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Gallstone-induced acute pancreatitis

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Abstract In the care of acute pancreatitis, a prompt search for the etiologic condition of the disease should be conducted. A differentiation of gallstone-induced acute pancreatitis should be given top priority in its etiologic diagnosis because it is related to the decision of treatment policy. Examinations necessary for diagnosing gallstone-induced acute pancreatitis include blood tests and ultrasonography. Early ERCP/ES should be performed in patients with gallstone-induced acute pancreatitis if a complication of cholangitis and a prolonged passage disorder of the biliary tract are suspected. The treatment for bile duct stones with the use of ERCP/ES alone is not recommended in cases of gallstone-induced pancreatitis with gallbladder stones. Cholecystectomy for gallstone-induced acute pancreatitis should be performed using a laparoscopic procedure as the first option as soon as the disease has subsided.

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Introduction

Research on the pathophysiology of acute pancreatitis has advanced dramatically during the last 20 years, and the number of randomized controlled studies (RCTs) on severe acute pancreatitis has steadily increased. The JPN guideline for the management of acute pancreatitis was published in Japanese on 2003, and in English on 2006, from the perspective of evidence-based clinical practice guidelines [1]. This paper incorporates the latest evidence, revises our guideline in relation to gallstone pancreatitis and represents the JPN Guidelines for the treatment of gallstone-induced acute pancreatitis.

Text

Chief causes of gallstone-induced pancreatitis

Gallstone-induced pancreatitis is thought to occur according to the following two mechanisms: (1) as a result of incarceration of common bile duct stones into the papilla (common pancreaticobiliary duct) followed by outflow disorders of pancreatic juice; (2) inflammation associated with cholangitis extending directly as far as the pancreas.

Diagnosis of gallstone-induced pancreatitis

CQ1 Which examinations are necessary for diagnosing gallstone-induced acute pancreatitis?

To begin with, blood tests and ultrasonography should be conducted. (Recommendation A)

A diagnosis of gallstone-induced acute pancreatitis is made when jaundice and elevated levels of ALP, γGTP and transamylase are detected by blood tests and common bile duct stones are visualized by (extracorporeal) ultrasonography (ultrasonography henceforth).

However, ultrasonography is not always able to visualize biliary stones in all cases. The ability of ultrasonography to visualize common bile duct stones decreases due to the presence of intestinal gas bubble imaging in the acute phase of pancreatitis. Common bile duct stones that induce acute pancreatitis are small sized, so visualization of the common bile duct by ultrasonography becomes difficult. Furthermore, in some cases, common bile duct stones are 'passed stones' that have already been excreted from the papilla to the duodenum. These considerations often make a diagnosis of gallstone-induced acute pancreatitis difficult. Therefore, ultrasonography should be conducted repeatedly or MRCP and EUS with higher sensitivity and specificity should be performed if ultrasonography has failed to visualize common bile duct stones, despite the presence of jaundice and elevated levels of the enzymes in the hepatobiliary system together with suspected gallstone-induced acute pancreatitis. There are cases in which ERCP is conducted on the assumption that endoscopic papillary treatment is to be provided.

Hematological examinations

There is a high possibility that gallstone-induced acute pancreatitis is present when the level of blood ALT is over 150 IU/L (48–93% for sensitivity, 34–96% for specificity, 1.4–12.0 for positive likelihood ratio and 1.8–4.9 for negative likelihood ratio) (Level 1c–2b) [2, 3], or when abnormal values were detected by blood tests in more than 3 of the items including bilirubin, ALP, γGTP, ALT, ALT/AST (85% for sensitivity, 69% for specificity, 2.7 for positive likelihood ratio, and 4.6 for negative likelihood ratio) [4]. Combination of ultrasonography and blood tests yields a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞ and negative likelihood ratio of 20.0–50.0, which enables the etiologic diagnosis of gallstone-induced acute pancreatitis (Level 2b) [4–6].

There is a report showing that blood trypsin-2-α1 antitrypsin complex/trypsinogen-1 ratio is useful in making the etiologic diagnosis of gallstone-induced acute pancreatitis because the level of blood trypsinogen increases specifically in blood trypsinogen-1 (Level 1b) [7].

