

BILIARY AND PANCREATIC

Extracorporeal shock wave lithotripsy is safe and effective for geriatric patients with chronic pancreatitis

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Key words

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Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas that is characterized by parenchymal fibrosis,

formation of pancreatic duct calculi, and progressive exocrine and endocrine dysfunction.¹ Obstruction of the main pancreatic duct (MPD) secondary to stones or stricture formation causes a rise in duct pressure resulting in pain.²

Abstract

Background and Aim: Pancreatic extracorporeal shock wave lithotripsy (P-ESWL) is a first-line treatment for chronic pancreatitis (CP) patients with pancreatic stones. However, the performance of P-ESWL in geriatric patients remains unclear. We aimed to evaluate the safety and efficacy of P-ESWL for them.

Methods: This prospective study was conducted in painful CP patients who underwent P-ESWL. Patients aged over 65 years were included in geriatric group; patients aged under 65 years were assigned to control group. For the long-term follow-up investigation, geriatric patients were matched with patients from the control group in a 1:1 ratio. Primary outcomes were complications of P-ESWL and pain relief. Secondary outcomes included stone clearance, physical and mental health, quality of life score, changes in exocrine and endocrine pancreatic function, and survival.

Results: From March 2011 to March 2016, P-ESWL was performed in 1404 patients (72 in the geriatric group and 1332 in the control group). No significant differences were observed in complications of P-ESWL between the two groups ($P = 0.364$). Among the 67 (67/72, 93.1%) geriatric patients who underwent follow up for 4.02 years, complete pain relief was achieved in 53 patients, which was not significantly different from that of matched controls (54/70; $P = 0.920$). The death in the geriatrics was significantly higher ($P = 0.007$), but none of them were correlated with P-ESWL.

Conclusions: P-ESWL is safe and effective for geriatric CP patients with pancreatic stones. It can promote significant pain relief and stone clearance and improve quality of life and mental and physical health.

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In 2013, the World Health Organization Health Report addressed the issue of global aging, and a large number of people will suffer from chronic diseases.³ The CP populations are also aging, with the mean age increasing year by year, especially in developed countries (Fig. S1).^{4–6} Unit root test was adopted to test the stationarity of these series, with $P < 0.05$ indicating stationary. America: $P = 0.457$; Europe: $P = 0.544$). In developing countries, the mean ages are similar (China: $P = 0.033$). This may be attributed to the alleviation of aging in developing countries in the past years. However, 13.2% of the CP patients in China were 65 years or older,^{7–9} which indicates that developing countries will also face the problem of aging in the next few years. Frequency of pancreatic duct stones were found increased depending on the age of the patients.^{10,11} However, elderly patients undergoing surgery are at higher risk to have adverse events and have an increased mortality compared with younger patients.¹² Because morbidity of major surgery in elderly patients is high, endoscopic approaches should be preferred for the management of CP or might be even the only option in some patients who cannot undergo surgery because of severe comorbidities.¹³

Pancreatic extracorporeal shock wave lithotripsy (P-ESWL) is minimally invasive, effective, and safe for the management of young adults and pediatrics with pancreatic stones.^{14,15} However, the safety and efficacy of P-ESWL in geriatric patients have not been previously reported.

The main concern with regard to the application of P-ESWL in geriatric patients is the potential for complications of the procedure, such as acute pancreatitis, perforation, bleeding, infection, and anesthesia-related side effects. The aim of our study was to evaluate the safety and efficacy of P-ESWL in the treatment of geriatric patients with pancreatic stones.

Methods

Study design. We performed a prospective cohort study to evaluate the outcome of geriatric patients with pancreatic stones who underwent P-ESWL in comparison with the outcome of all young patients who underwent P-ESWL within the same period. Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of Changhai Hospital. This study was registered on ClinicalTrials.gov (ID: NCT03373682).

Patients and data collection. The target population for P-ESWL was patients with painful CP and radiopaque stones of ≥ 5 mm. For CP patients who did not experience pain, interventions were performed only when complications such as biliary stricture, infection, or pancreatic pseudocyst enlargement occurred.¹⁶ Diabetes mellitus (DM) and/or steatorrhea were not indications for invasive treatment of CP. Patients with a suspected or established malignant mass or pancreatic ascites and pregnant patients were not considered for the P-ESWL treatment. The diagnosis of CP was established primarily based on computed tomography (CT), magnetic resonance imaging, or endoscopic ultrasound examinations according to the Asia-Pacific consensus.¹⁷ DM was diagnosed¹⁸ and managed¹⁹ according to the criteria of the American Diabetes Association. Medication management, sliding scale insulin, combined with nutrition support was carried

out for CP patients with diabetes. Steatorrhea was diagnosed when one of the following two conditions was met: (i) stench, oily chronic diarrhea²⁰ and (ii) positive result in quantification of fecal fat determination (fecal fat quantitation was performed within 3 days; patients with stool fat excretion over 14 g/day was diagnosed as steatorrhea). All of the patients were evaluated with CT scans prior to P-ESWL.

