

# Timing of laparoscopic cholecystectomy in patients with non-severe biliary pancreatitis

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## Abstract

**Introduction:** In patients with acute biliary pancreatitis (ABP), cholecystectomy is mandatory to prevent further biliary events, but the precise timing of laparoscopic cholecystectomy (LC) for non-severe disease remain a subject of ongoing debate.

**Aim:** To prove which method – early or delayed LC – is the method of choice in the non-severe disease by examining rates of gallstone-related complications, dissection difficulty, conversion rate, morbidity, mortality, and length of hospital stay.

**Material and methods:** We retrospectively analysed the data of patients diagnosed with non-severe ABP, who were followed and underwent LC in our department. Patients who met the inclusion criteria were divided in to the early (< 2 weeks) and the delayed groups (> 2 weeks).

**Results:** The patients in the early and delayed groups ( $n = 43/39$ ) were similar in terms of demographic characteristics, comorbidities, and severity of biliary pancreatitis. The mean time to surgery was 1.7 vs. 6.5 weeks in the early and late groups, respectively. Patients in the delayed group had a 17.9% readmission rate. The causes were acute pancreatitis (10.2%), cholangitis, and cholecystitis. The conversion and the difficult dissection rates were 11.6% vs. 12.8% and 13.95% vs. 20.51% in the early and delayed groups, respectively. Mortality was not observed in the groups. Morbidity rates were 4.6% vs. 5%, and mean length of hospital stay was 10 vs. 17 days in the early and delayed groups, respectively.

**Conclusions:** Delayed LC increases the rate of biliary events and early LC does not increase the operative difficulty or morbidity in patients with ABP.

## Introduction

Acute pancreatitis is a common gastrointestinal disease, with an incidence of 13 to 45 per 100,000 people [1]. The most frequent cause is stones in the gallbladder [2]. The American Gastroenterological Association and International Association of Pancreatology/American Pancreatic Association (IAP/APA) Working Group reported that the definitive treatment for acute biliary pancreatitis must include cholecystectomy to prevent recurrent biliary events [3, 4]. The main question in cases of mild to moderate acute biliary pancreatitis is the timing of laparoscopic cholecystectomy (LC). While some investigators have reported that delaying cholecystectomy can increase hospital readmission rates, others reported that earlier cholecystectomy may prevent recurrent biliary events without increasing the difficulty of surgery [5–9].

## Aim

To prove which method – early or delayed LC – is the method of choice in the non-severe disease by examining rates of gallstone-related complications, dissection difficulty, conversion rate, morbidity, mortality, and length of hospital stay.

## Material and methods

Ethical approval for this study was obtained from the Ondokuz Mayıs University (OMU) Faculty of Medicine Ethics Committee. The data of 1300 patients who had undergone LC in the General Surgery Department of the OMU Faculty of Medicine between 2006 and 2013 were retrospectively analysed.

The patients' age, sex, presence or history of comorbidities such as diabetes, hypertension, coronary artery disease, and cerebrovascular disease, ASA score,

alcohol use, presence of symptoms of abdominal pain, nausea and vomiting at admission, and serum levels of C-reactive protein (CRP), amylase, lipase, aspartate transaminase (AST), alkaline phosphatase (ALP),  $\gamma$ -glutamyl transferase (GGT), total bilirubin, direct bilirubin, triglycerides, calcium, blood urea nitrogen, and creatine, and the radiological diagnostic methods used and their findings were analysed.

Based on the presence of the signs and symptoms of pancreatitis accompanied by high serum amylase and lipase concentrations and also imaging-revealed stones in the gallbladder or common bile duct, 209 patients were classified as having acute gallstone pancreatitis.

The 82 patients, who were over 18 years of age, with no history of alcohol use, no concurrent hyperlipidaemia or signs of organ failure, and no findings of pancreatic necrosis on radiological imaging, who had first admission and follow-up and underwent cholecystectomy in our centre were included the study.

The early group was classified as patients who underwent cholecystectomy within 2 weeks of symptom onset. The delayed group was classified as patients who had an interval between initial conservative treatment and cholecystectomy longer than 2 weeks.

### Statistical analysis

The study data were coded and statistically analysed using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) software package. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation, and frequency data were expressed as number and percentage (%). In the statistical analyses, all mea-

sured variables were assessed for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk test. The independent-samples *t* test was used to compare the groups' means for normally distributed variables. The  $\chi^2$  and Fisher's exact test were used for comparisons of counted data. A *p*-value of less than 0.05 was regarded as statistically significant.

