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# The evaluation of ENGBD versus PTGBD in high-risk acute cholecystitis: A single-center prospective randomized controlled trial

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ABSTRACT

*Background:* Gallbladder drainage plays a key role in the management of acute cholecystitis (AC) patients. Percutaneous transhepatic gallbladder drainage (PTGBD) is commonly used while endoscopic naso-gallbladder drainage (ENGBD) serves as an alternative.

*Methods:* A single center, prospective randomized controlled trial was performed. Eligible AC patients were randomly assigned to ENGBD or PTGBD group. Randomization was a computer-generated list with 1:1 allocation. All patients received cholecystectomy 2−3 months after drainage. The primary endpoint was abdominal pain score, and the intention-to-treat population was analyzed. (ClinicalTrials.gov: NCT03701464).

*Findings:* Between Oct 1, 2018 and Feb 29, 2020, 22 out of 61 consecutive AC patients were enrolled in the final analysis. The mean abdominal pain scores before drainage, and at 24, 48, and 72 h after drainage in ENGBD were 6.9 ± 1.1, 4.3 ± 1.2, 2.2 ± 0.8 and 1.5 ± 0.5, respectively, while those of PTGBD were 7.4 ± 1.2, 6.2 ± 1.2, 5.3 ± 1.0 and 3.7 ± 0.9; and the mean gallbladder area tenderness scores were 8.4 ± 1.2, 5.7 ± 0.9, 3.5 ± 0.7, 2.5 ± 0.5 for ENGBD and 8.6 ± 0.9, 7.3 ± 1.0, 7.4 ± 0.5, 4.8 ± 0.9 for PTGBD. The mean abdominal pain and gallbladder area tenderness scores of the ENGBD significantly decreased than the PTGBD (group × time interaction $P<0.001$, respectively). ENGBD group presented lower post-operative hemorrhage and abdominal drainage tube placement rates (median (IQR) 15[5−20] vs 40[20−70]ml, 3*vs*9, $P = 0.03$), and pathological grade and lymphocyte count were observed ($P = 0.004$) between groups. No adverse events were observed in 3 months follow-up.

*Interpretation:* Compared to PTGBD, ENGBD group presented less pain, better gallbladder pathological grades and less surgical difficulties during cholecystectomy procedures.

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## 1. Introduction

Laparoscopic cholecystectomy (LC) is the fundus-first approach for acute cholecystitis (AC) [1], and it has been associated with significant morbidity and mortality rates in high-risk patients and those in advanced stages of cholecystitis [2]. Gallbladder drainage plays a key role in the management of these patients [3]. According to Tokyo Guidelines for management strategies for gallbladder drainage [4],

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**Research in context**

*Evidence before this study*

Gallbladder drainage plays a key role in the management of AC patients who have higher risks of morbidity and mortality rates. Although percutaneous transhepatic gallbladder drainage (PTGBD) is considered as a first-line alternative according to several important guidelines, endoscopic gallbladder drainage (EGBD) has also been used in high-volume institutes by skilled endoscopists to achieve gallbladder decompression. Its feasibility, safety, and efficacy had been described in several systematic reviews and randomized controlled trials.

*Added value of this study*

The effects of the two types of drainage methods on cholecystectomy remain uncertain, and no extensive evaluation has been reported. Hence this is the first prospective randomized controlled trial comparing ENGBD and PTGBD. The results of ENGBD and PTGBD were not significantly different in terms of technical success, clinical effectiveness and safety, and ENGBD was associated with less pain, better gallbladder pathological grades and lower difficulties cholecystectomy.

*Implications of all the available evidence*

ENGBD is administered as a minimally invasive method for gallbladder decompression via natural orifice, but its safety and efficiency has not been proven sufficiently due to a lack of direct comparison with PTGBD. Results of our randomized controlled trial showed that patients who underwent ENGBD have less pain, better compliance, better gallbladder pathological grades and less difficulties during cholecystectomy.

percutaneous transhepatic gallbladder drainage (PTGBD) should be considered as a first-line alternative, while endoscopic gallbladder drainage (EGBD) has also been a technique used in high-volume institutes by skilled endoscopists. EGBD, including endoscopic transpapillary gallbladder drainage (ETGBD) by using endoscopic nasogallbladder drainage (ENGBD) or endoscopic gallbladder stent (EGBS) and endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) [5], is an effective method for AC both technically and clinically and seems to be safer than traditional PTGBD according to a systematic review [6].

A prospective study indicated that EUS-GBD was comparable to PTGBD in terms of feasibility, efficacy and safety, but there was no prospective direct comparison of ENGBD or EGBS with PTGBD [7]. Although a randomized controlled trial confirmed that ENGBD and EGBS are both suitable for drainage [8], it is difficult for the gallbladder stent to fall off by itself during the waiting window from EGBS to cholecystectomy; [9] therefore, we conducted a prospective randomized controlled trial comparing ENGBD and PTGBD. Moreover, the effects of the two drainage methods on cholecystectomy remain uncertain, and there has been no extensive evaluation.

In this single-center trial, we aimed to observe the clinical effects of ENGBD and PTGBD for surgically high-risk patients with AC, not only peri-drainage but also peri-LC.

## 2. Material and methods

### 2.1. Study design

This was a randomized controlled, parallel, open-label trial conducted at the Surgical Endoscopy Center of the First Hospital of Lanzhou University, which performs more than 2000 endoscopic retrograde cholangiopancreatography (ERCP) procedures per year. The study was performed in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrial.gov under trial identification number NCT03701464. The ethics committee of the First Hospital of Lanzhou University approved the study, which was performed in accordance with a published protocol [10]. Written informed consent was obtained from the patient for using their data in scientific studies while protecting their anonymity before the procedure. The manuscript was prepared according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement.

