Prolonged versus delayed laparoscopic cholecystectomy for acute cholecystitis: Time to change the concept – A multicenter randomized controlled trial

Mohammed A. Omar[a*], Alaa A. Redwan[b], Ayman Kamal[c]
[a] General Surgery Department, Faculty of Medicine, South Valley University, Qena, Egypt
[b] General Surgery Department, Faculty of Medicine, Sohag University, Sohag, Egypt
[c] General Surgery Department, Faculty of Medicine, Helwan University, Helwan, Egypt

Abstract

Background: Laparoscopic cholecystectomy (LC) is the standard treatment for acute cholecystitis (AC) and is recommended within 72 hours (early LC, ELC) or six weeks (delayed LC, DLC) of symptom onset. Unfortunately, most patients presented after the 72 hours and refused initial conservative treatment until DLC. Evidence regarding LC beyond 72 hours (prolonged LC, PLC) is still insufficient.
Objectives: This study aimed to compare the outcomes of PLC and DLC in patients with AC 72 hours.
Patients and Methods: This trial included all patients treated with LC for AC after 72 hours of symptom onset. The patients were randomly divided into two groups according to the time of LC. After admission, PLC was performed as soon as possible, and DLC was postponed for at least six weeks after the initial conservative treatment.
Results: 354 patients were randomized into two groups. The overall morbidity was significantly lower in the PLC group. The mean length of the total hospital stays and duration of total antibiotic therapy was significantly shorter in the PLC group. The median total cost was significantly lower in the PLC group. In addition, PLC significantly promoted the early return to work. However, the mean operative time was significantly shorter in the DLC group. The groups had no significant differences in the conversion rate or complications.
Conclusions: PLC for AC after 72 hours of symptom onset is safe and associated with lower overall morbidity, shorter total hospital stay, shorter total antibiotic duration, reduced total cost, and fewer lost workdays than DLC.
Keywords: Acute cholecystitis; Prolonged laparoscopic cholecystectomy; Delayed laparoscopic cholecystectomy; 72 hours of symptom onset.

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***Correspondence:** mohamed_ali@med.svu.edu.eg
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Introduction

Gallbladder stone affects 10-15% of the adult population, and approximately 15-25% of these patients present with acute cholecystitis (AC) **(Okamoto et al., 2018).** Laparoscopic cholecystectomy (LC) is the treatment of choice for patients with AC **(Loozen et al., 2018; Okamoto et al., 2018).** However, there is a controversial debate regarding optimal timing **(Roulin et al., 2016; Bundgaard et al., 2021).**

Early laparoscopic cholecystectomy (ELC) is recommended for patients presented within 72 hours of symptom onset **(Miura et al., 2013; Okamoto et al., 2018; Pisano et al., 2020),** whereas initial conservative treatment followed by planned delayed laparoscopic cholecystectomy (DLC) after at least six weeks of symptom onset is recommended for patients who presented after 72-hours of symptom onset **(Okamoto et al., 2018).** ELC might be associated with significantly reducing morbidity and mortality rates, comparable conversion rates, shorter hospital stays, lower costs, and higher patient satisfaction than DLC **(Gutt et al., 2013; Wu et al., 2015; Roulin et al., 2016; Okamoto et al., 2018).**

Unfortunately, surgeons almost always encounter patients with AC after 72 hours of symptom onset because of patient and/or physician delay, and these patients usually consistently refuse conservative treatment and postpone LC **(Zhu et al., 2012; Cheng et al., 2021).** Additionally, 15-25% of these patients do not respond to conservative treatment and still need emergency cholecystectomy, whereas another 25-30% of these patients require re-hospitalization for recurrent attacks of AC or biliary-related complications such as biliary colic, acute biliary pancreatitis, acute cholangitis, and/or biliary obstruction during the interval waiting for DLC **(Zhu et al., 2012; Roulin et al., 2016; Okamoto et al., 2018),** which leads to higher total costs and more lost days of work **(Degrate et al., 2013; Gomes et al., 2013; Lucocq et al., 2022).** Moreover, chronic cholecystitis with adhesions, fibrosis, and anatomical distortion may lead to difficult dissection in DLC **(Cheruvu and Eyre-Brook 2002).** All studies focused on ELC and DLC and neglected the optimal treatment of the preceding group of patients (after 72 hours) with preexisting conditions, although they represent a significant proportion **(Zhu et al., 2012; Degrate et al., 2013; Gomes et al., 2013; Roulin et al., 2016).**

LC for AC after the theoretical optimal 72 hours from symptom onset (Prolonged LC, PLC) is thought to be more technically challenging and dangerous because of the distorted anatomy and altered pathology, where early edematous cholecystitis (first 2 to 3 days) progresses to suppurative and necrotizing cholecystitis (> 4 days), and this may be associated with increased perioperative complications and conversion rate **(Hadad et al., 2007; Kimura et al., 2007; Gonzalez-Rodriguez et al., 2009).** Therefore, many surgeons prefer the old policy of a cooling-off period before cholecystectomy **(Cheruvu and Eyre-Brook 2002).** In contrast, others believe that hyperemia and edema may help in dissection **(Gomes et al., 2013).**

The revised Tokyo Guidelines 2018 **(Okamoto et al., 2018)** recommended ELC for AC regardless of the duration of symptoms. The Danish National Board of Health 2019 **(Ainsworth 2019)** recommended both ELC and DLC when symptoms appeared more than three days ago. In addition, a few studies have shown that LC for AC can be performed safely after 72 hours of symptom onset **(Degrate et al., 2013; Gomes et al., 2013; Roulin et al., 2016).** We believe that more clinical trials are needed to evaluate the optimal treatment of AC after 72 hours of symptom onset. This randomized trial aimed to compare the outcomes of prolonged and delayed LC in patients with AC after 72 hours of symptom onset.

