

Efficacy of Different Pancreatic Interventional Treatments for Chronic Calcific Pancreatitis: A Two-Year Multicenter Retrospective Study

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Background: Extracorporeal shock wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) are the main treatments for chronic calcific pancreatitis (CCP). However, clinical outcomes remain unclear for patients underwent different interventional therapies based on these two techniques.

Methods: A total of 125 patients with CCP who underwent ESWL, ERCP or a combined treatment at two medical centers from January 2019 to January 2020 were considered. Patients were divided into four groups according to intervention types (ESWL-alone, ERCP-alone, ESWL-ERCP and ERCP-ESWL). A retrospective survey with a follow-up for 2 years was conducted. The main outcome measures were postoperative complications, abdominal pain and re-intervention during the follow-up. Possible prognostic factors were evaluated by multivariate analysis.

Results: Patients in ESWL-ERCP group had the highest complete pain relief rate (49.28%), the lowest pain frequency (1 time/year) and intensity (VAS-score, 1.84 ± 1.93) during the follow-up, which were statistically significant compared with the other three groups. ESWL-ERCP group also had the lowest postoperative complication rate (6%), while the highest complication rate (16%) was observed in ESWL-alone group. Both ESWL-alone and ESWL-ERCP group had significant lower frequencies of re-interventions (0.44 ± 0.73 , 0.57 ± 0.98 , respectively) after the initial treatments. An analysis of treatment-based prognostic factors found significant interactions between age, course of CCP, max pancreatic duct stone diameter, calcium, glycosylated hemoglobin (HbA1c) and triglyceride.

Conclusion: ESWL-ERCP was considered as the most effective interventional therapy for CCP with a better safety in a two-year follow-up. Prognostic factors may help to determine the patients who benefit by this technique.

Keywords: chronic calcific pancreatitis, ESWL, ERCP, follow-up

Introduction

Chronic calcific pancreatitis (CCP) is a progressive fibrotic disease of the pancreas characterized by fibrosis of the pancreatic parenchyma, formation of pancreatic duct stones, and progressive exocrine and endocrine function disorders. Studies have reported that pancreatic duct stones (PDS) account for up to 50–90% of patients with chronic pancreatitis (CP).¹ The presence of stones often obstructs the main pancreatic duct (MPD), leading to narrowing of the pancreatic duct and excessive pressure, which exacerbates tissue ischemia and calcification and causes pain.² Therefore, the removal of PDS is the key to relieving the pain among patients.³

In recent years, extracorporeal shock wave lithotripsy (ESWL) and endoscopic therapy (ERCP) lithotripsy have been introduced for the removal of PDS, and along with the continued maturation of the techniques, their effectiveness in stone removal and pain relief has gradually been proven.⁴ Several investigators have previously investigated ESWL alone and ESWL combined with ERCP treatment and have proposed the combined treatment as the first line of treatment for pancreatic duct stones.⁵ In recent years, the interventional treatments of PDS have developed into four main modalities,

including ESWL alone, ERCP alone, ESWL and subsequent ERCP, ERCP and subsequent ESWL. However, the long-term efficacy and safety differences between these four interventional treatments, and the strategies of how to select a specific treatment for a specific patient, remain to be further investigated.

In this study, we collected data from patients with CCP who received different pancreatic interventional treatment modalities and conducted a retrospective follow-up study for 2 years to evaluate the advantages and disadvantages in efficacy and safety for different treatments. Risk factors associated with the prognosis based on different treatments were also analyzed in order to help to provide better treatment options for patients.

Patients and Methods

Patients

Of the patients admitted to Shanghai Tenth People's Hospital and Shanghai Gong Li Hospital from January 2019 to January 2020, those who met the diagnostic criteria of chronic calcific pancreatitis⁶ were included in the study. Patients who fulfilled one or more of the following criteria were excluded: a) peripancreatic exudate > 2 cm; b) serum alkaline phosphatase more than twice the normal value; c) no pancreatic intervention (ESWL or ERCP) was performed during hospitalization; d) age <10 years or pregnancy or lactation; e) patients who had undergone pancreatic surgery and/or had been diagnosed with pancreatic cancer. Ultimately, 125 eligible patients were included. Figure 1 summarizes the flow of patients throughout the study. All patients gave written informed consent for participation in the study. The study complied with the Helsinki Declaration and was approved by the Institutional Review Board.

