Laparoscopic cholecystectomy for management of acute calculous cholecystitis within and after 3 days of symptom beginning: a retrospective study

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Objective
The aim of this study was to evaluate the competency and safety of surgical management of acute calculous cholecystitis (ACC) through laparoscopic cholecystectomy (LC) within and after 72 h of symptom onset. We are reviewing our experience by comparing the outcomes of both ways to carry out an ideal therapeutic strategy used for ACC.

Background
ACC is a very frequent surgical insult. The timing of surgery in the management of such condition is a subject of controversy among all surgeons. In this study, we tried to share in solving this conflict to implement the optimal timing of LC for ACC.

Patients and methods
The study includes 100 patients with ACC, divided according to the timing of LC into group E (50 patients), operated within 72 h of symptom onset and group L (50 patients), operated beyond 72 h of symptom onset. Patients in both groups monitored since admission, during operations, and along the postoperative (PO) period. The data collected include demographic data, clinical data, duration of symptoms before surgery, coexisting disease, laboratory and image results, operative data, PO complications, the length of stay in ICU and the total length of hospitalization.

Results
Fever and Murphy's sign were significantly greater in the early LC group. Initial total bilirubin and blood urea nitrogen are significantly higher (P=0.032 and 0.004, respectively) among the late LC group. The operative time and mean total hospital stay are significantly higher (P=0.005 and 0.010, respectively) in the late LC group compared with the early LC group. The rates of PO bile leakage and port-site infections were higher among patients of late LC group.

Conclusion
Emergent LC is a safe and reliable procedure for ACC within 72 h of symptom onset. Regarding the PO outcomes, financial costs and length of hospital stay, it is more helpful than LC beyond 72 h.

Keywords:
acute calculous cholecystitis, early laparoscopic cholecystectomy, laparoscopic cholecystectomy, late laparoscopic cholecystectomy

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Introduction

Gallstone disease has a prevalence stuck between 10 and 15%, and around 35% of patients develop problems or frequent symptoms in their life [1]. In 20% of cholelithiasis patients, acute calculous cholecystitis (ACC) occur with a wide discrepancy in severity [2]. Despite the high frequency of ACC, still, there is a significant controversy regarding its diagnosis and management [2]. Conservative treatment for ACC was followed by delayed cholecystectomy associated with numerous events [3]. About 20–26% of patients does not respond to medical treatment or develop prompt complications throughout the first admission and necessitate a pressing and technically challenging cholecystectomy [4]. If patients discharged home without operation after ACC, 15–30% were readmitted with recurrent manifestations and underwent an unplanned emergency cholecystectomy; the possibility of gallstone-related events include biliary colic in 70%, biliary tract obstruction occurs in 24%, and pancreatitis in 6% (4). At the times of delayed operation, dense fibrotic adhesions at Calot's triangle make interval laparoscopic cholecystectomy (LC) enormously difficult and risky [5].

According to Tokyo Guidelines 2013 (TG13), stated by the Japanese Society of Hepato-Biliary-Pancreatic

Surgery, the ideal management for ACC is early LC, mainly before 72 h of the symptom onset [6]. Conversely, surgical management for AC after 72 h of onset of symptoms is debatable. Due to the greater operative difficulty for delayed AC, surgery has been advised in an elective setting after 6–8 weeks or more; otherwise, LC can be performed carefully by a professional laparoscopic team [7]. A recent study has shown that emergent LC should be the first choice therapy for AC in patients who are fit for operative intervention; however, there are no report about the time of symptom onset [3]. Till now, few studies have compared the outcomes of LC implemented within and after 72 h of symptom onset [8]. In our present study, we try to evaluate the surgical outcomes of LC for ACC within and after 72 h of symptom onset.

Patients and methods

The current study completed at the General Surgery Department, Banha University Hospital in Egypt and King Saud Hospital in Saudi Arabia since January 2015 till May 2017. The present study includes 100 patients with ACC. After approval of the study protocol by the ethics committee and fully informed written patients' consent was obtained for participation in the study. Patients hospitalized through the emergency unit to the General Surgery Department, High-Dependency Unit or ICU according to the seriousness of patients' general condition at the time of admission.