### Results

The early group consisted of 43 patients. The delayed group consisted of 39 patients. There were no significant differences between the groups in terms of demographic characteristics, ASA scores, and comorbidities (Table I).

The most common presenting symptom was abdominal pain. Presenting symptoms did not differ significantly between the groups (*p* = 0.97). Mean amylase levels at first admission in the early and delayed groups were 1981  $\pm$ 1081.1 U/l and 1901  $\pm$ 1266.4 U/l, respectively. The mean time to normalization of amylase values was 5.76 days (2–18 days) in the early group and 4.9 days (2–13 days) in the delayed group (Table II).

In all patients, the presence of stones and biliary sludge in the gallbladder or bile ducts was demonstrated by at least one imaging method. Seventeen (39.5%) patients in the early group and 14 (35.8%) patients in the delayed group who had stones, biliary sludge, dilation, or stenosis in the common bile duct on ultrasonography, computed tomography, and/or magnetic resonance cholangiopancreatography (MRCP) examinations performed at time of admission or clinical signs consistent with accompanying cholangitis and obstruc-

**Table I.** Demographic characteristics and comorbidities

Parameter	Early group (n = 43)	Delayed group (n = 39)	P-value
Age [years]	54.8 $\pm$ 15.5 (18–86)	55.5 $\pm$ 16.4 (28–86)	0.826
Sex:			0.420
Male	15 (34.8%)	17 (43.5%)	
Female	28 (65.1%)	22 (56.4%)	
BMI [kg/m <sup>2</sup> ]	24	25	0.32
ASA Score:			0.883
I (healthy)	24 (55.8%)	21 (53.8%)	
II (mild systemic disease)	13 (30.2%)	12 (30.7%)	
III (severe systemic disease)	6 (13.1%)	6 (15.3%)	
Diabetes	12(27.9%)	10 (25.6%)	0.28
Hypertension	7 (16.2%)	8 (20.5%)	0.06
Coronary artery disease	9 (20.9%)	8 (20.5%)	0.81
Cerebrovascular disease	3 (6.9%)	2 (5.1%)	0.42

Student's *t* test,  $\chi^2$  test.

**Table II.** Comparison of presenting symptoms and biochemical parameters at first admission

Parameter	Early group (n = 43)	Delayed group (n = 39)	Normal values
Abdominal pain	43 (100%)	39 (100%)	$p = 0.97$
Nausea	31 (72.09%)	26 (66.6%)	
Vomiting	31 (72.09%)	25 (64.1%)	
AST [U/l]	207.6 ±188.4	164.0 ±143.8	8–46
ALP [U/l]	272.4 ±191.8	254.6 ±125.7	35–104
GGT [U/l]	234.5 ±195.7	271.5 ±259.3	5–36
Total bilirubin [mg/dl]	3.54 ±3.4	3.26 ±4.1	0.1–1.5
Direct bilirubin [mg/dl]	1.94 ±2.26	1.80 ±2.3	0.00–0.4
CRP [mg/l]	105.7 ±77.6	105.9 ±103.3	0–3
Amylase [U/l]	1981 ±1081	1901 ±1266.4	28–100
Lipase [U/l]	3276 ±2726	2907.5 ±2383	13–60

$\chi^2$  test. AST – aspartate aminotransferase, ALP – alkaline phosphatase, CRP – C-reactive protein, GGT –  $\gamma$ -glutamyl transpeptidase.

**Table III.** Diagnostic imaging and comparison of results

Parameter	Group I (n = 43)	Group II (n = 39)	P-value
Gallstones in gallbladder on USG	41 (95.3%)	38 (97.4%)	0.53
Bile sludge in gallbladder on USG	2 (4.65%)	1 (2.56%)	0.53
MRCP:	22 (51.1%)	22 (56.4%)	0.66
Stone in common bile duct	2 (9.09%)	3 (13.6%)	
Sludge in common bile duct	0 (0%)	1 (4.54%)	
ERCP	17 (39.53%)	14 (35.89%)	0.39
Papillotomy	17 (100%)	14 (100%)	
Gallstone	2 (11.7%)	7 (50%)	
Biliary sludge	4 (23.5%)	4 (28.5%)	
Debris	1 (5.8%)	1 (7.1%)	

Fisher's exact and  $\chi^2$  tests. USG – ultrasonography, MRCP – magnetic resonance cholangiopancreatography, ERCP – endoscopic retrograde cholangiopancreatography.

tive jaundice underwent endoscopic retrograde cholangiopancreatography (ERCP) (Table III).

