EUS-guided cholecystostomy versus endoscopic transpapillary cholecystostomy for acute cholecystitis in high-risk surgical patients

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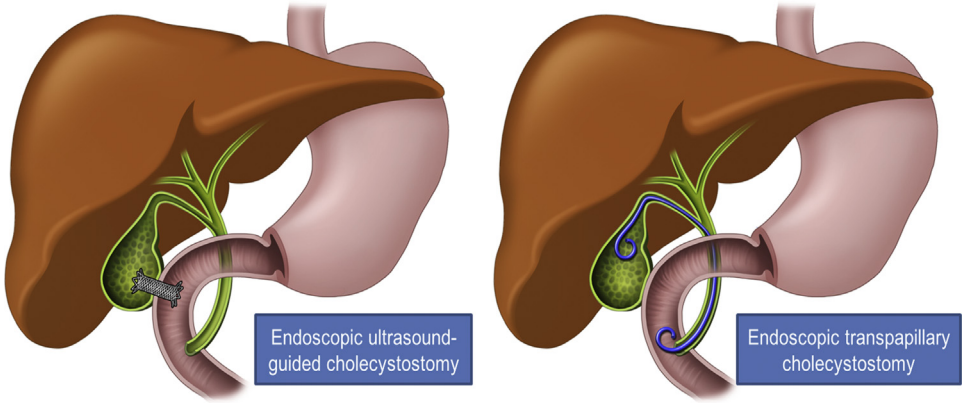
GRAPHICAL ABSTRACT



Background and Aims: Endoscopic gallbladder drainage (GBD) has been performed as an alternative to percutaneous drainage for acute cholecystitis. To date, there has been no comparative study between EUS-guided cholecystostomy (EUSC) and endoscopic transpapillary cholecystostomy (ETC). The aim of this study was to compare the outcomes of EUSC and ETC.

Methods: A retrospective review of an endoscopic GBD database prospectively collected at the Asan Medical Center (between July 2010 and December 2014) was performed to identify consecutive patients with acute cholecystitis who underwent attempted endoscopic GBD. Procedural and long-term outcomes were evaluated using inverse probability of treatment weighting (IPTW).

Results: A total of 172 patients (76 in the EUSC group and 96 in the ETC group) were included in this study. Seven patients who failed to undergo ETC crossed over to the EUSC group. After adjustment with the IPTW method, technical success (99.3% vs 86.6%, $P < .01$) and clinical success (99.3% vs 86%, $P < .01$) rates were significantly higher in the EUSC group than in the ETC group. The procedure-related adverse event rate was significantly higher in the ETC group (7.1% vs 19.3%, $P = .02$). The cholecystitis or cholangitis recurrence rate (12.4% vs 3.2%) was also higher in the ETC group than in the EUSC group, as identified using Cox analysis (hazard ratio, 3.01; 95% confidence interval, .73-12.9; $P = .04$).

Conclusions: In patients with acute cholecystitis who are unfit for surgery, EUSC may be a more suitable treatment method than ETC. (Gastrointest Endosc 2019;89:289-98.)

(footnotes appear on last page of article)

Although laparoscopic cholecystectomy is the criterion standard for management of acute cholecystitis, some patients are not fit for surgery because of their multiple comorbidities.[1] Percutaneous transhepatic cholecystostomy (PTC) can be used as an effective treatment option for decompression of the gallbladder and for controlling inflammation in acute cholecystitis until subsequent cholecystectomy can be performed in a stable patient. However, PTC may be not suitable for patients with massive ascites, coagulopathy or an anatomically inaccessible location.[2,3] Adverse event rates have been reported up to 12%, and it is associated with pneumothorax, bleeding, or bile peritonitis.[4] Moreover, continuous percutaneous drainage has several disadvantages, including patient discomfort and accidental catheter dislodgement.[1,5] In patients who have received PTC as a stand-alone treatment because of medical comorbidities precluding cholecystectomy, cholecystitis recurs in 22% to 47% of cases.[6]

Endoscopic management has been developed in the hope of obviating the necessity for a percutaneous drain and to improve the duration of the clinical benefit of gallbladder drainage (GBD). Several reports described the efficacy of endoscopic treatment of acute cholecystitis as an alternative to PTC, reporting that it can overcome the disadvantages.[1,2,5-8] Endoscopic GBD can be performed by 2 methods: EUS-guided cholecystostomy (EUSC) and endoscopic transpapillary cholecystostomy (ETC).[2] However, to date, no studies have compared the technical, clinical, and long-term results between both techniques. Therefore, the aim of this study was to compare the technical, clinical, and long-term outcomes of EUSC and ETC in patients with acute cholecystitis at high surgical risk, with inverse probability of treatment weighting (IPTW) analysis.

METHODS

Patients

Between July 2010 and December 2014, 172 consecutive patients with acute cholecystitis underwent EUSC or ETC (Fig. 1). The inclusion criteria for endoscopic GBD were acute cholecystitis, advanced malignancy and/or high-risk surgical patients (class III or IV on the American Society of Anesthesiologists Physical Status classification system), and age 20 years or older. EUSC was preferentially performed for acute cholecystitis resulting from malignant cystic duct obstruction or common bile duct (CBD) cancer, acute cholecystitis after bile duct metal stent placement, or unsuccessful and/or infeasible ETC. ETC was preferentially considered for acute cholecystitis with concomitant presence of CBD stones or high suspicion of CBD stones or acute cholecystitis not caused by bile duct malignancy. The exclusion criteria included an age less than 20 years and pregnancy.