Patients were admitted for clinical, laboratory, and radiological evaluation. Patients were examined generally besides local abdominal examination. Laboratory tests such as complete blood count, C-reactive protein, blood sugar, kidney function tests, liver enzymes, total and direct bilirubin, alkaline phosphatase and serum amylase were done. Diagnostic imaging was done by means of abdominal ultrasonography and/or computed tomography scans. Magnetic resonance cholangiopancreatography (MRCP) was carried out in selected cases to exclude common bile duct (CBD) stones subsequent to diagnosing ACC.

Preoperative endoscopic retrograde cholangio-pancreatography (ERCP) was done in two patients in group E and five patients in group L due to CBD stone and/or dilatation as revealed by preoperative MRCP. During ERCP, sphincterotomy was done, ballooning of CBD, stone/s extracted, washing of CBD, then leaves a stent for 3 months. In both groups, LC was implemented 1 or 2 days following ERCP.

Diagnosis of AC built on the occurrence of no less than two of the subsequent criteria: an acute pain in the upper abdomen besides the Murphy's sign, high core body temperature (>37.5°C) besides white blood cells (WBC) count more than 10×10^9/l and ultrasonography findings of gallstones as well as thick gallbladder (GB) wall (>4 mm), pericholecystic fluid and positive Murphy's sign on ultrasound probe.

Exclusion criteria in our present study were: patients with no gallstones, former upper abdominal operations, patients who underwent open cholecystectomy, age less than 18 years and more than 70 years, American Society of Anesthesiology (ASA) score more than IV, BMI greater than 35 kg/m^2, low-performance status, participation in an additional drug or device study and inability to offer informed consent. Also, we excluded patients with GB perforation or Mirizzi syndrome (preferred to do open cholecystectomy), patients with GB tumors or cholangitis (typically, to be managed conservatively first) and patients without complete data.

According to TG13 [9], the severity assessment of ACC graded, grade I (mild): AC with mild gallbladder (GB) inflammation with no organ dysfunction in a healthy patient; grade II (moderate): AC with one of the subsequent disorders: WBC count more than 18×10^9/l, tender mass in the right hypochondrium, onset of symptoms more than 72 h, biliary peritonitis, pericholecystic abscess, liver abscess, gangrenous GB or emphysematous GB; and grade III (severe): AC associated with dysfunctions in one of the subsequent systems/organs: neurological deterioration (diminished level of consciousness), cardiovascular impairment (hypotension necessitating dopamine 5 μg/kg/m or any dose of dobutamine); renal impairment (creatinine >2.0 mg/dl, oliguria), respiratory failure (PaO_2/FiO_2 ratio <300), bone marrow dysfunction (platelet count $<100\times10^9$/l), and hepatic function deterioration (international normalized ratio>1.5).

Preoperative assessment and preparation

On admission, all patients received intravenous broad-spectrum antibiotic as soon as the diagnosis of ACC was established. When clinically indicated, a urinary catheter and nasogastric tube were inserted. Our surgical unit's attitudes and practice of timing for cholecystectomy for patients suffering from the ACC was somewhat variable, some units tend to perform LC routinely within 72 h of symptom onset (hospital admission) unless there was a

contraindication for surgery, whereas other units tend to manage ACC conservatively and an appointment given to patients for interval LC within 6–8 weeks after discharge. In the later units, early LC is basically done upon patient's own request, when conservative medical management become unsuccessful (within or after 72 h) and when there is GB gangrene or perforation on the imaging studies.

Surgical procedure: laparoscopic cholecystectomy for acute calculous cholecystitis

Operations implemented by competent and experienced surgeons. Under general anesthesia, pneumoperitoneum created through 1.2 cm incision at the inferior aspect of the umbilicus, using blind puncture with a Veress needle, insufflation of CO_2 commenced up to 15 mmHg pressure. Four ports technique was used: 10 mm umbilical for a 0° scope, 10 mm three fingerbreadths inferior to the xiphoid process for working instruments, 5 mm on the right subcostal margin along the midclavicular line for a grasper, and 5 mm on the right subcostal margin along the anterior axillary line for retraction instruments. The patient's position adjusted to be in a reverse Trendelenburg with the left side down to permit colon and small bowel to drop away from the GB area. Since the GB was frequently distended, the fluid inside it aspired when necessary to allow better grasping. To produce a critical view of safety, the Calot's triangle dissected using a bipolar sealing device or ultrasonic dissection to isolate the cystic artery and cystic duct separately. At that time, both were clipped and divided. The GB separated from its bed with ultrasonic dissection or a monopolar electrocautery hook. To escape CBD injury, a retrograde cholecystectomy accomplished if there were dense adhesions at Calot's triangle. At the end of surgery, GB removed through the subxiphoidal incision, which was widened if needed. Hemostasis of the GB bed, saline lavage was done and then an abdominal drain was placed if indicated and the incisions closed. Conversion to open procedure accomplished through a long right subcostal incision when facing operative difficulties.

