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Peroral endoscopic myotomy (Z-POEM) versus flexible endoscopic septotomy (FES) for treatment of Zenker's diverticulum: does either make the cut? A systematic review and meta-analysis of outcomes

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Abstract

Background Endoscopic treatments of symptomatic Zenker's diverticulum (ZD) include flexible endoscopic septotomy (FES) and, more recently, peroral endoscopic myotomy (Z-POEM). Data comparing these techniques are limited. We conducted a meta-analysis evaluating FES vs. Z-POEM for symptomatic ZD.

Methods Multiple databases were searched from inception to September 2024. Our primary outcomes were clinical and technical success. Secondary outcomes included adverse events, length of hospital stay (LOS), procedure time, and recurrence. A random-effects model was used, and outcomes were represented as pooled rates, relative risk (RR) and standardized mean difference (SMD), along with 95% confidence intervals (CI).

Results Seven studies with 580 patients (Z-POEM=274, FES=306) were included. Mean age ranged from 68.9-74.9 years. The diverticulum size was not statistically different between the 2 groups: SMD -3.78 (-11.68 to 4.12), P=0.35. The pooled technical success was similar for Z-POEM and FES: RR 0.99 (95%CI 0.96-1.02; I^2=0%); P=0.4. Clinical success rate was significantly higher for Z-POEM compared to FES: RR 1.11 (95%CI 1.04-1.18; I^2=16%); P=0.001. There were no statistically significant differences between the 2 treatment modalities in pooled rate of recurrence, adverse events, LOS or procedural time.

Conclusions Our analysis shows that Z-POEM and FES in the treatment of symptomatic ZD are both associated with high technical success and a good safety profile, and have comparable procedural times and rates of recurrence. Z-POEM may offer higher rates of clinical success at follow up.

Keywords Zenker's diverticulum, Z-POEM, septotomy

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Introduction

Zenker's diverticulum (ZD), also known as hypopharyngeal diverticulum, is an acquired sac-like outpouching of the mucosa and submucosa in the posterior wall of the pharyngoesophageal junction. ZD is the leading type of esophageal diverticula, with an estimated prevalence of 0.01-0.11% [1,2], and predominantly afflicts elderly males, causing symptoms of dysphagia, regurgitation, coughing, aspiration and weight loss [3]. Treatment is often indicated for symptomatic patients, regardless of the size of the diverticulum.

Therapeutic approaches have included transcervical surgery, involving pharyngeal pouch excision, dating back to 1886 [4]. However, the need for a large neck incision, high morbidity

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rates and long postoperative hospital stays have led to advances in the management of ZD, with a shift towards minimally invasive techniques, including rigid and flexible endoscopic septotomy (FES) [5]. The rigid endoscopic approach has been shown to have several limitations, including the need for general anesthesia and significant rates of intraoperative failure (5-10%). Additionally, this approach may be technically more challenging in patients with smaller diverticuli (<3 cm) and those with inadequate jaw opening and restricted neck mobility [6,7].

During the last few decades, in an effort to overcome such limitations, FES has been established as a safe and effective alternative to both open surgery and rigid endoscopic treatments. While data suggest that 90% of patients achieve clinical resolution of symptoms with 1-2 treatment sessions after FES, the recurrence rate is estimated to be between 11% and 32% [8,9]. This relatively high rate of recurrence has been attributed to incomplete cricopharyngeal myotomy, due to the technical challenge of dividing the entire diverticular septum during FES without incurring a perforation. Consequently, Zenker's peroral endoscopic myotomy (Z-POEM) was recently introduced as an alternative to FES. With this technique, a mucosal incision is made that allows access to the submucosa and dissection around the diverticular septum. Once the septum is isolated, a full thickness myotomy is performed, followed by closure of the initial mucosal incision for restoration of luminal integrity. Comparative studies between FES and Z-POEM are scarce. We conducted a systematic review and meta-analysis assessing the effectiveness and safety of Z-POEM as compared to FES in the treatment of ZD.

Materials and methods

Search strategy

The literature was searched by a medical librarian for the concepts of ZD, peroral endoscopic myotomy and flexible endoscopic septotomy. Search strategies were created using a combination of keywords and standardized index terms. Searches were run on September 1, 2024, in ClinicalTrials.gov (2000+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Embase (1974+), Ovid Medline (1946+ including Epub ahead of print, in-process and other non-indexed citations), Scopus (1823+), Web of Science Core Collection (Science Citation Index Expanded 1975+ and Emerging Sources Citation Index 2015+), and the World Health Organization's clinical trial registry, ICTRP (2005+). Results were limited to the English language, based on the exclusion criteria, and a total of 201 citations were retrieved. Deduplication was performed in EndNote following the Bramer method (cited below), leaving 111 citations for screening [10]. The full search strategy is shown in Appendix 1. The PRISMA flowchart is provided as Supplementary Fig. 1 [11]. Reference lists of evaluated studies were examined to identify other studies of interest.

Study selection

In this meta-analysis, we only included comparative observational studies that reported on outcomes of FES and Z-POEM among patients with ZD. Studies were included irrespectively of follow-up time, country of origin, whether they were performed in an inpatient or outpatient setting, or published as full manuscripts or conference abstracts, as long as they provided the appropriate data needed for the analysis.

Our exclusion criteria were as follows: (1) individual studies reporting on outcomes of FES and Z-POEM; (2) individual case reports; (3) studies performed in the pediatric population (age <18 years); and (4) studies not published in English language. In case of multiple publications from a single research group reporting on the same patient cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained. The retained studies were decided upon by 2 authors, based on the publication timing (most recent) and/or the sample size of the study (largest). In situations where a consensus could not be reached, overlapping studies were included in the final analysis and any potential effects were assessed by sensitivity analysis of the pooled outcomes by leaving out 1 study at a time.