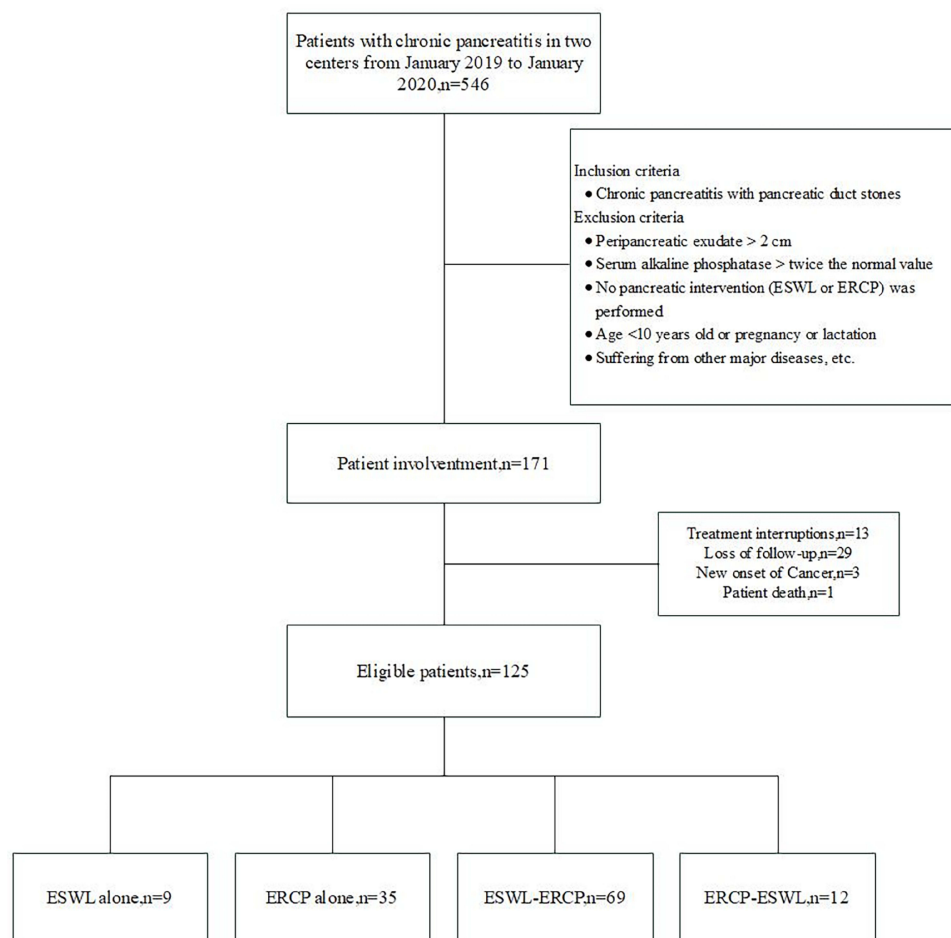


Figure 1 Patients flowchart of the study.

Pancreatic Interventional Treatments

All patients underwent pancreatic interventional lithotripsy treatments during the initial hospitalization, including ESWL, ERCP lithotripsy, or a combination of these two therapies. The times for ESWL/ERCP per patients were shown in [Supplementary Table 1](#). All interventions were carried out according to the standard procedures⁷ and performed by endoscopists who had received specialist training. The signs for technological success included two aspects. Firstly, the success of ESWL was defined as the application of high-energy ultrasound to successfully break up stones into fragments of <2mm in size. The success of ERCP was defined as successful access of the pancreatic duct by the duodenoscope, with the improvement of pancreatic duct drainage (complete stone extraction and/or stent placement). Secondly, clinical symptoms and serum biochemistry improved significantly after the treatment. Patients were divided into four groups according to different therapies: ESWL-alone, ERCP-alone, ESWL and subsequent ERCP (ESWL-ERCP), ERCP and subsequent ESWL (ERCP- ESWL).

Initial Evaluation

During the initial hospitalization, the baseline characteristics of the patients, course of CCP, serum biochemistry, diameter of the MPD, characteristics of PDS (location, quantity and diameter); ERCP procedures, ESWL data; and postoperative complications of the four treatments were recorded. Specifically, if there were multiple stones, the diameter of the largest one was noted. MPD was defined as dilated when it was greater than 3 mm in diameter. For combination treatment, complications that occur throughout the intervention are considered to be complications of combination treatment, whether they occur after ESWL or after ERCP. Based on previous studies, major complications were classified into four types (acute pancreatitis, infection, hemorrhage, and perforation).^{8,9} Infection is defined as a temperature greater than 38°C and lasting for more than 24 hours.¹⁰

Follow-Up Evaluation

The follow-up procedure began at the time of discharge and the endpoint was 2 years after the initial treatment. All patients were followed up every 6 months. At each visit, they were given a record of when the pain reappeared after the initial treatment, the frequency, duration and intensity of the pain and the frequencies of re-interventions during the follow-up period. We defined the interval between initial treatment and the first recurrence of pain as the duration of complete pain relief. Complete pain relief rate was the proportion of patients with complete pain relief to the total number of patients in each group. Pain intensity was recorded on a visual analogue scale (VAS).¹¹ A scale of 0 to 10 was used, where 0 indicated no pain, and 10 indicated severe, unbearable, continuous pain. A score of 0 to 1 was taken as no pain, 2 to 3 as mild pain, 4 to 6 as moderate pain, and 7 or more as severe pain. Re-intervention after the initial treatment included repeat ERCP or ESWL, but not surgical procedures. The procedure types and frequencies of re-interventions were recorded. Throughout the follow-up period, 0 reintervention was considered a complete clinical success, 1–5 times were considered a partial success and the rest were considered failures. Analysis of the characteristics and measurements of patients collected in the initial hospitalization were applied to determine the possible prognostic factors associated with the pain relief rate based on different types of interventions.

Statistical Analysis

All calculations were conducted by SAS software (version 9.2, Cary, NC). Continuous variables were expressed as the mean \pm standard deviation (mean \pm SD) in cases of a normal distribution and as the median and interquartile range (IQR) in cases of a skewed distribution. Categorical variables were described as percentages and compared using an χ^2 test or Fisher's exact test. The Kruskal–Wallis *H*-test was used to compare the difference between groups. The rate of complete pain relief was estimated by the Kaplan–Meier method, and any differences in relief were evaluated with a stratified Log rank test. Multivariable analyses with the Cox proportional-hazards model were applied to estimate the simultaneous effects of possible prognostic factors on pain relief. Considering the small sample size and low statistical power of the ESWL alone and ERCP-ESWL groups, the analysis of prognostic factors was only performed between ERCP alone and

ESWL-ERCP. R implements Kaplan–Meier curves and forest plots. A 2-tailed *p*-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The mean (standard deviation, range) age of the 125 patients with CCP was 42.63 (14.96, 11–84) years and most were male (94, 75.2%). Fifty-five (44%) patients consumed more than 20 grams of alcohol daily, while 58 (46.4%) were smokers. Diabetes was present in 49 (39.2%) of the subjects, while 10 (8%) with kidney stones. The median course of CCP was 3.75 (range:1 month–21 years) years. Most patients (104, 83.2%) had multiple PDS. Stones were mostly presented in pancreatic head region (84 patients, 67.2%). Proportion of patients reached complete ductal clearance after initial treatment was 76.8% (96 patients). Fatality rate overall was 2.1%. By the end of the follow-up period. The general characteristics of 125 patients before the treatment were shown in Table 1 and there was no statistically significant difference between the four groups.

