Original article

Timing of cholecystectomy after mild biliary pancreatitis

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Background: The aim of the study was to evaluate recurrent biliary events as a consequence of delay in cholecystectomy following mild biliary pancreatitis.

Methods: Between 2004 and 2007, patients with acute pancreatitis were registered prospectively in 15 Dutch hospitals. Patients with mild biliary pancreatitis were candidates for cholecystectomy. Recurrent biliary events requiring admission before and after cholecystectomy, and after endoscopic sphincterotomy (ES), were evaluated.

Results: Of 308 patients with mild biliary pancreatitis, 267 were candidates for cholecystectomy. Eighteen patients underwent cholecystectomy during the initial admission, leaving 249 potential candidates for cholecystectomy after discharge. Cholecystectomy was performed after a median of 6 weeks in 188 patients (75·5 per cent). Before cholecystectomy, 34 patients (13·7 per cent) were readmitted for biliary events, including 24 with recurrent biliary pancreatitis. ES was performed in 108 patients during the initial admission. Eight (7·4 per cent) of these patients suffered from biliary events after ES and before cholecystectomy, compared with 26 (18·4 per cent) of 141 patients who did not have ES (risk ratio 0·51, 95 per cent confidence interval 0·27 to 0·94; $P = 0·015$). Following cholecystectomy, eight (3·9 per cent) of 206 patients developed biliary events after a median of 31 weeks. Only 142 (53·2 per cent) of 267 patients were treated in accordance with the Dutch guideline, which recommends cholecystectomy or ES during the index admission or within 3 weeks thereafter.

Conclusion: A delay in cholecystectomy after mild biliary pancreatitis carries a substantial risk of recurrent biliary events. ES reduces the risk of recurrent pancreatitis but not of other biliary events.

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Introduction

Small gallstones and sludge are the most common cause of acute pancreatitis in the Western world[1,2]. Following an episode of biliary pancreatitis, patients may develop recurrent biliary events, such as recurrence of biliary pancreatitis, acute cholecystitis, cholangitis or biliary colic. To prevent these, international treatment guidelines advise cholecystectomy or endoscopic sphincterotomy (ES) following an episode of acute biliary pancreatitis[3–5]. Failure to provide definitive treatment may potentially put a patient at risk of a fatal episode of acute pancreatitis[6].

The appropriate timing of cholecystectomy in acute pancreatitis depends on the clinical course. After severe pancreatitis, with local complications such as pancreatic necrosis and systemic complications including respiratory failure, it is advisable to delay cholecystectomy until such complications have resolved[7]. After mild pancreatitis, without local and systemic complications, the optimal timing of cholecystectomy remains unclear. The aim is to minimize the risk of recurrent biliary events, but published guidelines differ with regard to the timing of cholecystectomy: during the initial admission or within 2, 3 or 4 weeks after discharge[3–5,8,9].

ES early in the course of mild biliary pancreatitis is indicated only for clearance of bile duct stones in the presence of obstructive jaundice or suspected cholangitis[3–5,8]. After recovery from pancreatitis, ES can be performed as an alternative to cholecystectomy in patients unfit for surgery, such as those with significant co-morbidity[3–5]. In patients with mild biliary pancreatitis who are fit for surgery, but have already undergone urgent ES for obstructive jaundice or suspected cholangitis, the use of cholecystectomy to prevent recurrent biliary events is debated. Some authors argue that, as ES is highly effective in preventing recurrent pancreatitis, cholecystectomy is not necessary in these patients[10,11]. Others draw a parallel with the situation in symptomatic gallstone disease, where a Cochrane review has clearly shown that cholecystectomy should always be performed after ES[12].

The primary aim of this study was to estimate the risk of recurrent biliary events occurring in the time between discharge after mild biliary pancreatitis and admission for cholecystectomy in a prospective multicentre cohort. Secondary aims were to evaluate the influence of ES on the recurrence of biliary events and to determine the incidence of recurrent biliary events after cholecystectomy.

