

## Review of clinical experience with acute cholecystitis on the development of subsequent gallstone-related complications\*

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**Background/aim:** Recently, surgery during admission has been advocated for acute cholecystitis, rather than delayed surgery after conservative treatment. This study was designed to perform early surgeries and analyze the criteria used for conservative management followed by delayed surgery.

**Materials and methods:** After implementation of a study with the aim of performing early surgery, a retrospective review using a prospective database during the period of June 2009 to June 2011 was established. Early surgery during index hospitalization was offered to all patients, except those having criteria for conservative management.

**Results:** There were 118 patients admitted for acute cholecystitis. Early and delayed surgeries were performed for 18 (15%) and 23 (20%) patients, respectively. Percutaneous cholecystostomy was performed for 10 (8%) patients with a success rate of 90% and significantly higher length of hospital stay ( $P = 0.001$ ). Gallstone-related complications developed in 33 (28%) patients, causing significantly higher readmission rates ( $P = 0.001$ ). Of the patients, 34 (29%) were neither operated on nor had complications. The subsequent cholecystectomy rate was calculated as 35%. The overall mortality rate was 1.7% for all groups.

**Conclusion:** Although surgical treatment of acute cholecystitis, either by early or delayed surgery, has some specific morbidity and mortality, it should be kept in mind that conservative treatment modalities have a higher rate of recurrences and subsequent complications, which all cause additional morbidity and mortality in patients.

**Key words:** Cholecystitis, acute, cholecystectomy, laparoscopic, cholecystostomy

### 1. Introduction

Acute cholecystitis (AC) is the most common complication of gallstones, requiring hospital admission and prompt intervention (1,2). Treatment options include early surgery during index admission, either by laparoscopic cholecystectomy (LC) or open cholecystectomy, or delayed cholecystectomy (surgery after a successful conservative treatment), or conservative approaches like treatment with antibiotics and percutaneous cholecystostomy (PC) for high-risk patients for surgery (3).

A high recurrence rate of gallstone complications after an initial hospitalization for AC attack necessitates surgical removal of the gallbladder by either an early or delayed approach (1,2,4,5). However, the medical history of patients who could not undergo cholecystectomy at

the time of initial presentation presents a unique set of challenges, including delayed presentation, significant comorbid illness, and increased morbidity associated with gallstone-related complications (2).

Early LC for AC has been increasingly studied in recent years. Many studies favored an early approach, which, when compared to delayed cholecystectomy, has similar complication rates and reduced overall length of hospital stay (LOHS) (1,6–12). However, the early approach has not been fully implemented since only 15% to 75% of patients with AC can be operated on upon initial hospitalization for many reasons, including patient comorbidities or older age (1,4,8,13–16). It has been reported that initial conservative management followed by DS after several weeks might also cause recurrent attacks of AC and other

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gallstone-related complications, requiring readmissions to the hospital while waiting for surgery (10,16).

We implemented this study with the aim of performing early surgery for AC patients and analyzing the criteria used for conservative management followed by delayed surgery. The main objectives of this paper are to assess accordance with the study criteria and to examine complications due to the effect of AC, which is thought to be a parameter that directly affects the results.

## 2. Materials and methods

A retrospective review of a prospectively collected database for patients admitted with a diagnosis of AC presenting for the first time to the Department of General Surgery at Ümraniye Education and Research Hospital was established. All consecutive patients admitted with AC diagnosis during the period of June 2009 to June 2011 were enrolled in the study. Written informed consent from each patient in the study was obtained. The study was approved by the local ethics committee.

Patients with coexisting acute biliary pancreatitis, choledocholithiasis, or acute cholangitis and patients who were taking anticoagulant medications, had acalculous AC, or had previous AC attacks were excluded from the study. A worksheet listing each patient's demographics, current illness, medical history, American Society of Anesthesiology (ASA) score, vital signs, laboratory results, and imaging studies was designed.

The diagnosis of AC was based on well-described clinical and laboratory parameters, including the presence of right upper quadrant pain and gallstones on ultrasonography, and additionally 2 of the following parameters: fever greater than 38 °C, elevated white blood cell (WBC) count greater than 10,000/mm<sup>3</sup>, or ultrasonographic findings of AC, including distended gallbladder (>4 cm in transverse diameter), thickened wall (>4 mm), or the presence of pericholecystic fluid.

