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Long-term clinical outcomes of extracorporeal shockwave lithotripsy and endoscopic retrograde cholangiopancreatography for pancreatic duct stone treatment in patients with chronic pancreatitis

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Summary

Background and Aims: Extracorporeal shock wave lithotripsy for pancreatic stones (P-ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) are the preferred therapeutic approaches for painful chronic pancreatitis (CP) with pancreatic stones. This study aimed to report the short- and long-term outcomes following P-ESWL and ERCP in a large cohort with CP.

Methods: Patients with painful CP and pancreatic stones >5 mm in size, who underwent P-ESWL and subsequent ERCP between March 2011 and June 2018, were included in this retrospective-prospective mixed observational study. The total stone clearance rates were recorded. All patients were followed up until the end of March 2024, with the visual analogue scale (VAS) for pain, pain type, quality-of-life scores and other relevant information recorded.

Results: A total of 2071 patients underwent P-ESWL, and 93.1% of them subsequently underwent ERCP during the study period. Patients were followed up for an average of 11.8 years from the onset of CP and 6.7 years from the first P-ESWL procedure. Complete stone clearance was achieved in 73.7% of the patients. At the end of the follow-up period, 70.1% of the patients achieved complete pain remission. Significant pain type conversion and lower VAS scores were observed in the patients

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after treatment. Quality-of-life scores and body mass indices increased after P-ESWL and ERCP.

Conclusions: P-ESWL and ERCP are effective and minimally invasive treatments for pancreatic stones in patients with painful CP. Most patients achieved complete pain relief, and pain-type conversion was common after treatment. (ClinicalTrials.gov: NCT05916547).

1 | INTRODUCTION

Chronic pancreatitis (CP) is a chronic inflammatory disease characterized by irreversible fibrosis of pancreatic tissues.[1] The major symptom affecting the quality of life of patients is abdominal pain, which occurs in approximately 80% of cases.[2] Refractory abdominal pain disrupts the normal lives of patients, impairs their psychological well-being, necessitates repeated hospitalizations, and increases their economic and medical burden. Consequently, the primary aim of CP treatment is to achieve abdominal pain remission.[3] Numerous factors contribute to the occurrence of abdominal pain, one of which is ductal hypertension caused by pancreatic stones in the main pancreatic duct (MPD).[4,5]

Pancreatic stones are a typical pathological feature of CP, with an incidence rate approaching 100% over the long-term clinical course.[6,7] Obstruction by pancreatic stones in the MPD impedes pancreatic fluid drainage, leading to MPD hypertension and ultimately resulting in abdominal pain. Removing pancreatic stones from the MPD and restoring pancreatic fluid drainage can alleviate abdominal pain.[4] Several methods exist for removing pancreatic stones, such as extracorporeal shockwave lithotripsy for pancreatic stones (P-ESWL), endoscopic treatment and surgery. P-ESWL and endoscopic retrograde cholangiopancreatography (ERCP) are preferred in patients with pancreatic stones because of their minimally invasive nature. According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines updated in 2018, P-ESWL and/or ERCP are recommended as first-line therapies for painful uncomplicated CP with an obstructed MPD in the head or body of the pancreas.[8] Specifically, P-ESWL is recommended for radiopaque obstructive MPD stones (>5 mm) located in the head or body of the pancreas, whereas ERCP is recommended for MPD stones (<5 mm) or radiolucent stones. In conventional clinical practice, ERCP is often performed after P-ESWL to remove fragmented stones. Several studies have reported the efficacy of P-ESWL and ERCP in patients with painful CP and pancreatic stones[9–37]; however, these studies were either small-sample or short-term and lacked long-term follow-up. More importantly, none of these studies reported the conversion of pain patterns after P-ESWL and ERCP.

Therefore, we conducted a retrospective-prospective mixed observational study to report the short- and long-term efficacies of P-ESWL and ERCP, exhibiting the conversion of pain patterns after P-ESWL and ERCP treatment based on the Changhai CP cohort.

2 | MATERIALS AND METHODS

2.1 | Patients and database

This retrospective–prospective mixed observational study was based on the Changhai CP Database (version 2.1, Yinma Information Technology Inc., Shanghai, China). Detailed information on the construction of the Changhai CP Database has been reported in previous studies.[6,14,38–40] Data of patients with CP who were admitted to Changhai Hospital between January 2000 and December 2004 were retrospectively collected according to the electronic medical record system, telephone, letter and email inquiries. The patients were prospectively enrolled in the database from January 2005. The clinical data were recorded and evaluated upon admission. In addition to spontaneous visits owing to complaints of discomfort associated with CP, all patients were periodically (at least annually) recalled for clinical check-ups and investigations. Imaging, including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), was recommended as the evaluation modality during each follow-up visit. Each revisit or evaluation via telephone inquiries for patients who did not return to Changhai Hospital was added to the CP database. Except for routine periodical follow-up, all patients underwent prospective concentrated follow-up from September 2023 to the end of March 2024 to obtain their latest status since their last admission for CP treatment. Patients with painful CP and pancreatic stones who underwent P-ESWL and subsequent ERCP between March 2011 and June 2018 at the Department of Gastroenterology at Shanghai Changhai Hospital were enrolled. Data on the basic information of patients, disease course and information related to P-ESWL and ERCP treatments were retrospectively collected from the database. Information after the last discharge from our centre was collected during the prospective concentrated follow-up.