Outcomes

Safety

Postoperative complications were analyzed to evaluate the safety of the four types of treatments (Figure 2). The most two common complications were infection and postoperative pancreatitis. Both the rate of postoperative hemorrhage and perforation were low and only found in patients undergoing ERCP alone. Patients in ESWL alone group had the highest postoperative complication rate (8% for both infection and acute pancreatitis, with no significant difference compared to the other three groups). ESWL-ERCP group had the lowest postoperative complication rate (4% for infection and 2% for acute pancreatitis). The two types of combined treatments had similar postoperative complication rate with no significant difference between them (Figure 2).

Efficacy

Complete Pain Relief

Kaplan-Meier demonstrated the difference in complete pain relief between the four treatment modalities. The result showed that the complete pain relief rate for ESWL-alone, ERCP-alone, ESWL-ERCP, and ERCP-ESWL were 44.44%, 25.71%, 49.28%, and 8.33%, respectively at the end of 2-year follow-up (*p*<0.05). As shown in Figure 3A, both the ESWL-alone group (*p*<0.05) and the ESWL-ERCP group (*p*<0.01) demonstrated significantly higher complete pain relief

Table 1 Base-Line Characteristics of the Patients with CCP

	ESWL Alone (n=9)	ERCP Alone (n=35)	ESWL-ERCP (n=69)	ERCP-ESWL (n=12)	<i>p</i> -value
Age, (median, IQR)	46 (23, 58.5)	39 (27, 54)	46 (33, 53)	38.5 (33.5, 47)	0.445
Course of CCP, (year, mean ±SD)	3.36±3.40	4.21±4.05	3.39±3.75	4.78±3.58	0.300
Male (n, %)	7 (77.78)	26 (74.29)	51 (73.91)	10 (83.33)	0.911
Alcoholism (n, %)	5 (55.56)	12 (34.29)	33 (47.83)	5 (41.67)	0.519
Smoking (n, %)	3 (33.33)	14 (31.43)	34 (49.28)	7 (58.33)	0.218
HbA1c % (mean ±SD)	8.37±2.83	6.48±1.36	7.32±1.68	7.56±1.95	0.066
Max stone diameter (mean ±SD)					
≤0.5cm	None	0.39±0.03	0.48±0.05	0.38±0.04	0.055
>0.5cm	1.11±0.58	1.03±0.48	1.39±0.77	1.18±0.86	0.448
MPD (mean ±SD)	8.50±2.08	8.01±1.82	8.30±2.77	6.70±1.80	0.445
Amylase (mean ±SD)	271.38±255.86	112.82±95.41	127.07±194.37	100.33±55.58	0.290
TG (mean ±SD)	1.07±0.45	1.62±1.35	1.47±1.56	1.42±0.27	0.109
Calcium (mean ±SD)	2.22±0.12	2.30±0.15	2.21±0.12	2.29±0.22	0.137

Abbreviations: ESWL, extracorporeal shock wave lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; MPD, main pancreatic duct; CCP, chronic calcific pancreatitis; TG, triglyceride.

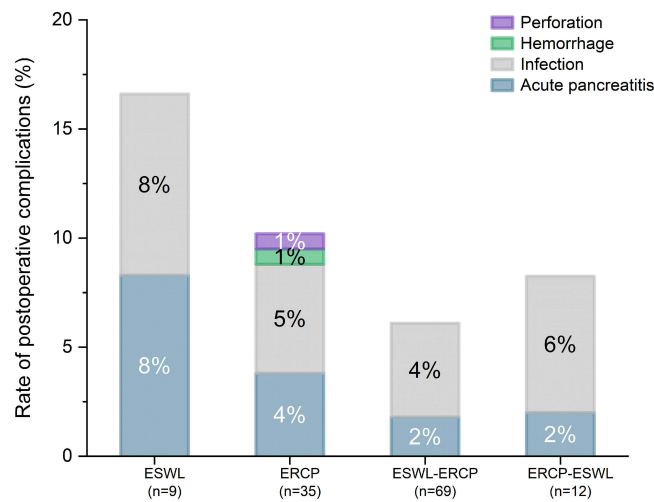


Figure 2 Rates of postoperative complications among different pancreatic interventional therapies.

