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Endoscopic Gallbladder Stenting to Prevent Recurrent Cholecystitis in Deferred Cholecystectomy: A Randomized Trial

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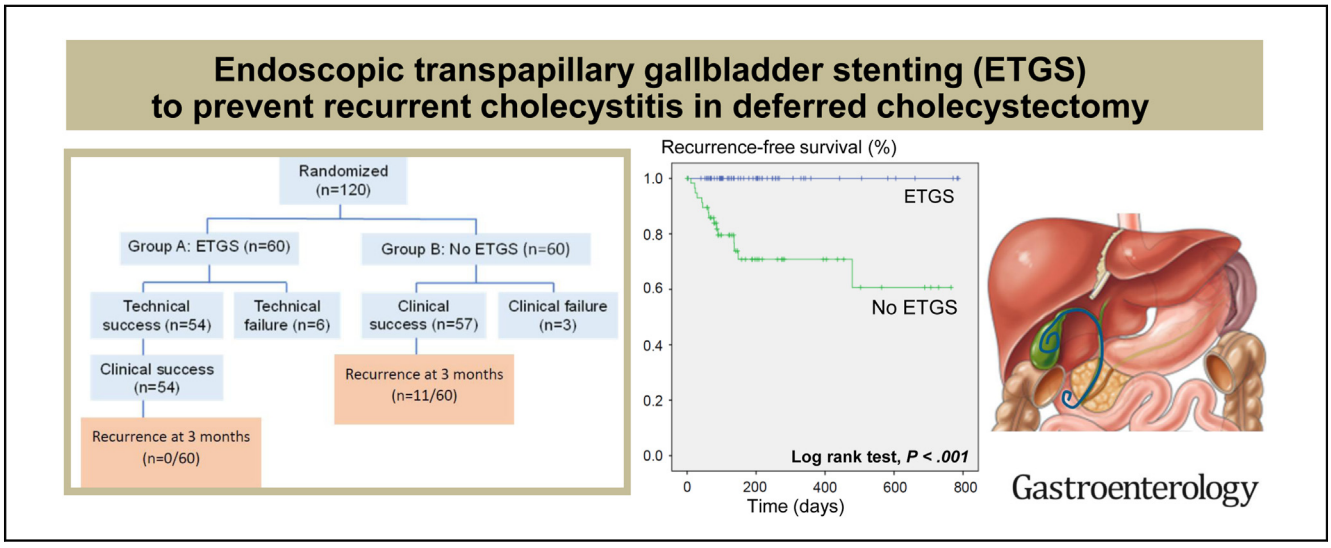
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e8. Learning Objective: Upon completion of this CME activity, successful learners will be able to evaluate knowledge about the use and difference in technical performance of many nonsurgical treatments for acute cholecystitis.



BACKGROUND & AIMS: Endoscopic transpapillary gallbladder stenting (ETGS) has been proposed as one of the adjunctive treatments, apart from antibiotics, before surgery in patients with acute cholecystitis whose cholecystectomy could not be performed or was deferred. Currently, there are no comparative data on the outcomes of ETGS in those who receive and do not receive ETGS. We aimed to compare the rates of recurrent cholecystitis at 3 and 6 months in these 2 groups. **METHODS:** Between 2020 and 2023, eligible acute calculous cholecystitis patients with a high probability of common bile duct stone, who were surgical candidates but could not have an early cholecystectomy during COVID-19 surgical lockdown, were randomized into groups A (received ETGS) and B (did not receive ETGS). A definitive cholecystectomy was performed at 3 months or later in both groups. **RESULTS:** A total of 120 eligible patients were randomized into group A (n = 60) and group B (n = 60). In group A, technical and clinical success rates were 90% (54 of 60) and 100% (54 of 54), respectively. Based on intention-to-treat analysis, group A had a significantly lower rate of recurrence than group B at 3 months (0% [0 of 60] vs 18.3% [11 of 60]; $P = .001$). At 3–6 months, group A showed a nonsignificantly lower rate of recurrent cholecystitis compared to group B (0% [0 of 32] vs 10% [3 of 30]; $P = .11$). **CONCLUSIONS:** ETGS could prevent recurrent cholecystitis in acute cholecystitis patients with common bile duct stone whose cholecystectomy was deferred for 3 months. In those who did not receive ETGS, the majority of recurrences occurred within 3 months. (Thaiclinicaltrials.org, Number TCTR20200913001)

Keywords: Transpapillary Gallbladder Stenting; Acute Cholecystitis.

Current guidelines recommend early laparoscopic cholecystectomy in patients with acute cholecystitis to prevent future potentially fatal attacks.[1,2] In real-life

Abbreviations used in this paper: **CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; ETGS, endoscopic transpapillary gallbladder stenting; EUS, endoscopic ultrasound; ITT, intention to treat; PP, per protocol.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Although a handful of retrospective series have demonstrated endoscopic transpapillary gallbladder stenting (ETGS) as a drainage option before surgery in acute cholecystitis patients who did not respond to antibiotics alone and when cholecystectomy could not be performed, there are no comparative outcomes of those receiving ETGS compared to those not receiving ETGS.

NEW FINDINGS

This is the first randomized controlled trial, to our knowledge, to show that in acute cholecystitis patients with common bile duct stone whose cholecystectomy was deferred, those receiving ETGS had a significantly lower rate of recurrence than those without ETGS at 3 months, and there was no difference in recurrence rates at 3–6 months between the 2 groups in those who were still waiting for surgery.

LIMITATIONS

The majority of patients in this study had a mild to moderate severity of acute cholecystitis and were not high-risk surgical candidates.

CLINICAL RESEARCH RELEVANCE

ETGS should be considered as a bridging treatment in mild to moderate acute cholecystitis patients with common bile stone whose cholecystectomy is deferred for 3 months.

