

Endoscopic ultrasound-guided gallbladder drainage, transpapillary drainage, or percutaneous drainage in high risk acute cholecystitis patients: a systematic review and comparative meta-analysis

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submitted 8.4.2019

accepted after revision 3.9.2019

Bibliography

DOI <https://doi.org/10.1055/a-1020-3932>

Published online: 23.10.2019 | Endoscopy 2020; 52: 96–106

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ISSN 0013-726X

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 Supplementary material

Online content viewable at:

<https://doi.org/10.1055/a-1020-3932>

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ABSTRACT

Background Endoscopic transpapillary gallbladder drainage (ETGBD) and endoscopic ultrasound-guided gallbladder drainage (EUSGBD) are alternatives to percutaneous gallbladder drainage (PCGBD) for patients with acute cholecystitis who are unfit for surgery. Data comparing these modalities are limited and have reported conflicting results.

Methods We searched multiple databases from inception to May 2019 to identify studies that reported on ETGBD, EUSGBD, and PCGBD in the management of acute cholecystitis in patients with a high surgical risk. Aims were to compare the pooled rates of technical success, clinical success, adverse events, and disease recurrence.

Results 1223 patients (22 studies), 557 patients (14 studies), and 13 351 patients (46 studies) were treated by ETGBD, EUSGBD, and PCGBD, respectively. The pooled technical and clinical successes were: ETGBD 83% (95% confidence interval [CI] 80.1–85.5, $I^2=29$) and 88.1% (95%CI 83.6–91.4, $I^2=50$), respectively; EUSGBD 95.3% (95%CI 92.8–96.9, $I^2=0$) and 96.7% (95%CI 94.0–98.2, $I^2=0$), respectively; and PCGBD 98.7% (95%CI 98.0–99.1, $I^2=0$) and 89.3% (95%CI 86.6–91.5, $I^2=84$), respectively. Clinical success with EUSGBD was significantly superior to the other approaches. All complications were comparable between the groups. Pancreatitis occurred with ETGBD in 5.1% (95%CI 3.5–7.3), whereas bleeding and perforation occurred with EUSGBD in 4.3% (95%CI 2.7–6.8) and 3.7% (95%CI 2.3–6.0), respectively. Stent migration occurred with PCGBD in 7.4% (95%CI 5.5–10.0).

Conclusion EUSGBD demonstrated better clinical success than ETGBD and PCGBD in the management of acute cholecystitis patients at high surgical risk.

Introduction

Acute cholecystitis is usually treated by laparoscopic cholecystectomy as the standard of care [1]. In situations where patients are not fit for surgery, percutaneous or endoscopic routes can be used to decompress the gallbladder. Percutaneous options for gallbladder drainage (GBD) include simple needle aspiration or percutaneous gallbladder drainage (PCGBD) that is traditionally done via interventional radiology with the placement of a double-pigtail plastic catheter as the drainage tool. Technical success rates with PCGBD range from 97% to 100%, with clinical success in the range of 56% to 100% [2].

PCGBD has its limitations, however. Adverse events in the range of 10%–12% have been reported, and worsening of cholecystitis is in the range of 25%–50% [3]. Endoscopic options to drain the gallbladder have evolved rapidly in recent years. Options include endoscopic transpapillary gallbladder drainage (ETGBD) and endoscopic ultrasound (EUS)-guided gallbladder drainage (EUSGBD). ETGBD and EUSGBD have the advantage of offering the patient internal drainage without the need for percutaneous tubes, with all of their attendant downsides.

Several studies have compared the performance of EUSGBD and/or ETGBD with that of PCGBD, with conflicting results [4–8]. As a result, the role of endoscopy in the management algorithm of acute cholecystitis has not been confirmed. Furthermore, data comparing ETGBD and EUSGBD are limited. We conducted this meta-analysis to better understand and compare the clinical outcomes of ETGBD, EUSGBD, and PCGBD in high-risk acute cholecystitis patients.