Methods

This was a retrospective observational study of adult patients with mild biliary pancreatitis. They were identified from a prospective database of patients with a primary attack of acute pancreatitis between March 2004 and March 2007 registered in one of 15 hospitals of the Dutch Pancreatitis Study Group[13]. These patients were potentially eligible for a randomized trial on probiotic prophylaxis[14]. The study was reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[15]. All patients gave written informed consent to participate and the ethics review board of each participating hospital approved the study.

In general, patients were treated with adequate fluid resuscitation and analgesics. They underwent abdominal ultrasonography and routine laboratory investigations during the first 3 days of admission and thereafter if necessary. Computed tomography (CT) was performed if there was no clinical improvement within a week of admission and thereafter on clinical indication. Patients were discharged from hospital once oral diet was tolerated, inflammatory parameters had normalized, and after sufficient clinical improvement as judged by the treating physician.

Treatment of biliary pancreatitis

The responsible physician decided if and when a cholecystectomy was necessary and whether the patient was fit for surgery. The study protocol did not provide guidelines on when to perform cholecystectomy, although the Dutch acute pancreatitis guideline published in 2005 advises cholecystectomy or ES in patients with mild biliary pancreatitis during admission or within 3 weeks thereafter[9]. If possible, cholecystectomy was performed laparoscopically. Intraoperative cholangiography was not carried out routinely.

ES was also performed at the discretion of the physician. The majority of endoscopic retrograde cholangiopancreatography (ERCP) procedures were performed during the first 24–72 h of admission. Indications for urgent ES have been described previously, and included obstructive jaundice or suspected cholangitis and predicted severe biliary pancreatitis[16].

Definition of pancreatitis

For this study, all prospective laboratory data and imaging results obtained during the first 72 h of admission were reviewed by two investigators. Acute biliary pancreatitis was defined as[16]: gallstones and/or sludge on ultrasonography or CT; a dilated common bile duct (CBD) on ultrasonography or CT (larger than 8 mm in diameter for patients aged 75 years or less; more than 10 mm in diameter for those aged over 75 years); or two of the following three laboratory abnormalities: serum bilirubin level greater than 40 μmol/l, alanine aminotransferase (ALT) level greater than 100 units/l with ALT level greater than the aspartate aminotransferase level, and alkaline phosphatase level greater than 195 units/l with a γ-glutamyltransferase level greater than 45 units/l. Other causes of pancreatitis or indications for chronic pancreatitis had to be absent.

Study outcomes

Mild pancreatitis was defined as pancreatitis without local complications such as necrosis or organ failure[17]. Criteria for predicted severe pancreatitis were an Acute Physiology And Chronic Health Evaluation (APACHE) II score of at least 8, or an Imrie score of 3 or more, or a C-reactive protein level greater than 50 mg/l[18–20]. Biliary events included recurrent biliary pancreatitis, acute cholecystitis, cholangitis and symptomatic cholelithiasis requiring admission to hospital. Recurrent biliary pancreatitis was diagnosed when at least two of the following three criteria were present: typical epigastric abdominal pain, increase

in serum amylase or lipase level to more than three times the upper limit of normal, or confirmatory findings on cross-sectional abdominal imaging. Cholecystitis was defined as signs of peritonitis in the right upper abdomen with a positive Murphy's sign in combination with fever and a raised white blood cell count[21]. Symptomatic cholelithiasis requiring admission was defined as the presence of biliary colic or other complaints caused by the presence of gallstones in the CBD[22]. Cholangitis was defined as acute abdominal pain, serum bilirubin level greater than 40 μmol/l and/or a dilated CBD on ultrasonography or CT and temperature greater than 38·5°C[16].

Data collection

Clinical data were collected prospectively at the time of patient inclusion. All CT images were reviewed by one experienced radiologist to assess the presence of peripancreatic or pancreatic necrosis and to determine the CT severity index[23]. Follow-up was completed in January 2009. Postdischarge data concerning readmissions for gallstone complications were obtained from the medical records during site visits at the end of follow-up. If a patient was transferred to another hospital, the transferring hospital was contacted for information on possible readmission during follow-up.