Acute cholecystitis was diagnosed according to the Tokyo guidelines, which are based on a combination of typical symptoms and imaging findings.[9] None of the included patients showed improvement after 24 hours of conservative management with bowel rest, fluid replacement, and intravenous antibiotics.[6,10] Written informed consent was obtained from all patients before the procedure. This study was approved by the institutional review board of our center (IRB no. 2016-1152). The data were prospectively collected and retrospectively analyzed in this study.

EUSC procedure

All procedures were performed by 3 experienced endosonographers (S.S.L., D.H.P., and T.J.S.), who have carried out more than 1000 ERCP and 500 EUS procedures for pancreatobiliary diseases annually, using a conventional linear array echoendoscope (GF-UCT240 or 260; Olympus Optical, Tokyo, Japan) with fluoroscopic guidance. Patients were under conscious sedation with intravenous midazolam and meperidine. The initial puncture was made at the prepyloric antrum of the stomach or the bulb of the duodenum, to access the gallbladder body or neck while avoiding any intervening vessels. A 19-gauge needle (EUSN-19-T; Cook Endoscopy, Winston-Salem, NC) was used to puncture the gallbladder through the gastric or duodenal wall. Bile was aspirated and sent for microbacterial culture. Contrast media was then injected into the gallbladder under fluoroscopic guidance to confirm access. A .035-inch guidewire (Jagwire; Boston Scientific, Natick, Mass) or .025-inch guidewire (Visiglide; Olympus, Tokyo, Japan) was passed through the needle and coiled in the gallbladder. After removal of the needle, a 6F or 7F bougie (Soehendra Biliary Dilatation Catheter; Cook Endoscopy) was inserted and then removed to dilate the tract. If there was resistance to advancing the 6F bougie, a triple-lumen needle-knife (Microtome; Boston Scientific) with a 7F shaft diameter was used to dilate the tract using a brief burst of pure cutting current over the guidewire. If resistance was felt during stent advancement, a 4-mm biliary balloon dilator (Hurricane; Boston Scientific) was used to achieve sufficient dilation of the tract to facilitate the advancement of the stent. A modified covered self-expandable metal stent with antimigrating flare (BONA-AL Stent; Standard Sci-Tech Inc, Seoul, Korea) was placed over the guidewire (Fig. 2). The length of the inserted stent was decided by approximation of the distance between the gallbladder and the stomach or duodenum with extra length (10-15 mm), considering fluctuation of the distance because of bowel movement, based on EUS.[6,8] Patients started food intake 24 hours after the procedure if adverse events did not occur.

ETC procedure

All ETC procedures were also performed by experienced endoscopists (S.S.L., D.H.P., and T.J.S.). All procedures were performed with the patient under conscious sedation with intravenous midazolam and meperidine. For transpapillary drainage, biliary cannulation was performed with a duodenoscope (JF-260V or TJF-260V; Olympus Optical). After successful deep cannulation of the CBD, endoscopic sphincterotomy and balloon-occluded cholangiography were performed to find the orifice of the cystic duct. Then, the

