

Early Versus Delayed Cholecystectomy for Acute Cholecystitis, Are the 72 hours Still the Rule?

A Randomized Trial

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Objective: The aim of this study was to compare clinical outcomes of early versus delayed laparoscopic cholecystectomy (LC) in acute cholecystitis with more than 72 hours of symptoms.

Background: LC is the treatment of acute cholecystitis, with consensus recommendation that patients should be operated within 72 hours of evolution. Data however remain weak with no prospective study focusing on patients beyond 72 hours of symptoms.

Methods: Patients with acute cholecystitis and more than 72 hours of symptoms were randomly assigned to early LC (ELC) or delayed LC (DLC). ELC was performed following hospital admission. DLC was planned at least 6 weeks after initial antibiotic treatment. Primary outcome was overall morbidity following initial diagnosis. Secondary outcomes were total length of stay, duration of antibiotic therapy, hospital costs, and surgical outcome. **Results:** Eighty-six patients were randomized (42 in ELC and 44 in DLC group). Overall morbidity was lower in ELC [6 (14%) vs 17 (39%) patients, $P = 0.015$]. Median total length of stay (4 vs 7 days, $P < 0.001$) and duration of antibiotic therapy (2 vs 10 days, $P < 0.001$) were shorter in the ELC group. Total hospital costs were lower in ELC (9349€ vs 12,361 €, $P = 0.018$). Operative time and postoperative complications were similar (91 vs 88 min; $P = 0.910$) and (15% vs 17%; $P = 1.000$), respectively.

Conclusions: ELC for acute cholecystitis even beyond 72 hours of symptoms is safe and associated with less overall morbidity, shorter total hospital stay, and duration of antibiotic therapy, as well as reduced cost compared with delayed cholecystectomy (NCT01548339).

Keywords: 72 hours symptoms, acute cholecystitis, early versus delayed laparoscopic cholecystectomy, randomized trial

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If the definitive treatment of acute cholecystitis is laparoscopic cholecystectomy (LC), the timing of surgery remains controversial. A long-standing dogma stipulated that patients should be operated within 72 hours of symptoms. This was also based on anatomic-pathological observation: following edematous cholecystitis during the first 2 to 4 days of symptoms, necrotizing and then suppurative cholecystitis develops,¹ making LC potentially more dangerous. In a retrospective study on acute cholecystitis, the conversion rate to laparotomy increased according to the delay from onset of symptoms until surgery.²

Data however remain weak on the specific management of acute cholecystitis beyond 72 hours of symptoms, with only a few retrospective case-control studies reporting that LC can safely be performed after 72 hours of symptoms.^{3–5} A recently published meta-analysis reported that early LC for acute cholecystitis might be associated with shorter hospital stay, lower hospital costs, and higher patient satisfaction. However, all existing randomized studies included only patients with less than 72 hours of symptoms, or did not discriminate patients according to the length of symptoms.⁶ On the basis of the currently available literature, the updated Tokyo guidelines classify an acute cholecystitis as grade II/moderate with duration of complaints of more than 72 hours, and proposed delayed LC, or early LC when advanced laparoscopic technique was available.⁷ Therefore, prospective data were needed to establish the specific management of acute cholecystitis beyond 72 hours of symptoms.

The objective of the present prospective randomized trial was to compare clinical and surgical outcomes of early versus delayed LC in acute cholecystitis with more than 72 hours symptoms.

METHODS

Study Design

A single center, parallel-group, with balanced randomization (1:1) study performed at the University Hospital of Lausanne (CHUV), a tertiary referral center in Switzerland.

The study was approved by the institutional ethics committee (#252/08). Every patient provided written informed consent before enrollment. The trial was registered under clinicaltrials.gov (NCT01548339). The trial was conducted and the results presented according to the CONSORT guidelines.⁸

Study Population

Patients older than 16 years and able to provide informed consent, with symptoms of acute cholecystitis lasting more than 72 hours before admission, were eligible. There was no upper limit of symptoms duration. The diagnosis of acute cholecystitis was established according to Tokyo guidelines,⁹ with local (murphy's sign/right upper quadrant pain) and systemic (fever/elevated C-reactive protein/white blood cell) signs of inflammation and confirmed by ultrasound. The abdominal ultrasound was performed by trained radiologists. Characteristic findings of acute cholecystitis were thickening of the gallbladder wall and pericholecystic fluid or radiological murphy's sign, associated with biliary stone. The exclusion criteria were severe sepsis, immunosuppression, perforated cholecystitis, biliary peritonitis, cholangitis, acute pancreatitis, and pregnancy.