After the first episode of acute pancreatitis, 7 (17.9%) patients in the delayed group were readmitted due to gallstone-related diseases. Four (10.2%) patients had recurrent biliary pancreatitis, 1 (5.1%) patient had acute cholangitis, and another 1 (2.5%) had acute cholecystitis. Six of those patients had undergone ERCP/ endoscopic sphincterotomy (ES) at first admission

(Table IV). Recurrent biliary pancreatitis occurred at 1, 2, 4, and 12 weeks after discharge. Acute cholangitis occurred in the first week after discharge.

The mean time to surgery was 1.7 weeks in the early group and 6.5 weeks in the delayed group, with 28% of the operations performed in week 4, 23% in week 6, and 20% in week 8.

The conversion rate was 11.6% ( $n = 5$ ) in the early group and 12.8% ( $n = 5$ ) in the delayed group

**Table IV.** Gallstone-related recurrent diseases in patients in the delayed cholecystectomy group who did and did not undergo ERCP/ES at first admission

Variable	ES (n = 14)	No ES (n = 25)	Risk rate	P-value
Biliary disease	6	1	18 (1.63–464.1)	0.005
Pancreatitis	3	1	6.55 (0.5–184.4)	0.122
Cholangitis	2	0	–	0.122
Cholecystitis	1	0	–	0.36

**Table V.** Reasons for conversion

Variable	Group I (n = 5)	Group II (n = 5)	P-value
Bile duct anomaly	1 (2.85%)	1 (3.44%)	0.73
Haemorrhage from gallbladder bed	1 (2.85%)	0	0.524
Difficult dissection	3 (8.57%)	4 (13.7%)	0.532

$\chi^2$  test.

( $p = 0.87$ ). Reasons for conversion in the early group included difficult dissection, bile duct anomaly, and haemorrhage from the gallbladder bed. In the delayed group, the reasons were difficult dissection and bile duct anomaly. There was no statistically significant difference between the groups in terms of reasons for conversion (Table V). Three (10%) of the cholecystectomies in the early group and 4 (16%) in the delayed group involved dissection difficulties, but the procedures could be completed laparoscopically. The overall difficult dissection was 13.95% in the early group and 20.51% in the delayed group ( $p = 0.043$ ). Operative time was longer in the delayed group (116  $\pm$ 18.7 min. vs. 100  $\pm$ 25.2;  $p = 0.02$ ).

In the early group, the morbidity rate was 4.6% ( $n = 2$ ), including postoperative bleeding and surgical site infection, which were managed with conservative treatment. This rate was 5% ( $n = 2$ ) in the delayed group. The cause in both cases was Strasberg type-A injury, and 1 patient underwent ERCP while the other was treated surgically (2.5%).

Median total hospital length of stay was 10 days (range: 2–21 days) in the early group and 17 days (range: 7–41 days) in the delayed group. The difference between the groups was statistically significant ( $p = 0.048$ ).

There was no mortality in either group.

## Discussion

There is ongoing controversy regarding the timing of cholecystectomy in patients with acute biliary pancreatitis, and available guidelines have different recommendations about the ideal timing [10–12]. For decades, surgeons justified interval cholecystectomy based on the idea that cholecystectomy performed at initial presentation led to higher surgical morbidity and unnecessary conversion due to the oedema caused by acute pancreatitis. Different studies [13–15] reported surgical success rates with laparoscopic surgery of 76% to 92%, while those of interval cholecystectomy were between 53% and 82%. In the present study, success rates of laparoscopic surgery in the early and delayed cholecystectomy groups were 85.7% and 82.7%, ( $p = 0.43$ ) respectively. Although it did not result in a signifi-

cant difference in conversion rates, the total proportion of patients with difficult dissection was significantly higher in the delayed group (20.51%) compared to the early group (13.95%). Based on our study, we believe that the interval cholecystectomy approach causes more difficulty with dissection.

