (at the cutoff value of 0.85) in discriminating the retreatment group from the non-retreatment group (Fig. 4a). Among the 20 patients with a VSR <0.85 , 10 (50.0%) underwent retreatment after ESWL, whereas among the 22 patients with a VSR ≥ 0.85 , 3 (13.6%) underwent retreatment after ESWL. There was a statistically significant difference between these two

Table 3. Logistic Regression Analysis for Recurrence after ESWL in Chronic Pancreatitis Patients.

Variable		Univariate analysis		Multivariate analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Age	<63 years	3.682 (0.911-14.88)	0.067	5.732 (1.107-29.68)	0.037
Sex	Male	0.196 (0.016-2.392)	0.202		
BMI	<21.1 kg/m ²	0.583 (0.154-2.214)	0.428		
Etiology	Alcohol	0.716 (0.167-3.061)	0.652		
Diabetes	Yes	0.321 (0.073-1.414)	0.133		
Stones					
Number	Single	1.150 (0.239-5.540)	0.862		
Distribution	≥2 areas	1.436 (0.386-5.339)	0.589		
Maximum diameter	≥10.3 mm	1.969 (0.518-7.488)	0.320		
MPD stricture	Yes	2.095 (0.378-11.62)	0.397		
Stent placement	Yes	3.852 (0.719-20.62)	0.115		
Serum amylase	≥90 U/L	1.250 (0.337-4.639)	0.739		
Serum albumin	≥4.2 g/dL	0.743 (0.199-2.779)	0.659		
Total cholesterol	≥160 mg/dL	0.476 (0.118-1.929)	0.299		
SATI	<28.4 cm ² /m ²	0.800 (0.216-2.969)	0.739		
VATI	<25.2 cm ² /m ²	3.187 (0.794-12.80)	0.102		
VSR	<0.85	6.333 (1.413-28.39)	0.016	9.122 (1.680-49.54)	0.010
MA	<43.7 HU	0.670 (0.176-2.542)	0.556		
L3-SMI	<45.1 cm ² /m ²	0.314 (0.078-1.260)	0.102		

Each continuous variable was divided into two categories according to median value. Only variable, age, with a univariate value of $p < 0.10$ was allowed to enter the multivariate analysis. ESWL: extracorporeal shock wave lithotripsy, OR: odds ratio, CI: confidence interval, BMI: body mass index, MPD: main pancreatic duct, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, VSR: visceral to subcutaneous adipose tissue area ratio, MA: muscle attenuation, HU: Hounsfield unit, L3-SMI: skeletal muscle index at the third lumbar vertebra

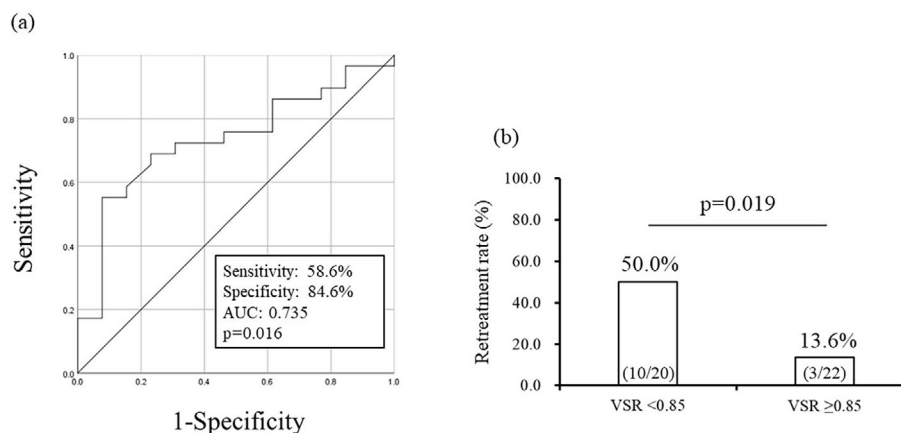


Figure 4. (a) Receiver operating characteristic curve for predicting retreatment after ESWL in 42 chronic pancreatitis patients with pancreatolithiasis. (b) A comparison of retreatment rates between patients with a VSR of < 0.85 and those with a VSR of ≥ 0.85 . AUC: area under the curve, ESWL: extracorporeal shock wave lithotripsy

groups ($p = 0.019$) (Fig. 4b).

