ORIGINAL ARTICLE

Early laparoscopic cholecystectomy reduces hospital stay in mild gallstone pancreatitis. A randomized controlled trial

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Abstract

Background: Two strategies for same-admission cholecystectomy in mild gallstone pancreatitis (MGP) exist: early surgery (within 48–72 h from admission) and delayed surgery until resolution of symptoms and normalization of pancreatic tests.

Methods: This was a single-center, open-label RCT. Patients with MGP according to revised Atlanta classification-2012 and SIRS criteria were randomly assigned to early laparoscopic cholecystectomy (E-LC) within 72 h from admission or delayed laparoscopic cholecystectomy (D-LC). Laparoscopic-endoscopic rendezvous was performed when common bile duct stones were found at systematic intraoperative cholangiography. The primary outcome was length of stay (LOS), and the secondary outcomes were complications at 90 days, need for ERCP/choledocolithiasis, conversion, and re-admission. One year of follow-up was carried-on.

Results: At interim analysis, 52 patients were randomized (26 E-LC, 26 D-LC). E-LC versus D-LC was associated with a significantly shorter LOS (median 58 versus 167 h; $P = 0.001$). There were no differences in ERCP necessity for choledocolithiasis between the two approaches (E-LC 26.9% versus D-LC 23.1%, $P = 1.00$). No differences in postoperative complications were found.

Conclusions: E-LC approach in patients with MGP significantly reduced LOS and was not associated with clinically relevant postoperative complications.

Trial registration: clinicaltrials.gov (NCT02590978).

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Introduction

Acute pancreatitis is the third most common gastrointestinal cause for hospital admission in the United States of America even above acute appendicitis. It has a variable incidence of 14–45/100,000 inhabitants[1,2]; up to 70% is secondary to gallbladder stones or sludge.[3] Chile has one of the world's highest prevalence of gallstones affecting 27% of the adult population and leading to a high incidence of pancreatitis: from 28 to 62/100,000 inhabitants.[4,5] There is consensus regarding same-admission cholecystectomy in MGP given an unacceptable 17%–33% recurrent gallstone-related complications and re-admissions within first month from discharge of patients who are not treated with surgery. This strategy is supported by recent RCTs and guidelines.[6–11]

Cholecystectomy in a hostile field can lead to a potential increase in perioperative complications. Concerns regarding this issue arise from Ranson's studies where either cholecystectomy or common bile duct (CBD) exploration at the first week had a mortality of 9.1% and 67% in mild and severe pancreatitis, respectively.[12]

Thirty years later, in the era of computed tomography (CT) and laparoscopic surgery, some groups have challenged these concerns suggesting that E-LC for MGP should be done within 48–72 h of admission. Other groups discourage this approach arguing that an increase in surgery difficulties secondary to edema and ileus might lead to high morbi-mortality.[13,14] Moreover, it remains unclear whether the severity assessment can be properly conducted within the first 24–48 h when the

patient can still develop necrosis or organ failure precluding early surgery.[15–17] In contrast, several retrospective studies[18–21] and one randomized trial[22] have shown interesting results including a reduced LOS without morbidity increase. None of these studies included patients with CBD stones suspicions. We conducted this RCT to evaluate whether E-LC can reduce LOS in patients with MGP versus conventional D-LC regardless of CBD stones risk.

Methods

Design

This was a single-center, randomized, open-label controlled trial conducted at the service of surgery of a teaching hospital from the University of Chile (Santiago, Chile). The aim of this study was to compare E-LC (within 72 h from admission) and D-LC for LOS and surgical outcomes. The study protocol was approved by the Ethics Committee of the Hospital del Salvador. It followed the Principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment. The study was registered on ClinicalTrails.gov in December 2015 (NCT02590978).