Data abstraction and quality assessment

Data on study-related outcomes from the individual studies were abstracted independently onto a standardized form by at least 2 authors. Authors cross-verified the collected data for possible errors and 2 authors did the quality scoring independently. The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [12]. This quality score consisted of 8 questions, the details of which are provided in Supplementary Table 1. As the included studies were observational in design, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was followed (Appendix 2) [13,14].

Outcomes assessed

Our primary outcomes were to assess the clinical and technical success of both FES and Z-POEM. Technical success

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was defined as successful completion of all procedural steps, or the ability to sever the septum between the ZD and esophagus and successfully complete the cricopharyngeal myotomy for Z-POEM or standard FES. Clinical success was defined as improvement in the Eckardt Score to ≤2 or the dysphagia score to ≤1, a decrease in the Dakkak and Bennett dysphagia score [14] to ≤1 (or to 0 in patients with baseline score of 1) or, in those patients with no dysphagia at baseline, complete resolution of other symptoms or an increase in functional oral intake scale and, conversely, a reduction in Eckardt score and stage. Secondary outcomes included pooled and comparative rates of 1) symptom recurrence; 2) overall adverse events; 3) length of hospital stay (LOS) in days; 4) procedure time in min; and 5) size of diverticulum.

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case, following the methods suggested by DerSimonian and Laird and using the random-effects model. 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 [15]. We assessed heterogeneity between study-specific estimates using the Cochran Q statistical test for heterogeneity, 95% confidence interval (CI) and I^2 statistics [16-19], in which values of <30%, 30-60%, 61-75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. We assessed publication bias, qualitatively, by visual inspection of funnel plots, and quantitatively, by the Egger test. When publication bias was present, further statistics using the fail-safe N test and Duval and Tweedie's "Trim and Fill" tests were used to ascertain the impact of the bias [20]. 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 the effect size changed substantially but the final finding would still remain the same, and severe if the basic final conclusion of the analysis was threatened by the bias [21]. A Knapp-Hartung 2-tailed P-value of <0.05 was considered statistically significant and the R^2 value was calculated to study the goodness of fit. All analyses were performed using RStudio (R version 4.1.1).

Results

Search results and population characteristics

A total of 52 full-length articles were evaluated, from which 7 studies with 580 patients (58% male) were included in the final analysis. Overall, 274 patients underwent Z-POEM and 306 underwent FES. Mean age ranged from 68.9-74.9 years. Follow up ranged from 3.4-24 months. Full details of the patients' characteristics are summarized in Tables 1 and 2.

Table 1 Study details and patient characteristics

Study, year [ref.]	Design	Total patients		Sex (male/female)		Age		Follow up
		Z-POEM	FES	Z-POEM	FES	Z-POEM	FES	
Kahaleh, 2022 [22]	Retrospective, multicenter, March 2017 until November 2020, USA	52	49	56/45		74.9±11.32 [Mean]	72.82±11.1 [Mean]	3.4 months (Z-POEM), 7.9 months (FES) [Mean]
Al Ghamdi, 2022 [23]	Retrospective, multicenter, January 2016 and September 2019, USA	119	86	67/52	48/38	72.49 (13.23) [Mean]	72.21 (12.37) [Mean]	9.3 months (9.9) [Mean]
Swei, 2023 [24]	Retrospective, single-center, 2015 and 2018, USA	13	15	10/3	10/5	69.9±11.5 [Mean]	72.2±9.1 [Mean]	24 months (9 Z-POEM), 12 months (12 Z-POEM, 13 FES)
Maselli, 2021 ABS [27]	Retrospective, single-center, February 2011 to December 2019, Italy	35	107	19/16	66/41	68.9 (14.1) [Mean]	68.9 (12) [Mean]	24 months
Desai, 2019 ABS [26]	Retrospective, single-center, 2013-2016, India	7	8	9/6		71.4 years (range 67-81)		18 months
Aslan, 2019 ABS [25]	Retrospective, single-center, October 2015 and October 2018, Turkey	9	20	NR	NR	NR	NR	NR
Sarkis, 2024 [28]	Retrospective, single-center, 07/2016 and 08/2023, USA	39	21	24/15	9/12	70.3 (11.8)	73.7 (13.2)	18 months

ABS, abstract; NR, not reported; FES, flexible endoscopic septotomy

Table 2 Study outcomes

Study, year [ref.]	Technical success		Clinical success		Diverticulum size (cm)		Procedure time (min)		Length of stay (days)		Adverse events		Recurrence/reintervention	
	Z-POEM	FES	Z-POEM	FES	Z-POEM	FES	Z-POEM	FES	Z-POEM	FES	Z-POEM	FES	Z-POEM	FES
Kahaleh, 2022 [22]	51/52	49/49	48/52	41/49	NR	NR	42.51 (18.75) [Mean]	44 (20.20) [Mean]	1.5 (1)	1.9 (1.3)	5/52	15/49	3/52	7/49
Al Ghamdi, 2022 [23]	113/119	82/86	102/110	65/75	3.49±1.47	2.87±1.23	46.13 (20.34) [Mean]	33.72 (22.34) [Mean]	1.66 [SD 1.55]	1.47 [SD 0.97]	20/119	2/86	15/102	6/65
Swei, 2023 [24]	13/13	15/15	13/13	13/15	2.4±0.6	2.5±0.8	43.9±13.7 [Mean]	60.2±22.4 [Mean]	NR	NR	0/13	1/15	0/9	NR
Maselli, 2021 ABS [27]	NR	NR	32/35	86/107	1.4±6.8	17.5±11.1	13.6 (6.3) [Mean]	19.7 (7.3) [Mean]	NR	NR	1/35	3/107	NR	NR
Desai, 2019 ABS [26]	NR	NR	7/7	3/8	0.26	0.55	49	34.5	1.1	2.5	1/7	5/8	0/7	3/8
Aslan, 2019 ABS [25]	NR	NR	9/9	16/20	NR	NR	NR	NR	NR	NR	5/9	1/20	0/9	3/20
Sarkis, 2024 [28]	38/39	21/21	10/14	15/18	2.94 (1.37)	2.82 (1.22)	48.75 (3.75)	43.75 (8.75)	1 (0)	1.25 (0.25)	2/39	6/21	3/39	2/20