Written informed consent was obtained from all enrolled patients. This study was approved by the Ethics Committee of the Shanghai Changhai Hospital (CHEC2023-143).

2.2 | Definitions

CP was diagnosed according to the Asia-Pacific consensus.[41] Alcoholic CP was diagnosed when alcohol consumption exceeded 80 g/day in males and 60 g/day in females for a minimum of 2 years in the absence of other causes.[42] The diagnosis of hereditary,

post-traumatic, hyperlipidaemia-related and anatomically induced CP was consistent with previous reports.[38,40] Idiopathic CP was diagnosed when none of the aforementioned causes were detected. The abdominal pain patterns included recurrent acute pancreatitis, recurrent pain, recurrent acute pancreatitis and recurrent pain, and chronic pain.[43] The frequency of abdominal pain was categorized as several times annually, monthly or weekly. Abdominal pain severity was assessed using a visual analogue scale (VAS).

2.3 | Treatment procedure

P-ESWL was first performed in patients with painful CP at Shanghai Changhai Hospital in March 2011. Patients diagnosed with painful CP and at least one large pancreatic stone (>5 mm in diameter) located in the head or body of the pancreas underwent P-ESWL performed by three gastroenterologists (LHH, BY and HC) using an electromagnetic lithotripter (Compact Delta II; Dornier Med Tech., Wessling, Germany) equipped with a bi-dimensional fluoroscopic targeting facility. Patients underwent repeated P-ESWL sessions on consecutive days until the therapeutic goal of fragmenting pancreatic stones into particles <3 mm in diameter was achieved. The patients were anaesthetized with flurbiprofen and remifentanil administered via transvenous injection during the P-ESWL procedure. Shock waves were limited to a maximum of 5000 shocks per P-ESWL session, with an intensity set between one and six and a frequency of 60–120 shocks per minute. Each P-ESWL session lasted 60–90 min. Following the completion of the final P-ESWL session and confirmation of pancreatic stones being <3 mm through radiography, patients underwent ERCP to remove any residual stone fragments and address MPD stricture, if necessary.[8] ERCP is often performed twice with the first ERCP to remove stone fragments and the placement of stents, if required and the second ERCP to remove the pancreatic stent. At our centre, ERCP is performed according to the guideline as consistently as possible.[44] A 10-Fr plastic stent is placed for 1 year as much as possible when dominant MPD stenosis exist. A 7-Fr or 8.5-Fr plastic stent is chosen to improve MPD stenosis in patients with severe pancreatic strictures, in whom a 10-Fr plastic stent cannot be placed safely. Multiple plastic stents can be implanted side-by-side in patients with refractory strictures. Usually, the pancreatic stent is removed after 1 year. The stent can be removed or replaced at any time when unexpected conditions occur, such as stent migration or obstruction. Endoscopic treatment is terminated when complete runoff of the contrast material is observed after removal of the pancreatic stent and no obvious MPD stricture exists. For patients without MPD stenosis but with high risk of post-ERCP pancreatitis, a preventive 5-Fr plastic stent is placed in order to facilitate pancreatic duct drainage and prevent the occurrence of post-ERCP pancreatitis.[45,46] In these patients, radiographic examination is arranged 2 weeks later to observe whether the stent had dropped into the intestinal channel. However, ERCP after P-ESWL is exempted under the following conditions: First, the pancreatic duct was found to be fluent without strictures or significant distortions based on ERCP history at other hospitals before admission to our centre. Fragmented stones would flow out spontaneously in such patients, making ERCP after P-ESWL unnecessary. Second, ERCP is not often considered for patients with rerouting of the gastrointestinal tract due to a history of gastrointestinal surgery, unless spontaneous stone removal is insufficient. Third, ERCP will not be performed in patients who develop severe complications after P-ESWL. Finally, other special conditions can also lead to exemption from ERCP, such as the personal unwillingness of the patients to undergo ERCP.

2.4 | Outcome measures

Symptom evaluation and investigation were conducted following each P-ESWL and ERCP procedure. Complications and their respective treatments were documented 30 days after P-ESWL and ERCP. All patients were prospectively followed up from September 2023 to the end of March 2024, during which the VAS scores, abdominal pain type, quality-of-life score and other relevant information were recorded. Short-term outcomes included pancreatic stone clearance rate, whereas long-term outcomes included pain relief, pain type, quality-of-life score, pancreatic exocrine and endocrine function, changes in pancreatic stones and death. The clearance rate of the pancreatic stones was evaluated during ERCP following P-ESWL. The complete clearance rate was defined as the removal of >90% of the MPD stone volume, whereas the partial clearance rate was defined as the removal of 50%–90% of the stone volume. Clearance was considered failed if <50% of the stone volume was removed.[47] If patients were unable to undergo ERCP after P-ESWL and radiography could not determine the stone volume, the stone clearance rate was recorded as an indeterminate factor. The pain relief was evaluated at the end of the follow-up period. Complete relief was defined as an Izbicki pain score was ≤10, whereas partial relief was defined as an Izbicki pain score >10 with a decrease of >50%.[48,49] Quality-of-life score was evaluated based on a brief scale of 0 to 100, where higher scores indicate better quality of life.[28]

