SYSTEMATIC REVIEW AND META-ANALYSIS

Trial sequential analysis of EUS-guided gallbladder drainage versus percutaneous cholecystostomy in patients with acute cholecystitis

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Background and Aims: Meta-analytic comparison of EUS-guided gallbladder drainage (EUS-GBD) versus percutaneous gallbladder drainage (PT-GBD) for acute cholecystitis (AC) brings the risk of spurious results if too few studies are included. Trial sequential analysis (TSA) can overcome this, providing information about its credibility.

Methods: Comparative studies between EUS-GBD, using lumen-apposing metal stents, and PT-GBD for AC until July 2021 were used for conventional meta-analysis and TSA, which allowed the use of monitoring boundaries and the estimation of the required information size (RIS) needed to prove credibility.

Results: Four studies accrued 535 patients. Technical success was in favor of PT-GBD (relative risk [RR], .967; $P = .036$), but TSA estimated that 1663 participants would be needed to avoid a Type I error (false positive). Clinical success was similar (RR, .965; $P = .146$), and TSA supported the absence of any demonstrable superiority of one therapy rather than a Type II error (false negative). EUS-GBD reduced overall adverse events (RR, .424; $P < .001$) and unplanned readmissions (RR, .215; $P < .001$), and TSA confirmed the avoidance of a Type I error, with early RIS achievement, providing necessary credibility. EUS-GBD had fewer reinterventions (RR, .244; $P < .001$), but a Type I error was not avoided, needing additional 97 patients to the accrued 535 to prove credibility.

Conclusions: PT-GBD can provide superior technical success than EUS-GBD if a very large sample size is accrued, thus limiting the single-patient benefit. Clinical success is probably equivalent. EUS-GBD convincingly decreased overall adverse events and unplanned readmissions, whereas the need for reinterventions requires additional studies. (Gastrointest Endosc 2021;■:1-8.)

The criterion standard in the treatment of acute cholecystitis (AC) is laparoscopic cholecystectomy. However, not all patients are suitable for surgery because they are often elderly, with comorbidities, and/or with overall clinical conditions that suggest delaying or even avoiding cholecystectomy. In such cases, gallbladder drainage may be a therapeutic option, possibly followed by delayed laparoscopic cholecystectomy once the patient's general condition has improved. Alternatively, it may represent the only therapy for high-risk patients who will never be considered for surgery. Approaches applied to drain the gallbladder are percutaneous cholecystostomy

Abbreviations: AC, acute cholecystitis; AE, adverse events; EUS-GBD, EUS-guided gallbladder drainage; LAMS, lumen-apposing metal stent; PT-GBD, percutaneous gallbladder drainage; RCT, randomized controlled trial; RIS, required information size; RRR, relative risk reduction; TSA, trial sequential analysis.

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(percutaneous gallbladder drainage [PT-GBD]), EUS-guided endoscopic drainage (EUS-guided gallbladder drainage [EUS-GBD]), and ERCP transpapillary gallbladder drainage. To date, several comparative studies have suggested that EUS-GBD may provide better results than PT-GBD[1] and that both had a proven highest likelihood of technical and clinical success in respect to ERCP transpapillary gallbladder drainage.[2] However, such comparisons are still in their exploratory phase, so it is not yet possible to draw firm and solid conclusions.

The possibility of pooling data from different studies, through meta-analysis, may be a useful effort for a more complete understanding of the results after EUS-GBD and PT-GBD in the treatment of AC. Unfortunately, the credibility of meta-analyses is low when few comparative studies are available, so that the effects of an intervention can often be falsely overestimated (Type I error) or falsely underestimated (Type II error), because of low statistical power as a consequence of failure to reach the required number of participants.[3,4] The trial sequential analysis (TSA) of a meta-analysis can correct these problems.[3-6] A simple way to think about TSA in meta-analyses is in the methods and conduction of a randomized controlled trial (RCT). For such a clinical study, investigators derive a sample size calculation based on event rate, predicted effect size, Type I error, and the desired statistical power. TSA requires these same assumptions to derive a power calculation for a meta-analysis. In TSA, studies, rather than patients, are included in chronologic order and managed as subsequent interim analyses relative to the required number of participants. This methodology allows the application of monitoring (benefit, harm, and futility) and conventional boundaries and finally allows the calculation of the required number of participants based on the predefined intervention effect, adjusting it for the heterogeneity observed in the included studies.