ABS, abstract; NR, not reported; FES, flexible endoscopic septotomy; SD, standard deviation

Characteristics and quality of included studies

All included studies were retrospective in design. Four were published as full-length manuscripts and 3 were published as conference abstracts [22-28]. Two studies were multicenter [22,23] and 5 studies were single-center [24-28]. Four studies originated in the USA, and 1 each in India, Turkey, and Italy. Based on the Newcastle-Ottawa scoring system, 6 studies were of high quality and one study was of low quality (Supplementary Table 1).

Meta-analysis outcomes

Primary outcomes

1. Clinical success (7 studies). The overall pooled clinical success was significantly higher among patients undergoing Z-POEM compared to FES: 92.1% (95%CI 87.9-94.9; I^2=0%) vs. 81.8% (95%CI 77-85.9; I^2=46%), respectively; RR 1.11 (95%CI 1.04-1.18; I^2=16%), P=0.001 (Fig. 1).
2. Technical success (4 studies). There was no statistically significant difference in the overall pooled technical success between Z-POEM and FES: 96.4% (95%CI 93-98.2; I^2=0%) vs. 98.6% (95%CI 78.9-99.9; I^2=0%), respectively; RR 0.99 (95%CI 0.96-1.02; I^2=0%), P=0.4 (Fig. 2).

Secondary outcomes

3. Recurrence (5 studies). We found a higher rate of clinical recurrence among patients undergoing FES compared to Z-POEM: 13% (95%CI 8.6-19.1; I^2=14%) vs. 7.8% (95%CI 3.5-16.8%; I^2=0%). However, the difference between the 2 techniques was not statistically significant: RR 0.7 (95%CI 0.29-1.66; I^2=20%), P=0.42 (Supplementary Fig. 2).
4. Overall adverse events (7 studies). There was no statistically significant difference in the overall pooled rate of adverse events between Z-POEM, 10% (95%CI 4-22%; I^2=62%) and FES: 11.2% (95%CI 3.7-29.2%; I^2=85%); RR 0.88 (95%CI 0.24-3.2; I^2=76%), P=0.42 (Supplementary Fig. 3).
5. LOS (3 studies). There was no statistically significant difference in the LOS between the 2 techniques: SMD -0.09 (95%CI -0.66 to 0.49; I^2=75.6%), P=0.77 (Supplementary Fig. 4).
6. Procedure time (5 studies). Mean procedure time ranged from 13.6-49 min for Z-POEM and from 19.7-60.2 min for FES. There was no statistically significant difference in the procedure time between the 2 techniques: SMD 0.12 (95%CI -8.21 to 8.47; I^2=92%), P=0.97 (Supplementary Fig. 5).
7. Size of diverticulum (4 studies). The size of the diverticulum in the FES group was greater, but the difference was not significant: SMD -3.78 (95%CI -11.68 to 4.12; I^2=97%), P=0.35 (Supplementary Fig. 6).

We performed a subgroup analysis with exclusion of all abstracts, following which the results with respect to our

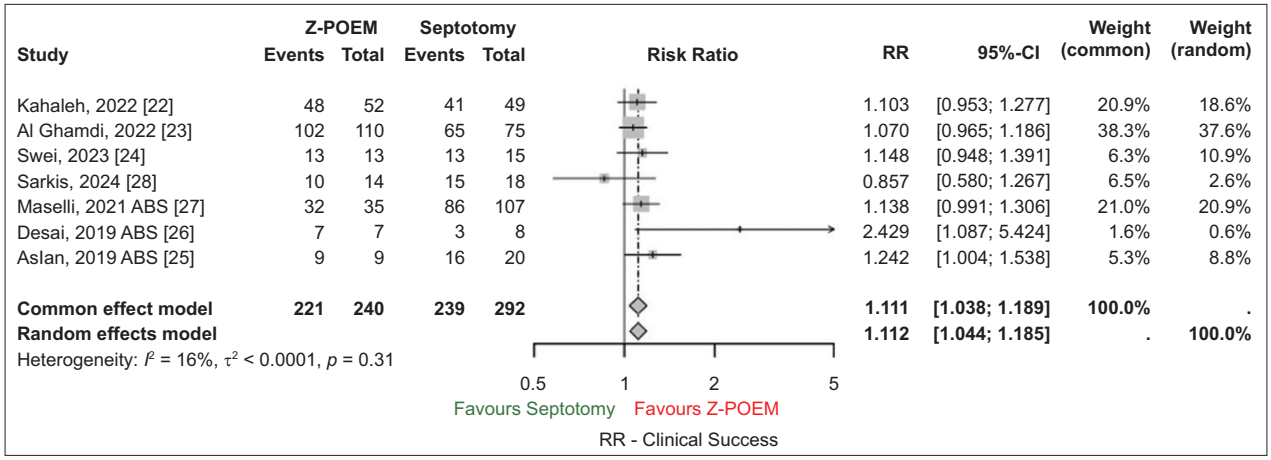

Figure 1 Forest plot showing clinical success
RR, relative risk; CI, confidence interval; Z-POEM, Zenker's peroral endoscopic myotomy