2.5 | Statistical analysis

Depending on the type of numeric data, either Student's *t*-test or the nonparametric Mann–Whitney *U*-test was used to compare continuous variables across distinct groups. To compare categorical variables in different groups with varying sample sizes, either Chi-squared analysis or Fisher's exact test was employed. Statistical significance was set at $p < 0.05$. Data analysis was conducted using SPSS 27.0 (SPSS, Chicago, Illinois, USA) and R software (version 4.2.1).

3 | RESULTS

3.1 | Baseline information of patients

A total of 2071 patients who underwent P-ESWL between March 2011 and June 2018 were included in this study. The demographic

and clinical profiles of the patients are shown in Table 1. Among them, 13.1% were adolescents at the onset of CP. Approximately, half of the patients had a history of smoking or alcohol consumption. Abdominal pain was the most prevalent initial manifestation (85.4%). Most CP cases (60.4%) were classified as idiopathic. Prior to treatment, 19.6% of patients presented with steatorrhea, whereas 24.2% had diabetes mellitus (DM). All patients experienced abdominal pain, with the most common type being recurrent acute pancreatitis with the ratio of 34.5%, followed by recurrent pain with the ratio of 34.3%, and then recurrent acute pancreatitis and recurrent pain with the ratio of 27.2% prior to treatment. Chronic pancreatic pain was the least frequently reported pain type in this study. Most patients in this cohort had a low Charlson Comorbidity index (CCI), with >90% of patients having a CCI of less than two.

Details of the P-ESWL and ERCP procedures are presented in Table 2. Of the 5002 P-ESWL procedures performed on 2071 patients; 262 complications were reported, with the majority being mild. Only 81 patients experienced moderate-to-severe complications. A total of 1929 of 2071 patients (93.1%) underwent ERCP after P-ESWL, with a technological success rate of 86.5%. Among these patients, 4.0% (78/1929) experienced post-ERCP complications, including 69 cases of post-ERCP pancreatitis, seven cases of bleeding and two cases of infection. The reasons for the missing ERCP data in 142 patients varied, including abnormal anatomic structure of the stomach or pancreas, post-P-ESWL complications, spontaneous clearance of stones observed via X-ray examination prior to ERCP, and other personal reasons. Nearly half of the patients underwent ERCP within 48 h of the last P-ESWL procedure.

3.2 | Efficacy

For the 2071 patients who underwent P-ESWL, complete stone clearance was achieved in 73.7%; 13.2% had a partial stone clearance rate and 7.3% experienced failed stone clearance. The stone clearance rate was indeterminant for 5.8% patients (Table 3).

The long-term efficacies of P-ESWL and ERCP are shown in Table 3. Long-term efficacy was evaluated in approximately 80.3% (1664/2071) of patients with complete follow-up data. The abdominal pain patterns significantly improved after P-ESWL and ERCP. In total, 70.1% of patients experienced complete pain relief after treatment. The proportion of patients with recurrent acute pancreatitis decreased from 35.3% to 11.3% after treatment, whereas the proportion of patients experiencing recurrent pain decreased from 34.2% to 19.2%. For patients with recurrent acute pancreatitis and recurrent pain, the proportion decreased from 27.5% to 3.7%, whereas for patients with chronic pancreatic pain, the proportion decreased from 2.9% to 0.8%. The abdominal pain pattern converted after P-ESWL and ERCP treatment (Figure 1), with the most significant transformation being the conversion to 'without pain'.

To investigate the potential factors associated with pain relief in patients who completed follow-up, the correlation between smoking cessation, alcohol abstinence, pancreatic enzyme replacement therapy (PERT) and pain relief was tested in patients with complete data on smoking, drinking and PERT. The results revealed no significant relationship between smoking cessation and pain relief, or alcohol abstinence and pain relief. However, PERT treatment was associated with pain relief (Table S1).

In addition, the frequency of pain and the proportion of patients with high VAS pain scores decreased after treatment. The number of patients using analgesics, median number of hospital admissions and median number of days absent from work also decreased after treatment. The quality-of-life score and mean body mass index increased after treatment (Table 3).

3.3 | Follow-up

The emerging events in patients who completed follow-up and provided complete or partial data by March 2024 are listed in Table 4. During the long-term follow-up, 213, 120, 84, 36 and 27 patients developed DM, steatorrhea, pancreatic pseudocysts, biliary strictures and sinistral portal hypertension, respectively. A total of 174 patients experienced pancreatic stone recurrence 2 years after complete stone clearance. Thirty-five patients were diagnosed with pancreatic cancer during the follow-up. During the follow-up period, 59 and 15 patients underwent ERCP and P-ESWL, respectively. Twenty-four patients underwent surgery for newly developed events. Sixty-five patients underwent both ERCP and P-ESWL for recurrent pancreatic stones.