### 2.2. Participants and operators

According to the Tokyo Guidelines (TG) 2018 flowchart [1], the following patients who were not suitable for early or urgent cholecystectomy and needed gallbladder drainage were included: partial Grade II (moderate) and Grade Ⅲ (severe) AC patients who were symptomatic greater than 72 h, and symptoms could not be relieved by antibiotics administer and general supportive care. Particularly, Grade III AC patients with impaired liver or kidney functions and coagulopathies were included. (Table 1); or present no negative predictive factors but have American Society of Anesthesiologists (ASA) physical status classification [13] score $\geq$ 3 (a patient with severe systemic disease and even a constant threat to life; a moribund patient who is not expected to survive without the operation; a declared brain-dead patient whose organs are being removed for donor purposes) (Supplementary Table 1), or a Charlson comorbidity index [14] (CCI) $\geq$4.

**Table 1**
TG18/TG13 severity grading for acute cholecystitis [11].

| TG18/TG13 severity grading for acute cholecystitis | Whether to be included |
|---|---|
| Grade III (severe) acute cholecystitis | |
| "Grade III" acute cholecystitis is associated with dysfunction of any one of the following organs/systems: | |
| 1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine $\geq$5 lg/kg per min, or any dose of norepinephrine | × |
| 2. Neurological dysfunction: decreased level of consciousness | × |
| 3. Respiratory dysfunction: $PaO_2/FiO_2$ ratio <300 | × |
| 4. Renal dysfunction: oliguria, creatinine >2.0 mg/dl | √ |
| 5. Hepatic dysfunction: PT-INR >1.5 | √ |
| 6. Hematological dysfunction: platelet count <100,000/$mm^3$ | √ |
| Grade II (moderate) acute cholecystitis | |
| "Grade II" acute cholecystitis is associated with any one of the following conditions: | |
| 1. Elevated WBC count (>18,000/$mm^3$) | √ |
| 2. Palpable tender mass in the right upper abdominal quadrant | √ |
| 3. Duration of complaints >72 h[a] | √ |
| 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis) | × |
| Grade I (mild) acute cholecystitis | |
| "Grade I" acute cholecystitis does not meet the criteria of "Grade III" or "Grade II" acute cholecystitis. It can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure | × |

Cited from Yokoe et al. [12]: the TG13 severity assessment criteria of acute cholecystitis was judged from numerous validation studies as useful indicators in clinical practice and adopted as TG18severity assessment criteria without any modification. To judge predictive factors of acute cholecystitis on flowchart in Grade III, serum total bilirubin level is required to measure.

[a] Laparoscopic surgery should be performed within 96 h of the onset of acute cholecystitis.

Exclusion criteria included the following: age <18 or >90 years, pregnant or breastfeeding, severe obesity (body mass index ≥ 35 kg/$m^2$), pre-existing condition such as bile duct stone, acute pancreatitis, gastrointestinal bleeding or perforation, any malignancy, severe liver disease, coagulation dysfunction (international normalized ratio > 1.5) and thrombocytopenia (<50 × $10^9$/L), taking anticoagulation or antiplatelet drugs, and previous gastrectomy and choledochojejunostomy. All patients or their legal representatives provided written informed consent after being familiarized with the drainage procedures and study participation.

PTGBD was performed by a professional and trained ultrasound interventional physician (YNY). ERCP and cholecystectomy were completed by an endoscopic surgeon team with more than 10 years of ERCP and 20 years of LC experience (400 ERCP procedures and 450 LC procedures per year at present).

### 2.3. Randomization and masking

Randomization was performed by an independent statistician using a computer-generated randomization list with 1:1 allocation, stored and placed into 22 sealed, opaque envelopes independently. Patients and physicians were not masked because of the nature of the intervention (position and shape of the drainage tube). However, outcome assessors were masked to treatment allocation.

### 2.4. Procedures

PTGBD was guided by ultrasound. An 18-gauge needle was inserted into the gallbladder, a 0.035-in. guidewire was coiled into the gallbladder, and a 9 Fr dilator expanded the skin. Then, an 8 F 20 cm catheter was placed. Patients in the ENGBD group were sedated by the intravenous administration of sufentanil and propofol, followed by selective bile duct cannulation. A 0.025- or 0.035-in. guidewire was advanced into the cystic duct and subsequently into the gallbladder, withdrawing the catheter. A 5 Fr naso-gallbladder catheter was inserted into the gallbladder along the guidewire (Fig. 2). When ENGBD was technically unsuccessful or clinically ineffective, endoscopic naso-biliary drainage (ENBD), PTGBD and EUS-GBD, [15] were used as alternative procedures.

All participants were monitored by an attending physician in accordance with recent guidelines and previous clinical experience, including sufficient infusion, maintenance of the electrolyte balance, antibacterial agents, monitoring of respiratory and hemodynamics, and correction of acidosis and complications. In particular, there was no strict recommendation for the extubation time, and the ENGBD group was extubated when clear bile drained from the naso-gallbladder tube, which was always 1–2 weeks after drainage based on our experience. Patients in the PTGBD group were extubated during cholecystectomy to prevent biliary fistula. Additionally, no consensus was reached about the optimal timing of cholecystectomy after drainage. Because most studies [16-18] determined that a short interval duration between PTGBD and LC can increase the intraoperative difficulty, we required all patients to undergo cholecystectomy 2–3 months after drainage so that edema and inflammation around the gallbladder subsided completely. We followed up all patients at least 3 months after cholecystectomy.

### 2.5. Outcomes

The primary outcome was the abdominal pain score, which was defined as abdominal pain felt by the patients from the supine to the standing position. All the pain scores, which were based on the visual analog scale [19], were assessed within 2 h before drainage and 24, 48, and 72 h post-drainage in conscious and communicating patients by a specially trained nurse who devoted herself to the objectivity and authenticity of the scores. The assessment was performed as follows: a 10-cm line was drawn on a piece of paper, and one end of the line was marked with the number 0, indicating no pain; the other end was marked with the number 10, indicating the most severe pain; the middle part indicated different degrees of pain. Patients who could not see the numbers on the paper marked the location according to how they felt about the pain and the nurse gave a score based on the mark. In particular, all pain assessments were performed without the administration of a pain killer or after analgesics for at least 6 h.