BASIC RESEARCH RELEVANCE

Although there is a potential benefit of ETGS beyond 3 months in those who are still not receiving cholecystectomy, the real clinical benefits beyond 3 months in those with more severe acute cholecystitis and never-surgery candidates remain to be determined.

practice, the median time to cholecystectomy in such patients ranged from 60 to 180 days in several centers.[3–6] Reasons for deferred cholecystectomy include unstable patient medical status at presentation due to severe sepsis and limited availability of operative theater and scheduling, especially during the COVID-19 surgical lockdown.[7–16] Several organizations, such as the British Intercollegiate General Surgery Guidance, Society of American Gastrointestinal and Endoscopic Surgeons, and European Association for Endoscopic Surgery, advocated for more conservative management rather than surgery for patients with acute cholecystitis during the pandemic whenever possible.[17–19] During the COVID-19 period, 73% of patients with acute cholecystitis received a conservative strategy of antibiotic treatment alone (58%) and percutaneous cholecystostomy (15%) for patients not responding to antibiotics.[20] A previous retrospective study of 226 patients with acute cholecystitis who had cholecystectomy deferral demonstrated recurrent cholecystitis in 13.7% of cases during a median follow-up of 308.5 days after receiving only antibiotic treatment. Early recurrence was also documented in 8.4% of patients within the first 3 months while waiting for elective cholecystectomy.[21] Among gallstone disease patients with deferred cholecystectomy after common bile duct (CBD) clearance, cholecystitis was the most frequent (47%) recurrence of biliary events, with the first episode occurring at a median time of 29.5 days (interquartile range, 15–82).[22]

Percutaneous cholecystostomy has been the mainstay treatment for temporary gallbladder drainage in patients with acute cholecystitis who are poor surgical candidates at the time of diagnosis and have shown subsequent clinical improvement.[1] The percutaneous approach has been shown to carry a high rate of procedure-related adverse events of up to 20% in the long term, such as tube dislodgement, early occlusion, or leakage.[23–26] Because approximately one third of both cholecystostomy tube dislodgement (32.5%) and occlusion (30%) occur within 1 month after percutaneous cholecystostomy,[24] reinterventions are required in those who are waiting for cholecystectomy for longer than 3 months.

To obviate cholecystostomy tube–related issues, an endoscopic approach is an alternative treatment for gallbladder drainage in acute cholecystitis patients at moderate to high risk for surgery that can be done by either endoscopic transpapillary gallbladder stenting (ETGS) or endoscopic ultrasound (EUS)–guided transmural gallbladder stenting.[1] EUS-guided transmural gallbladder stenting offers permanent gallbladder drainage, but surgeons need to close the fistula tract when a future cholecystectomy is performed. Given its ability to preserve gallbladder anatomy, ETGS provides an effective bridge therapy before elective cholecystectomy.[9] Among acute cholecystitis patients with concomitant CBD stone who need endoscopic retrograde cholangiopancreatography (ERCP), ETGS can be performed in the same session with 1 duodenoscope.[9,27–31] However, there has been no prospective trial of ETGS in acute cholecystitis patients who were fit for surgery but for whom cholecystectomy was deferred.

The primary objective of our study was to compare the rate of recurrent cholecystitis at the 3-month follow-up after ETGS in acute cholecystitis patients with deferred cholecystectomy who received and did not receive ETGS. The secondary objectives were to compare the rate of recurrent cholecystitis at 6 months after ETGS in those who still did not have cholecystectomy and determine postprocedural outcomes, such as technical success rate, clinical success rate, and procedure-related adverse events of ETGS.

Materials and Methods

We enrolled acute calculous cholecystitis patients with a high probability of CBD stone at our institution between November 2020 and February 2023. All patients were evaluated by the surgical team before ERCP. Eligible criteria included patients with acute cholecystitis who had a high probability of CBD stone and had cholecystectomy deferral (at 3 months or later after the onset of symptoms) for reasons such as potential reversible biliary sepsis and limited operative scheduling, especially during the COVID-19 pandemic. We used the Tokyo Guidelines 2018 to diagnose acute cholecystitis; the presence of

right upper quadrant abdominal pain with tenderness, fever, leukocytosis and compatible transabdominal ultrasonography or computed tomography of the abdomen.[32] The severity of acute cholecystitis was classified as grade 1 (mild), 2 (moderate), or 3 (severe) based on the Tokyo Guidelines 2018. The presence of a high probability of CBD stone was determined by using the American Society for Gastrointestinal Endoscopy criteria, including CBD stone seen on imaging, acute cholangitis, or total bilirubin of >4 mg/dL with dilated CBD.[33] Exclusion criteria before randomization included gallbladder perforation, septic cholangitis in never-surgery candidates (American Society of Anesthesiologists physical status of >3), severe coagulopathy, previous ERCP with CBD stone removal, and refusal to participate in the study.

After obtaining written informed consent from eligible patients, an investigator used sealed opaque envelopes with a block size of 4 in a 1:1 ratio for randomization. The randomization was performed just before the ERCP procedure started and before cholangiogram was obtained but not intraprocedurally because we believed that if the randomization was done after cholangiogram, in the cases with large CBD stones and difficult cystic duct anatomy, the performing endoscopist may be biased and exclude them to make the success rate of ETGS higher than usual. Eligible patients were randomly categorized into 1 of 2 groups: group A (those who received ETGS) and group B (those who did not receive ETGS). The patients or endoscopists could not be blinded because of the nature of the interventions. Once acute cholecystitis was diagnosed, intravenous antibiotics (third generation cephalosporin or equivalent) were administered. All patients were admitted to the hospital. ERCP was done within 72 hours after the time of diagnosis in both groups. In group A, ERCP with stone removal was performed before transpapillary gallbladder stent placement. In group B, ERCP with stone removal was performed without transpapillary gallbladder stent placement. For patients in group A with failed ETGS and group B who still had ongoing sepsis after antibiotic treatment alone, same-admission cholecystectomy (if the operative theater was available) or percutaneous cholecystostomy was reserved as salvage therapy. In groups A and B, with clinical response following ERCP, all patients received the standard of care in the same manner during hospitalization. After discharge, patient clinical status was followed on an outpatient basis at 1, 3, and 6 months and then every 6 months until definitive cholecystectomy was performed. Patients were censored at the time of their last visit until August 2023 or when they had a definitive cholecystectomy. The study protocol was reviewed and approved by the institutional review board, Faculty of Medicine, Chulalongkorn University (institutional review board no. 678/63) and was registered prospectively at the National Clinical Registry (TCTR20200913001). Every 6 months, the data and safety monitoring committee of our institutional review board monitored the adverse occurrences of the study participants as well as the study conduct and progression of this randomized trial.