Patients and methods

Study design

This study was a multicenter, parallel-group, open-label, with equal randomization (1:1), randomized controlled trial (RCT). This study was approved by the Institutional Ethics Committee of the Qena Faculty of Medicine, South Valley University, Egypt (ID: SVU/MED/SUR011/4/23/4/611). This study was conducted per the Declaration of Helsinki, and the results were reported per the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines **(Schulz et al., 2010).** This trial was registered in the ClinicalTrials.gov database (ID: NCT05736003). Written informed consent was obtained from all patients before enrollment.

Study participants

This study included all consecutive patients who underwent LC for AC between January 2019 and December 2022 at three tertiary centers in Egypt. The inclusion criteria were patients diagnosed with the first attack of AC after 72 hours of symptom onset, American Society of Anesthesiologists (ASA) scores of I-III, and those aged 20-70 years. Patients with a common bile duct stone/s, acute biliary pancreatitis, cholangitis, perforated gallbladder, biliary peritonitis, pregnancy, or a previous upper abdominal surgery were excluded.

Sample size and randomization

We calculated the sample size with https://clincalc.com/Stats/SampleSize.aspx, with an estimated overall morbidity rate (15% vs. 34%) with a power of 90%, a reliability of 0.05, and an estimated 5% loss to follow-up. Randomization was performed by nurses who were not involved in the study. The nurses randomly assigned the patients to either the PLC or DLC group by opening a sealed opaque envelope from an opaque box containing the given group's information (designated as PLC or DLC). All envelopes were prepared at a 1:1 ratio, carefully jumbled, and placed in a box. Blinding was not performed (Fig. 1).

Preoperative assessment

AC was diagnosed according to the Tokyo Guidelines 2018 (TG18) criteria **(Okamoto et al., 2018)**, i.e., one local sign of inflammation (Murphy's sign or right upper quadrant pain/tenderness/mass), one systemic sign of inflammation (temperature > 38 °C, leukocytosis > 18,000 mm^3, or C-reactive protein (CRP) > 5 mg/L), and an affirmative radiological criterion of AC (gallbladder stone or debris, thickened gallbladder wall ≥ 4 mm, pericholecystic fluid, sonographic positive Murphy's sign, and no evidence of a dilated ductal system). Laboratory tests included complete blood count, random blood sugar, coagulation profile, renal function tests, liver function tests, serum amylase, CRP, and serological markers. Radiological evaluations included abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) performed by expert radiologists. AC severity was graded as mild, moderate, or severe according to TG18 **(Okamoto et al., 2018)**.

In both groups, medical therapy in the form of intravenous antibiotics, analgesics, and fluids was administered once the diagnosis was confirmed. The recommended antibiotics are third-generation cephalosporins and metronidazole. In the PLC group, LC was performed on the index hospital admission within a maximum of 24 hours of admission. In contrast, in the DLC group, patients were treated conservatively and discharged once the symptoms were controlled with a switch from intravenous to oral medications for 10 days. For these patients, readmission for LC was planned for at least 6 weeks after symptom onset. In cases of failure of conservative treatment, urgent LC was performed. In cases of recurrent AC attacks while waiting for DLC, a second trial of conservative treatment was proposed, and urgent LC was completed if it failed.

Operative procedure

Consultant surgeons performed all surgeries with at least 10 years of experience in LC. LC was performed according to the SAGES Safe Cholecystectomy Program. LC was performed using the 3-ports technique, and an additional fourth or fifth port was used in complex cases. The pathological findings of simple, phlegmonous, or gangrenous cholecystitis were recorded according to the surgeon's judgment. The adhesion score was evaluated according to **Nair et al. (1974),** whereas LC difficulty was graded according to the Nassar scale **(Nassar et al., 1995).** Needle aspiration and decompression of the distended gallbladder were performed, and a sample for culture sensitivity was obtained. Intraoperative cholangiography (IOC) was conducted in the selected patients. Subtotal cholecystectomy was performed with dense adhesions and difficult Calot's triangle dissection. The surgeons decided to convert to open cholecystectomy. The gallbladder was removed through the epigastric port using an endoscopic bag. A subhepatic drain was placed only selectively. All specimens were subjected to histopathological examination.

Postoperative assessment

Oral fluids were administered as tolerated. All patients received 3rd generation cephalosporin until culture sensitivity appeared for 5-7 days postoperatively. The subhepatic drain was removed in the absence of discharge. The patient was discharged once oral fluid was tolerated and the pain was controlled with oral analgesia.

Outcomes

The primary outcome was overall morbidity. The secondary outcomes were the conversion rate, operative time, morbidity, mortality, total hospital stay length, duration of antibiotic therapy, total cost, and number of lost work days. Complications were any undesired events during or within 30 days of the surgery. Complications were graded according to the Clavien-Dindo scoring system (CDS) **(Dindo et al., 2004).** The overall morbidity included the failure of initial conservative treatment, emergency consultation, unplanned hospital readmission, subtotal cholecystectomy, and intra- and postoperative complications. Failure of the initial conservative treatment for patients with DLC was defined as the need to proceed to urgent LC. The surgical hospital stay was from the day of admission to the day of discharge after surgery, and the medical hospital stay was defined as the duration of the initial conservative treatment or unplanned hospital readmission for patients with DLC. The total length of hospital stay included surgical and medical hospital stays. The surgical cost is the cost of the surgery and postoperative medical treatment. The medical costs included the costs of preoperative medical therapy, emergency consultation, and unplanned readmission. The total cost includes the surgical and medical costs. The costs were calculated in Egyptian Pounds (EGP) and converted into dollars (USD) at an exchange rate of 1 USD=15 EGP.