The secondary outcomes included the gallbladder area tenderness score (defined as the pain score of patients lying supine when the doctor examined and pressed the abdomen of the gallbladder area), the technical success rate (defined as the outflow of more than 50 mL of bile from the drainage tube within 24 h after the drainage operation), the clinical remission rate (defined as an improvement in typical clinical symptoms, laboratory tests, and imaging studies after drainage), bridge stage relapse (defined as cholecystitis recurrence during the window from the clinical remission of drainage to cholecystectomy), gallbladder integrity (defined as partial cholecystectomy or no mucosal destruction), open conversion (defined as the surgical team's decision to switch to open surgery for safety reasons), pathological grade (defined as post-operative gallbladder pathology reported as simple inflammatory, suppurative or gangrenous), and lymphocyte count reflecting objectively the severity of chronic inflammation (defined as the average number of lymphocytes randomly selected from 10 fields of view in HE-stained pathology slides under a 200x microscope).

Safety outcomes were pancreatitis, bleeding, perforation, biliary leakage, drainage tube accidents peri-drainage, intraoperative common bile duct injury, postoperative bleeding, biliary leakage, and infection peri-cholecystectomy.

### 2.6. Statistical analysis

The sample size calculation was based on the primary outcome (i.e., abdominal pain score). According to the research by Jang et al. [7], and using the method provided by Luo et al. [20] and Wan et al. [21], the mean post-procedure pain score in the PTGBD group was 5.4 ± 3.1, and the mean post-procedure pain score in the ENGBD group was 1.3, as shown by Itoi et al. [8]. Using a theoretical sample size for a two-sample design, we determined that 9 participants were needed in each group to obtain 80% power and a 5% significance level. Allowing for a 10% loss to follow-up, we planned to recruit 22 patients (11 in each group). A predefined statistical analysis plan was followed. Dichotomous variables are reported as counts and percentages. Continuous variables are presented as medians and interquartile ranges (IQRs). The primary analysis was a comparison between ENGBD and PTGBD for abdominal pain remission based on an intention-to-treat principle. A linear mixed model was fitted by PROC MIXED. This model was adjusted for the fixed effects of treatment group, time (0, 24, 48, or 72 h), and treatment*time interaction. An unstructured covariance pattern was selected for the repeated measurements as the least restrictive structure, which resulted in a better model fit based on log-likelihood values than more constrained patterns. Estimates of the difference in pain scores between treatment groups were assessed overall and at individual time points. Fisher's exact test was used for dichotomous variables, and the Wilcoxon test was used for rank data. For quantitative data, a two-tailed Student's *t*-test was used if the data followed a normal distribution and if the homogeneous total variance was satisfied; otherwise, the Wilcoxon test was used. All statistical analyses were performed with SAS 9.4. *P* values less than 0.05 were considered to indicate statistical significance.

### 2.7. Role of the funding source

The funder of the study had no role in study design, patient recruitment, data collection and analysis, interpretation of the data,

or writing of the report. The corresponding author (WM and PY) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## 3. Results

Between Oct 1, 2018, and Feb 29, 2020, 61 consecutive patients were diagnosed with AC, 39 patients were excluded after screening, and the remaining 22 patients were randomly assigned to receive ENGBD or PTGBD and included in the final analysis (Fig. 1). Endoscopic drainage was successfully performed in 10 patients of experimental group, with a technical success rate of 90.9% due to guide wire could not enter the gallbladder duct opening after repeated attempts in one patient of the ENGBD group, thus endoscopic nasobiliary drainage was performed.

Baseline demographic and clinical characteristics were comparable between the two groups (Table 2). The mean abdominal pain scores of the ENGBD group before drainage and 24, 48, and 72 h after drainage were 6.9 ± 1.1, 4.3 ± 1.2, 2.2 ± 0.8 and 1.5 ± 0.5, respectively, while those of the PTGBD group were 7.4 ± 1.2, 6.2 ± 1.2, 5.3 ± 1.0 and 3.7 ± 0.9, respectively (Fig. 3), with mean difference (95% CI) of −0.5 (−1.6, 0.5), −1.9 (−3.0, −0.9), −3.1 (−3.9, −2.3), −2.3 (−3.0, −1.6), respectively (Table 3). The mean gallbladder area tenderness scores of the ENGBD group before drainage and 24, 48, and 72 h after drainage were 8.4 ± 1.2, 5.7 ± 0.9, 3.5 ± 0.7 and 2.5 ± 0.5, respectively, while those of the PTGBD group were 8.6 ± 0.9, 7.3 ± 1.0, 7.4 ± 0.5 and 4.8 ± 0.9, respectively (Fig. 3), with mean difference (95% CI) of −0.3 (−1.2, 0.7), −1.5 (−2.4, −0.7), −3.8 (−4.4, −3.3), −2.3 (−2.9, −1.6), respectively (Table 3). There were significant interactions between group and time ($P < 0.001$) for both scores, which suggested that abdominal pain scores and gallbladder area tenderness scores of the ENGBD decrease faster than the PTGBD.

The technical success rates of ENGBD (10/11) and PTGBD (11/11) were similar ($P = 1.00$); in 1 patient, ENGBD failed due to the inability of the guidewire to enter the opening of the cystic duct after repeated attempts, and ENBD was performed. The median and inter quartile range (IQR) operation time of drainage in the ENGBD group (38 [35–60] minutes) was significantly longer than that in the PTGBD group (16 [14–20] minutes) ($P < 0.001$), and the ENGBD group had 12 (9–20) minutes of X-ray exposure time, while the PTGBD group did not ($P < 0.001$). All 22 patients achieved clinical remission ($P = 1.00$). One patient with pancreatitis in the ENGBD group and 3 patients (one patient had a small amount of bloody bile in the drainage tube, one patient had drainage tube blockage and fever symptoms, and the other patient underwent the drainage tube fell off one month later.) in the PTGBD group experienced drainage-related adverse events ($P = 0.59$). In the ENGBD and PTGBD groups, suppurative bile was drained in 7 and 6 patients, respectively, 10 and 9 patients, respectively, were positive for bile bacterial culture, and the median (IQR) lengths of hospitalization peri-drainage were 6.0 (5.0–7.0) and 7.0 (6.0–10.0) days, respectively ($P > 0.05$). One patient in the ENGBD group underwent analgesic intervention, whereas 11 patients in the PTGBD group underwent analgesic intervention. The median (IQR) drainage cost of the ENGBD group was 18505 (17,963–19,024) renminbi, which was much higher than that of the PTGBD group (9709, 9007–12,708) renminbi; $P < 0.001$). One patient in the ENGBD group experienced bridge stage relapse (Table 4).