Methods

Search strategy

We conducted a comprehensive search of several databases and conference proceedings including EBM reviews, Embase, Medline, Scopus, Web of Science, and ClinicalTrials.gov (earliest inception to May 2019). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklists [9, 10] by using a predefined protocol to identify studies reporting on GBD in high risk patients diagnosed with acute cholecystitis. An experienced medical librarian using inputs from the study authors helped with the literature search. The PRISMA and MOOSE checklists are provided in the supplementary appendix (see the online-only supplementary material).

Details of the search strategy including the key words used are detailed in the supplementary appendix. The search was restricted to studies in human subjects and published in the English language in peer-reviewed journals. Two authors (B.P.M. and S.T.) independently reviewed the title and abstract of studies identified in primary search and excluded studies that did not address the research question, based on prespecified exclusion and inclusion criteria. The full text of remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus, and in discussion with a co-author.

The bibliographic sections of the selected articles, as well as the systematic and narrative articles on the topic, were manually searched for additional relevant articles.

Study selection

We included studies that evaluated the performance of ETGBD, EUSGBD, and PCGBD in patients with acute cholecystitis who were considered high risk for immediate cholecystectomy owing to age and/or underlying chronic disease processes such as malignancy. Studies were included irrespective of the presence or absence of gallstones, underlying liver cirrhosis, inpatient/outpatient setting, geography, or abstract/manuscript status, as long as they provided data needed for the analysis.

Exclusion criteria were: 1) studies on GBD for malignant stricture of the bile ducts, 2) studies with a sample size of fewer than 10 patients, 3) studies conducted in a pediatric population (age < 18 years), and 4) studies not published in the English language.

In cases of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included. Primary authors were contacted via email for further clarification if needed.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least three authors (B.P.M., S.R.K. and S.T.), and two authors (S.R.K. and B.P.M.) completed the quality scoring independently.

For randomized trials and case–control studies, data collection was performed as number of reported events (n) out of total number of patients (N) from each study. The collected data were treated akin to single group cohort studies and therefore we used the Newcastle–Ottawa scale for cohort studies to assess the quality of data for bias [11]. This quality score consisted of eight questions, the details of which are provided in **Table 1** s in the online-only supplementary material.

Outcomes assessed

The following outcomes were assessed for ETGBD vs. EUSGBD vs. PCGBD: pooled rate of technical success, pooled rate of clinical success, pooled rate of adverse events, pooled rate of disease recurrence, pooled rate of all-cause mortality.

Assessment methodology and definitions

The collected data were matched between the groups (ETGBD, EUSGBD, and PCGBD) before statistical analysis. Although, this model of comparison is indirect and should be considered weak when compared with a randomized controlled trial, the approach is comparable to a retrospective case–control study with matched groups [12].

Acute cholecystitis diagnosis

Patients were diagnosed as having acute cholecystitis based on the following criteria derived from the Tokyo guidelines: clinical symptoms of right upper quadrant and/or epigastric pain or tenderness; signs of systemic inflammation including fever

and high white blood cell count or high levels of C-reactive protein; and positive findings associated with distended gallbladder, thickening of the wall of the gallbladder or, fluid around the gallbladder, as confirmed on abdominal ultrasonography or computed tomography and/or positive Murphy's sign [13].

Definition of outcomes

Technical success was defined as successful placement of the catheter into the gallbladder with confirmed drainage. Clinical efficacy was evaluated based on the improvement in white blood cell count, serum bilirubin levels, C-reactive protein levels, and improvement in patient symptoms. The clinical success rate was calculated for patients in whom technical success was achieved, and not for all patients in whom drainage was attempted.

Recurrence of acute cholecystitis was defined as the new onset of typical symptoms of acute cholecystitis and/or cholangitis with imaging findings after a documented clinical success.

Adverse events were defined as any procedure-, drain- or stent-related event. When reported, the American Society of Gastrointestinal Endoscopy (ASGE) lexicon definitions were used to classify the data [14].