Patients aged older than 65 years who underwent P-ESWL treatment from March 2011 to March 2016 were included in the geriatric group,²¹ whereas patients less than 65 years who underwent P-ESWL treatment in the same period were assigned to the control group. Demographic data and the disease course of the CP, including the onset, manifestations, diagnosis, and previous treatments, were recorded in detail upon admission to the hospital. In addition, the visual analog scale (VAS) pain score, quality of life score, and Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) questionnaire were completed.

To evaluate the long-term outcomes of P-ESWL in geriatric patients, we matched the geriatric group with patients from the control group in a 1:1 ratio. The matching principles were sex, type of abdominal pain, and location of the stones.

For patients in the geriatric group and patients selected as the matched controls, revisits were required annually after P-ESWL therapy. During the revisits, contrast-enhanced CT of the pancreas was performed, and follow up data, including the disease course of the CP after P-ESWL, VAS pain score, usage of medication, disease-related inability to work, quality of life score, and SF-36 questionnaire, were recorded. In November 2017, we evaluated the patients in the geriatric group and the matched control group included in this study.

Treatment strategy. In this study, all of the patients involved were treated with P-ESWL after admission to the hospital. P-ESWL was performed using a third-generation electromagnetic lithotripter (Compact Delta II; Dornier Med Tech, Wessling, Germany). After they had received intravenous sedation analgesia (remifentanyl and flurbiprofen), the patients were treated in the supine position with the shock head touching the abdomen from above. Pancreatic duct stones were targeted by the lithotripter using fluoroscopy.

For each individual patient, the P-ESWL session was repeated on consecutive days until the stone was fragmented to ≤ 3 mm in diameter. No more than 5000 shocks at an intensity of 6 (16 000 kV) on a scale of 1–6, at a frequency of 120 shocks/min were delivered during each therapeutic session. The duration of each session was 60–90 min.^{15,22} Radiation protection was provided by adhering to the European Society of Gastrointestinal Endoscopy guidelines.²³

For patients in the geriatric group, a pancreatic surgery team was on call for elective surgery during the study in case of severe complications. Also, the emergent surgery team was prepared for all patients. Endoscopic retrograde cholangiopancreatography (ERCP) was routinely performed 48 hours after the last P-ESWL. The treatment principle for the ERCP mainly followed the European Society of Gastrointestinal Endoscopy guidelines.²⁴

Outcome measures. A standardized evaluation of symptoms and investigations was carefully performed after every P-

ESWL session and after the ERCP that was performed post-P-ESWL. Any complications and relevant treatments were documented during the subsequent 30 days after P-ESWL and ERCP.

The primary outcomes were complications of P-ESWL^{14,15} (Table S1) and pain relief. Secondary outcomes were stone clearance, physical and mental health, quality of life score, changes in exocrine and endocrine pancreatic function, and death.

Pain relief at the end of the follow-up period was classified as complete relief (Izbicki pain score ≤ 10) or partial relief (Izbicki pain score > 10 after a decrease of $> 50\%$).^{25,26} Stone clearance was evaluated at the ERCP performed post-P-ESWL, with complete clearance defined as clearance of $> 90\%$ of the MPD stone volume, whereas partial clearance was defined as clearance of 50–90% of the stone volume. Quality of life scores were assessed by the patients and ranged from 0 to 100, with higher scores indicating a better quality of life.²⁷ Physical and mental health was assessed according to the scores on the SF-36 questionnaire.

Statistical analysis. Depending on the distributional properties, outcome measures were expressed as the mean \pm standard deviation or as median values with ranges. For normally distributed continuous data, statistical significance was assessed by the Student's *t*-test; for categorical data, significance was assessed by the chi-squared test with Yates' correction when appropriate or by the Fisher's exact test; and for non-normally distributed continuous data, statistical significance was assessed by the Wilcoxon test. All reported *P* values are two-sided. A *P* value of < 0.05 was established as the significance level. Missing follow-up data were considered to be missing at random.

Results

From March 2011 to March 2016, P-ESWL was performed in 1404 patients (72 in the geriatric group and 1332 in the control group).

Baseline characters. The demographic and clinical characteristics of the patients in the two groups differed significantly. The percentage of abdominal pain as initial symptom was lower in the geriatric group (22.2% vs 36.6%), while chronic pancreatic pain (5.6% vs 1.5%) and DM (15.3% vs 10.0%) were higher ($P = 0.010$). Regarding the type of pain,²⁸ the percentage of recurrent pain (RP) and recurrent acute pancreatitis plus RP were lower in the geriatric group, while chronic pancreatic pain and without pain were higher (Table 1).