Endoscopic Transpapillary Gallbladder Stenting Technique

All procedures were performed by 1 of our 4 experienced endoscopists (R.R., P.P., P.A., W.R.) under conscious sedation, each of whom had performed more than 200 ERCPs per year (>3000 ERCPs in career). After biliary sphincterotomy and successful CBD stone removal were completed, a transpapillary gallbladder stent was placed during the same session. As detailed in our earlier study,[6,28] the ETGS approach consisted of 3 steps: cystic duct cannulation, guidewire placement in the gallbladder, and gallbladder stent placement (Figure 1). After successful CBD stone removal, balloon-occluded cholangiogram was performed to identify the cystic duct insertion. When the occlusion balloon was placed below the cystic duct insertion, cystic duct cannulation was attempted using either a 0.035-inch guidewire (Jagwire, Boston Scientific) or a 0.025-inch guidewire (angled VisiGlide, Olympus) under fluoroscopic guidance. If the use of the balloon catheter and guidewire failed, a bendable-tip catheter, such as the Ultratome XL (Boston Scientific) or a Swing Tip cannula (Olympus), was subsequently applied with a 0.025-inch guidewire (angled VisiGlide) for cystic duct cannulation. In cases where cystic duct cannulation could not be achieved within 10 minutes under fluoroscopy, we performed a single operator peroral cholangioscopy (SpyGlass DS Direct Visualization System, Boston Scientific) to identify the cystic duct orifice and facilitate cystic duct cannulation, as previously described in our ETGS protocol.[6,28] After contrast injection to confirm successful cystic duct cannulation, the guidewire was looped in the gallbladder. The catheter was then slowly advanced over the guidewire through the cystic duct into the gallbladder. If the cholangiogram revealed a tortuous cystic duct, we manipulated the catheter with the guidewire to keep the cystic duct straightened before stent placement. If a small cystic duct was present, a 4F–7F graduated dilator (Soehendra, Cook Endoscopy) was used for cystic duct dilation before inserting the stent. A 7F, 15-cm, double-pigtail plastic stent was then advanced over the guidewire into the gallbladder. If a 7F graduated dilator could not dilate a small cystic duct, a 5F single-pigtail plastic stent was used. The proximal end of the stent was inserted into the gallbladder while the distal end of the stent was placed in the second part of the duodenum. Technical success was defined as successful insertion of the stent in the appropriate location confirmed by endoscopy or radiography. Clinical success was defined as symptoms and laboratory abnormalities (leukocytosis and liver function tests) resolved within 72 hours after ETGS. Procedure-related adverse events were defined according to the American Society for Gastrointestinal Endoscopy lexicon.[34]

Follow-Up and Outcomes Measurement

After the procedure, patients from groups A and B were hospitalized with antibiotic treatment and resumed diet within 24 hours in cases with no procedure-related adverse events. During hospitalization, they all received the same standard of care. Before discharge, patients were advised to return to the hospital if they experienced recurrent symptoms, such as abdominal pain and/or fever. All patients were followed for their clinical response in the outpatient clinic at 1, 3, and 6 months and then every 6 months until definitive cholecystectomy was performed. When patients did not appear at their appointed clinical visits, a follow-up telephone call was conducted to evaluate the potential of recurrence, other new developed morbidities, and death. In group A, plain film of the abdomen was done at 3 months after ETGS to confirm the stent position. We did not perform regular stent exchange if patients had no clinical evidence of recurrent cholecystitis or cholangitis. In cases where recurrent

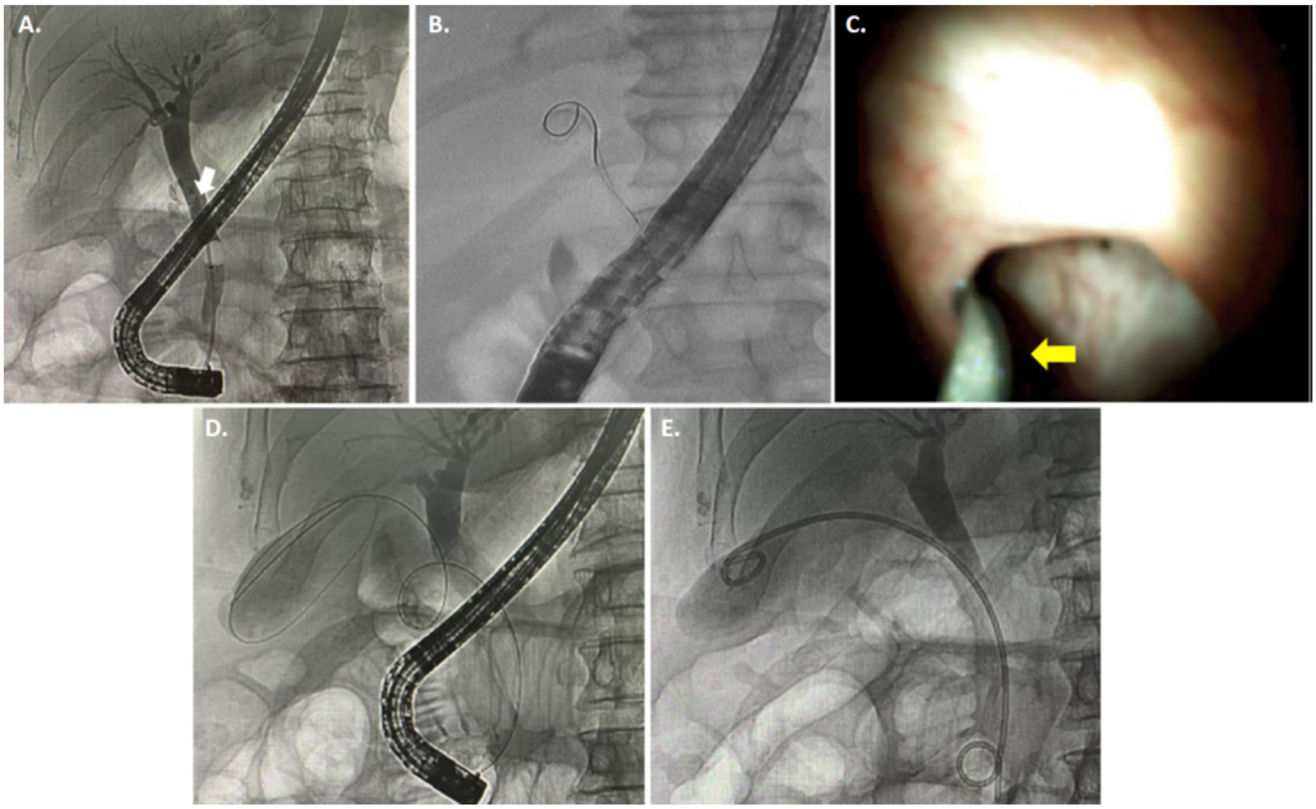

Figure 1. Three steps of the ETGS technique. (*A*) Cystic duct insertion (*white arrow*) on balloon-occluded cholangiogram. (*B*) Cystic duct cannulation under fluoroscopic guidance. (*C*) Cystic duct cannulation under cholangioscopic guidance (*yellow arrow*). (*D*) Guidewire placement in the gallbladder. (*E*) Gallbladder stent placement.