In the present study, the available literature comparing EUS-GBD through lumen-apposing metal stents (LAMSs) versus PT-GBD for AC was used to initially estimate the pooled results through conventional meta-analysis and then, more importantly, to assess the credibility of these results through the TSA. This approach defines the level of confidence with which to interpret the results published to date.

METHODS

Search strategy

The study was conducted and reported according to the Cochrane Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Meta-analysis of Observational Studies in Epidemiology guidelines. A comprehensive e-literature search, limited to the English language, was conducted by 1 investigator (E.D.) for articles published through July 2021 using PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. The details of the search are provided in Appendix 1 and Supplementary Figure 1 (available online at www.giejournal.org). Further research was conducted through a manual check of references. A gray literature search was not attempted. Articles were selected for full text review based on title and abstract.

Inclusion and exclusion criteria

Comparative cohorts, RCTs, or observational cohort studies that compared the efficacy and safety between EUS-GBD and PT-GBD in nonsurgical patients with AC were considered because these procedures are proven to have the highest likelihood of technical and clinical success.[2] Only US-guided endoscopic transmural drainage of the gallbladder using metal stents was included, excluding studies reporting transpapillary drainage. Studies were included if they reported the outcome measures of technical success, clinical success, overall adverse events (AEs; defined as any event occurring during or after the procedure), unplanned readmission, and the need for reoperation. Two investigators (E.D. and M.S.) independently identified the original articles for eligibility and validity review. Any disagreements between the reviewers were discussed with a third reviewer (C.B.) for final consent.

Trial sequential meta-analysis

This methodology adopts the sequential analysis method commonly used for interim analyses of RCTs but applying the concept to meta-analyses. TSA differs from RCT sequential analysis in that the enrolled units are not represented by patients but by studies that are included in chronologic order. The analysis is repeated cumulatively after new studies are added. The final number of participants in the meta-analysis constitutes the accrued information size.

Similar to RCTs, the TSA of the meta-analyses is based on an anticipated a priori intervention effect, on the basis of which the sample size is estimated to be subsequently detected with adequate power. This sample size in the TSA is the required information size (RIS), which is the number of events (or patients) from the included studies necessary to accept or reject the a priori statistical hypothesis.[3-6] RIS is calculated through the heterogeneity-adjustment factor to adjust for heterogeneity among the included trials. The heterogeneity-adjustment factor is calculated as the total variance in a random-effects model divided by the total variance in a fixed-effects model. Finally, the RIS adjusted for heterogeneity between trials (random) is calculated by multiplying the nonadjusted RIS (fixed) for the heterogeneity-adjustment factor.[5] When calculating RIS, the Type I error was set at 5% and the power at 80%.

The a priori anticipated intervention effect is crucial. Generally, trials with high-bias risk (ie, inadequate generation of the allocation sequence, inadequate allocation

