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Original research

Optimal timing of cholecystectomy after necrotising biliary pancreatitis

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ABSTRACT

Objective Following an episode of acute biliary pancreatitis, cholecystectomy is advised to prevent recurrent biliary events. There is limited evidence regarding the optimal timing and safety of cholecystectomy in patients with necrotising biliary pancreatitis.

Design A post hoc analysis of a multicentre prospective cohort. Patients with biliary pancreatitis and a CT severity score of three or more were included in 27 Dutch hospitals between 2005 and 2014. Primary outcome was the optimal timing of cholecystectomy in patients with necrotising biliary pancreatitis, defined as: the optimal point in time with the lowest risk of recurrent biliary events and the lowest risk of complications of cholecystectomy. Secondary outcomes were the number of recurrent biliary events, periprocedural complications of cholecystectomy and the protective value of endoscopic sphincterotomy for the recurrence of biliary events.

Results Overall, 248 patients were included in the analysis. Cholecystectomy was performed in 191 patients (77%) at a median of 103 days (P25–P75: 46–222) after discharge. Infected necrosis after cholecystectomy occurred in four (2%) patients with persistent peripancreatic collections. Before cholecystectomy, 66 patients (27%) developed biliary events. The risk of overall recurrent biliary events prior to cholecystectomy was significantly lower before 10 weeks after discharge (risk ratio 0.49 (95% CI 0.27 to 0.90); p=0.02). The risk of recurrent pancreatitis before cholecystectomy was significantly lower before 8 weeks after discharge (risk ratio 0.14 (95% CI 0.02 to 1.0); p=0.02). The complication rate of cholecystectomy did not decrease over time. Endoscopic sphincterotomy did not reduce the risk of recurrent biliary events (OR 1.40 (95% CI 0.74 to 2.83)).

Conclusion The optimal timing of cholecystectomy after necrotising biliary pancreatitis, in the absence of peripancreatic collections, is within 8 weeks after discharge.

Significance of this study

What is already known on this subject?

- ► After an episode of mild biliary pancreatitis, same-admission cholecystectomy is advised to prevent recurrent biliary events.
- ► Cholecystectomy after acute necrotising pancreatitis is potentially associated with an increased risk of complications.
- ► In patients with necrotising biliary pancreatitis, there is no high-level evidence for the optimal timing of cholecystectomy.

What are the new findings?

- ► In current clinical practice, the presence or absence of peripancreatic collections are often not evaluated before cholecystectomy.
- ► The risk of recurrent biliary events, particularly recurrent pancreatitis is high and increases when cholecystectomy is postponed, with a turning point at 8 weeks after discharge.
- ► Delaying cholecystectomy did not reduce the risk of periprocedural complications including infected necrosis.

How might it impact on clinical practice in the foreseeable future?

- ► Before cholecystectomy, assessment of the presence or absence of peripancreatic collections should be performed.
- ► Cholecystectomy, in the absence of peripancreatic collections, is preferably performed before 8 weeks after discharge due to the increased risk of recurrent biliary events.
- ► Endoscopic sphincterotomy does not reduce the risk of recurrent biliary events in patients with necrotising biliary pancreatitis.

INTRODUCTION

Gallstones and biliary sludge are the most common cause of pancreatitis.[1 2] In order to avoid recurrent biliary events after an episode of biliary pancreatitis, such as cholangitis, recurrent acute pancreatitis and acute cholecystitis, international guidelines advise to perform a cholecystectomy.[3–5] A randomised trial in patients with mild biliary pancreatitis has shown that same-admission cholecystectomy is safe and reduces recurrent biliary events, especially recurrent pancreatitis, as compared with interval cholecystectomy.[6] In patients with necrotising biliary pancreatitis, however, there is no high-level evidence regarding the optimal timing of cholecystectomy.[7]

With respect to the appropriate timing of cholecystectomy, a risk assessment between recurrent biliary events and the potentially higher risk of (surgical) complications (especially in case of persistent peripancreatic collections) should be performed.

A recent systematic review of 11 guidelines demonstrated that only four guidelines specify a time frame for performing a cholecystectomy in patients with peripancreatic collections.[8] Namely, to delay surgery until these collections have completely resolved or at least 6 weeks after onset of disease in case of persistent collections.[5 9–11] The remaining seven guidelines merely state that clinicians should postpone cholecystectomy until local and/or systemic signs of inflammation have subsided.

The recommendations from these guidelines are based on six studies that compare early with delayed cholecystectomy in necrotising biliary pancreatitis. These studies were published between 1978 and 2007.[12–17] These studies have several limitations: sample sizes are relatively small (<50 patients in five out of six studies), use of different definitions for disease and for 'early' and 'delayed' cholecystectomy, and lastly in some studies a more aggressive treatment strategy was used compared with current practice.[8]

When cholecystectomy is not (yet) considered possible, endoscopic sphincterotomy (ES) may reduce the risk of recurrent biliary events but the protective value in patients with necrotising biliary pancreatitis remains unclear.[18]

Therefore, the aims of this study are to determine the optimal timing of cholecystectomy in patients with necrotising biliary pancreatitis inferred from the association between the timing and occurrence of recurrent biliary events and procedural-related complications, and to determine the protective value of ES in preventing recurrent biliary events.

METHODS

Study design

This is a post hoc analysis of a prospective observational cohort study to investigate the optimal timing of cholecystectomy in patients after necrotising biliary pancreatitis. The study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[19]

Study population

Adult patients with moderate severe or severe acute biliary pancreatitis with peripancreatic collections were selected from a cohort of acute pancreatitis patients. Patients were either included in a previous trial of the Dutch Pancreatitis Study Group (PANTER, PYTHON, TENSION) or included in the registration cohort of patients potentially eligible for inclusion in the PANTER-trial in the time period between 2005 and 2014.[20–22]

Patients with severe and moderate severe acute biliary pancreatitis according to the revised Atlanta Classification, with a CT severity index (CTSI) score of three or more were included. Acute pancreatitis was defined according to the revised Atlanta Classification.[23 24] A biliary aetiology was assumed if patients fulfilled any of the following criteria: (1) gallstones and/or sludge diagnosed on imaging (eg, transabdominal ultrasound or CT), (2) a dilated common bile duct (CBD) (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) or (3) a serum alanine aminotransferase (ALT) level >2 times higher than normal values at admission, in absence of other causes of acute pancreatitis or signs of chronic pancreatitis.[25–28] The CTSI score is the sum of the scores obtained with the Balthazar Score and the evaluation of pancreatic necrosis, the full scoring system can be found in online supplemental table S1.[29] The following patients were excluded: patients who died during index admission before the cholecystectomy, patients who had less than 3 months follow-up after discharge and did not undergo cholecystectomy within those 3 months and patients who had already undergone cholecystectomy before the first episode of biliary pancreatitis.

Patient and public involvement

Due to the post hoc nature of this study, patients have not been directly involved in the design. However, the Dutch Pancreatitis Study Group has close ties with the Dutch Association for patients with pancreatic disease, the 'Alvleesklier vereniging'. This association was actively involved in the design of the above-mentioned trials and registration cohort.

Data collection

Clinical data were collected prospectively during patients' inclusion in the various trials. An expert radiologist (TLB) reviewed all CT images to assess the CTSI, the presence and location of peripancreatic collections, and to determine the presence of gas within peripancreatic collections. Data on readmissions for biliary complications and cholecystectomy were obtained from the medical records at the end of follow-up in 2019. If a patient was transferred to a different hospital at any time during follow-up, all the required follow-up data were retrieved from those institutions.

