Earlier surgery improves outcomes from painful chronic pancreatitis

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Abstract
The timing of surgery for painful chronic pancreatitis (CP) may affect outcomes. Clinical course, subjective pain scores, and pancreatic function were retrospectively compared and analyzed between patients undergoing either early or late surgery (<3 or ≥3 years from diagnosis) for painful CP in a single center from 2007 to 2012. The early surgery group (n=98) more frequently than the late group (n=199) had abdominal pain with jaundice (22.4% vs 9.5%, \(P=0.002\)) and pancreatic mass +/- ductal dilatation (47% vs 27%, \(P<0.001\), but less frequently abdominal pain alone (73.5% vs 85.9%, \(P=0.009\)), ductal dilatation alone (31% vs 71%, \(P<0.001\)), parenchymal calcification (91.8% vs 100%, \(P<0.001\)) or exocrine insufficiency (60% vs 72%, \(P=0.034\)); there were no other significant differences. The early group had longer hospital stay (14.4 vs 12.2 days, \(P=0.009\)), but no difference in complications. Significantly greater pain relief followed early surgery (complete 69% vs 47%, partial 22% vs 37%, none 8% vs 16%, \(P=0.01\)) with lower rates of exocrine (60% vs 80%, \(P=0.005\)) and endocrine insufficiency (36% vs 53%, \(P=0.033\)).

Our data indicate that early surgery results in higher rates of pain relief and pancreatic sufficiency than late surgery for chronic pancreatitis patients. Frey and Berne procedures showed better results than other surgical procedures.

Abbreviations: CP = chronic pancreatitis, ISGPF = International Study Group on Pancreatic Fistulae, PD = pancreaticoduodenectomy, POPF = postoperative pancreatic fistula, PPPD = pylorus-preserving, SD = standard deviation.

Keywords: chronic pancreatitis, endocrine pancreatic insufficiency, exocrine pancreatic insufficiency, pain relief, surgery

1. Introduction
Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas with an increasing annual incidence characterized by intractable pain and poor quality of life.\[1\] As the disease progresses there is continuous destruction of the pancreatic parenchyma, chronic pain, local complications (including duodenal, biliary and pancreatic duct obstruction, and pancreatic pseudocysts), compromised pancreatic exocrine and endocrine function, as well as an increased risk for pancreatic cancer.\[1,2\] The associated co-morbidities, recurrent symptomatic episodes, and socioeconomic impact make CP one of the most resource intensive diseases to manage.\[3\]

One key goal of the management of CP is to mitigate pain,\[1,4–6\] as it is the predominant symptom and its severity significantly correlates with poor quality of life.\[7\] Unfortunately, the mechanisms of pain secondary to CP have not been fully elucidated, resulting in suboptimal clinical efficacy of targeted treatments.\[4\] Traditionally, a conservative step-up approach has been advocated to treat painful CP, with surgery regarded as an option when other treatments have failed.\[1,5,6\] The initial choices of analgesic medications are nonsteroidal anti-inflammatory drugs.\[4\] But, a large proportion of patients prove refractory to medical therapy.\[1,6\] Endoscopic therapy is often performed in such patients in an effort to relieve pancreatic and/or bile duct obstruction and symptomatic pseudocysts.\[1,5,6\] Randomized controlled studies\[5–11\] however, have shown that surgery (either resection or drainage) results in significantly greater and more durable pain relief than endotherapy.\[1,10,11\]

There is some evidence to suggest that early surgery is more effective than later surgery in preserving exocrine function in experimental CP.\[12\] A recent meta-analysis has shown that early surgery is associated with an increased likelihood of complete pain relief together with reduced rates of pancreatic insufficiency and re-intervention.\[13\] A multicentre retrospective study of 266 patients with CP demonstrated that early surgery within 3 years was more beneficial for pain relief, pancreatic function, and quality of life.\[14\] Nevertheless other studies suggest or advocate a step-up approach using antioxidants,\[15–18\] adjuvant analgesics,\[19\] pancreatic enzyme supplements,\[20,21\] and endoscopy...
therapy,[16,21] resorting to surgery at a later stage for those who fail the conservative management.