The location, size, and number of stones were not significantly different between the two groups. The age of the geriatric patients who underwent P-ESWL was 71.329 ± 4.420 years (range 65.6–81.7 years). Geriatric patients were subjected to fewer shocks (9812 ± 5000 vs $11\,176 \pm 7429$; $P = 0.031$) per person compared with the control group patients (Table 2).

The coexisted diseases were significantly more common in geriatric patients (77.8% vs 38.9%, $P < 0.001$), especially hypertension ($P = 0.001$), myocardial infarction or cardiac decompensation ($P = 0.005$), cerebral ictus or subdural hematoma ($P = 0.023$), gallbladder diseases ($P = 0.007$), and spinal diseases ($P = 0.023$, Table S2).

Safety. Although coexisted diseases were more common in geriatric patients, no significant differences were observed between the geriatric and control groups regarding the safety of P-ESWL. The overall and specific complications of P-ESWL have no significant differences between geriatric and control groups (8.3% vs 11.9%; $P = 0.364$) (Table 3). In the geriatric group, six complications of P-ESWL occurred in six patients (6/72; 8.3%), with three of these patients presenting with mild post-ESWL pancreatitis (PEP), one presenting with severe PEP and two presenting with mild infection.

All of the patients were referred for ERCP. No significant differences were observed between the geriatric group (1/72; 1.4%) and the control group (38/1332; 2.9%) in terms of post-ERCP complications ($P = 0.453$).

Efficacy. During the ERCP performed post-P-ESWL, complete clearance of the stones was achieved in 73.6% of the patients in the geriatric group (53/72) and 81.9% in the matched controls (59/72; $P = 0.395$) (Table 4).

The median follow-up period was 4.02 years (range 0.23–6.58 years) for the geriatric group and 4.03 years (0.26–6.79 years) for the matched controls. One of the geriatric patients died from cardiac decompensation 2 months after P-ESWL, and one of the control patients died from liver metastases cancer with unknown primary tumor 3 months after P-ESWL, leading to the follow-up period less than 1.5 years. Five patients in the geriatric group and 2/72 matched controls were lost to follow up. Among the 67 patients (93.1%) receiving ongoing follow up in the geriatric group, complete pain relief was achieved in 53 patients (53/67; 79.1%), and significant differences were not observed compared with the matched controls (54/70; 77.1%; $P = 0.920$) (Table 5). One geriatric patient and one matched control later underwent surgery because of recurrent abdominal pain. The geriatric patient underwent exploration of the pancreatic duct and taking-off stone. The matched control patient who needed surgery underwent distal pancreatectomy.

In the geriatric group, the pain frequency ($P < 0.001$), VAS pain score ($P < 0.001$), and absences from work (median 26.200 days vs 3.134 days; $P = 0.002$) decreased significantly, and the scores for quality of life (67.791 ± 16.819 vs 82.866 ± 14.790 ; $P < 0.001$), physical health (72.746 ± 13.033 vs 78.537 ± 13.173 ; $P = 0.012$), and mental health scores based on the SF-36 (68.910 ± 16.601 vs 80.164 ± 12.301 ; $P < 0.001$) improved after the P-ESWL. The body mass index (BMI) of the geriatric patients improved significantly at follow up ($P = 0.001$, Table 6).

During the follow up, the death in the geriatric group (11/67, 16.4%) was significantly higher compared with the matched control group (2/70, 2.9%; $P = 0.007$). In the geriatric group, one patient died from severe acute pancreatitis, and one patient died from cachexia from undernourishment caused by prolonged steatorrhea, which are correlated directly with CP (Table 7).

Discussion

P-ESWL has been successfully applied in the treatment of pancreatic stones since 1987 and is now recommended as the first-line therapy for young patients with uncomplicated painful CP and