A total of 128 patients died during the follow-up period (Table 4). The most frequent cause of death was cancer, including pancreatic and other organ cancers. The second most common causes of death were cardiovascular and cerebrovascular diseases. The third most frequent cause of deaths was CP-related complications, including severe steatorrhea and acute CP attacks.

4 | DISCUSSION

P-ESWL and ERCP have been recognized as the first-line treatments for painful pancreatic stones in patients with CP.[8] The latest clinical trial involving 106 patients with CP found that P-ESWL with ERCP provided modest short-term pain relief in patients with painful CP.[50] However, long-term follow-up data from large-sample studies are lacking. More importantly, pain-type conversion after P-ESWL and ERCP has not been reported. This is the first retrospective-prospective mixed observational study with a long-term follow-up to evaluate the efficacy of P-ESWL and ERCP for painful pancreatic stones in patients with CP and to explore pain type conversion after treatment. The short-term endpoints revealed satisfactory pancreatic stone clearance rates and safety of P-ESWL and ERCP, whereas the long-term endpoints showed that complete pain relief was achieved in most patients, and pain frequency and VAS pain scores decreased after P-ESWL and ERCP treatment.

TABLE 1 Baseline Characteristics of 2071 patients with chronic pancreatitis prior to treatment.

Items	Overall ($n = 2071$)	Male ($n = 1485$)	Female ($n = 586$)	p value
Age at the onset of CP (years)	37.575 (26.014, 47.542)	39.033 (28.953, 48.660)	30.414 (20.071, 43.656)	<0.001
Age at the diagnosis of CP (years)	43.378 (32.222, 52.025)	45.041 (35.677, 53.018)	37.238 (25.545, 48.898)	<0.001
Adolescent	271 (13.1%)	151 (10.2%)	120 (20.5%)	<0.001
Smoking history	1073 (51.8%)	1061 (71.4%)	12 (2.0%)	<0.001
Alcohol consumption history	1051 (50.7%)	1017 (68.5%)	34 (5.8%)	<0.001
Initial manifestations				
Abdominal pain	1768 (85.4%)	1273 (85.7%)	495 (84.5%)	0.719
Endocrine/Exocrine dysfunction	250 (12.1%)	176 (11.9%)	74 (12.6%)	
Others	53 (2.6%)	36 (2.4%)	17 (2.9%)	
Aetiology				
Alcoholic CP	605 (29.2%)	590 (39.7%)	15 (2.6%)	<0.001
Idiopathic CP	1250 (60.4%)	772 (52.0%)	478 (81.6%)	
Others	216 (10.4%)	123 (8.3%)	93 (15.9%)	
Steatorrhea	406 (19.6%)	303 (20.4%)	103 (17.6%)	0.144
DM	502 (24.2%)	366 (24.6%)	136 (23.2%)	0.491
Biliary stricture	97 (4.7%)	80 (5.4%)	17 (2.9%)	0.016
Pancreatic pseudocyst	296 (14.3%)	239 (16.1%)	57 (9.7%)	<0.001
Pancreatic sinistral portal hypertension	35 (1.7%)	28 (1.9%)	7 (1.2%)	0.272
Morphology of MPD				
Pancreatic stone(s) alone	1074 (51.9%)	747 (50.3%)	327 (55.8%)	0.046
MPD stenosis and stone(s)	268 (12.9%)	195 (13.1%)	73 (12.5%)	
Complex pathologic changes[a]	491 (23.7%)	375 (25.3%)	116 (19.8%)	
Indeterminant	238 (11.5%)	168 (11.3%)	70 (11.9%)	
Type of pain				
Recurrent acute pancreatitis	715 (34.5%)	557 (37.5%)	158 (27.0%)	<0.001
Recurrent pain	710 (34.3%)	448 (30.2%)	262 (44.7%)	
Recurrent acute pancreatitis and recurrent pain	564 (27.2%)	415 (27.9%)	149 (25.4%)	
Chronic pancreatic pain	82 (4.0%)	65 (4.4%)	17 (2.9%)	
Severe acute pancreatitis	52 (2.5%)	42 (2.8%)	10 (1.7%)	0.142
Successful MPD endoscopic drainage	501 (24.2%)	368 (24.8%)	133 (22.7%)	0.318
Successful MPD surgical drainage	112 (5.4%)	77 (5.2%)	35 (6.0%)	0.475
DM in first-/second-/third-degree relatives	236 (11.4%)	159 (10.7%)	77 (13.1%)	0.117
Pancreatic diseases in first-/second-/third-degree relatives (excluding hereditary CP)	121 (5.8%)	68 (4.6%)	53 (9.0%)	<0.001
Charlson Comorbidity Index				
None: CCI score (0)	963 (46.5%)	632 (42.6%)	331 (56.5%)	<0.001
Mild: CCI score (1, 2)	959 (46.3%)	739 (49.8%)	220 (37.5%)	
Moderate: CCI score (3, 4)	144 (7.0%)	112 (7.5%)	32 (5.5%)	
Severe: CCI score (5+)	5 (0.2%)	2 (0.1%)	3 (0.5%)	

Abbreviations: CCI, Charlson Comorbidity Index; CP, chronic pancreatitis; DM, diabetes mellitus; MPD, main pancreatic duct; P-ESWL, extracorporeal shockwave lithotripsy for pancreatic stones.

