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ORIGINAL ARTICLE

Failure to perform index cholecystectomy during acute cholecystitis results in significant morbidity for patients who present with recurrence

Alfredo Escartín, Marta González, Ana Pinillos, Elena Cuello, Pablo Muriel, Jaume Tur, Mireia Merichal, Nuria Mestres, María-Carmen Mías & Jorge-Juan Olsina

General Surgery Department, IRBLleida-University Hospital Arnau de Vilanova, Avenue Alcalde Rovira Roure 80, Lleida, Spain

Abstract

Background: Although index cholecystectomy is considered the treatment of choice for acute cholecystitis (AC), many hospital systems struggle to provide such a service. The aim of this study was to analyze the effect of failure to perform index cholecystectomy in patients presenting with acute cholecystitis.

Methods: Between June 2010 and December 2015, all patients presenting to one hospital with an initial attack of AC were enrolled into a prospective database. Patient's records were reviewed up until point of delayed cholecystectomy or for a minimum of 24 months after the initial presentation with AC. Recurrent AC was defined as early (<6 weeks from initial discharge) or late (>6 weeks from initial discharge).

Results: In total 998 patients presented with AC, 409 (41%) of whom were discharged without index cholecystectomy. Eighty-three (20%) patients presented with AC recurrence (ACR). Compared to the first AC episode, patients were more likely to present with grade III AC and suffer significantly greater morbidity ($p < 0.05$ for all comparisons). A prior history of biliary disease was associated with ACR ($p = 0.002$). ACR occurred early in 48 (58%) patients and delayed in 35 (42%) patients.

Conclusions: Twenty percent of patients discharged without cholecystectomy after their first attack of ACR will develop recurrence within the first two years. Half of ACR will occur within 6 weeks. Patients who present with ACR are more likely to develop more severe AC and are likely to suffer greater morbidity as compared to their first attack.

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Correspondence

Alfredo Escartín Arias, Hepato-bilio-pancreatic Surgery Unit, Surgery Department, IRBLleida-University Hospital Arnau de Vilanova, Avenue Alcalde Rovira Roure 80, 25198 Lleida, Spain. E-mail: aescartin.lleida.ics@gencat.cat

Introduction

Although laparoscopic cholecystectomy is the technique of choice for acute cholecystitis (AC), including in elderly patients,[1–4] it is not always performed during the AC episode. A Cochrane review[5] found no significant differences between early and late laparoscopic cholecystectomy, but did find trials indicating that early laparoscopic cholecystectomy during AC seems safe and may shorten the total hospital stay.[3,5–12] However, patient comorbidity, severity of disease, suspicion or presence of choledocholithiasis, patient or surgeon refusal or poor health system design sometimes lead to patients being treated with a combination of antibiotics, analgesia, percutaneous drainage and delayed cholecystectomy.[13]

After medical treatment of AC, it is considered safe to perform cholecystectomy more than 6 weeks after resolution of the symptoms.[6] However, this is not always possible due to the appearance of new episodes of AC or other biliary complications.[1,10,14,15] In patients with AC who did not undergo emergency surgery, a new episode of AC will occur in around 20% of patients, and if biliary complications are included, this number increases to 30%.[14]

The objective of the present study was to analyze patients with non-operated AC who required a new hospital admission for recurrence of AC, in order to analyze the characteristics of the recurrence, to investigate if there is any factor that can predict recurrence, and to assess how the appearance of a recurrence of AC affects the time of the scheduled cholecystectomy.

Patients and methods

A prospective patient registry set up by the General Surgery department of the Arnau de Vilanova hospital in Lleida, Spain. In 2010, the department modified its protocol for diagnosis, classification and treatment of AC according to the Tokyo guidelines[16] and designed a database for prospective data collection.