Data sheets for patients generated comprised: (a) demographic data; age, sex, BMI, ASA score, coexisting disease, and duration of symptoms up to surgery; (b) clinical data, such as core body temperature, Murphy's sign, and a palpable abdominal mass; (c) laboratory tests such as WBC count, blood urea nitrogen (BUN), international normalized ratio, total/direct bilirubin, alkaline phosphatase, amylase, aspartate transaminase, and alanine transaminase; (d) preoperative radiological findings, including ultrasonography/MRCP as well as ERCP; (e) operative data included the duration of operation, intraoperative bleeding and rate for conversion from LC to open cholecystectomy; (f) postoperative (PO) notes of concern documented regarding PO complications and length of stay. For statistical analysis, the gathered data entered into a database in the form of variables.

Patients categorized according to the timing of LC into two groups. Group E, including 50 patients who underwent LC within 72 h of symptom onset and group L, including 50 patients who underwent LC after 72 h of symptom onset. The analysis of the collected data was planned to compare between both patient groups.

Postoperative care

(1) Most patients shifted postoperatively to ordinary ward beds under close monitoring. However, some patients who were haemodynamically unstable were shifted to ICU.
(2) Patients managed with current enhanced recovery after surgery protocols.
(3) Patients encouraged for quick ambulation.
(4) Close observation of pulmonary function and SpO_2 monitoring.
(5) The intravenous antibiotic was continued for 24 h after surgery.
(6) Deep vein thrombosis (DVT) prophylactic measures (mechanical and chemical) applied according to protocols.
(7) On the first PO day, urine catheter was removed, oral fluid and soft fat-free diet were allowed.
(8) Drains were removed on the second PO day or when it became minimal (<50 ml in 24 h).
(9) Patients discharged home by the second PO day with advice to keep on a fat-free diet for 3 months at least.
(10) Outpatient clinic follow-up every week after discharge and sustained until patients became fully improved and had no more PO complaints.

Statistical analysis

Data presented as mean±SD, ranges, numbers, and ratios. Results were analyzed using Wilcoxon's ranked test for unrelated data (Z-test) and χ^2-test for numerical data. Statistical analysis conducted using the SPSS (version 21) for Windows statistical package (IBM Corp., Armonk, NY, USA). The P value less than 0.05 was considered as statistically significant.

Results

The study contained 100 patients with ACC, divided into two equal groups (50 patients in each group) according to the timing between the symptom onset and LC. Group E, for LC within 72 h and group L, for LC beyond 72 h of symptom onset.

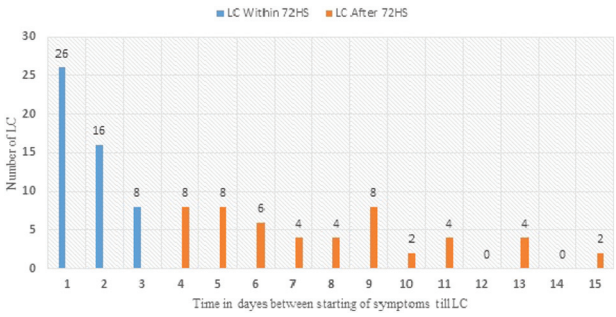
No difference regarding age, sex, ASA score or BMI between patients of both groups. Basic findings of clinical examination and medical history were nearly similar as well among both groups. However, the mean core body temperature and the positive Murphy's sign were significantly greater in group E compared with group L. Preoperative demographic and clinical data are clearly mentioned in Table 1.

In the early LC group, more than 50% of operations were performed within 24 h of symptom onset, whereas 32 and 16% of LC were done in the second and third days, respectively. On the other hand, 52% of LC in the delayed group were done between the fourth and seventh days of symptom onset and the remaining 48% were implemented in the subsequent week (Fig. 1).

Initial preoperative serum total bilirubin and BUN were significantly higher among patients of group L than patients of group E (P=0.032 and 0.004, respectively). However, there were no significant differences between both groups regarding other initial laboratory or radiological investigations. Preoperative ERCP was done in two patients in group E and five patients in group L. Preoperative laboratory and radiological data are summarized in Table 2.