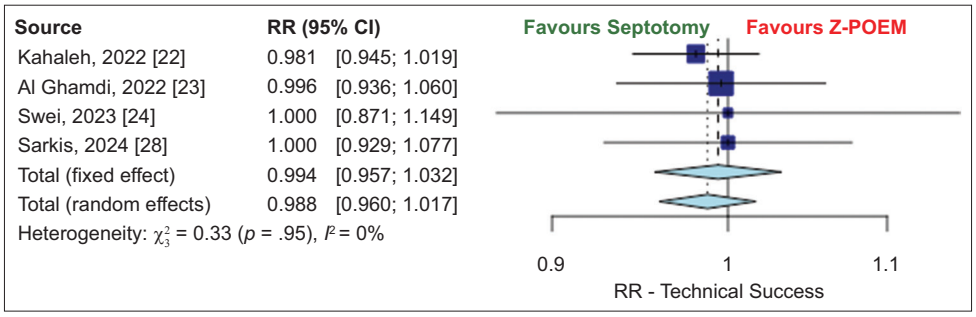

Figure 2 Forest plot showing technical success
RR, relative risk; CI, confidence interval; Z-POEM, Zenker's peroral endoscopic myotomy

primary and secondary outcomes were as follows: clinical success 91.5% (95%CI 86.6-94.7%) vs. 85.4% (95%CI 78.9-90.1%), RR 1.08 (95%CI 1.01-1.17), P=0.04; technical success 96.4% (95%CI 93-98.2%) vs. 98.6% (95%CI 78.9-99.9%), RR 0.98 (95%CI 0.96-1.02), P=0.36; recurrence 9.5% (95%CI 4.9-17.5%) vs. 11.2% (95%CI 6.9-17.7%), RR 0.88 (95%CI 0.35-2.21), P=0.79; adverse events 10% (95%CI 5-20%) vs. 12% (95%CI 3.6-33.4%), RR 0.65 (95%CI 0.11-3.81); and procedure time SMD -0.22 (95%CI -15.62 to 15.16), P=0.9770.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any single study had a dominant effect on the meta-analysis, we excluded 1 study at a time and analyzed its effect on the main summary estimate. In this analysis, no single study significantly affected our primary outcomes (Supplementary Fig. 7A,B).

Heterogeneity

We assessed the dispersion of the calculated rates using the I^2 percentage values. Overall, low to moderate heterogeneity was found in the pooled and comparative rates of technical and clinical success, as well as recurrence. Furthermore, considerable to substantial heterogeneity was found in the pooled and comparative rates of adverse events, LOS, procedure times and size of diverticulum. These findings can probably be explained by variation in procedural techniques as well as operator experience.

Publication bias

Publication bias was not assessed, since the number of studies included in our analysis was less than 10.

Discussion

Although endoscopic therapy for ZD has been gaining traction over recent years, there are limited data supporting the optimal treatment approach for ZD. Our meta-analysis shows that, while both Z-POEM and FES are technically feasible modalities for symptomatic ZD, in expert hands, Z-POEM was associated with a higher clinical success rate, while it had comparable procedural time, adverse events and recurrence rates.

FES was initially introduced in 1995 and involves division of the septum between ZD and esophagus [29]. In view of the high success rates, combined with decades of experience, the 2020 guideline from the European Society of Gastrointestinal Endoscopy recommended flexible endoscopic treatment as first-line therapy for symptomatic ZD [30]. On the other hand, Z-POEM is a relatively new application of POEM for ZD, and was recommended only for research purposes, given the lack of data at the time. Similarly, the technology status report by the American Society for Gastrointestinal Endoscopy concluded that, while the flexible endoscopic approach is better than surgical or rigid endoscopic methods, emerging techniques such as Z-POEM would need direct comparison with FES in clinical studies. The main criticism of FES revolves around the potential for recurrence, in the range of 11-32%, which has been often attributed to an incomplete extension of the septotomy to the level of the fundus of the diverticulum, prompted by concerns about mediastinal leak and challenging mucosal closure [31]. On the other hand, a major benefit proposed for Z-POEM was greater safety due to the intact overlying mucosa and prevention of mucosal perforation with submucosal tunneling; however, there was a concern that this technique was more technically challenging and time-consuming as compared to FES [32]. In our analysis, we found that Z-POEM was associated with a higher clinical success rate than FES, probably attributable to the ability to perform a complete septotomy. This may also be a contributing factor to the trend towards a higher recurrence of symptoms following FES.

Keeping these factors in mind, and when assessing comparative studies cumulatively, our results showed that both techniques were technically successful in over 90% of cases. Additionally, we found that the clinical success was significantly higher in the Z-POEM group (92.1%) than in the FES group (81.8%). It is interesting to note that a previous single-arm meta-analysis by Ishaq *et al* reported a symptomatic success rate of 91% for FES in patients with ZD, which is much higher than the rate observed in our study [9]. A likely explanation of this finding could be the heterogeneity in the definition of "clinical success" used in the studies. While Ishaq *et al* defined clinical success as "symptomatic improvement in dysphagia and/or regurgitation with or without using scoring grades such as Dakkak and Bennett", we used additional criteria, such as Eckardt and dysphagia scores, to incorporate the maximum number of studies possible. Furthermore, we included studies with small sample sizes, which may have shifted the significance in favor of Z-POEM.