Table 1 General characteristics of the geriatric group and the control group

	Geriatric group (n = 72)	Control group (n = 1332)	P value
Age at onset of CP, years [†]	62.675 ± 11.649	34.408 ± 13.897	< 0.001
Age at diagnosis of CP, years [†]	68.828 ± 6.839	40.007 ± 13.016	< 0.001
Age at which stone(s) were identified, years [†]	69.285 ± 5.758	40.239 ± 12.911	< 0.001
Male	54 (75.0%)	948 (71.2%)	0.484
BMI	20.446 ± 2.636	20.884 ± 2.884	0.208
Alcohol			0.114
0 g/day	39 (54.2%)	737 (55.3%)	
0–20 g/day	1 (1.4%)	52 (3.9%)	
20–80 g/day	17 (23.6%)	191 (14.3%)	
> 80 g/day	15 (20.5%)	352 (26.4%)	
Smoking history	36 (50.0%)	642 (48.2%)	0.766
Etiology [‡]			0.469
ICP	54 (75.0%)	867 (65.1%)	
ACP	12 (16.7%)	336 (25.2%)	
Abnormal anatomy of pancreatic duct	5 (6.9%)	92 (6.9%)	
HCP	1 (1.4%)	35 (2.6%)	
Post-traumatic CP	0 (0.0%)	2 (0.2%)	
Initial symptoms of CP			0.010
Acute pancreatitis	28 (38.9%)	532 (39.9%)	
Abdominal pain without significantly increased serum amylase	16 (22.2%)	487 (36.6%)	
Chronic pancreatic pain	4 (5.6%)	20 (1.5%)	
Diabetes mellitus	11 (15.3%)	133 (10.0%)	
Steatorrhea	6 (8.3%)	90 (6.8%)	
Others	7 (9.7%)	70 (5.3%)	
Type of abdominal pain (19)			0.003
RAP	20 (27.8%)	337 (25.3%)	
RP	16 (22.2%)	402 (30.2%)	
RAP and RP	13 (18.1%)	386 (29.0%)	
CPP	9 (12.5%)	63 (6.2%)	
Without pain	14 (19.4%)	124 (9.3%)	
Severe acute pancreatitis	4 (5.6%)	42 (3.2%)	0.265
Diabetes mellitus	26 (36.1%)	386 (29.0%)	0.195
Steatorrhea	13 (18.1%)	329 (24.7%)	0.201
Regional portal hypertension	1 (1.4%)	31 (2.3%)	0.627
Common bile duct stricture	16 (22.2%)	150 (11.3%)	0.005
Pancreatic pseudocyst	10 (13.9%)	191 (14.3%)	0.915
DM in first-degree/second-degree/third-degree relatives	10 (13.9%)	214 (16.1%)	0.623
Pancreatic diseases in first-degree/second-degree/third-degree relatives (excluding HCP)	3 (4.2%)	71 (5.3%)	0.667

[†]Mean ± SD.

[‡]The etiology of 17 patients were both alcoholic CP and abnormal anatomy of pancreatic duct. They were included under abnormal anatomy of pancreatic duct. Three of them are geriatrics, and 14 of them are in the control group.

ACP, alcoholic chronic pancreatitis; CP, chronic pancreatitis; DM, diabetes mellitus; CPP, chronic pancreatic pain; HCP, hereditary chronic pancreatitis; ICP, idiopathic chronic pancreatitis; RAP, recurrent acute pancreatitis; RP, recurrent pain; SD, standard deviation.

radiopaque stones ≥ 5 mm obstructing the MPD.²⁴ The safety and efficacy of P-ESWL have been demonstrated in numerous studies, but data for geriatric patients have not been previously reported.^{1,14,15,27,29} Our study is the first to report the safety and efficacy of P-ESWL in geriatrics.

With the global aging, the CP patients were also aging, especially in developed countries. The mean age of CP patients increased gradually in the USA and Europe during recent decades. The mean age even demonstrated 58 years in a national study of CP in Dutch (Fig. S1).⁶ P-ESWL is a safe and effective treatment for geriatric patients with pancreatic stones, which may improve

their quality of life, as well as physical and mental health. The risk of complications relating to P-ESWL was not increased in geriatric patients, and the efficacy of P-ESWL was demonstrated by the significant pain relief and effective stone clearance. The outcome was similar to the results of previous P-ESWL studies in young patients.^{15,29–31}

The characteristics of CP have some differences in geriatric and young patients. With the declining of endocrine function in geriatrics,^{10,32} DM and steatorrhea were more common as the initial symptom of CP, while abdominal pain was more common in young patients. Elderly CP patients were reported with less severe

Table 2 Details of pancreatic extracorporeal shock wave lithotripsy

	Geriatric group (n = 72)	Control group (n = 1332)	P value
Location of stone(s)			0.264
Head	46 (63.9%)	944 (70.9%)	
Body/tail	3 (4.2%)	26 (2.0%)	
Head and at least another location	23 (31.9%)	362 (27.2%)	
Size of stones (diameter)			0.478
0.5–1.0 cm	32 (44.4%)	630 (47.3%)	
1.0–2.0 cm	26 (36.1%)	519 (39.0%)	
2.0–3.0 cm	10 (13.9%)	145 (10.9%)	
≥ 3.0 cm	4 (5.6%)	38 (2.9%)	
Number of stones			0.766
Single	10 (13.9%)	169 (12.7%)	
Multiple	62 (86.1%)	1163 (87.3%)	
Age at performance of ESWL, years [†]	71.329 ± 4.420	41.851 ± 12.645	< 0.001
Time from onset of CP to ESWL, years [†]	8.654 ± 11.271	7.443 ± 7.156	0.375
Time from identification of stone(s) to ESWL, years [†]	2.044 (0.014–25.786)	1.612 (0.000–23.225)	0.370
Number of shocks, years [†]	9812 ± 5000	11176 ± 7429	0.031
Number of ESWL sessions, years [†]	2.000 (1–5)	2.000 (1–10)	0.443

[†]Mean ± SD.[‡]Median ± range.