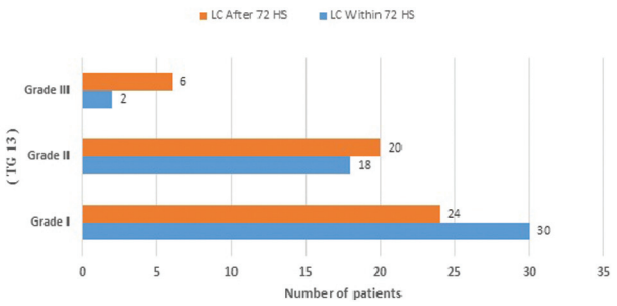
According to Tokyo Severity Grading (TG13) of ACC, GB was mildly inflamed in around 50% of patients in both groups. However, in 40% of group E and 36% of group L, the GB was moderately inflamed. A little percentage of patients in both groups suffered severe ACC, 4% in group E and 12% in group L (Fig. 2).

Figure 1



Distribution of cases, according to the time between starting of symptoms till laparoscopic cholecystectomy. LC, laparoscopic cholecystectomy.

Figure 2



Distribution of patients, according to Tokyo severity grading (TG13). LC, laparoscopic cholecystectomy.

Table 1 Patients' demographic and preoperative clinical data

Data	Group E	Group L	*P* value
N=100 [*n* (%)]	50 (50)	50 (50)	
Age (years)	40.44±13.66 (23–65)	41.2±13.96 (20–64)	0.689
Sex			
Males	22 (44)	20 (40)	NS
Females	28 (56)	24 (60)	NS
BMI (kg/m^2)	31.36±2.64 (26–35)	31.08±2.19 (28–35)	0.719
ASA score	1.72±0.74 (1–3)	1.96±0.73 (1–3)	0.440
Fever	38.25±0.63 (37.5–39.8)	37.46±0.47 (37.7–38.5)	0.016
Palpable tender mass	8 (16)	18(36)	0.002
Murphy's sign (+)	48 (96)	42 (84)	0.018
Coexisting disease[a]			
Diabetes mellitus	10 (20)	12 (24)	NS
Ischemic heart disease	2 (4)	4 (8)	NS
Hypertension	5 (10)	6 (12)	NS
COPD	3 (6)	4 (8)	NS
Renal impairment	1 (2)	3 (6)	NS

Data are presented as mean±SD and numbers; ranges and percentages are in parentheses. ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease. [a]Some cases had more than one coexisting disease.

In both groups, the majority of patients passed the operations smoothly without major intraoperative complications. The operative time in the delayed LC group was significantly higher (P=0.005) compared with the early LC group; however, there was a no significant difference between both groups regarding intraoperative complications, conversion rate, drain insertion rate, or ICU admission days. The mean total hospital stay was significantly higher (P=0.010) between patients of delayed LC group compared with the early LC group (Table 3).

Two patients of each group experienced PO bleeding (coming through the abdominal drain) ranging between 150 and 440 ml over the first 3 PO days and bleeding was managed conservatively. One patient from the delayed group suffered PO biliary leakage through the drain ranged between 10 and 110 ml/day over the first 5 PO days. On the sixth PO day, bile leakage stopped completely, abdominal ultrasonography was done and revealed no free fluid in Morison's pouch and laboratory results were normal, then the drain was removed. Hospital-acquired respiratory tract infection was recorded in two patients of group E and three patients of group L. In spite of applying DVT prophylactic measures, one patient of the late LC group suffered PO DVT in her left leg on the fourth PO day and managed with a therapeutic dose of subcutaneous clexane (Fig. 3).

Discussion

The most common infectious disease of the GB is the ACC. It is initiated by three chief mechanisms: cystic duct obstruction by gallstones, lysolecithin release, or ascending bacterial infection [9]. Formerly, the ideal time intended for LC for patients with ACC was 6–8 weeks after clinical improvement of acute inflammatory attack to permit the improvement of the acute phase reaction of the GB [10]. Conversely, in recent years, numerous studies have verified that early LC for ACC is harmless with morbidity and