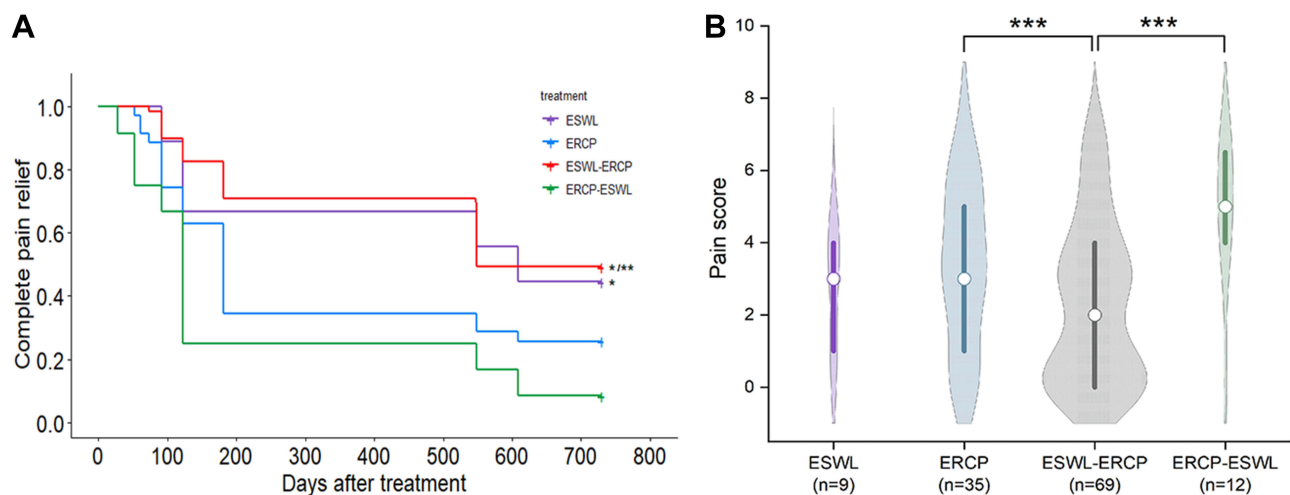


Figure 3 The evaluation of pain management between four different pancreatic interventional therapies for CCP during the follow-up. **(A)** Comparison of complete pain relief rates (*Compared to ERCP-ESWL group, $p < 0.05$; **Compared to ERCP group, $p < 0.05$). **(B)** Comparison of pain scores (*** $p < 0.001$).

rates compared with the ERCP-ESWL group throughout the follow-up. In addition, the relief rate of patients in the ESWL-ERCP group was significantly higher than the ERCP alone group ($p < 0.01$). There was no significant difference in complete pain relief between the remaining groups.

Frequency of Pain Relapse and Pain Score

As listed in Table 2, although there was an increase in the pain recurrence in all groups during the 2-year follow up, ESWL-ERCP group kept the lowest proportion of patients with pain relapse (28.99% for 1st year and 50.72% for the 2nd year). ESWL alone group also presented lower proportion of patients with pain relapse among the four groups. However, the ERCP-ESWL group had the highest proportion of pain relapse at 91.67% (11 patients). The difference between the four groups was statistically significant (Table 2). In addition, patients in the ERCP-ESWL group had the highest frequency of pain attack (3 times/year) and the pain score (4.92 ± 2.02), while patients underwent ESWL-ERCP had the least frequency of pain attack (1 times/year) and the pain score (1.84 ± 1.93) during the follow-up period ($p < 0.001$). Furthermore, it can be intuitively seen that patients in the ESWL-ERCP group endured better pain management during the follow-up period, with the majority of scores distributed between 0 and 2 (Figure 3B).

Table 2 Efficacy Evaluation of the Patients with CCP During the Two-Years Follow-Up Between the Different Interventions

	ESWL Alone (n=9)	ERCP Alone (n=35)	ESWL-ERCP (n=69)	ERCP-ESWL (n=12)	p-value
Patients with pain relapse, n (%)					
At 1 year	3 (33.33)	22 (62.86)	20 (28.99)	9 (75.00)	0.001
At 2 years	5 (55.56)	26 (74.29)	35 (50.72)	11 (91.67)	0.014
Frequency of pain episodes (times/year, median, IQR)	1 (3.50)	1 (3.00)	1 (1.00)	3 (4.25)	0.001
Pain score (mean \pm SD)	2.78 \pm 1.72	3.37 \pm 2.29	1.84 \pm 1.93	4.92 \pm 2.02	0.000
Frequency of re-interventions (times/year, mean \pm SD)	0.44 \pm 0.73	2.11 \pm 2.03	0.57 \pm 0.98	2.08 \pm 1.93	0.000
Complete clinical success, n (%)	5 (55.56)	9 (25.71)	41 (59.42)	3 (25.00)	0.004

Abbreviations: ESWL, extracorporeal shock wave lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography, re-interventions refer to treatment including MPD clearance at ERCP and repeat ESWL.

Re-Interventions

Pancreatic re-intervention during the follow-up period was also analyzed to evaluate the efficacy of different treatments. Patients in the ESWL-alone group had the least frequency of re-interventions (0.44 ± 0.73) among the four groups. Patients underwent ESWL-ERCP also had a similar low frequency of re-interventions (0.57 ± 0.98), with no significant difference compared with those underwent ESWL-alone (Table 2). The frequencies of re-interventions were significant lower in both ESWL-ERCP and ESWL-alone group than in the other two groups ($p < 0.01$, Figure 4A). According to our definition, the intervention with the highest complete clinical success rate was ESWL-ERCP (41 patients, 59.42%), followed by ESWL-alone (5 patients, 55.56%), which were both significant higher than ERCP-alone and ERCP-ESWL ($p < 0.01$, Figure 4B). ERCP-ESWL had the lowest complete clinical success rate (3 patients, 25%) among the four interventions (Table 2).