[a]MPD stenosis, stone(s) and dilation.

TABLE 2 Procedural characteristics of P-ESWL and ERCP.

	n	%
Age at the first performance of P-ESWL (years)	44.937 (33.989, 53.362)	
Number of P-ESWL sessions	2 (1.000, 11.000)	
Location of stone(s)		
Head	1453	70.2
Body/tail	47	2.3
Head and at least another location	571	27.6
P-ESWL complications	262	5.2
Mild	181	69.1
Moderate	73	27.9
Severe	8	3.1
Performing post P-ESWL ERCP	1929	93.1
Failed	67	3.5
Only finished pancreatography	23	1.2
Failed deep pancreatic cannulation	142	7.4
Failed stone extraction	29	1.5
Success in stone extraction	1668	86.5
Dorsal pancreatogram	148	7.7
Pancreatic duct stricture dilation		
Balloon dilation	313	16.2
Bouginage	416	21.6
Stents placement	1204	62.4
Single stent	1185	61.5
5F	339	28.6
7F	560	47.3
8.5F	208	17.6
10F	78	6.6
Multiple stents	19	1.0
Sphincterotomy		
Major pancreatic sphincterotomy	1291	66.9
Minor papilla sphincterotomy	113	5.9
Minor papilla cannulation	186	9.6
Biliary stenting	64	3.3
Stone extraction		
By balloon	1322	68.5
By basket	346	17.9
Post-ERCP complications	78	4.0
Post-ERCP pancreatitis	69	3.6
Mild	60	87.0
Moderate	9	13.0
Bleeding	7	0.4
Mild	6	85.7
Moderate	1	14.3
Infection	2	0.1
Mild	2	100.0
Reasons for patients missing ERCP		
Abnormal anatomic structure of stomach or pancreas	39	27.5
Post P-ESWL complications	20	14.1
Spontaneous clearance of stone(s)	53	37.3
Other reasons	30	21.1
Time between P-ESWL and ERCP		
0	38	2.0
<24 h	359	18.6
24–48 h	580	30.1
>48 h	952	49.4
Technological success	1668	86.5

Abbreviations: ERCP, Endoscopic retrograde cholangiopancreatography; P-ESWL, pancreatic extracorporeal shock wave lithotripsy.

The complete pancreatic stone clearance rate in our study was 73.7%, which is relatively satisfactory. However, 7.3% of the patients did not achieve stone clearance, potentially for several reasons. First, the physical characteristics of the stones made fragmentation difficult. Stones with higher CT numbers corresponded to harder stones and larger stone fragments.[51] Stones with a density >820.5 Hounsfield units have been reported to respond less effectively to P-ESWL.[52] Second, the abnormal anatomy of the MPD may have caused difficulties in targeting the pancreatic stones and stone passage. Third, some patients experienced moderate-to-severe complications after the initial P-ESWL procedure, which interfered with further P-ESWL or ERCP treatment and led to incomplete stone clearance. Finally, pancreatic stones are often located in the MPD, side branches, or parenchyma of the pancreas. Stones in the MPD, side branches and parenchyma can be fragmented into smaller fragments during P-ESWL. Some small fragments in the side branches may flow into the MPD and be removed by ERCP or spontaneously flow into the intestine. However, some larger fragments in the side branches and parenchyma may not have flowed out. Therefore, complete stone clearance was not achieved in these patients. Surgery is the only treatment option for patients in whom stone clearance has failed.

As P-ESWL was first performed at Changhai Hospital in 2011, several studies have reported stone clearance rates. The stone clearance rates in previous reports were 72.4%,[16] 67.24% and 87.31% (pancreatic pseudocyst and control groups, respectively),[22] and 86.1% and 94.4% (paediatric and match groups, respectively).[34] Over the years, the technique has not changed significantly and the stone clearance rate was similar to that in the current study (73.7%). Other cohort studies reported similar results. Tandan et al. reported that complete stone clearance was achieved in 72.6% (3722/5124) of the patients.[30] Yamamoto et al. reported that overall stone clearance was achieved in 79% patients.[37] Bick et al. reported that 86.7% of their patients had a technical success rate in stone clearance.[10] In a study by Cahen et al., complete stone extraction was accomplished in 89% (16/18) of patients with pancreatic stones.[49] In the study by Issa et al., complete ductal clearance was achieved in 62% (24/39) of the patients who were treated endoscopically.[37] In a study by Talukdar et al., complete pancreatic ductal clearance was achieved in 88% (46/52) of patients.[50] Thus, the stone clearance rate in our

TABLE 3 The short-term and long-term efficacy of P-ESWL and ERCP for treatment of chronic pancreatitis.