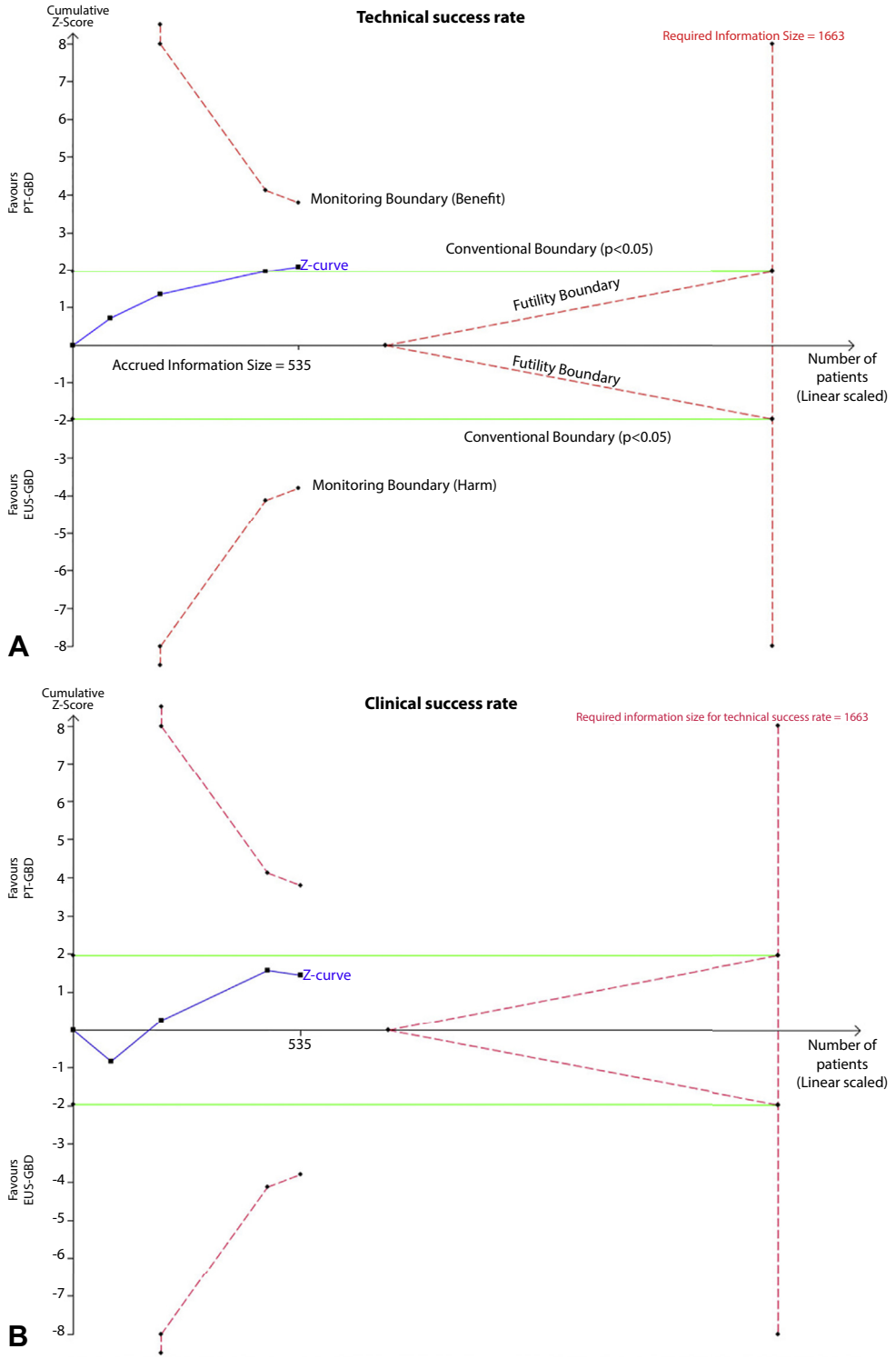

Figure 1. Trial sequential analysis (TSA) of technical and clinical success rates. The accrued information size is the number of patients in the meta-analysis. For technical success, the last point of the cumulative Z-curve (*blue line*) surpassed the conventional boundary (*green line*) returning a $P < .05$; however, this point was within the monitoring boundaries (*dotted red lines*). Therefore, a statistical difference occurred in the conventional meta-analysis that was absent in TSA, thus not avoiding a false-positive result. The required information size (RIS) was estimated as 1663 patients to prove with credibility that technical success is truly in favor of PT-GBD. For clinical success, the RIS was estimated as >10,000 patients and defined here as 1663 for graphic representation. The cumulative Z-curve remained within conventional boundaries ($P > .05$) and far from futility boundaries. Thus, the result from conventional meta-analysis means no effect or lack of power. *EUS-GBD*, EUS-guided gallbladder drainage; *PT-GBD,* percutaneous gallbladder drainage.