Despite the higher complexity of Z-POEM as compared to FES, and some studies suggesting a longer procedure time and more adverse events with Z-POEM, our study did not find significant differences between the 2 treatment groups. This may be related to the expert proficiency of the endoscopists, and highlights the importance of adequate training [33]. As a result, the current adoption rate of Z-POEM among interventionalists is variable, with some using it only for salvage cases after prior surgical myotomy, or in patients without large ZD pouches. Nevertheless, it is reassuring that the overall adverse events were comparable in the Z-POEM (10%) and FES (11.2%) groups, comprising mostly bleeding episodes. Along similar lines, the hospital LOS did not differ between the 2 treatment strategies. Prior studies have clearly alluded to technical challenges of Z-POEM [34,35], and it is important to highlight that our data were derived primarily from select expert centers, which probably influenced our results.

Over a variable follow up of 3.4-24 months in the included studies, our results showed a numerically higher rate of symptom recurrence in patients undergoing FES (13%) compared to Z-POEM (7.8%). These pooled rates are consistent with a previous meta-analysis of 20 studies on FES (recurrence 11%), and a recent long-term study on Z-POEM (recurrence 6.7%), with a mean follow up of around 3 years [9]. Even though non-significant, this difference in recurrence may be due to the possibility of small remnant muscular septum in the FES group [23]. It would be important to evaluate the cost-effectiveness of the Z-POEM and FES strategies, as recurrent symptoms and the need for any additional procedures could increase the total cost for patients.

Our study has the largest pooled sample size of patients in whom Z-POEM and FES techniques for symptomatic ZD were compared. A prior meta-analysis showed similar results to ours; however, the authors included a study assessing modified Z-POEM [36], in which septal mucosal incision with muscular interruption was performed, which could technically have different outcomes compared to standard Z-POEM [37]. We performed a subgroup analysis with exclusion of the abstracts to further validate our results and found that the findings were congruent with our primary and secondary outcomes.

Nevertheless, our analysis also had some limitations. First, the results of this study are subject to the same inherent selection bias, as the included studies are retrospective in design. Second, in 1 of the included studies, a peroral endoscopic septotomy (POES) approach was utilized [27]. This is a modification of the "standard" Z-POEM approach, in which the initial mucosotomy must be created approximately 1-3 cm proximal to the septum, at the boundaries between the pharynx and the upper esophageal sphincter. In this area, muscular spasm as well as anatomical limitations may reduce the ability to properly open and close the mucosal incision. During POES, to gain direct access to the ZD muscular septum without the need of long tunneling starting at pharyngeal level, the mucosal cut is performed alongside the long axis of the septum and directly on top of it. Third, since most of the data were from single-center studies, our results may not be generalizable in routine clinical practice. Furthermore, although the studies specified that the procedures were performed by experienced endoscopists, no further detail was provided. Hence, it is difficult to ascertain whether there was significant heterogeneity in terms of operator experience. Fourth, only abstracts were available for 3 of the included studies; however, the reported outcomes were clearly defined for inclusion in this meta-analysis. Finally, there was variability in the definition of "clinical success" by study authors (e.g., "complete resolution of regurgitation symptoms" by Desai *et al*), and in the duration of follow up, which may have influenced our results.

We believe that in expert hands, Z-POEM may be a feasible alternative for symptomatic ZD patients, with a possibly higher

clinical success rate compared with FES. Both the treatment approaches had similar technical success rate, procedural time, adverse events and symptom recurrence rate. This meta-analysis should be interpreted keeping in mind the inclusion of only observational data with variable follow ups. Additional long-term comparative prospective data are needed to fully understand the optimal treatment for patients with symptomatic ZD. Importantly, there may not be a "one type fits all" answer, as the best approach may depend on multiple patient- and operator-dependent factors.

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Summary Box

What is already known:

- Endoscopic treatments of symptomatic Zenker's diverticulum include flexible endoscopic septotomy (FES) and peroral endoscopic myotomy (Z-POEM)
- Data comparing these techniques are limited

What the new findings are:

- Clinical success rate was significantly higher for Z-POEM compared to FES
- There were no statistically significant differences between the 2 treatment modalities in the pooled rate of technical success, recurrence, adverse events, length of hospital stay, or procedural time

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Supplementary material

Appendix 1 Literature search strategy

ClinicalTrials.gov - classic site* (2000+):

(zenker OR zenkers OR zenker's) AND (peroral OR "per oral" OR orifice OR POEM OR ZPOEM) AND (septotomy OR FES)

Cochrane Central Register of Controlled Trials (CCTR) via Ovid (1991+)):

#	Query	Results from 7 Feb 2024
1	(((Zenker* or ?esophag* or pharyn* or hypopharyn* or pulsion) adj2 (diverticul* or pseudodiverticul*)) or (zenker* adj1 pouch)).ab, hw, ti.	28
2	(((peroral or per-oral or orifice*) adj3 (endoscop* or myotom*)) or POEM* or ZPOEM*).ab, hw, ti.	868
3	(septotom* or FES).ab, hw, ti.	1,252
4	1 and 2 and 3	1

Embase via Ovid (1974+):

#	Query	Results from 7 Feb 2024
1	Zenker diverticulum/	2,012
2	(((Zenker* or ?esophag* or pharyn* or hypopharyn* or pulsion) adj2 (diverticul* or pseudodiverticul*)) or (zenker* adj1 pouch)).ab, kf, ti, dq.	3,205
3	or/1-2	3,575
4	peroral endoscopic myotomy/or myotomy/ or esophagus myotomy/or natural orifice transluminal endoscopic surgery/	10,566
5	(((peroral or per-oral or orifice*) adj3 (endoscop* or myotom*)) or POEM* or ZPOEM*).ab, kf, ti, dq.	11,601
6	or/4-5	16,781
7	(septotom* or FES).ab, kf, ti, dq.	9,617
8	3 and 6 and 7	102
9	limit 8 to english language	97