Enrolment and Randomization

Patients were assessed for eligibility at the emergency station by the surgeon on-call once the diagnosis of acute cholecystitis was

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established. A dedicated study nurse assigned randomly to early (ELC group) or delayed (DLC group) LC, by picking out of a box and opening a sealed opaque randomization envelope. The details of the allocated treatments (“early” or “delayed”) were given on cards contained in sealed opaque envelopes. All sealed opaque envelopes were previously prepared with a 1 : 1 ratio, well shuffled, and put into a box by the dedicated study nurse. No blinding was performed.

Interventions

In both groups, antibiotic treatment according to institutional guidelines was given systematically once diagnosis was established. LC was performed using a 3-ports technique¹⁰ without routine cholangiography. All surgeons of the department performed LC under supervision of an attending surgeon without distinction between the 2 randomized groups.

In both groups, intravenous antibiotic treatment was administered upon diagnosis of acute cholecystitis. The recommended antibiotic was amoxicillin/clavulanic acid, with possible modification when required according to institutional guidelines (http://www.chuv.ch/min/min_home/min-professionnels-sante/min-prof-guide-antibiotherapie.htm). In the ELC group, LC was performed during daytime as soon as possible following admission. After LC, antibiotic therapy was stopped unless contraindicated by local abscess/bacteriemia. Patients were discharged once the pain was controlled by oral medication. In the DLC group, antibiotic therapy was administered for 10 to 14 days, and LC was planned at least 6 weeks following initial diagnosis.

Outcomes/Study Endpoints

The primary composite outcome was overall morbidity, defined as any adverse event occurring from time of diagnosis until the 30th postoperative day. Overall morbidity included failure of initial antibiotic treatment in the DLC group requiring emergency cholecystectomy, unplanned hospital readmission or emergency consultation while awaiting delayed LC, as well as any postoperative complications within 30 postoperative days. Secondary outcomes were total length of hospital stay, duration of antibiotic therapy, and in-hospital costs, as well as surgical characteristics (postoperative complications, operative time and conversion rate). Postoperative 30-day morbidity was graded according to the Clavien classification.¹¹ A follow-up visit at 30 postoperative days was scheduled.

A dedicated study nurse prospectively entered data in a specific computerized database, which was completed by the first 2 investigators (D.R. and A.S.).

Sample Size and Statistical Analysis

Sample size calculation was based on a noninferiority hypothesis with an estimated increase of 4% on overall morbidity associated with early LC. Adopting a power of 80%, a 2-sided type I error (α) of 0.05, the calculated sample size was 466 patients. An intermediary analysis was planned after 50 patients, and in case of a significant decrease in overall morbidity associated with ELC, a new sample size calculation based on a superiority hypothesis would be performed.

Descriptive statistics were reported as absolute number for categorical variables, and as mean (\pm standard deviation, SD) or median (interquartile range, IQR) for continuous variables whenever appropriate. Categorical variables were analyzed with Fisher exact test. Normal and non-normal continuous variables were compared by Student *t* test and Mann-Whitney *U* test, respectively.

Hospital costs included all costs during primary hospitalizations, secondary planned hospitalizations in the DLC group, and, if applicable for unplanned readmission. Cost data were obtained from the hospital accounting database and available for each patient. Ambulatory costs were unavailable and were not included in the cost

analysis. Costs were calculated in Swiss francs (CHF), and converted in Euros (€) at an exchange rate of 1€ = 1.20CHF. The nonparametric bootstrap method to test with standard *t* test and to derive confidence intervals for difference in arithmetic mean costs has been advocated for moderate sample size,¹² and was used for cost analysis.