To determine the relative merits of early and late surgery we analyzed 297 patients who had surgery for CP retrospectively to determine[11] whether early surgery offered better pain control and preservation of pancreatic function than late surgery, and[22] which surgical procedure (resection only or resection +/- drainage or drainage only) was more effective when performed early.

2. Methods

2.1. Patients and data collection

Consecutive CP patients diagnosed by disease history and radiological findings who underwent surgery at West China Hospital between February 2007 and February 2012 were considered for inclusion in this retrospective study. Demographics, symptoms at admission, pancreatic functional status, surgical procedures undertaken, intra- and postoperative outcomes were determined. Risk factors for CP were classified according to the TIGAR-O classification system.[22] Patients were excluded from the study if the diagnosis of CP was not confirmed histologically, if pancreatic cancer was detected on histology, if patients were excluded if the diagnosis of CP was not confirmed histologically, if pancreatic cancer was detected on histology, if there was inadequate information or patients were lost to follow-up during 3 years after surgery. Patients were also excluded if they had any surgical procedures on the pancreas prior to the index operation for CP. All the identified patients were followed-up in outpatient clinic and/or by telephone for at least 3 years postoperatively. The research protocol was approved by the institutional review board of West China Hospital and informed consent from patients was waived due to retrospective use of anonymized data. The study followed the STROBE guidelines.

2.2. Patient management and surgical procedures

Patients in West China Hospital with a disease history of CP confirmed radiologically (CT and/or MRI) and with intractable pain are candidates for surgery; we have used narcotic analgesia and endotherapy with surgery as an alternative or subsequently, depending on clinical and radiological features. Pancreatectoduodenectomy (PD) and pylorus-preserving pancreatectoduodenectomy (PPPD) were offered for inflammatory enlargement of the pancreatic head, especially when calcifications were predominantly in the head. Beger’s procedure was offered for calcifications located in the head of the pancreas with or without associated enlargement of the pancreatic head; the Berne procedure was an alternative determined intraoperatively. Frey’s procedure was offered when calcifications were located throughout the pancreas with or without pancreatic head enlargement, and with or without a dilated main pancreatic duct. The Partington–Rochelle procedure was undertaken as an alternative for a dilated main pancreatic duct in patients with no pancreatic head enlargement.

2.3. Outcome measures

The primary endpoint was pain relief, assessed at the end of follow-up using the Izbicki pain score as described by Caven et al.[10] with minor modifications and as reported by the patients. It was defined as complete pain relief (Izbicki pain score, ≤ 10 or pain level decrease of 100%), partial (Izbicki pain score > 10 and pain level decrease > 50%) or no relief (Izbicki pain score > 10 and pain level decrease of < 50%).

Secondary end points were intra- and postoperative outcomes including pancreatic function. Postoperative pancreatic fistula (POPF) was defined by the International Study Group on Pancreatic Fistulae (ISGPF A, B, and C) definition.[23] Exocrine insufficiency was defined as faecal elastase levels < 200 μg/g, or the presence of steatorrhoea, or the need for pancreatic enzyme replacement therapy (> 1 year history; overt steatorrhoea without treatment). Endocrine insufficiency was defined by the presence of prediabetes (fasting serum glucose levels > 6.0 mmol/L in capillary blood or > 6.9 mmol/L in venous plasma on 2 different days) or overt diabetes mellitus. Both exocrine insufficiency and endocrine insufficiency were defined as described by Caven et al.[10], those who had pancreatic insufficiency at both baseline and follow-up (insufficiency persisted); those who did not have insufficiency at baseline but in whom insufficiency developed during follow-up (insufficiency developed); those who had insufficiency at baseline but not at follow-up (insufficiency resolved), and those who did not have insufficiency at baseline or follow-up (sufficiency persisted). Quality of life was measured by the European Organisation for Research and Treatment of Cancer’s quality-of-life questionnaire.[24]

2.4. Statistical analysis

Based on data from previous studies,[14,25] early surgery was defined as surgery performed ≤ 3 years following diagnosis, while late surgery was > 3 years. Continuous data are presented as mean± standard deviation (SD) or median with range depending on normal or skewed distributions, respectively. Categorical variables are described as numbers and in percentages. Mann–Whitney U and Chi-square (or Fisher’s exact test) tests were used for continuous and categorical data comparisons, respectively. Intention-to-treat analysis was performed before removal of dead patients before follow-up. A P value <.05 was considered to be statistically significant. The analyses were performed using IBM SPSS 22.0 statistical software (IBM, Armonk, NY).