Prognostic Factors

To determine the possible prognostic factors associated with the long-term efficacy, we assessed the interaction between patients' base-line characteristics and two main types of pancreatic interventions (ERCP alone and ESWL-ERCP). As shown in Figure 5, each square represents the estimated treatment effect (pain relief), the horizontal lines represent the

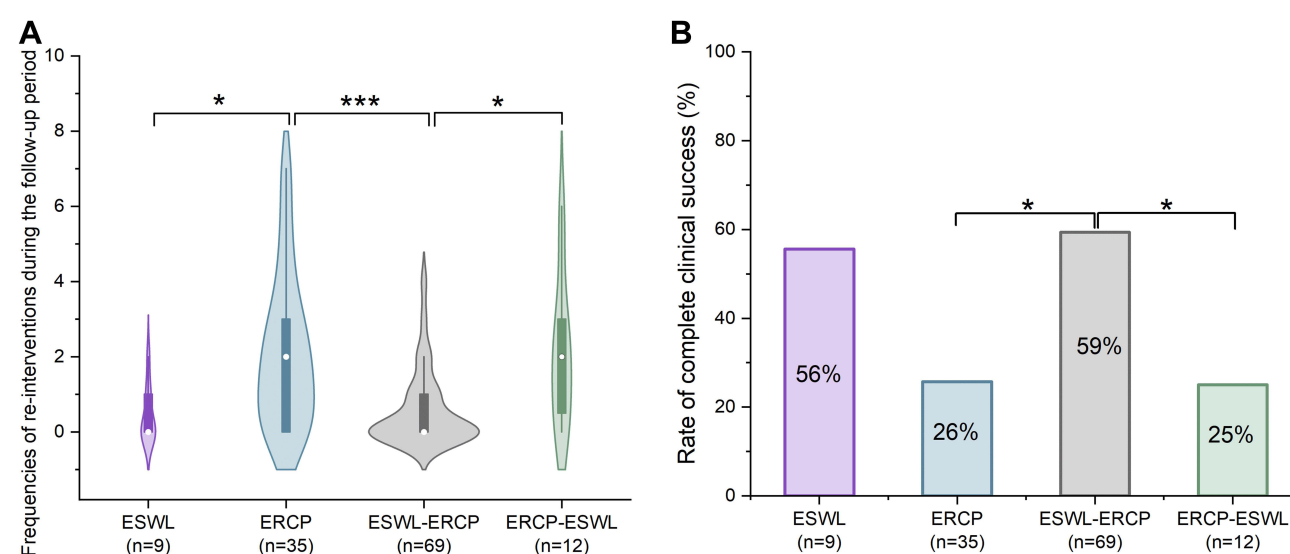


Figure 4 The evaluation of re-intervention between four different pancreatic interventional therapies for CCP during the follow-up. (A) Comparison of the frequencies of re-interventions (* $p < 0.05$, *** $p < 0.001$). (B) Comparison of complete clinical success (* $p < 0.05$).