Acute pancreatitis treatment

Initial treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis and included resuscitation and analgesia.[5] Guidelines on timing of cholecystectomy were not provided within the study protocols; cholecystectomy was performed at the discretion of the treating clinician. The decision to proceed with a cholecystectomy was made when a patient was deemed fit for surgery by the treating surgeon and after consultation of an anaesthesiologists, taking into account the physical condition of the patient with normalisation of dietary intake, resolution of infection and the absence of clinical or laboratory signs of active inflammation. Cholecystectomy was performed laparoscopically if deemed feasible. An intraoperative cholangiography was not performed routinely. The indication for ES varied between hospitals and local guidelines, and was left at the discretion of the clinician. Patients with infected peripancreatic necrosis and/or collections were treated conservatively with surgical, radiological or endoscopic interventions if deemed necessary according to the study protocols of randomised trials or according to the treating clinician. Follow-up of the evolution of peripancreatic collections before cholecystectomy was left to the discretion of the treating clinician.

Study outcomes

The primary endpoint of the study was the optimal timing of cholecystectomy inferred from the association between its timing and the occurrence of recurrent biliary events before cholecystectomy, and procedural-related complications. Optimal timing was defined as: the optimal point in time with the lowest risk of recurrent biliary events and the lowest risk of complications of cholecystectomy. The secondary endpoint of the study was the assessment of the effect of ES on the occurrence of biliary events.

Definitions

Biliary events included choledocholithiasis needing endoscopic retrograde cholangiopancreatography (ERCP), cholangitis,

Box 1 TG18 diagnostic criteria for acute cholecystitis

A. Local signs of inflammation: Murphys' sign or right upper quadrant mass, pain or tenderness
B. Systemic signs of inflammation:
   – (1) fever, (2) elevated C reactive protein, (3) elevated white blood cell count
C. Imaging findings characteristic of acute cholecystitis

Definite diagnosis: one item in A+one item in B+C
Cited from Yokoe *et al*[30]

acute cholecystitis and recurrent acute biliary pancreatitis. Choledocholithiasis had to be identified on imaging (endoscopic) ultrasound, CT, magnetic resonance cholangiopancreatography (MRCP) or MRI, and an ERCP had to be performed. Acute cholecystitis was defined according to the 2018 Tokyo classification (box 1).[30] Cholangitis was defined as: acute abdominal pain, serum bilirubin level greater than 40 μmol/L and/or a dilated CBD and/or choledocholithiasis on ultrasound, CT, endoscopic ultrasound or MRCP/MRI in combination with a body temperature greater than 38·5°C with chills of 39·0°C or higher regardless of chills and without an obvious other cause for fever.[31] The same criteria as for the first episode were used to determine the biliary aetiology of the recurrent pancreatitis. Between the first episode and recurrent episode, the patient should have been pain-free and the new episode should be presented with acute abdominal pain with either an amylase or lipase serum level of ≥3 times the upper limit or proven acute pancreatitis on imaging. Biliary leakage was defined according to the Amsterdam criteria.[32] When either blood transfusion, radiological and/or surgical intervention or conversion was required this was defined as bleeding. Infected necrosis was defined by either: (1) a positive culture of peripancreatic necrotic tissue obtained through fine-needle aspiration or, (2) a positive culture of peripancreatic necrotic tissue obtained from the first drainage procedure or operation, or (3) the presence of gas within collections on CT. Occurrence of infected necrosis after cholecystectomy was defined as an infection that developed within 1 month after the cholecystectomy.

Statistical analysis

All analyses were performed using SPSS Statistics V.24.0 (IBM Corporation). Continuous data were reported as medians with interquartile ranges (P25–P75) when not normally distributed or as mean with standard deviation (SD (±)) when normally distributed. Categorical data are shown as frequency and percentages. Between-group differences were analysed using the Mann-Whitney U (non normal distribution) or unpaired t-test (normal distribution) test for continuous data, and Fisher's exact test or χ^2 test for categorical data. Risk ratios and Odds Ratios were calculated with their respective 95% Confidence Intervals. The optimal timing of cholecystectomy was determined through the calculation of risk ratios of biliary events and adverse events at the various time points that a cholecystectomy was performed. We started calculating the risk ratios from 2 weeks before the 25th percentile to 2 weeks before the median with a 2-week interval. This amounted to 4, 6, 8, 10 and 12 weeks, respectively. A two-sided $p<0.05$ was considered statistically significant. Multivariable logistic regression was performed with ES as main variable and serum bilirubin and serum ALT levels during the first 48 hours of admission as co-variables to ascertain the protective value of ES.

RESULTS

In total, 945 patients with acute pancreatitis were enrolled in the registry and pre-mentioned randomised trials, of whom 328 patients had necrotising biliary pancreatitis with peripancreatic collections and a CTSI score >3. As shown in figure 1, 80 patients met the exclusion criteria, 37 patients died during index admission due to multiorgan failure, 8 patients underwent cholecystectomy during necrosectomy for infected pancreatic necrosis and were therefore excluded from analysis (figure 1). Baseline characteristics of the included and excluded patients are provided in online supplemental table S2. Baseline characteristics of the 248 candidates eligible for cholecystectomy are provided in table 1. Mean follow-up was 76 (±30) months.

Current practice

Of the 248 patients with necrotising biliary pancreatitis and peripancreatic collections, 191 (77%) patients underwent cholecystectomy. Cholecystectomy was performed at a median of 103 days (P25–P75: 46–222) after discharge. In 57 (23%) patients, no cholecystectomy was performed during initial admission or follow-up. Patients who had no cholecystectomy were older ($p<0.01$), had a higher American Society of Anesthesiologists grade ($p=0.01$), higher Acute Physiology And Chronic Health Evaluation-II (APACHE-II) scores at admission ($p<0.01$) and more often infected necrosis ($p=0.01$). Overall mortality was 13%, 3 (1%) patients died from the (ongoing) necrotising pancreatitis. Baseline characteristics of patients with and without cholecystectomy and with reasons for omitting cholecystectomy are presented in online supplemental tables S3, S4.

Follow-up abdominal imaging to assess the development of peripancreatic collections prior to cholecystectomy was not performed in all patients. In 42% of the 191 patients who underwent cholecystectomy, no imaging was performed, despite the fact that in 69% of these patients collections were present during index admission. In 59 (31%) patients, abdominal imaging was performed within 14 days before cholecystectomy, with persistent peripancreatic collections in 28 (15%) patients. Of these patients, infection of peripancreatic collections occurred in 4 (14%).

Association between the timing of cholecystectomy and recurrent biliary events

During admission for acute pancreatitis, 19 (8%) patients were diagnosed with cholecystitis and 9 (4%) patients with cholangitis. A total of 57 of 248 (23%) patients had a biliary event after their initial episode of acute pancreatitis, of whom 56 were readmitted. Recurrent biliary pancreatitis occurred in 21 (9%) patients, cholangitis in 13 (5%), cholecystitis in 18 (7%) patients and 28 (11%) patients underwent an ERCP for choledocholithiasis. There was no significant difference in the occurrence of recurrent pancreatitis between patients with pancreatic necrosis or peripancreatic necrosis alone (12 (9%) vs 9 (8%); $p=0.82$), also no significant difference was found between patients with <50% pancreatic necrosis or ≥50% pancreatic necrosis (10 (10%) vs 3 (18%); $p=0.40$). The median time between discharge and first recurrent biliary event was 85 (P25–P75: 32–256) days.