3. Results

3.1. Characteristics of included patients

The patient selection process is shown in Figure 1. The initial screen included 417 CP patients. Eighty patients were excluded because they were lost to follow-up or there was insufficient information to determine long-term outcome. A further 31 patients were excluded either because of pancreatic/periampullary cancer, or they had undergone previous surgery, or histopathology was not obtained. A total of 306 patients with CP were included. Four patients died postoperatively in the early surgery group before follow-up: 2 abdominal cavity bleeding after PD, 1 gastrointestinal bleeding after PPPD, 1 gastrointestinal leakage (abdominal cavity infection and respiratory failure) after Beger’s procedure; 4 died in the late surgery group: 2 gastroduodenal artery rupture after PD, 1 lung infection after PD, 1 liver and renal failure after Beger’s procedure. Thus complete data were available for analysis from 297 patients. The year in which surgery was performed had no significant impact on the allocation of early or late surgery group (each year P > .05). The preoperative patient characteristics are outlined in Table 1. There were no statistically significant differences in age, gender, TIGAR-O classification, pain pattern and endocrine insufficiency, and the presence of both pancreatic head mass and ductal...
dilatation between the early and late surgery groups. There was a higher proportion of patients in the early surgery group who had abdominal pain with jaundice (22.4% vs 9.5%, \( P = .002 \)), pancreatic head mass (26.5% vs 11.1%) or pancreatic duct stone without ductal dilatation or mass (20.4% vs 15.6%), but lower proportion with abdominal pain alone (73.5 vs 85.9%), pancreatic duct dilatation alone (30.6% vs 70.9%) and parenchymal calcification (91.8% vs 100%) when compared to the late surgery group (all \( P < .05 \)). The proportion of patients with exocrine insufficiency was significantly lower in the early surgery group as compared to the late surgery group (60.2% vs 72.4%, \( P = .034 \)), while there was no difference in endocrine insufficiency (25.5% vs 31.2%, \( P > .05 \)).

### 3.2. Intra- and postoperative complications

Patients underwent surgery at a median 25 months (range 11–36) from initial CP diagnosis in the early surgery group compared with 81 months (range 45–122) in the late surgery group. There was no difference in follow-up time between the 2 surgery groups (65 months [36–96] vs 73 months [36–89], \( P > .05 \)). Details of the intra- and postoperative complications and length of hospital stay are provided in Table 2. There were no significant differences in the mean operation time, intraoperative blood transfusion, volume of transfused packed red blood cells and the overall volume of transfused packed red blood cells.

### Table 1

**Characteristics of CP patients prior to surgery.**

| Patient characteristics | Total n = 297 | Early n = 98 | Later n = 199 | \( P \) value |
|-------------------------|--------------|-------------|---------------|-------------|
| **Gender, n (%)**       |              |             |               |             |
| Male                    | 216 (72.7)   | 74 (75.5)   | 142 (71.4)    | .450        |
| Female                  | 81 (27.3)    | 24 (24.5)   | 57 (28.6)     |             |
| **Age in years, mean ± SD** | 47 ± 12.4   | 47.2 ± 11.3 | 48 ± 9.2      | .521        |
| **Symptoms**            |              |             |               |             |
| Abdominal pain alone    | 243 (81.8)   | 72 (73.5)   | 171 (85.9)    | .009        |
| Abdominal pain + jaundice | 41 (13.8)  | 22 (22.4)   | 19 (9.9)      | .002        |
| **Key radiological appearance** |            |             |               |             |
| Mass alone              | 48 (16.2)    | 26 (26.5)   | 22 (11.1)     | .001        |
| Ductal dilatation       | 171 (57.6)   | 30 (30.6)   | 141 (70.9)    | < .001      |
| Mass + ductal dilatation| 51 (17.2)    | 20 (20.4)   | 31 (15.6)     | .299        |
| Ductal stone without dilatation or mass | 27 (9.1) | 22 (22.4) | 5 (2.5) | < .001 |
| Parenchymal calcification | 289 (97.3) | 90 (91.8) | 199 (100) | < .001 |
| **TIGAR-O classification, n (%)** | | | | .870 |
| Toxic-metabolic (alcohol and smoking) | 118 (39.7) | 37 (37.8) | 81 (40.7) | |
| Idiopathic              | 142 (47.8)   | 49 (50)     | 93 (46.7)     |             |
| Hereditary              | 1 (0.3)      | 0 (0)       | 1 (0.5)       |             |
| Autoimmune              | 1 (0.3)      | 1 (1)       | 0 (0)         |             |
| Recurrent or severe acute pancreatitis | 23 (7.7) | 7 (7.1) | 16 (8) | |
| Obstructive             | 5 (1.7)      | 2 (2)       | 3 (1.5)       |             |
| **Pain pattern, n (%)** |              |             |               | .517        |
| Continuous              | 174 (58.6)   | 60 (61.2)   | 114 (73.7)    |             |
| Intermittent            | 123 (41.4)   | 38 (38.8)   | 85 (26.3)     |             |
| **Exocrine function, n (%)** | | | | .034 |
| Insufficiency           | 203 (68.4)   | 59 (60.2)   | 144 (72.4)    |             |
| Normal                  | 94 (31.7)    | 39 (39.8)   | 55 (27.6)     |             |
| **Endocrine function, n (%)** | | | | .315 |
| Insufficiency           | 87 (29.3)    | 25 (25.5)   | 62 (31.2)     |             |
| Normal                  | 210 (70.7)   | 73 (74.5)   | 137 (68.8)    |             |