Statistical analysis

The number and timing of cholecystectomies, and biliary events before cholecystectomy, in patients with mild biliary pancreatitis were analysed. A further analysis was carried out with patients stratified according to whether or not they had undergone ES during the initial admission. In addition, ES during the initial admission was incorporated into a multivariable logistic regression model, with serum bilirubin and serum ALT levels during the first 48 h of admission as co-variables. The treatment strategies for biliary events, the rate of laparoscopic cholecystectomy, the number of readmissions after cholecystectomy and adherence to the Dutch guideline were assessed.

Continuous data are presented as median (interquartile range), and risk ratios and odds ratios with 95 per cent confidence intervals. Between-group differences were analysed using the Mann–Whitney *U* test for continuous data, and Fisher's exact test for categorical data. Two-sided $P < 0{\cdot}050$ was considered statistically significant. Analyses were performed with SPSS® version 15.0 (SPSS, Chicago, Illinois, USA).

Results

Some 731 patients with a primary episode of acute pancreatitis were enrolled in the study; 203 patients with severe pancreatitis were excluded, leaving 528 patients with mild pancreatitis. A biliary aetiology was established in 308 patients (58·3 per cent), of whom a further 41 patients were excluded (*Fig. 1*). Demographic and clinical characteristics of the 267 candidates for cholecystectomy, either during admission or after discharge, are shown in *Table 1*. The minimum follow-up was 22 months (median 39 (28–48) months).

Timing of cholecystectomy

Of 267 patients with mild biliary pancreatitis eligible for cholecystectomy, 206 (77·2 per cent) patients underwent the procedure. Eighteen patients (6·7 per cent) had cholecystectomy during the initial admission for mild biliary pancreatitis, leaving 249 candidates for cholecystectomy after discharge. Cholecystectomy was performed after a median of 6 (4–13) weeks in 188 (75·5 per cent) of these 249 patients. Sixty-one (22·8 per cent) of 267 patients did

Table 1 Baseline characteristics of 267 patients who were candidates for cholecystectomy during admission or after discharge

	No. of patients*
Age (years)†	59 (41–72)
Women	160 (59·9)
ASA grade	
I (healthy)	140 (52·4)
II (mild systemic disease)	104 (39·0)
III (severe systemic disease)	23 (8·6)
Predicted severity of pancreatitis	
APACHE-II†‡	6 (3–9)
Imrie/modified Glasgow score†	2 (1–3)
C-reactive protein (mg/l)†§	123 (37–232)
CT performed	142 (53·2)
CT severity index†	3 (2–4)
Highest liver enzymes during first 48 h of admission†	
Bilirubin (μmol/l)	38 (20–65)
AST (units/l)	176 (69–314)
ALT (units/l)	237 (99–438)
AP (units/l)	153 (101–242)
GGT (units/l)	309 (122–513)
Length of hospital stay (days)†	9 (5–14)
Follow-up (months)†	39 (28–48)

*With percentages in parentheses unless indicated otherwise; †values are median (interquartile range). ‡Highest score on day of admission. §Highest value during first 48 h. ASA, American Society of Anesthesiologists; APACHE, Acute Physiology And Chronic Health Evaluation; CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, γ-glutamyltransferase.