Data from all patients diagnosed with acute calculous cholecystitis, who presented at the General Surgery department of the hospital Arnau de Vilanova between June 2010 and December 2015 and met the selection criteria were included in the database. The criterion for including patients in the database was referral from the emergency room with primary diagnosis of acute calculous cholecystitis. The exclusion criteria were recurrence of AC, AC as secondary diagnosis, acalculous AC, and concomitant acute cholangitis, pancreatitis, gastro-intestinal cancer or bile duct diseases.

For the current study, patients included in the database who did not undergo initial surgery were selected for further analysis. History of biliary diseases was defined as prior episodes of acute pancreatitis, acute cholangitis or obstructive jaundice. Acute cholecystitis recurrence (ACR) was defined as a new AC occurring after clinical resolution of the symptoms with normal laboratory values and discharge of the patient. Early recurrence was defined as recurrence occurring within 6 weeks, which is the recommended minimum time to wait before operating on the patients. Delayed recurrence was defined as recurrence occurring after 6 weeks or more. Delayed cholecystectomy (DC)[5] was defined as a cholecystectomy performed electively from the sixth week after resolution of the AC. Follow-up of the patients was ended after cholecystectomy in patients who underwent surgery (emergency surgery during an episode of AC or scheduled after the resolution of the symptoms). In non-operated patients, the minimum follow-up was 24 months. For all patients, complications and mortality of the AC episode occurring within 30 days were taken into account.

The following data that we regarded as potentially important in ACR were collected: age and gender, disease severity grade, medical history, physical status according to the classification of the American Society of Anesthesiologists (ASA), history of biliary disease, presence of choledocholithiasis, use of antibiotics, microbiological test results, duration of antibiotic therapy, length of inpatient stay and readmissions. Obesity was not considered. Fitness of the patients was categorized according to the ASA physical status classification score: good physical status (ASA score $\leq$ II) and poor physical status (ASA score > II). Complications were evaluated according to the Clavien–Dindo scale.[17]

Diagnosis

Patients who presented in the emergency room with signs and symptoms compatible with AC underwent a blood test (including transaminases, blood cell count and coagulation study) and abdominal sonography. Abdominal computed tomography scanning and/or magnetic resonance cholangiography were performed when deemed necessary.

Diagnosis was made based on clinical (Murphy's sign, acute upper abdominal pain, right hypochondrial tenderness, fever > 37.5 °C), laboratory (white blood cell count greater than 10×10^9/L), and ultrasound criteria (edematous and >5 mm thickened gallbladder, distended gallbladder, positive sonographic Murphy's sign, pericholecystic fluid, and gallstones).[18] All patients were classified into Grade I (mild), Grade II (moderate) and Grade III (severe) AC according to the Tokyo Guidelines:[18] **Grade I AC** does not meet the criteria for "grade II" or "grade III" AC. **Grade II AC** is associated with any one of the following conditions: (1) elevated WBC count (>18 000/mm^3); (2) palpable tender mass in the right upper abdominal quadrant; (3) duration of complaints > 72 h; (4) marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). **Grade III AC** is associated with dysfunction of any one of the following organs/systems: (1) cardiovascular dysfunction: hypotension requiring treatment with dopamine $\geq$ 5 μg/kg per minute, or any dose of norepinephrine; (2) neurological dysfunction: decreased level of consciousness; (3) respiratory dysfunction: PaO_2/FiO_2 ratio < 300; (4) renal dysfunction: oliguria, creatinine > 2.0 mg/dL; (5) hepatic dysfunction: PT international normalized ratio > 1.5; (6) hematological dysfunction: platelet count < 100 000/mm^3.

Management in the emergency room

All patients were initially assessed in the emergency room, where intravenous fluid therapy, analgesia, proton pump inhibitor and antimicrobial treatment were started.[19] Later, they were admitted to the hospital ward to start antibiotic treatment or to undergo urgent cholecystectomy, according to the clinical judgment and the patient's wish. Patients with grade III AC were treated on a case-by-case basis, with admission to the intensive care unit when necessary.