*Early vs late.*

\( SD = \) standard deviations.

\( P \) value in bold indicates early vs late was significant different at level of 0.05.
complication rate between the 2 groups. The early surgery group had a higher incidence of grade A POPF (13.2% vs 7%, \( P = .079 \)) and was associated with a longer hospital stay (mean 14.4 vs 12.2 days, \( P = .009 \)) compared to the late surgery group.

### 3.3. Endpoints

Izbicki pain scores at follow-up were significantly lower in the early surgery group compared to the late surgery group (24 \( \pm \) 14 vs 31 \( \pm \) 16, \( P = .031 \); Table 2). Complete or partial pain relief was achieved in 91.8% of patients in the early surgery group, significantly higher than 83.9% in the late surgery group (\( P = .01 \)). A much higher proportion of patients in the early surgery group had complete pain relief (69.4% vs 46.7%, \( P < .001 \)), and the proportion of patients with no pain relief in the early surgery group was smaller (8.2% vs 16.1%, \( P = .06 \)).

Early surgery was followed by a reduced incidence of exocrine insufficiency (60.2% vs 80.39%, \( P = .005 \)) and endocrine insufficiency (35.7% vs 52.7%, \( P = .033 \)), with a trend of a higher rate of resolution of both exocrine and endocrine insufficiency in the early surgery group (Table 2). Early surgery group also showed a better quality of life than later surgery group (Table 2).

### 3.4. Comparison of the impact of individual surgical procedures on pain relief

The influence of different surgical procedures on postoperative pain relief in the early and late surgery groups was analyzed and is summarized in Table 3. There were no significant differences in pain relief between the early and late surgery groups when only resections (PD, PPPD and Beger’s procedure) or drainage procedures (Partington–Rochelle) were compared. In contrast, patients undergoing a combination of resection with drainage (Frey and Berne procedures) experienced significantly greater pain relief in the early surgery group compared to the late surgery group (Frey \( P = .031 \), Berne \( P = .028 \)). There were no statistically significant differences in pain relief between different early surgical interventions likely due to small patient numbers. There was however a trend toward complete pain relief following Frey (82.6%), Berne (75.9%), and Partington–Rochelle (70%) procedures when compared with other procedures (50%–61.5%).

### 3.5. Comparison of individual surgical procedures on pancreatic function

The impact of different surgical procedures on postoperative pancreatic exocrine and endocrine function is summarized in Table 4. Similar to the findings obtained for pain relief, patients undergoing Frey and Berne procedures in the early surgery group had consistently high rates of exocrine (Frey \( P = .001 \), Berne \( P = .02 \)) and endocrine (Frey \( P = .037 \), Berne \( P = .049 \)) function preservation when compared with patients undergoing the same procedures in the late surgery group. This was not the case for the other surgical procedures, with the exception of patients undergoing Beger’s procedure in the early surgery group who had significantly better preservation of endocrine function (\( P = .038 \)). Intention-to-treat analyses including patients who died did not change any findings on endpoints.