Our clinic adopted a policy of early cholecystectomy for patients admitted with AC in 2009. Early surgery was defined as LC performed in the acute stage after diagnosis of AC within 72 h of onset of symptoms during the index hospitalization and was offered to all patients, except those having the criteria for conservative management (Table 1). The treatment protocol for patients who could not be operated on at the initial hospitalization for AC was conservative management with bowel rest, analgesia, antibiotics, and intravenous fluids. After relief of the acute attack, patients were discharged and an appointment was arranged for their readmission for delayed surgery after 6–8 weeks.

Patients initially were classified into 2 groups: those who were operated on laparoscopically during initial hospitalization were defined as the early surgery (ES)

**Table 1.** Criteria used for conservative management.

| Criteria                           | n <sup>§</sup> |
|------------------------------------|----------------|
| More than 72 h duration of history | 33             |
| Age 70 or older                    | 29             |
| ASA 3                              | 24             |
| ASA 4                              | 3              |
| Usage of anticoagulant agents      | 2              |
| Pregnancy                          | 1              |
| Lack of approval for treatment     | 1              |
| Incompatible with criteria         | 38             |

§: One or more criteria in 1 patient.

group, and those who could not be operated on were defined as the conservative group. We also divided the conservative group into 4 subgroups: those who were operated on after the interval period, referred to as the delayed surgery (DS) group; those who had PC applied, referred to as the PC group; those who were treated because of gallstone-related complications, referred to as the complicated group; and those who were neither operated on nor had complications for at least 6 months after the discharge from initial hospitalization, referred to as the conservative-only group.

PC was applied for the patients for whom the conservative treatment failed, which was defined as a worsening of clinical signs and laboratory tests. Clinical improvement within 48–72 h after administration of PC was used to define the success rate of PC.

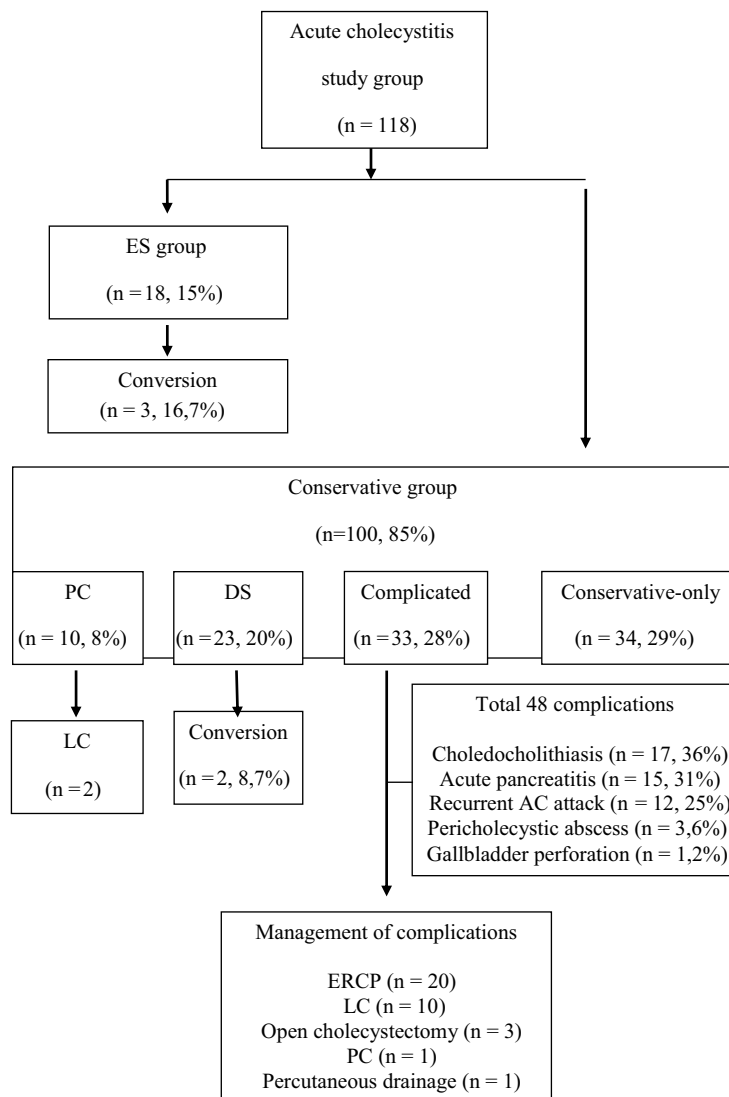
The outcome measures for all groups were analyzed regarding LOHS during index admission, number of additional hospitalizations (readmissions) required either for gallstone-related problems during conservative treatment or operative complications of AC itself, and mortality rate for all patients. Open versus LC, conversion to open surgery, and development of perioperative complications were evaluated for the patients who underwent early or delayed surgery. The number of delayed surgeries in all subgroups of the conservative group was calculated using subsequent cholecystectomy rates. The number of the patients who were not operated on during initial hospitalization without clear criteria for conservative management (protocol violation) was calculated as the failure rate. Hospitalizations due to the development of gallstone-related complications such as recurrent AC, choledocholithiasis, acute biliary pancreatitis, and pericholecystic abscess were recorded for the conservative group and calculated as the gallstone-related readmission rate.