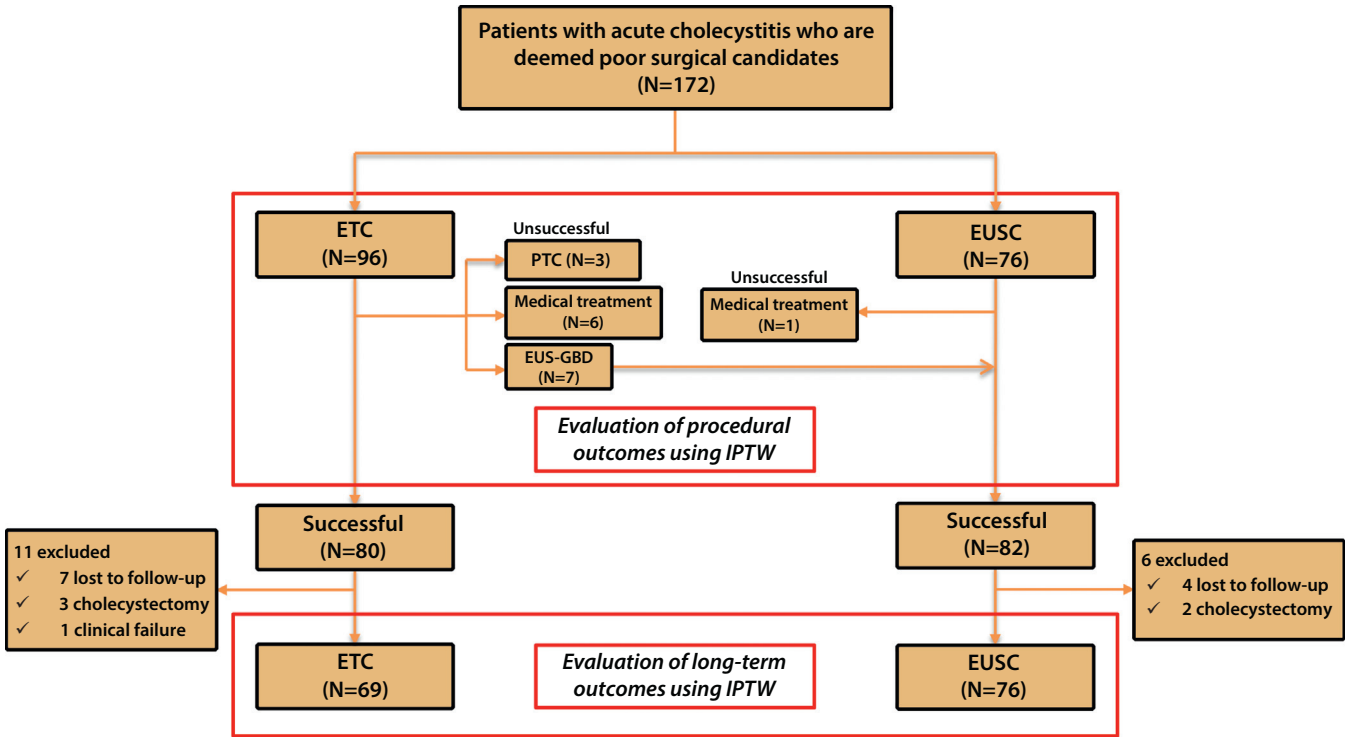


Figure 1. Flow chart of patients through the study of endoscopic gallbladder drainage. *ETC*, Endoscopic transpapillary cholecystostomy; *EUSC*, EUS-guided cholecystostomy; *PTC*, percutaneous transhepatic cholecystostomy; *IPTW*, inverse probability of treatment weighting.

insertion of a guidewire (Jagwire [Boston Scientific] or Visiglide [Olympus]) into the gallbladder via the cystic duct was attempted, using various catheters such as a standard catheter, pull-sphincterotome, or rotating sphincterotome. After successful cystic duct cannulation, contrast media was injected to confirm gallbladder. The catheter device was carefully advanced into the cystic duct over the guidewire, and the guidewire and catheter device were further advanced as far as possible to straighten the cystic duct. If gallbladder cannulation was achieved and the guidewire was coiled in the gallbladder, a 7F double-pigtail plastic stent (Zimmon; Wilson-Cook Medical, Winston-Salem, NC) was placed into the gallbladder (Fig. 3). Patients started food intake 24 hours after the procedure if adverse events did not occur.

Follow-up

Patient follow-up was based on outpatient examinations every 6 months or whenever adverse events developed. Blood tests and simple abdominal radiographs were performed every 6 months, and abdominal CT or US was additionally performed in patients with adverse events. Scheduled stent exchange or removal was not performed in this study. Reintervention was considered when symptomatic biliary problems such as cholangitis or cholecystitis developed.

Definition of outcomes

The main outcomes measures were technical success, clinical success, procedural adverse events, stent-related late adverse events, and recurrence of cholecystitis. Technical success was defined as successful placement of the stent across the stomach or duodenum into the gallbladder for EUSC and successful placement of the stent into the gallbladder via the cystic duct for ETC, along with adequate flow of radio contrast and bile through the stent. Clinical success was defined as complete resolution of clinical symptoms with normalization of laboratory tests. Procedural adverse events were defined as any procedure-related adverse events that occurred within 2 weeks, including bleeding, bile peritonitis, pneumoperitoneum, and perforation. Stent-related late adverse events were defined as any stent-related adverse events occurring later than 2 weeks after stent placement, including stent migration, occlusion, or acute cholecystitis.[11]

Recurrence of cholecystitis was defined as the recurrence of typical symptoms with characteristic imaging findings. Reintervention was defined as any type of endoscopic, percutaneous, or surgical procedure that was required to improve GBD after placement of the self-expandable metal stent for EUSC or after placement of the plastic stent for ETC. The procedure time was measured for EUSC as the time from echoendoscope insertion to successful transmural stent placement and for ETC as the time from duodenoscope insertion to successful transpapillary stent placement. Stent patency was calculated according to the interval (days) between the time of stent placement and the time of stent occlusion, stent migration, or patient death. If a patient demonstrated no clinical symptoms related to stent