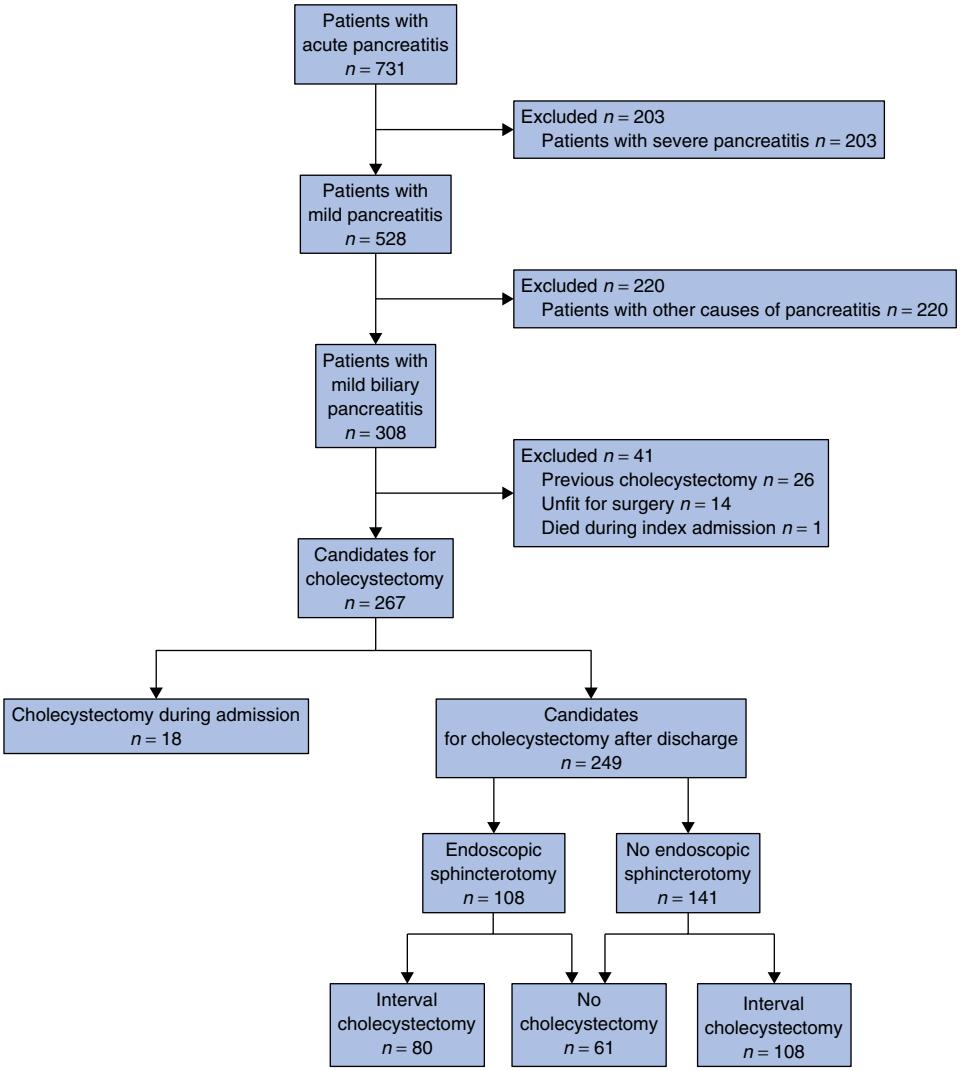

Fig. 1 Study population

not have a cholecystectomy during follow-up: 28 patients who had and 33 who did not have ES (*Fig. 1*).

Recurrent biliary events

Biliary events requiring readmission before cholecystectomy are summarized in *Table 2*. Among the 18 patients who underwent cholecystectomy during the initial admission, no biliary events were documented in the short interval between recovery from pancreatitis and cholecystectomy. Thirty-four (13·7 per cent) of 249 candidates for cholecystectomy after discharge were readmitted owing to biliary events. Twenty-four patients (9·6 per cent) had an attack of recurrent biliary pancreatitis, two (0·8 per cent) were readmitted for acute cholecystitis and eight (3·2 per cent) with symptomatic cholelithiasis. No patient developed cholangitis during the study. The median time between discharge and readmission was 31 (11–76) days. Sixteen readmissions (6·4 per cent) occurred within 4 weeks of discharge (*Table 2*).

Role of endoscopic sphincterotomy

ES was performed during primary admission in 108 (43·4 per cent) of 249 patients who were candidates for cholecystectomy after discharge (*Fig. 1*). Stones or sludge were found in the CBD during ERCP in 51 (47·2 per cent) of these patients. A stent was placed in the CBD in three of the patients who had early ES. Reasons for biliary stents were incomplete removal of CBD stones in two patients

Table 2 Recurrent biliary events in 249 candidates for cholecystectomy after discharge

	No. of patients*
No. of recurrent biliary events‡	34 (13·7)
Recurrent biliary pancreatitis	24 (9·6)
Acute cholecystitis	2 (0·8)
Symptomatic cholelithiasis	8 (3·2)
Cholangitis	0 (0)
Time of onset of recurrent biliary events after discharge	
Within 2 weeks	11 (4·4)
Within 4 weeks	16 (6·4)
Within 6 weeks	21 (8·4)
Within 10 weeks	26 (10·4)
Time after discharge (days)†	31 (11–76)

*With percentages in parentheses unless indicated otherwise; †values are median (interquartile range). ‡Readmissions for recurrent biliary events before cholecystectomy or before end of follow-up without cholecystectomy.

and contraindication to ES because of coagulopathy in one. None of the patients underwent ES as an elective procedure after discharge for prevention of recurrent biliary events.