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random effects model [15]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [16]. Statistical significance to the difference between the cohorts assessed was set a priori at a *P* value of ≤ 0.05 as determined by the statistical software based on the analyzed outcomes between the cohorts. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity, 95% prediction interval (PI), which deals with the dispersion of the effects [17–19], and the *I*² statistics [20, 21]. For this, values of <30%, 30%–60%, 61%–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [22]. Publication bias was ascertained, qualitatively, by visual inspection of a funnel plot and quantitatively by the Egger test [23]. When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's "Trim and Fill" test was used to ascertain the impact of the bias [24]. Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there was no bias. The impact was reported as minimal if both versions were estimated to be the same, modest if effect size changed substantially but the final finding would still remain the same, and severe if the basic final conclusion of the analysis is threatened by the bias [25].

All analyses were performed using Comprehensive Meta-Analysis software, version 3 (BioStat, Englewood, New Jersey, USA).

Results

Search results and population characteristics

From an initial total of 2591 studies, 129 records were screened and 101 full-text articles were assessed. A total of 72 studies were included in the final analysis [3–8, 26–91]. The flow diagram of study selection is shown in **Fig. 1 s**.

In our search process, we encountered at least seven studies that had overlapping cohorts [8, 28, 33, 60, 92–94]. The most comprehensive study was included in this analysis. The studies by Irani et al. [5], and Dollhopf et al. [28], had potential overlap of patients managed with EUSGBD at the Prince of Wales Hospital, Hong Kong. Both studies were included in the analysis and any potential statistical bias was evaluated by sensitivity analysis. In the study by Kedia et al. [34], endoscopic GBD (combination of ETGBD and EUSGBD) was compared with PCGBD, and the data on PCGBD were extracted.

Overall, 22 studies provided data on ETGBD [3, 4, 29, 30, 32, 35–41, 43, 59, 63, 74, 76, 80, 82, 85–87], 14 studies provided data on EUSGBD [5–8, 26–28, 31, 33, 41, 42, 44, 59, 85], and 46 studies provided information on PCGBD for the analysis [3–8, 30, 34, 45–58, 60–62, 64–73, 75, 77–79, 81, 83, 84, 88–91].