The risks of a recurrent biliary event before and after cholecystectomy at 4, 6, 8, 10 and 12 weeks, respectively are summarised in table 2. The risk of a recurrent biliary event after discharge was lower (risk ratio 0.49 (95% CI 0.27 to 0.90); $p=0.02$) when the cholecystectomy was performed within 10 weeks after discharge. The risk of recurrent pancreatitis before cholecystectomy was lower when cholecystectomy was performed within

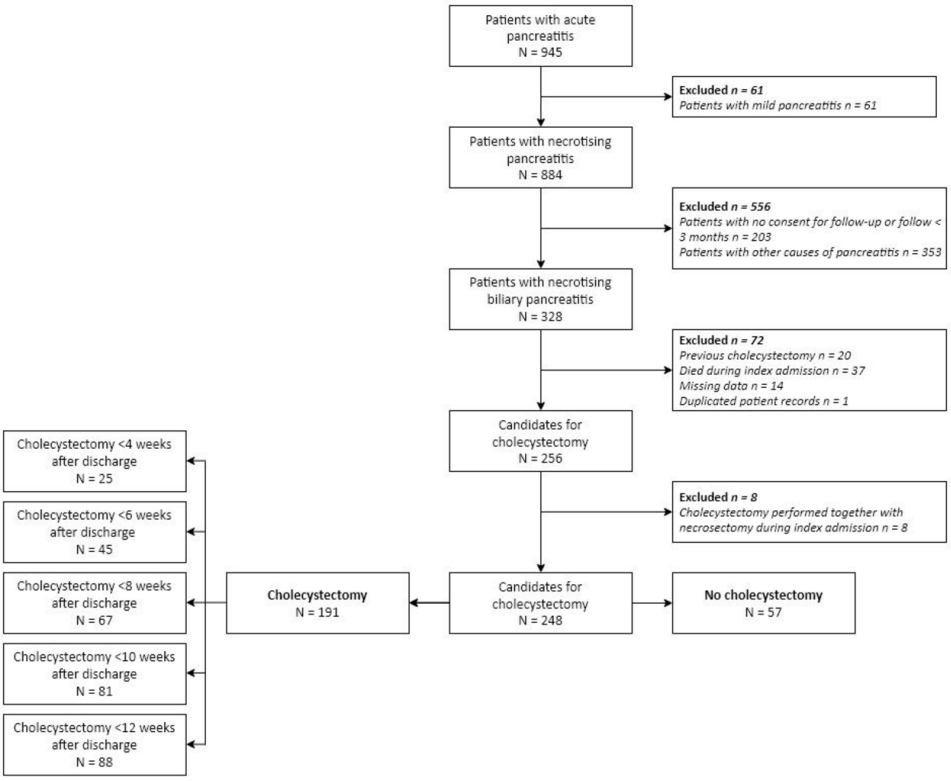

Figure 1. Inclusion flowchart.

8 weeks after discharge (risk ratio 0.14 (95% CI 0.02 to 0.99); p=0.02). One patient had pre-existing heart failure and died of organ failure during readmission for cholecystitis. In the group of patients who did not underwent cholecystectomy, recurrent biliary events occurred in 13 (23%) patients. Obstructive choledocholithiasis was seen in 5 (9%), cholecystitis in 3 (5%), cholangitis in 3 (5%) and recurrent pancreatitis in 6 (11%) patients. Recurrent biliary events after cholecystectomy are listed in online supplemental table S5. Baseline characteristics of patients divided over a 2-week time timing interval are presented in online supplemental table S6.

Timing of cholecystectomy and complications

Difficulty and complications of cholecystectomy before and after cholecystectomy at 4, 6, 8, 10 and 12 weeks, respectively, in 191 patients with necrotising biliary pancreatitis are shown in table 3. In total, 22 out of 166 (13%) of the laparoscopic cholecystectomies were converted to an open procedure and 25 (13%) primary open cholecystectomies were performed. A subtotal cholecystectomy was performed in 8(4%) patients. Complications of cholecystectomy (including infected necrosis) occurred in 22 (12%) patients, of whom 6 (3%) had an intraoperative and/or postoperative bleeding and 7 (4%) had a bile duct injury (type A, 5 patients; type B, 2 patients). Infected necrosis within 31 days after laparoscopic cholecystectomy occurred in four (2%) patients, in one patient laparoscopic procedure was converted to an open cholecystectomy. The risk of complications of cholecystectomy (including infected necrosis) did not decrease significantly over time. There was no significant difference in the occurrence of adverse events (with and without infected necrosis) between the patients with pancreatic necrosis and peripancreatic necrosis alone (15 (12%) vs 11 (9%); p=0.68 and 8 (6%) vs 6 (5%); p=0.79, respectively).

Role of ES

ES was performed in 117 (47%) patients of 248 patients with necrotising biliary pancreatitis after a median of 1 day (P25–P75: 0–21). Indication for ES is listed in online supplemental table S7. The same number of patients underwent ES in the early cholecystectomy group (<10 weeks after discharge) compared with the delayed group (>10 weeks after discharge) (34 (42%) vs 83 (50%); p=0.89). ES was performed during the index admission in 92 (79%) patients, and 70 (60%) patients had an ES within 1 day after admission. In 21 (18%) patients in whom an ES was performed, biliary events had occurred before performing ES. Baseline characteristics of patients who had ES and those who did not were comparable, except for APACHE-II score and serum bilirubin and alkaline phosphatase levels. During ERCP, gallstones were found in the CBD in 57 (48%) and sludge was seen in the CBD in 32 patients (27%). None of the patients underwent an ES as an elective procedure for the prevention of recurrent biliary events. We observed no statistical difference in the percentage of patients with CBD stones at ERCP between those with ≥50% necrosis (47 patients, 51%) and those <50% (10 patients, 59%) (p=0.21). Out of 117 patients that underwent ES, 87 also underwent cholecystectomy. The proportion of cholecystectomies was comparable between patients with and without ES: 87 of 117 (74%) versus 104 of 131 (79%), respectively. The median time to cholecystectomy was 99 days (P25–P75: 52–189) in patients who had ES and 108 days (P25–P75: 37–244) days in patients who did not undergo ES. The occurrence of recurrent biliary events did not differ between patients who had ES and those who did not (risk ratio 1.16 (95% CI 0.73 to 1.85); p=0.54; Table 4). ES had no protective value on the occurrence of biliary events overall (adjusted OR 1.44 (95% CI 0.74 to 2.83)) or on the occurrence of recurrent pancreatitis (adjusted OR 0.36 (95% CI 0.08 to 1.59)). This was independent of the timing of ES before cholecystectomy.

Table 1 Baseline characteristics of 248 patients with necrotising biliary pancreatitis

	Overall n=248
Age (years)	60 (±15)
Women	116 (47)
BMI (n=161, (16%))	27 (25–31)
ASA grade on admission	
1	104 (42)
2	126 (51)
3	18 (7)
First episode of pancreatitis	245 (99)
History of abdominal surgery	51 (21)
Liver enzymes at admission	
Bilirubin (µmol/L) (n=221, 89%)	28 (17–50)
AST (units/L) (n=210, 85%)	174 (80–314)
ALT (units/L) (n=223, 90%)	199 (84–379)
AP (units/L) (n=219, 88%)	122 (91–172)
GGT (units/L) (n=219, 88%)	303 (160–552)
Predicted severity of pancreatitis on admission	
APACHE-II	8 (±4)
Imrie score	3 (±2)
Imaging severity	
CT severity index	6 (4–8)
Parenchymal necrosis	130 (52)
<30% necrosis	57 (23)
30%–50% necrosis	37 (15)
>50% necrosis	38 (15)
Extra pancreatic necrosis only	118 (48)
ICU admission	87 (35)
Organ failure	65 (26)
Infected necrosis before cholecystectomy	109 (44)
Invasive intervention for infected necrosis	108 (44)
Length of initial hospital stay (days)	23 (13–68)
Follow-up (months)	76 (±30)

Data are presented as n (%), mean (±SD) or median (IQR: P25–P75). Note: data were available for all 248 patients unless differently specified.
ALT, alanine aminotransferase; AP, alkaline phosphatase; APACHE, Acute Physiology And Chronic Health Evaluation; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; ICU, intensive care unit.