Follow-up: The patients were followed-up for 30 days postoperatively.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 26.0, Inc., Chicago, IL, USA). Normally distributed data were confirmed using the Shapiro-Wilk test. Categorical variables are expressed as frequencies (n) and percentages (%) and were compared using the chi-square test. Normally distributed variables are expressed as mean ± standard deviation (SD) and were compared using Student's t-test. Non-normally distributed variables are expressed as the median and interquartile range (IQR, Q1-Q3) and were compared using the Mann-Whitney U test. Statistical significance was determined at a *p*-value ≤ 0.05.

Results

Patient flow: Between January 2019 and December 2022, 437 consecutive AC patients were assessed for eligibility. After applying the exclusion criteria, 354 patients were randomly assigned to the PLC or DLC group (n=177). In the PLC group, five patients failed to undergo surgery, whereas in the DLC group, 41 patients failed to undergo delayed surgery. Based on this surgical failure, all parameters were analyzed based on intention-to-treat (n=354), except for operative parameters, which were analyzed based on a modified intention-to-treat (n=308) (**Fig. 1**).

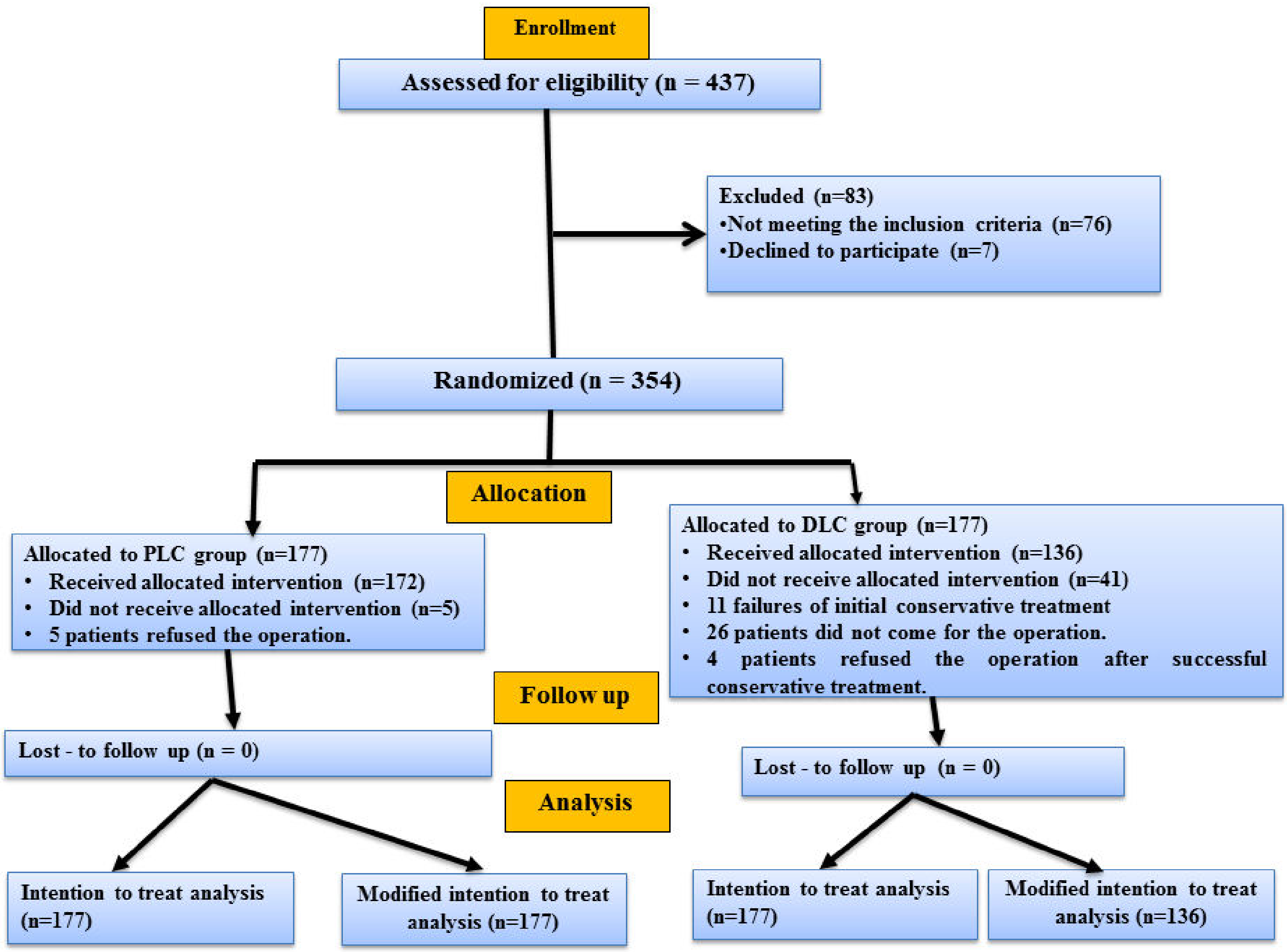

Fig.1. Consort flow diagram.