CP, chronic pancreatitis; ESWL, extracorporeal shock wave lithotripsy; SD, standard deviation.

Table 3 Pancreatic extracorporeal shock wave lithotripsy complications in the geriatric and control groups

Complications	Geriatric group (n = 72)	Control group (n = 1332)	P value
Type			
PEP	4 (5.6%)	124 (9.3%)	0.196
Infection	2 (2.8%)	14 (1.1%)	0.196
Bleeding	0	2 (0.2%)	0.900
Perforation	0	4 (0.3%)	0.810
Steinstrasse	0	11 (0.8%)	0.599
Others	0	0	—
Severity			0.058
Mild	5 (6.9%)	114 (8.6%)	
Moderate	0	42 (3.2%)	
Severe	1 (1.4%)	2 (0.2%)	
Total	6 (8.3%)	158 (11.9%)	0.364
complications			

PEP, post-extracorporeal shock wave lithotripsy pancreatitis.

pain,^{33,34} which lead to more patients without pain in the geriatric group, while RP and recurrent acute pancreatitis plus RP were much less than in the control group.

Coexisted diseases were more common in geriatric patients (Table S2). Cardiac and pulmonary problems have been demonstrated to increase among elderly patients. As the cardiac and pulmonary problems in geriatrics make the anesthetizing more challenging, lower concentration may be chosen during the sedation. It was reported that morbidity and mortality associated with interventions shows a higher rate among elderly compared with young adults. In the present study, the vital signs for the geriatric patients were carefully monitored, and anesthesia-related

Table 4 Findings and procedural characteristics of ERCP after pancreatic extracorporeal shock wave lithotripsy

	Geriatric group (n = 72)	Matched controls (n = 72)	P value
MPD stricture	38 (52.8%)	55 (76.4%)	0.003
ERCP procedure			
Endoscopic papillotomy	51 (70.8%)	44 (61.1%)	0.218
Bougie dilation	10 (15.6%)	15 (22.7%)	0.304
Balloon dilation	17 (26.6%)	14 (21.2%)	0.474
Stone extraction	40 (62.5%)	38 (57.6%)	0.567
Pancreatic stent	32 (50.0%)	42 (63.6%)	0.116
Successful drainage	65 (90.3%)	60 (83.3%)	0.218
Stone clearance			0.395
Complete [†]	53 (73.6%)	59 (81.9%)	
Partial [‡]	8 (11.1%)	7 (9.7%)	
Failed [§]	11 (15.3%)	6 (8.3%)	

[†]Clearance of > 90% of MPD stone volume.[‡]Clearance of 50–90% of MPD stone volume.[§]Clearance of < 50% of MPD stone volume.

MPD, main pancreatic duct; ERCP, endoscopic retrograde cholangiopancreatography.

complications were not observed in any of the geriatric group patients. These coexisted diseases in the geriatrics did not increase the risk of P-ESWL.

Although there is no significant difference in the number of P-ESWL sessions between geriatric and young patients, the geriatric patients required fewer shock waves in their P-ESWL to achieve successful stone fragmentation. This result may be

Table 5 Pain relief and further treatment at follow up

	Geriatric group (n = 67)	Matched controls (n = 70)	P value
Pain relief			0.920
Complete [†]	53 (79.1%)	54 (77.1%)	
Partial [‡]	8 (11.9%)	10 (14.3%)	
No	6 (8.6%)	6 (9.0%)	
Further ERCP(s) [§]	4 (6.0%)	3 (4.3%)	0.654
Further surgery	1 (1.5%)	1 (1.4%)	0.975

[†]Izbicki pain score ≤ 10.

[‡]Izbickipain score > 10 after a decrease of > 50%.

[§]Most ERCPs were performed for the replacement or withdrawal of pancreatic stents combined with clearance of the main pancreatic duct.

ERCP, endoscopic retrograde cholangiopancreatography.

attributed to more idiopathic CP in geriatric patients, which characterized by much slower rate of calcification than alcoholic CP.³⁵ Another possible reason is that diminished production of bicarbonate and enzymes in pancreatic secretion were observed in geriatric patients.³⁶ This may lead to a softer texture of pancreatic stones, which need less energy.