The following antibiotic treatment protocol was followed:[20,21] Grade I: ceftriaxone + metronidazole; Grade II: ceftriaxone + metronidazole (ertapenem in patients > 75 years old or with risk factors); Grade III: piperacillin/tazobactam. In case of allergy: gentamycin + metronidazole in Grade I–II; tigecycline + quinolone in Grade III. If no cholecystectomy was performed, treatment duration was 4–7 days, usually until normalization of white blood cell count and reduction of the initial reactive protein C levels by half. If cholecystectomy was

performed, antibiotic treatment was discontinued 24 h after surgery, but in case of emphysematosis, vesicular necrosis, perforation or pericholecystic abscess it was maintained for 4–7 days after surgery.

Treatment options

Laparoscopic cholecystectomy was the standard treatment for patients with grade I or grade II AC, while treatment of grade III AC was determined on an individual basis. However, for various reasons, such as advanced age, significant comorbidity burden, concurrent anticoagulant treatment, concomitant choledocholithiasis, symptom duration at admission >7 days or patient's refusal to be operated on, some patients continued antibiotherapy without undergoing surgery. The on-duty surgeons were experienced surgeons, but for the above reasons or due to lack of experience in hepatobiliary laparoscopic surgery it was sometimes decided to continue medical treatment when there was no life-threatening emergency, given the fact that laparoscopic cholecystectomy in AC may be complex.

Patients with evidence of choledocholithiasis were given antibiotic treatment and underwent urgent endoscopic biliary sphincterotomy to drain the bile duct and to allow for laparoscopic cholecystectomy without the need for bile duct exploration. Ultrasound-guided cholecystostomy was performed in patients who could not be operated on and for whom gallbladder drainage was judged indispensable. The cholecystostomy was clamped when there was a small flow of clean bile, and the catheter was withdrawn in the consultation room after the third week. In patients whom more than 400 cc of bile per day continued to discharge, magnetic resonance cholangiography was performed to rule out obstructive choledocholithiasis.

Medical treatment

In admitted patients who did not undergo surgery, treatment included antibiotic therapy according to the protocol, analgesia with paracetamol and metamizole, prophylaxis of thromboembolic disease and proton pump inhibitor administration. Oral intake of water was initiated upon admission if the patient did not present nausea or vomiting, with progressive increase of liquid and food intake according to oral tolerance.

Statistical methods

Since this was an exploratory study, no formal sample size calculations were made. Quantitative variables were expressed as medians and ranges, and qualitative variables were expressed as frequencies and percentages. Categorical variables were compared using chi square or Fischer's exact test. Continuous variables were compared using the Mann Whitney U test. Level of statistical significance was set at $p < 0.050$. Risk of ACR was calculated from the date of first AC discharge using the Kaplan–Meier method and compared with the log-rank test. Patients who underwent DC or died after discharge were censored.

Results

Patient disposition

A total of 998 patients diagnosed with AC were entered into the local registry between June 2010 and December 2015. The decision making and outcomes are shown in Fig. 1. Among the 582 patients operated on for the first episode of AC, after 30 days of hospital follow-up a total of 9 (1.5%) patients presented with biliary complications: 6 choledocolithiases (detected by cholangitis, pancreatitis or jaundice) and 3 biliary stenoses. In total 409 (42%) patients were discharged without symptomatology and with normalized blood test values, and therefore presented a risk of ACR. Of these 409 patients, the median age was 81 (17–99) years and 229 (56%) were male. One hundred twenty-five patients underwent planned DC before ACR at a median of 17 (6–171) weeks. The median follow-up of non-operated patients was 19 (1–73) months. A total of 83 patients (20%) presented with ACR, and 44 patients (11%) presented with other biliary disease. Of those 83 patients, 38 (46%) had unplanned DCduring a subsequent acute admission. Of 45 non-operated ACR patients, 8 (10%) presented with a third episode of AC. The median time to ACR was 1.2 (0.5–24) months. Forty-eight (58%) patients presented with early ACR.