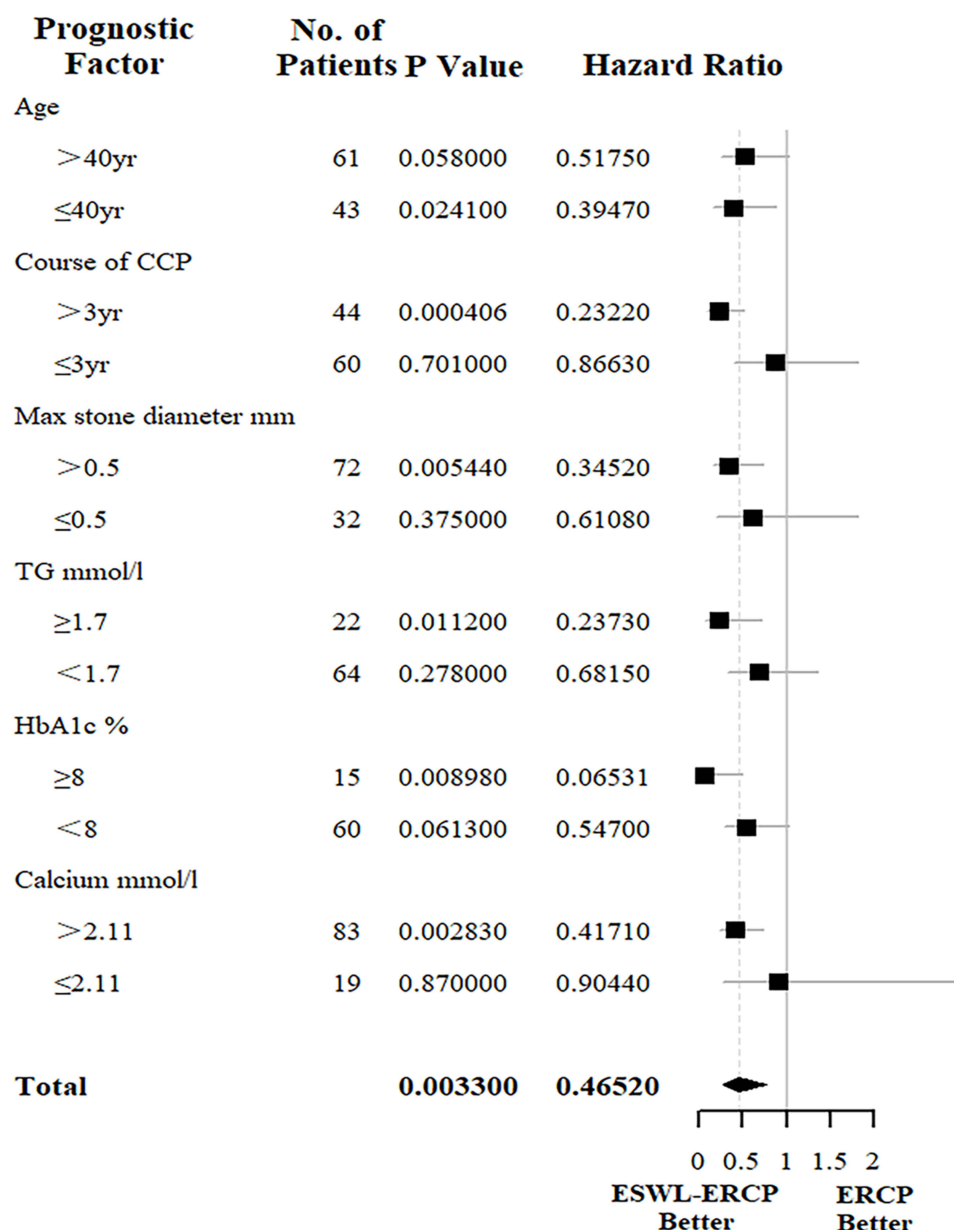


Figure 5 Hazard ratios for pain relief in patients in the ESWL-ERCP group as compared with the ERCP alone group.

95% confidence intervals, and the diamond corresponds to the 95% confidence intervals for the entire group of patients. Hazard ratios for pain were calculated for patients in the ESWL-ERCP group compared to the ERCP-alone group. It can be observed that ESWL-ERCP tended to provide a definitive pain relief benefit for patients with age ≤ 40 years (hazard ratio = 0.39 (0.17–0.88); $p=0.02$), course of CCP >3 years (hazard ratio = 0.23 (0.10–0.52); $p=0.0004$), hyperglycemia (hazard ratio = 0.07 (0.008–0.51); $p=0.009$), hypercalcemia (hazard ratio = 0.42 (0.23–0.74); $p=0.003$), hypertriglyceridemia (hazard ratio = 0.24 (0.07–0.72); $p=0.01$) and with large pancreatic duct stones (>5 mm) (hazard ratio = 0.34 (0.16–0.73); $p=0.005$).

Discussion

In recent years, interventional treatment of PDS has evolved into four main modalities: ESWL alone, ERCP alone, ESWL and subsequent ERCP, and ERCP and subsequent ESWL.¹² However, there is still a lack of studies comparing the long-term efficacy and safety of these four interventions. Therefore, we conducted a retrospective follow-up study of 125

patients with CCP, which included all four interventions simultaneously for the first time and subdivided the combined treatment into two separate regimens for comparison. The aim of the study was to evaluate the advantages and disadvantages of the different treatment modalities in terms of efficacy and safety. We also analyzed the risk factors associated with prognosis based on the different treatments, with a purpose to provide some valuable clinical options for treatment strategies for specific patients.

Previous studies have reported that the general features of CCP include a predilection for young male adults, a short duration of disease,¹³ and its tendency to form denser stones in the pancreatic duct early in the course of the disease.¹⁴ Long-term irritation from stones affected the exocrine and endocrine function of the pancreas and nearly 40% of patients had diabetes at presentation.¹⁵ Comparing the clinical characteristics of the patients in the four groups, we found that the majority of patients in this study were younger (≤ 45 years), male patients-dominated ($>75\%$), with generally short duration of the disease (3–4 years), and high prevalence of diabetes (39.2%), which is consistent with the previous data. In Western countries, alcohol is considered to be the main cause of CCP.¹⁶ A large number of studies have confirmed that the consumption of large amounts of alcohol accelerates the development of calcification in the pancreatic ducts among patients with CCP.^{17,18} However, our study found that in addition to alcohol, nearly half of the patients have a history of smoking, indicating tobacco is also a possible major factor for the cause of CCP in China, which may be related to the abundance of tobacco consumption in our country. A national epidemiological survey by Hirota et al¹⁹ reported that smoking increases the incidence of diabetes and pancreatic calcification in CCP patients, but the exact mechanism is unclear and more research is needed to further investigate.

As the two most common complications after pancreatic interventional treatments, postoperative pancreatitis and infection were observed in all four groups of patients. Previous studies have reported that the incidence of postoperative pancreatitis reached 15.5% in the patients with first ESWL session, compared to 4.2% in combination therapy.^{20,21} The results of our study are similar to previous data, but with a lower overall complication rate. Analysis of the potential reasons for this may be the low frequency and number of shock waves for the ESWL procedure in our study (no more than 60 shocks per minute and a maximum of 5000 shocks in a single session). Studies have found that a decrease in frequency (60 shocks per minute to 90 shocks per minute) is likely to increase the success rate of fragmentation and improve safety.²² In the subgroup analysis, we observed lower complications with combined treatments when comparing to the treatment alone. On the one hand, the use of post-ERCP accelerates the removal of stones compared to ESWL alone and avoids the aforementioned side effects due to natural process. On the other hand, the use of ESWL alleviates the difficulties of interventional procedures due to large stones compared to ERCP alone. The reasons for the higher incidence of infection in both the ESWL alone and ERCP-ESWL groups (6–8%) may be the exposure to the risk of pancreatic juice outflow obstruction and repeated mechanical injury during waiting for the natural stone removal. Perforation and hemorrhage are relatively rare complications of ERCP, with an incidence of 1%, which is similar to the rates reported in previous studies.²³