cholecystitis occurred, all patients were re-evaluated by the surgical team for same-admission cholecystectomy before considering stent exchange.

The rate of recurrent cholecystitis at the 3-month follow-up was measured in groups A and B as the primary outcome. Secondary outcomes included the rates of recurrent cholecystitis at the 6-month follow-up (in the remaining patients of the 2 groups) and postprocedural outcomes, such as technical success rate, clinical success rate, and procedure-related adverse events of ETGS. Recurrent cholecystitis was defined as having cholecystitis occurring after ETGS. Primary outcome (recurrent cholecystitis) was first evaluated by emergency room or inpatient attending physicians who were technically blinded to the study as primary assessors because the patients returned to the hospital at any time when they developed any unexpected medical illnesses. They used the diagnosis of recurrent cholecystitis based on the Tokyo Guidelines 2018 and confirmed by on-call junior gastroenterology fellows who were also blinded to the patients' group allocations if the recurrence developed before 3 months. After 3 months, the stent position was checked in all who underwent ETGS by a plain film of the abdomen, and then the study group was revealed to hospital personnel. Ultimately, before study analysis, the medical charts, ERCP findings, and all imaging results were further reviewed by a group of independent senior gastroenterology fellows who were not involved in this study to confirm the diagnosis of the primary and secondary outcomes. If cholecystitis reoccurred and same-admission cholecystectomy was still not available, ERCP was performed with stent exchange in group A, whereas antibiotic treatment alone was offered in group B. In cases of unsuccessful medical treatment in those with recurrence in group B, further management was determined at the discretion of the attending physicians, surgeons, and endoscopists, which included ETGS or percutaneous cholecystostomy or EUS-guided transmural gallbladder stenting.

Statistical Analysis

The rate of recurrent cholecystitis in acute cholecystitis patients who did not receive ETGS was assumed to be 13.7%,[21] and the rate of recurrent cholecystitis in patients with acute cholecystitis who received ETGS was assumed to be 0.2%,[35] based on the available data of ETGS in acute cholecystitis patients published during 2007–2018. A sample size of 120 (60 in each group) was estimated to enable the detection of a 13.5% difference in recurrence rates between the 2 groups at a 2-sided significance level of 5% with 80% statistical power.

Continuous variables are reported as mean with standard deviation or median with range and were compared between the 2 groups using the Student *t* test. Categorical variables are presented as number and percentage and were compared between the 2 groups using the chi-square test or the Fisher exact test. Differences were considered significant at the level of .05. Intention-to-treat (ITT) and per-protocol (PP) analyses were performed. We calculated the recurrence-free survival curve using the Kaplan-Meier method with the log-rank significance test. SPSS version 23 (IBM) was used for the analysis. All authors had access to the study data and reviewed and approved the final manuscript.

Results

A total of 142 patients with acute calculous cholecystitis with a high probability of CBD stone were enrolled at our institute. Despite limited operating room slots, our surgeons were able to perform a few cholecystectomies per month during the peak of the COVID-19 pandemic. Thus, 22 patients were excluded before randomization, including those who had an elective cholecystectomy within 1 month (n = 15), irreversible hemodynamic instability (n = 6), and gallbladder perforation (n = 1) (Figure 2). We randomized 120 eligible patients into group A (those receiving ETGS: n = 60) and group B (those not receiving ETGS: n = 60). Baseline characteristics were not different between groups A and B, including mean age (64.9 ± 15.6 vs 60.2 ± 16.2 years; P = .11), male sex (34 [56.7%] vs 30 [50%]; P = .46), Charlson comorbidity index (3 [range, 0–8] vs 2.5 [range, 0–7]; P = .23), and severity (grade 1/2/3) of cholecystitis (36/20/4 vs 44/14/2; P = .28) (Table 1). Indications for ERCP also did not differ between the 2 groups, including the presence of CBD stone on imaging (16 [26.7%] vs 14 [23.3%]; P = .67), acute cholangitis (29 [48.3%] vs 27 [45%]; P = .71), and a total bilirubin level of >4 mg/dL with dilated CBD (16 [26.7%] vs 19 [31.7%]; P = .55). Mean number of gallstones in the gallbladder (3.1 ± 1.5 vs 2.8 ± 1.5; P = .42) and the largest gallstone size (7.9 ± 6.4 mm vs 9.6 ± 6.5 mm; P = .18) were not different between both groups. Concomitant CBD stone was found during the index ERCP in 37 (61.7%) and 35 (58.3%) in groups A and B, respectively (P = .71), which were successfully removed. The presence of cystic duct stone showed no significant difference between group A and group B [5 (8.3%) vs 7 (11.6%); P = .76].

