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Meta-analysis

Role of Peroral Endoscopic Myotomy in Advanced Achalasia Cardia With Sigmoid and/or Megaesophagus: A Systematic Review and Metanalysis

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Background/Aims
Sigmoid esophagus and/or megaesophagus are considered as an advanced stage in the natural history of achalasia cardia. The role of peroral endoscopic myotomy (POEM) in these subset of patients is emerging. We performed a systematic review and metanalysis to study the efficacy of POEM in advanced achalasia cardia with sigmoid and megaesophagus.

Methods
A literature search in PubMed and Embase was done from inception till August 3, 2021 to look for studies reporting exclusively on the role of POEM in advanced achalasia cardia with sigmoid and/or megaesophagus. The random effect method with inverse variance approach was used for the computation of pooled prevalence. For 2 groups' analysis of continuous outcome standardized mean difference was used as the summary measure.

Results
Eleven studies with 428 patients were included for analysis. The pooled technical and clinical success was 98.27% (95% CI, 96.19-99.22; I^2 = 0%) and 89.38% (95% CI, 84.49-92.86; I^2 = 26%) and on subgroup analysis into sigmoid and megaesophagus it was (98.06% [95% CI, 95.41-99.19; I^2 = 0%], 98.47% [95% CI, 92.72-99.69; I^2 = 0%] and 87.92% [95% CI, 80.68-92.70; I^2 = 37%], 88.36% [95% CI, 62.62-97.17; I^2 = 77%]) respectively. The clinical success at < 1 year and 1-3 year follow-up was 89.37% (95% CI, 82.82-93.61; I^2 = 0%) and 88.66% (95% CI, 81.65-91.22; I^2 = 46%) respectively. There was a significant reduction in the post-POEM scores with standardized mean difference for Eckardt score (4.81), for integrated relaxation pressure at 4 seconds (1.93), and for lower esophageal sphincter pressure (2.06).

Conclusions
POEM is an effective modality of treatment even in the subset of patients of advanced achalasia cardia with sigmoid and megaesophagus.

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Key Words
Esophageal achalasia; Follow-up studies; Myotomy

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Introduction

With over a decade of experience and robust data showing excellent safety and efficacy, peroral endoscopic myotomy (POEM) is now considered as the first line treatment for achalasia cardia.[1] Around 10% of patients with prolonged duration of disease develop advanced achalasia cardia where there can be either excessive dilatation of the esophagus (megaesophagus with diameter > 6 cm) or the axis of the esophagus becomes tortuous taking shape of sigmoid (like sigmoid colon) or both.[2,3] Traditionally, esophagectomy has been considered the treatment option for this patient cohort, however, it is fraught with high morbidity and mortality.[4] Due to the extreme tortuosity one would expect difficulty in performing POEM in this subset of patients. Over the years as more and more experience has been gained with POEM for achalasia, we now have some data showing good efficacy even in this subset of advanced achalasia with sigmoid shape and megaesophagus.[5] Hence, this systematic review and metanalysis was planned to study the efficacy and safety of POEM in the treatment of advanced achalasia cardia with sigmoid and/or megaesophagus.

Methodology for Systematic Review and Meta-analysis

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology guidelines were followed for this systematic review and meta-analysis.

We searched the literature for articles that reported exclusively on the role of peroral endoscopic myotomy in advanced achalasia cardia with sigmoid and/or megaesophagus on PUBMED and EMBASE. The search terms used for PUBMED were "advanced achalasia OR Sigmoid achalasia OR Sigmoid esophagus OR Megaesophagus) AND (Peroral myotomy OR Peroral endoscopic myotomy OR POEM)" while for EMBASE were (sigmoid esophagus OR Advanced achalasia OR sigmoid achalasia OR megaesophagus) AND Peroral endoscopic myotomy. The search was done from inception until August 3, 2021.

Two authors (H.S.M. and J.S.) independently searched for articles to be included for the analysis. After comparing the articles screened by both authors, the final list for full text reading was prepared. Any overlap or discrepancy about the data was discussed with and cleared by other co-authors (P.K.M. and V.S.).

We selected those studies published as full text/abstracts in English language that included ≥ 5 cases reporting on the role of POEM in the treatment of advanced achalasia cardia with sigmoid and/or megaesophagus. We excluded those studies that included case reports with < 5 cases, review articles, letter to editor without original data, commentary, articles published in non-English language, and articles that did not exclusively report on the role of POEM in advanced achalasia cardia with sigmoid and/or megaesophagus.