Patients

All patients aged 18–70 admitted between January 2016 and October 2017 with first episode of MGP were evaluated for eligibility. The diagnosis and severity was based upon the revised Atlanta classification-2012 and SIRS criteria (see below, *Severity Assessment*).[23] Acute pancreatitis was diagnosed when at least two out of three criteria were met: acute upper abdominal pain, elevated serum amylase/lipase levels (more than three times the upper limit of normal range), and evidence of pancreatitis on any imaging modality. All patients underwent abdominal ultrasonography (US) upon admission and the biliary etiology was confirmed when stones or sludge were present in the gallbladder. All other etiologies were excluded. Exclusions criteria were: 1) SIRS, immediate exclusion if $\geq$2 of following were met: heart rate >90/min, respirations >20/min, fever or white blood count <4000 or >12,000/mm^3 or core temperature <36 °C or >38 °C, or one of SIRS criteria positive after 24 h of additional observation time, (2) cholecystitis at US, (3) suspected/confirmed cholangitis according to Tokyo Guidelines,[24] (4) history of Roux-en-Y gastric by-pass or open supraumbilical surgery, (5) acute alcohol consumption, (6) chronic hepatic/pancreatic disease, (7) comorbidities contraindicating emergency surgery, (8) mental condition that precludes informed consent, (9) pregnancy, (10) patient refusal, or (11) no endoscopist availability. No exclusions were made based on choledocolithiasis risk.

Severity assessment

We based the severity assessment on the revised Atlanta classification-2012 and SIRS criteria. According to this, MGP was defined as the absence of organ failure and local/systemic complication. Patients with organ failure were defined as those with a Marshall score $\geq$2 for one of three organ systems (respiratory, cardiovascular, or renal).

Systemic complications were defined as any chronic disease exacerbation triggered by pancreatitis. Local complications were defined as acute peri-pancreatic fluid collection, pancreatic and/or peri-pancreatic necrosis, necrotic collection, walled-off necrosis, splenic and portal vein thrombosis, and intestinal ischemia. For local complication assessment, all candidates underwent a contrast-enhanced abdominal CT after 24 h from the onset of symptoms.

Positive SIRS was an exclusion criterion. The presence of only one of four SIRS criteria was observed for 24 additional hours and the exclusion was definitive if it remained after medical care. Patients with more than 48 h from the onset of symptoms at the moment of recruitment without any severity criteria were considered to have had sufficient evolution time regardless of whether this time passed at the hospital or not.

Randomization

The study coordinator performed the recruitment and informed consent process. The patients were randomized once they met the eligibility criteria and gave informed consent. Randomization was conducted using a centralized web-based software via variable permuted blocks. Neither the participants nor the investigators were blinded to the group allocation due to the invasive nature of the interventions and the logistics involved in the procedures.

Therapeutic approaches

Both groups received standard medical care with intravenous fluid therapy, analgesia (NSAID), anti-emetics, and fasting. Oral feeding was restarted progressively from the second day if abdominal pain/nausea decreased. No antibiotics were used. In the E-LC group, surgery was performed within 72 h from admission. In the D-LC group, surgery was planned after complete resolution of abdominal tenderness, oral feeding, and a downward trend in pancreatic laboratory values.

Procedures

A standard 4-port LC was performed with systematic intraoperative cholangiography (IOC) in all patients. CBD stones images and/or lacks of duodenal filling with CBD dilatation on IOC were considered indications for biliary exploration via laparoscopic-endoscopic rendezvous (LERV) approach. In this procedure, the direct cannulation of the papilla of Vater and the sphincterotomy is obtained using a guide wire introduced through the cystic duct. All surgeries and IOC findings were recorded and were performed by staff surgeons from the HPB Department. We considered subjects for discharge on postoperative day one when the patients had decreasing pain managed with oral analgesia, adequate oral intake, and unremarkable physical exam.

Outcomes

The primary endpoint was LOS. Secondary endpoints were divided into intraoperative endpoints (operative time, IOC findings, ERCP necessity, and conversion to open cholecystectomy) as well as post-operative complications (bleeding, biliary leakage, abdominal and wound infection, medical complications, and re-admissions at 90 days). We used the Clavien-Dindo classification as the complications registry. Outpatient follow-ups were carried on post-operative days 7, 30, and 90. Telephone follow-ups were performed one year after surgery.