Statistical analyses were performed with a computerized software package using Excel (Office XP from Microsoft). Statistical calculations were performed using the Number Cruncher Statistical System (2007) and PASS (2008) statistical software. A one-way ANOVA test was used for analysis of normally distributed and descriptive continuous variables, which were expressed as mean  $\pm$  standard deviation (SD), medians, frequencies, and ranges. A Kruskal–Wallis test was used for comparison of descriptive variables without normal distribution. A Mann–Whitney U test was used to detect the groups that caused differences. The chi-square test was used to assess an association between qualitative variables. Differences were considered statistically significant if the P value was equal to or less than 0.05.

### 3. Results

During the study period, 118 patients suffering from acute calculous cholecystitis were treated in our department. The study population consisted of 65 females (55%) and 53 males (45%) with a median age of 58 years (range: 18–87 years). Early surgery was performed in 18 (15%) patients, and the remaining patients were initially managed in a conservative manner (conservative group; n = 100, 85%). Delayed surgery and PC were performed for 23 (20%) and 10 (8%) patients, respectively. Gallstone-related complications (complicated group) developed in 33 (28%) patients. Thirty-four (29%) patients (conservative-only group) were neither operated on nor developed complications (Figure).

Demographic variables, ASA scores, and WBC counts of the patients are detailed in Table 2. Although no



**Figure.** Study flowchart.

**Table 2.** Demographic data and clinical parameters of all patients admitted with AC.

| n = 118                                            | ES group            | Conservative group (n = 100) |                     |                     |                     | P      |
|----------------------------------------------------|---------------------|------------------------------|---------------------|---------------------|---------------------|--------|
| Subgroups                                          |                     | PC group                     | DS group            | Complicated group   | Conservative-only   |        |
| n (%)                                              | 18/15               | 10/8                         | 23/20               | 33/28               | 34/29               |        |
| Female/male ratio                                  | 1                   | 0.25                         | 1.56                | 1.1                 | 2.1                 | 0.112  |
| Age, mean $\pm$ SD (range)                         | 55 $\pm$ 12 (37–76) | 71 $\pm$ 10 (57–87)          | 54 $\pm$ 16 (29–86) | 58 $\pm$ 19 (18–86) | 58 $\pm$ 18 (19–84) | 0.090  |
| ASA score, mean $\pm$ SD (median)                  | 1.7 $\pm$ 0.7 (2)   | 2.5 $\pm$ 0.5 (3)            | 1.7 $\pm$ 0.8 (2)   | 2.1 $\pm$ 1.0 (2)   | 2.1 $\pm$ 0.6 (2)   | 0.030* |
| WBC count, /mm <sup>3</sup> , mean $\pm$ SD        | 13,244 $\pm$ 4905   | 15,280 $\pm$ 5112            | 12,657 $\pm$ 6210   | 11,367 $\pm$ 4145   | 13,937 $\pm$ 4780   | 0.143  |
| LOHS, mean $\pm$ SD (median)                       | 3.9 $\pm$ 1.6 (4)   | 12.6 $\pm$ 5.5 (12)          | 4.9 $\pm$ 2.3 (4)   | 9.2 $\pm$ 8.3 (6)   | 4.6 $\pm$ 1.8 (4)   | 0.001* |
| Number of hospitalizations, mean $\pm$ SD (median) | 0.06 $\pm$ 0.23 (0) | 0.08 $\pm$ 0.78 (1)          | 1.04 $\pm$ 0.02 (1) | 1.33 $\pm$ 1.05 (1) | 0.06 $\pm$ 0.23 (0) | 0.001* |

\*: Statistically significant.