The technical success rate of ETGS in group A was 90% (54 of 60) with a 100% (54 of 54) clinical success rate (Table 2). Of those who underwent ETGS (n = 60), 18 (30%) required additional cholangioscopic guidance for cystic duct cannulation. Of those receiving successful ETGS (n = 54), 53 patients received a 7F stent placement except for one who had a 5F stent insertion due to having a small cystic duct. ETGS could not be achieved in 6 patients because of failure to pass the guidewire through the tortuous cystic duct (n = 5) and inability to pass the stent (5F) through the very small cystic duct (n = 1). Six patients with unsuccessful ETGS received antibiotic treatment alone (n = 5) and same-admission cholecystectomy (n = 1) (Figure 2). In group B, 95% (57 of 60) of patients had clinical success after ERCP with CBD stone removal (without ETGS). Three patients required further intervention, including same-admission cholecystectomy (because of the sudden availability of an operative theater) (n = 1) and percutaneous cholecystostomy because of ongoing severe sepsis despite successful ERCP with CBD stone removal (n = 2). Procedure-related adverse events were not different between groups A and B (13 [21.7%] vs 8 [13.3%]; P = .23), including periprocedural transient hypoxemia (5 [8.3%] vs 3 [5%]; P = .72); mild post-ERCP pancreatitis (6 [10.2%] vs 4 [6.7%]; P = .51), which was treated conservatively; and postsphincterotomy bleeding (2 [3.3%] vs 1 [1.7%]; P = 1.0) requiring diluted epinephrine injection at the same session. Although the additional procedure time for ETGS in group A was 3.7 ± 7.2 minutes, there was no statistical difference in mean total procedural time (39.2 ± 22.3 [range, 10–100] minutes vs 35.5 ± 15.1 [range, 10–70]

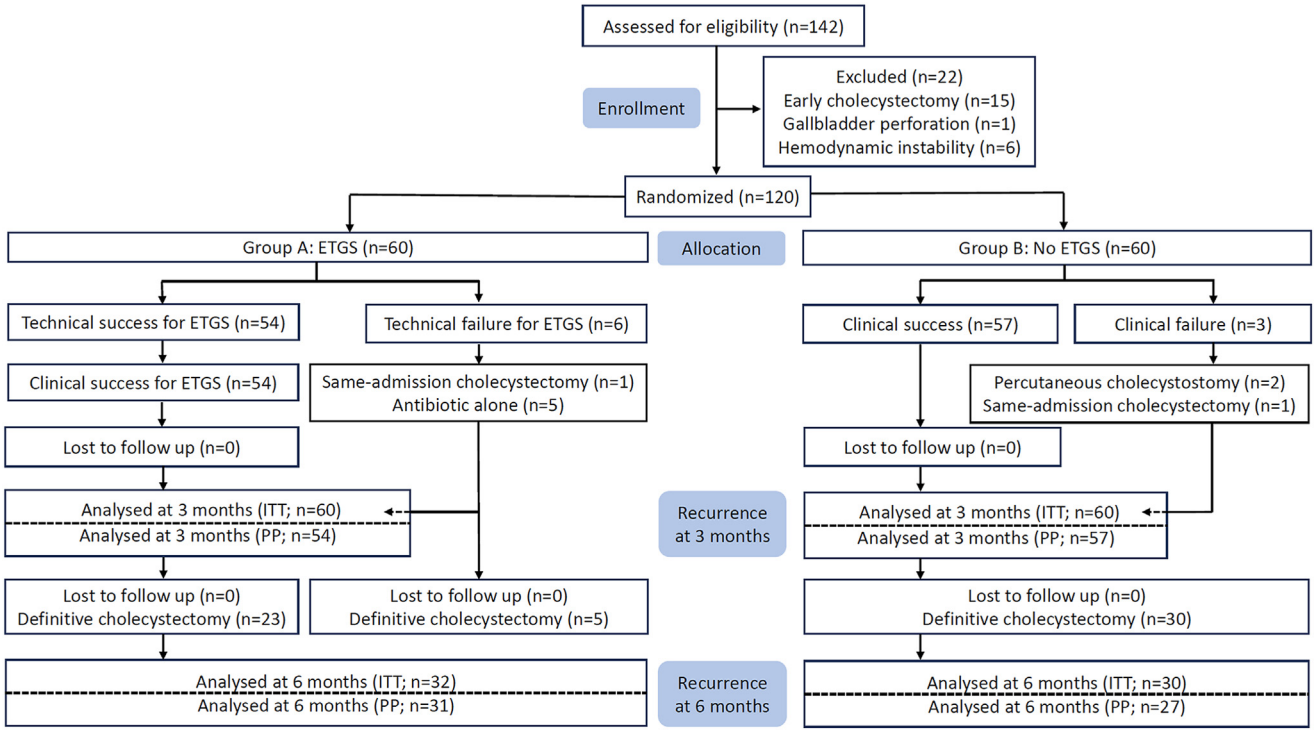

Figure 2. Flowchart of eligible patients with acute cholecystitis and a high probability of CBD stone whose cholecystectomy was deferred.

Table 1. Baseline Characteristics of Acute Cholecystitis Patients With a High Probability of CBD Stone Whose Cholecystectomy Was Deferred

Characteristics	Group A: allocated to ETGS (n = 60)	Group B: allocated to no ETGS (n = 60)	*P* value
Age, *y*, mean (SD)	64.9 (15.6)	60.2 (16.2)	.11
Male, n (%)	34 (56.7)	30 (50)	.46
Charlson comorbidity index, median (range)	3 (0–8)	2.5 (0–7)	.23
Severity of acute cholecystitis based on the Tokyo Guidelines 2018			.28
Grade 1	36 (60)	44 (73.4)	
Grade 2	20 (33.3)	14 (23.3)	
Grade 3	4 (6.7)	2 (3.3)	
Indication for ERCP, n (%)			
CBD stone seen on imaging	16 (26.7)	14 (23.3)	.67
Acute cholangitis	29 (48.3)	27 (45)	.71
Total bilirubin level > 4 mg/dL and dilated CBD	16 (26.7)	19 (31.7)	.55
Imaging findings			
Type of imaging studies before ERCP, n (%)			.19
Transabdominal ultrasound	36	31	
Computed tomography	22	29	
Magnetic resonance imaging	2	0	
Number of gallstones, mean (SD)	3.1 (1.5)	2.8 (1.5)	.42
The largest gallstone size, *mm*, mean (SD)	7.9 (6.4)	9.6 (6.5)	.18
Endoscopic findings, n (%)			
Concomitant CBD stone	37 (61.7)	35 (58.3)	.71
Passing CBD stone with or without biliary sludge	23 (38.3)	25 (41.7)	.71
Cystic duct stone	5 (8.3)	7 (11.6)	.76

SD, standard deviation.

minutes; $P = .08$) between the 2 groups. The median length of hospitalization (5 [range, 1–21] days vs 4 [range, 1–76] days; $P = .93$]) did not differ between groups A and B.