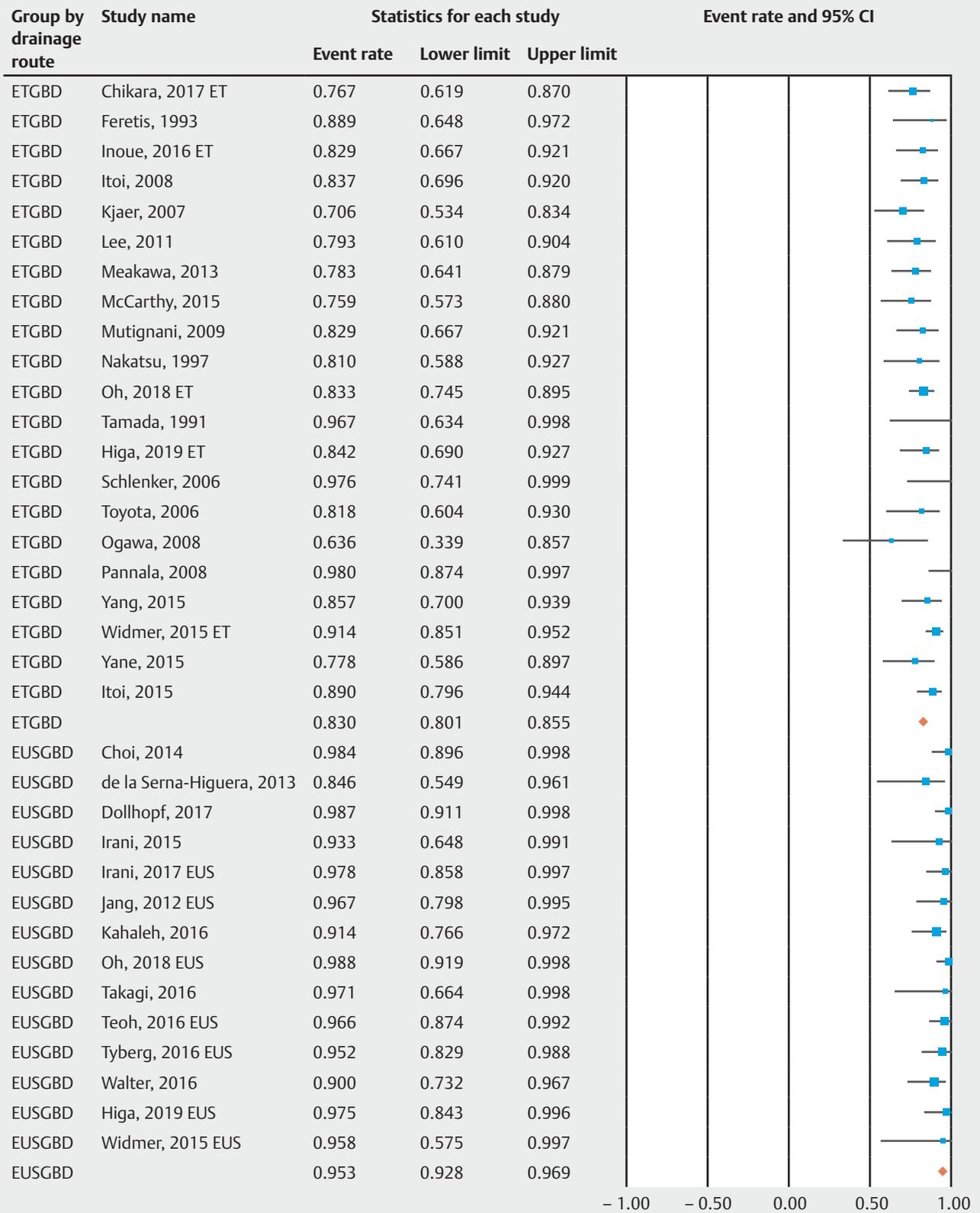
Baseline population characteristics were comparable between the three groups. The mean and/or median age ranged from 65 years to 85 years, with a predominantly male population (61%). Basic population characteristics are described in **Table 2 s**.

Characteristics and quality of included studies

Seven of the 72 studies were prospective [6, 8, 29, 36, 44, 63, 86], including one randomized study [63], and the rest were retrospective in nature. A total of 14 studies [3, 5, 7, 8, 28, 31, 33, 36, 44, 53, 63, 79, 85, 91] were from multicenter settings and the rest were single-center studies. One study was population based from the National Inpatient Sample (NIS) database [47]. All studies reported adequately on the clinical outcomes, assessment, and the basic patient factors were comparable between the study groups. Based on the risk of bias scoring system, 37 studies were considered of high quality [3, 5–8, 26, 28, 30, 31, 33, 34, 36, 37, 39, 41, 44, 45, 48, 52, 53, 58–61, 63–65, 68, 69, 71, 75–78, 80, 85, 90], 33 studies were of medium quality [4, 27, 29, 32, 35, 38, 40, 42, 43, 46, 49–51, 54–57, 62, 66, 67, 70, 72, 74, 79, 81–84, 86–89, 91], and two studies were considered to be of low quality [47, 73]. The detailed assessment of study quality is given in **Table 1 s**.

Meta-analysis outcomes

A total of 15 131 patients were included in the analysis from 72 studies [3–8, 26–91], 1223 patients from 22 studies were treated with ETGBD [3, 4, 29, 30, 32, 35–41, 43, 59, 63, 74, 76, 80, 82, 85–87], 557 patients from 14 studies were treated by EUSGBD [5–8, 26–28, 31, 33, 41, 42, 44, 59, 85], and 13 351 patients from 46 studies were treated by PCGBD [3–8, 30, 34, 45–58, 60–62, 64–73, 75, 77–79, 81, 83, 84, 88–91].