DISCUSSION

This is the first large nationwide multicentre cohort study based on prospectively collected data on the timing of cholecystectomy in patients with necrotising biliary pancreatitis. We found that cholecystectomy is delayed in the majority of patients with necrotising biliary pancreatitis up to a median of a 100 days after discharge. This is in line with current guidelines, which state that cholecystectomy should be delayed at least 6 weeks or until peripancreatic collections are resolved.[8] Our study, however, also shows that in current clinical practice the presence or absence of peripancreatic collections is often not re-evaluated before cholecystectomy.

Our main findings are that the risk of biliary events, particularly recurrent pancreatitis, increases when cholecystectomy is postponed, with a turning point at 8 weeks after discharge for recurrent pancreatitis and 10 weeks for recurrent biliary events overall. The latter risk increases significantly from 19% before 10 weeks to 31% after 10 weeks after discharge. The present results show that the risk of biliary events increases beyond 8 weeks after discharge. The reason for this tipping point at 8 weeks could not be readily extracted from the study data. A possible explanation might be that patients with smaller bile stones are at particular risk for early stone migration. It also may be related to the fact that patients after having been severely ill and fed by means of (par)enteral nutrition, after discharge will resume their own diet with increased caloric density and fat content possibly provoking early gall stone migration.

To our knowledge, no prospective comparative studies have been published on the occurrence of biliary events in patients with necrotising biliary pancreatitis, making it difficult to compare our results with the literature. In contrast, the risk of recurrent biliary events in patients with mild pancreatitis and a delayed cholecystectomy has been investigated in several prospective studies. Three studies showed that the readmission rate for biliary events before cholecystectomy was significantly higher in the group of patients who underwent delayed cholecystectomy.[18 33 34] These findings were confirmed in the multicentre randomised PONCHO trial, where same-admission cholecystectomy for mild acute biliary pancreatitis was compared with interval cholecystectomy (6 weeks after discharge). Herein, 17% of patients had recurrent biliary events in the interval group versus 5% in the same admission group.[6] Overall, these and our results confirm that delaying cholecystectomy exposes a patient to a higher risk of recurrent biliary events, both in mild and moderate to severe biliary pancreatitis, although the optimal timing differs according to disease severity.

Other major factors to take into consideration with regard to the timing of cholecystectomy are procedural complications and the risk of infection of peripancreatic necrosis.

The results of this study show that cholecystectomy after acute necrotising pancreatitis is a challenging procedure that is often associated with complications, most importantly bleeding (3%) and bile duct injury (4%). Furthermore, surgeons often chose a primary open procedure (13%) and conversion from a laparoscopic to an open procedure occurred in 13% of cases. However, as shown in table 3, the timing of cholecystectomy did not appear to be associated with a higher risk of these complications or infected necrosis. We believe that according to the results of our study, a cholecystectomy after severe pancreatitis cannot be compared with a routine cholecystectomy. It is conceivable that (past) inflammation and peripancreatic collections lead to more adhesions, poorer visibility and demarcation of anatomical structures during cholecystectomy or even altered anatomy of the biliary duct system. It might be difficult to gain access to the hepatic hilum and a difficult dissection, especially in patients who underwent invasive treatment for infected necrosis (eg, drainage, necrosectomy). To prepare for the latter eventualities, preoperative imaging (CT or MRI) can be performed to evaluate the biliary anatomy (combined with the evaluation of the collections). A difficult procedure should be assumed when preparing for cholecystectomy after necrotising pancreatitis. This should be taken into account when preparing and counselling the patient for surgery, choosing the surgical team and the timing of the cholecystectomy. We believe that if a large collection is present in or near the head of the pancreas or when there is intra-abdominal involvement, this can also lead to a more difficult dissection in these patients. Furthermore, if the patient has had interventions for infected necrosis (eg, drainage or necrosectomy), conversion to an open procedure might be preferable.

According to current guidelines, follow-up imaging in patients with biliary pancreatitis and collections appears the most appropriate in case of relevant clinical findings or when invasive treatment is anticipated, rather than routine follow-up.[35] In clinical

Table 2 Recurrent biliary events before cholecystectomy in 248 patients with necrotising biliary pancreatitis with cholecystectomy at 4, 6 8, 10 and 12 weeks after discharge, respectively

	<4 weeks n=25	>4 weeks n=223	<6 weeks n=45	>6 weeks n=203	<8 weeks n=67	>8 weeks n=181	<10 weeks n=81	>10 weeks n=167	<12 weeks n=88	>12 weeks, n=160
Overall biliary events	2 (8)	55 (25)	8 (18)	49 (24)	10 (15)	47 (26)	11 (14)	46 (28)	11 (13)	46 (29)
	RR 0.32 (0.08 to 1.25), p=0.08		RR 0.74 (0.38 to 1.45), p=0.44		RR 0.58 (0.31 to 1.07), p=0.09		RR 0.49 (0.27 to 0.90), p=0.02		RR 0.44 (0.24 to 0.80), p<0.01	
Choledocholithiasis	0 (0)	28 (13)	4 (9)	24 (12)	6 (9)	22 (12)	6 (7)	22 (13)	6 (7)	22 (14)
	p=0.09		RR 0.75 (0.27 to 2.06), p=0.80		RR 0.74 (0.31 to 1.74), p=0.65		RR 0.56 (0.24 to 1.33), p=0.21		RR 0.50 (0.21 to 1.18), p=0.14	
Cholecystitis	2 (8)	16 (7)	4 (9)	14 (7)	4 (6)	14 (8)	5 (6)	13 (8)	5 (6)	13 (8)
	RR 1.12 (0.27 to 4.57), p=0.70		RR 1.29 (0.45 to 3.73), p=0.75		RR 0.77 (0.26 to 2.26), p=0.79		RR 0.79 (0.29 to 2.15), p=0.80		RR 0.70 (0.26 to 1.90), p=0.61	
Cholangitis	0 (0)	13 (6)	1 (2)	12 (6)	1 (2)	12 (7)	1 (1)	12 (7)	1 (1)	12 (8)
	p=0.37		RR 0.38 (0.05 to 2.82), p=0.47		RR 0.23 (0.03 to 1.70), p=0.20		RR 0.17 (0.02 to 1.30), p=0.07		RR 0.15 (0.02 to 1.15), p=0.04	
Recurrent pancreatitis	0 (0)	21 (10)	1 (2%)	20 (10)	1 (2)	20 (11)	1 (1)	20 (12)	1 (1)	20 (13)
	p=0.14		RR 0.23 (0.03 to 1.64), p=0.14		RR 0.14 (0.02 to 0.99), p=0.02		RR 0.10 (0.01 to 0.76), p<0.01		RR 0.09 (0.01 to 0.67), p<0.01	
Readmission for biliary event	2 (8)	54 (24)	9 (20)	47 (23)	12 (18)	44 (24)	13 (16)	43 (26)	13 (15)	43 (27)
	RR 0.33 (0.09 to 1.27), p=0.08		RR 0.86 (0.46 to 1.63), p=0.84		RR 0.74 (0.42 to 1.31), p=0.31		RR 0.62 (0.36 to 1.09), p=0.11		RR 0.55 (0.31 to 0.97), p=0.04	

Data are presented as n (%)
RR, risk ratio.

practice, however, follow-up of peripancreatic collections is often omitted, even when cholecystectomy is planned.