Primary Outcomes

No patients were lost to follow-up in either group at 3 months (Figure 2). In group A, 6 patients with unsuccessful

Table 2. Postprocedural Outcomes of Acute Cholecystitis Patients With a High Probability of CBD Stone Whose Cholecystectomy Was Deferred

Outcomes	Group A: allocated to ETGS (n = 60)	Group B: allocated to no ETGS (n = 60)	*P* value
Technical success, n (%)	54 (90)	—	—
Under fluoroscopic guidance	36 (60)	—	—
Additional cholangioscopic guidance	18 (30)	—	—
Technical failure, n (%)	6 (10)	—	—
Clinical success, n (%)	54 of 54 (100)	57 of 60 (95)	.62
Procedure-related adverse events, n (%)	13 (21.7)	8 (13.3)	.23
Transient hypoxemia	5 (8.3)	3 (5)	.72
Mild pancreatitis	6 (10.2)	4 (6.7)	.51
Postsphincterotomy bleeding	2 (3.3)	1 (1.7)	1.0
Total procedure time, *min*, mean (SD)	39.2 (22.3)	35.5 (15.1)	.08
Length of hospital stay, *d*, median (range)	5 (1–21)	4 (1–76)	.93

SD, standard deviation.

Table 3. Primary and Secondary Outcomes of Acute Cholecystitis Patients With a High Probability of CBD Stone Whose Cholecystectomy Was Deferred Who Received and Did Not Receive ETGS

Outcomes	Group A: allocated to ETGS (n = 60)	Group B: allocated to no ETGS (n = 60)	*P* value
Primary outcomes			
Recurrent cholecystitis at 3 months, ITT analysis, n (%)	0 of 60	11 of 60 (18.3)	.001
Recurrent cholecystitis at 3 months, PP analysis, n (%)	0 of 54	11 of 57 (19.3)	.001
Secondary and other outcomes			
Recurrent cholecystitis at 3–6 months, ITT analysis, n (%)	0 of 32	3 of 30 (10)	.11
Recurrent cholecystitis at 3–6 months, PP analysis, n (%)	0 of 31	3 of 27 (11.1)	.09
Overall recurrent cholecystitis, n (%)	0	15[a] (25)	<.001
Time to recurrent cholecystitis, median (range)	—	63 (11–479)	
Definitive cholecystectomy, n (%)	42 (70)	44 (73.3)	.69
Time to cholecystectomy, *d*, median (range)	121 (92–665)	123 (91–709)	.57
Conversion to open cholecystectomy, n (%)	2 of 42 (4.8)	1 of 44 (2.3)	.61
Overall surgical complications, n (%)	4 of 42 (9.5)	1 of 44 (2.3)	.19
Perioperative complications, n (%)	2 of 42 (4.8)	0 of 44	.24
Postoperative complications, n (%)	2 of 42 (4.8)	1 of 44 (2.3)	.61
Follow-up time, *d*, median (range)	172 (95–786)	133 (92–765)	.29

[a]One patient had recurrent cholecystitis after 12 months (at day 479).

ETGS had clinical response with antibiotic treatment alone (n = 5), and 1 underwent same-admission cholecystectomy because of ongoing sepsis. In group B, 2 patients with ongoing sepsis despite antibiotic treatment underwent percutaneous cholecystostomy, and 1 had same-admission cholecystectomy. Those with failed ETGS or who required additional interventions (6 in group A and 3 in group B) were excluded from the PP analysis. At 3-month follow-up, group A had a significantly lower rate of recurrent cholecystitis when compared to group B based on the ITT analysis (0% [0 of 60] vs 18.3% [11 of 60]; $P = .001$) (Figure 2 and Table 3). When using the PP analysis, at the 3-month follow-up, group A also had a significantly lower rate of recurrent cholecystitis when compared to group B (0% [0 of 54] vs 19.3% [11 of 57]; $P = .001$) (Figure 2 and Table 3). The number needed to prevent recurrent cholecystitis at 3 months was 6 (1/0.183). Based on the plain film follow-up at 3 months, no stent migration was observed in group A. In group B, 11 patients developed recurrent cholecystitis on days 11, 22, 24, 29, 43, 45, 62, 63, 78, 86, and 90. Of those who developed recurrent cholecystitis (n = 11) in group B, 4 patients with recurrent cholecystitis (severity grade 1) received a cholecystectomy during the same index admission, and 1 (severity grade 3) had a percutaneous cholecystostomy because of unstable condition for surgery. The remaining 6 patients (severity grade 1) were managed with antibiotic treatment and then underwent definitive cholecystectomy at 3–6 months after the onset of recurrence.

Secondary Outcomes

During the follow-up period of 3–6 months, 28 of 60 (46.7%) and 30 of 60 (50%) patients received definitive cholecystectomy (Figure 2) with a median time to cholecystectomy of 103 (92–166) days and 98 (91–172) days in groups A and B, respectively. No patients were lost to follow-up in groups A and B at 3–6 months. In group B, 3 patients developed recurrent cholecystitis at days 136, 137, and 148 during the 3–6-month periods (Figure 2 and Table 3). At the 6-month follow-up, which focused on the recurrent rate after 3 months, group A had a lower rate of recurrent cholecystitis than group B, although this difference did not reach statistical significance with either the ITT analysis (0% [0 of 32] vs 10% [3 of 30]; $P = .11$) or the PP analysis (0% [0 of 31] vs 11.1% [3 of 27]; $P = .09$). Of those who had recurrent cholecystitis (n = 3) at 3–6 months in group B, 1 patient (severity grade 2) underwent percutaneous cholecystostomy because of gangrenous cholecystitis with liver abscess before cholecystectomy, and 2 patients (severity grade 1) received antibiotic treatment and then underwent definitive cholecystectomy at 7 months after the onset of recurrence.