► Fig. 1 Technical success rates of gallbladder drainage methods.

► **Table 1** Meta-analysis results.

	Technical success	Clinical success	Adverse events	Recurrence
Pooled rates, % (95%CI, I^2)				
▪ ETGBD	83% (80.1–85.5, 29) (21 studies, 851 patients)	88.1% (83.6–91.4, 50) (22 studies, 1223 patients)	9.6% (5.9–15.3, 27) (21 studies, 1209 patients)	4.6% (2.8–7.4, 53) (22 studies, 1223 patients)
▪ EUSGBD	95.3% (92.8–96.9, 0) (14 studies, 557 patients)	96.7% (94.0–98.2, 0) (14 studies, 557 patients)	12.4% (6.9–21.1, 6) (13 studies, 546 patients)	4.2% (2.4–7.4, 0) (14 studies, 557 patients)
▪ PCGBD	98.7% (98.0–99.1, 0) (33 studies, 2203 patients)	89.3% (86.6–91.5, 84) (38 studies, 11800 patients)	15.1% (11.1–20.3, 95) (39 studies, 11997 patients)	10.8% (8.3–13.9, 76) (37 studies, 3677 patients)
P value of statistical significance				
▪ ETGBD vs. EUSGBD	0.001	0.001	0.32	0.99
▪ ETGBD vs. PCGBD	0.001	0.59	0.12	0.001
▪ EUSGBD vs. PCGBD	0.001	0.001	0.56	0.001
CI, confidence interval; ETGBD, endoscopic transpapillary gallbladder drainage; EUSGBD, endoscopic ultrasound-guided gallbladder drainage; PCGBD, percutaneous gallbladder drainage.				

► **Table 2** Pooled rate of adverse events subtypes.

	ETGBD	EUSGBD	PCGBD
Pooled rates, 95%CI, I^2 %			
Bleeding	1.9% (1.1–3.1, 0) (21 studies, 1209 patients)	4.3% (2.7–6.8, 0) $P = 0.02$ (13 studies, 546 patients)	2% (1.5–2.7, 0) (37 studies, 3597 patients)
Perforation	2% (1.2–3.2, 0) (21 studies, 1209 patients)	3.7% (2.3–6.0, 0) $P = 0.04$ (13 studies, 546 patients)	2% (1.4–2.9, 0) (36 studies, 3524 patients)
Bile leak/bile peritonitis	1.4% (0.8–2.5, 0) (21 studies, 1209 patients)	2.9% (1.6–5.1, 0) (13 studies, 546 patients)	2.7% (2.1–3.5, 0) (37 studies, 3597 patients)
Pancreatitis	5.1% (3.5–7.3, 17) $P = 0.003$ (21 studies, 1209 patients)	1.4% (0.7–3.1, 0) (13 studies, 546 patients)	1.1% (0.7–1.7, 0) (36 studies, 3524 patients)
Stent occlusion	1.8% (0.9–3.6, 0) (20 studies, 1171 patients)	2.6% (1.2–5.6, 0) (12 studies, 506 patients)	1.8% (1.1–2.8, 56) (36 studies, 3524 patients)
Stent migration	2.2% (1.2–3.9, 0) (20 studies, 1171 patients)	2.7% (1.3–5.4, 0) (13 studies, 546 patients)	7.4% (5.5–10.7, 79) $P = 0.01$ (38 studies, 3977 patients)
Mortality	16.6% (10.5–25.2, 77) (13 studies, 884 patients)	26% (16.7–38.1, 86) $P = 0.001$ (9 studies, 398 patients)	11.2% (8.7–14.1, 83) (37 studies, 3597 patients)
CI, confidence interval; ETGBD, endoscopic transpapillary gallbladder drainage; EUSGBD, endoscopic ultrasound-guided gallbladder drainage; PCGBD, percutaneous gallbladder drainage; P values shown for statistically significant differences only.			