concealment, or inadequate double blinding) overestimate intervention effects compared with trials with low-bias risk.[3] To avoid this, a solution is to derive an intervention effect from studies with adequate allocation concealment.[3] In brief, allocation concealment refers to blinding to the randomization sequence so the person randomizing the patient does not know what the next treatment allocation will be.

Once the a priori anticipated intervention effect is established, the Z-value is updated with each additional published study added to the meta-analysis, providing the cumulative Z-curve (Fig. 1). The Z-value is the test statistic where a $|Z| = 1.96$ corresponds to a $P = .05$; the higher the Z-value, the lower the P value. This Z-curve is then checked for crossover in 3 boundaries: the naïve (horizontal) boundaries, which correspond to a nominal $P = .05$; the monitoring boundaries, which are sequential monitoring boundaries calculated on the a priori intervention effect and are distinguished in benefit/harm boundaries; and the futility boundaries, which are the adjusted threshold for nonsuperiority and noninferiority tests.[7,8]

When the Z-curve crosses the naive boundaries, P will be <.05 (Fig. 1A). If the Z-curve lies within futility boundaries and the appropriate RIS is reached, it can be easily concluded that the intervention does not have an effect. However, if the result of the meta-analysis is negative but the appropriate RIS is not reached, then the intervention has no effect or has a lack of power (Fig. 1B). If the Z-curve crosses monitoring boundaries, it means that the treatment has evident benefit (or harm) in respect to the control group (Fig. 2).

A meta-analysis was conducted applying the fixed-effects model because this was considered more appropriate than random effects for meta-analyses with a relatively small number of included studies and because TSA was not aimed at generalization of results. TSA was conducted using the Trial Sequential Analysis software provided by the Copenhagen Trial Unit.[6]

RESULTS

After removal of duplicate records, 596 articles were identified through the research strategy (Appendix 1, available online at www.giejournal.org). After applying the exclusion criteria, 563 articles were rejected, and 33 studies remained for abstract review. After an abstract review, 11 studies remained for full-text eligibility. Finally, 9 studies met the inclusion criteria after assessment of the full articles and were considered for data extraction. Of those 9, 3 studies reporting outcomes after drainage with stents other than LAMSs[9-11] and 1 study that reported mixed results from transpapillary and transmural EUS-GBD[12] were excluded. Additionally, another study from 2016[13] was subsequently updated and enlarged in 2019,[14] and the latter was retained for the analyses. The analysis finally included 3 observational studies[14-16] and 1 RCT,[17] resulting in an accrued information size of 535 participants (245 undergoing EUS-GBD and 290 undergoing PT-GBD). The only RCT was the DRAC-1 trial,[17] and after quality assessment this was deemed as the only study with a low risk of bias for allocation concealment (Table 1). Consequently, effect sizes from this study were used as a priori information for TSA.

Technical success

Conventional meta-analysis resulted in a relative risk (RR) of EUS-GBD over PT-GBD of .967 (95% confidence interval [CI], .937-.998; $P = .036$), thus in favor of PT-GBD. As can be noted from Figure 1A, the RIS calculated by TSA was of 1663 participants, thus above the accrued information size of 535 patients enrolled. The Z-curve crossed the conventional test boundary remaining below the benefit monitoring boundary. Therefore, there was a statistical difference in both conventional meta-analysis and TSA, but further information is required because a Type I error cannot be excluded.