	Pre-treatment	Post-treatment	*p*
Stone clearance			
Complete	—	1527 (73.7%)	N/A
Partial	—	273 (13.2%)	
Failed	—	151 (7.3%)	
Indeterminant	—	120 (5.8%)	
Type of pain			
Recurrent acute pancreatitis	588 (35.3%)	176 (10.6%)	<0.001
Recurrent pain	569 (34.2%)	319 (19.2%)	
Recurrent acute pancreatitis and recurrent pain	458 (27.5%)	62 (3.7%)	
Chronic pancreatic pain	49 (2.9%)	13 (0.8%)	
Without pain	0	1094 (65.7%)	
Pain frequency			
No pain	0	1094 (65.7%)	0.145
Several times a year	1503 (90.3%)	523 (31.4%)	
Several times a month	96 (5.8%)	24 (1.4%)	
Several times a week	65 (3.9%)	23 (1.4%)	
VAS pain score[a]			
0	0	1094 (65.7%)	0.009
1–3	218 (13.1%)	156 (9.4%)	
4–6	361 (21.7%)	218 (13.1%)	
7–10	1085 (65.2%)	196 (11.8%)	
Usage of analgesics	153 (9.2%)	52 (3.1%)	<0.001
Median number of hospital admissions	2 (1, 4)	0 (0, 0)	<0.001
Median number of days absent from work	20 (8, 40)	0 (0, 0)	<0.001
Life quality score	70 (60, 80)	85 (80, 90)	<0.001
Mean body mass index (kg/m^2)	20.901 (19.025, 22.922)	21.493 (19.721, 23.661)	<0.001
Abdominal pain relief after P-ESWL			
None	—	44 (2.6%)	N/A
Partial relief	—	453 (27.2%)	
Completely relief	—	1167 (70.1%)	

Abbreviations: P-ESWL, pancreatic extracorporeal shock wave lithotripsy; VAS, visual analogue scale.

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

study was similar to those reported in other studies, including randomized controlled trials (RCTs).

For patients with failed stone clearance or consistent pain after P-ESWL and ERCP, peroral pancreatoscopy-guided lithotripsy, including laser lithotripsy or electrohydraulic lithotripsy (EHL) directly under peroral pancreatoscopy (POPS), may become a new non-surgical treatment choice. Pancreatoscopy-guided laser lithotripsy and EHL have been reported previously.[53–57] As the new technique provides direct visualization and direct intraductal lithotripsy, the fragmentation of complex difficult-to-extract and cast-like stones which often cause failure of stone clearance in traditional P-ESWL and ERCP treatments becomes possible. However, these techniques may pose difficulties and risks. Shock waves may cause inadvertent injury or perforation of the pancreatic duct wall if the probe is not deployed close to the stone or away from the ductal wall. The intensities of the shock wave and laser light are also important for avoiding severe complications. In addition, positioning the endoscope to visualize the stones next to the papilla in patients with stones located mainly in the pancreatic head may be difficult. Thus, experience and skill are important in performing pancreatoscopy-guided lithotripsy. Despite these difficulties, pancreatoscopy-guided lithotripsy is a promising alternative treatment for pancreatic stones.