Twenty-two participants were readmitted to our department for cholecystectomy 2–3 months after drainage, and open conversion occurred in 2 patients: 1 patient in the ENGBD group and 1 patient in the PTGBD group ($P = 1.00$). The median (IQR) duration of cholecystectomy was 50 (47–90) min in the ENGBD group and 70 (50–104) min in the PTGBD group ($P = 0.25$). The median (IQR) volume of hemorrhage during cholecystectomy in the ENGBD group was 15 (5–20) ml, which was significantly less than that in the PTGBD group (40, 20–70) ml; $P = 0.03$). Two patients in the ENGBD group experienced

**Table 2**
Baseline clinical features.

| | ENGBD ($n = 11$) | PTGBD ($n = 11$) | $P$ |
|---|---|---|---|
| Sex (male/female) | 8/3 | 7/4 | 1.00 |
| Age (years) | 63 (52–82) | 61 (53–80) | 0.84* |
| BMI (kg/m$^2$) | 23.2 (21.6–26.0) | 23.4 (21.5–24.8) | 0.69* |
| Comorbidities | | | |
| Coronary disease | 4 | 2 | 0.64 |
| Chronic pulmonary disease | 6 | 7 | 1.00 |
| Hypertension | 5 | 4 | 1.00 |
| Diabetes | 1 | 0 | 1.00 |
| ASA | | | 0.62 |
| II | 2 | 3 | |
| III | 9 | 8 | |
| CCI | | | 0.54 |
| 5 | 9 | 10 | |
| 6 | 2 | 1 | |
| Severity grade | | | 0.62 |
| II | 8 | 9 | |
| III | 3 | 2 | |
| First episode | 6 | 4 | 0.67 |
| Fever | 9 | 7 | 0.64 |
| Onset before drainage (day) | 7.0 (5.0–9.0) | 5.0 (5.0–8.0) | 0.22* |
| Multiple stone | 7 | 4 | 0.40 |
| Gallbladder wall thickness (mm) | 5 | 6 | 0.74 |
| Long diameter of gallbladder (mm) | 109 (89–118) | 98 (87–113) | 0.28* |
| WBC ($10^9$/L) | 12.0 (11.0–14.2) | 11.1 (10.0–13.7) | 0.45* |
| Neutral percentage | 83.1 (75.7–88.7) | 81.0 (70.3–91.6) | 0.84* |
| CRP (mg/L) | 50.1 (21.6–175.2) | 48.1 (20.1–155.4) | 0.58* |
| Platelet count ($10^9$/L) | 125 (99–136) | 133 (100–158) | 0.45* |
| TBIL (umol/L) | 10.4 (6.1–16.7) | 8.1 (5.3–10.9) | 0.38* |
| DBIL (umol/L) | 2.7 (0.6–6.0) | 3.0 (2.3–4.6) | 0.79* |

Data are median (IQR: Inter-quartile range) or n;.
* Wilcoxon rank sum tests. Others are Fisher's exact test.