There were no significant differences in patient demographics or clinical characteristics between the two groups at first hospital admission, (**Table. 1**). The median times from symptom onset to LC were 6 and 115 days in the PLC and DLC groups, respectively ($P < 0.001$). Overall, 184 patients (59.7%) underwent a four-port laparoscopic approach (75% vs. 40.4%), and 124 patients (40.3%) underwent surgery using a three-port technique (25% vs. 59.6%) ($P < 0.01$). Clinically, in the PLC group, the majority (68.6%) of the patients had phlegmonous cholecystitis, whereas, in the DLC group, the majority (77.9%) had simple cholecystitis ($P < 0.001$). The PLC group had significantly more adhesions and a more difficult LC than the DLC group ($P = 0.01$). The median operative time was significantly longer in the PLC group (110 vs. 87 min, $P < 0.001$). Acute cholecystitis was the most common histological diagnosis (58.7%) in the PLC group, whereas chronic cholecystitis was the most common histological diagnosis (77.9%) in the DLC group ($P < 0.01$). The median surgical hospital stay was significantly longer in the PLC group (3 vs. 2 days, $P < 0.01$), (**Table.2**).

Table 1. Patients demographics and clinical characteristics at first hospital admission

Variables	**PLC (n=177)**	**DLC (n=177)**	***P*-value**
Age (years) [1]	46.4 ± 7.8	47.2 ± 8.2	0.456
Sex (Female) [2]	102 (57.6)	98 (55.4)	0.69
BMI (Kg/m^2) [3]	27 (25-28)	27 (25-28)	0.746
ASA score [2]			0.545
I	118 (66.7)	123 (69.5)	
II	46 (26)	42 (23.7)	
III	13 (7.3)	12 (6.8)	
History of abdominal surgery [2]	66 (37.3)	75 (42.4)	0.761
Severity grade of TG18 [2]			0.1
II (moderate)	167 (94.4)	169 (95.5)	
III (severe)	10 (5.6)	8 (4.5)	
Laboratory findings			
WBC (10^3 ml) [3]	11.3 (7.2-14.9)	12.1 (8.3-16.1)	0.21
CRP (mg/dL) [3]	15.2 (4.6-26.3)	19.3 (9.6-27.8)	0.63
Bilirubin (mg/dL) [3]	1.4 (0.7-1.9)	1.7 (0.0-2.8)	0.09
Amylase (U/L) [1]	52.5 ± 18.9	49.7 ± 15.7	0.51
Charlson Comorbidity Index [3]	0 (0–1)	0 (0–1)	0.83
Smoking [2]	35 (19.8)	41 (23.2)	0.43

PLC: Prolonged Laparoscopic Cholecystectomy, DLC: Delayed Laparoscopic Cholecystectomy, BMI: Body Mass Index, ASA: American Society of Anesthesiologists, TG18: Tokyo Guidelines 2018, WBC: White Blood Count, CRP: C Reactive Protein.
[1] Mean ± SD, [2] n (%), [3] Median (Q1-Q3)

Selective IOC was performed in 12 patients (3.9%) because of suspected bile duct injuries or stones. Four cholangiograms revealed common bile duct stones, and the patients were managed by stone extraction with intraoperative ERCP; three revealed partial CBD injury, and intraoperative ERCP and stenting managed the patients, and five were normal. The overall incidence of conversion to open cholecystectomy was 3.2%. The causes of conversion were the failure of Calot's triangle dissection due to severe adhesions and inflammation (n=5), suspected common bile duct injury (n=2), severe bleeding (n=1) in the PLC group, and severe adhesion to the duodenum and suspicion of intestinal injury (n=1), and suspected common bile duct injury (n=1) in the DLC group. There were no significant differences in IOC, conversion rate, blood loss and transfusion, gallbladder perforation, abdominal drainage, complications, postoperative intervention, surgical costs, and postoperative antibiotic duration, **(Table.2)**.

Table 2. Operative characteristics

Variables	**PLC (n=172)**	**DLC (n=136)**	***P*-value**
Time from the onset of symptoms to operation (days)[1]	6 (5-7)	115 (78-166.5)	**0.001**
Number of ports [2]			**0.01**
Three	43 (25)	81 (59.6)	
Four	129 (75)	55 (40.4)	
Clinical pathological diagnosis [2]			**0.001**
Simple	52 (30.2)	106 (77.9)	
Phlegmonous	118 (68.6)	30 (22.1)	
Gangrenous	2 (1.2)	0 (0)	
IOC [2]	9 (5.2)	3 (2.2)	0.19
Conversion to open cholecystectomy [2]	8 (4.7)	2 (1.5)	0.071
Blood loss (ml) [2]			0.493
< 400 ml	170 (98.8)	134 (98.5)	
> 400 ml	2 (1.2)	2 (1.5)	
Blood transfusion (unit) [2]	2 (1.2)	2 (1.5)	0.245
Adhesion scores [2]			**0.01**
Mild (grade 0-1)	68 (39.5)	111 (81.6)	
Moderate (grade 2-3)	101 (58.7)	22 (16.2)	
Severe (grade 4)	3 (1.8)	3 (2.2)	
The difficulty of cholecystectomy [2]			**0.01**
Grade 1	5 (2.9)	28 (20.6)	
Grade 2	48 (27.9)	65 (47.8)	
Grade 3	105 (61)	41 (30.1)	
Grade 4	14 (8.2)	2 (1.5)	
Gallbladder perforation [2]	3 (1.7)	2 (1.5)	0.67
Abdominal drain [2]	141 (82)	73 (53.7)	0.09
Operative time (min) [1]	110 (96-125)	87 (74-95)	**0.001**
Histological diagnosis [2]			**0.01**
Acute cholecystitis	101 (58.7)	0 (0)	
Acute on top of chronic cholecystitis	58 (33.7)	30 (22.1)	
Chronic cholecystitis	13 (7.6)	106 (77.9)	
Complications [2]	18 (10.5)	8 (5.9)	0.231
Grade I	7 (4.1)	3 (2.2)	
Grade II	6 (3.5)	3 (2.2)	
Grade III a/b	5 (2.9)	2 (1.5)	
Grade IV a/b	0 (0)	0 (0)	
Grade V	0 (0)	0 (0)	
Postoperative intervention [2]	3 (1.7)	1 (0.7)	0.61
Surgical hospital stays [1]	3 (2-3)	2 (1-2)	**0.01**
Surgical cost (USD) [1]	1000 (1000-1200)	1000 (1000-1000)	0.1
Postoperative antibiotic duration (d) [1]	7 (5-8)	7 (6-8)	0.76