Clinical success

The pooled RR for clinical success was .965 (95% CI, .920-1.012; $P = .146$). TSA reported in Figure 1B shows that at the accrued information size of 535 enrolled participants, the cumulative Z-curve was far from futility boundaries. The RIS was estimated as >10,000 patients, meaning that, to date, the absence of superiority of 1 treatment over the alternative could mean no effect of the intervention or lack of power.

Overall AEs

The pooled RR for overall AEs was .424 (95% CI, .323-.555; $P < .001$), thus evidently in favor of EUS-GBD. The cumulative Z-curve crossed the benefit boundary early (Fig. 2A), confirming the absence of a Type I error. Additionally, after having crossed the benefit boundary, the Z-curve remained above it, confirming that the meta-analytic finding was conclusive. The RIS was of 80 patients. The relative risk reduction (RRR) was 57.6% (Table 2). These figures show that EUS-GBD reduces overall AEs in 1 patient for every 4 treated compared with PT-GBD. Assuming an RRR of 20%, the RIS to establish the superiority of EUS-GBD would be 1031 patients.

Unplanned readmission

EUS-GBD reduced unplanned readmissions with an RR of .215 (95% CI, .137-.337; $P < .001$). TSA showed that the trend of the cumulative Z-curve was very similar to that of AEs (Fig. 2B). An RIS of 89 patients was necessary to claim consistency of this finding, and subsequent studies provided additional confirmation. The final RRR was 78.5% (Table 2). Under these circumstances, EUS-GBD reduces unplanned readmissions in 1 patient for