Baseline characteristics of patients who had ES and those who did not were comparable, except for levels of liver-related serum enzymes which were higher in the ES group during the first 48 h of admission (*Table 3*). The rate of interval cholecystectomy did not differ between patients with and without ES: 80 (74·1 per cent) of 108 *versus* 108 (76·6 per cent) of 141 respectively ($P = 0·658$). The median time to cholecystectomy was 6 (4–12) weeks in patients who had ES, compared with 7 (4–14) weeks in those who did not ($P = 0·168$).

Patients who had ES developed fewer recurrent biliary events before cholecystectomy, primarily owing to a reduced risk of biliary pancreatitis. Two patients developed recurrent pancreatitis before cholecystectomy in the ES group compared with 22 in the group without ES: risk ratio 0·18 (0·05 to 0·68; $P < 0·001$) (*Table 4*). The potential protective effect of ES on the development of biliary events was explored in a multivariable logistic regression model including serum bilirubin and serum ALT levels during the first 48 h of admission as co-variables. In the multivariable model, ES significantly reduced the risk of recurrent biliary events (odds ratio 0·38, 0·16 to 0·91; $P = 0·029$). Univariable analysis was carried out to explore whether patients at risk of recurrent biliary events after ES could be identified. Predicted severity of pancreatitis, high liver enzyme levels and the presence of stones or sludge during ES were tested, but none was associated with recurrent biliary events (data not shown).

Table 3 Baseline characteristics of patients who did or did not undergo endoscopic sphincterotomy

	ES ($n = 108$)	No ES ($n = 141$)	P§
Age (years)*	57 (41–73)	59 (41–72)	0·834¶
Women	70 (64·8)	79 (56·0)	0·192
ASA grade			
I (healthy)	58 (53·7)	74 (52·5)	0·898
II (mild systemic disease)	44 (40·7)	53 (37·6)	0·694
III (severe systemic disease)	6 (5·6)	14 (9·9)	0·341
Predicted severity of pancreatitis			
APACHE-II*†	6 (3–10)	6 (4–9)	0·504¶
Imrie/modified Glasgow score*	2 (1–3)	2 (1–3)	0·847¶
C-reactive protein (mg/l)*‡	141 (55–244)	124 (29–231)	0·422¶
CT performed	61 (56·5)	72 (51·1)	0·442
CT severity index*	3 (2–4)	3 (2–4)	0·645¶
Highest liver enzyme levels during first 48 h of admission*			
Bilirubin (μmol/l)	54 (31–91)	29 (16–52)	< 0·001¶
AST (units/l)	222 (151–336)	129 (49–289)	< 0·001¶
ALT (units/l)	319 (159–495)	190 (70–391)	< 0·001¶
AP (units/l)	203 (121–298)	135 (88–209)	< 0·001¶
GGT (units/l)	388 (233–594)	247 (100–450)	< 0·001¶
Length of hospital stay (days)*	9 (6–16)	9 (5–13)	0·207¶
Total length of follow-up (months)*	39 (28–48)	39 (31–48)	0·287¶

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). †Highest score on day of admission. ‡Highest value during first 48 h. ES, endoscopic sphincterotomy; ASA, American Society of Anesthesiologists; APACHE, Acute Physiology And Chronic Health Evaluation; CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, γ-glutamyltransferase. §Fisher's exact test, except ¶Mann–Whitney *U* test.