Ultrasonography

As described above, in most cases, combination of ultrasonography with blood biochemical tests yields a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞ and negative likelihood ratio of 20.0–50.0, which enables the etiologic diagnosis of gallstone-induced acute pancreatitis (Level 2b) [5, 6]. Furthermore, there is a difference from report to report in the visualization rate of common bile duct stones (20–90%) by ultrasonography, so gallstone-induced pancreatitis should not be ruled out, even if ultrasonography has failed to detect biliary stones and bile duct dilatation (Level 1b–4) [8–10]. Therefore, ultrasonography should be performed repeatedly or MRCP should be conducted when gallstone-induced pancreatitis is suspected, even if the initial ultrasonography has failed to visualize biliary stones.

CT

Because CT cannot visualize biliary stones in many cases (sensitivity of 40–53%), it is not suitable for diagnosing gallstone-induced acute pancreatitis (Level 1b) [5, 10].

MRI/MRCP

Sensitivity in visualizing common bile duct stones is 20% for CT and 40% for MRCP, but is 80% for MRI/MRCP; for this reason there is an opinion that recommends MRI/MRCP as a procedure for determining indications for endoscopic papillary treatment (ERCP/ES) (Level 1b) [11]. Compared with ERCP, MRCP does not require manipulation of the papilla, so that it is able to visualize common bile duct stones in a relatively early phase of the disease because it is a minimally invasive procedure without carrying the risk of worsening the condition of acute pancreatitis.

EUS

EUS is superior to ultrasonography in terms of ability to visualize common bile duct stones (Level 1b–2b) [8, 12, 13]. In cases in which ultrasonography has failed to identify the etiology, common bile duct stones can be visualized in 59–78% of cases by performing EUS (Level 1b–3b) [12, 14, 15]. ERCP and EUS have been considered to be gold standards for making a detailed examination of biliary stones. However, the biliary tract is not able to be visualized by ERCP in some cases (14%) while detailed examinations can be carried out by EUS in all the cases that are involved (Level 1b) [16]. As mentioned above, ERCP performed at the time of an attack of acute pancreatitis is likely to further worsen inflammation.

ERCP

When jaundice and hepatic disorders are observed and the presence of common bile duct stones is strongly suspected, ERCP/ES should be performed on the assumption that endoscopic treatment of gallstone-induced pancreatitis is to be conducted. When ERCP/ES is not available, patients should be transferred to a medical facility which is in a position to perform it. There is also an opinion that recommends combined use of intraductal ultrasonography (IDUS) with ERCP on the basis of data showing that the rate of visualization of common bile duct stones is 95% for ERCP and 95% for ERCP in combination with IDUS (Level 1b) [10]. However, pancreaticography should be avoided as far as conditions permit when ERCP/EC is performed for gallstone-induced pancreatitis.

Treatment of biliary stones in gallstone-induced pancreatitis

Endoscopic treatment

CQ2 Should early ERCP+ES be performed in gallstone-induced acute pancreatitis?

Early ERCP + ES should be performed in gallstone-induced acute pancreatitis when complications of cholangitis or prolonged passage disorder of the biliary tract is suspected. (Recommendation B). Usefulness of early ERCP + ES is not supported in cases that are different from the above cases.

Of those patients in whom a diagnosis of gallstone-induced acute pancreatitis has been made or acute pancreatitis is suspected, ERCP with/without endoscopic sphincterotomy (ERCP/ES) should be performed according to the present knowledge in patients with complicated cholangitis and in patients with recurrent jaundice or its aggravation along with suspected prolongation of a passage disorder of the biliary tract. It is considered that benefits of ERCP/ES are particularly great in patients with severe acute pancreatitis. An advanced medical facility where care of acute pancreatitis is provided should always be in a position to provide ERCP/ES.

Meta-analysis

As far as an early ERCP/ES in acute pancreatitis is concerned, 4 RCTs were performed until 1997 (Level 1b) [17–20] (Table 1). Meta-analyses conducted by these RCTs (Level 1a) [21–23] reported that the incidence and mortality rates were favorable in an ERCP/ES group [21] and the incidence of complications decreased significantly only in severe cases after severity had been stratified (41.8 vs. 31.3%, $P = 0.03$) [22], a significant difference was observed in the incidence of complications (57.1 vs. 18.2% $P = 0.001$) [22] (OR = 0.27, 95% CI = 0.14–0.53) [23] and the mortality rate (17.9 vs. 3.6%, $P = 0.03$) [22].