Statistics and sample size calculation

The study was powered for LOS. Based on a previous study,[22] the sample size needed for the comparison of the average LOS was calculated using an expected standard deviation of three days, a power of 80%, a confidence level of 95%, and treatment effect duration of 1.7 days. Using the O'Brien-Fleming method, a required sample size of 100 patients was obtained with an interim analysis after 50 patients. According to this method, the study could be terminated after 50 patients if there was a difference in LOS with an alpha level of 0.005.[25] The quantitative variables were described using median and range, and the categorical variables by distribution of absolute and relative frequencies. The Wilcoxon–Mann–Whitney test was used for the comparison of quantitative variables and the Fisher's test for categorical variables. Statistical analyses were performed using STATA12 (StataCorp, Texas, USA).

Results

From January 2016 to November 2017, 146 patients with biliary pancreatitis were assessed for eligibility. The flowchart of the study population is shown in Fig. 1. Fifty-two eligible patients were enrolled and randomly assigned: 26 to the E-LC group and 26 patients to the D-LC group. Both groups were comparable in terms of demographics, liver laboratory, and images findings at admission (Table 1). All randomized patients completed the assigned interventions. There was no conversion to open cholecystectomy and the median operative times were similar between groups (E-LC, 72.5 versus D-LC, 77 min; $P < 0.542$). Inflammatory intraoperative findings were more common in the E-LC group than in the D-LC group (Table 2). One 36-year-old female assigned to the E-LC group had peritoneal fat necrosis plaques and gallbladder edema. IOC showed CBD stones or lack of duodenal filling in 7 (26.9%) of 26 patients in the E-LC group as compared with 6 (23.1%) of 26 patients in the D-LC group ($P = 1.0$). Following the study protocol, patients with positive IOC findings underwent an intraoperative CBD exploration through LERV approach confirming CBD stones in all cases. CBD stones retrieval was successful in almost every patient except for one 53-year-old female from the D-LC group; biliary endoprosthesis was left for a further endoscopic revision. This patient was discharged on the second post-operative day without any complications. ERCP was repeated two months later, and biliary endoprosthesis with residual CBD stones were extracted for a clean retrograde cholangiography.

Regarding the primary outcome of the study, the median LOS was significantly shorter in patients undergoing E-LC as compared with the D-LC group (58 vs. 167 h; $P < 0.001$). No surgery or ERCP-related complications occurred. No differences were found in postoperative complications between groups. Three patients in the D-LC group and one in the E-LC group had minor medical complications (Clavien-Dindo $\leq$II) at discharge. No major complications were registered (Table 3).

Interim analysis

As described previously, we performed an interim analysis after recruitment of 52 patients. The resulting *P*-value fulfilled the cut-off value needed to finish the study.

90 days follow up

All patients completed the follow-up schedule. Here, 2/52 patients (one from each group) described the onset of intermittent diarrhea but without alarming symptoms; these were spontaneously resolved. Two patients were re-admitted within this time. The first was a 65-year-old male in the E-LC group with no declared history of high corticosteroid doses for nasal polyposis. He was readmitted five days after surgery for infectious diarrhea and treated successfully with antibiotics. The other was a 53-year-old woman with retained CBD stones (described above).

12-month follow up

A 78.8% (41/52) of 12-month follow up was achieved. There were no re-admissions related to gastrointestinal diseases. Five patients presented diarrhea and three of these recovered spontaneously (two from the E-LC group and one from the D-LC group) and the other two (D-LC group) underwent a complete study by a gastroenterologist with no positive findings. Two more patients (one from each group) were followed up for chronic non-specific pain ruling out any organic disease. Finally, one 65-year-old male from the E-LC group was readmitted for elective vascular surgery six months after MGP.