International Clinical Trials Registry Platform (ICTRP) from the World Health Organization (2005+) – *standard interface*:

zenker* AND (peroral OR (per oral) OR orifice* OR POEM* OR ZPOEM*) AND (septotom* or FES)

MEDLINE via Ovid (1946+ and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily):

#	Query	Results from 7 Feb 2024
1	Zenker Diverticulum/	1,116
2	(((Zenker* or ?esophag* or pharyn* or hypopharyn* or pulsion) adj2 (diverticul* or pseudodiverticul*)) or (zenker* adj1 pouch)).ab, kf, ti.	2,878
3	or/1-2	3,013
4	Myotomy/or Natural Orifice Endoscopic Surgery/	4,130
5	(((peroral or per-oral or orifice*) adj3 (endoscop* or myotom*)) or POEM* or ZPOEM*).ab, kf, ti.	7,141
6	or/4-5	9,612
7	(septotom* or FES).ab, kf, ti.	7,268
8	3 and 6 and 7	27
9	limit 8 to english language	27

Scopus via Elsevier (1823+):

((TITLE-ABS-KEY ((zenker* OR esophag* OR oesophag* OR pharyn* OR hypopharyn* OR pulsion) W/2 (diverticul* OR pseudodiverticul*)) OR TITLE-ABS-KEY (zenker* W/1 pouch))) AND ((TITLE-ABS-KEY ((peroral OR per-oral OR orifice*) W/3 (endoscop* OR myotom*)) OR TITLE-ABS-KEY (poem* OR zpoem*))) AND (TITLE-ABS-KEY (septotom* OR fes)) AND (LIMIT-TO (LANGUAGE, "English"))

Web of Science Core Collection via Clarivate Analytics (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+):

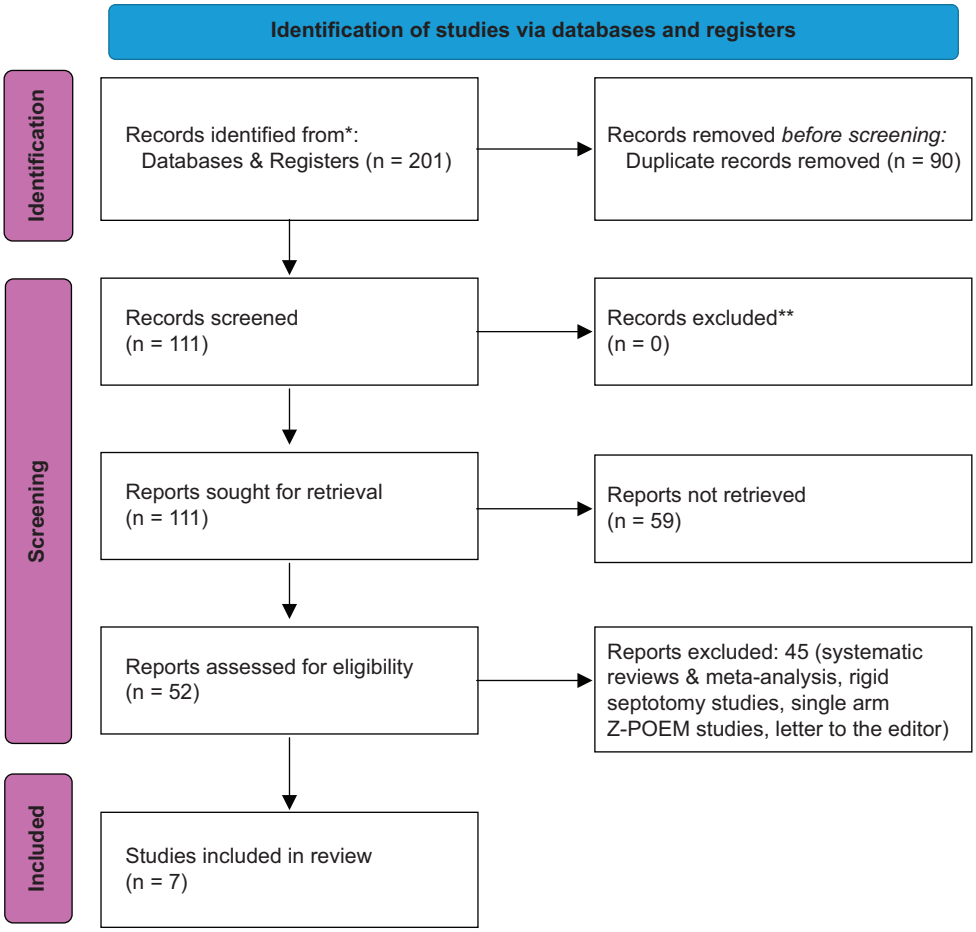
#4	#1 AND #2 AND #3 and English (Languages)
#3	septotom* or FES (Topic)
#2	(peroral or per-oral or orifice*) NEAR/3 (endoscop* or myotom*) (Topic) or POEM* or ZPOEM* (Topic)
#1	(Zenker* or $esophag* or pharyn* or hypopharyn* or pulsion) NEAR/2 (diverticul* or pseudodiverticul*) (Topic) or zenker* NEAR/1 pouch (Topic)