According to the conclusions obtained by recent meta-analyses that paid attention to the sampling and end points of cases involved [24–26], early ERCP/ES decreases the incidence of complications only in severe cases but it has no effect on the mortality rate (Level 1a) [24]. In gallstone-induced acute pancreatitis without cholangitis, early ERCP/ES does not decrease the incidence of complications or the mortality rate irrespective of severity (Level 1a) [25], and irrespective of severity, early ERCP/ES decreases the incidence of local complications including infected pancreatic necrosis, pancreatic abscess and pancreatic pseudocysts (Level 1b) [26].

Table 1 Comparison of the incidence of complications and mortality rate in a group that underwent early ERCP/ES and a group that underwent conservative treatment in RCTs

Reporters	Years reported	Indications	Timing of EEI	Number of cases EEI versus ECM (severe)	Incidence of complications (%)		Mortality rate (%)	
					EEI (mild/severe)	ECM (mild/severe)	EEI (mild/severe)	ECM (mild/severe)
Neoptolemos [17]	1988	Gallstone-induced acute pancreatitis	Hospitalization <72 h	59 versus 62 (25 vs. 28)	16.9* (11.8/24.0)	33.9 (11.8/60.7)	1.7 (0/4.0)	8.1 (0/17.9)
Fan [18]	1993	Acute pancreatitis	Hospitalization <24 h	97 versus 98 (41 vs. 40)	17.5 (14.3/22.0)	28.6 (10.3/57.5)	5.2 (0/12.2)	9.2 (0/22.5)
Nowak [19]	1995	Gallstone-induced acute pancreatitis without papillary incarceration	Hospitalization <24 h	103 versus 102	16.9*	36.3	2.3*	12.8
Fölsch [20]	1997	Gallstone-induced acute pancreatitis T-Bil <5 mg/dL	Onset <72 h	126 versus 112 (26 vs. 20)	46.0	50.9	11.1	6.3
Zhou [27]	2002	Gallstone-induced acute pancreatitis	Hospitalization (<24 h)	20 versus 25 (7 vs. 7)	5.0* (0/14.3)	20.0 (0/71.4)		
Acosta [29]	2006	Gallbladder stones-related acute pancreatitis with symptoms of papillary incarceration	Onset <24–48 h	30 versus 31 (3 vs. 3)	6.7*	29.0	0	0
Oria [30]	2007	Gallstone-induced acute pancreatitis with passage disorder, without cholecystis	Onset <72 h	51 versus 51 (17 vs. 21)	21.6	17.6	5.9 (0/17.6)	2.0 (0/4.8)

EEI early endoscopic intervention (ERCP/ES), *ECM* early conservative management

* $P < 0.05$

Recent RCTs

A small RCT (Level 2b) (Table 1) [27] conducted to examine the incidence of complications, length of hospital stay and medical costs by assigning patients to either a group ($n = 20$) receiving ERCP/ES within 24 h following hospitalization and a group ($n = 25$) receiving conservative treatment found that the incidence of complications, as well as a length of hospital stay and medical costs, decreased significantly in severe cases in the ERCP/ES group.

According to an RCT (Level 2b) [28] that studied acute pancreatitis of which the causes are not limited by assigning patients either to a group that underwent EST 24 h after hospitalization or to a group that did not undergo EST, the number of days required until the disappearance of abdominal pain, the number of days for the amylase level in blood and urine tests to return to normal and the length of hospital stay were significantly shorter in the EST group. The rate of disappearance of acutely collected fluid and the rate of improvement detected by CT were also significantly superior in the EST group. However, there are no evaluations that separately confirmed the incidence and mortality rate in terms of severity.

An RCT (Level 2b) [29] (Table 1) was conducted to examine gallstone-induced acute pancreatitis accompanying papillary obstruction in terms of the incidence of complications associated with the timing of ERCP/ES. Patients with a prolonged passage disorder of the biliary tract were assigned either to a group that underwent ERCP/ES within 24–48 h after onset of the disease or to a group in which ERCP/ES was conducted when the passage disorder was found to have persisted for more than 48 h until the 48 h of observation. The results show that no death occurred in either group but that the incidence of early complications was significantly lower in the early treatment group (26 vs. 3%, $P = 0.026$) and the overall incidence of the complications was lower (29 vs. 7%, $P = 0.043$). The incidence of early and late complications was significantly higher in cases where obstruction persisted for more than 48 h, cholecystectomy was delayed and the length of hospital stay was long.