Studies investigating the relation between early cholecystectomy and infected necrosis are mostly retrospective in design and sample sizes are small.[12–17] This is reflected in a 2013 Cochrane review stating that there is 'no evidence to support or refute early cholecystectomy for patients with necrotising pancreatitis'.[7] Early cholecystectomy in acute necrotising pancreatitis has its risks, as seen both in literature and in clinical practice. Previous studies have shown that persisting inflammation/peripancreatic collections can lead to a more difficult surgical dissection, increasing the risk of bile duct injuries and other complications. Furthermore, to prevent complications, patients need to be 'fit for surgery', which might not be the case very early after an episode of necrotising pancreatitis. In our study, the evaluation of the pancreatic and peripancreatic collection over time after necrotising pancreatitis was not performed in a consistent manner, making it difficult to draw definitive conclusions. The safety of a very early cholecystectomy in light of the presence of collections and subsequent the risk of developing infected necrosis is still up for debate.

Furthermore, infected necrosis occurred in four patients, in three patients prophylactic antibiotics were administered during cholecystectomy. In one patient, information regarding antibiotic administration was not available. Given the low number of events, the added value of periprocedural antibiotics could not be evaluated. If there are no collections present, infected necrotising pancreatitis cannot develop. Therefore, we would recommend standard follow-up imaging (4 weeks after discharge) to evaluate the presence or absence of (peri)pancreatic collections after acute biliary pancreatitis. Subsequently, cholecystectomy should be performed as early as possible when no collections are present. If there are still collections present, imaging should be repeated after 2–4 weeks until collections are resolved. For patient with persistent collections, however, the risk of waiting and the risk of performing a cholecystectomy should be weighted, taking into consideration the size and location of collections. These recommendations are summarised in the flowchart in figure 2.

Nealon and colleagues prospectively followed 151 patients with acute necrotising biliary pancreatitis and associated collections, comparing early cholecystectomy (before resolution or established persistence of pseudocyst) with a delayed cholecystectomy (>6 weeks after admission or after resolution of pseudocysts). They found that an early cholecystectomy was associated with a higher risk of infected necrosis (16 out of 78 patients (21%) vs 3 out of 109 (3%)) and concluded that a cholecystectomy should be delayed until the collections either resolve or persist beyond 6 weeks.[16] There are substantial differences between the patients investigated in our study compared with those in the study by Nealon *et al*. In the latter study, patients who underwent early cholecystectomy were referred from other hospitals. This most likely caused inclusion bias, since patients in whom a successful early cholecystectomy was performed in the referring hospitals were not included in this study. Moreover, all patients were admitted to the intensive care unit indicating a group of more severely ill patients.

Another difference is that patients in the delayed group had persistent peripancreatic collections (n=53/89) and underwent open cholecystectomy combined with cystenterostomy. These low numbers of infected necrosis in their delayed group might be related to the simultaneous treatment of collections.

Contrary to previous studies, ES did not prevent recurrent biliary events. Patients in this study underwent ES only for clear indications such as retained CBD stones, there were no ERCP procedures performed solely to prevent recurrent biliary events. Therefore, bias due to confounding by indication might have played a role in the limited effect of ES found in our study. Nevertheless, a proportion of the patients who did undergo ES, developed biliary events afterwards, which shows that ES does not abolish the risk of biliary events.

Multiple studies, including a systematic review, conclude that the incidence of recurrent pancreatitis after ES was decreased compared with the overall incidence of recurrent pancreatitis

Table 3 Difficulty cholecystectomy and adverse events in 191 patients after necrotising biliary pancreatitis with cholecystectomy at 4, 6 8, 10 and 12 weeks after discharge, respectively

	<4 weeks n=25	>4 weeks n=166	<6 weeks n=45	>6 weeks n=146	<8 weeks n=67	>8 weeks n=124	<10 weeks n=81	>10 weeks n=110	<12 weeks n=88	>12 weeks n=103
Overall adverse events	3 (12)	19 (11)	3 (7)	19 (13)	7 (10)	15 (12)	8 (10)	14 (13)	9 (10)	13 (13)
	RR 1.05 (0.33 to 3.29), p=1.00		RR 0.51 (0.16 to 1.65), p=0.30		RR 0.86 (0.37 to 2.01), p=0.82		RR 0.78 (0.34 to 1.76), p=0.65		RR 0.81 (0.36 to 1.81), p=0.66	
Abscess or biloma	1 (4)	15 (9)	1 (2)	15 (10)	4 (6)	12 (10)	5 (6)	11 (10)	6 (7)	10 (10)
	RR 0.44 (0.06 to 3.21), p=0.70		RR 0.22 (0.03 to 1.59), p=0.12		RR 0.62 (0.21 to 1.84), p=0.43		RR 0.62 (0.22 to 1.71), p=0.43		RR 0.70 (0.27 to 1.86), p=0.60	
Infected necrosis*	2 (8)	2 (1)	2 (4)	2 (1)	2 (3)	2 (2)	2 (3)	2 (2)	2 (2)	2 (2)
	RR 6.64 (0.98 to 45.04), p=0.08		RR 3.24 (0.47 to 22.38), p=0.24		RR 1.85 (0.27 to 12.84), p=0.61		RR 1.36 (0.20 to 9.44), p=1.00		RR 1.17 (0.17 to 8.14), p=1.00	
Adverse events during cholecystectomy	1 (4)	13 (8)	1 (2)	13 (9)	3 (5)	11 (9)	4 (5)	10 (9)	4 (5)	10 (15)
	RR 0.0.51 (0.07 to 3.74), p=0.70		RR 0.25 (0.03 to 1.86), p=0.19		RR 0.51 (0.15 to 1.75), p=0.39		RR 0.54 (0.18 to 1.67), p=0.40		RR 0.45 (0.15 to 1.44), p=0.27	
Bleeding	1 (4)	5 (3)	1 (2)	5 (3)	3 (4)	3 (2)	3 (4)	3 (3)	3 (3)	3 (3)
	RR 1.33 (0.16 to 10.90), p=0.57		RR 0.65 (0.08 to 5.41), p=1.00		RR 1.85 (0.38 to 8.92), p=0.43		RR 1.36 (0.28 to 6.56), p=0.70		RR 1.17 (0.24 to 5.65), p=1.00	
Bile duct injury	1 (4)	6 (4)	1 (2)	6 (4)	1 (2)	6 (5)	1 (1)	6 (6)	1 (1)	6 (6)
	RR 1.11 (0.14 to 8.81), p=1.00		RR 0.54 (0.07 to 4.37), p=1.00		RR 0.31 (0.04 to 2.51), p=0.43		RR 0.23 (0.03 to 1.84), p=0.24		RR 0.20 (0.02 to 1.59), p=0.13	
Difficulty cholecystectomy										
Adhesions (n=179, %)	18 (72)	105 (68)	27 (63)	96 (71)	40 (63)	83 (72)	48 (62)	75 (74)	51 (61)	72 (76)
	RR 1.06 (0.81 to 1.38), p=0.82		RR 0.89 (0.69 to 1.15), p=0.35		RR 0.87 (0.69 to 1.08), p=0.24		RR 0.85 (0.69 to 1.05), p=0.14		RR 0.80 (0.65 to 0.99), p=0.04	
Gall spill (n=179, %)	12 (48)	83 (54)	27 (63)	68 (50)	35 (55)	60 (52)	43 (56)	52 (51)	48 (57)	47 (50)
	RR 0.89 (0.58 to 1.37), p=0.67		RR 1.26 (0.94 to 1.67), p=0.16		RR 1.05 (0.79 to 1.39), p=0.76		RR 1.10 (0.83 to 1.44), p=0.55		RR 1.16 (0.88 to 1.52), p=0.37	
Conversion to open (n=185, %)	3 (12)	19 (11)	4 (9)	18 (12)	6 (9)	16 (13)	8 (10)	14 (13)	8 (9)	14 (14)
	RR 1.01 (0.32 to 3.17), p=1.00		RR 0.71 (0.25 to 1.99), p=0.60		RR 0.69 (0.29 to 1.68), p=0.48		RR 0.77 (0.34 to 1.74), p=0.65		RR 0.66 (0.29 to 1.49), p=0.37	
Subtotal cholecystectomy (n=180, %)	0 (0)	8 (5)	1 (2)	7 (5)	1 (2)	7 (6)	1 (1)	7 (7)	2 (2)	6 (6)
	p=0.60		RR 0.46 (0.06 to 3.60), p=0.68		RR 026 (0.03 to 2.06), p=0.26		RR 0.19 (0.02 to 1.52), p=0.14		RR 0.38 (0.08 to 1.84), p=0.29	
Drain placement (n=182, %)	4 (16)	29 (18)	5 (12)	28 (19)	6 (9)	27 (22)	9 (12)	24 (22)	11 (13)	22 (21)
	RR 0.87 (0.33 to 2.25), p=1.00		RR 0.58 (0.24 to 1.40), p=0.26		RR 0.41 (0.18 to 0.94), p=0.03		RR 0.51 (0.25 to 1.04), p=0.08		RR 0.58 (0.30 to 1.13), p=0.12	