Appendix 2 MOOSE Checklist

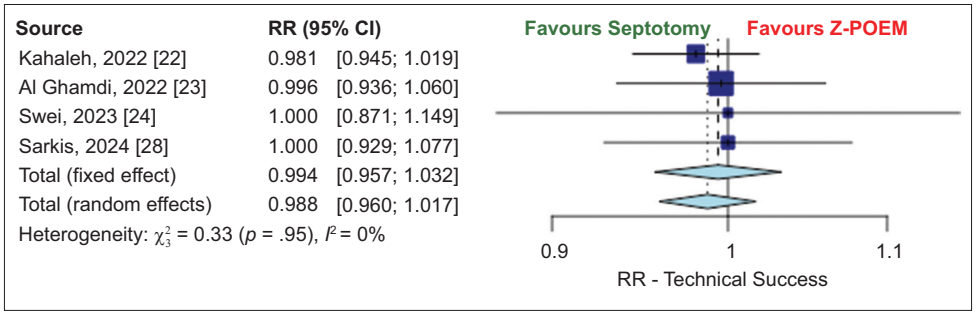
Item No	Recommendation	Reported on Page No
	Reporting of background should include	
1	Problem definition	4-5
2	Hypothesis statement	5
3	Description of study outcome (s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	6
	Reporting of search strategy should include	
7	Qualifications of searchers (e.g., librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	-NA-
13	List of citations located and those excluded, including justification	8-9, Suppl Figure 1
14	Method of addressing articles published in languages other than English	-NA-
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	-NA-
	Reporting of methods should include	
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5-6
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7
22	Assessment of heterogeneity	8
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8
24	Provision of appropriate tables and graphics	Tables 1-2, Figures 1-2
	Reporting of results should include	
25	Graphic summarizing individual study estimates and overall estimate	Figure 1 and 2 Suppl Figure 3 and 7
26	Table giving descriptive information for each study included	Table 1 and 3
27	Results of sensitivity testing (e.g., subgroup analysis)	12-13
28	Indication of statistical uncertainty of findings	12-13

Supplementary Table 1 Newcastle-Ottawa scale quality assessment

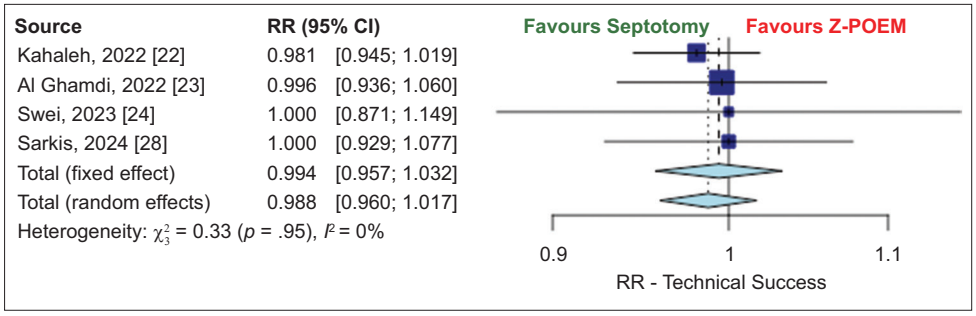
Study, year [ref.]	Selection				Comparability	Outcome			Score	Quality
	Representativeness of the average adult in community	Cohort size	Information on clinical outcomes	Outcome not present at start	Factors comparable between the groups	Adequate clinical assessment	Follow-up time	Adequacy of f ollow up	MAX=8	High>6, Medium 4 to 6, Low<4
	Population based: 1; Multi-center: 0.5; Single-center: 0	>40 patients: 1; 39 to 20: 0.5; <20: 0	Information with clarity: 1; Information derived from percentage value: 0.5; Unclear: 0	not present: 1; present: 0	yes: 1; no: 0	yes: 1; no: 0	yes: 1; not mentioned: 0	All patients followed-up: 1; >50% followed-up: 0.5; < 50% followed-up OR not mentioned: 0		
Kahaleh, 2022 [22]	0.5	1	1	1	1	1	1	1	7.5	High
Al Ghamdi, 2022 [23]	0.5	1	1	1	1	1	1	1	7.5	High
Swei, 2023 [24]	0.5	0.5	1	1	1	1	1	1	7	High
Maselli, 2021 ABS [27]	0	1	1	1	1	1	1	1	7	High
Desai, 2019 ABS [26]	0	0	1	1	1	1	1	1	6	Medium
Aslan, 2019 ABS [25]	0	0.5	1	1	1	0	0	0	3.5	Low
Sarkis, 2024 [28]	0	1	1	1	1	1	1	1	7	High



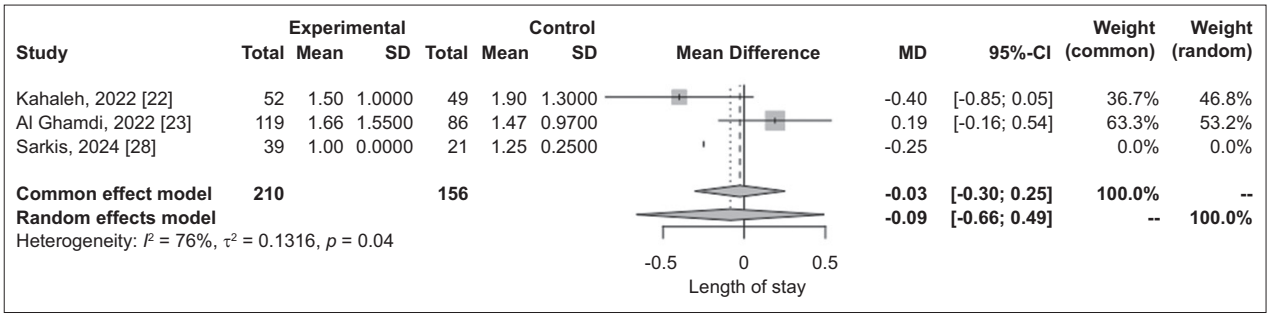
Supplementary Figure 1 PRISMA flow diagram
Z-POEM, Zenker's peroral endoscopic myotomy