An RCT (Level 1b) [30] (Table 1) was conducted in patients who were hospitalized 48 h after onset of gallstone-induced acute pancreatitis not accompanied by cholangitis and who had, at the time of hospitalization, a bile duct diameter of $\geq$8 mm and a blood bilirubin level of $\geq$1.2 mg/dL. Patients were assigned either to a group of patients who underwent ERCP/ES within 72 h following hospitalization or to a group of patients who underwent conservative treatment. The results failed to find a significant difference in the SOFA score ($P = 0.87$), the severity detected by CT ($P = 0.88$), the incidence of localized complications (6 vs. 6%, $P = 0.99$), the overall incidence of complications (21 vs. 18%, $P = 0.80$) and the mortality rate (6 vs. 2%, $P = 1$).

From these reports, ERCP/ES is expected to be useful in cases with severe gallstone-induced acute pancreatitis accompanied by a prolonged passage disorder of the bile duct.

Alternative biliary drainage

Besides ERCP/ES, various types of procedures for biliary drainage are employed widely in Japan. At present, there is no report comparable to the above RCTs in terms of the level of quality, although there is a study that asserts the usefulness and safety of endoscopic nasobiliary drainage (ENBD) as an emergency treatment for incarcerated bile stones (Level 4) [31].

An RCT that compared the usefulness of ERCP/ES conducted within 72 h after onset of gallstone-induced severe acute pancreatitis and that of percutaneous transhepatic gallbladder drainage (Level 1b) [32] suggested that the success rate, incidence of complications and mortality rate are similar in either procedure, and that percutaneous transhepatic gallbladder drainage is useful as an alternative procedure to biliary drainage in a community in which endoscopic treatment is not available.

Safety of ERCP/ES

According to a recent national survey (Level 4) [33] investigating incidental diseases related to gastrointestinal endoscopy in Japan, the incidence of incidental diseases detected by diagnostic ERCP and therapeutic ERCP was 0.202 and 0.717%, respectively, and the mortality rate was 0.0065 and 0.052% of the overall death rate.

The safety of ERCP/ES in an acute phase of pancreatitis is asserted in a study comparing patients who underwent early ERCP/ES (within 48 h after onset of the disease) and patients who underwent elective ERCP/ES (Level 4) [34], in reports of ERCP/ES performed within 24–72 h after onset of the disease (Level 4) [35] and in a retrospective study that investigated a large number of cases in the acute phase of pancreatitis (Level 4) [36]. Also, the RCTs mentioned already in this article (Level 1b) [17–20, 27–30, 32] have found that no complications occurred that were associated with procedures and were direct causes of death and that the risk associated with ERCP/ES conducted in the early phase of pancreatitis cannot be regarded as being particularly high. Advanced medical institutions with experienced and appropriate specialists along with specialized facilities and staff are required so that they can cope with emergency ERCP/ES and bleeding that may follow. On the other hand, there is a trial that has studied the usefulness of EUS prior to ERCP/ES, in which study

ERCP/ES was conducted only when EUS indicated the presence of common bile duct stones (Level 1b) [37]. This trial is likely to contribute to a decrease in the potential risk of this procedure.

Summary

According to the present knowledge, unlimited use of early ERCP/ES is not supported. Its use should be limited to patients with symptoms such as the occurrence of jaundice or its prolongation that points to suspected passage disorder of the biliary tract and patients with a complication of cholangitis.

Surgical treatment after resolution of gallstone-induced pancreatitis

Necessity of surgical treatment

CQ3 Is selection of ES alone possible instead of cholecystectomy to prevent gallstone-induced pancreatitis with gallbladder stones?

When there is no special reason for not being able to perform cholecystectomy, ERCP + ES alone is not recommended. (Recommendation D)

Some reports have discussed the adequacy of observing the clinical course of gallstone-induced acute pancreatitis only by ERCP/ES. Some studies (Level 4) [38, 39] that reported on the observation of the clinical course of gallstone-induced acute pancreatitis conducted by using ES alone found no recurrence of pancreatitis during the 2–4 years of observation in elderly patients and patients with a high surgical risk, and claimed the usefulness of ES.

According to a prospective cohort study ($n = 117$, Level 2b) [40] of gallstone-induced acute pancreatitis, recurrent pancreatitis occurred in 2 cases of a group that underwent cholecystectomy and in one case of a group that underwent ERCP + ES alone during the 3 years of observation, and complications in the biliary system occurred in 3.6 and 11.6%, respectively, showing that the rate of occurrence was high in the ERCP + ES alone group, although the difference was not significant. Two reports (Level 4) [41, 42] that prospectively observed patients with gallstone-induced acute pancreatitis in whom ERCP + ES was performed alone found that recurrent pancreatitis occurred only in 1.5% of the patients during the 3–4 years of observation, but that some sorts of disorders of the biliary system of unknown origin occurred in 33.0%, and 12.5% of patients underwent cholecystectomy during the observation period. In both reports, many of the patients of the ERCP + ES alone group were composed of those that avoided early cholecystectomy for the reason that their surgical risk was high.