P-ESWL was safe for geriatric patients. The common complications of P-ESWL include PEP, bleeding, infection, steinstrasse, and perforation (Table S1).³⁷ In this study, the same intensity of shock wave was applied in both the geriatric group and the control group, and significant differences were not observed in the complication rate. As for the post-ERCP complications, post-ERCP

Table 7 Cause of death at follow up

Cause of death	Geriatric group (n = 67)	Matched controls (n = 70)	P value
Cancer of			
Lung	2 (3.0%)	0	
Esophagus	1 (1.5%)	0	
Liver metastases [†]	0	1 (1.4%)	
Cerebral glioma	1 (1.5%)	0	
Cerebral infraction	1 (1.5%)	0	
MI or cardiac decompensation	2 (3.0%)	0	
Severe acute pancreatitis	1 (1.5%)	0	
Cachexia from undernourishment [‡]	1 (1.5%)	0	
Unknown	2 (3.0%)	1 (1.4%)	
Total	11 (16.4%)	2 (2.9%)	0.007

[†]The primary tumor is unknown.

[‡]Caused by a prolonged steatorrhea.

pancreatitis only occurred in 1.4% of geriatric patients, which was much lower than the control group, as well as previous studies.³⁸ This result may be attributed to that large amount of geriatric patients have endocrine and exocrine insufficiency. With the pancreatic function “burning out” in the long term, it is less likely to have acute pancreatitis attack.³⁹ Therefore, we conclude that this shock wave intensity and ERCP treatment post-ESWL were safe for geriatric patients.

Table 6 Prognostic outcomes of pancreatic extracorporeal shock wave lithotripsy treatment in the geriatric group

	Pre-ESWL (n = 67)	Post-ESWL (n = 67)	P value
Pain frequency [†]			< 0.001
0	14 (20.9%)	53 (79.1%)	
1	40 (59.7%)	13 (19.3%)	
2	3 (4.5%)	0 (0.0%)	
3	10 (14.9%)	1 (1.5%)	
VAS pain score [‡]			< 0.001
0	14 (20.9%)	53 (79.1%)	
1–3	4 (6.0%)	3 (4.5%)	
4–6	11 (16.4%)	4 (6.0%)	
7–10	38 (56.7%)	7 (10.4%)	
Number of days absent from work (median + range)	26.299 (0–385)	3.134 (0–90)	0.002
Quality of life score [§]	67.791 ± 16.819	82.866 ± 14.790	< 0.001
SF-36 quality of life score [¶]			
Physical health component	72.746 ± 13.033	78.537 ± 13.173	0.012
Mental health component	68.910 ± 16.601	80.164 ± 12.301	< 0.001
Weight, kg	57.422 ± 9.890	62.336 ± 11.395	0.009
Body mass index	20.432 ± 2.660	22.239 ± 3.437	0.001
Steatorrhea	11 (16.4%)	13 (19.4%)	0.458
Diabetes	26 (38.8%)	30 (44.8%)	0.484

[†]Pain frequency was classified into four levels: 0, no pain; 1, several times a year; 2, several times a month; 3, several times a week.

[‡]SF-36 physical and mental health component scores range from 0 to 100, with higher scores indicating better physical and mental states.

[§]The VAS ranges from 0 to 10, with higher scores indicating more severe pain.

[¶]Quality of life scores range from 0 to 100, with higher scores indicating better quality of life.

ESWL, extracorporeal shock wave lithotripsy; SD, standard deviation; SF-36, 36-item Short-Form General Health Survey; VAS, visual analog scale.

Pancreatic extracorporeal shock wave lithotripsy was effective for geriatric patients. No significant differences were observed in the stone clearance, successful drainage, and pain relief between the geriatric and matched control groups. After P-ESWL, pain frequency and VAS pain score have significantly reduced in the geriatrics, while the quality of life, physical and mental health, and BMI have improved significantly.

It was showed a large increase in mortality rate with age.⁴⁰ During the follow up, 11 geriatric patients died. Although it was obviously more than that in the matched control group ($n = 2$), only two patients directly died from complications of CP. Other patients mostly died from extrapancreatic tumor (4/11, 36.4%) and cardio-cerebral vascular events (3/11, 27.3%). Earlier studies agree on cancer being the main cause of death.^{41,42} Pancreatic cancer was reported markedly increased in CP patients,⁹ but it was not detected in the present study. Digestive diseases were also reported the main cause of death in CP patients,⁴³ but they were not found in the present study. All of the causes of death in both groups in the present study have no relationship with P-ESWL.