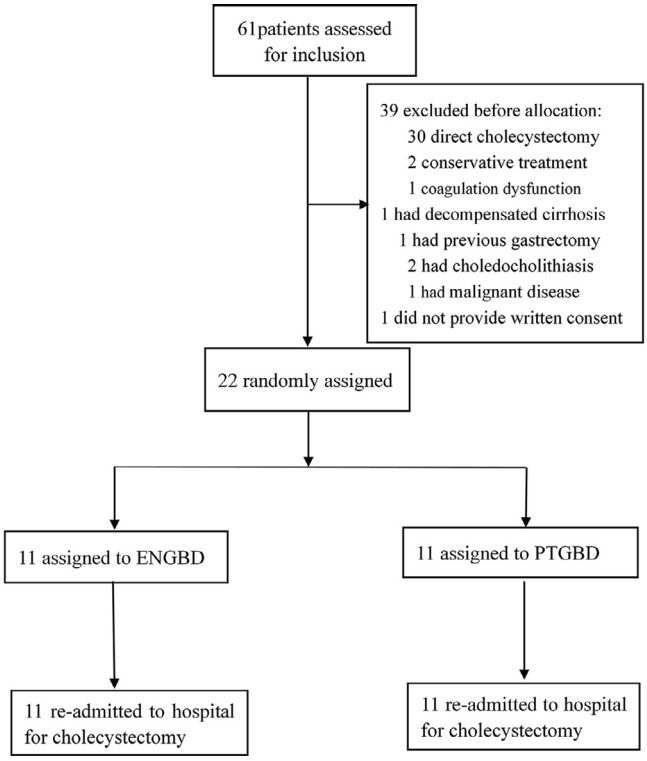


**Fig. 1.** Flow diagram of the study.

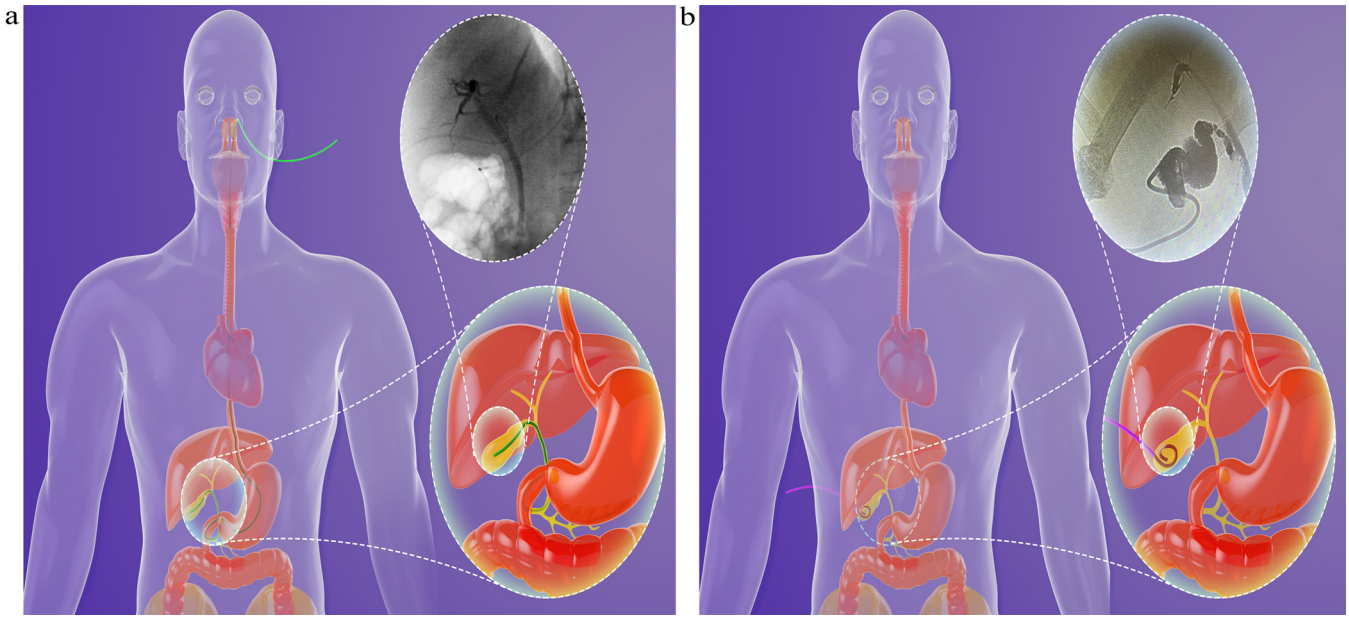


**Fig. 2.** ENGBD (a) and PTGBD (b) procedures.

**Table 3**
Change of abdominal pain score and gallbladder area tenderness score in ENGBD and PTGBD.

| Outcomes | ENGBD ($N$ = 11) | PTGBD ($N$ = 11) | Mean difference (95%CI) |
|---|---|---|---|
| Abdominal pain score[a] | | | |
| 0 h | 6.9 ± 1.1 | 7.4 ± 1.2 | −0.5 (−1.6, 0.5) |
| 24 h | 4.3 ± 1.2 | 6.2 ± 1.2 | −1.9 (−3.0, −0.9) |
| 48 h | 2.2 ± 0.8 | 5.3 ± 1.0 | −3.1 (−3.9, −2.3) |
| 72 h | 1.5 ± 0.5 | 3.7 ± 0.9 | −2.3 (−3.0, −1.6) |
| Gallbladder area tenderness score[b] | | | |
| 0 h | 8.4 ± 1.2 | 8.6 ± 0.9 | −0.3 (−1.2, 0.7) |
| 24 h | 5.7 ± 0.9 | 7.3 ± 1.0 | −1.5 (−2.4, −0.7) |
| 48 h | 3.5 ± 0.7 | 7.4 ± 0.5 | −3.8 (−4.4, −3.3) |
| 72 h | 2.5 ± 0.5 | 4.8 ± 0.9 | −2.3 (−2.9, −1.6) |

Mixed model: Abdominal pain score and Gallbladder area tenderness score as dependent variables; fixed factors: group, time (continuous), group × time interaction; random effect: subject id.
Data were presented as means ± SD (Standard Deviation) for ENGBD and PTGBD.
All tests are Wilcoxon rank sum tests.
[a] $P$<0.001 for group × time, $P$ = 0.01 for group, $P$<0.001 for time.
[b] $P$<0.001 for group × time, $P$ = 0.045 for group, $P$<0.001 for time.

**Table 4**
Clinical outcomes of peri-drainage.

| | ENGBD ($n$ = 11) | PTGBD ($n$ = 11) | $p$ |
|---|---|---|---|
| Technical success | 10 | 11 | 1.00 |
| Procedure duration (min) | 38 (35–60) | 16 (14–20) | <0.001* |
| Radiation exposure time (min) | 12 (9–20) | 0 (0–0) | <0.001* |
| Clinical remission | 11 | 11 | 1.00 |
| Antibiotic use | 11 | 11 | 1.00 |
| Analgesic intervention | 1 | 11 | <0.001 |
| Adverse events | 1 | 3 | 0.59 |
| Pancreatitis | 1 | 0 | 1.00 |
| Bleeding | 0 | 1 | 1.00 |
| Clogged tube | 0 | 1 | 1.00 |
| Shed tube | 0 | 1 | 1.00 |
| Purulent bile | 7 | 6 | 1.00 |
| Positive bile bacterial culture | 10 | 9 | 1.00 |
| Hospital stay (day) | 6 (5–7) | 7 (6–10) | 0.23* |
| Drainage cost (rmb) | 18,505 (17,963–19,024) | 9709 (9007–12,078) | <0.001* |
| Bridge stage relapse | 1 | 0 | 1.00 |

Data are median (IQR: Inter-quartile range) or n;.
* Wilcoxon rank sum tests. Others are Fisher's exact test.

choledocholithiasis during the peri-cholecystectomy period, whereas no patient in the PTGBD group did ($P$ = 0.48). Two patients in the ENGBD group and 5 patients in the PTGBD group had tight adhesion under direct vision during the operation ($P$ = 0.36). Nine patients in the ENGBD group and 7 patients in the PTGBD group maintained gallbladder integrity ($P$ = 0.64). Three patients in the ENGBD group had abdominal drainage tubes after cholecystectomy, whereas 9 patients in the PTGBD group did ($P$ = 0.03). No LC-related adverse events occurred in the ENGBD or control group after cholecystectomy; the median (IQR) lengths of hospitalization peri-cholecystectomy were 3.0 (3.0–5.0) and 5.0 (3.0–7.0) days, respectively ($P$ = 0.12). There was a statistically significant difference in the pathological grade of the gallbladder between the two groups ($P$ = 0.01); in the ENGBD group, 2 patients showed suppurative pathology, and 9 patients had a purely inflamed gallbladder; in the PTGBD group, 6 patients showed suppuration pathology, 2 patients had a gangrenous gallbladder, and only 3 patients had a simply inflamed gallbladder (Table 5). Additionally, the median (IQR) lymphocyte count in the ENGBD group was significantly less than that in the PTGBD group (20.6 [17.8–30.6] vs 33 [31.8–36], $P$ < 0.004) (Fig. 4).