Outcome

The aim of this systematic review and meta-analysis is to assess the efficacy of POEM for advanced achalasia cardia with sigmoid and/or megaesophagus. The outcomes assessed were: technical success; clinical success; change in Eckardt score (ES), integrated relaxation pressure at 4 seconds (4s-IRP) and lower esophageal sphincter pressure (LESP) pre and post-POEM procedure.

The Outcome Definitions Used in the Study Are as Follows

(1) The technical success was defined as completion of all the steps of POEM including myotomy and (2) the clinical success was defined as a reduction in the ES ≤ 3 post-POEM. The ES is based on 4 symptoms each given score of 0 to 3 with maximum score of 12.[6] The 4s-IRP and LESP are recorded from the standard software of high-resolution manometry.[7] In addition we also noted the adverse event rate and was defined as per the American Society of Gastrointestinal Endoscopy (ASGE) lexicon[8] or International Per Oral Endoscopic Myotomy Survey Classification (IPOEMS)[9] or Clinical practice guidelines for POEM and Japan Clinical Oncology Group post-operative complications (JCOG PC) criteria[10,11] or noted as observational data. Apart from this, we looked for the following information: type of study (single/multicentre), type of sigmoid esophagus (Type 1 and Type 2 as per the CT classification–where Type 1 has only single bend and a single lumen on axial cut of CT, while Type 2 is S shaped and 2 lumens can be seen on axial CT image;[12] sigmoid and advanced sigmoid as per the descriptive rules of esophageal achalasia–where depending on the α angle [angle between 2 straight lines drawn along the long axis of the esophagus] it is defined a sigmoid when the α angle is < 135^{o} and > 90^{o}[13] and advanced sigmoid when the α angle is < 90^{o} and megaesophgus if diameter is > 6 cm[14]), type of achalasia cardia as per the Chicago classification version 3.0,[7] duration of symptoms in months, average diameter of the esophagus, previous treatments

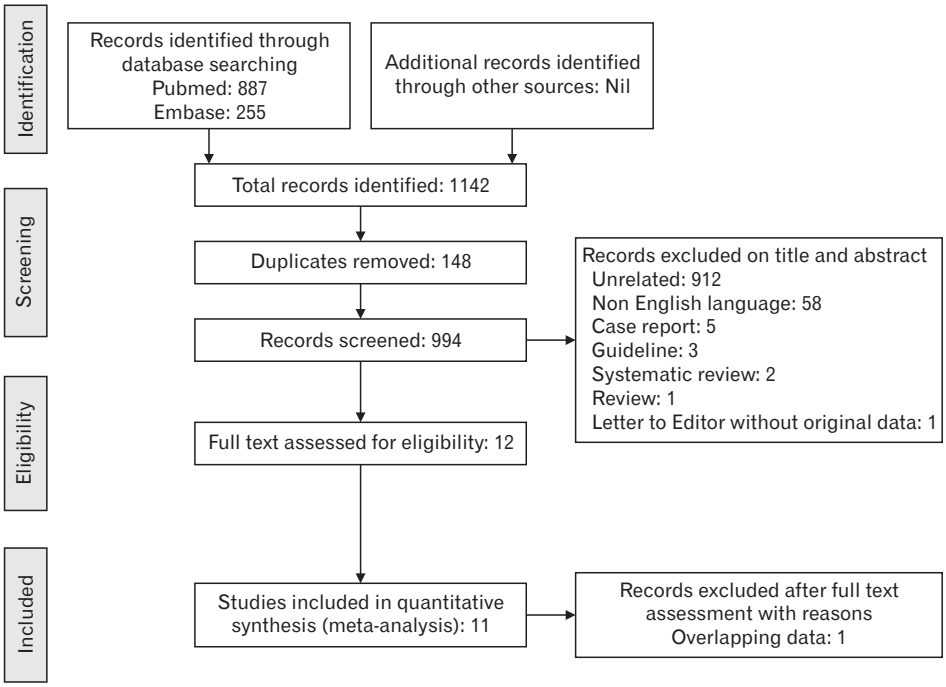

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) figure showing the flow of studies included in the meta-analysis.

received, pre- and post-ES, pre- and post-4s-IRP, pre- and post-LESP, duration of follow-up, myotomy length, and definition used for sigmoid esophagus by individual study. For missing data in abstracts, we contacted the authors through electronic mail.

We also performed separate subgroup analysis of studies that reported on sigmoid esophagus and those that reported on megaesophagus. Apart from this, based on the follow-up period available we performed subgroup analysis of clinical success into 2 groups, viz, clinical success with follow-up < 1 year and that with follow-up between 1-3 years.