### 4. Discussion

Our study clearly demonstrates that early surgery results in more effective pain relief and better preservation of pancreatic exocrine
and endocrine function. The study, the largest comparing early versus late surgery for painful CP to date, also demonstrates that drainage and resection (e.g., Frey and Berne procedures) had better outcomes than resection or drainage alone.

The early surgery group was comparable to the late surgery group with respect to the operation time, intraoperative blood transfusion, transfused red volume of packed blood cells, duration of intensive care unit stay, and the overall complication rate, which indicate that it was safe. The incidence of POPF B/C was similar in both groups, but early surgery was associated with a higher incidence of POPF A, and thus with a longer hospital stay. This may be because in CP at an earlier stage the pancreas tends to have more functional units, less fibrosis (soft pancreas) and the exocrine pancreas is able to produce more fluid. It has been demonstrated that the soft pancreas has a higher POPF rate after surgery than the hard pancreas.\(^26\)

### Table 3

| Procedures                  | No relief | Partial relief | Complete relief | P value |
|-----------------------------|-----------|----------------|-----------------|---------|
| Resection, n (%)            |           |                |                 |         |
| PD                          |           |                |                 | 1.000   |
| Early (n = 9)               | 1 (11.1)  | 3 (33.3)       | 5 (55.6)        |         |
| Late (n = 19)               | 4 (21.1)  | 5 (26.3)       | 10 (52.6)       | .704    |
| PPPD                        |           |                |                 |         |
| Early (n = 13)              | 2 (15.4)  | 3 (23.1)       | 8 (61.5)        |         |
| Late (n = 18)               | 3 (16.7)  | 7 (38.9)       | 8 (44.4)        | .436    |
| Beger                       |           |                |                 |         |
| Early (n = 14)              | 1 (7.1)   | 6 (42.9)       | 7 (50)          |         |
| Late (n = 35)               | 8 (22.9)  | 12 (34.3)      | 15 (42.9)       |         |
| Resection + drainage, n (%) |           |                |                 | .031    |
| Frey                        |           |                |                 |         |
| Early (n = 23)              | 0 (0)     | 4 (17.4)       | 19 (82.6)       |         |
| Late (n = 30)               | 5 (16.7)  | 10 (33.3)      | 15 (50)         |         |
| Berne                       |           |                |                 | .028    |
| Early (n = 29)              | 3 (10.3)  | 4 (13.8)       | 22 (75.9)       |         |
| Late (n = 69)               | 9 (31.3)  | 27 (39.1)      | 33 (47.8)       |         |
| Drainage, n (%)             |           |                |                 | .328    |
| Partington–Rochelle         |           |                |                 |         |
| Early (n = 10)              | 1 (10)    | 2 (20)         | 7 (70)          |         |
| Late (n = 28)               | 3 (10.7)  | 13 (46.4)      | 12 (42.9)       |         |

PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy.

P value in bold indicates early vs late for Frey and Berne was significant different at level of 0.05, respectively.