Technical success

The calculated pooled rate of technical success was 83% (95%CI 80.1–85.5, 95%PI 72.3–90.2, $I^2 = 29$) with ETGBD, 95.3% (95%CI 92.8–96.9, 95%PI 92.6–97, $I^2 = 0$) with EUSGBD, and 98.7% (95%CI 98.0–99.1, 95%PI 98.1–99.1, $I^2 = 0$) with PCGBD. The technical success with EUSGBD was superior to that with ETGBD ($P = 0.001$), whereas the PCGBD technical success was superior to both ETGBD and EUSGBD ($P = 0.001$) (► **Fig. 1**, ► **Table 1**).

Clinical success

The calculated pooled rate of clinical success was 88.1% (95%CI 83.6–91.4, 95%PI 70.3–95.9, $I^2 = 50$) with ETGBD, 96.7% (95%CI 94.0–98.2, 95%PI 93.6–98.3, $I^2 = 0$) with EUSGBD, and 89.3% (95%CI 86.6–91.5, 95%PI 68.8–96.9, $I^2 = 84$) with PCGBD. The clinical success with EUSGBD was superior to both ETGBD and PCGBD ($P = 0.001$), whereas the clinical success with ETGBD and PCGBD were comparable ($P = 0.59$) (► **Fig. 2**, ► **Table 1**).



► Fig. 2 Clinical success rates of gallbladder drainage methods.

► **Table 3** Pooled results from the analysis of prospective studies (total 7 studies, 331 patients).

	Technical success	Clinical success	Adverse events	Recurrence
Pooled rates, 95%CI, I^2 %				
▪ ETGBD (4 studies, 87 patients)	84.3% (77.3–89.5, 0)	81.7% (74.1–87.5, 12)	12.6% (54.9–28.6, 78)	2.6% (0.8–7.8, 0)
▪ EUSGBD (3 studies, 102 patients)	93.5% (86.3–97.1, 0)	97.7% (91.3–99.4, 0)	12.2% (4.4–29.7, 0)	6.1% (2.7–13.3, 0)
▪ PCGBD (2 studies, 142 patients)	98.3% (93.3–99.6, 0)	87.7% (80.9–92.3, 45)	9.1% (2.4–28.8, 45)	7.3% (3.9–13.3, 15)
P value of statistical significance				
▪ ETGBD vs. EUSGBD	0.001	0.003	0.97	0.23
▪ ETGBD vs. PCGBD	0.001	0.28	0.73	0.11
▪ EUSGBD vs. PCGBD	0.001	0.02	0.86	0.72
CI, confidence interval; ETGBD, endoscopic transpapillary gallbladder drainage; EUSGBD, endoscopic ultrasound-guided gallbladder drainage; PCGBD, percutaneous gallbladder drainage.				

Adverse events, disease recurrence, and mortality

Data on adverse events were extracted and classified according to the ASGE lexicon definitions when possible. The majority of the studies, however, did not follow the ASGE lexicon definitions. Data were extracted as reported in the original studies. Details of the adverse event data extracted are provided in **Table 3s**.

The calculated pooled rates of all adverse events between ETGBD, EUSGBD, and PCGBD were comparable (► **Table 1, Fig. 2s**). In the analysis of the adverse events subtypes, the P value was statistically significant in the pooled rates of pancreatitis with ETGBD (5.1%, 95%CI 3.5–7.3, $I^2=17$, $P=0.003$), bleeding with EUSGBD (4.3%, 95%CI 2.7–6.8, $I^2=0$, $P=0.02$), perforation with EUSGBD (3.7%, 95%CI 2.3–6.0, $I^2=0$, $P=0.04$), and stent migration with PCGBD (7.4%, 95%CI 5.5–10.0, $I^2=79$, $P=0.01$). The results for the pooled rates of adverse event subtypes with ETGBD, EUSGBD, and PCGBD are summarized in ► **Table 2** (see also **Fig. 3s, Fig. 4s, Fig. 5s, Fig. 6s, Fig. 7s, Fig. 8s**).