Pain management and frequency of re-intervention were the main indicators for the efficacy of CCP in our study. Our findings indicated that the four treatments are effective in relieving the pain in chronic calcific pancreatitis, but with variable results. Both ESWL-ERCP and ESWL alone groups showed advantages in pain control and reduction of re-intervention frequencies at 2 years, which is consistent with the findings of some previous studies.²⁴ Several scholars considered that the ESWL combined with endoscopy is the standard of care in the management of large stones in the MPD.¹² Guidelines in many countries have also been revised to recommend combination therapy as the first-line treatment for pancreatic duct stones.²⁵ The majority of our patients also opt for combination therapy; however, the sequencing of ERCP and ESWL has the potential to influence the outcome of treatment. Throughout the follow-up period, we found a significantly lower rate of complete pain relief in the ERCP-ESWL group than in the ESWL-ERCP group, and a markedly higher frequency of pain recurrence and re-intervention in the ERCP-ESWL group. Reviewing the development of the disease and the treatment process in both groups, we found that the patients treated with ERCP-ESWL had different degrees of pancreaticobiliary obstruction at presentation, and the early application of ERCP played an important role in relieving the obstruction and alleviating the pain in the acute phase. Analyzing the reasons for the poor efficacy in pain management in this group, we believe that the instrumentation in the pancreatic duct and the hydrostatic pressure generated by the contrast agent during the initial ERCP²⁶ are the two most important factors

contributing to the further pancreatic injury, which tends to induce the secretion of proteolytic enzymes in the pancreatic duct, exacerbating the edema of the duct and duodenal papilla.²⁷ ESWL based on this pathological basis may exacerbate the tissue damage and reduces the possibility of natural stone removal from the pancreatic ducts. It has been reported that residual stones in pancreatic duct are the main cause of recurrence of pain and the need for re-intervention in patients.²⁸ In contrast, the patients underwent ESWL followed by ERCP lithotripsy tends to achieve complete removal of small calcified foci from the pancreatic duct, which improved the long-term prognosis of the patient to some extent. Overall, our study concluded that the clinical outcome of ESWL-ERCP appears to be better. However, due to the small sample size of ERCP-ESWL, future studies with more cases may be needed to confirm this difference.

As mentioned earlier, ESWL-ERCP and ESWL have similar results in terms of efficacy in the present study. Then the question of whether ERCP is necessary after ESWL has been repeatedly raised. The results of an RCT by Dumonceau et al²⁹ showed that additional ERCP lithotripsy after ESWL increased the risk of recurrent pancreatic pain and the cost of treatment for patients compared to ESWL alone, so at one point, the investigators recommended eliminating the addition of ERCP. However, as ERCP technology has matured over the past decades, similar findings have not emerged. Most updated guidelines treat the proposal to abolish ERCP with a weak recommendation.³⁰ Considering the similarity in the efficacy of treating CCP with ESWL-ERCP, we believe that ESWL alone is feasible for stones that are not associated with pancreatic stenosis and that it is possible to shorten the hospitalization and reduce the cost of care. Whereas, in cases of pancreatic stenosis, ESWL alone cannot remove all the stone fragments and ERCP should also be combined to facilitate the expulsion of stones. From the point of view of complications, prolonged mechanical friction may induce infection and pancreatitis during the expulsion of stones after ESWL alone, whereas additional ERCP has the opportunity to facilitate the process and reduce such complications. Although ERCP may not be essential for all patients, as a technique with a better safety and guaranteed efficacy ESWL-post-ERCP might be the preference in most cases.

To help to provide better treatment options for CCP, risk factors associated with the prognosis based on different types of interventions (ERCP-alone vs ESWL-ERCP) were also analyzed in the present study. As the two main pancreatic interventions in our study, they are also currently the two most widely used treatments in our country.³¹ Our study showed that ESWL-ERCP tended to improve the complete pain relief rate among patients with stones that was more than 5 mm in diameter, which was in line with some guidelines.³⁰ In addition, we found that combination therapy was more effective for patients with a course of CCP >3 years and hypercalcemia. The reason for this is that a long course of disease tends to result in larger stones and more severe pancreatic duct stenosis. And previous studies have shown that high calcium levels also promote the formation and development of larger stones.³² The results also showed ESWL-ERCP tended to significantly improve complete pain relief in patients younger than 40 years old. Elderly patients are more likely to experience complications and co-morbidities, tending to be less tolerant of the combined treatment procedure, which might be the reasons for decreased efficacy. In a subgroup analysis of HbA1c and triglyceride, we found that ESWL-ERCP seemed to have a more striking benefit than ERCP alone in relieving pain for patients with hyperglycemia and/or hypertriglyceridemia. Previous studies have indicated that hyperglycemia and hypertriglyceridemia, as risk factors for chronic pancreatitis, tend to increase the stone burden and pancreatic duct stenosis of patients,^{33,34} so the combination therapy might be the better choice for this group of patients.

This study has several limitations. First, the total number of patients that we collected, especially for ESWL alone and ERCP-ESWL groups, was small. Second, it was a retrospective study and the measurements were mainly recalled by the patients, which was relatively subjective and may lead to inaccurate and biased data. A prospective cohort study based on large sample of patients will be needed to validate the results in the future. Third, we did not distinguish very well whether the types of complications in combination treatment were all due to the combination procedure. Some complications may arise from a single treatment rather than a combined modality. To a certain extent, it may lead to some bias in the data.

In conclusion, both ESWL-ERCP and ESWL alone achieved better clinical outcomes in terms of pain control and re-intervention, and the combined treatment appeared to have a better safety profile. ESWL-ERCP may be more suitable for patients with age ≤ 40 years, course of CCP >3 years, hyperglycemia, hypercalcemia, hypertriglyceridemia and with large pancreatic duct stones. A further large prospective study will be needed to confirm the efficacy and reliability of

different pancreatic interventions for pancreatic ductal calculi, which could be helpful for providing better treatment options for patients.

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Disclosure

The authors declare that they have no competing interests.