PLC: Prolonged Laparoscopic Cholecystectomy, DLC: Delayed Laparoscopic Cholecystectomy, IOC: Intra-Operative Cholangiogram, USD: United States dollar.
[1] Median (Q1-Q3), [2] n (%).

The Overall morbidity was significantly reduced in PLC [20 (11.3 %) vs. 52 (29.4%) patients, $P < 0.001$]. Two patients underwent subtotal cholecystectomy in the PLC group due to severe adhesions and inflammation, and 18 patients developed complications. In the DLC group, 11 patients (6.2%) failed to improve with the initial conservative treatment. They were treated with emergency interval LC, and 33 patients (18.6%) were re-evaluated in the emergency room for biliary colic (11 patients, 6.2%), recurrent attacks of AC (13 patients, 7.3%), and biliary-related complications (9 patients, 5.1%) before the planned secondary hospitalization. Patients with biliary colic were treated medically as outpatients, whereas others were readmitted. In total, 13 patients were readmitted with another AC attack and treated medically; five were readmitted with calcular obstructive jaundice and ERCP; and four were readmitted with acute biliary pancreatitis and treated medically. The median total hospital stay (3 vs. 7 days, $P < 0.001$), the median total antibiotic duration (7 vs. 19 days, $P < 0.001$), and the median number of admissions (1 vs. 2, $P < 0.001$) were significantly lower in the PLC group, and this was reflected on significantly lower median total cost (1350 vs. 2000 USD, $P < 0.001$). PLC was significantly associated with a decreased median number of lost work days (15 vs. 22 days, $P < 0.001$),(**Table.3**).

Table 3: Primary and secondary outcomes

Variable	PLC (n=177)	DLC (n=177)	P-value
Overall morbidity [1]	20 (11.3)	52 (29.4)	**0.001**
Failure of initial conservative treatment	0 (0)	11 (6.2)	
Emergency consultation	0 (0)	11 (6.2)	
Unplanned readmission	0 (0)	22 (12.4)	
Subtotal cholecystectomy	2 (1.1)	0 (0)	
Complications	18 (10.2)	8 (4.5)	
Hospital stays (d) [2]			
Medical hospital stay	0 (0-0)	5 (5-7)	**0.0001**
Total hospital stay	3 (2-3)	7 (6-8)	**0.001**
Antibiotic therapy duration (d) [2]			
Preoperative antibiotic duration	1 (1-1)	10 (8-10)	**0.0001**
Total antibiotic duration	7 (5-8)	19 (13-25)	**0.001**
Number of hospital admissions [2]	1 (1-1)	2 (2-3)	**0.001**
Total ICU admission [1]	3 (1.7)	2 (1.1)	0.12
Cost (USD) [2]			
Medical cost	300 (300-350)	1000 (850- 1200)	**0.0001**
Total cost	1350 (1200-1450)	2000 (1900-2200)	**0.001**
Total lost days of work [2]	15 (12-15)	22 (19-27)	**0.001**

PLC: Prolonged Laparoscopic Cholecystectomy, DLC: Delayed Laparoscopic Cholecystectomy, ICU: Intensive care Unit, USD: United States dollar, ICU: Intensive care Unit.
[1] n (%), [2] Median (Q1-Q3),

Discussion

This study assessed the impact of LC timing on the overall morbidity of AC after 72 hours of symptom onset. PLC significantly reduced the overall morbidity, total hospital stay, antibiotic duration, hospital admissions, total cost, and total number of lost work days. DLC was significantly associated with fewer ports, ease of dissection, fewer adhesions, and reduced operative time.