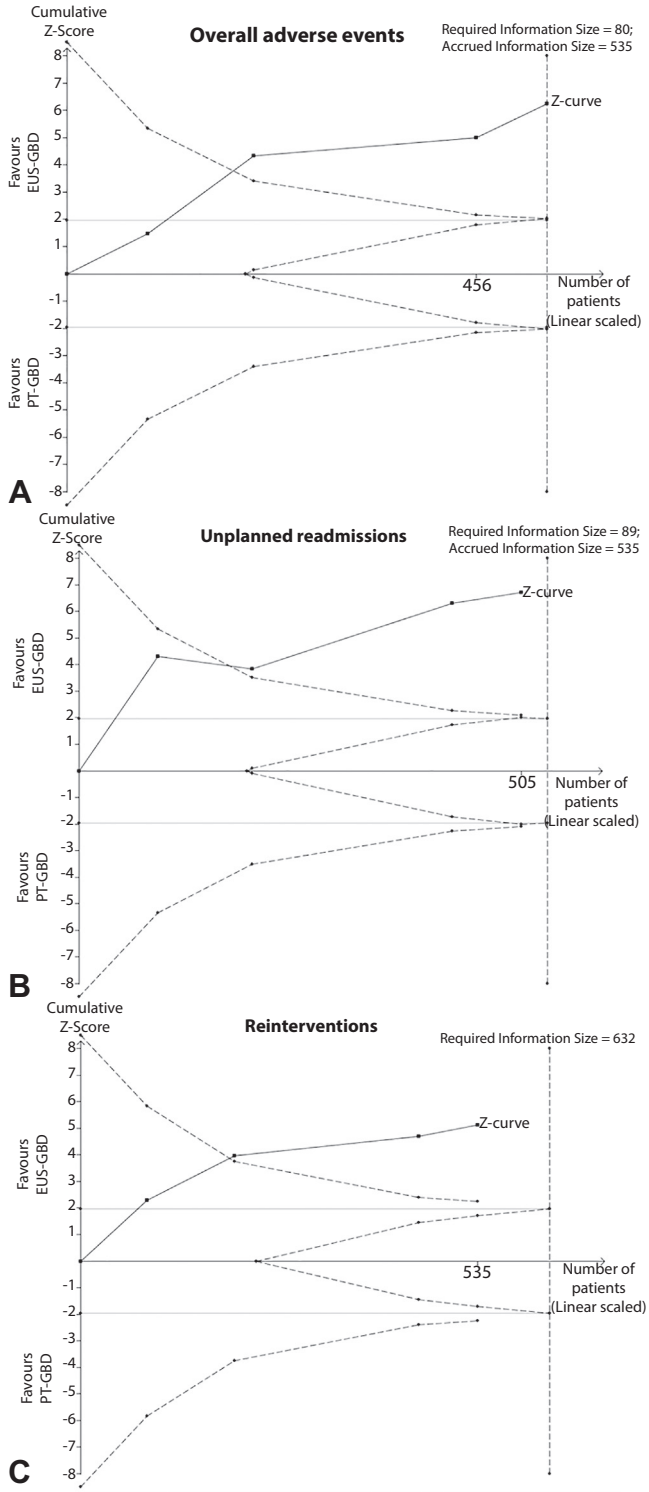

Figure 2. Trial sequential analysis of overall adverse events, unplanned readmissions, and reinterventions. For overall adverse events and unplanned readmission, the Z-curve crossed the benefit boundary early with an estimated required information size of 80 and 89 patients, respectively, largely lower than the accrued sample of 535, providing credibility of meta-analytic results. *EUS-GBD*, EUS-guided gallbladder drainage; *PT-GBD,* percutaneous gallbladder drainage.

every 3 treated with PT-GBD. Assuming an RRR of 20%, the RIS to establish the superiority of EUS-GBD would be 1284 patients.

Reinterventions

EUS-GBD determined a reduction in reinterventions in comparison with PT-GBD, with an RR of .244 (95% CI, .142-.418; $P < .001$). The cumulative Z-curve crossed the benefit boundary early remaining considerably above it (Fig. 2C). The RIS was 632, not so far from the accrued sample of the meta-analysis of 535 patients. The final RRR was 75.6% (Table 2). Type I error was implausible, and EUS-GBD provides a benefit in 1 patient for every 6 in respect to PT-GBD. Assuming an RRR of 20%, the RIS to establish the superiority of EUS-GBD would be >10,000 patients.

DISCUSSION

The management of patients with AC deemed not able to tolerate cholecystectomy because of poor premorbid conditions is currently under investigation. A common strategy is to treat these patients conservatively and eventually perform gallbladder drainage if sepsis cannot be controlled. Over the past decade, PT-GBD was the most common approach adopted, but more recently EUS-GBD emerged as an effective option with potential advantages over PT-GBD. However, the evidence supporting 1 approach over the other is currently poor because only 1 small RCT was provided in literature. The possibility to integrate and summarize results from an individual study can increase the knowledge in this field, but meta-analyses are not free from errors and biases. With this study, we tried to improve the clinical evidence of gallbladder drainage[18] and at the same time to evaluate confidence in the results, giving indications for future clinical studies.

Technical success was found in favor of PT-GBD, but the RIS was 3 times larger than the accrued information size. Does this mean superiority of PT-GBD? A previous meta-analysis, which did not include the DRAC-1 trial, affirmed that EUS-GBD had comparable effectiveness with PT-GBD for high-risk surgical patients with AC in terms of the technical success rate.[1] That meta-analysis included the study from Jang et al,[9] which used nasobiliary drainage or pigtail stents but not metallic stents, and from Kedia et al,[12] in which mixed data of transmural and transpapillary procedures were presented. In the present study, only studies using LAMSs were analyzed. Implanting of LAMSs is a technically challenging procedure, requiring skills in both diagnostic and interventional EUS, with an adequate learning curve to optimize results.[19,20] Consequently, the results of conventional meta-analyses are worth consideration; that

TABLE 1. Summary of studies included in the present conventional meta-analysis and trial sequential analysis