There are 3 RCTs of an ERCP + ES alone group in which indications were not limited to acute pancreatitis and a group that underwent cholecystectomy. The first report (Level 1b) [43] that concerns patients above 70 years of age (an average of 80 years) found that pancreatitis did not occur in either group during the 17 months of observation but that disorders of the biliary system occurred in 21% of the ERCP + ES alone group and 6% of the cholecystectomy group. The report concluded that cholecystectomy is desirable for elderly patients. The second RCT (Level 1b) [44] found that there was no occurrence of pancreatitis during the 2 years of observation but that there was a high rate of recurrence of symptoms associated with the biliary system in the ERCP + ES alone group (47 vs. 2%). The last report (Level 1b) [45] concerns patients above 60 years of age and shows that there was no occurrence of pancreatitis but that there was a high rate of recurrence of symptoms associated with the biliary system in the ERCP + ES alone group (24 vs. 7%).

Under these conditions, it is thought that in the absence of a special reason for not performing cholecystectomy, observation by performing ERCP + ES alone should be refrained from in cases of gallstone-induced pancreatitis, though the rate of recurrence is not said to be high.

Timing of cholecystectomy

CQ4 Which is the adequate timing for performing cholecystectomy in gallstone-induced pancreatitis?

Cholecystectomy should be performed as soon as resolution of gallstone-induced acute pancreatitis has been achieved. (Recommendation B)

Cholecystectomy has been the first option for gallstone-induced pancreatitis for the reason that cholelithiasis is one of the chief causes of acute pancreatitis. Acute pancreatitis accompanying gallstones is considered to be an indication for treatment of gallstones to prevent its recurrence. There are some opinions concerning the timing of cholecystectomy. One of them asserts that cholecystectomy should be performed as soon as the disease has occurred, while another opinion claims that it should be performed in an elective fashion while waiting for the resolution of inflammatory reaction. An RCT (Level 1b) [46] that supports early surgery found no difference in the incidence of complications (8.3 vs. 10.3%) and the mortality rate (2.8 vs. 6.9%) between the two groups on the basis of the comparison of the group that underwent early surgery within 72 h following hospitalization (early surgery group) and the group that underwent elective surgery after 3 months following hospitalization (elective surgery

group), and concluded that surgery can be performed even in the acute phase. On the other hand, an RCT (Level 1b) [47] that supports elective surgery reports, on the basis of comparison between an early surgery group that underwent surgery within 48 h following hospitalization and a delayed (elective) surgery group that underwent surgery after 48 h following hospitalization, that both the incidence of complications and the mortality rate were high (30.1 vs. 5.1% and 15.1 vs. 2.4%, respectively) in the early surgery group. However, this conclusion is unacceptable because outcomes of treatment are very poor in severe cases.

There is a recent report of a study concerning the benefit of shortening the length of hospital stay in patients who underwent laparoscopic cholecystectomy for gallstone-induced mild pancreatitis (retrospective cohort study, Level 4) [48]. The study asserts the benefit of shortening the length of hospital stay in the early surgery group (surgery is conducted according to the policy that it is to be performed if there is a tendency of improvement in abdominal tenderness and the amylase level, that is, surgery is conducted after an average of 1.8 days following hospitalization) and a benefit in the elective surgery group (surgery is conducted after the blood amylase level has returned to normal, that is, after an average of 2.8 days following hospitalization). On the other hand, there is another report (retrospective cohort study, Level 4) [49] that asserts the benefit associated with elective open laparoscopic cholecystectomy in terms of occurrence of moderate–severe complications. At present, emergency or early ECP/ES is recommended in indicated patients, so that necessity of performing surgery in the acute phase has decreased remarkably. (Refer to the previous section).

On the other hand, elective surgery has two options, that is, surgery performed during the one-time hospitalization period and surgery performed after waiting for another hospitalization after having spent sufficient time for convalescence. Pancreatitis recurs in 32–31% of patients while waiting for surgery (it occurs at the high rate within 6 weeks) (Level 4) [50–52]. In patients with gallstone-induced mild pancreatitis not accompanied by complications, search for the biliary tract and cholecystectomy should be conducted as soon as resolution of pancreatitis has been achieved even if the disease is severe.