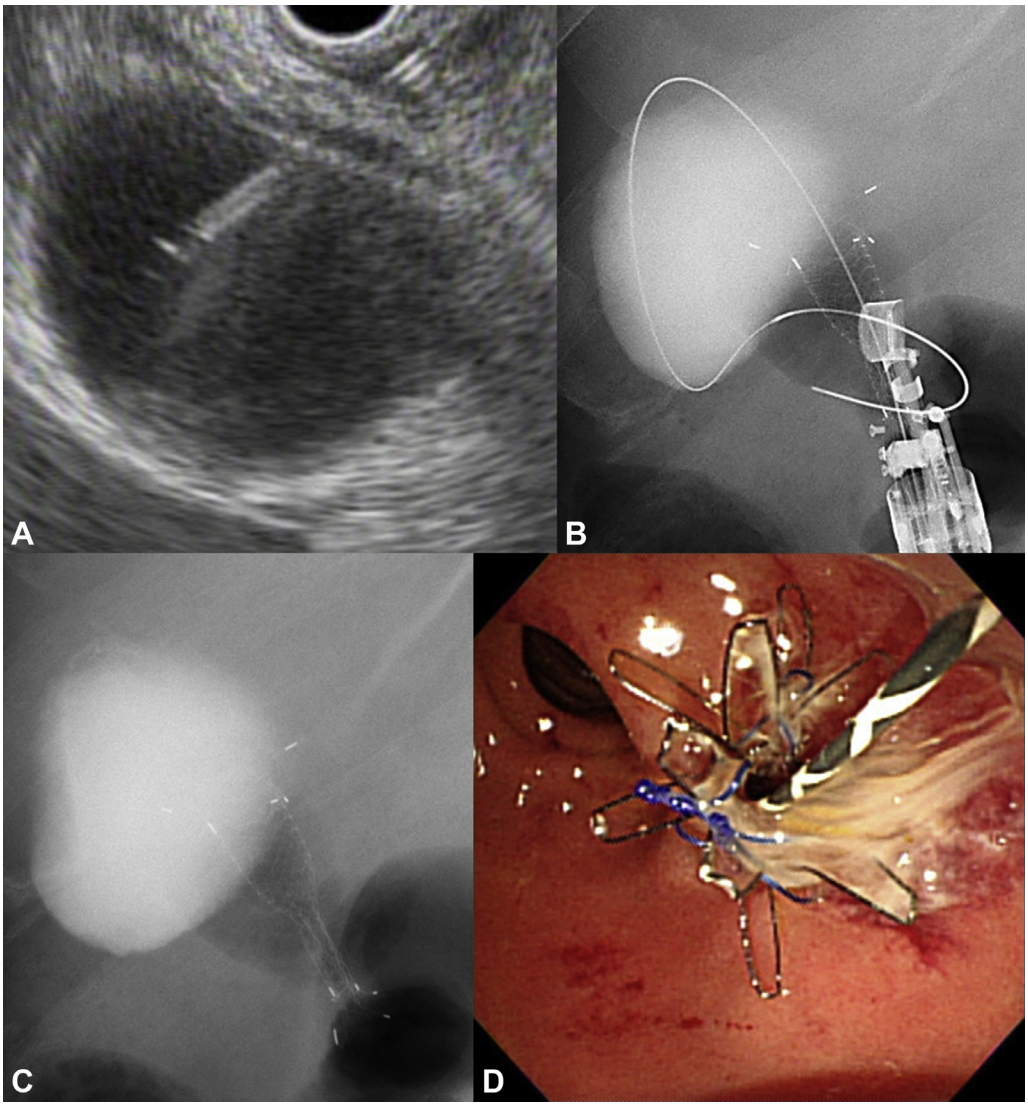


Figure 2. EUS-guided transmural cholecystostomy with a self-expandable metal stent. **A,** EUS-guided puncture of the distended gallbladder with a 19-gauge needle. **B,** A self-expandable metal stent is placed over the guidewire under fluoroscopic guidance. **C,** Fluoroscopic image after placement of a self-expandable metal stent. **D,** Endoscopic image showing the duodenal end of the stent.

malfunction, the duration of stent patency was regarded as equal to the survival time.

Statistical analysis

Results are expressed as mean and standard deviation. Unadjusted baseline characteristics, procedural outcomes, and long-term outcomes were compared between the EUSC and ETC groups. Categorical variables were compared using a χ^2 test and the Fisher exact test. Continuous parameters were compared using the Student *t* test and the Mann-Whitney U test. Cox regression analysis was used to compare late adverse event rate and cholecystitis recurrence rate.

Propensity scores to estimate the probability that patients would be selected for ETC on the basis of their characteristics were developed with the use of logistic regression to adjust for between-group differences in the baseline characteristics of the patients.[12] Details of the individual variables included in the propensity model are provided in Table 1. The propensity scores were used to determine the IPTW, which was then used as the primary tool to adjust for differences between the 2 treatment groups.[13] The IPTW, which was implemented to create balance, involved weighting each patient who underwent ETC by the inverse of the probability that a patient would be selected for ETC and weighting each patient who underwent EUSC by the inverse of the probability that a patient would be selected for EUSC. A $P < .05$ was considered to be statistically significant. Statistical analyses were performed using SPSS Statistics 22.0 (SPSS Inc, Chicago, Ill) and the R statistical package (V.3.1.2).

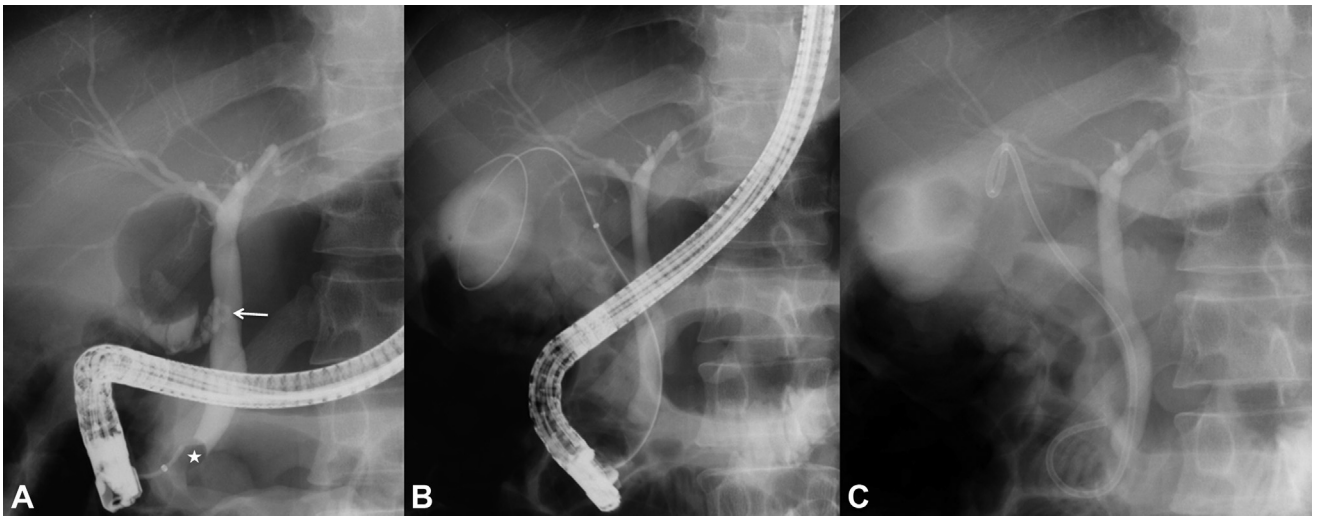


Figure 3. Endoscopic transpapillary cholecystostomy. **A,** Balloon (*star*) occluded cholangiogram showing cystic duct (*arrow*). **B,** A guidewire advanced from the cystic duct to the gallbladder. **C,** A 7F double-pigtail stent is placed in the gallbladder.