Table 4 Recurrent biliary events in patients who did or did not undergo endoscopic sphincterotomy before cholecystectomy

	ES* ($n = 108$)	No ES* ($n = 141$)	Risk ratio†	P§
Biliary events‡	8 (7·4)	26 (18·4)	0·51 (0·27, 0·94)	0·015
Recurrent pancreatitis	2 (1·9)	22 (15·6)	0·18 (0·05, 0·68)	< 0·001
Cholecystitis	2 (1·9)	0 (0)	2·33 (2·02, 2·69)	0·187
Symptomatic cholelithiasis	4 (3·7)	4 (2·8)	1·16 (0·57, 2·35)	0·730

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Readmissions for biliary events before cholecystectomy or before end of follow-up without cholecystectomy. ES, endoscopic sphincterotomy. §Fisher's exact test.

Clinical course and treatment of biliary events

The median duration of readmission for the 34 patients with recurrent biliary events was 8 (4–12) days. No patient died during readmission or thereafter, and none developed necrotizing pancreatitis or organ failure.

Of 24 patients who developed recurrent pancreatitis, 17 eventually underwent cholecystectomy, three patients underwent ES during readmission and cholecystectomy 3 months thereafter, one patient underwent ES alone, and in three patients no ES or cholecystectomy was performed. The eight patients who were readmitted with symptomatic cholelithiasis were treated with cholecystectomy. The two patients readmitted with cholecystitis underwent cholecystectomy.

Cholecystectomy

There were 18 open and 188 laparoscopic cholecystectomies, of which 15 (8·0 per cent) were converted to an open procedure.

Biliary events after cholecystectomy

Eight (3·9 per cent) of 206 patients were readmitted with recurrent biliary events after a median of 31 (8–44) weeks following cholecystectomy. Three patients developed recurrent biliary pancreatitis, four were readmitted for symptomatic choledocholithiasis and one had cholangitis. One of the 18 patients who had cholecystectomy during the initial admission developed recurrent pancreatitis within a month of the procedure.

Furthermore, 26 (8·4 per cent) of a total of 308 patients with mild biliary pancreatitis had a cholecystectomy before the study, of whom three were readmitted with symptomatic cholelithiasis.

Adherence to Dutch guideline

Some 142 (53·2 per cent) of 267 patients were treated in accordance with the Dutch guideline, which recommends cholecystectomy or ES during admission or within 3 weeks thereafter. Four of these patients (2·8 per cent) did not have planned cholecystectomy within 3 weeks after discharge, but during readmission for a biliary complication. Excluding these four patients, 138 patients (51·7 per cent) were treated according to the Dutch guideline.

Adherence to the guideline differed between hospitals, especially the proportion of patients who had urgent ES. However, no significant differences in baseline characteristics were found between patients who were treated in accordance with the guideline and those who were not. Type of hospital (university *versus* non-university) did not influence guideline adherence (data not shown).

Discussion

The main finding of this multicentre study on the timing of cholecystectomy in mild biliary pancreatitis was that 13·7 per cent of patients were readmitted for biliary events when cholecystectomy was performed at a median of 6 weeks after discharge. This included an almost 10 per cent risk of recurrent pancreatitis. If ES was performed during the initial admission, the risk of biliary events was significantly reduced but not eliminated. Furthermore, there was a low risk of recurrent biliary events after cholecystectomy. Finally, this study showed that compliance with the Dutch guideline was poor.

Surgeons who advocate cholecystectomy 6 weeks after discharge argue that very early cholecystectomy is associated with a more difficult dissection, potentially leading to more conversions and more complications, such as bile duct injuries[24]. They accept the risk of recurrent biliary events, arguing that these can usually be treated by simple cholecystectomy. It has also been suggested that patients should be given time to recover fully from an episode of acute pancreatitis. On the other hand, surgeons advocating cholecystectomy during the initial admission argue that recurrent biliary pancreatitis may be severe

and potentially fatal[6]. There is evidence to suggest that early cholecystectomy might even be associated with a less difficult dissection than delayed cholecystectomy[25].

Unfortunately, no prospective comparative studies have been published to settle this debate. A recent investigation from Boston suggested that an interval of 2 weeks between discharge and cholecystectomy might be too long[26]. In the present study, 11 patients (4·4 per cent) were readmitted within 2 weeks after discharge.