Table 2 Patients' preoperative laboratory and radiological data

Data (NR)	Group E	Group L	*P* value
WBCs (4–11×10^9/l)	18.67±5.64 (12.9–34.2×10^9/l)	15.73±3.52 (11.5–2.6×10^9/l)	0.632
ALT (0–41 U/l)	42.69±14.8 (23–88)	60.52±27.2 (26–142)	0.053
AST (0–40 U/l)	38.72±24.5 (12–92)	42.28±24.1 (16–135)	0.262
Total bilirubin (<1.4 mg/dl)	1.76±0.74 (1–3.4)	1.9±1.1 (1–5.2)	0.032
Direct bilirubin (<0.2 mg/dl)	1.18±0.82 (0.1–2.8)	1.7±1.05 (0.3–4.5)	0.280
ALP (40–130 U/l)	90.9±68.7 (41–320)	116.9±85.4 (30–412)	0.492
Amylase (28–100 U/l)	127.9±97.6 (30–425)	126.8±117.4 (30–512)	0.423
BUN (10–20 mg/dl)	17.08±6.34 (10–31)	19.36±6.10 (11–31)	0.004
INR (0.8–1.1)	1.12±0.16 (1.1–1.5)	1.26±0.24 (1–1.9)	0.183
MRCP/ultrasonography findings			
Gallstones	50 (100)	50 (100)	
Thick-wall gallbladder	42 (84)	44 (88)	0.846
Pericholecystic fluid	34 (68)	30 (60)	0.840
CBD dilatation	4 (8)	8 (16)	0.676
Preoperative ERCP	4 (8)	10 (20)	0.002

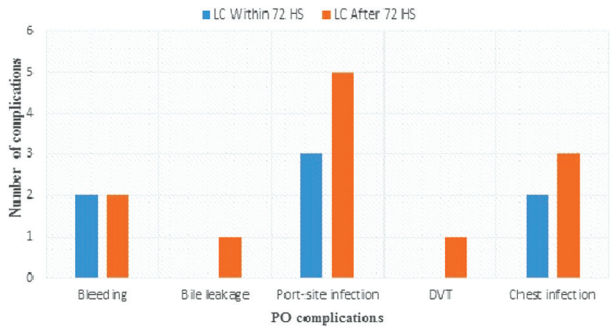
Data are presented as mean±SD and numbers; ranges and percentages are in parentheses. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; INR, international normalized ratio; MRCP, magnetic resonance cholangiopancreatography; NR, normal range; WBC, white blood cells.

Table 3 Operative and postoperative data

Data	Group E (*n*=50)	Group L (*n*=50)	*P* value
Operative time (min)	85.1±25.08 (45–125)	110.4±21.4 (75–160)	0.005
Intraoperative complications			
Blood loss	83.8±8.9 (10–210)	90.4±46.3 (20–200)	0.026
Biliary tract injury	0.0	1 (2)	NS
Conversion to an open procedure	1 (2)	3 (6)	0.739
Drain			
n (%)	29 (58)	35 (70)	0.764
Duration	1.48±2.9 (1–4)	1.84±0.3 (1–5)	0.001
ICU admission (days)	0.36±0.9 (1–3)	0.56±1.6 (1–4)	0.831
Total hospital stay (days)	5.24±1.66 (3–10)	9.6±3.69 (6–21)	0.010

Data are presented as mean±SD and numbers; ranges and percentages are in parentheses.

Figure 3



Postoperative 30 days complications. PO, postoperative.

mortality resembling those of LC in a delayed elective setting [11]. Ohta *et al.* [12], in a retrospective study, compared four timing groups of LC for management of ACC (within 72 h, 4–14 days, 3–6 weeks, and after 6 weeks subsequent to symptom onset), they found that the ideal timing is less than or equal to 72 h, compared with LC implemented later. According to the TG13 which is summarized by Yamashita *et al.* [6], management of ACC depend on the severity of the disease. Early LC soon after admission (within 72 h) for grade I (mild) and grade II (moderate) ACC. However, for grade III (severe) ACC, urgent management of system/organ dysfunction and GB drainage for control of severe local inflammation followed by delayed elective LC [6].