TABLE 1. Baseline characteristics of the enrolled patients

	Unadjusted cohort			Cohort adjusted with the use of inverse probability weighting			
	EUSC (n = 83)	ETC (n = 96)	*P* value	EUSC (n = 83)	ETC (n = 96)	*P* value	SMD
Age, y, mean ± SD	68.4 ± 11.4	65.6 ± 14.4	.15	67.9 ± 12.5	68.1 ± 12.7	.91	.02
Gender, male	33 (39.8)	66 (68.8)	<.01	45.8 (55.2)	49.9 (51.9)	.67	.07
Cause of cholecystitis			<.01			.35	.14
Calculous	50 (60.2)	80 (83.3)		61.4 (74)	76.7 (79.9)		
Acalculous	33 (39.8)	16 (16.7)		21.6 (26)	19.3 (20.1)		
Presence of CBD stone	6 (7.2)	28 (29.2)	<.01	9.7 (11.7)	16.8 (17.5)	.27	.17
Presence of liver cirrhosis	3 (3.6)	9 (9.4)	.15	8.3 (10)	5.6 (5.9)	.3	.15
Anticoagulation treatment	7 (8.4)	6 (6.3)	.58	5.7 (6.9)	6.7 (6.9)	.99	<.01
Causes underlying high surgical risk			<.01			.65	.14
ASA III	12 (14.5)	53 (55.2)		24.4 (29.3)	33.2 (34.6)		
ASA IV	15 (18.1)	23 (24)		19.2 (23.1)	17.6 (18.3)		
Advanced malignancy	56 (67.5)	20 (20.8)		39.4 (47.5)	45.2 (47.1)		
Cholangiocarcinoma	27 (32.5)	1 (1)		17.3 (20.8)	1.4 (1.5)		
Gallbladder cancer	10 (12)	1 (1)		5.8 (7)	5.3 (5.5)		
Pancreatic cancer	7 (8.4)	1 (1)		4.4 (5.3)	7 (7.2)		
Leukemia	3 (3.6)	0		3.1 (3.7)	0		
Hepatocellular carcinoma	2 (2.4)	5 (5.2)		2.4 (2.8)	6.2 (6.5)		
Prostate cancer	2 (2.4)	1 (1)		1.3 (1.6)	.8 (.9)		
Lung cancer	2 (2.4)	1 (1)		1.3 (1.6)	.8 (.9)		
Advanced gastric cancer	1 (1.2)	5 (5.2)		1.9 (2.3)	16.8 (17.5)		
Colon cancer	1 (1.2)	2 (2.1)		.7 (.9)	3 (3.1)		
Ovarian cancer	1 (1.2)	1 (1)		1.1 (1.4)	2.3 (2.4)		
Renal cell carcinoma	0	2 (2.1)		0	1.5 (1.6)		

Values are n (%) unless otherwise defined.

ETC, Endoscopic transpapillary cholecystostomy; *EUSC*, EUS-guided cholecystostomy; *SMD*, standardized mean difference; *SD*, standard deviation; *CBD*, common bile duct; *ASA*, American Society of Anesthesiologists.

*Seven patients who failed to undergo ETC crossed over to EUSC.

TABLE 2. Comparison of procedural outcomes of ETC and EUSC by intention to treat analysis

	Unadjusted cohort			Cohort adjusted with the use of inverse probability weighting		
	EUSC (n = 83)	ETC (n = 96)	*P* value	EUSC (n = 83)	ETC (n = 96)	*P* value
Technical success rate	82 (98.8)	80 (83.3)	<.01	82.5 (99.3)	83.1 (86.6)	<.01
Clinical success rate	82 (98.8)	79 (82.3)	<.01	82.5 (99.3)	82.6 (86)	<.01
Procedure time, min, mean ± SD	18.3 ± 4.9	19.5 ± 9.6	.31	17.7 ± 5.3	19.3 ± 9.3	.15
Procedural adverse events	6 (7.2)	9 (9.4)	.75	5.9 (7.1)	18.5 (19.3)	.02
Acute pancreatitis	0	8 (8.3)		0	18 (18.8)	
Pneumoperitoneum	3 (3.6)	0		4 (4.8)	0	
Recurrent biliary pain	2 (2.4)	1 (1.1)		1.4 (1.7)	.5 (.6)	
Perforation	1 (1.2)	0		.5 (.7)	0	

Values are n (%) unless otherwise defined.
ETC, Endoscopic transpapillary cholecystostomy; *EUSC*, EUS-guided cholecystostomy; *SD*, standard deviation.

RESULTS

Patient characteristics

Between July 2010 and December 2014, 4552 patients underwent surgical cholecystectomy. A total of 172 patients were enrolled for participation in this study during study periods. Of these patients, 76 underwent EUSC and 96 underwent ETC. Seven of 16 patients who failed to undergo ETC crossed over to the EUSC group. The baseline characteristics of the patients are summarized in Table 1. The 2 groups differed significantly in terms of gender, cause of unfitness for surgery, cause of cholecystitis, and presence of CBD stones.

Procedural outcomes

The procedural outcomes and adverse events are summarized in Table 2. Technical success rate (EUSC, 98.8% [82/83], vs ETC, 83.3% [80/96]; $P < .01$) and clinical success rate by intention to treat analysis (EUSC, 98.8% [82/83], vs ETC, 82.3% [79/96]; $P < .01$) were significantly higher in the EUSC group than in the ETC group. However, there was no statistical difference in clinical success rate by per-protocol analysis between both groups (82/82 [100%] vs 79/80 [98.8%], $P = .49$). The procedure time was not significantly different between both groups (EUSC, 18.3 ± 4.9 minutes, vs ETC, 19.5 ± 9.6 minutes; $P = .31$).