Several, mostly retrospective, studies have suggested that there is a substantial risk of recurrent biliary events after discharge from hospital following an episode of mild biliary pancreatitis and before interval cholecystectomy[27–29]. None reported on the period after cholecystectomy. The present study has shown that there is a small risk of recurrent biliary events after cholecystectomy. These events are most likely caused by retained CBD stones. Another possible explanation for recurrent biliary pancreatitis occurring months to years after cholecystectomy is formation of new stones in the bile duct[30].

It is of interest that ES reduced the risk of recurrent pancreatitis in this study. However, most patients with mild biliary pancreatitis do not need urgent ES as this is indicated only in the event of suspected cholangitis or retained CBD stones. Nonetheless, in patients who undergo urgent ES, the question has been raised whether cholecystectomy should be performed early or even at all. In a meta-analysis of five randomized trials in patients without pancreatitis, patients who underwent cholecystectomy after ES had less biliary pain, cholecystitis, cholangitis and even mortality compared with a wait-and-see policy[12]. No randomized trial has compared cholecystectomy with a wait-and-see policy in patients with mild biliary pancreatitis who have undergone ES. A single-centre study from Sweden showed that, of 109 patients with biliary pancreatitis who had ES without planned cholecystectomy, only one had recurrent pancreatitis[10]. However, 45 patients developed other recurrent biliary events, of whom 20 later underwent cholecystectomy. In a study from Ohio, no significant difference in recurrent pancreatitis was found between 38 patients who had ES *versus* 83 who underwent cholecystectomy[11]. In the present study, although ES significantly reduced the risk of recurrent pancreatitis, 7·4 per cent of patients still had recurrent biliary events. Early cholecystectomy may be indicated to prevent such biliary events, which are associated with patient discomfort, hospital admission and additional costs.

As a result of the varying study outcomes, international guidelines differ on when to perform a cholecystectomy[3–5]. More recent guidelines tend to recommend early cholecystectomy, either during the hospital admission or within 2 weeks after discharge. Nonetheless, in general adherence to such guidelines is low. After the release of the UK guidelines for acute pancreatitis, several studies reported that early cholecystectomy was performed in only a minority of patients[31–34]. In studies from the USA and Australia, cholecystectomy was performed too late and only in a minority of patients[35,36]. However, a recent audit from Scotland claimed that a majority of surgeons perform cholecystectomy in accordance with guideline recommendations[37]. In the present study adherence was poor as only half of all patients were treated in accordance with the Dutch guideline. A substantial proportion of patients had no cholecystectomy during follow-up. In accordance with the intention-to-treat principle, these patients were not excluded from the analyses and calculations were based on all patients who were candidates for cholecystectomy.

This study has some limitations. Although it was a non-randomized cohort study, the population consisted of consecutive prospectively registered patients with a primary attack of acute pancreatitis. The emphasis was on recruiting patients with predicted severe pancreatitis potentially eligible for a randomized trial on probiotic prophylaxis[14]. As a consequence, the number of patients with predicted severe disease in the cohort may have been relatively high, as reflected by the median C-reactive protein values and the median CT severity index. Nevertheless, the results are unlikely to be influenced by this as all patients in the study fulfilled the criteria for mild biliary pancreatitis. Patient selection could have influenced the timing of cholecystectomy or the decision to perform ES. However, multivariable analysis adjusting for liver-related serum enzyme levels showed a significant reduction in recurrent biliary events following ES.

This study has shown that a delay in cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of recurrent biliary events. ES, if performed during the initial admission, might reduce the risk of recurrent pancreatitis but does not decrease the likelihood of other biliary events. There is a small risk of recurrent biliary events even after cholecystectomy.

Collaborators

In addition to the authors, the following clinicians participated in this study: B. van Ramshorst, B. L. Weusten and R. Timmer (St Antonius Hospital, Nieuwegein), L. M. Akkermans, G. A. Cirkel, V. Zeguers, A. Roeterdink, H. G. Rijnhart, M. P. Schwartz, M. S. van Leeuwen and B. U. Ridwan (University Medical Centre Utrecht,

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