Data were analyzed with Statistical Package for Social Sciences (SPSS 21.0, Inc., Chicago, IL) and Prism 6.03 (GraphPad Software, Inc., La Jolla, CA). Power size calculation was performed with G*Power.¹³

RESULTS

Patient Flow

Between February 12, 2009, and December 9, 2014, 375 consecutive patients admitted for acute cholecystitis were assessed for eligibility. There were 213 patients with exclusion criteria, among them 127 patients who presented within 72 hours of symptoms, 25 patients with severe sepsis, 13 patients with concomitant acute pancreatitis, 28 patients with associated cholangitis, 6 patients with perforated gallbladder or biliary peritonitis, 5 patients under immunosuppression, 8 patients unable to provide informed consent due to language or dementia, and 1 pregnant patient. Further, 76 patients declined to participate or failed to be screened. There were 86 patients randomized to ELC ($n = 42$) or DLC ($n = 44$) (Fig. 1). In the ELC group, 1 patient refused LC following randomization and was further lost following initial hospitalization. In the DLC, 6 patients did not receive the complete initial conservative treatment with delayed LC. Among them, 3 patients had persistent or increasing pain under antibiotic therapy requiring emergency LC. Two patients refused the delayed LC following successful antibiotic therapy treatment. Both patients were seen at the ambulatory consultation after discharge from the primary hospitalization, and no further follow-up was planned. One patient presented with anaphylactic shock with cardiac arrest during anesthesia induction and cholecystectomy was not performed. All patients who had LC were seen or contacted for the 30th postoperative day follow-up visit. The primary (overall morbidity) and secondary outcomes analysis for duration of antibiotic therapy, length of hospital stay, as well as hospital costs, were intention-to-treat ($n = 86$). The analysis of the surgical procedure and related surgical outcomes was performed on a modified intention-to-treat analysis and included only patients with cholecystectomy ($n = 82$).

Recruitment

The planned intermediary analysis was performed in December 2011, after the inclusion of 54 patients. A statically significant difference of the main outcome (overall morbidity) was observed in favor of the early LC group with a *P* value of 0.044. As the outcome was significantly worse in 1 group, a recalculation of the sample size was performed according to the original protocol submitted to the ethical committee before the initiation of the trial. A sample size calculation based on the superiority hypothesis of early LC in terms of overall morbidity with a proportion of 0.22 for early LC versus 0.48 for delayed LC was performed. On the basis of the same power of 80% and a 1-sided type I error (α) of 0.05, the calculated sample size with an anticipated loss of follow-up of 5% was 86 patients. The trial was terminated after 86 randomized patients on December 9, 2014. The last postoperative follow-up was performed on January 20, 2015.

Baseline Demographics and Clinical Characteristics

Median age of the overall population was 58.5 years. Baseline demographics and clinical characteristics were similar in both groups (Table 1).