Discussion

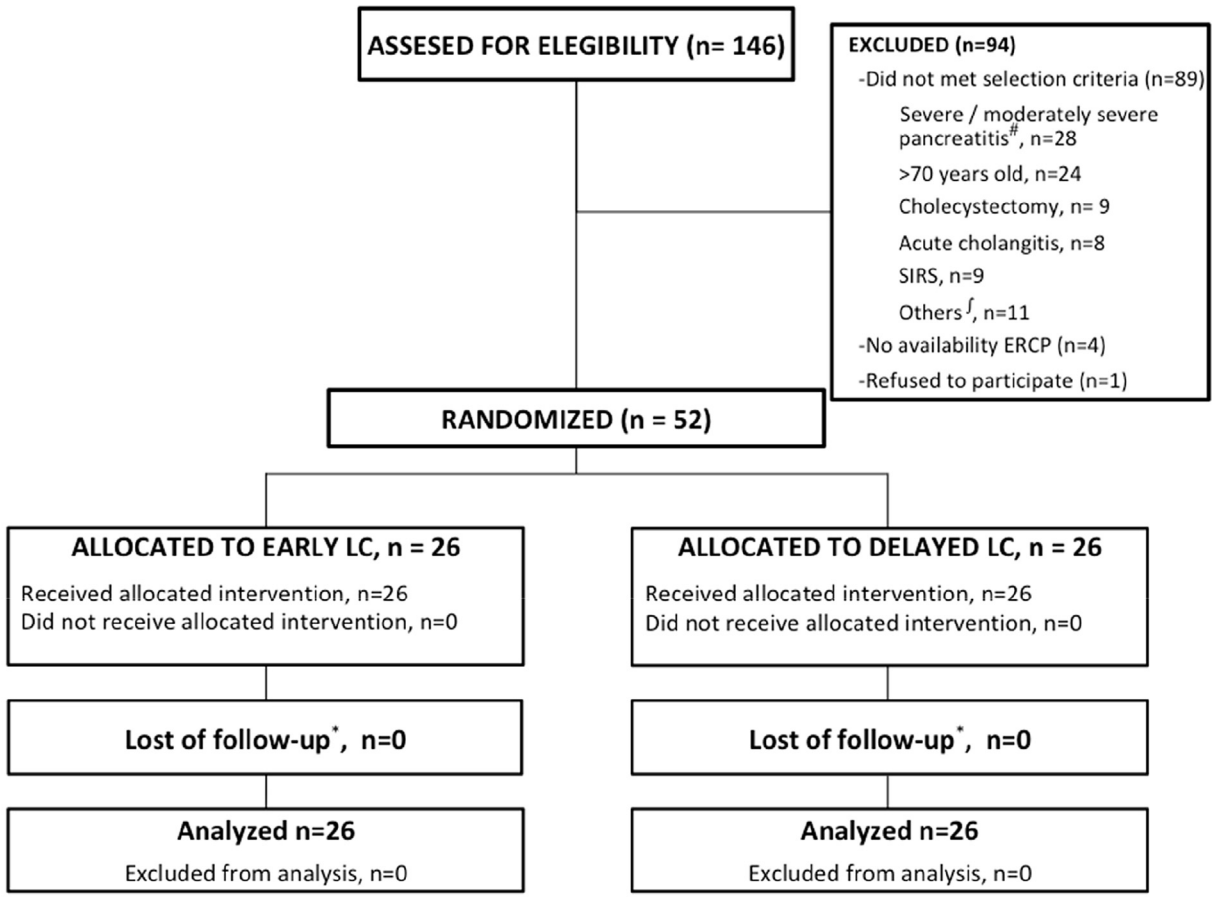
This single-center randomized trial shows that patients with MGP regardless of the CBD stones risk can be treated early reducing LOS to less than 50% versus standard care without clinically relevant morbidity. Moreover, CBD stones frequency at systematic IOC was not different between groups and was handled successfully using the laparoscopic-endoscopic approach.

Cholecystectomy during index admission for MGP is the standard treatment for these patients but optimal timing for surgery during this time period has not been studied in detail. Concerns remain about increased risk of surgical complications in this setting due to local inflammation, unrecognized

pancreatic local complications, and surgery as a second inflammatory trigger.