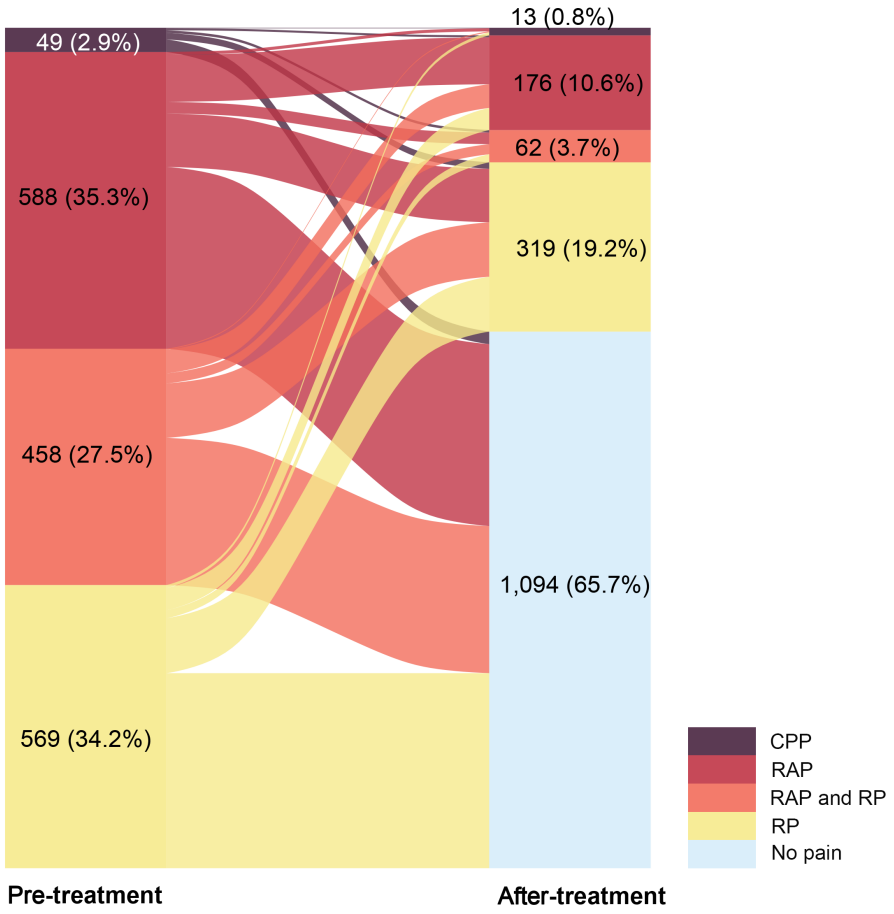

FIGURE 1 The pain-type conversion of patients from pre-treatment to after-treatment. CPP, chronic pancreatic pain; RAP, recurrent acute pancreatitis; RAP and RP, recurrent acute pancreatitis and recurrent pain; RP, recurrent pain.

Pancreatoscopy-guided laser lithotripsy has been performed at our centre as a new technique since 2023 and some studies from our centre may be reported in the future.

In our study, 70.1% of patients achieved complete pain relief after P-ESWL and ERCP, which was also similar to other published cohort studies. Vaysse et al. reported that 76% of the patients achieved success, as defined by the resolution of pain.[33] Tandan et al. reported that 82.6% of patients were pain free at 6-month follow-up after P-ESWL and ERCP treatment.[30] Yamamoto et al. reported that 94% of patients experienced pain relief.[37] Gurav et al. reported that 68.1% of the patients experienced pain relief after ESWL and ERCP with pancreatic duct stent placement.[58] However, prior RCTs have not reported satisfactory results for the following reasons.[49,50,59] These RCTs focused on patients with severe and chronic pain and not all pain types in patients with CP with stones. In a study by Cahen et al., patients with severe-recurrent pancreatic pain insufficiently relieved by non-narcotic analgesics or requiring opiates were included.[49] In a study by Issa et al., patients with severe pain due to obstructive CP and a dilated pancreatic duct who recently started opioids because of progressive pain despite non-opioid medication were eligible for enrollment.[59] The median duration of strong opioid use and weak opioid use was 0.8 and 2.0 months, respectively, which reflected the severity of pain in these patients. In a study by Talukdar et al., patients who had chronic abdominal pain characteristic of CP with a pain intensity greater than three on a 0–10 visual analogue scale, who met the criteria for chronic pain (pain ≥3 days per week for ≥3 months), and had obstruction of the pancreatic duct due to intraductal stones with dilation of the duct proximal to the obstruction, were enrolled.[50] Conversely, the current study and cohort studies in other countries reported results in all patients with P-ESWL who experienced all degrees of pain. In our study, 34.5%, 34.3% and 27.2% of patients had recurrent acute pancreatitis, recurrent pain, and recurrent acute pancreatitis and recurrent pain, respectively (Table 1). Only 4.0% of the patients experienced chronic pancreatic pain in terms of pain type. Regarding pain frequency, 90.3% of the patients experienced pain several times a year instead of several times a week (a feature of chronic pain). Moreover, only 9.2% of patients used analgesics before P-ESWL and ERCP, which also reflected the low rate of patients with severe pain. Patients with severe chronic pain may experience neuropathic pain, which may fail to respond to P-ESWL and ERCP and require different approaches. In addition, pancreatic pain over a long disease course can affect the peripheral and central nervous systems, leading to neuropathy and sensitization. Pain becomes refractory once central sensitization occurs. Thus, the patients in our study were different from those in the aforementioned RCTs (only patients with severe pain were enrolled), which contributed to the distinct results of P-ESWL and ERCP between our study and the RCTs.

TABLE 4 Clinical events, treatment and mortality in 1843 patients during follow-up.

	n	%
Newly diagnosed DM	213	11.6
Newly diagnosed steatorrhea	120	6.5
Newly diagnosed pancreatic pseudocyst	84	4.6
Newly diagnosed biliary stricture	36	2.0
Newly diagnosed sinistral portal hypertension	27	1.5
Newly diagnosed pancreatic stone(s)[a]	174	9.4
Newly diagnosed pancreatic cancer	35	1.9
Invasive treatment		
Further ERCP	59	3.2
Further P-ESWL	15	0.8
Further surgery	24	1.3
Further ERCP + P-ESWL	65	3.5
Death		
Cancer	58	3.147
Pancreatic cancer	30	51.724
Lung cancer	11	18.966
Other cancers[b]	17	29.310
Cardiovascular and cerebrovascular diseases	17	0.922
Complications related to CP	14	0.760
Death by misadventure	2	0.109
Gastrointestinal haemorrhage	1	0.054
Other[c]	36	1.953

Abbreviations: ERCP, Endoscopic retrograde cholangiopancreatography; DM, diabetes mellitus; P-ESWL, pancreatic extracorporeal shock wave lithotripsy.