Techniques of cholecystectomy and procedures for searching for the biliary tract

CQ5 Which operative techniques should be used for cholecystectomy after resolution of gallstone-induced pancreatitis has been achieved?

Laparoscopic cholecystectomy is the first option. (Recommendation B)

Laparoscopic surgery has been introduced actively in gallstone-induced acute pancreatitis. By totaling the data of retrospective studies conducted to date (Level 1b–4) [53–58], it was found that the rate of successful completion of laparoscopic cholecystectomy (LC) was 94.5% (79–100%), the incidence of complications was 5.5% (0–10%) and the mortality rate was 0.4% (0–2.5%) (Table 2), showing that this procedure is as successful as or more successful than open surgery.

CQ6 Which procedures are adequate for the search for the biliary tract and treatment of common bile duct stones in patients who underwent laparoscopic cholecystectomy?

According to present knowledge, selection of adequate procedures is made at the discretion of operators.

Traditionally, laparoscopic cholecystectomy (LC) and intraoperative cholangiography (IOC) plus incision of the common bile duct performed when common bile duct stones are detected have been standard procedures. However, introduction of LC has given rise to multiple options for the search for the biliary tract and treatment of common bile duct stones. The following 4 procedures are most representative. However, owing to the improvement in the diagnostic ability of MRCP, invasive search for the biliary tract such as ERCP and IOC is not always required.

1. ERCP/ES is conducted prior to surgery, while LC is performed after the diagnosis has been made and common bile duct stones have been removed.
2. Instead of ERCP, LC is performed along with IOC. When common bile duct stones are detected, LC is changed to open cholecystectomy.
3. When common bile duct stones are detected by IOC, LC is continued until its completion. ES is conducted intraoperatively or postoperatively.
4. When common bile duct stones are detected by IOC, lithotripsy through cystic-duct or with common bile duct incision is performed in a laparoscopic fashion.

There is an opinion that the LC procedure should be performed only when the presence of common bile duct stones is suspected by blood and biochemical tests or when common bile duct stones are observed (Level 1b) [58]. Furthermore, there are reports showing that the use of ERCP is likely to be adequate because the positive rate of common bile duct stones is high in the acute phase of gallstone-induced pancreatitis and the negative rate of common bile duct stones is low after remission of the disease has been achieved (Level 4) [59]. Also, the potential risk of ERCP should be taken into consideration (Level 4) [60]. An RCT (Level 1b) [58] that studied procedures and postoperative ERCP + ES for gallstone-induced acute

Table 2 Prospective cohort studies on laparoscopic cholecystectomy applied to gallstone-associated acute pancreatitis

References	Number of patients	Timing of surgery (days after the onset)	Completion rate (%)	Conversion rate (%)	Operation time (min)	Morbidity (%)	Mortality (%)	CBD exploration[d]
Rhodes et al. [53]	16	10 (4–34)[a]	100	0	50 (30–120)	0	0	15/1
Tate et al. [54]	24	7 (3–24)[a]	87.5	12.5	76 (NA)	8	0	23/0
Ballestra-Lopez et al. [55]	40	3.4/15[b,c]	100	0	86 (45–210)	10	2.5	0/40
Ricci et al. [56]	51	NA	100	0	NA	1.9	0	40/47
Uhl et al. [57]	48	10 (4–29)[a]	79	21	80 (30–225)	7.9	0	0/33
Chang et al. [58]	59	NA	100	0	NA	3.4	0	0/58

NA not assessed

[a] Median (range); [b] Mean; [c] Mild/severe disease; [d] Preoperative ERC/intra-operative cholangiogram

pancreatitis (mild to moderate severity) asserts the superiority of the LC procedure in terms of the length of hospital stay and costs. A retrospective cohort study (Level 4) [61] that examined 2 groups of patients with gallstone-induced mild pancreatitis in whom LC was performed using the technique within 2 weeks after onset and after 2 weeks following onset found favorable results in both groups. Laparoscopic treatment is very likely to become a standardized procedure along with the improvement in technical skill of operators as well as development of ideas. As for selection of procedure 2–4 when common bile duct stones have been detected by IOC, there is nothing for it but to rely on operators' skill. There is a high possibility that LC will make remarkable progress and become a standardized procedure (Level 4) [62]. Further collection of data is required concerning the safety, invasiveness, rate of successful execution and adequate selection of cases involved.

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