Most previously published studies **(Gutt et al., 2013; Miura et al., 2013; Wu et al., 2015; Loozen et al., 2018; Okamoto et al., 2018; Pisano et al., 2020)** have recommended ELC for treating AC within 72 hours of symptom onset. ELC might be associated with a significant reduction in morbidity and mortality rates, comparable conversion rates, shorter overall hospitalization, lower overall cost, and higher patient satisfaction than DLC **(Degrate et al., 2013; Wu et al., 2015; Roulin et al., 2016; Okamoto et al., 2018; Bundgaard et al., 2021; Lucocq et al., 2022).**

DLC after at least six weeks of initial successful conservative treatment is recommended for patients presenting after 72 hours of symptom onset **(Okamoto et al., 2018).** Unfortunately, data revealed that 20-25% of these patients have a potential risk of failed initial conservative treatment, recurrent attacks of AC in those who had initial successful conservative treatment, or development of biliary-related complications before the elective procedure, which may require emergency interval surgery, medical consultation, or hospital readmission **(Lee et al., 2008; Gurusamy et al., 2010; Lucocq et al., 2022).** Moreover, half of the patients requiring emergency interval surgery have significantly higher morbidity and conversion rates **(Cao et al., 2015).** In addition, many of these patients may have poor compliance and communication or drop out of follow-up assessments at the outpatient clinic. Occasionally, these patients will be regular visitors to the hospital emergency rooms, resulting in not only repeated readmissions with subsequent increased overall hospital costs but also more lost productive work days **(Lee et al., 2008).**

There is no consensus regarding the definition of "early". It was defined variably as a surgical intervention from 24 hours up to 7 days, either from symptom onset or from admission time **(Degrate et al., 2013; Skouras et al., 2012),** and these two-time frames are significantly different. Therefore, the optimal time for ELC remains controversial, although it is advised to be within 72 hours of symptom onset **(Lee et al., 2008; Zhu et al., 2012).**

In clinical practice, ELC within 72 hours of symptom onset can be applied only in lower proportions of patients (15-20%) **(Degrate et al., 2013; Cheng et al., 2021).** In our study, only 45 patients (10.3%) presented within 72 hours of symptom onset and underwent ELC. Often, these patients present or are referred by physicians 72 hours after symptom onset, have comorbidities that necessitate preoperative consultations and preparation with other specialties, have concomitant common bile duct stones that necessitate preoperative ERCP, or take anticoagulant medications that must be discontinued before surgery. Furthermore, most hospitals lack resources for emergency surgery, with the longstanding belief of surgeons and physicians that AC is not a surgical emergency **(Cao et al., 2016).** For all the above reasons, these patients missed their "golden 72 hours" when they visited the doctor, and failure to perform ELC indicates DLC for these patients in many centers **(Zhu et al., 2012; Degrate et al., 2013; Cheng et al., 2021).**

Theoretically, within 72 hours of AC, tissue hyperemia and edema might facilitate the dissection of Calot's triangle, while after that, the adhesion, fibrosis, and even necrosis might interfere with the safe dissection **(Gomes et al., 2013). Gomes et al. (2013)** and **Banz et al. (2011)** reported a non-significant difference in the clinicopathological diagnoses of simple, phlegmonous, and gangrenous cholecystitis between the ELC and DLC groups. It demonstrates different degrees of gallbladder inflammation between patients and suggests that the severity of gallbladder inflammation is not time-dependent. LC can be performed safely by an expert laparoscopic surgeon at any time without a 72-hour limit **(Banz et al., 2011; Gomes et al., 2013).**

Despite the large number of studies on LC for AC, only a few have focused on the subset of patients who were presented with AC after the 72-hour limit **(Casillas et al., 2008).**

A randomized controlled trial by **Roulin et al. (2016)** assessed ELC (after 72 hours) and DLC (after six weeks) for AC after 72 hours of symptom onset. They reported comparable operative time, conversion rate, and postoperative complications between the two groups. They reported that ELC was associated with a significant decrease in overall morbidity (14% vs. 39%, $P < 0.01$), mostly because of complications that occurred while waiting for delayed surgery. There was also a significant reduction in the median total length of hospital stay (4 vs. 7 days, $P < 0.001$), duration of antibiotic therapy (2 vs. 10 days, $P < 0.001$), and total cost (9.349 vs. 12.361 €, $P < 0.01$). They recommended ELC for AC during the daytime by an expert laparoscopic surgeon regardless of the duration of symptoms. **Degrate et al. (2013)** retrospectively assessed the outcomes of LC for AC at different times. The study included 316 patients classified into two groups: Group 1 (initial admission LC) included 262 patients (82.9 %), and Group 2 (DLC after at least four weeks) included 54 patients (17.1 %). They reported a similar conversion rate, operative time, and overall morbidity rate between the groups. They revealed a significantly longer total hospital stay in group 2 (9 vs. 11 days, $P = 0.005$), as 37% of these patients needed urgent re-evaluation, and 25.9% required hospital readmission while awaiting DLC. They concluded that the conversion rate and postoperative morbidity do not appear to be affected by the timing of cholecystectomy for AC and that 72 hours should not be regarded as a strict limit for performing LC, provided that the operation is performed during the initial hospitalization.