[a]Pancreatic stone(s) reoccurrence 2 years after complete clearance.

[b]This included four patients with oesophageal cancer, two patients with gastric cancer, one patient with liver cancer, two patients with brain cancer, one patient with oral cancer, one patient with thyroid cancer, one patient with prostate cancer, one patient with renal carcinoma, one patient with malignant bone tumour, one patient with leukaemia, one patient with laryngocarcinoma and one patient with unknown cancer (the detailed information was not provided by the patients' family members).

[c]This included 29 patients with unknown causes of deaths (the detailed information was not provided by the patients' family members), three patients with COVID-19, two patients with other pneumonia and two patients with ketoacidosis.

Our study found a pain-type conversion after treatment. Most patients with the four types of pain experienced complete pain relief, with their pain type converting to 'no pain'. The pain type in a small proportion of patients with recurrent acute pancreatitis transitioned to recurrent pain and chronic pancreatic pain. The pain type of some patients with recurrent acute pancreatitis and recurrent pain converted to recurrent pain and chronic pancreatic pain. Additionally, the pain type in a small proportion of patients with chronic pancreatic pain converted to recurrent pain and recurrent acute pancreatitis and recurrent pain after treatment. Although the 'burn-out' hypothesis suggests that many patients with CP may achieve a lasting pain-free status during the disease course, the hypothesis is not universally accepted because a notable fraction of patients experience ongoing abdominal pain even after 10 or more years of disease.[60] Therefore, we believe that the combined therapy of P-ESWL and ERCP yielded satisfactory pain relief and resulted in pain-type conversion.

Our study has some limitations. First, we did not perform exact tests for pancreatic exocrine function, such as faecal elastase 1, in these patients. Thus, we only recorded the symptoms of patients (steatorrhea), which represents a severe stage of pancreatic exocrine function. Therefore, the rate of exocrine insufficiency may have been underestimated. Second, all P-ESWL and ERCP procedures were performed by experienced gastroenterologists at Changhai hospital, limiting the generalizability of the results to other small centres with fewer patients. Third, pain relief and pain type conversion in patients with CP after treatment may be influenced by many confounding factors, such as lifestyle and psychological changes. However, it was difficult to evaluate these factors in an observational study. Nevertheless, we explored the relationship between smoking cessation, alcohol abstinence and pain relief; however, the results were not statistically significant. Nonetheless, more stringent randomized controlled clinical trials should be conducted to explore the pure influence of treatment on pain relief and pain type conversion. Finally, as the patient data were extracted from the database, there may have been a selection bias, and some data may have been incomplete. Although imaging, including ultrasonography, CT or MRI, was recommended as an evaluation modality during each follow-up visit, imaging was not compulsory, and some patients may not have completed the imaging examination, which may have caused the underestimation of stone recurrence and other structural changes of the pancreas. For patients who did not return to the Changhai Hospital, follow-up and evaluation were completed via telephone inquiries. In particular, the last concentrated follow-up was conducted through telephone inquiries; thus, there may have been some information bias. For instance, patients may report the absence of recurrent pancreatic stones or pseudocysts if they had no obvious symptoms and did not undergo imaging examinations. Specifically, among 1843 patients who completed follow-up and provided complete or part of data by March 2024, 645 patients underwent CT scans; 37 patients, MRI scans; 350 patients, both CT and MRI scans; 37 patients, both CT scans and ultrasound examinations; and 55 patients, both MRI scans and ultrasound examinations, whereas 719 did not undergo any examinations during the concentrated follow-up. This may have led to an underestimation of the number of patients with conditions such as recurrent stones and pancreatic pseudocysts.

In conclusion, P-ESWL and ERCP are effective minimally invasive treatments for pancreatic stones in patients with painful CP. Most patients achieved complete pain relief and pain-type conversion after treatment.

AUTHOR CONTRIBUTIONS

Yu Liu: Data curation; methodology; formal analysis; funding acquisition; writing – original draft; writing – review and editing;

investigation. **Xiao-Yi Yin:** Investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation. **Jia-Hui Cui:** Investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation. **Teng Wang:** Investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation. **Xiao-Yue Feng:** Investigation; visualization; software; data curation. **Jin-Hui Yi:** Investigation; visualization; software; data curation. **Jin-Jie Xu:** Investigation; validation; software; data curation. **Song-Ling Zhang:** Investigation; validation; software; data curation. **Pei-Dong Han:** Investigation; validation; formal analysis; data curation. **Dan Wang:** Investigation; validation; formal analysis; data curation. **Run-Hui Liu:** Conceptualization; writing – review and editing; project administration; data curation; resources. **Fang-Yu Wang:** Project administration; data curation; resources; conceptualization. **Zhao-Shen Li:** Conceptualization; writing – review and editing; project administration; resources; supervision. **Liang-Hao Hu:** Conceptualization; funding acquisition; writing – review and editing; project administration; supervision; resources.

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DATA AVAILABILITY STATEMENT

Data would be available to other researchers upon reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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