All participants were followed up for more than 3 months, and there was no recurrence of cholangitis, biliary pancreatitis, cholecystitis, or other diseases.

## 4. Discussion

PTGBD is a frequently performed gallbladder decompression option for surgically high-risk patients with AC, [22] but it is prohibited for patients with ascites, coagulopathy, Chilaiditi syndrome, decompensated liver cirrhosis, portal hypertension or malignant tumors [23]. Patients who received PTGBD have higher risk of bleeding when combined with coagulopathy at the time of treatment [4]. While this risk is lower when performing ENGBD, which uses natural orifice, cystic duct, for gallbladder decompression, [24,25] but its

**Table 5**
Clinical outcomes of peri-cholecystectomy.

| | ENGBD ($n$ = 11) | PTGBD ($n$ = 11) | $p$ |
|---|---|---|---|
| Duration of cholecystectomy (min) | 50 (47–90) | 70 (50–104) | 0.25* |
| Hemorrhage (ml) | 15 (5–20) | 40 (20–70) | 0.03* |
| Choledocholithiasis | 2 | 0 | 0.48 |
| Abdominal drainage tube | 3 | 9 | 0.03 |
| Tight adhesion | 2 | 5 | 0.36 |
| Gallbladder integrity | 9 | 7 | 0.64 |
| Exploration of common bile duct | 2 | 0 | 0.48 |
| Open conversion | 1 | 1 | 1.00 |
| Pathological grade | | | 0.01* |
| 1 (simple inflammatory) | 9 | 3 | |
| 2 (suppurative) | 2 | 6 | |
| 3 (gangrenous) | 0 | 2 | |
| Lymphocyte count | 20.6 (17.8–30.6) | 33 (31.8–36) | 0.004* |
| Adverse events | 0 | 0 | 1.00 |
| Hospital stay (day) | 3.0 (3.0–5.0) | 5.0 (3.0–7.0) | 0.12* |

Data are median (IQR: Inter-quartile range) or n;.
* Wilcoxon rank sum tests. Others are Fisher's exact test.

safety and efficiency have not been proven sufficiently due to a lack of direct comparison with PTGBD. We designed the current study, which was a prospective randomized controlled trial, to compare the clinical outcome of ENGBD and PTGBD.

We demonstrated that the abdominal pain score of the ENGBD group was significantly lower than that of the PTGBD group, consistent with a previous study [26] that indicated that EGBD was associated with almost 50% less pain than PTGBD. This finding could be explained by the following two aspects. First, the PTGBD puncture point is located in the right subcostal region, where people are very sensitive to pain and stimulation. In addition, PTGBD forcibly punctures along the skin-liver-gallbladder path, while ENGBD follows the natural path of the digestive tract, causing little damage to tissues and organs and relatively mild abdominal pain [27]. Notably, compared with PTGBD, which requires local anesthesia only, ENGBD, which requires moderate to deep anesthesia, may burden or even threaten patients with high-risk AC.

We included patients with Grade III AC who were combined with coagulopathies, impaired liver or kidney functions. In patients with oliguria or elevated serum creatinine levels, aggressive preoperative fluid therapy was applied to correct their kidney function status. Patients with coagulopathies and low platelet counts within the range of 50–100 $\times$ $10^9$/L were included, while the patients who had platelet counts less than 50 $\times$ $10^9$/L were excluded [28]. The unique advantage of ENGBD is to remove cystic duct obstruction and the same goal cannot be achieved by LC and PTGBD. Besides, ENGBD is a subtype of natural orifice transluminal endoscopic surgery (NOTES) and presents lower risk of bleeding when compared with LC and PTGBD, especially in patients with severe coagulopathies [27].

A mature clinical technique needs to strike a balance in three aspects: high technical success rate, high clinical remission rate and low adverse event rate [29]. The technical success rate, clinical remission rate, and drainage-related adverse events rate of ENGBD and PTGBD were comparable. One patient in the ENGBD group experienced technical failure because the guidewire could not enter the opening of the cystic duct after repeated attempts. Then, ENBD was performed, and the terminal end of the nose-biliary duct was located at the lower position of the common bile duct (below the opening of the cystic duct). The patient achieved clinical remission after conservative supportive treatment; this outcome made sense because the side hole of the nose-biliary duct partially drains the inflammatory bile into the gallbladder, which may make the "gallbladder-common bile duct-nose-biliary duct" smooth to a certain extent. No serious adverse events occurred in 22 participants. A female patient in the ENGBD group developed mild pancreatitis, but she recovered after 3 days of treatment with conventional drugs. One patient in the PTGBD group had a small amount of bloody bile in the drainage tube, which was relieved after hemostasis medication was given, and another patient had drainage tube blockage and fever symptoms, which were relieved after adjusting the drainage tube again under the guidance of ultrasound. In another patient, the drainage tube fell off one month after drainage, causing only slight abdominal pain. Pancreatitis is an important complication of ERCP, [30] and the guidewire to the cystic duct and drainage tube to the gallbladder may cause mechanical damage to the opening of the pancreatic duct; therefore, it is necessary to master these skills and operate gently to reduce and alleviate pancreatitis. For patients in high post-ERCP pancreatitis (PEP) [30] group, rectal indomethacin is routinely administered 30 min before ERCP. Compared with the PTGBD group, the ENGBD group had a longer drainage operation time and X-ray exposure time, and the hospitalization costs [31] related to drainage were higher, which may also be prominent reasons restricting the popularity of endoscopic drainage.