Other Outcomes

After the 12-month follow-up, no recurrent cholecystitis had occurred in group A, whereas 1 patient in group B developed recurrent cholecystitis at day 479 and had same-admission cholecystectomy. After 12 months, through August 2023, group A had no significant difference in the rate of recurrent cholecystitis compared to group B (0% [0 of 18] vs 6.2% [1 of 16]; $P = .47$), with a median follow-up period of 139 days (range, 92–786 days) (Table 3). Among those with recurrence in group B (n = 15), the median time to recurrent cholecystitis was 63 days (range, 11–479 days). Overall, there were no differences in the proportion of patients receiving definitive cholecystectomy after 3 months (42 [70%] vs 44 [73.3%]; $P = .69$), the median time to cholecystectomy (121 days [range, 92–665 days] vs 123 days [range, 91–709 days]; $P = .57$), and the median time to follow-up (172 days [range, 95–786 days] vs 133 days [range, 92–765 days]; $P = .29$) in groups A and B. Based on

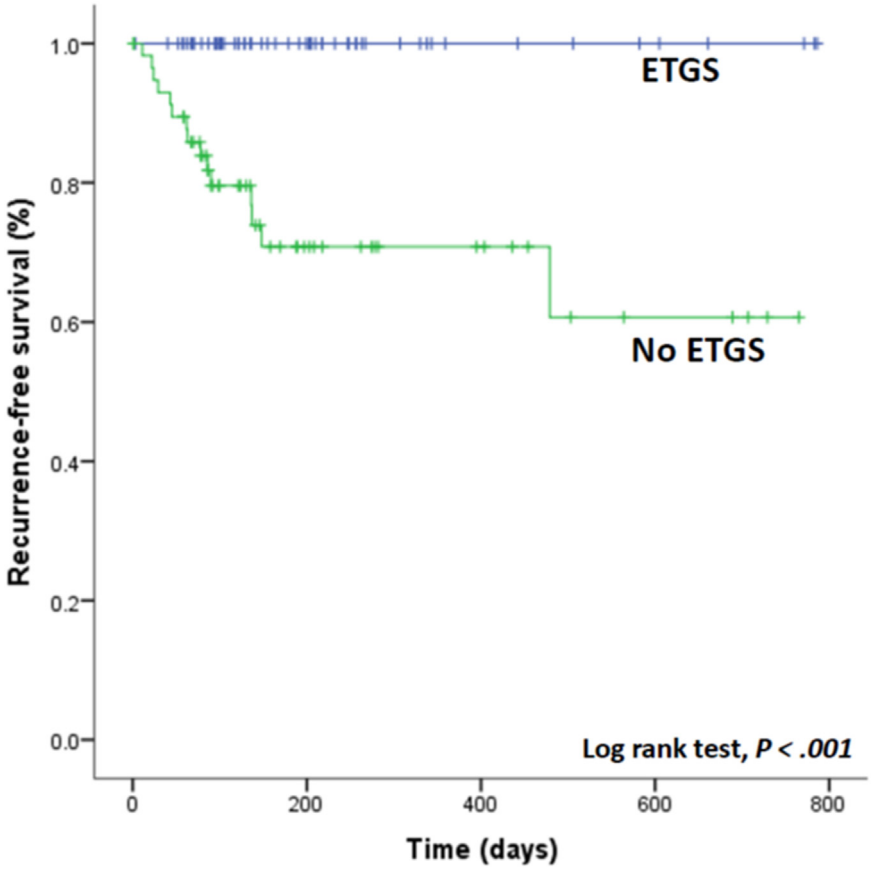

Figure 3. Kaplan-Meier analysis demonstrating the recurrence-free survival curve in acute cholecystitis patients with a high probability of CBD stone who had clinical success in groups A and B (n = 111).

Kaplan-Meier analysis of acute cholecystitis patients with a high probability of CBD stone who had clinical success in groups A and B (n = 111), the overall rate of recurrence was significantly higher in group B compared to group A (log-rank test, $P < .001$) (Figure 3).

Of those who underwent definitive cholecystectomy in group A (n = 42) and group B (n = 44), the overall surgical complications were not significantly different between the 2 groups (4 of 42 [9.5%] vs 1 of 44 [2.3%]; $P = .19$). The proportion of conversion to open surgery was not different between groups A and B (2 of 42 [4.8%] vs 1 of 44 [2.3]; $P = .61$). Of those with surgical complications in group A (n = 4), 2 patients had perioperative complications that were converted to open surgery, including right portal vein injury (n = 1), which was successfully repaired during the operation, and injury to the aberrant right hepatic duct (n = 1) with bile leak, which was successfully managed by ERCP with stent placement after surgery. The remaining 2 patients received laparoscopic cholecystectomy but developed postoperative complications, including bile leak (n = 1) requiring ERCP with stent placement and subhepatic collection (n = 1) requiring percutaneous drainage. One patient in group B was converted to open surgery because of severe inflammation and adhesion at the gallbladder and surrounding structures and was found to have bile leak after surgery, which was resolved by conservative management.

Discussion

Although our previous retrospective study of 234 patients with gallstone-related disease (acute cholecystitis = 147) with high surgical risk who received ETGS showed no recurrent cholecystitis at the 6-month follow-up after ETGS,[6] there were no prospective trials comparing the outcomes of those having ETGS plus antibiotic vs conservative treatment with antibiotics alone in acute cholecystitis patients who are surgical candidates. To address this research gap, we conducted this randomized controlled trial to evaluate the benefit of ETGS in patients with acute cholecystitis who had cholecystectomy deferral. Our study demonstrated that those receiving ETGS had a significantly lower rate of recurrent cholecystitis than those who did not receive ETGS in both ITT (0% [0 of 60] vs 18.3% [11 of 60]; $P = .001$) and PP analysis (0% [0 of 54] vs 19.3% [11 of 57]; $P = .001$) at the 3-month follow-up. No significant difference in the recurrence rate between 3 and 6 months was noted. A possible explanation for the efficacy of ETGS is that even if the stent gets occluded, the bile flow from the gallbladder could still run along the stent that straightens the tortuous cystic duct. In addition, the stent could prevent additional stone migration from the gallbladder to the cystic duct. These findings highlight ETGS as a possible effective bridging treatment to prevent recurrent cholecystitis in patients with acute cholecystitis who have been waiting for cholecystectomy for 3 months.

Similar to the previous studies of ETGS,[6,10,13] adverse events related to ETGS in our study were mainly pancreatitis, which was reported in a comparable range to post-ERCP pancreatitis rates among patients receiving standard ERCP. We observed no guidewire-related duct perforation in the current study. Likewise, our previous retrospective study of 234 gallstone-related disease patients with high surgical risk or cholecystectomy deferral who received ETGS showed a lower rate of guidewire-related duct perforation (n = 4; 1.7%), which was managed conservatively, when compared to the risk of cystic duct perforation in the earlier study (9.2%).[36] Cystic duct injury may be caused by the sharp tip of the stiff wire during passage through the tortuosity and the acute angle of the cystic duct. Based on these data, a gentle manipulation of the guidewire using a soft-tip guidewire is recommended for patients with difficult cystic duct anatomy.