Author (year)	Study	Therapy	No. of cases	Technical success n (%)	Clinical success n (%)	Overall adverse events n (%)	Unplanned readmission n (%)	Reinterventions n (%)	Allocation concealment bias
Irani (2017)[15]	Retrospective	EUS-GBD	45	44 (100)	43 (95.6)	8 (17.8)	6 (13.3)	11 (24.4)	High
		PT-GBD	45	45 (100)	41 (91.1)	14 (31.1)	22 (48.9)	26 (57.8)	
Teoh (2017)[16]	Retrospective	EUS-GBD	59	57 (96.6)	53 (89.8)	19 (32.2)	4 (6.8)	1 (1.7)	High
		PT-GBD	59	59 (100)	56 (94.9)	44 (74.6)	42 (71.2)	16 (27.1)	
Siddiqui (2019)[14]	Retrospective	EUS-GBD	102	96 (94.1)	92 (90.2)	11 (10.8)	4 (3.9)	1 (1.0)	High
		PT-GBD	146	143 (97.9)	141 (96.6)	35 (24.0)	29 (19.9)	15 (10.3)	
Teoh (DRAC-1) (2020)[17]	Randomized controlled trial	EUS-GBD	39	38 (97.4)	36 (92.3)	10 (25.6)	6 (15.4)	1 (2.6)	Low
		PT-GBD	40	40 (100)	37 (92.5)	31 (77.5)	20 (50.0)	8 (20.0)	

The accrued information size was 535 patients (245 submitted to EUS-GBD and 290 submitted to PT-GBD). The DRAC-1 trial[17] was the only study with a low risk of bias for allocation concealment. Consequently, effect sizes from this study were used as anticipated effect sizes in the trial sequential analysis.
EUS-GBD, EUS-guided gallbladder drainage; *PT-GBD*, percutaneous gallbladder drainage.

TABLE 2. Effects of EUS-GBD over PT-GBD resulting from meta-analysis on main outcome measures considering all retrieved studies

Outcome measure	Relative risk (95% confidence interval)	*P* value	I^2 (%)	D^2 (%)	Events in the PT-GBD group (%)	RRR (%)	Number needed to treat
Technical success	.976 (.937-.998)	.036	0	0	99.4 (97.9-100)	−2.4	42
Clinical success	.965 (.920-1.012)	.146	11	14	95.2 (92.3-97.6)	−3.5	30
Overall adverse events	.424 (.323-.555)	.001	0	0	42.4 (36.7-48.2)	57.6	4
Unplanned readmission	.215 (.137-.337)	.001	5	5	38.0 (32.4-43.8)	78.5	3
Reinterventions	.244 (.142-.418)	.001	65	84	20.7 (16.1-25.6)	75.6	6

I^2 and D^2 are 2 different measures of heterogeneity/difference among included studies. RRR is the relative risk reduction of EUS-GBD over PT-GBD. Number needed to treat is the number of patients needed to treat to prevent 1 additional bad outcome in comparison with the alternative. It is calculated as the inverse of absolute risk reduction (ARR). For example, EUS-GBD has a number needed to treat of 4 for overall adverse events over PT-GBD because the proportion of events dropped from 42.4% to 18.0% with EUS-GBD (corresponding to the RRR of −57.6%) resulting in an ARR of 24.4. The inverse of 24.4 is 4, meaning that 4 people must be treated with this approach to prevent 1 additional adverse event in respect to PT-GBD.
EUS-GBD, EUS-guided gallbladder drainage; *PT-GBD*, percutaneous gallbladder drainage; *RRR*, relative risk reduction.

is, PT-GBD provides higher technical success with a 0% of heterogeneity between studies included, but TSA suggests that a much larger sample of patients, up to 1663, should be enrolled to provide firm conclusions. At present, the possibility of a Type I error cannot be excluded.