A systematic review [32] showed that the technical success rate of ENGBD was 80.9%, while that of this study was 90.9%. We considered that the following four points could contribute to the success of

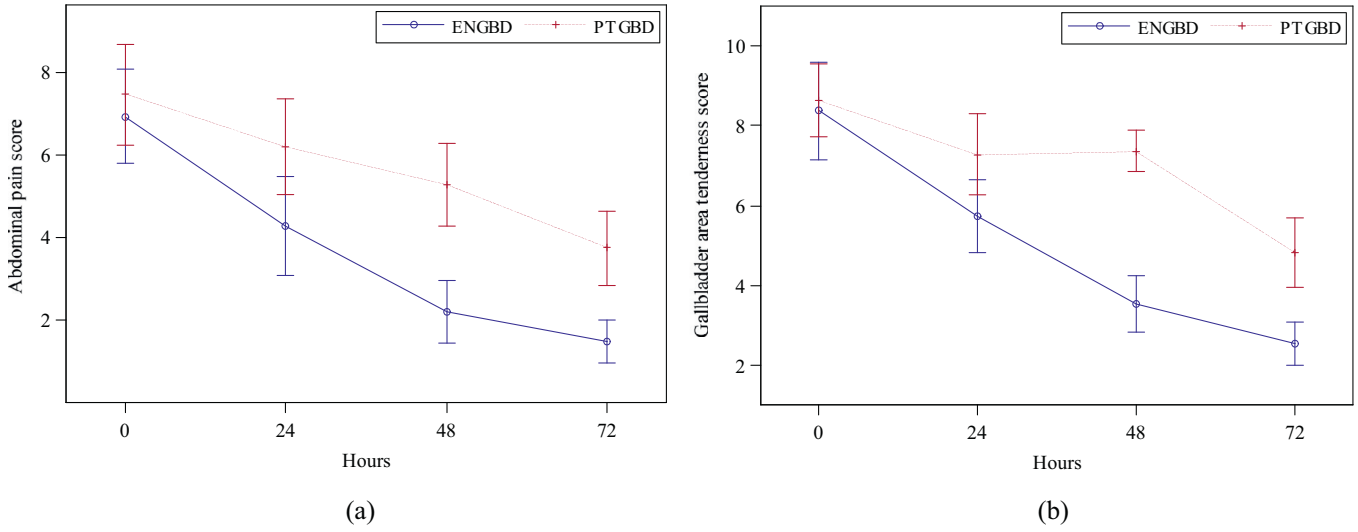


**Fig. 3.** Participants' abdominal pain score (a) and gallbladder area tenderness score (b); Y-axes: Data are expressed as the mean ± standard deviation.

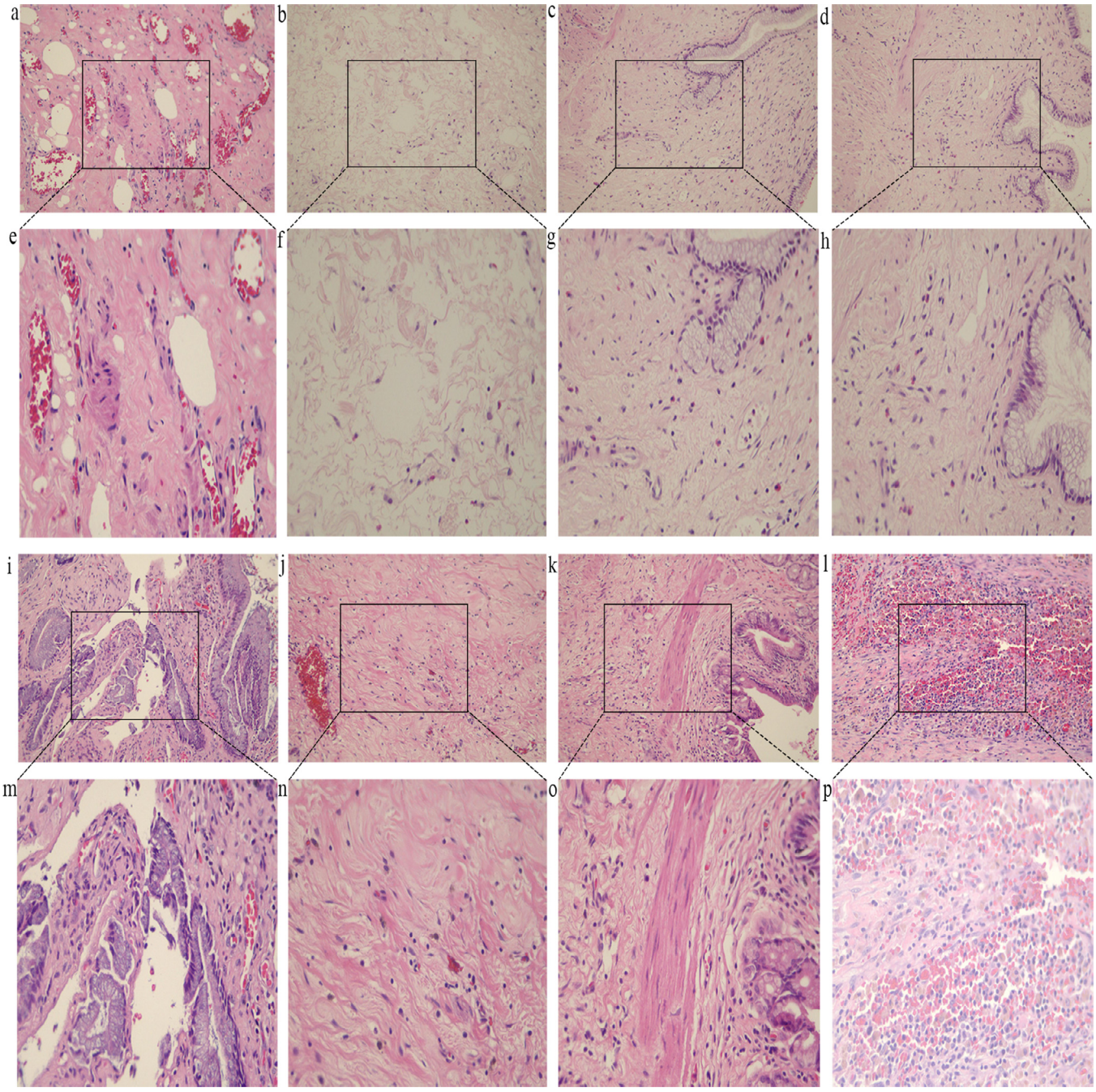


**Fig. 4.** Lymphocyte count. a–d, pathological results of four patients who received ENGBD (200* field of view); e–h, pathological results of four patients who received ENGBD (400* field of view); i–l, pathological results of four patients who received PTGBD (200* field of view); m–p, pathological results of four patients who received PTGBD (400* field of view).