In the EUSC group, the procedure failed in 1 patient (1.2%) because of accidental loss of the guidewire during stent placement. ETC failed in 16 patients (16.7%) because of selective cystic duct cannulation failure (n = 12) or nonvisualization of the cystic duct because of cystic duct obstruction (n = 4).

After adjustment of IPTW analysis, the technical success rate (EUSC, 99.3%, vs ETC, 86.6%; $P < .01$) and clinical success rate (EUSC, 99.3%, vs ETC, 86%; $P < .01$) were still higher in the EUSC group. The mean procedural time was not statistically different between both groups (EUSC, 17.7 ± 5.3 minutes, vs ETC, 19.3 ± 9.3 minutes; $P = .15$).

TABLE 3. Comparisons of the baseline characteristics of patients with PEP and without PEP in the endoscopic transpapillary gallbladder drainage group

	Patients with PEP (n = 8)	Patients without PEP (n = 88)	*P* value
Age, y, mean ± SD	75.9 ± 9.6	64.7 ± 14.4	.03
Gender, male	6 (75)	60 (68.2)	.69
Cause of cholecystitis			.1
Calculous	5 (62.5)	75 (85.2)	
Acalculous	3 (37.5)	13 (14.8)	
Presence of CBD stone	1 (12.5)	27 (30.7)	.28
Causes underlying high surgical risk			<.01
ASA III	2 (25)	51 (57.9)	
ASA IV	1 (12.5)	22 (25)	
Advanced malignancy	5 (62.5)	15 (17.1)	
Pancreatobiliary malignancy	1 (12.5)	2 (2.3)	
Nonpancreatobiliary malignancy	4 (50)	13 (14.8)	

Values are n (%) unless otherwise defined.
PEP, Post-ERCP pancreatitis; *SD*, standard deviation; *CBD*, common bile duct; *ASA*, American Society of Anesthesiologists.

Procedural adverse events

The procedural adverse event rates of EUSC (7.2%, 6/83) and ETC (9.4%, 9/96) were similar ($P = .75$). In the EUSC group, pneumoperitoneum occurred in 3 patients (3.6%), duodenal perforation in 1 patient (1.2%), and recurrent biliary pain in 2 patients (2.4%). Patients who experienced recurrent biliary pain underwent endoscopic examination, and food reflux was identified 8 days after stent placement in 1 patient. Therefore, an additional

TABLE 4. Baseline characteristics of the patients who were evaluated for long-term outcomes

	Unadjusted cohort			Cohort adjusted with the use of inverse probability weighting			
	EUSC (n = 76)	ETC (n = 69)	*P* value	EUSC (n = 76)	ETC (n = 69)	*P* value	SMD
Age, y, mean ± SD	68.3 ± 11.6	65.2 ± 14.9	.18	68.2 ± 12.4	68.4 ± 12.8	.94	.01
Gender, male	30 (39.5)	50 (72.5)	<.01	40.5 (53.3)	35 (50.7)	.76	.05
Cause of cholecystitis			<.01			.33	.16
Calculous	45 (59.2)	57 (82.6)		53.6 (70.5)	53.5 (77.6)		
Acalculous	31 (40.8)	12 (17.4)		22.4 (29.5)	15.5 (22.4)		
Presence of CBD stone	6 (7.9)	19 (27.5)	<.01	9.1 (11.9)	10.6 (15.4)	.55	.1
Presence of liver cirrhosis	3 (3.9)	5 (7.3)	.61	5.6 (7.4)	3 (4.4)	.45	.13
Anticoagulation treatment	7 (9.2)	4 (5.8)	.65	5.9 (7.8)	5.3 (7.7)	.98	<.01
Causes underlying high surgical risk			<.01			.64	.16
ASA III	11 (14.5)	37 (53.6)		19.9 (26.2)	21.4 (31.1)		
ASA IV	12 (15.8)	15 (21.7)		15.6 (20.6)	10.4 (15.1)		
Advanced malignancy	53 (69.7)	17 (24.7)		40.5 (53.3)	37.1 (53.8)		
Follow-up periods, mo, mean ± SD	18.6 ± 21.1	25.5 ± 21.9	.07	21.9 ± 21.5	20.7 ± 19.7	.73	.06

Values are n (%) unless otherwise defined.
ETC, Endoscopic transpapillary cholecystostomy; *EUSC*, EUS-guided cholecystostomy; *SMD*, standardized mean difference; *SD*, standard deviation; *CBD*, common bile duct; *ASA*, American Society of Anesthesiologists.

double-pigtail plastic stent was placed through the metal stent to prevent food reflux. In the other patient with recurrent biliary pain, the proximal end of the metal stent was shown to be stuck to the gallbladder wall on cholecystogram through the metal stent lumen. An additional double-pigtail plastic stent was placed through the metal stent lumen to maintain stent patency. The single case of duodenal perforation was because of accidental loss of the guidewire access during stent placement. Endoscopic closure was performed using hemoclips, immediately upon recognition of the iatrogenic duodenal perforation. The patient improved after conservative treatment. Patients who experienced pneumoperitoneum recovered completely with conservative treatment within 2 days. There was no significant bleeding or bile leakage after the procedure in the EUSC group.