Few studies have compared E-LC with D-LC. A meta-analysis from Randial *et al.* included three retrospectives studies and one RCT; 207 patients operated within 48 h from admission and 429 operated after 48 h. The LOS was significantly shorter in the E-LC group as compared with D-LC, and there were no differences in the complication rate.[26] The study from Aboulian *et al.*[22] included in this meta-analysis is the only RCT until this work. Here, 50 patients with MGP according to Ranson's score were assigned to E-LC and D-LC. Patients with suspected CBD stones were excluded (total bilirubin >4 mg/dL or CBD stone in US). The E-LC group had a significantly shorter median LOS than the D-LC group (3 versus 4 days; $P = 0.0016$). No intraoperative or postoperative complications were registered on any arm. CBD stones detected on systematic IOC were extracted with a postoperative ERCP (E-LC, 6/25 versus D-LC, 3/25; $P = 0.27$).

There were important differences between the former study and our work. First, we used the revised Atlanta classification-2012 complemented with SIRS. Moreover, we used a systematic contrast-enhanced abdominal CT after 24 h from the onset of symptoms for local complication assessment. Of 28 people excluded for severe or moderately-severe gallstone pancreatitis, 16 patients had local complications at abdominal CT (Fig. 1). Surprisingly, 10 patients from this group had no organ failure or SIRS. These findings and other studies challenge the need to wait 72 h to perform the abdominal CT.[8] Second, we did not exclude patients according to CBD stone risk. Using only "bilirubin



LC, laparoscopic cholecystectomy
Marshall score ≥2, n=18
Local complications, n=16 (n=7, pancreatic/peri-pancreatic necrosis; n=7 peri-pancreatic collections; n=1 venous mesenteric thrombosis; n= 1, emphysematous pancreatitis)
∫ n=3, previous open supraumbilical surgery; n=3, comorbidities contraindicating emergency surgery; n=3, acute alcohol consumption; n=1, chronic hepatic/pancreatic disease; n=1 no CT availability.
* 90 days follow-up.

Figure 1 Flowchart of study participants

Table 1 Demographics and admission values of the study participants

Characteristic	Early LC (n = 26)	Delayed LC (n = 26)
Age, years, median (range)	39.5 (24–65)	44.5 (20–67)
Female, *n* (%)	19 (73.1)	20 (76.9)
Body mass index, kg/m^2, median (range)	29.2 (17.5–40.6)	28.2 (24.6–40.3)
Duration of symptoms,[a] hours, median (range)	24 (16–29)	22 (15–33)
Comorbidities, *n* (%)	9 (34.6)	7 (26.9)
MAP, mmHg, median (range)	94.5 (62–105)	92 (86–115)
Heart rate, beats/min, median (range)	76 (56–102)	76 (71–109)
Temperature °C, median (range)	36.3 (36–37.1)	36.2 (36–37.3)
APACHE II score, median (range)	5 (5–7)	5 (3–7)
WBC, median (range)	11,450 (4000–20,200)	9550 (4600–19,500)
Total bilirubin, mg/dL, median (range)	2.5 (0.22–7.8)	3.6 (0.44–9.82)
ALP, U/L, median (range)	207 (74–874)	229 (70–523)
GGT, U/L, median (range)	406 (24–1947)	346 (38–1312)
AST, U/L, median (range)	223 (20–1184)	205 (24–946)
ALT, U/L, median (range)	360 (28–1243)	295 (22–1301)
Lipase, mg/dL, median (range)	2613 (189–35,548)	1763 (234–39,947)
CRP, mg/L, median (range)	12.1 (0.7–286)	13.2 (0.6–135)
Images		
Abdominal-US		
CBD stones, *n* (%)	3 (11.5)	1 (3.8)
CBD diameter, mm, median (range)	5 (4–15)	5 (5–15)
Abdominal-CT		
CBD stones, *n* (%)	1 (3.8)	1 (3.8)
CBD diameter, mm, median (range)	5 (3–15)	5 (4–19)

LC, laparoscopic cholecystectomy; MAP, mean arterial pressure; WBC, white blood cell; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; US, ultrasonography; CBD, common bile duct; CT, computed tomography.
[a] Before admission.

>4 mg/dL" as an exclusion criterion would have excluded 18/52 subjects. Only 12/52 patients in our trial had normal bilirubin levels. Despite these differences, our results confirm previous findings supporting the early surgical approach in MGP.