Regarding clinical success, the CI of the comparison between EUS-GBD and PT-GBD includes 1, resulting in a *P* value of .146 at the accrued information size. With this result, can it be said that EUS-GBD and PT-GBD are equivalent in achieving clinical success? Some considerations are needed to answer this question. The necessary prerequisite for achieving clinical success is achieving technical success. Consequently, the previously discussed results for technical success are applicable to this result as well. It is foreseeable that if adequate data for technical success are reached and PT-GBD demonstrates superiority over EUS-GBD, clinical success could also be influenced in this direction. On the other hand, having a larger lumen, EUS-GBD can improve clinical success compared with PT-GBD because of the possibility of better drainage of the gallbladder, intraluminal lavage, and eventual stone clearance. The fact that the size of the required information calculated via TSA is very large (>10,000) suggests that these 2 conflicting aspects, 1 in favor of PT-GBD and 1 in favor of EUS-GBD, could dissolve the size of the final effect of an approach over the alternative. Considering these observations, it can be argued that EUS-GBD and PT-GBD are equivalent in determining the clinical success rate.

The superiority of EUS-GBD over PT-GBD on overall AEs is one of the most robust findings of the present study. Heterogeneity was 0% and robustness was reinforced by the TSA result, which showed that the Type I error was reasonably avoided and that a benefit was gained early with an RIS of only 80 patients. A benefit of EUS-GBD in terms of AE reduction can be observed in 1 patient for every 4 compared with PT-GBD, and this can be considered a very large effect size. This TSA also provided confirmation on the integrity of the DRAC-1 study design, which was built on 1-year overall AEs and enrolled a total sample of 79 patients.[17] Because the overall AEs were lower in the EUS-GBD group, the predictable consequence is that unplanned readmission would also be lower than that of

patients undergoing PT-GBD and that this benefit can be observed in 1 patient for every 3 treated. Furthermore, re-operations can be avoided in 1 patient for every 6 treated. All of these aspects converge to reduce the direct costs of EUS-GBD, reducing the higher costs because of the treatment itself.[21]

Limitations of the present study are shared with other previous meta-analyses conducted on this topic,[1,22] which are the limited number of included studies, their retrospective nature in most cases, and the differences between EUS-GBD and PT-GBD patients outside the only available RCT. All of these aspects converge to determine a significant heterogeneity that would bias final meta-analytic results. However, differently from previous reports, here we tried to handle heterogeneity through TSA because the RIS is adjusted for the heterogeneity detected in included studies, finally providing the confidence to place into conventional meta-analytic results together with the required sample size needed to exclude Type I and Type II errors. Another specific limitation regards the impossibility to robustly use in-hospital stay in the present study. This was an a priori decision based on the fact that studies always reported in-hospital stay as medians and, unfortunately, often without ranges. These data could have been transformed in means and standard deviations necessary for meta-analysis using appropriate formulae, but the lack of range prevented it.[23] In addition, it was conceivable that variations in hospital stay also depended on differences in postdrainage protocols, discharging criteria, and social support.[1] Considering that the aim of the present study was to provide some robustness to meta-analyses through TSA, the use of these data would have been a contradiction. We are aware that hospitalization is a major driver of costs related to the procedures,[21] but focusing on a more objective outcome represents a more reliable approach. Overall, the suggestion can be that hospital length requires a clear definition, eventually encoding it as the proportion over a predetermined threshold. Finally, we hasten to add that the present TSA results are not to be considered definitive, because any further study in this regard should be added to the current analysis as if it were a new interim analysis. This would lead to a new estimate of the RIS in relation to the new effect size and the new heterogeneity detected. However, some results are robust enough to deserve prompt clinical consideration in the routine clinical practice.

In conclusion, the present meta-analysis and TSA showed that PT-GBD can be superior to EUS-GBD in providing technical success, but this is evident only when a very large sample size is achieved, thus limiting the number needed to treat to observe a single benefit. Clinical success is probably equivalent. The advantage of EUS-GBD on the reduction of overall AEs and unplanned readmissions is large enough to be considered for future recommendations. The need for reinterventions requires additional studies.

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