drainage: first, if the stones are tightly stuck to the cystic duct and neck of the gallbladder, ENGBD should be avoided; second, endoscopic sphincterotomy should not be selected before the wire is inserted into the cystic duct; otherwise, the bile in the common bile duct will be emptied, the common bile duct will no longer be filled, and the opening of the cystic duct in the common bile duct will be occluded, making it difficult to enter the cystic duct; in addition, the low confluence of the cystic duct and common bile duct, which is equivalent to shortening the distance of the guidewire bending in the "tunnel" of the common bile duct, is conducive to the technical success rate; finally, it is very important to identify the direction in which the cystic duct flows into the common bile duct. A previous study [33] of 226 patients who received ENGBD noted that if the cystic duct was located on the left side of or below the common bile duct, the operation would become more difficult. A Japanese study on a small sample [34] also reported that if the cystic duct was located on the upper right side of the bile duct, the technique was relatively easy.

We creatively discovered that the ENGBD group had significant advantages in the abdominal drainage tube placement rate, gallbladder pathology and hemorrhage compared with the PTGBD group during the peri-cholecystectomy period. We hypothesized that since ENGBD operated along the natural cavity without damaging the gallbladder serosa and mucosa, the destruction of inflammatory factors would be limited to the mucosa as much as possible. On the one hand, the pathological performance of ENGBD was significantly superior to that of PTGBD, as confirmed by the pathological grade and lymphocyte count. On the other hand, the difficulty of

cholecystectomy may also be reduced, which was manifested by a significantly lower hemorrhage volume and abdominal drainage tube placement rate. In contrast, PTGBD damages the serosal and mucosal tissues to a certain extent, and inflammatory cells are likely to infiltrate and destroy the gallbladder wall tissue; therefore, cholecystectomy, which is mainly serous membrane separation, may become difficult.

There was no difference between the ENGBD and PTGBD groups in other indicators during the peri-cholecystectomy period, such as the duration of cholecystectomy, tight adhesion, LC-related adverse events, gallbladder integrity, length of hospitalization, and open conversion rate. One patient in each group experienced open conversion and neither had superficial or deep intra-abdominal infections. The patient in the PTGBD group formed a dense fiber bundle between the gallbladder and surrounding tissues, which was difficult to forcefully separate and caused more bleeding in the surgical field. The patients who experienced open conversion in the ENGBD group had common bile duct stones, and the possibility of a cholecystoduodenal fistula was considered under laparoscopic vision, which was confirmed after open conversion. The team performed cholecystectomy, duodenal serosal repair, and exploration of the common bile duct to retrieve the stones. The other patient with choledocholithiasis underwent ENBD, and AC recurred during the waiting period of the bridge stage. Both patients with common bile duct stones received ENGBD. To determine whether the drainage route would make gallstones easily fall into the common bile duct and increase the recurrence rate of cholecystitis in the bridge stage, high-level research is still needed.

This study had two limitations. First, it was conducted by only one endoscopic surgical team in a single center. Although it was a well-designed, prospective randomized controlled study, it may not be appropriate to extrapolate our results to other centers because endoscopists have variable levels of clinical experience and understanding of ENGBD and PTGBD, and some endoscopic teams need assistance from surgeons to complete LC successfully. Second, the sample size of the prospective study was small. Thus, future multicenter randomized clinical trials with large sample sizes are needed to validate our results. Comparison of ENGBD and PTGBD drainage methods, ENGBD is an effective drainage modality for patients with acute cholecystitis requiring gallbladder drainage and is an important addition to existing drainage modalities.

In conclusion, ENGBD and PTGBD were not significantly different in terms of technical success, clinical effectiveness, and safety in the peri-drainage period. However, patients in the ENGBD group had less pain, greater compliance and certain advantages in gallbladder pathology grade and difficulties from cholecystectomy. ENGBD could be a safe and effective alternative treatment to PTGBD for patients with AC who are unsuitable for emergency cholecystectomy. However, based on the limits of the current study, large sample, multicenter studies are still needed.

## 5. Contributors

PLM, YYL, XZZ and YWL contributed equally. PLM, YYL, XZZ, YWL, HPW, JWL, PY and WBM: protocol development, drafting of this manuscript, critical revision of the manuscript for significant intellectual content. PLM, YYL, XZZ YWL, MY, ZJD, LG, NNM and TYL: conducted clinical trials, patient enrollment and acquired data. PLM, YYL, XZZ, YWL, PY, WCZ, XL and WBM: providing personnel, environmental support and tools and instruments that are vital for the project. PLM, MY, HPW: taking responsibility in statistical analysis, logical interpretation and presentation of the results. PLM, XZZ, ZJD, LG, NNM and FW: taking responsible for pathology and figures. PLW, YYL, XZZ, YWL, TYL, YL, JWL, PY and WBM: reviewing the article before submission not only for spelling and grammar but also for its intellectual content. PLM, LYY, PY and WBM: taking responsibility in the execution of the trials and patient follow-up. PLM, YYL, PY, WBM, JWL, WCZ and XL: constructing an idea or hypothesis for the manuscript, providing critical revision.

## Declaration of Interests

No conflict of interest was declared by the authors.

## Data sharing statement

Except for the patients' privacy, some fields in data, the study protocol, statistical analysis plan, data dictionary and deidentified results of these analyses are available for scientific researchers upon reasonable request through the first or corresponding author. The data will be kept for three years after the publication of the article.


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## Supplementary materials

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