SD: Standard deviation, ASA: American Society of Anesthesiology, WBC: white blood cell, LOHS: length of hospital stay.

significant differences among the groups in age and sex were found, older age ( $P = 0.09$ ), male predominance ( $P = 0.112$ ), and higher WBC count ( $P = 0.143$ ) were noted in the PC group. Patients in the PC group had statistically significant higher ASA scores than the other patients ( $P = 0.03$ ).

A history of more than 72 h of duration of AC, an age of 70 or older, and ASA score of 3 or more were the most common conditions to force conservative management followed by delayed surgery (Table 1). In 38 patients, there were no clear criteria, with a failure rate of 38%.

Conversion to open surgery occurred in 3 (16.7%) and 2 (8.7%) patients in the ES and DS groups, respectively. Conversion in the ES group was higher than in the DS group; however, this difference did not reach statistical significance ( $P = 0.634$ ). There were no operative mortalities and no major surgical complications in any of the groups. There was 1 wound and 1 lower respiratory tract infections in the DS group, which were managed conservatively, and 1 retained stone in the common bile duct, which was managed by endoscopic retrograde cholangiopancreatography (ERCP). There was 1 wound infection and 1 retained stone in the common bile duct in the ES group, which were managed conservatively. The overall complication rate did not differ between the 2 surgery groups ( $P > 0.05$ ).

PC was technically successful in 9 of 11 interventions (82%) in 10 patients. Clinical improvement within 48–72 h was detected in all except 1 patient, with a success rate of 90%. There was 1 case of acute cholangitis while the catheter was in place and 1 case of AC after removal of the catheter. The latter patient died of uncontrollable biliary sepsis. LC was performed in 2 patients while their PC catheters were in place.

Forty-eight complications developed in 33 patients with a gallstone-related readmission rate of 28%. Among these complications, choledocholithiasis (36%), acute biliary pancreatitis (31%), and recurrent AC attacks (25%) were most common. The others were pericholecystic abscess in 3 and gallbladder perforation in 1. These complications developed during the treatment of the first attack, during the interval period for DS, or after the interval period in 13, 13, and 7 patients, respectively. For the treatment of gallstone-related complications, we performed ERCP in 20 patients, LC in 10, open cholecystectomy in 3, PC in 1, and percutaneous abscess drainage in 1.

LOHS was significantly longer in the PC group than the other groups ( $P < 0.001$ ) (Table 1). Mean LOHS for the complicated group was also statistically longer than the other groups, except the PC group ( $P < 0.001$ ). Mean LOHS in the ES group was shorter than in the DS group, although this difference did not reach statistical significance ( $P = 0.135$ ). The number of additional hospitalizations for the complicated group was  $1.33 \pm 1.05$ , which was statistically higher than in the other groups, except the DS group, which required at least 1 additional hospitalization for each LC ( $P < 0.001$ ) (Table 1).

Subsequent cholecystectomy rate was calculated as 35% by adding 20, 13, and 2 cholecystectomies in the DS, complicated, and PC groups, respectively. There were 2 deaths, 1 in the PC group and the other in the complicated group, in which emergency open cholecystectomy was performed due to gallbladder perforation. The overall mortality rate was 1.7% for all groups. The mean follow-up period for all patients was 11 months, with a range of 1 to 26 months.

#### 4. Discussion

Acute calculous cholecystitis is a common disease in emergency surgical consultations and is treated by cholecystectomy. It has been shown that early cholecystectomy is effective, safe, and feasible in the majority of cases (2,4,15–20). However, due to largely logistic and administrative considerations, AC patients are treated conservatively in many centers (3). Although high-risk patients were considered as poor surgical candidates, many low- to medium-risk patients with AC were not operated on for many reasons, like the inexperience of the surgical team, unavailability of early access to emergency operating rooms, or perceived risk of higher complications and higher conversion rates (10,12). All these contributory factors give rise to cholecystectomy rates of 15%–75% in patients with AC during initial hospitalization, depending on the hospital size (1,4,10,14–17). Although we aimed to perform early surgery for AC during initial hospitalizations, it could be done in only 15% of the patients. After exclusion of the patients with clear criteria for conservative management, we had a failure rate of 38%. We agree with other recommendations that for successful implementation there should be a multidisciplinary approach among the surgical team and other departments like emergency services, anesthesiology, intensive care units, and the operating room (1).