In the ETC group, 8 patients (8.3%) experienced post-ERCP pancreatitis (PEP), which improved after conservative treatment. Recurrent biliary pain occurred in 1 patient (1.1%) at 3 days after ETC. A partially distally migrated stent was verified by simple abdominal radiography, and a plastic stent exchange was therefore performed. In the subgroup analysis of patients with PEP, the proportion of patients with advanced malignancy was statistically higher in patients with PEP than in patients without PEP (62.5% [5/8] vs 17.1% [15/88], $P < .01$; Table 3). After adjustment, the procedural adverse event rates were significantly higher in the ETC group (EUSC, 7.1%, vs ETC, 19.3%; $P = .02$).

Long-term outcomes

Eleven patients (EUSC, n = 4; ETC, n = 7) were lost to follow-up, despite attempts to contact them. Five patients were excluded from follow-up because of cholecystectomy. Elective laparoscopic cholecystectomy was performed with curative intent for 2 patients in the EUSC group and 3 patients in the ETC group. Therefore, the long-term outcomes were evaluated in the remaining 145 patients who achieved clinical success (EUSC, n = 76; ETC, n = 69). The patients evaluated for long-term outcomes were readjusted according to the significant differences in baseline characteristics, and the results are shown in Table 4. There was no statistical difference between the groups with respect to the mean follow-up periods (EUSC, 18.6 ± 21.1 months, vs ETC, 25.5 ± 21.9 months; $P = .07$).

The long-term outcomes are described in Table 5. The cholecystitis or cholangitis recurrence rate was higher in the ETC group than in the EUSC group, although it did not reach statistical significance (hazard ratio [HR], 3.53; 95% CI, .99-12.5; EUSC, 3.9% [3/76, recurrent cholecystitis in 3], vs ETC, 17.4% [12/69, recurrent cholecystitis in 10 and recurrent cholangitis in 2]; $P = .05$). These symptomatic patients underwent reintervention. In the EUSC group, 3 patients experienced recurrent cholecystitis because of stent strut fracture (n = 2) or stent occlusion because of food impaction (n = 1). In patients with stent strut fracture, additional metal stents were placed within the original self-expandable metal stent. In a patient with stent occlusion, double-pigtail plastic stents placement through the metal stent was performed. In the ETC group, 10 patients experienced recurrent cholecystitis because of distal stent migration (n = 6) or stent occlusion (n = 4). Recurrent cholangitis with CBD stones occurred in 2 patients. Among the patients who experienced recurrent cholecystitis, plastic

TABLE 5. Cox proportional hazard regression model for long-term outcomes

	Unadjusted cohort					Cohort adjusted with the use of inverse probability weighting				
	HR	95% CI	EUSC* (n = 76)	ETC* (n = 69)	*P* value	HR	95% CI	EUSC* (n = 76)	ETC* (n = 69)	*P* value
Recurrence of cholecystitis or cholangitis	3.53	.99-12.5	3 (3.9)	12 (17.4)	.05	3.01	.73-12.9	2.4 (3.2)	8.6 (12.4)	.04
Recurrence of cholecystitis			3 (3.9)	10 (14.5)				2.4 (3.2)	7.2 (10.5)	
Recurrence of cholangitis			0	2 (2.9)				0	1.3 (1.9)	
Asymptomatic stent-related adverse events	.53	.09-3.23	3 (3.9)	3 (4.3)	.49	.25	.03-2.37	3 (3.9)	1.8 (2.7)	.68

HR, Hazard ratio, *ETC*, endoscopic transpapillary cholecystostomy; *EUSC*, EUS-guided cholecystostomy.
*Values are n (%).

stent exchange was performed in 6 patients. Stent removal and medical treatment was performed in 3 patients because of failed cystic duct selection. PTC was performed in 1 patient because of intolerability for endoscopic treatment. Two patients experienced recurrent CBD stones, and stone removal and stent exchange was performed.

The asymptomatic stent-related adverse event rate was similar between the 2 groups (HR, .53; 95% CI, .09-3.23; EUSC, 3.9% [3/76], vs ETC, 4.3% [3/69]; $P = .49$), with asymptomatic distal stent migration occurring in 3 patients in both the EUSC and ETC groups. These asymptomatic patients did not require additional treatments. The stent patency was similar in both groups (EUSC, 14.8 ± 16.8 months, vs ETC, 15.5 ± 18.1 months; $P = .81$). After adjustment using the IPTW method, the cholecystitis or cholangitis recurrence rate was higher in the ETC group than in the EUSC group (HR, 3.01; 95% CI, .73-12.9; EUSC, 3.2%, vs ETC, 12.4%; $P = .04$), whereas stent patency was similar in both groups (EUSC, 13.2 ± 15.2 months, vs ETC, 14.9 ± 16.8 months; $P = .49$).

DISCUSSION

In the present study, EUSC showed significantly higher technical and clinical success rates than ETC. In terms of the recurrence of cholecystitis and cholangitis, EUSC showed more favorable results than ETC. To the best of our knowledge, this study was the first to compare the outcomes of EUSC and ETC. To improve the validity of the results, we performed IPTW analysis to reduce potential confounding factors that might have influenced the chance of being treated with a specific procedure. Therefore, EUSC can be considered an effective and safe treatment for acute cholecystitis and as a definitive treatment for high surgical risk patients or patients with advanced malignancy.