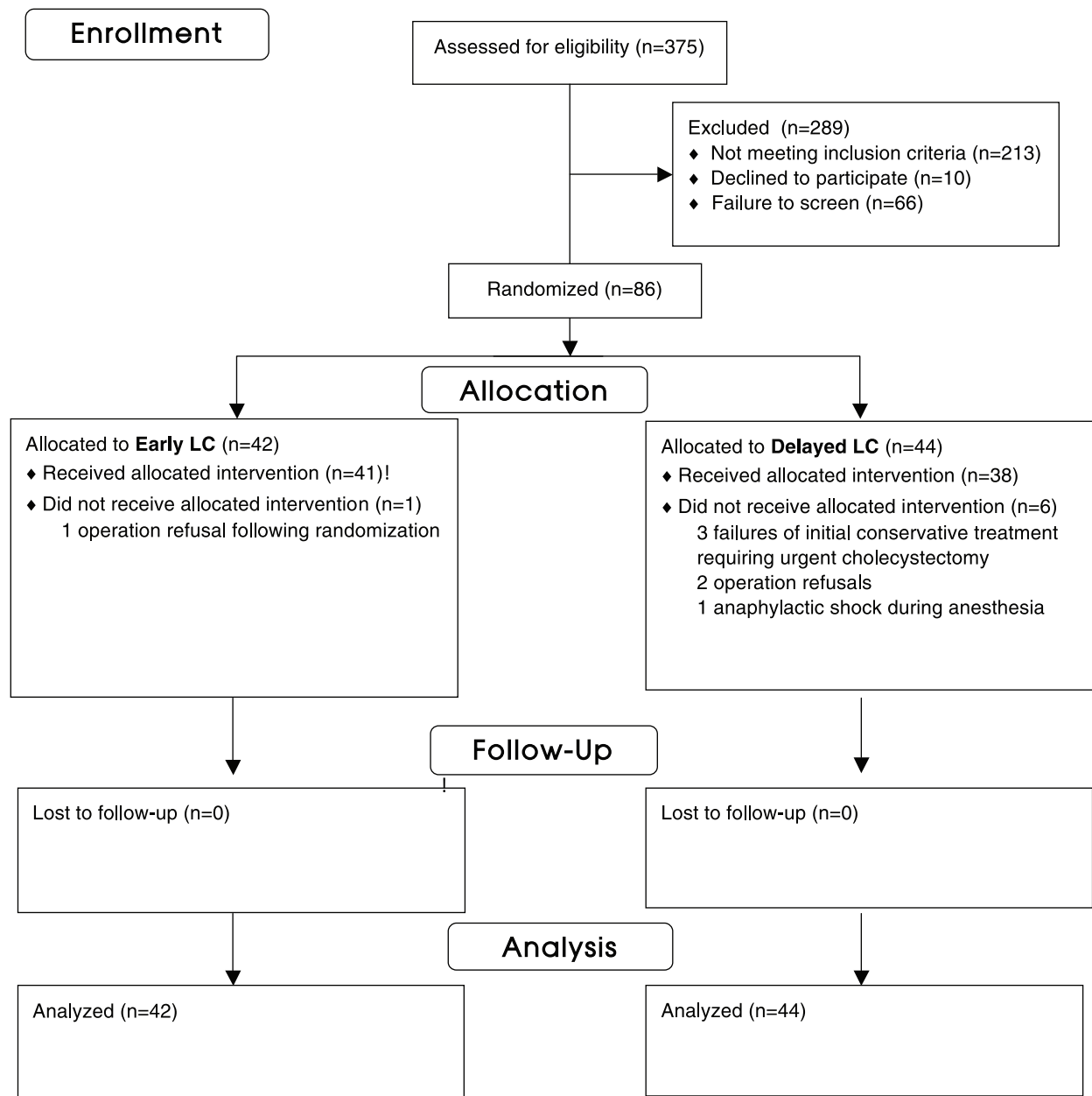


FIGURE 1. CONSORT flow diagram. Randomized controlled trial of early versus delayed laparoscopic cholecystectomy (LC) for acute cholecystitis with more than 72 hours of symptoms.

Overall Morbidity From Initial Diagnosis Until Postoperative Follow-up

Overall morbidity was reduced in ELC [6 (14%) vs 17 (39%) patients, $P = 0.015$]. In the DLC, there were 13 patients (29.5%) with nonresolution of symptoms under initial conservative treatment or recurrence of symptoms during the waiting period (Table 2). Among patients requiring an emergency consultation/hospitalization while awaiting delayed cholecystectomy, 3 patients had recurrent symptomatic cholelithiasis requiring urgent consultation, and 1 among them was hospitalized for analgesia. Moreover, 4 patients had recurrent acute cholecystitis treated with antibiotic therapy and cholecystectomy, 2 patients presented with acute biliary pancreatitis, and 1 with

obstructive cholangitis treated by antibiotics and endoscopic retrograde cholangiopancreatography with a further planned LC. As 3 patients in the DLC group with unplanned readmission while waiting delayed LC due to recurrent acute cholecystitis also presented with postoperative complications, the total number of patients with morbidity was 17 in the DLC group. The median interval (IQR) between the date of first admission and delayed surgery was 58 (42 to 98) days.

Duration of Antibiotic Therapy, Length of Stay, and Hospital Costs

Median total length of stay (4 vs 7 days, $P < 0.001$) and duration of antibiotic therapy (2 vs 10 days, $P < 0.001$) were shorter

TABLE 1. Baseline Characteristics Comparing Patients With Early Versus Delayed Laparoscopic Cholecystectomy

	ELC (n = 42)	DLC (n = 44)	P
Age, mean (SD), yr	55.8 (16.8)	57.9 (16.6)	0.564
Male gender, n (%)	24 (57)	25 (57)	1.000
Body mass index, mean (SD), kg/m ²	28.2 (5.5)	27.6 (4.3)	0.596
Hypertension, n (%)	15 (36)	12 (27)	0.488
Diabetes, n (%)	4 (10)	4 (9)	1.000
Cardiac disease*, n (%)	7 (17)	9 (20)	0.784
Pulmonary disease†, n (%)	5 (12)	2 (5)	0.260
Chronic renal insufficiency, n (%)	0	2 (5)	0.236
Cerebrovascular attack, n (%)	2 (5)	0	0.494
Charlson comorbidity index, median (IQR)	0 (0–1)	0 (0–1)	0.413
ASA grade I–II, n (%)	40 (95)	42 (95)	1.000
Previous intrabdominal operation, n(%)	7 (17)	9 (20)	0.784
Length of symptoms, median (IQR), d	4 (3–7)	4 (3–5)	0.385

*Rhythmic, valvular, or ischemic cardiopathy.