Data are presented as n (%).
*Within 31 days after cholecystectomy.
RR, risk ratio.

without ES. It was concluded that ES might be as effective in reducing the incidence of recurrent acute biliary pancreatitis compared with cholecystectomy, but is inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy was deemed superior to either of the treatments alone.[36–38]

Our study has several limitations. First, it comprises a post hoc analysis although of prospectively collected data. Consecutive patients from a set time period admitted to one of the participating hospitals were included in this study, a subset of patients was included in the PANTER-trial and TENSION-trial, which included patients for invasive interventions in infected necrotising pancreatitis.[22 39] Therefore, the prevalence of infected necrosis before cholecystectomy was relatively high in this cohort. This may have led to a larger group of more seriously ill patients. However, our results show that also in severely ill patients with necrotising pancreatitis recurrent biliary events often occur and that performing a late cholecystectomy does not reduce the risk of adverse events. Second, timing of cholecystectomy was determined by the treating clinicians and might have been influenced by logistic constraints (eg, waiting time for the cholecystectomy) to perform early surgery leading to an underrepresentation of patients with early cholecystectomy. Third, due to low overall post-cholecystectomy infected necrosis rates, we could not compare the effect of early versus late cholecystectomy on infection rates. This would require a much larger study cohort.

CONCLUSION

There is a substantial risk of recurrent biliary events in the waiting period for cholecystectomy in patients with necrotising biliary pancreatitis. Our results indicate that the optimal timing of cholecystectomy, in the absence of peripancreatic collections, is within 8 weeks after discharge. We did not observe a role for ES to reduce the risk of recurrent biliary events in patients with necrotising biliary pancreatitis.

Table 4 Recurrent biliary events before cholecystectomy in 248 patients with necrotising biliary pancreatitis who did or did not undergo sphincterotomy

	ES n=117	No ES n=131	Risk ratio, p value
Recurrent biliary event (after ES*)	28 (24)	27 (21)	RR 1.16 (0.73 to 1.85), p=0.54
Obstructive choledocholithiasis	11 (9)	11 (8)	RR 1.12 (0.50 to 2.49), p=0.83
Cholecystitis	11 (9)	9 (7)	RR 1.37 (0.59 to 3.19), p=0.49
Cholangitis	5 (4)	5 (4)	RR 1.12 (0.33 to 3.77), p=1.00
Recurrent pancreatitis	3 (3)	8 (6)	RR 0.42 (0.11 to 1.55), p=0.22

Data are presented as n (%).
*After endoscopic sphincterotomy in patients who underwent sphincterotomy after admission, overall recurrent biliary events in patient who did not undergo sphincterotomy.
ES, endoscopic sphincterotomy; RR, risk ratio.

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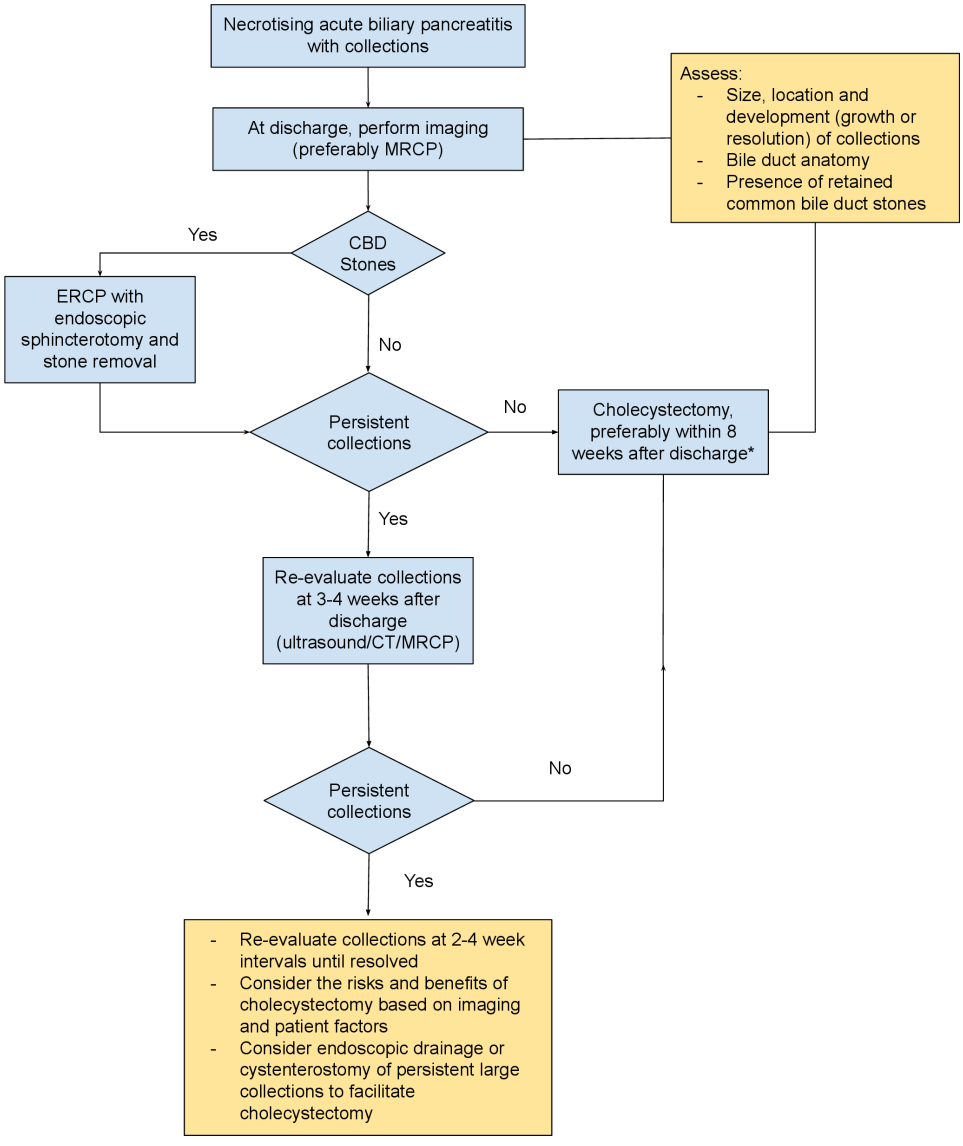