Severity assessment

One of the most critical aspects of early surgery in MGP is the accuracy in predicting the severity. The Atlanta-2012 severity classification requires 48 h of observation and works retrospectively. Here, a minimal of 48 h of evolution from the onset of symptoms was required for the assessment regardless of whether this time occurred at home or after admission—this is different from the original concept. We believe that this "48-h window" time-lapse is the key for correct severity assessment.

In addition, many groups have validated the SIRS criteria as a severity predictor. Persistent SIRS is associated with 25% mortality versus 8% for transient SIRS in pancreatitis.[10,30] Much earlier, Yaghoubian *et al.* used a heart rate >110 beats/minute which is part of SIRS criteria as an exclusion criterion.[31] This group validated this strategy with more than 300 patients in different studies showing no severity progression or mortality in MGP.[18–20,22] Based on this data, we associated the revised Atlanta classification-2012 with SIRS criteria to increase its accuracy. Here, one 36-year old female assigned to the E-LC group with no local complications at abdominal CT at 40-h from onset of symptoms had necrotic peritoneal fat plaques at laparoscopy. Cholecystectomy and post-operative observation were uneventful, and she was discharged on the second postoperative day. Follow-up CT performed ten days after discharge only showed postsurgical changes. No re-admission or gastrointestinal disorders were registered at 90 days and 1-year follow-up. This patient had no exclusion criteria but presented at admission with leukocytosis and elevated C-protein reactive (CRP = 288 mg/L). According to protocol, 24 h of additional observation was completed to resolve leukocytosis facilitating her inclusion in the study. Despite the excellent outcome of this patient, we are aware that there are still some patients with intermediate severity not detected by scoring systems. Using a CRP limit of 100 mg/L as

Table 2 Operative results

Results	Early LC ($n = 26$)	Delayed LC ($n = 26$)	Total ($n = 52$)	*P* value
LC, *n* (%)	19 (73.1)	20 (76.9)	39 (75)	0.500
LERV, *n* (%)	7 (26.9)	6 (23.1)	13 (25)	1.000
Operative time, minutes, median (range)	72.5 (40–183)	77 (50–150)	75 (40–183)	0.542
LC	65 (40–120)	75 (50–90)	70 (40–120)	0.401
LERV	105 (45–183)	112 (77–150)	110 (45–183)	0.883
Intraoperative findings, *n* (%)				
Acute cholecystitis	1 (3.8)	0 (0.0)	1 (1.9)	0.501
Gallbladder edema	19 (73.1)	8 (30.7)	27 (51.9)	0.003
Ascites	3 (11.5)	0 (0.0)	3 (5.7)	0.115
Necrotic peritoneal fat plaques	1 (3.8)	0 (0.0)	1 (1.9)	0.501
Conversion, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
CBD findings in IOC, *n* (%)				
CBD stones images	5 (19.2)	6 (23.1)	11 (21.1)	0.513
Lack of duodenum filling + CBD dilatation	2 (7.7)	0 (0.0)	2 (3.8)	0.244

LC, laparoscopic cholecystectomy; LERV, laparoscopic-endoscopic rendezvous; CBD, common bile duct; IOC, intraoperative cholangiography.

Table 3 Length of stay, complications, and re-admissions

Results	Early LC ($n = 26$)	Delayed LC ($n = 26$)	*P* value
Length of stay, hours, median (range)	58 (26–109)	167 (98–325)	<0.001
Time admission to surgery, hours, median (range)	35 (7–70)	140 (87–278)	<0.001
Complication at discharge, *n* (%)	1 (3.8)	3 (11.5)	0.612
Clavien-Dindo $\leq$ II			
Allergic rush	1	1	
Urine retention		2	
Re-admission at 90-days, *n* (%)	1 (3.8)	1 (3.8)	1.000
Acute diarrhea	1		
Retained CDB stones[a]		1	

LC, laparoscopic cholecystectomy; CBD, common bile duct.
[a] Programmed re-admission for stent retrieval and CBD stones extraction.