The probability of recurrence over time and by prior history of biliary diseases is shown in Fig. 2. The actuarial risk of recurrence was 13%, 17%, 20% and 23% at 2, 6, 12 and 24 months.

Risk factors for recurrence of acute cholecystitis

Patients treated without index cholecystectomy were divided into those with ACR (n = 83) vs no ACR and no DC (n = 201) to determine potential risk factors for ACR (Table 1).

In the 83 patients who developed ACR the severity of AC and outcomes of the first and subsequent admission were compared (Table 2).

Comparison between early and delayed recurrences

There was early recurrence in 48 patients (58%) and delayed recurrence in 35 patients (42%) (Table 3).

Discussion

The aim of the present study was to determine the outcomes of those patients who presented with AC but did not undergo index cholecystectomy. In addition, an attempt was made to determine who was at risk of early recurrence and would present at the hospital again prior to delayed cholecystectomy. The main findings of this study were that 20% of patients present with ACR, and recurrences are of greater severity as defined by the Tokyo guidelines and are associated with increased morbidity compared to the first admission, including a 6% mortality associated with a second recurrence.

It is the authors view that the optimal treatment for AC is early laparoscopic cholecystectomy, since it reduces hospital stay and

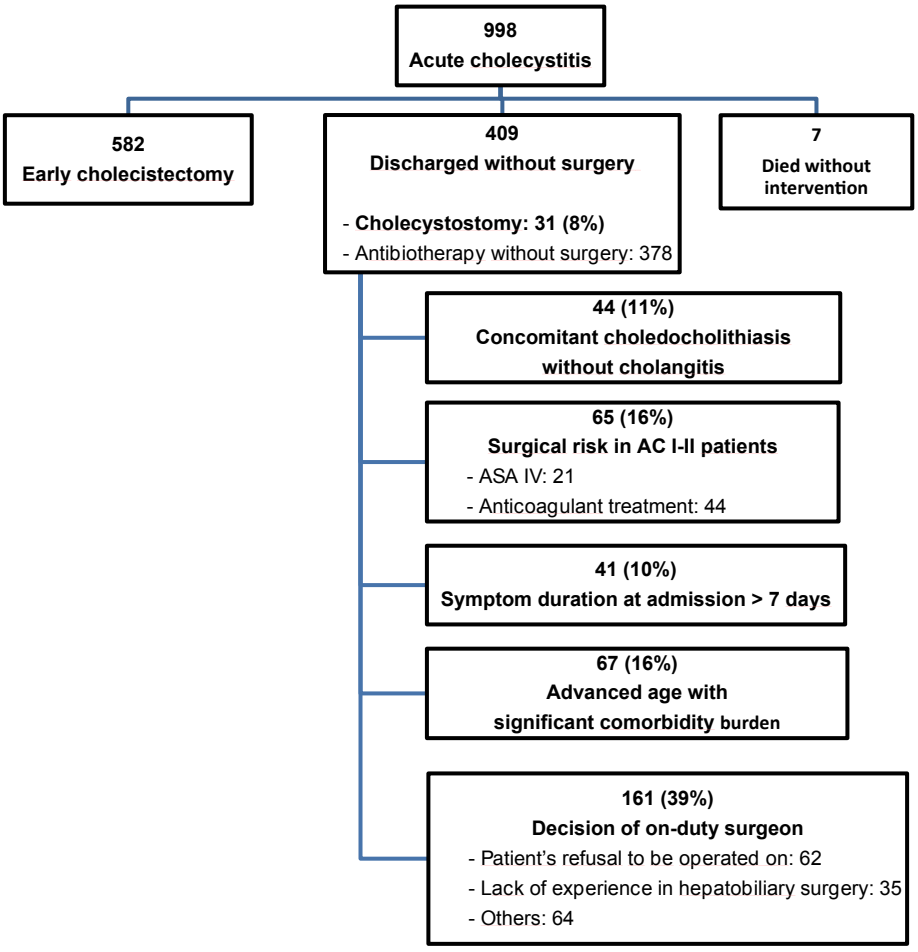

Figure 1 Flowchart detailing the reasons why patients were not operated on after the first episode of acute cholecystitis