Figure 2 Flowchart on follow-up after necrotising biliary pancreatitis and timing of cholecystectomy. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

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Supplementary material

Table S1 CT Severity Index (CTSI)	
Pancreatic inflammation	**Pojnts**
Normal pancreas	0
Focal or diffuse enlargement of pancreas	1
Peripancreatic inflammation	2
Single acute fluid collection	3
Two or more acute fluid collections	4
Pancreatic Necrosis	
No necrosis	0
≤30% necrosis	2
>30-50% necrosis	4
>50% necrosis	6

Based on Bollen et al. 2011 [29]

Table S2. Baseline characteristics of patients who were included and excluded*			
	Included N = 248	Excluded N = 71	P-value
Age	60 (±15)	66 (±13)	<0.01
Women	116 (47%)	32 (45%)	0.89
BMI (n = 164, 65%)	27.1 (25 – 31)	27.5 (26 – 30)	0.92
ASA grade			
1	104 (42%)	26 (37%)	0.58
2	126 (51%)	32 (45%)	0.59
3	18 (7%)	11 (16%)	0.03
History of abdominal surgery	51 (21%)	34 (48%)	<0.01
Predicted severity of pancreatitis			
APACHE-II	8 (±4)	10 (7 – 15)	<0.01
Imrie score	3 (±2)	4 (±2)	<0.01
Imaging severity			
CT severity index	6 (4 – 8)	6 (4 – 10)	0.01
Parenchymal necrosis	130 (52%)	40 (56%)	0.14
<30% necrosis	57 (23%)	5 (7%)	<0.01
30 – 50% necrosis	37 (15%)	15 (21%)	0.07
>50% necrosis	38 (15%)	20 (28%)	<0.01
ICU admission	87 (35%)	53 (75%)	<0.01
Organfailure	65 (26%)	50 (70%)	<0.01
Liver enzymes at admission			
Bilirubin (µmol/l)	28 (17 – 50)	31 (19 – 55)	0.83
AST (units/l)	174 (80 – 314)	256 (±206)	0.40
ALT (units/l)	199 (84 – 379)	211 (59 – 386)	0.90
AP (units/l)	122 (91 – 172)	122 (90 – 202)	0.74
GGT (units/l)	303 (160 – 552)	288 (129 – 518)	0.62
Occurrence infected necrosis	109 (44%)	42 (59%)	0.01
Invasive intervention for infected necrosis	104 (42%)	42 (59%)	<0.01
Length of initial hospital stay in days	23 (13 – 68)	36 (16 – 85)	0.18
Follow-up (months)	76 (±30)	49 (±66)	<0.01

*Patients excluded after identifying necrotising biliary pancreatitis (n = 328); previous cholecystectomy (n = 20), died during index admission (n = 37), missing data (n = 37).
Data are presented as median (interquartile range: P25 – P75) or mean (± standard deviation).
BMI body mass index, *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* gamma-glutamyl transferase, *ICU* Intensive Care Unit
Note: data was available for all 250 patients unless differently specified.

Table S3. Reasons for not having a cholecystectomy in 57 patients	
Death shortly after index admission	22 (39)
Risk of complications deemed too high	19 (33)
Cholecystectomy was not indicated (according to the treating clinician)	11 (19)
Shriveled gallbladder	22 (39)
Unknown	22 (39)
Data are presented as n (%).	

Table S4. Baseline characteristics of 248 patients who did and did not undergo cholecystectomy

	Cholecystectomy N = 191	No cholecystectomy N = 57	P-value
Age	58 (48 – 67)	72 (62 – 79)	<0.01
Women	88 (46%)	28 (49%)	0.76
BMI (n = 164, 65%)	26.8 (25 – 31)	27.7 (25 – 31)	0.44
ASA grade			
1	87 (46%)	17 (30%)	0.05
2	95 (50%)	31 (54%)	0.55
3	9 (5%)	9 (16%)	0.01
History of abdominal surgery	37 (19%)	14 (25%)	0.46
Predicted severity of pancreatitis			
APACHE-II	7 (4 – 10)	9 (7 – 12)	<0.01
Imrie score	2 (1 – 4)	3 (2 – 3))	0.13
Imaging severity			
CT severity index	4 (4 – 8)	6 (4 – 8)	0.09
Parenchymal necrosis	96 (50%)	34 (60%)	0.23
<30% necrosis	45 (24%)	12 (21%)	0.86
30 – 50% necrosis	27 (14%)	10 (18%)	0.53
>50% necrosis	25 (13%)	13 (23%)	0.09
ICU admission	62 (33%)	25 (44%)	0.12
Organfailure	50 (26%)	15 (26%)	1.00
Liver enzymes at admission			
Bilirubin (µmol/l) (n = 221, 89%)	28.5 (17 – 50)	27 (17 – 50)	0.83
AST (units/l) (n = 210, 85%)	182 (84 – 312)	163 (60 – 326)	0.80
ALT (units/l) (n = 223, 90%)	222 (89 – 395)	175 (44 – 349)	0.17
AP (units/l) (n = 219, 88%)	121 (87 – 172)	125 (96 – 185)	0.35
GGT (units/l) (n = 219, 88%)	334 (176 – 568)	237 (111 – 499)	0.08
Occurrence infected necrosis	75 (39%)	34 (60%)	0.01
Invasive intervention for infected necrosis	73 (38%)	31 (54%)	0.03
Length of initial hospital stay in days	21 (13 – 58)	41 (16 – 92)	0.04
Follow-up (months)	85 (70 – 98)	77 (42 – 95)	0.02

Data are presented as median (interquartile range: P25 – P75).
BMI body mass index, *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* gamma-glutamyl transferase, *ICU* Intensive Care Unit
Note: data was available for all 250 patients unless differently specified.

Table S5. Recurrent biliary events after cholecystectomy in 191 patients	
Overall number of patients with recurrent biliary events	20 (11%)
Choledocholithiasis	9 (5%)
Cholangitis	2 (1%)
Recurrent pancreatitis	22 (12%)
Data are presented as n (%). Different biliary events may occur in 1 patient.	