### Table 4

| Procedures                  | Exocrine function | Endocrine function | P value |
|-----------------------------|-------------------|---------------------|---------|
|                            | Insufficiency persisted | Insufficiency developed | Suficiency resolved | P value |
|                            | Insufficiency persisted | Insufficiency developed | Suficiency resolved | P value |
| Resection, n (%)            |                   |                     |                   |         |
| PD                          |                   |                     |                   | .630    |
| Early (n = 9)               | 5 (62.5)          | 3 (25.0)            | 0 (0)             | 3 (37.5) |
| Late (n = 19)               | 12 (63.2)         | 4 (21.1)            | 0 (0)             | 3 (15.8) |
| PPPD                        |                   |                     |                   | .524    |
| Early (n = 13)              | 8 (57.1)          | 3 (21.4)            | 2 (14.3)          | 1 (7.1)  |
| Late (n = 18)               | 12 (63.2)         | 2 (10.5)            | 1 (5.3)           | 4 (21.1) |
| Beger                       |                   |                     |                   | .582    |
| Early (n = 14)              | 7 (50)            | 2 (14.3)            | 3 (21.4)          | 2 (14.3) |
| Late (n = 35)               | 22 (62.9)         | 5 (14.3)            | 3 (8.6)           | 5 (14.3) |
| Resection + drainage, n (%) |                   |                     |                   | .011    |
| Frey                        |                   |                     |                   | .037    |
| Early (n = 23)              | 10 (43.5)         | 0 (0)               | 3 (13)            | 10 (43.5) |
| Late (n = 30)               | 22 (73.3)         | 3 (10)              | 1 (3.3)           | 4 (13.3) |
| Berne                       |                   |                     |                   | .020    |
| Early (n = 29)              | 11 (37.9)         | 3 (10.3)            | 4 (13.8)          | 11 (37.9) |
| Late (n = 69)               | 47 (68.1)         | 7 (10.1)            | 4 (5.8)           | 11 (15.9) |
| Drainage, n (%)             |                   |                     |                   | .049    |
| Partington–Rochelle         |                   |                     |                   | .644    |
| Early (n = 10)              | 5 (50)            | 2 (20)              | 1 (10)            | 2 (20)   |
| Late (n = 28)               | 18 (66.7)         | 2 (7.4)             | 2 (7.4)           | 5 (18.5) |

PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy.
A major challenge in the management of CP patients is the treatment of pain. The pain in CP is multifactorial with a number of proposed mechanisms, although by the time patients present there is often a significant neuropathic component. Neural plasticity, neural inflammation, and an altered distribution of sympathetic and sensory fibres are seen in CP and these changes correlate with the severity of neuropathic pain. Patients with CP exhibit central hyperalgesia and alterations in brain resting activity, which decrease their pain threshold. Traditionally it was considered that pain in CP would ultimately resolve spontaneously or “burn out,” owing to progressive destruction of the pancreatic parenchyma. More recent data indicate that repeated episodes of pancreatic inflammation lead to peripheral and central nociceptive nerve sensitisation, which leads to a chronic pain state that might be avoided by earlier intervention. Narcotic analgesics commonly used to treat unresolved pain are associated with addiction and unfavourable side effects, including opioid hyperalgesia. Recent meta-analyses indicate that the antineuropathic pain medications pregabalin, and pancreatic enzyme replacement therapy have little effect on pain relief. An improved understanding of the patterns of pain in CP is needed and the Dutch CARE trial presently underway, seeks to address this. CP patients in whom pain is refractory to medications and endotherapy eventually undergo surgery, often as a last resort. Recently, surgery has been shown to be superior to endotherapy for both short- and long-term pain control in randomized trials, in a meta-analysis based on these trials. Intermediate and long-term follow-up studies have shown that patients undergoing resection with or without drainage procedures have sustained pain relief with substantially improved quality of life. Our CP patients who had intractable pain following medical management and endotherapy were advised to have surgery; in our study, the complete and partial pain relief rates were similar to or higher than in previous studies. We used a cut-off of 3 years to define early and late surgery, in keeping with previous studies; many of our patients had little response to medical management and had undergone one or more endoscopic interventions by this time. Other studies have suggested that surgical intervention prior to the start of opioid dependence might be beneficial, but this study could be considered too early to justify a major resection plus drainage procedures (both Frey and Berne procedures) had better outcomes when performed early.

This study has several limitations. It was performed retrospectively and the sample sizes in the individual surgical groups were small, which may have resulted in some bias. The early and late surgical groups did have differences prior to surgery, especially in pancreatic morphology, but this has been shown not to relate to pain severity or the response to intervention. We did not obtain precise data for symptom onset, narcotic medicine and endotherapy prior to operation for comparisons. Data on quality of life, one of the better parameters to assess treatment effects in CP, were not available. The validated PANQOLI tool is now available and should be used in future studies. The results of the prospective, multicenter randomized controlled trial comparing early surgery and an optimised step-up approach are eagerly awaited. Unfortunately this trial has used the Izbicki pain score, as in the present study, which assesses only 4 aspects of pain. A more comprehensive pain assessment tool is required to capture all important aspects of pain, since pain is the primary indication for intervention and the reduction of pain is the primary endpoint of intervention studies. While our data indicate the benefits of early surgery and the surgical procedures that are most effective, these findings need to be confirmed in prospective randomized controlled trials.

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