Risk of Bias and Quality Assessment of Studies

We used the Joanna Briggs Index for critical appraisal of case series and cohort studies to assess the quality of studies (2 independent authors H.S.M. and J.S. performed the appraisal). For assessment of publication bias, the funnel plot was used and quantitative analysis was done with Egger's test.

Statistical Analysis

The statistical analysis was conducted using R version 4.1.0 and in addition to the base package, the "meta" package was used for the analysis. The random effect method with inverse variance approach was used for the computation of pooled prevalence. The prevalences were logit transformed before computing summary. For 2 groups' analysis of continuous outcomes (pre- and post-), standardized mean difference (SMD) was used as the summary measure and was calculated by the Hedges' g method and the computation of summary across studies was performed by random effect method with inverse variance approach was used. Both I^2 and *P*-value of significance were used for the assessment of heterogeneity or metanalysis. For I^2, a value of $> 50\%$ and for *P*-value of significance a value < 0.1 were kept for assessing heterogeneity for different variables. Sensitivity analysis was performed for data showing marked heterogeneity.

Results

After screening total 1142 studies we finally included 11 studies (9 full text and 2 abstracts) with 428 patients for meta-analysis. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart for the included studies. Table 1 shows the detailed demographic data of the included studies.[3,14-22] The study that fulfilled the inclusion criteria but was excluded with reason for exclusion is found in (Supplementary Table).[16,23] Of these 11 studies, 9 were single center retrospective and 1 each was single center prospective and multicenter retrospective.

Table 1. Detailed Demographic Characteristics of the Included Studies

Name and year	Type of study	Number of patients	Type of sigmoid	Type of AC-I/II/III/unidentified	Duration of symptoms	Esophageal diameter	Previous treatment[a]	Pre/Post-ES	Pre/Post-4s-IRP	Pre/Post-LESP	Duration of follow-up	Clinical success	Technical success	Procedure time	Myotomy length[b]	Length of hospital stay	Orientation of myotomy	Thickness of myotomy	AE$	Definition of sigmoid/advanced AC
Fujiyoshi et al,[19] 2020	Single center retrospective	108	All type 2	28/8/1/71	17.4 (7.7-29.0) yr	48.1 ± 17.5 mm	B-49, H-10	5.0 ± 2.5/ 1.1 ± 1.0 (2 mo)	15.7 ± 9.9/ 8.6 ± 5.5	19.9 ± 13.9/ 14.6 ± 7.7	1 yr	At 2 mo: 82/92 (89.1), at 1 yr: 43/49 (87.8)	107	95.9 ± 32.1 min	E-7 (5-9), G-3 (2-3)	4 (4-5) day	NA	NA	6	Enormously dilated and tortuous esophagus in barium esophagram and double esophageal lumen in some CT slices
Ueda et al,[14] 2021	Single center retrospective	11	S1-6, S2-4, ST-1	10/1	15 (2-41) yr		B-4	6 (2-10)/ 2 (0-4)	23 (11-34)/ 9 (3-21)		1 yr	7 (63.6)	11	71 (39-100)	9 (4-16)		NA	NA	2	S1, the esophagus was significantly dilated, tortuous with single lumen on CT; S2, double lumen seen on CT
Sanaka et al,[21] 2021	Single center retrospective	20		6/10/0/3	5.0 (2.0, 13.0) years median IQR	4.5 (3.02, 5.45)	BO-6, B-4, H-6, BB-1, CR-5	7.0 (6.0, 10.0)/ 0.0 (0.0, 2.0)	15.6 (10.5, 30.5)/ 3.9 (1.9, 10.3)	33.4 (8.9, 53.3)/ 14.2 (10.8, 16.5)	2 mo	17 (94.4)	20	89.5 (65.2, 103.7)	8.5 (8.0, 9.7)	1.0 (1.0, 1.0)	Anterior except for those with post LHM status	Selective circular	0	Sigmoid type when the angle was < 135° and advanced sigmoid when angle < 90
Qiu et al,[22] 2021	Single center retrospective	112	All advanced AC > 6 cm	47/63/2	6.5 (3.0, 13.0) yr	7.1 (6.4, 8.3) cm	B-20, BO-7, H-4, S-4, P-4	8.0 (6.0-9.0)/ 1.0 (0.0-2.0)		29.5 ± 11.6/ 14.2 ± 11.8	31 (21.0, 47.0) mo	94/101 (93.1)	112	45.5 (35.8, 60.3) min	7.0 (5.0-8.0) cm	7.0 (7.0-8.0) day	NA	Full thickness	10	Advanced achalasia defined as megaesophagus with max diameter ≥ 6 cm
Liu D et al,[5] 2021	Single center retrospective	50	Megaeso-24, sig-19, sig mega-7	NA	91 (6, 600)		B-8, H-5, BH-1	7 (3-11)/ 1 (0-11)			25.3 (6-50) mo	41 (82.0)	50	43 (16-163) min	8 (5-14)	5.5 (3-11)	NA	Full thickness	9	Esophagus lumen with a diameter of ≥ 6 cm and/or sigmoid in shape
Tang et al,[17] 2016	Single center retrospective	11	NA	NA	21 (18-36) mo	NA	NA	NA	NA	NA	23 (12.0-37.5) mo	11 (100.0)	11	56.8 (49-70) min	5.2 (5-6) cm	NA	NA	NA	NA	NA
Yoon HJ et al,[15] 2020	Multi-i-center retrospective (2 centers)	13	Sig-8, A Sig-15	NA	165.7 (228)	67.6 ± 27.5	B-5	7 (4-10)/ 0.5 (0-2)	17.5 ± 7.8/ 8.8 ± 8.2	NA		13 (100.0)	13	NA	NA	< 5 day	NA	NA	0	Achalasia was defined as sigmoid type when the angle was < 135° and advanced sigmoid when angle < 90°
Nabi et al,[16] 2021	Single center retrospective	32	Sig-22, A Sig-10	21/6/0/5	111.25 ± 41.75 (range 48-228) mo		B-13, H-3	6.81 ± 1.554/ 0.97 ± 0.93	23.60 ± 13.42/ 8.57 ± 5.58	34.45 ± 13.24/ 13.99 ± 5.25	34.03 ± 13.78 mo	27 (84.0), long term > 3 yr: 8 (72.7)	32	62.69 ± 32.71 min	9.78 ± 3.71	NA	NA	NA	2	Achalasia was defined as sigmoid type when the angle was < 135° and advanced sigmoid when angle < 90°