Table S6. Baseline characteristics of 248 patients with necrotising biliary pancreatitis over a two-week interval timing of cholecystectomy

	<4 weeks N = 25	>4 weeks N = 223	<6 weeks N = 45	>6 weeks N = 146	<8 weeks N = 67	>8 weeks N = 124	<10 weeks N = 81	>10 weeks N = 110	<12 weeks N = 88	>12 weeks N = 103
Age	53 (+14)	61 (+15)	53 (+14)	61 (+14)	55 (+15)	62 (+14)	56 (+15)	62 (+14)	56 (+15)	62 (+14)
Women	10 (40%)	106 (48%)	24 (53%)	92 (45%)	37 (55%)	79 (44%)	45 (56%)	71 (43%)	48 (55%)	68 (43%)
BMI (n = 161, %)	27 (24 – 29)	27 (25 – 31)	27 (25 – 32)	27 (25 – 31)	27 (25 – 31)	27 (25 – 31)	27 (25 – 31)	28 (25 – 31)	27 (25 – 32)	28 (25 – 31)
ASA grade										
1	9 (36%)	95 (43%)	20 (44%)	84 (41%)	30 (45%)	74 (41%)	38 (47%)	66 (40%)	42 (48%)	62 (39%)
2	15 (60%)	111 (50%)	23 (51%)	103 (51%)	34 (51%)	92 (51%)	40 (49%)	86 (52%)	43 (49%)	83 (52%)
3	1 (4%)	17 (8%)	2 (4%)	16 (8%)	3 (5%)	15 (8%)	3 (4%)	15 (9%)	3 (3%)	15 (9%)
First episode of pancreatitis	25 (100%)	220 (99%)	45 (100%)	200 (99%)	67 (100%)	178 (98%)	81 (100%)	164 (98%)	88 (100%)	157 (98%)
History of abdominal surgery	6 (24%)	45 (20%)	13 (29%)	38 (19%)	16 (24%)	35 (19%)	18 (22%)	33 (20%)	19 (22%)	32 (20%)
Liver enzymes at admission										
Bilirubin (µmol/l) (n = 221, 89%)	26 (18 – 57)	28 (17 – 50)	29 (18 – 46)	28 (17 – 50)	32 (19 – 53)	26 (17 – 50)	30 (18 – 51)	26 (17 – 50)	30 (18 – 50)	26 (17 – 50)
AST (units/l) (n = 210, 85%)	137 (49 – 245)	184 (82 – 319)	193 (68 – 320)	170 (82 – 311)	204 (84 – 317)	162 (76 – 313)	195 (95 – 315)	163 (74 – 310)	185 (84 – 297)	168 (75 – 320)
ALT (units/l) (n = 223, 90%)	193 (106 – 350)	204 (81 – 384)	217 (95 – 437)	194 (74 – 375)	237 (132 – 441)	178 (70 – 362)	223 (95 – 438)	188 (68 – 357)	217 (95 – 433)	189 (71 – 363)
AP (units/l) (n = 219, 88%)	132 (103 – 181)	121 (90 – 172)	132 (103 – 192)	119 (88 – 172)	132 (103 – 202)	115 (84 – 169)	129 (100 – 202)	119 (89 – 547)	127 (89 – 195)	119 (91 – 168)
GGT (units/l) (n = 219, 88%)	352 (210 – 590)	295 (153 – 549)	307 (202 – 578)	303 (153 – 549)	362 (203 – 605)	286 (153 – 535)	336 (183 – 576)	292 (153 – 547)	319 (175 – 568)	297 (153 0 550)
Predicted severity of pancreatitis										
APACHE-II	7 (+4.5)	8 (+4)	7 (+4)	8 (+4)	7 (+4)	8 (+4)	7 (+4)	8 (+4)	7 (+4)	8 (+4)
Imrie score	2 (1 – 3)	3 (2 - 4)	2 (+1)	3 (+2)	4 (4 – 5)	6 (4 – 8)	2 (+1)	3 (+2)	2 (1 – 3)	6 (4 – 8)
Imaging severity										
CT severity index	4 (4 – 6)	6 (4 – 8)	4 (4 – 6)	6 (4 – 8)	4 (4 – 5)	6 (4 – 8)	4 (4 – 4)	6 (4 – 8)	4 (4 – 5)	6 (4 – 8)
Parenchymal necrosis	9 (36%)	121 (54%)	13 (29%)	117 (58%)	17 (25%)	113 (62%)	19 (24%)	111 (67%)	22 (25%)	108 (68%)
<30% necrosis	5 (20%)	52 (23%	7 (16%)	50 (25%)	10 (15%)	47 (26%)	11 (14%)	46 (28%)	11 (13%)	46 (29%)
30 – 50% necrosis	2 (8%)	35 (16%)	3 (7%)	24 (17%)	4 (6%)	33 (18%)	5 (6%)	32 (19%)	6 (7%)	31 (19%)
>50% necrosis	2 (8%)	36 (16%)	3 (7%)	35 (17%)	4 (6%)	34 (19%)	4 (5%)	34 (20%)	6 (7%)	32 (20%)
ICU admission			2 (4%)	85 (42%)	5 (8%)	82 (45%)	11 (14%)	76 (46%)	13 (15%)	74 (46%)
Organ failure	1 (4%)	64 (29%)	2 (4%)	63 (31%)	4 (6%)	61 (34%)	6 (7%)	59 (35%)	8 (9%)	57 (36%)
Infected necrosis before cholecystectomy	3 (12%)	64 (29%)	5 (11%)	104 (51%)	8 (12%)	101 (56%)	9 (11%)	100 (60%)	11 (13%)	98 (61%)
Invasive intervention for infected necrosis	2 (8%)	102 (46%)	4 (9%)	100 (49%)	7 (10%)	97 (54%)	8 (10%)	96 (58%)	10 (11%)	94 (59%)
Length of initial hospital stay in days	17 (12 – 23)	25 (14 – 75)	15 (9 - 22)	31 (16 - 80)	16 (10 – 23)	39 (17 - 88)	16 (10 – 23)	45 (18 – 93)	16 (10 – 23)	47 (18 - 93)
Follow-up (months)	92 (81 – 101)	82 (59 - 96)	90 (77 - 99)	82 (59 - 96)	90 (79 – 99)	80 (56 – 96)	90 (77 – 98)	80 (53 – 96)	91 (78 – 99)	80 (51 – 95)

Data are presented as n (%), mean (±SD), or median (interquartile range). Note: data was available for all 248 patients unless differently specified.

BMI body mass index, *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* gamma-glutamyl transferase, *ICU* Intensive Care Unit

Table S7. Indication for ERCP in 117 patients	
Prevention progression biliary pancreatitis*	6 (5%)
Prevention progression biliary pancreatitis with abnormal liver function tests	30 (26%)
Prevention progression biliary pancreatitis with abnormal liver function tests and cholestasis	26 (22%)
Abnormal liver function tests	3 (3%)
Abnormal liver functions tests and cholestasis	4 (3%)
Obstructive icterus	5 (4%)
Cholangitis with abnormal liver function tests	3 (3%)
Cholangitis with abnormal liver function tests and cholestasis	5 (4%)
Status after pancreatitis with choledocholithiasis (no known liver function tests)	4 (3%)
Status after pancreatitis, abdominal pain (colic), abnormal liver function tests	4 (3%)
Prevention of recurrent biliary events	5 (4%)
Unknown indication with abnormal liver function test	3 (3%)
Unknown indication with abnormal liver function tests and cholestasis	5 (4%)
Unknown indication with no known liver function tests	11 (9%)
Other#	3 (3%)
Data are presented as n (%). * no known liver function test or no abnormal liver function test # Evaluation of the pancreatic duct in 1 patient, rendezvous procedure in 1 patient, status after pancreatitis according to the current guidelines in 1 patient,	