Especially in the acute period, complications can still occur at a substantial rate after LC [16, 17]. Among the most important of these are complications related to the bile ducts, which have been reported at rates between 0.2% and 1.5% [16]. However, 2 more recent studies [18, 19] indicated that early laparoscopic cholecystectomy did not increase the postoperative complication rate. We also observed that early laparoscopic cholecystectomy did not increase the postoperative complication rate (4.6% vs. 5%). At the same time, in the delayed group complication rate related to the bile duct (Strasberg Type A) was 5% and the reoperation rate was 2.5%. This shows that early LC does not increase morbidity in patients with non-severe ABP.

An evaluation of studies on the timing of cholecystectomy in non-severe biliary pancreatitis cases shows that one of the topics focused on is safety and another is the risk of recurrent diseases associated with gallstones while waiting for interval cholecystectomy. In our study, the frequency of gallstone-related recurrent diseases was 17.9% among patients who underwent interval cholecystectomy, and different studies have reported rates varying between 14% and 61% [13–15]. In a recent study [20], the most common cause of re-admission was acute pancreatitis. When the frequency of recurrent biliary events was evaluated in our study, the most common cause was also acute pancreatitis, at 10.2%. This was followed by acute cholangitis and acute cholecystitis. The 4 patients with biliary pancreatitis presented again at 1, 2, 4, and 12 weeks after discharge. In a study with a mean post-discharge time of 19 days for recurrent biliary pancreatitis [13], it was reported that 12.5% of cases occurred in the first week, 31% in the second week, and 50% in the fourth week, and the frequency of recurrent disease within 2 weeks after discharge from the first admission was 33%.

The median total hospital length of stay in our study was significantly higher in patients who underwent late cholecystectomy, due to their 17.9% readmission rate. If

these patients had undergone cholecystectomy at initial presentation or at an earlier time, these readmissions would have been prevented.

Despite numerous randomized studies, there is no consensus in meta-analyses or international guidelines on the role and timing of ERCP in acute biliary pancreatitis [21]. However, according to the American Society for Gastrointestinal Endoscopy, early ERCP plays no role in the evaluation and treatment of mild to moderate pancreatitis without clear evidence of the presence of a stone in the common duct [7]. In a study evaluating the effect of ERCP/ES in the prevention of gallstone-related recurrent diseases [13], patients in the interval cholecystectomy group who did and did not undergo ERCP/ES were compared. It was determined that ES reduced the incidence of recurrent pancreatitis but did not completely eliminate it, while it substantially increased the frequency of acute cholecystitis. Schachter *et al.* [22] reported that in their study group of 19 patients who underwent early ERCP, none of the patients had any gallstone-related recurrent events during a waiting period of 8 to 12 weeks. In a study of 58 patients who underwent interval cholecystectomy, Srinathan *et al.* [23] reported that biliary or pancreatic complications occurred in 14 (24%) patients and that the complication rate was higher among patients who underwent ERCP. Moretti *et al.* [24] demonstrated that ERCP was not superior to conservative treatment in mild to moderate pancreatitis and that it only reduced the development of pancreatitis-related complications in patients with severe pancreatitis. In our study, the use of ERCP was limited to patients with cholangitis, patients with a high probability of having stones in the common bile duct, and patients with cholestasis. No significant difference was detected between the groups in terms of the frequency of ERCP. Of 7 patients who underwent interval cholecystectomy and had gallstone-related recurrent conditions, 6 underwent ERCP/ES at the time of first admission. One patient did not undergo ERCP/ES. Of the 6 patients who did, 3 developed acute pancreatitis, 2 developed cholangitis, and 1 developed cholecystitis. The patient who did not undergo ES developed acute pancreatitis.

As a single-centre retrospective study the size of the study is small, and this leads to weak statistical power. Also, according to the patients' data, although we suggested that the timing of the surgery during the first admission or the interval period depends on the patient's decision, we could not explain the exact reason for delaying the surgery, which might raise concerns for selection bias.

Based on the results of our study, early laparoscopic cholecystectomy in patients with non-severe ABP reduces the frequency of recurrent biliary events and total length of hospital stay compared with delayed cholecystectomy. Moreover, it does not cause any differences in the success of laparoscopic cholecystectomy or the frequency of complications. Thus, we believe that the early laparoscopic cholecystectomy approach, preferably at first presentation, is a safe and effective method in patients with non-severe biliary pancreatitis.

## Conflict of interest

The authors declare no conflict of interest.

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