It is a fact that early definitive treatment of AC decreased LOHS and reduced readmission rates, both improving patient care and decreasing costs (1,2,11,14,15). We did not detect any significant difference in morbidity and operative mortality between early and delayed surgery for AC, in accordance with others (1). In this study, there was a shorter LOHS in the ES group than in the DS group, albeit not statistically significantly so, possibly due to the small size of the study population.

Although early and delayed surgery both appear to be safe and effective, high incidences of failure (>20%), recurrent AC attacks, and readmissions (>30%) should be considered during conservative treatment (2,4,11,14,15). It was reported that the 2-year gallstone-related readmission rate was as high as 38% in patients without cholecystectomy after AC, which is in accordance with the present study's rate of 28% (1,2,10,18). These findings should serve to warn surgeons about future possible problems if they do not perform early definitive treatment for AC. Although early surgery may pose some additional risk for AC patients, these patients might be faced with more risks in the case of gallstone-related complications requiring many interventions.

Bile duct injuries and other surgical complications such as bile leak and bleeding were reported at higher rates when LC was carried out in an acutely inflamed gallbladder (9,13,14,19). However, series from specialized centers

reported very low to zero bile duct injury rates for early laparoscopic treatment of AC (4,8). In a metaanalysis of randomized controlled trials, no significant difference was found with respect to bile duct injury, bile leak requiring ERCP, other surgical complications, and conversion rate (15). Although there were more bile duct injuries and bile leaks requiring ERCP in this analysis, these were all statistically insignificant. Rates of major and minor surgical complications after early and delayed surgery in the present study were the same, but these results were interpreted cautiously because of the small number of the patients in each group. The statistically insignificant high conversion rate for early surgery in this study might be due to the complexity of AC and the experience of the surgical team, but conversion rates in the ES and DS groups were within the accepted ranges reported in the literature (15,17).

Most gallstone-related complications developed during the interval period for delayed surgery, an indicator of the unpredictable course of AC. However, in almost one-fifth of our patients (7 patients among 33), the complications were noted after the interval period. Therefore, we suggest that surgery should not be delayed after the interval period to prevent future gallstone-related complications.

Regarding the timing of surgery in AC, it is accepted that a duration of the symptoms for AC of not more than 72 h is important for the safety of LC with regard to major complications and conversion rates (10–15). Therefore, the day of onset of symptoms was accepted as a reference point in the present study. However, there were also some studies in which early surgery could be performed for AC, regardless of the duration of symptoms and without higher rates of complication or conversion rates. As an explanation for such a policy, there was wide subjectivity and difficulty in determining the exact duration of, the onset of symptoms. Therefore, this issue should be clarified by detailed studies (1,10,11,13).

PC essentially replaces open cholecystectomy, especially for high-risk patients and those who fail to improve under conservative treatment (3,5,8,9,20,21). Generally, age above 70, male sex, and ASA scores of 3 or more are accepted as the factors that predict the need for PC at admission and through the follow-up (3,5,11,13,15). In the present study, the application of PC was required, especially in elderly male patients whose ASA scores and WBC counts were higher, but we could not show any significant difference because of the small number of the patients in the PC group. This approach may be used as a bridge treatment for subsequent delayed surgery with low mortality, or it may be the definitive treatment of gallstone diseases, especially for critically ill patients (9,18,21). With the use of PC, it was reported that relief of sepsis could be achieved in 90% of the patients. However, recurrent cholecystitis attacks might develop after removal of the

catheter in more than half of the patients (9,20). Because of this finding, it was recommended that PC catheters be left in place until the time of operation to prevent recurrence of symptoms (20).

The main limitation of the present study was its retrospective and nonrandomized design. Initial treatment strategy of the patients was determined based on their clinical conditions. A decision for early surgery was made only in suitable cases.

In conclusion, AC should be treated in an appropriate way for each patient. Although surgical treatment of AC, either by early or delayed surgery, has some specific morbidity and mortality, it should be kept in mind that conservative treatment modalities have higher rates of recurrences and subsequent complications, which all cause additional morbidity and mortality for patients. A prospective randomized study is needed in order to specify more objective scientific parameters.

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