The calculated pooled rate of disease recurrence was 4.6% (95%CI 2.8–7.4, $I^2=53$) with ETGBD and 4.2% (95%CI 2.4–7.4, $I^2=0$) with EUSGBD. The rates were comparable between ETGBD and EUSGBD ($P=0.99$), whereas the calculated pooled rate of disease recurrence with PCGBD was 10.8% (95%CI 8.3–13.9, $I^2=76$), which was significantly more ($P=0.001$) than with ETGBD or EUSGBD (► **Table 1, Fig. 9s**).

The pooled all-cause mortality rate was 16.6% (95%CI 10.5–25.2, $I^2=77$) with ETGBD, 26% (95%CI 16.7–38.1, $I^2=86$) with EUSGBD, and 11.2% (95%CI 8.7–14.1, $I^2=83$) with PCGBD. The pooled all-cause mortality rate with EUSGBD was significantly greater ($P=0.001$) when compared with ETGBD or PCGBD (► **Table 2, Fig. 10s**).

Analysis of prospective studies

No significant change was noted to the pooled rates except for the observed statistical significance of disease recurrence, which is now comparable between the groups. The observed heterogeneity was noted to decrease in the analysis of clinical success with ETGBD and PCGBD from prospectively designed studies. The results are summarized in ► **Table 3**.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity. Therefore, the inclusion or exclusion of either one of the studies by Irani et al. [5] and/or Dollhopf et al. [28] resulted in essentially the same pooled results.

Heterogeneity

We assessed dispersion of the calculated rates using the prediction interval (PI) and I^2 percentage values. The PI gives an idea of the range of the dispersion and I^2 tell us what proportion of the dispersion is true vs. chance [19]. The pooled rates of technical and/or clinical success with ETGBD, EUSGBD, and PCGBD had narrow PIs with minimal to no heterogeneity. The pooled rates of adverse events and disease recurrence with PCGBD had considerable heterogeneity. The all-cause mortality data with all the modalities were also noted to have considerable heterogeneity.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias (**Fig. 11s**, Egger's 2-tailed $P=$

0.001). Further statistics using the fail-Safe N test and Duval and Tweedie's "Trim and Fill" test revealed that the impact of the possible publication bias appeared to be minimal and would not change the calculated estimate or the conclusion of this meta-analysis.

Discussion

Our study demonstrates that EUSGBD has significantly better clinical success rates than ETGBD and/or PCGBD in the treatment of acute cholecystitis in high risk surgical patients. To the best of our knowledge, this study is the first meta-analysis comparing the outcomes of ETGBD, EUSGBD, and PCGBD.

Based on our analysis, EUSGBD demonstrated significantly superior technical success rate when compared with ETGBD (95.3% vs. 83.0%, $P = 0.001$). There are multiple explanations for this observation. The selective cannulation of the cystic duct can be technically difficult, especially in the presence of impacted stones and/or the tortuous nature of the cystic duct with its spiral valves of Heister. EUSGBD, on the other hand, is not affected by cystic duct anatomy. Nevertheless, EUSGBD has its own technical challenges including the need to identify an ideal site for transmural drainage and the technical demands of transmural stent placement. Accumulating experience with the procedure has shown promising results with regard to technical success [8]. Recent guidelines do recommend EUSGBD as a first-line modality in centers with high experience in the procedure [95].

Our analysis of clinical success revealed that EUSGBD demonstrated a significantly superior pooled rate when compared with ETGBD (96.7% vs. 88.1%, $P = 0.001$). This observation could be related to the recent widespread use of dedicated metal stents with flared ends in EUSGBD. By preventing migration, these stents provide sustained drainage of the gallbladder compared with double-pigtail plastic stents. Lumen-apposing metal stents generally have an overall wider diameter, aiding better drainage of gallbladder contents. The majority of the included studies were retrospective in nature and a selection bias on the use of ETGBD for common bile duct stones was unavoidable.