There is no doubt that the reduction of operative times and amounts of blood loss would participate in patient safety and improves the overall outcomes. In our study, operative time and the total amount of intraoperative blood loss were significantly higher (P=0.005 and 0.026, respectively) in the delayed LC group compared with the early LC group. Besides, the conversion rate and intraoperative complications in the delayed LC group were higher than the early LC group. This confirms the more safety of early LC for ACC (within 72 h) than beyond 72 h of symptom onset. The shorter operative time in early LC can be explained by the truth that inflammation accompanying AC makes an edematous plane nearby the GB, thus smoothing its dissection during operation. While in delayed operations, progress of the inflammation, and hence organization of the firm adhesions, result in scarring and contraction, making the GB cemented with the adjacent structures with distortion of normal anatomy leading to operative difficulty and inability to generate a critical view of safety. These findings go with Shunsuke *et al.* [13], who concluded from their study in comparison of early LC and late LC, that late LC was accompanied with longer operation time, more blood loss, more biliary injury, and greater conversion rate compared with early LC. However, their patients who underwent late LC had satisfactory surgical outcomes [13]. On the other hand, Alper *et al.* [14] found that although the operative time in early LC can be longer, there was no significant difference between the early and delayed LC groups regarding rates for conversion to open cholecystectomy and operation time. Also, the incidence of serious intraoperative complications was analogous to the delayed LC. However, they concluded that early LC still looks more advantageous than late intervention [14].

In our study, there were no noteworthy differences regarding the PO morbidities in both groups. However, the total PO complications (hemorrhage, bile leak, chest infections, DVT, and surgical site infections) were higher in the delayed LC group compared with early LC group (12 vs 7, respectively). On the reverse, Zafar *et al.* [15] found that PO complications were more frequent with early LC than delayed LC and they attributed this to the initially significant greater body temperatures and serum levels of conjugated bilirubin in the early LC group which were the only significant preoperative differences between both patient groups in their study. On the other hand, de Mestral *et al.* [16] agree with us in the same results and found that PO complications were significantly higher among patients of emergent early LC compared with late LC group.

In our present work, we found that the total hospital stay was significantly lower in early LC than delayed LC (P=0010). By the way, the short hospitalization will affect positively on the patient's PO quality of life (QOL). This goes with Zhu *et al.* [8] who mentioned that a recent survey assessing surgical approaches for management of acute cholecystitis (AC), total hospital stay was established to be shorter for a group of patients who underwent early (emergency) cholecystectomy at the time of the first admission compared with patients who had delayed elective cholecystectomy. Similar to the results of our present study and the above clinical studies, Samraj *et al.* [17] found that duration of hospital stay was significantly shorter and management-related costs were lesser with early LC compared with delayed LC for ACC. Along with the clinical studies, the meta-analyses of randomized clinical trials in the literature revealed that early LC (24–72 h of disease onset) offers advantages over delayed LC (beyond 72 h of disease onset) in the form of lesser total hospital stay, lower conversion rates, and fewer PO complications [18]. Siddiqui *et al.* [19] analyzed four clinical studies

comprising 375 patients of ACC who were managed at different periods following disease onset and found a shorter hospital stay in early LC. In a best-evidence subject that investigated 92 papers (retrospective cohort studies, meta-analyses, prospective controlled study, and randomized control trials), it was established that early LC for ACC is advantageous regarding the length of hospital stay without rises in morbidity or mortality [18]. Some recent studies have investigated the financial costs of early compared with delayed LC in the management of ACC. Masayuki *et al.* [20] mentioned that early LC is less pricey with superior outcomes regarding the QOL. An additional study from Canada established the better patient QOL and considerable cost savings with early LC. In our present study, due to a shorter duration of total hospital stay and near absence of conservative treatment in early LC, we conclude that management-related expenses were lesser in the early LC group [21]. According to Ansaloni *et al.* [22], the Scientific Board of the 2nd World Congress of the World Society of Emergency Surgery on August 2013, depending on the evidence involved in the guidelines, it can be specified that early LC is the best management method for ACC. However, the surgical therapy of ACC is limited to patients who are in good condition for urgent surgery. In cases of patients not fit for urgent LC (grade III according to TG13), World Society of Emergency Surgery agree with TG13 in management procedures which have been mentioned before [22].

We cannot deny that the current study had some restrictions regarding the small sample size and cost analysis was not based on a systematic decision model. However, the results of this study should offer a source for large-scale clinical studies and additional cost analysis matching early versus delayed LC for ACC, which is one of the most common procedures in surgical practice.

Conclusion

Emergent LC is a safe and a reliable management procedure for ACC within 72 h of symptoms onset. It was established that it is more advantageous than delayed LC (beyond 72 h) in terms of patient safety, financial costs, and length of hospital stay without rises in morbidity or mortality.

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Conflicts of interest
There are no conflicts of interest.

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