Discussion

Pancreatolithiasis is a sequela of CP, and its formation causes increased intraductal pressure that can lead to pain and complications, such as pancreatic pseudocysts. ESWL is now the accepted standard of care for the management of pancreatolithiasis worldwide; however, one of the limitations

of this procedure is the high recurrence rate (5). To our knowledge, this is the first study to evaluate the association between body composition parameters and the prediction of retreatment after ESWL. In summary, we found that the VSR can be a useful marker for predicting the need for retreatment of patients with CP after ESWL.

Previous studies have reported that there are some risk factors for stone recurrence following ESWL. Yamamoto et al. reported that the recurrence rate was significantly higher

in non-elderly patients (<65 years old) than in elderly patients (≥65 years old) (8). Similarly, in the present study, age <63 years old was one of the factors identified as being associated with retreatment after ESWL. Therefore, non-elderly patients need to be carefully monitored after ESWL. Regarding the etiology of CP, the stone recurrence rate of alcohol-induced CP is known to be higher than that of non-alcohol-induced CP (8). In patients with alcohol-induced CP, continued alcohol abuse is a risk factor for stone recurrence following ESWL (7). In the present cohort, stone recurrence was found in 10 of 32 cases of alcohol-induced CP and in 3 of 10 cases of non-alcohol-induced CP, showing no significant difference between the groups. In addition, the relationship between continued alcohol consumption and stone recurrence could not be examined in patients with alcohol-induced chronic pancreatitis due to insufficient interviews. MPD stricture is reported as another risk factor for stone recurrence following ESWL (8, 19). Yamamoto et al. divided recurrence cases into those within one year of treatment and those after one year and found that the recurrence rate within one year was significantly higher in cases with MPD stricture than in those without (8). In the present cohort, although there were many cases (32/42 cases) of MPD stricture, there were 5 cases of retreatment within 1 year, all of which involved MPD stricture. MPD stricture is thought to cause a poor outflow of pancreatic juice and stasis, which may lead to early recurrence.

Recent reports indicate the relationship between body composition and pancreatic diseases. Sternby et al. examined the association between body composition and disease severity in 454 patients with acute pancreatitis and found that mean MA was only correlated with disease severity (20). Choi et al. reported that preoperative sarcopenia and postoperative accelerated muscle loss were associated with a poor overall survival after pancreatic cancer resection (21). In this study, we found that the VSR was associated with retreatment following ESWL in patients with CP.

The mechanism of pancreatic stone formation in patients with CP has been speculated. In CP, an increase in protein secretion, including pancreatic stone proteins and lactoferrin, appears in the pancreatic juice (22). With the onset of pancreatitis, trypsinogen (inactive form) becomes trypsin (active form), which changes soluble pancreatic stone proteins into an insoluble form. It is believed that the increase in insoluble pancreatic stone proteins and lactoferrin facilitates the formation of protein plugs and eventually pancreatic stones. However, lactoferrin is known to have an effect on visceral fat. Ono et al. reported that enteric-coated lactoferrin tablets decreased visceral fat accumulation in obese patients, and *in vitro* studies suggested that this was due to the promotion of lipolysis and the anti-adipogenic activity of lactoferrin (23, 24). In the present study, the VSR was positively correlated with the VATI but not the SATI. Given these findings, it can be inferred that patients in the retreatment group showed a low VSR due to visceral fat loss caused by the high lactoferrin concentration in pancreatic juice, making

them prone to pancreatic stone formation after treatment. In the future, we will study the lactoferrin concentrations in pancreatic juice.

Several limitations associated with the present study warrant mention. First, this was a single-center retrospective study and included a small number of patients. Thus, there might have been some selection bias. Second, age was also an independent factor associated with retreatment after ESWL. The VSR is known to increase with age (25), making it a potential confounder of our results. Third, most of the patients in this cohort were men, so whether or not the results of this study apply to women with CP is currently unclear. Fourth, the effect of ESWL on the pancreatic endocrine and exocrine functions has not been studied.

In conclusion, the VSR is useful as a predictor of retreatment after ESWL. Given the high recurrence rate of ESWL treatment for pancreatolithiasis, a body composition assessment prior to ESWL treatment seems important in clinical practice to help identify patients likely to require retreatment.

The authors state that they have no Conflict of Interest (COI).

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