Our analysis of the adverse event subtypes revealed that EUSGBD had a significantly higher potential to cause bleeding (4.3%, $P = 0.02$) and perforation (3.7%, $P = 0.04$) compared with ETGBD, whereas ETGBD had a significantly higher rate of post-procedure pancreatitis compared with EUSGBD (5.1%, $P = 0.003$). It should be stated that the transmural nature of EUSGBD de facto creates an iatrogenic perforation of the stomach or the duodenum to the gallbladder, but that these perforations need to be made in a very controlled manner. Post-ETGBD pancreatitis is a well-established adverse event related to the fact that the procedure is performed as part of an ERCP. The pooled rates of all adverse events, and disease recurrence were comparable between ETGBD and EUSGBD.

Where does our analysis stand in relation to PCGBD? In this study, we have assessed our calculated outcomes with ETGBD and EUSGBD in relation to PCGBD, thereby contributing to the growing literature comparing endoscopic GBD with PCGBD.

Technical success with PCGBD (98.7%) was significantly better than with ETGBD (83.0%) or EUSGBD (95.3%; $P = 0.001$). Clinical success with PCGBD (89.3%) was comparable to ETGBD (88.1%; $P = 0.59$), but significantly inferior to EUSGBD (96.7%; $P = 0.001$). Stent migration and/or dislodgement was a significantly frequent problem in PCGBD patients (7.4%; $P = 0.01$) and the pooled rate of disease recurrence was significantly greater with PCGBD (10.8%; $P = 0.001$) compared with ETGBD (4.6%) or EUSGBD (4.2%). In summary, although technically sound, PCGBD demonstrated significant stent dislodgement and disease recurrence, in addition to an inferior clinical success rate compared with endoscopic options, especially EUSGBD.

How does our study compare to other published works in literature? The only other published study that compared ETGBD, EUSGBD, and PCGBD is the three-way comparative study by Siddiqui et al. [92], which reported similar results to our study in terms of technical success; however, ETGBD seemed to have significantly lower clinical success compared with PCGBD and EUSGBD. Unlike any other study published to date, we report the pooled all-cause mortality rates. We noted that the all-cause mortality in patients who underwent EUSGBD was 26%, despite the very high clinical success rate (96.7%), and was significantly more than ETGBD (16.6%) or PCGBD (11.2%; $P = 0.001$). This result, however, needs to be interpreted with caution as it is limited by considerable heterogeneity and not all studies reported mortality data. Based on the study's clinical success definition, patients undergoing EUSGBD responded well with minimal disease recurrence. However, the probable explanation for the 26% all-cause mortality is that the majority of EUSGBD studies were conducted in patients in whom the overall survival was low to begin with and the studies adequately followed up their patients to report a mortality event, unlike the ETGBD and/or PCGBD studies.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data, rigorous evaluation of study quality, and statistics to establish and/or refute the validity of the results of our meta-analysis. Heterogeneity was minimal to zero in the overall primary outcome analysis and we were able to demonstrate the study design (prospective and retrospective) as the main reason behind the observed heterogeneity. There were limitations to this study, most of which are inherent to any meta-analysis. The included studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. Our analysis included studies that were retrospective in nature, which contributed to selection bias.

In conclusion, based on our meta-analysis of the various GBD modalities in the management of acute cholecystitis patients with high risk for surgery, EUSGBD demonstrated superior clinical success compared with ETGBD and/or PCGBD. Significant risk of perforation and bleeding can be expected with EUSGBD, whereas acute pancreatitis risk is significantly higher with ETGBD. PCGBD in this patient population was associated with a significantly higher chances of disease recurrence and stent dis-

lodgement. The all-cause mortality seemed to be significantly more in the EUSGBD cohort; however, this was limited by considerable heterogeneity. We, therefore, recommend that EUSGBD be used as one of the first-line approaches when treating this patient population and is preferably performed in centers with high expertise owing to the chances of rare but serious adverse events.

Competing interests

Dr. Adler is a consultant for Boston Scientific.

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