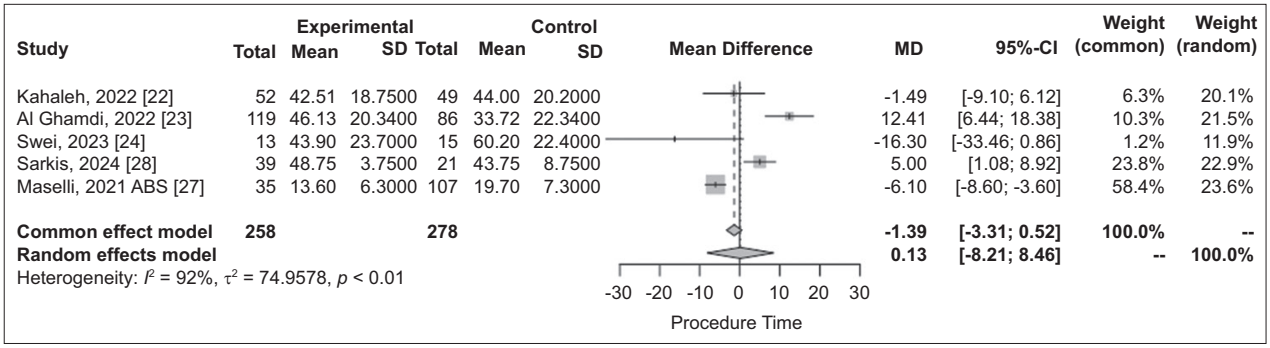
Supplementary Figure 2 Relative risk (RR), recurrence
RR, relative risk; CI, confidence interval; Z-POEM, Zenker's peroral endoscopic myotomy



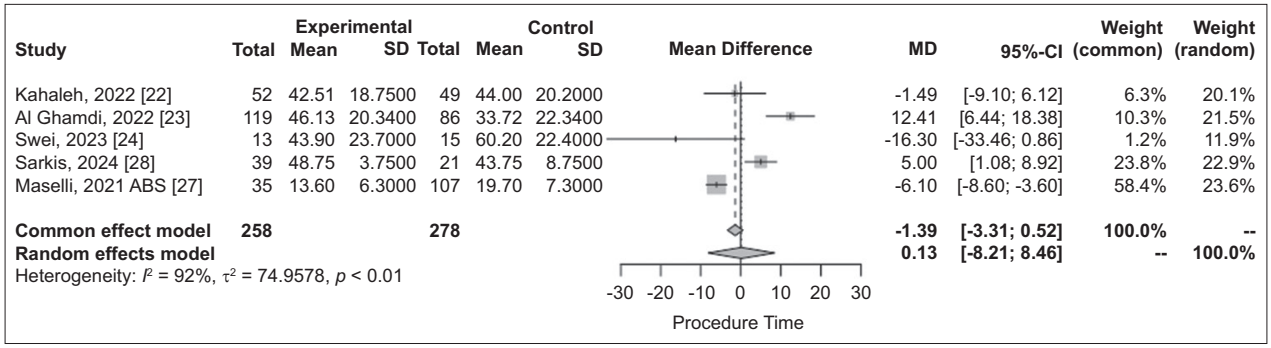
Supplementary Figure 3 Relative risk (RR), overall adverse events
RR, relative risk; CI, confidence interval; Z-POEM, Zenker's peroral endoscopic myotomy



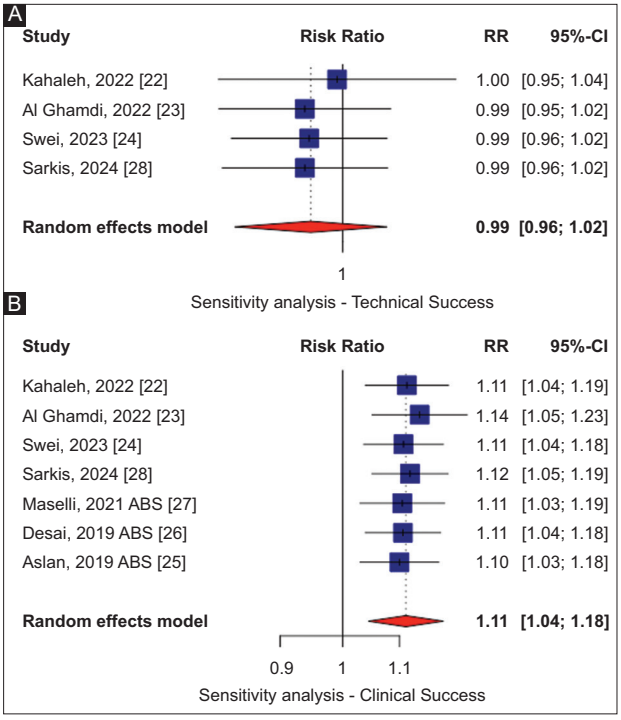
Supplementary Figure 4 Standardized mean difference (MD), length of hospital stay
SD, standard deviation; CI, confidence interval



Supplementary Figure 5 Standardized mean difference (MD), procedure time
SD, standard deviation; CI, confidence interval



Supplementary Figure 6 Standardized mean difference (MD), size of diverticulum
SD, standard deviation; CI, confidence interval



Supplementary Figure 7 Sensitivity analysis
RR, relative risk; CI, confidence interval