References

1. Ammann RW, Muench R, Otto R, et al. Evolution and regression of pancreatic calcification in chronic pancreatitis. A prospective long-term study of 107 patients. *Gastroenterology*. 1988;95:1018–1028.
2. Kloppel G. Pathology of chronic pancreatitis and pancreatic pain. *Acta Chir Scand*. 1990;156:261–265.
3. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. *Gut*. 2011;60:77–84.
4. Tandan M, Reddy DN, Santosh D, et al. Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi—a large single center experience. *Indian J Gastroenterol*. 2010;29:143–148.
5. Moole H, Jaeger A, Bechtold ML, et al. Success of extracorporeal shock wave lithotripsy in chronic calcific pancreatitis management: a meta-analysis and systematic review. *Pancreas*. 2016;45:651–658.
6. Tandon RK, Sato N, Garg PK. Chronic pancreatitis: Asia-Pacific consensus report. *J Gastroenterol Hepatol*. 2002;17:508–518.
7. Li BR, Liao Z, Du TT, et al. Risk factors for complications of pancreatic extracorporeal shock wave lithotripsy. *Endoscopy*. 2014;46:1092–1100.
8. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc*. 1991;37:383–393.
9. Kozarek RA, Brandabur JJ, Ball TJ, et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. *Gastrointest Endosc*. 2002;56:496–500.
10. Parida SK, Pottakkat B, Raja K, et al. Bacteriological profile of pancreatic juice in patients with chronic pancreatitis. *JOP*. 2014;15:475–477.
11. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: myths, truths and clinical relevance. *Scand J Pain*. 2016;13:67–75.
12. 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.
13. Tandan M, Reddy DN, Talukdar R, et al. Long-term clinical outcomes of extracorporeal shockwave lithotripsy in painful chronic calcific pancreatitis. *Gastrointest Endosc*. 2013;78:726–733.
14. Ong WC, Tandan M, Reddy V, et al. Multiple main pancreatic duct stones in tropical pancreatitis: safe clearance with extracorporeal shockwave lithotripsy. *J Gastroenterol Hepatol*. 2006;21:1514–1518.
15. Balakrishnan V, Nair P, Radhakrishnan L, et al. Tropical pancreatitis - a distinct entity, or merely a type of chronic pancreatitis? *Indian J Gastroenterol*. 2006;25:74–81.
16. Marinov V, Gaidarski R, Draganov K. Some aspects of the etiology and the pathogenesis of chronic pancreatitis. *Khirurgia*. 2011;1:12–21.
17. Lankisch MR, Imoto M, Layer P, et al. The effect of small amounts of alcohol on the clinical course of chronic pancreatitis. *Mayo Clin Proc*. 2001;76:242–251.
18. Schreiber F, Gurakuqi GC, Pristautz H, et al. Sonographically-guided extracorporeal shockwave lithotripsy for pancreatic stones in patients with chronic pancreatitis. *J Gastroenterol Hepatol*. 1996;11:247–251.
19. Hirota M, Shimosegawa T, Masamune A, et al. The seventh nationwide epidemiological survey for chronic pancreatitis in Japan: clinical significance of smoking habit in Japanese patients. *Pancreatol*. 2014;14:490–496.
20. Sauerbruch T, Holl J, Sackmann M, et al. Extracorporeal lithotripsy of pancreatic stones in patients with chronic pancreatitis and pain: a prospective follow up study. *Gut*. 1992;33:969–972.
21. Ohara H, Hoshino M, Hayakawa T, et al. Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones. *Am J Gastroenterol*. 1996;91:1388–1394.
22. Li K, Lin T, Zhang C, et al. Optimal frequency of shock wave lithotripsy in urolithiasis treatment: a systematic review and meta-analysis of randomized controlled trials. *J Urol*. 2013;190:1260–1267.
23. Guda NM, Reddy DN, Kumar A. Complications of ERCP. *Indian J Gastroenterol*. 2014;33:1–9.
24. van Huijgevoort N, Veld JV, Fockens P, et al. Success of extracorporeal shock wave lithotripsy and ERCP in symptomatic pancreatic duct stones: a systematic review and meta-analysis. *Endosc Int Open*. 2020;8:E1070–E1085.
25. Kitano M, Gress TM, Garg PK, et al. International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatol*. 2020;20:1045–1055.
26. Bockman DE, Buchler M, Malfertheiner P, et al. Analysis of nerves in chronic pancreatitis. *Gastroenterology*. 1988;94:1459–1469.
27. Arata S, Takada T, Hirata K, et al. Post-ERCP pancreatitis. *J Hepatobiliary Pancreat Sci*. 2010;17:70–78.
28. Drewes AM, Bouwense S, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatol*. 2017;17:720–731.

29. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. *Gut*. 2007;56:545–552.
30. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018. *Endoscopy*. 2019;51:179–193.
31. Guo JY, Qian YY, Sun H, et al. Optimal timing of endoscopic intervention after extracorporeal shock-wave lithotripsy in the treatment of chronic calcified pancreatitis. *Pancreas*. 2021;50:633–638.
32. Sarles H. Etiopathogénie des pancréatites chroniques nutritionnelles [Etiopathogenesis of chronic nutritional pancreatitis]. *Reprod Nutr Dev*. 1987;27:611–625. French.
33. Chang YT, Chang MC, Su TC, et al. Lipoprotein lipase mutation S447X associated with pancreatic calcification and steatorrhea in hyperlipidemic pancreatitis. *J Clin Gastroenterol*. 2009;43:591–596.
34. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatol*. 2013;13:336–342.

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