In addition, in a recent retrospective cohort study by **Bundgaard et al. (2021)**, 222 patients (89.5%) underwent ELC, and 26 (10.5%) underwent DLC (after six weeks). ELC was divided into three subgroups according to the duration from symptom onset to cholecystectomy: group A (< 3 days, n=111), group B (3-5 days, n=77), and group C (> 5 days, n=34). They reported no significant difference in the conversion rate, morbidity, or mortality between ELC and DLC or in the ELC subgroup analysis. They reported significantly longer operative times in groups B (97 vs. 113 min, $P = 0.02$) and C (97 vs. 121 min, $P = 0.004$) than in group A; however, there was no significant difference between the ELC and DLC groups. They reported a significantly longer mean total hospital stay in group B (3.1 vs. 4.1 days, $P < 0.001$) and group C (3.1 vs. 5.6 days, $P = 0.002$) than in group A. Additionally, the total hospital stay was significantly longer in the DLC group (3.8 vs. 9.9 days, $P < 0.001$) than in the ELC group. They concluded that ELC for AC (even 5 days after symptom onset) is safe and has comparable complication and conversion rates to DLC and should be the preferred choice for AC regardless of the duration of symptoms. **Ohta et al. (2012)** reviewed the medical records of 100 patients who underwent LC for AC. The patients were divided into four groups. Group 1, patients undergoing LC within 72 hours of symptom onset (n=11); group 2, between 4 days and 2 weeks (n=20); group 3, between 3 and 6 weeks (n=52); and group 4, > 6 weeks (n=17). They revealed similar conversion rates, blood loss, operative time, morbidity, and mortality among the four groups. They reported a significantly shorter mean hospital stay in groups 1 and 2 (8.8 & 18.5 days) than in groups 3 and 4 (31.4 & 49.1 days), ($P < 0.01$) and a statistically significantly shorter mean hospital stay in group 3 than in group 4 ($P < 0.01$). They concluded that ELC within 72 hours is the best time to perform LC for AC and that the best time for patients who cannot have an ELC is probably as soon as they can tolerate LC. The authors did not support the conventional delayed timing of LC for 6-12 weeks. A retrospective study by **Lee et al. (2008)**, including 202 consecutive patients, reported the outcomes of LC performed for AC. The patients were divided into three groups: group 1 (45 patients), LC within 72 hours; group 2 (55 patients), LC between 4 days and 5 weeks; and group 3 (102 patients), LC after 5 weeks. Group 3 had a significantly shorter mean total hospital stay than both other groups (3.1 vs. 4.3 vs. 1.7 days, $P < 0.001$), as well as a significantly shorter postoperative stay than group 1 (2.4 vs. 2 vs. 1.4 days, $P = 0.03$). This difference was explained based on those receiving surgery during their initial hospitalization, spending more time in the hospital for the initial work-up, and waiting for an open operating room. He reported no statistically significant differences in complication and conversion rates among the three groups. They concluded that patients who present with AC should undergo surgery during the same admission period, regardless of the duration of symptoms, and that this would not necessitate a long postoperative recovery period **(Lee et al., 2008).** A recent meta-analysis of 77 case-control studies **(Cao et al., 2016)** reported a significant reduction in morbidity, mortality, blood loss, conversion rates, and length of hospital stay in ELC (within 72 hours) compared with DLC (after 4 weeks). In addition, a subgroup analysis of ELC (within 72 hours) and PLC (within 7 days) versus DLC (after 4 weeks) reported a significant reduction in morbidity, mortality, and length of hospital stay in the ELC and PLC groups. They concluded that LC for AC within 72 hours is optimal, and even if patients are operated on within 7 days after symptom onset, surgical outcomes are still good compared to DLC. They concluded that the duration of AC symptoms should not influence the surgeon's decision to perform early cholecystectomy.

A recent study by **Yuksekdag et al. (2021)** assessed the effects of LC timing for AC. Patients were classified into three groups based on the time from symptom onset. Group 1: LC within 3 days (n=22); Group 2: LC between the 4th and 7th days (n=24); and Group 3: LC after 7 days (n=11). They reported significantly shorter operative time and hospital stay in group 1 than in both groups 2 (50 vs. 74 min, $P < 0.05$ & 1.9 vs. 4.5 days, $P < 0.001$) and group 3 (50 vs. 132 min, $P < 0.001$ & 1.9 vs. 7.2 days, $P < 0.001$), and significantly shorter operative time and hospital stay in group 2 than in group 3 (74 min vs. 132 min, $P < 0.001$ & 4.5 vs. 7.2 days, $P < 0.05$). There were no statistically significant differences in postoperative complications among the three groups. They concluded that LC can be performed safely within seven days of symptom onset. In a retrospective study by **Cheng et al. (2021)**, 104 patients with AC were analyzed. They were divided into an ELC group (within 72 hours) and a PLC group (after 72 hours). There were no differences between the two groups in conversion rates, operative time, morbidity rate, mortality rate, and operative costs. However, the PLC was associated with longer postoperative and total hospital stay (7.0 vs. 6.0 days, $P = 0.03$) and (11 vs. 8 days, $P <$ 0.01), respectively, and subsequently higher total costs (40.400 vs. 31.100 Yuan, $P < 0.01$). They concluded that PLC is safe and feasible as an ELC for patients with AC, but it is also associated with longer hospital stays and higher total costs.

Our study revealed a significant increase in both the number of ports (P < 0.01) and operative time (110 vs. 87 min, P < 0.001) in the PLC group, which is most likely a direct reflection of the significantly increased clinicopathological severity (P < 0.001), operative difficulty (P < 0.01), and dense adhesions (P < 0.01) encountered during PLC. Male sex, old age, a thick gallbladder wall > 5 mm, recurrent inflammation, and gangrenous cholecystitis were risk factors for conversion to open surgery during LC for AC **(Yuksekdag et al., 2021).** In cases of difficult dissection, we never hesitate to convert to open cholecystectomy to avoid serious consequences, and this conversion should not be considered a complication or treatment failure but rather a wise decision **(Popkharitov 2008).** The conversion rates mentioned in a large meta-analysis ranged from 3%-20% **(Papi et al., 2004).** The conversion rate in this study was comparable to this range, with no significant difference (4.7% vs. 1.5%, P = 0.07) between the two groups. The incidence of intervention for postoperative complications after LC is very low, usually associated with missed common bile duct injuries or bleeding **(Brooks et al., 2013).** In our study, four patients developed postoperative bile duct leaks, which ERCP, sphincterotomy, and biliary stenting managed. The reported incidence of postoperative intervention was approximately 1% **(Khan et al., 2009),** consistent with our findings (1.7% vs. 0.7%, P = 0.6). No deaths occurred in either group.