the risk of readmission to the hospital for biliary pathology.[3,5,8–11,14,22] However, due to various circumstances such as the significant associated comorbidity (higher with increasing age[3,23]), concomitant choledocholithiasis with no option of endoscopic extraction available (present in around 10%–20% of patients[1,3]) or patient refusal because of slight symptoms or due to the short time elapsed since the onset of symptoms (3–7 days, depending on the studies consulted[1,6]), there are times when index laparoscopic cholecystectomy is not possible. However the current study showed that patient choice was a common reason given. This suggests adequately consenting patients about the likely outcomes of delaying surgery needs to be part of the consent process. In addition improving hospital systems to ensure appropriately trained surgeons, access to endoscopic retrograde cholangiopancreatography, and optimizing comorbidities could all result in improved outcomes. In addition to the reasons previously described, one should realize that laparoscopic cholecystectomy in AC can be a complex procedure, so that experienced surgeons who do not usually perform biliary procedures may decide not to perform these procedures when there is no life-threatening situation. In this regard, it is interesting to read a survey among the members of the Spanish Association of Surgeons that analyzed the preferences of Spanish surgeons for surgical management of AC.[24]

With regard to early laparoscopic cholecystectomy, several studies defend DC, because the authors are of the opinion that the interval is sufficiently long to resolve the inflammatory process so that the cholecystectomy can be done more safely. However, this interval is very variable; a retrospective study carried out by Wang *et al.*[15] observed that DC varies between a few weeks and a few months after AC, and they noted that most studies place it between 6 and 12 weeks; other authors define DC as cholecystectomy after initial conservative treatment or cholecystectomy after resolution of the symptoms. Based on these data, Wang *et al.*[15] defined DC as operations performed at least 1 week after symptom onset. However, in the current study ACR occurred as early as the second week after resolution of the first episode. Half of the patients in this study recurred within 6 weeks, prior to the planned DC. In addition to 20% of admissions due to ACR an additional 11% of patients were readmitted for other complications related to biliary lithiasis, which may be associated with an even higher morbidity and mortality than in