There are several limitations of our study. First, given the observational study design (cohort study), there is an inherent selection bias, and the follow-up data for the entire control group were not acquired. Second, multiple confounders are present that can affect the quality of life, mental and physical health, and BMI in these geriatric patients. Third, lack of genetic testing data prevents more intensive study of the disease. Fourth, the need for an ERCP post-P-ESWL is still controversial, and this requires there to be a large-scale multicenter randomized controlled trial.

In conclusion, P-ESWL is a minimally invasive, safe, and effective procedure for the management of geriatric pancreatic stones, which can safely achieve significant pain relief and stone clearance. None of the deaths during the follow up were correlated with P-ESWL. What is more, the therapy promotes quality of life and mental and physical health in these patients, which may benefit the geriatric patients.

References

- Tandan M, Reddy DN, Talukdar R *et al.* Long-term clinical outcomes of extracorporeal shockwave lithotripsy in painful chronic calcific pancreatitis. *Gastrointest. Endosc.* 2013; **78**: 726–33.
- Kloppel G. Pathology of chronic pancreatitis and pancreatic pain. *Acta Chir. Scand.* 1990; **156**: 261–5.
- World Health Report. World Health Organization 2013.
- Owens JL Jr, Howard JM. Pancreatic calcification: a late sequel in the natural history of chronic alcoholism and alcoholic pancreatitis. *Ann. Surg.* 1958; **147**: 326–38.
- Machicado JD, Chari ST, Timmons L, Tang G, Yadav D. A population-based evaluation of the natural history of chronic pancreatitis. *Pancreatology: official journal of the International Association of Pancreatology (IAP) [et al]* 2017.
- Ahmed Ali U, Issa Y, van Goor H *et al.* Dutch Chronic Pancreatitis Registry (CARE): design and rationale of a nationwide prospective evaluation and follow-up. *Pancreatology: official journal of the International Association of Pancreatology (IAP) [et al]* 2015; **15**: 46–52.
- Hao L, Pan J, Wang D *et al.* Risk factors and nomogram for pancreatic pseudocysts in chronic pancreatitis: a cohort of 1998 patients. *J. Gastroenterol. Hepatol.* 2017; **32**: 1403–11.
- Hao L, Bi YW, Zhang D *et al.* Risk factors and nomogram for common bile duct stricture in chronic pancreatitis: a cohort of 2153 patients. *J. Clin. Gastroenterol.* 2017.
- Hao L, Zeng XP, Xin L *et al.* Incidence of and risk factors for pancreatic cancer in chronic pancreatitis: a cohort of 1656 patients. *Dig. Liver Dis.: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver.* 2017; **49**: 1249–56.
- Gloor B, Ahmed Z, Uhl W, Buchler MW. Pancreatic disease in the elderly. *Best Pract. Res. Clin. Gastroenterol.* 2002; **16**: 159–70.
- Chantarojanasiri T, Hirooka Y, Ratanachu-Ek T, Kawashima H, Ohno E, Goto H. Evolution of pancreas in aging: degenerative variation or early changes of disease? *J. Med. Ultrason.* (2001) 2015: 177–83.
- Lukens FJ, Howell DA, Upender S, Sheth SG, Jafri SM. ERCP in the very elderly: outcomes among patients older than eighty. *Dig. Dis. Sci.* 2010; **55**: 847–51.
- Finkelmeier F, Tal A, Ajouaou M *et al.* ERCP in elderly patients: increased risk of sedation adverse events but low frequency of post-ERCP pancreatitis. *Gastrointest. Endosc.* 2015; **82**: 1051–9.
- Wang D, Bi YW, Ji JT *et al.* Extracorporeal shock wave lithotripsy is safe and effective for pediatric patients with chronic pancreatitis. *Endoscopy* 2017; **49**: 447–55.
- Dumonceau JM, Andriulli A, Elmunzer BJ *et al.* Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline—updated June 2014. *Endoscopy* 2014; **46**: 799–815.
- Ito T, Ishiguro H, Ohara H *et al.* Evidence-based clinical practice guidelines for chronic pancreatitis 2015. *J. Gastroenterol.* 2016; **51**: 85–92.
- Tandon RK, Sato N, Garg PK. Chronic pancreatitis: Asia-Pacific consensus report. *J. Gastroenterol. Hepatol.* 2002; **17**: 508–18.
- Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014; **37**: S81–90.
- Munshi MN, Florez H, Huang ES *et al.* Management of diabetes in long-term care and skilled nursing facilities: a position statement of the American Diabetes Association. *Diabetes Care* 2016; **39**: 308–18.
- Affronti J. Chronic pancreatitis and exocrine insufficiency. *Prim. Care* 2011; **38**: 515–37 ix.
- World Health Organization: Proposed working definition of an older person in Africa for the MDS Project. <http://www.who.int/healthinfo/survey/ageingdefnolder/en/>.
- Yang YG, Hu LH, Chen H *et al.* Target-controlled infusion of remifentanyl with or without flurbiprofen axetil in sedation for extracorporeal shock wave lithotripsy of pancreatic stones: a prospective, open-label, randomized controlled trial. *BMC Anesthesiol.* 2015; **15**: 161.
- Dumonceau JM, Garcia-Fernandez FJ, Verdun FR *et al.* Radiation protection in digestive endoscopy: European Society of Digestive Endoscopy (ESGE) guideline. *Endoscopy* 2012; **44**: 408–21.
- Dumonceau JM, Delhaye M, Tringali A *et al.* Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2012; **44**: 784–800.
- Bloechle C, Izbicki JR, Knoefel WT, Kuechler T, Broelsch CE. Quality of life in chronic pancreatitis—results after duodenum-preserving resection of the head of the pancreas. *Pancreas* 1995; **11**: 77–85.
- Cahen DL, Gouma DJ, Nio Y *et al.* Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N. Engl. J. Med.* 2007; **356**: 676–84.
- Seven G, Schreiner MA, Ross AS *et al.* Long-term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. *Gastrointest. Endosc.* 2012; **75**: 997–1004 e1.
- Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system