We agree with **Gutt et al. (2013) and Roulin et al. (2016)** that overall morbidity is the most important outcome for which LC success should be evaluated. Failure of the initial conservative treatment, necessitating emergency interval LC, or recurrent episodes of biliary-related complications requiring emergency consultation and/or unplanned readmission during the waiting period for DLC could be interpreted from the patient's perspective as treatment failure. Moreover, since subtotal cholecystectomy, which is practically a drainage procedure, was not the target operation, we considered it a treatment complication. In this study, the overall incidence of morbidity supported PLC (11.3% vs. 29.4%, P < 0.001). A Cochrane review **(Gurusamy et al., 2010)** reported that the incidence of patients suffering from biliary-related complications while waiting for the DLC was 23.3 %. In comparison, a population-based analysis by **de Mestral et al. (2013)** reported 14%, 19%, and 29% at 6, 12, and 48 weeks, respectively. In our study, the incidence of gallstone-related complications was 18.6%. Eleven patients (6.2%) required only emergency consultation, and 22 (12.4%) required hospital readmission. In our study, subtotal cholecystectomy was performed only in two patients in the PLC group because of the difficult dissection of the gallbladder. We believe that cholecystectomy should not be performed at the expense of increased complications.

Many studies have reported that delaying surgery from symptom onset increases the incidence of readmission by approximately 20-30% and, consequently, the overall hospital stay **(Gurusamy et al., 2010; Banz et al., 2011; Degrate et al., 2013).** In our analysis, PLC patients had a significantly shorter total hospital stay than DLC patients (3 vs. 7 days, P < 0.001). This result is expected, as the total hospital stay for the DLC group included at least two admissions, one during the initial acute attack with conservative treatment until improvement and discharge and the second for the planned elective surgery **(Cao et al., 2015).** The median number of readmissions was significantly higher (1 vs. 2 days, P < 0.001) in the DLC group.

Undoubtedly, the longer the hospital stays, the greater the health costs generated. Many previous studies have reported significantly increased overall costs for DLC due to the price of doctor emergency consultation for similar attacks, unplanned readmission, and increased total antibiotic duration **(Wilson et al., 2010; Sutton et al., 2017; Kerwat et al., 2018)**, not to mention the indirect costs and economic burden associated with hospitalization, such as lost salary with more time away from work and societal expenditures **(Banz et al., 2011; Cao et al., 2015; Gallagher et al., 2019).** In our analysis, we found a significantly decreased median total cost in the PLC group (1350 vs. 2000 $, $P < 0.001$), mainly due to a significantly decreased median total antibiotic duration (7 vs. 19 days, $p < 0.01$). In addition, patients in the DLC group lost 7 more days from work than those in the PLC group (15 vs. 22 days, $P < 0.001$), mainly due to two hospital admissions. The PLC promotes a quicker return to work and maximizes financial gain.

LC for AC after the optimal 72-hours window is safe, and patients will benefit from surgery compared to conservative treatment followed by delayed surgery. The duration of symptoms in AC should not influence the surgeon's decision to perform a cholecystectomy. One of the main suggested reasons for delaying surgery for AC 72 hours after symptom onset is the increased risk of serious complications, such as bile duct injury and bile leak, which this study denies and proves the opposite. In recent years, many hospitals have changed their AC management policy by providing emergency operating rooms and expert laparoscopic surgeons. We need to work together to change the old concept of surgeons regarding the management of AC and spread the culture of cholecystectomy for AC, regardless of the time of presentation, intending to improve outcomes and provide the best quality of life for our patients.

Strengths and limitations

Our study has several strengths. To the best of our knowledge, this study is one of the few randomized controlled studies in an emergency setting evaluating the outcomes of LC for AC after the golden 72 hours. This trial was a multicenter study with a large sample size and high statistical power. Both the intention and modified intention-to-treat analyses were used to provide a proper explanation of the results. Finally, the data collected from our collaborating centers had an exact homogeneous timing and endpoint. These circumstances make our study unique and raise the likelihood that our conclusions will be valid. However, this study has some limitations. First, the short follow-up period did not allow the evaluation of late complications. Second, we could not distinguish between different postoperative complications, such as biliary leak and biliary stricture, which require many patients for appropriate data. Third, there is insufficient data for patients initially treated conservatively; they were improved and subsequently lost to complete the study. Finally, the duration of symptom onset was based on patient history, and the decision to convert to open surgery was at the discretion of the operating surgeon. Despite these limitations, our data reflect a real-world clinical scenario and have excellent generalizability that can be applied to all countries with high laparoscopic surgery standards.

Conclusion

In conclusion, LC for AC after 72 hours of symptom onset is safe, feasible, and associated with lower overall morbidity, shorter total hospital stay, shorter total antibiotic duration, fewer hospital admissions, and reduced total cost, as well as a rapid return to work compared with conservative treatment and delayed surgery. Although DLC was associated with a significantly increased number of ports and operative time, this was not compared with other benefits. These results encourage LC in patients with AC, irrespective of symptom onset, in the presence of skilled laparoscopic surgeons.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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