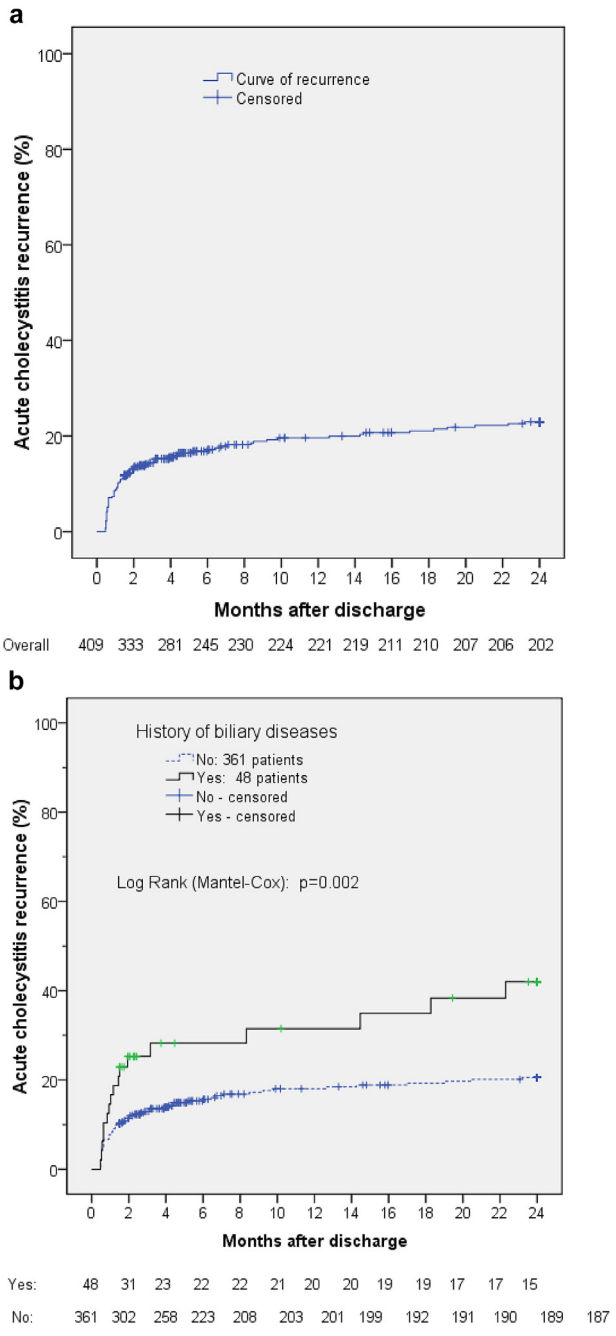

Figure 2 Risk or recurrence of acute cholecystitis. a. Kaplan–Meier plot of overall recurrence of acute cholecystitis. b. Kaplan–Meier plot of recurrence in subgroups of patients with or without a history of biliary disease prior to the first episode of AC. In both plots, censored patients who underwent IC are indicated

the initial episode of AC and that will require a significant amount of care and expenses.

Studies that analyze the characteristics of ACR, and the criteria for ACR are not well defined.[14,15] The current study defined recurrence as a new episode with diagnostic criteria of AC[18] that occurred after the clinical and analytical resolution of the first episode of AC. Regarding the frequency of ACR, the numbers in the literature are conflicting, although they are around 10–25%.[1,5,13,14] In a large population-based analysis, the probability of a gallstone-related event by 6 weeks, 12 weeks, and 1 year after discharge was 14%, 19%, and 29% respectively, with increased risk in younger patients.[14] The presence of a history of prior biliary disease (acute pancreatitis, acute cholangitis or obstructive jaundice) prior to the first episode of AC was found to be related to ACR. This may be due to the presence of local inflammatory alterations or to changes in the flora due to previous inflammatory processes and antibiotic treatments. The current study did not find risk factors for ACR reported by other authors[15,23] (such as age, severity, morbidity of the patient, and duration of previous antibiotic treatment), and therefore was unable to define a group of patients that could benefit from performing DC early. Although it is thought that percutaneous cholecystostomy may serve as the definitive treatment for AC and some ACR studies did not include patients who underwent cholecystostomy,[15] in the authors experience cholecystostomy did not decrease the risk of recurrence. When comparing characteristics of the ACR with the first episode of AC, ACR occurs with grade III AC up to twice as frequently (18%).Regarding the first episode of AC, no differences were observed in length of hospital stay or antibiotic treatment.

The Kaplan Meier curves show that most recurrences appear in the first 2–3 months, probably because from the sixth week on DC begin to be performed, as the censored data in the curve show. The curves also show that the risk is significantly higher in patients with a history of biliary disease. Although other authors define early recurrence as recurrence that occurs within 100 days,[17] the current study defined it as 6 weeks. In fact, more than half of the recurrences (58%) occurred before that time, which prevented these patients from receiving optimal treatment with DC.[22] Only age was related to the appearance of an early recurrence. Other factors, such as the severity or the duration of antibiotic treatment[15] of the first episode, did not influence the time to recurrence. Both early and late recurrences evolved in a similar way. In view of these results, advancing the moment of the DC without waiting for the sixth week, especially in patients <80 years old and in healthy elderly, would probably help reduce the rate of recurrence. A new study is required to corroborate this hypothesis.

The main limitation of the present study is that it was not possible to monitor all patients from the first year of AC regarding DC, given that these scheduled cholecystectomies may have been performed in different centers. Nevertheless, it was possible to collect the clinical manifestations of all biliary recurrences, since all serious or complex pathologies of the health region are admitted to centrally to the tertiary hospital.