Table 1. Continued

Name and year	Type of study	Number of patients	Type of sigmoid	Type of AC-I/II/III/ unidentified	Duration of symptoms	Esophageal diameter	Previous treatment[a]	Pre/ Post-ES	Pre/ Post-4s-IRP	Pre/ Post-LESP	Duration of follow-up	Clinical success	Technical success	Procedure time	Myotomy length[b]	Length of hospital stay	Orientation of myotomy	Thickness of myotomy	AE,$	Definition of sigmoid/ advanced AC
Maruyama et al,[20] 2020	Single center retrospective	16	Sig-16 (A Sig-5)	4/3/1	NA		B-5	4.9 ± 2.1/ 0.4 ± 0.6	17.6 ± 9.2/ 7.9 ± 5.5	19.4 ± 10.2/ 9.2 ± 6.4	2 mo	16 (100.0)	16	SG-94.7 ± 31.4	11.7 ± 2.5	6.9 ± 3.4	NA	Selective circular	4	Achalasia was defined as sigmoid type when the angle was < 135° and advanced sigmoid when angle < 90°
Lv et al,[24] 2016	Single center retrospective	23	Type 1-19, Type 2-4	3/11/1	8 (2-25) yr	58.2 mm	B-6, D-1, BO-1, H-1, S-1	7 (4-11)/1			18 (12-42) mo	22 (95.6)	23	67.6 (45-120) min	10 cm	5 (3-10) day	Posterior	Full thickness	9	S1, the esophagus was significantly dilated, tortuous with single lumen on CT; S2, double lumen seen on CT
Hu et al,[18] 2015	Single center prospective	32	Type 1-29, Type 2-3	NA	13.4 yr (1 mo-50 yr)		B-14, BO-3, H-3, S-3	7.8 (4-12)/ 1.4 (0-5)		37.9 (21.9-70.3)/ 12.9 (7.7-22.5)	30.0 (24-44) mean range	30 (96.8)	32	63.7 (22-130)	E-8.0 (5-11), G-2.3 (2-5), T-10.3 (7-14)	3.9 (1-29)	Posterior	Full thickness	15	S1, the esophagus was significantly dilated, tortuous with single lumen on CT; S2, double lumen seen on CT

[a]B, balloon dilation; H, Hellers; BO, botox; S, self expanding metal stent; P, peroral endoscopic myotomy; BH, both dilatation and Hellers; D, drugs; BB, botox and dilation; CR, controlled radial expansion and dilatation by Savary Gillard dilator.
[b]E, esophagus; G, gastric; T, total.
AC, achalasia cardia; ES, Eckardt score; 4s-IRP, integrated relaxation pressure at 4 seconds; LESP, lower esophageal sphincter pressure; NA, not available; AE, adverse events; IQR, interquartile range; SG, Savary Gillard; LHM, laparoscopic Heller myotomy.
Data are expressed as n, n (%), median (range), mean ± SD, or median (IQR 25th, 75th).