†Asthma, chronic obstructive pulmonary disease, obstructive sleep apnea.

ASA indicates American Society of Anesthesiologists.

in the ELC group. The mean difference in hospital costs was 3012€ per patient in favor of ELC ($P = 0.018$). In the DLC group, 3 LCs were performed on an ambulatory basis.

Surgical Procedure and Perioperative Complications

There was no statistically significant difference in surgical characteristics and surgery-related outcomes (Table 3). Operative time and postoperative complications were similar (91 vs 88 min; $P = 0.910$) and (15% vs 17%; $P = 1.000$), respectively. The median postoperative length of stay was significantly shorter in the elective DLC group (2 vs 4 days; $P < 0.001$).

DISCUSSION

This randomized controlled trial focusing on acute cholecystitis with more than 72 hours of symptoms found that ELC was associated with a significant reduction in overall morbidity, mostly in relation with complications occurring during waiting time until surgery in the DLC group. Moreover, the total duration of antibiotic therapy and length of stay, as well as costs were significantly reduced by an ELC. There were no significant differences in operative time or perioperative complications between ELC versus DLC.

The present study is to the best of our knowledge the first randomized controlled trial including only acute cholecystitis patients with more than 72 hours of symptoms. It is currently

established from previous randomized trials that early cholecystectomy is the best management of acute cholecystitis.^{6,14,15} However, the definition used in previous randomized studies to differentiate ELC versus DLC had a high degree of variability: ELC was either based on the apparition of symptoms or on the admission day, with an interval until the operation varying from 24 hours to 7 days. The definition of ELC used in meta-analysis^{6,14} was LC performed within 7 days of the onset of symptoms, and when compared with DLC, ELC was associated with a reduction in length of stay and work days lost, as well as costs⁶ without increase of conversion or perioperative complications. The optimal timing to perform LC for acute cholecystitis was analyzed in prospectively gathered databases that encompassed more than 120,000 patients.^{16–18} However, they all considered time from admission to operation, but not the duration of symptoms until admission, when concluding to the benefits of ELC.

The dogma of 72 hours of symptoms was previously challenged in retrospective studies.^{3–5,19} Reduced total length of stay, similar rates of conversion, and postoperative complications were associated with ELC versus DLC in patients beyond 72 hours of symptoms.^{3,5,19} A further retrospective study including 61 patients operated before and after the 72 hours boundary found no differences between them and concluded that the degree of inflammation was not necessarily time-dependent.⁴ This might provide an explanation why ELC even beyond 72 hours of symptoms was not associated with an increased conversion rate or bile duct injury.

The primary outcome, overall morbidity, was in favor of ELC, mainly due to complications during the initial conservative treatment or the waiting time until planned LC. This morbidity, described as gallstone-related morbidity during the waiting period, occurred in 18.3% according to the Cochrane review,¹⁴ comparable to the 29.5% described in this study. These patients subjected to such a non-resolution of symptoms under initial conservative treatment or recurrence of symptoms during the waiting period requested an emergency LC with a high conversion rate of 45%.¹⁴

Some limitations of this study should be addressed. With a low recruitment rate (about 14 patients/yr), 6 years were needed to complete the trial. This was partially explained by strict inclusion criteria. In fact, in a country with high medical density, most patients presented to the emergency department within 72 hours of symptoms. There were also some failures to screen, inherent difficulty of randomized prospective trial in emergency setting.

The choice of a composite primary outcome of overall morbidity encompassing failure of initial conservative treatment, unplanned hospital readmission or emergency consultation, and postoperative complications has to be justified. This outcome was the most closely adapted to the patient's point of view. Indeed, failure of initial antibiotic therapy requesting emergency unplanned operation, or occurrence of a biliary-related complication during the

TABLE 2. Overall Morbidity, Total Duration of Antibiotic Therapy, Length of Stay, and Hospital Costs