In conclusion, at least 20% of non-operated patients presenting with acute calculous cholecystitis will present with recurrence. There are no risk factors that predict recurrence, but

Table 1 Risk factors for recurrence of acute cholecystitis based on factors present at first attack of cholecystitis[a]

	Without Recurrence n = 201	With recurrence n = 83	p
Age, years	84 (26–99)	82 (17–98)	0.082
Age > 80, years	139 (69%)	49 (59%)	0.156
Male gender	106 (52%)	47 (57%)	0.578
Diabetes	55 (27%)	24 (29%)	0.523
Poor physical status	114 (57%)	42 (51%)	0.342
History of biliary disease	15 (7%)	17 (20%)	0.002
Choledocholithiasis	23 (11%)	7 (8%)	0.425
Symptom days at admission	2 (0–30)	3 (0–14)	0.081
AC grade			
Grade I	91 (45%)	34 (41%)	0.561
Grade II	96 (48%)	43 (52%)	0.586
Grade III	14 (7%)	6 (7%)	0.912
Positive blood culture n (%)	18/51 (35%)	10/24	0.638
Cholecystostomy	21 (10%)	6 (7%)	0.473
Days of antibiotic therapy	7 (2–22)	7 (3–20)	0.807
Days of hospital stay	4 (1–30)	5 (1–33)	0.557
30-day complications	11 (5%)	11 (13%)	0.024

[a] All data from first admission.

Table 2 Characteristics of the AC recurrences and comparison with the first episode of AC

	First episode n = 83	Recurrent AC n = 83	p
Choledocholithiasis	7 (8%)	1 (1%)	0.031
Symptom days at admission	3 (0–14)	1 (0–14)	0.000
AC grade III	6 (7%)	15 (18%)	0.034
Positive blood culture	10/24	12/23	0.485
Positive bile culture	6/7	23/28	0.854
Cholecystectomy	0 (0%)	39 (47%)	0.000
Cholecystostomy	6 (7%)	4 (5%)	0.579
Days of antibiotic therapy	7 (3–20)	6 (2–23)	0.303
Days of hospital stay	5 (1–33)	4 (0–33)	0.996
30-day complications	8 (10%)	17 (21%)	0.041
30-day mortality	–	5 (6%)	–
30-day readmission	4 (5%)	5/78 (6%)	0.665

more than half of the ACRs will present within the first 6 weeks after discharge. The population exposed to recurrence will be older patients with worse functional status, and grade III AC will be more frequent than in the first episode, which will result in increased morbidity and potential increase in mortality, in addition to the health costs associated with hospital readmission.

Table 3 Comparison between early and late recurrences

	Early <6 weeks n = 48	Delayed >6 weeks n = 35	p
Patient characteristics			
Age, years	79 (17–98)	86 (18–97)	0.042
Age > 80 years	22	27	0.004
Male gender	27	20	0.952
Diabetes	11	13	0.115
Poor physical status	23	19	0.546
History of biliary disease	11	6	0.572
Choledocholithiasis	6	1	0.135
First AC characteristics			
AC grade III	3	3	0.646
Positive blood culture	4/14	6/10	0.146
Cholecystostomy	5	1	0.157
Days of antibiotic therapy	7 (3–16)	7 (3–20)	0.398
Days of hospital stay	5 (2–27)	4 (1–33)	0.130
30-day complications	5	3	0.718
Recurrence AC characteristics			
AC grade III	8	5	0.896
Positive blood culture	4/14	8/9	0.005
Positive bile culture	15/20	8/8	0.175
Cholecystectomy	27	12	0.045
Days of antibiotic therapy	5 (2–22)	8 (2–23)	0.138
Days of hospital stay	4 (0–33)	4 (2–31)	0.266
30-day complications	8	8	0.548
30-day mortality	4	1	0.395
30-day readmission	3/44	2/36	0.845

All this reinforces the idea that early laparoscopic cholecystectomy should be the treatment of choice in the first episode of AC if there is no physiological or system contraindication.

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Conflict of interests

The authors declare no conflict of interests.

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