In this study, EUSC showed significantly higher technical success rate than ETC (98.8% vs 83.3%, $P < .01$). The clinical success rate by intention-to-treat analysis was significantly higher in the EUSC group (EUSC, 82/83 [98.8%], vs ETC, 79/96 [82.3%]; $P < .01$), which may be because of relatively lower technical success rate of ETC. There was no statistical difference in clinical success rate by per-protocol analysis between both groups (EUSC, 82/82 [100%], vs ETC, 79/80 [98.8%]; $P = .49$). Although ETC has advantages such as single-step drainage of the gallbladder concomitant with the CBD stone removal and physiologic drainage without the creation of a fistula, ETC is technically challenging, especially the cannulation and traversal of the cystic duct.[2,14] A recent review reported a technical success rate of 83% for ETC.[14] The relatively lower technical success rate of ETC may be because of tumor involvement, impacted stones, a previously inserted metal stent, or tortuosity of the cystic duct.[7] On the other hand, EUSC showed a higher technical success rate because it is not affected by the configuration of cystic duct.[5] Although EUSC has inherent technical difficulties, these may be overcome as experience of the procedure accumulates.[15] According to a recent guideline, EUSC could be considered in high-volume institutes by experienced endosonographers.[16] In this study, all procedures were performed by highly experienced endoscopists. If these procedures were performed by inexperienced endosonographers, results may be different from current favorable results.

Our higher technical and clinical success rate of EUSC may also be related with a dedicated metal stent with large flared ends. Use of the modified stents with right-angle flared ends may have prevented migration.[8] On the other hand, the application of plastic stent or standard tubular biliary metal stent may lower the clinical outcomes of EUSC. Furthermore, EUSC can avoid potentially serious ERCP-related adverse events such as PEP and cystic duct perforation.[5]

In the present study, patients who underwent ETC had more CBD stones at the time of intervention than those who underwent EUSC (29.2% vs 7.2%, $P < .01$). This was because of the treatment strategy, that is, when CBD stones were observed or suspected, ETC was preferentially considered. For these reasons, the proportion of CBD stones differed between the groups. Based on our results, we suggest that ETC should be used in selected candidates with combined CBD stones or suspected choledocholithiasis. In addition, ETC might be a safer procedure than EUSC in patients with coagulopathy because it does not require needle puncture or tract dilation. In this study, the proportion of patients receiving anticoagulation treatment was similar in both groups. No postprocedural bleeding occurred in all patients. In a recent study by Kahaleh et al,[17] postprocedural bleeding developed in patients with plastic stent placement but not in patients with metal stent placement. The mechanical tamponade effect of the metal stent may achieve hemostasis in patients receiving anticoagulation treatment.

The incidence of procedural adverse events was similar in both groups; however, such events occurred more frequently in the ETC group after adjustment. A plausible explanation is that patients who experienced PEP may not be suitable for ETC. The proportion of advanced malignancy was statistically higher in patients with PEP than in patients without PEP (62.5% [5/8] vs 17.1% [15/88], $P < .01$). ETC may not be feasible in patients with cystic duct obstruction caused by tumor invasion.[7] Furthermore, ETC was performed in nonpancreatobiliary cancer patients with normal-caliber CBDs, which is related to the risk factor of PEP.[18] This tendency is likely to have been emphasized after adjustment. Therefore, EUSC should be preferentially considered in patients who have potential risk factors of PEP with advanced malignancy to avoid ERCP-related adverse events.

In this study, there was a tendency for cholecystitis or cholangitis recurrence to develop more frequently in the ETC group than in the EUSC group (EUSC vs ETC: 3.9% [3/76] vs 17.4% [12/69]; $P = .051$). After adjustment for confounding biases, the cholecystitis or cholangitis recurrence rate was statistically higher in the ETC group (HR, 3.01; 95% CI, .73-12.9; EUSC, 3.2%, vs ETC, 12.4%; $P = .04$). Our results suggest that EUSC is more suitable than ETC as a definitive treatment in patients with high surgical risk or advanced malignancy because unnecessary interventions, such as stent exchange or removal, may be avoided after EUSC.

Although asymptomatic stent migration occurred in both groups, there was no statistically significant difference. In the EUSC group, asymptomatic stent migration developed in 3 of 76 cases. There is a possibility that the cholecystoenteric fistula tract had matured, and therefore recurrence of symptoms did not occur. A recent study demonstrated that the recurrence of cholecystitis after stent removal 4 weeks after self-expandable metal stent placement was not common, found in only 1 of 12 patients (8.3%) who underwent EUSC.[19]

This study has several limitations. First, it is a retrospective analysis from a single institution. Thus, we could not control selection bias and confounding factors. However, we did use propensity score matching and IPTW to enable us to analyze outcomes between EUSC and ETC. Second, this study was conducted in a tertiary center, and procedures were performed by experienced endosonographers. Therefore, our results may not be directly extrapolated to other centers with different expertise in EUSC and ETC.

Although we found the long-term outcomes of ETC to be inferior to those of EUSC, in patients with acute cholecystitis combined with CBD stones, gallbladder decompression is performed in the same session as the removal of CBD stones through ERCP, with this clinical practice having a reduced patient burden. It is therefore beneficial for patients in terms of medical cost benefit. Thus, it is reasonable to attempt ETC first if CBD stones are suspected.

In conclusion, EUSC and ETC were both safe and effective for the acute phase treatment of acute cholecystitis in high surgical risk patients. However, considering the long-term follow-up and risk of recurrence, EUSC may be more helpful for patients who cannot undergo surgery. Given our favorable data, further randomized trials are warranted to verify these promising results.

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Abbreviations: CI, confidence interval; CBD, common bile duct; ETC, endoscopic transpapillary cholecystostomy; EUSC, EUS-guided cholecystostomy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; GBD, gallbladder drainage; PEP, post-ERCP pancreatitis; PTC, percutaneous transhepatic cholecystostomy.

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