Outcomes	ELC (n = 42)	DLC (n = 44)	OR (95% CI)	P
Overall morbidity, n (%)	6 (14.3)	17 (38.6)*	0.26 (0.0–0.76)	0.015
Failure of initial treatment	0 (0)	3 (6.8)	0.14 (0–2.79)	0.242
Unplanned readmission/emergency consultation awaiting delayed cholecystectomy	0 (0)	10 (22.7)	0.04 (0–0.68)	0.001
Postoperative complications	6 (14.3)	7 (15.9)	0.88 (0.27–2.88)	1.000
Total antibiotic duration, median (IQR), d	2 (1–5)	10 (10–14)	—	<0.001
Total hospital length of stay, median (IQR), d	4 (3–4)	7 (5–11)	—	<0.001
Total hospital costs, mean cost per patient (95% CI), €	9349 (7865–11,142)	12,361 (10,753–14,253)	—	0.018

*Three patients with unplanned readmission while awaiting DLC also presented with postoperative complications.

CI indicates confidence interval; OR, odds ratio.

TABLE 3. Surgical Characteristics and Surgery-related Outcomes

	ELC (n = 41)	DLC (n = 41)	OR (95% CI)	P
Operative time, median (IQR), min	91 (70–114)	88 (71–118)	—	0.910
Peroperative cholangiography, n (%)	7 (17)	2 (4.9)	4.02 (0.8–20.7)	0.155
Pathological diagnosis			—	<0.001
Acute cholecystitis, n (%)	22 (53.7)	10 (24.4)		
Acute on chronic cholecystitis, n (%)	15 (36.6)	0		
Chronic cholecystitis, n (%)	4 (9.8)	31 (75.6)		
Conversion to laparotomy, n (%)	1 (2.4)	0 (0)	3.07 (0.1–77.8)	1.000
Bile duct injury/leak, n (%)	0 (0)	1 (2.4)	0.33 (0–8.2)	1.000
Postoperative complications, n (%)	6 (14.6)	7 (17)	0.83 (0.3–2.7)	1.000
Grade I	2	3		
Grade II	2	1		
Grade III a/b	1	2		
Grade IV a/b	1	1		
Grade V	0	0		
Postoperative length of stay, median (IQR), d	4 (3–4)	2 (2–3)	—	<0.001
Postoperative readmission, n (%)	0 (0)	2 (4.8)	0.19 (0–4.1)	0.494

Postoperative complications graded by severity according to the Clavien classification.¹¹

waiting time, would be interpreted by the patient as treatment failure. Postoperative complications were also taken into account, as proceeding to an ELC should not be done at the expense of a potential increase of perioperative complication, which was not the case in this study. Moreover, a composite primary outcome of overall morbidity was previously described in another randomized trial comparing immediate versus delayed cholecystectomy irrespectively of the length of symptoms, where morbidity was defined as the occurrence of any of the clinically relevant complications from the day of inclusion until the postoperative visit.¹⁵ Another limitation is that the study was underpowered to detect a difference in surgical complications. Such a prospective trial, based on bile-duct injury and leakage rates, would request for adequate statistics more than 50,000 patients.¹⁴

The results of this study suggest applying the recommendation of ELC irrespectively of the duration of symptoms. For safety reasons, the approach in our institution was to perform surgery during daytime, when sufficient surgical laparoscopic expertise is available, as it was shown previously that in acute cholecystitis, nighttime LC was associated with higher conversion rate.²⁰ This might provide a possible argument for the low conversion rate observed in our study with only 1 conversion in the ELC group, as compared with the 13% to 15% conversion rate described in the literature.⁶

In conclusion, ELC for acute cholecystitis even beyond 72 hours of symptoms is safe and associated with less overall morbidity, shorter total hospital stay and duration of antibiotic therapy, as well as reduced cost compared with DLC. ELC without any time limit between onset of symptoms and operation may be recommended.

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DISCUSSANTS

G. Torzilli (Rozzano, Italy):

The authors aimed to clarify the best surgical policy between early versus delayed laparoscopic cholecystectomy (LC) in patients presenting symptoms of acute cholecystitis lasting more than 72 hours. These patients correspond to a subgroup classified as carriers of grade II (moderate) cholecystitis according to the Tokyo Guidelines: indeed, symptoms lasting for more than 72 hours are criteria for classifying a cholecystitis as moderate and for planning a delayed LC (DLC). Therefore, analyzing its impact conveys with no doubt an element of originality. Furthermore, methodologically, the study is a randomized controlled trial (RCT), with a suitable sample size for an interim analysis. Results showed that early LC (ELC) was associated with an overall lower morbidity albeit similar surgical outcome. On the contrary, the restrictive inclusion criteria justify the low recruitment rate. In terms of major morbidity, it is unclear from the Table whether in the DLC group a bile leak or a bile duct injury occurred: the latter may sustain a team's reluctance to conversion. This rather than suggesting a selection bias could be the explanation for the low rate of conversion. My opinion is that this study is original, and methodologically properly carried out, with results that provide important insights for completing the actual guidelines.