the exclusion criteria might improve severity assessment as described in other studies.[6,7]

CBD stones and ERCP

The role of early routine ERCP in gallstone pancreatitis without cholangitis is a controversial issue. The meta-analysis of Burstow *et al.*[32] reviewed 11 RCTs and showed non significant decrease in overall complications of early ERCP in MGP (OR 0.67; 95%CI: 0.43–1.03). Nevertheless, we used a LERV approach but only in those patients where CBD stones were highly suspected according to the IOC findings (presence of CBD stones and/or lack of duodenal filling/CBD dilatation). LERV allow to treat patients with gallstones and CBD stones in a single-stage procedure with proven benefits (lower morbidity, post-ERCP pancreatitis, and LOS).[33] This has been well supported only in patients with cholelithiasis and concurrent choledocholithiasis, but there is still low quality level of evidence for MGP. Although this study was not focused on LERV performance, our results and the current evidence raise the need of more investigations in this area.

The E-LC has several benefits for patients and health insurers. The most obvious advantage is related to the reduction of LOS and faster health recovery with an early return to work. Additionally, one-time LC with IOC resolves a common diagnosis issue about CBD stones suspicion saving unnecessary image studies as magnetic resonance cholangiography. One-year follow up of our patients demonstrate that IOC is a reliable method for ruling out CBD stones. Moreover, a single-stage surgery is an efficient strategy for CBD stones and decreases the surgical and anesthetic risk leading to a remarkable positive impact in costs.

This trial has some limitations beginning with the single center design and local practices such as the routinely use of IOC and immediate availability of intraoperative ERCP. These aspects might reduce the external validity of our findings. Moreover, our study was not sufficiently powered to detect surgical-related morbidity as would be desirable. Design a trail to evaluate the safety of early approach would need a large sample size to demonstrate any differences if there were any. Nevertheless, we believe that the LOS is a good surrogate marker of all patient outcomes. Related to the discharge criteria, the non-blinded design of this study might bias the recovery time in the two groups. The LOS in E-LC group was 2,4 days (median), which reflects an uneventful evolution. We did a rigorous 30 and 90-days follow-up and no differences were found related to complications or re-admissions, supporting that discharge was not rushed. On the other hand, when comparing our controlled group with *early surgery* trials[22] (commented above) or those that focused on surgery within same-admission, there are small differences in LOS. For instance, Da Acosta *et al.*[6] compared same-admission surgery to interval cholecystectomy (surgery differed to four weeks after MGP). In the same-admission arm, which is comparable to D-LC group of our trial, patients were eligible for surgery when no need for opioid analgesics and tolerance of a normal oral diet was achieved. These clinical criteria are similar to those used in our study. Same-admission arm was operated on day 6 (median) with a total LOS of 8 days (median). In the present study, D-LC group was operated on day 5,8 (median) from admission and had a LOS of 6,9 days (median), which is very similar than previously reported (see Table 3).

This study offers complementary data supporting early cholecystectomy in the setting of MGP. The combined use of severity assessment scores such as the revised Atlanta classification-2012, SIRS criteria, and a "48-h window" observation can shorten the LOS without clinically relevant morbidity.

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Authors' contributions

Francisco Riquelme, MD: Conception and design, analysis and interpretation, writing the article, and approving the final version of the manuscript.

Boris Marinkovic, MD: Conception and design, analysis and interpretation, writing the article, and approving the final version of the manuscript.

Marco Salazar, MD: Conception and design, collecting the data, critical revision of the article, and approving the final version of the manuscript.

Waldo Martínez, MD: Collecting the data, critical revision of the article, and approving the final version of the manuscript.

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Jorge Muñoz, MD: Collecting the data, critical revision of the article, and approving the final version of the manuscript.

Andrea Canals, MD: Collecting the data, analysis and interpretation, critical revision of the article, and approving the final version of the manuscript.

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Conflicts of interest

Drs. Riquelme, Marinkovic, Salazar, Martínez, Catán, Uribe-Echevarría, Puelma, Muñoz, Canals, Astudillo and Uribe have nothing to declare.

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