- based on a review of previous classifications of the disease. *J. Gastroenterol.* 2007; **42**: 101–19.
- 29 Hu LH, Ye B, Yang YG *et al.* Extracorporeal shock wave lithotripsy for Chinese patients with pancreatic stones: a prospective study of 214 cases. *Pancreas* 2016; **45**: 298–305.
- 30 Lillemoe KD. Pancreatic disease in the elderly patient. *Surg. Clin. North Am.* 1994; **74**: 317–44.
- 31 Schmitz-Moormann P, Himmelmann GW, Brandes JW *et al.* Comparative radiological and morphological study of human pancreas. Pancreatitis like changes in postmortem ductograms and their morphological pattern. Possible implication for ERCP. *Gut* 1985; **26**: 406–14.
- 32 Franken FH. Geriatric pancreatitis. *Z. Gerontol.* 1982; **15**: 118–21.
- 33 Kamisawa T, Yoshiike M, Egawa N *et al.* Chronic pancreatitis in the elderly in Japan. *Pancreatol: official journal of the International Association of Pancreatology (IAP) [et al]* 2004; **4**: 223–7 discussion 7–8.
- 34 Otte M. Chronic pancreatitis and pancreatic carcinoma in the elderly. *Praxis* 2005; **94**: 943–8.
- 35 Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMaggio EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; **107**: 1481–7.
- 36 Grassi M, Petraccia L, Mennuni G *et al.* Changes, functional disorders, and diseases in the gastrointestinal tract of elderly. *Nutr. Hosp.* 2011; **26**: 659–68.
- 37 Li B-R, Liao Z, Du T-T *et al.* Risk factors for complications of pancreatic extracorporeal shock wave lithotripsy. *Endoscopy* 2014; **46**: 1092–100.
- 38 Zhao ZH, Hu LH, Ren HB *et al.* Incidence and risk factors for post-ERCP pancreatitis in chronic pancreatitis. *Gastrointest. Endosc.* 2017; **86**: 519–24 e1.
- 39 Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology* 1999; **116**: 1132–40.
- 40 Bang UC, Benfield T, Hyldstrup L, Bendtsen F, Beck Jensen JE. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. *Gastroenterology* 2014; **146**: 989–94.
- 41 Rosch T, Daniel S, Scholz M *et al.* Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. *Endoscopy* 2002; **34**: 765–71.
- 42 Thuluvath PJ, Imperio D, Nair S, Cameron JL. Chronic pancreatitis. Long-term pain relief with or without surgery, cancer risk, and mortality. *J. Clin. Gastroenterol.* 2003; **36**: 159–65.
- 43 Nojgaard C, Bendtsen F, Becker U, Andersen JR, Holst C, Matzen P. Danish patients with chronic pancreatitis have a four-fold higher mortality rate than the Danish population. *Clin. Gastroenterol. Hepatol.: the official clinical practice journal of the American Gastroenterological Association* 2010; **8**: 384–90.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Mean ages of CP patients in different countries. This scatter plot was based on the ages and times reported by each study of CP (References see Supplementary material 1). Unit root test was adopted to test the stationarity of these series, with $P < 0.05$ indicating stationary. They were analyzed by using the tseries package of R, version 3.2.4 (<http://www.rproject.org/>; America: $P = 0.457$; Europe: $P = 0.544$; China: $P = 0.033$; India: $P = 0.809$). CP = chronic pancreatitis.

Table S1. Definitions of major adverse events of pancreatic extracorporeal shock wave lithotripsy.

Table S2. Coexisted diseases at pancreatic extracorporeal shock wave lithotripsy (P-ESWL).