Response From D. Roulin (Lausanne, Switzerland):

Thank you Professor Torzilli for your kind comments. Indeed, our low recruitment rate was partly explained by precise inclusion criteria, as a significant amount of patients presented with less than 72 hours of symptoms. Moreover, this prospective randomized trial was conducted in an emergency setting, which made recruitment more difficult. Concerning the bile duct injury, it was a leakage from cystic duct that occurred in 1 patient with delayed cholecystectomy, and which was successfully treated by endoscopic retrograde cholangiopancreatography. A conversion would probably not have prevented this leak. Our conversion rate (1%) was low and was comparable to retrospective data describing conversion rate between 0% and 12% in delayed LC.

M. Büchler (Heidelberg, Germany):

It is evidence-based that we operate early when it comes to acute cholecystitis. In 13 RCTs and 1 meta-analysis, this has been shown. You have confirmed these findings. What I cannot understand is what specifically the content of your trial is.

Response From D. Roulin (Lausanne, Switzerland):

The originality of our study was the inclusion criteria focusing only on patients with acute cholecystitis beyond the long-standing dogma of 72 hours of symptoms. Among previous RCTs, none of these included exclusively this group of patients.

C. Bruns (Cologne, Germany):

Can you explain again how you did the patient's calculation ending up with 86 analyzed patients coming from 488 included

patients? Did you change the statistical study design, or did you have dropouts?

With respect to the clinical symptoms, you rely on the patient's information, in particular regarding their estimation of duration of the symptoms such as longer than 72 hours.

How can you be sure that the information of the patients is correct?

It might also be that some patients experienced clinical symptoms in particular pain much earlier, however, do not mention this. How do you handle this subjective information, which is of importance for the key message of the study?

Response From D. Roulin (Lausanne, Switzerland):

We started with a noninferiority trial because we did not have previous data to formulate our hypothesis. In methodology, an intermediate analysis was planned. After intermediate analysis, there was a significant advantage in favor of early cholecystectomy. Therefore, we had to recalculate the sample size with, this time, a superiority trial hypothesis. This explained the lower number of patients to be included. Regarding the duration of symptoms, we had to rely on what patients reported when they were admitted to the emergency department. This is of course, as any symptom, a subjective information.

P.-A. Clavien (Zurich, Switzerland):

Dr. Roulin, congratulations to you and the Lausanne's team for putting together this challenging and clinically relevant trial. My question focused on your very low conversion rate with only 1 conversion out of 40 cases. To me, this is a too low figure for patients presenting with acute cholecystitis, and who underwent delayed laparoscopic surgery. I am suspicious that—perhaps due to difficulty in recruitment—you included patients, who did not fulfilled the criteria for acute cholecystitis, but rather presented only with symptomatic cholelithiasis. This number, despite the fact that you mention reported range between 0% and 12%, is hard to believe. Can you comment on how certain you are that all cases were indeed acute cholecystitis?

Response From D. Roulin (Lausanne, Switzerland):

It is true that we had 1 conversion only, occurring in delayed LC. We carefully assessed our data and all included patients had elevated inflammatory parameters on admission. Moreover, anatomic-pathological analysis of every removed gallbladder confirmed cholecystitis. There were no patients with simple cholelithiasis in this trial.

J. Pratschke (Berlin, Germany):

Congratulations to your work. I would like to stress once again on 2 points. The first is, if I remember it correctly, you had a recruiting time of over 8 years for this study, so what is the reason for that, because cholecystectomy is not a rare operation. Second, what is really the novelty of this study, because there have been other publications addressing this problem, please comment.

Response From D. Roulin (Lausanne, Switzerland):

Actually, the inclusion period was 6 years. We only included emergency acute cholecystitis beyond 72 hours, and not other all cholecystectomies performed in our institution. Moreover, we also had to face a high rate of drop-out because of emergency. The novelty of this study was to focus on patients beyond 72 hours of symptoms, because it remains a diagnostic criterion used in the guidelines for the management of acute cholecystitis. This lack of specific data made the analysis of this specific group of patients important.