Among endoscopic and percutaneous approaches for gallbladder drainage in patients with acute cholecystitis with high surgical risk, patients receiving percutaneous cholecystostomy had the highest rate of recurrence, which usually developed within 3 months compared to EUS-guided transmural gallbladder stenting and ETGS (10.8%–17.1% vs 1%–4.5% vs 3.2%–4.6%, respectively).[25,26,37,38] When a revision of percutaneous cholecystostomy was needed, the causes were tube dislodgement and occlusion, which accounted for up to 30% within 1 month.[24] Given that percutaneous cholecystostomy is associated with a significantly high number of reinterventions due to tube dislodgement and occlusion,[24] which increases the rate of recurrent cholecystitis (17%),[25,29] readmission (50%),[24] and total length of hospital stays,[23,24] this strategy may not be a suitable choice in those who are still waiting for surgery longer than 1 month. Even though the tube is still patented, percutaneous cholecystostomy is associated with postprocedure pain because of the discomfort of an external drainage catheter.[23,39]

EUS-guided transmural gallbladder stenting is another endoscopic option, but it can result in permanent fistula and can cause gallbladder adherence to the surrounding structures (duodenum or stomach, depending on the EUS punctured site). Technically, a fistula needs repair with a risk for postoperative leak.[39,40] Although it is feasible, this may make future cholecystectomies more difficult or require additional closure of fistula. The rate of conversion to open cholecystectomy after EUS-guided transmural gallbladder stenting has been documented to range from 2.9% to 9%.[41,42] In a recent retrospective study by Kunda et al[43] in 81 cases of cholecystectomy preceded by EUS-guided transmural gallbladder stenting, although all fistula closed spontaneously in most cases, additional closure was performed during laparoscopy to ensure the seal in 85% of the cases. In contrast, ETGS can preserve gallbladder and nearby structures. In our study, there were no differences in the rate of conversion to open surgery (4.8% vs 2.3%; $P = .61$) and surgical complications (9.5% vs 2.3%; $P = 19$) between those who received and did not receive ETGS. In our opinion, EUS-guided transmural gallbladder stenting should be reserved only for acute cholecystitis patients who are unsuitable for surgery indefinitely (never surgery) and require permanent gallbladder drainage. Percutaneous cholecystostomy or ETGS can serve as a bridging option for gallbladder drainage in those who had cholecystectomy deferral within 1 month. Given the higher rate of 30-day adverse events associated with percutaneous cholecystostomy, ETGS should be the preferred option for temporary gallbladder drainage, particularly in patients with acute cholangitis and cholecystitis who are planning an elective cholecystectomy and will experience a waiting time of longer than 1 month.

Our study has some limitations. First, our primary outcome was the short-term follow-up (3 months) after ETGS in acute cholecystitis patients whose cholecystectomy was deferred. At 3–12 months, approximately two-thirds of patients in each group underwent definitive cholecystectomy. Nevertheless, no recurrent cholecystitis occurred in the remaining patients receiving ETGS after the 12-month follow-up. Second, the majority of the patients in our study had mild to moderate severity of acute cholecystitis. Because of a very small number of patients with severe cholecystitis (4 and 2 in groups A and B, respectively), we could not confirm the effectiveness of ETGS in patients who were presented with severe acute cholecystitis. Third, although our study showed a high success rate of gallbladder stent placement, in fact, technical success rate for cystic duct cannulation under fluoroscopic guidance was not high (60%) and is comparable to that in other reported studies.[27–30,44–46] We had a low threshold to use a cholangioscope to facilitate cystic duct cannulation after failed fluoroscopic guidance without using other special techniques such as steerable catheter, catheter with multiple exits for wires, and balloon occlusion with additional bouncing wire from below. In addition, ETGS procedures were performed by experienced endoscopists who had performed more than 100 ETGS procedures before entering in this study. Hence, our ETGS protocol may be limited in its generalizability to other units because of different expertise and limited access to special instruments, such as cholangioscopes and other advanced devices for ETGS. Multicenter studies in community settings are required to support similar outcomes. Fourth, we were unable to blind the assigned groups to the performing endoscopists. This may affect the technical success rate of ETGS but should not influence the rate of recurrent cholecystitis after successful ETGS, which was the primary outcome of this study. Technically, all patients were blinded to the recruitment until follow-up because in group A, a plain film of the abdomen was done at 3 months after ETGS to confirm the stent position. As a result, we were unable to blind the patients in this group after the 3-month follow-up. Fifth, our study was not powered to detect noninferiority in terms of adverse events, and larger studies are needed to assess this. Finally, we did not perform a cost-effectiveness analysis of ETGS. Recently, a cost-effectiveness study among ETGS vs EUS-guided transmural gallbladder stenting vs percutaneous cholecystostomy in acute cholecystitis patients who were poor surgical candidates showed that ETGS (US$40,086) and EUS-guided transmural gallbladder stenting (US$57,808) were more

cost-effective, requiring US$1312 per hospitalization day averted, compared to percutaneous cholecystostomy (US$53,712).[47] However, EUS-guided transmural gallbladder stenting required an additional US$8950 to prevent 1 additional day of hospitalization when compared to ETGS.[47] Although ETGS provided better cost-effectiveness compared to EUS-guided transmural gallbladder stenting and percutaneous cholecystostomy during a 3-month follow-up, the use of an additional cholangioscopy during ETGS in some patients was not included in this cost-effectiveness analysis.[47] Further studies are needed to confirm the cost utility of additional cholangioscopic guidance for ETGS and long-term cost-effectiveness of ETGS.

In conclusion, our study demonstrated that ETGS is safe and provides high efficacy in preventing recurrent cholecystitis at 3 months, and there was no difference in recurrence rates at 3–6 months in mild to moderate acute cholecystitis patients with CBD stone whose cholecystectomy is deferred.

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The authors disclose no conflicts.

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Data Availability
Individual participant data, analytic methods, and study materials will not be shared. An earlier version of these data was accepted for oral presentation at the annual meeting of Digestive Diseases Week, 2023, Chicago, Illinois.