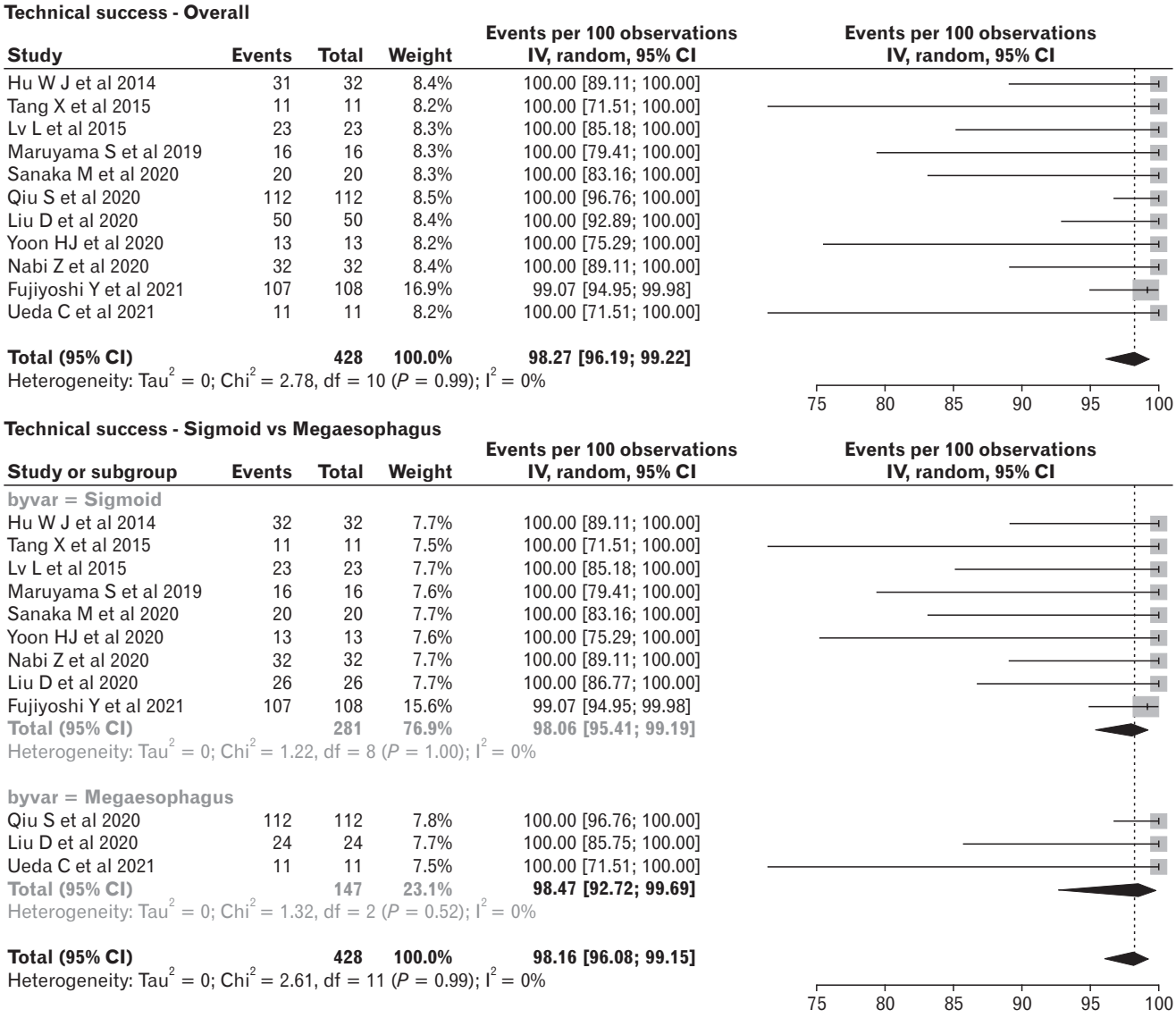

Figure 2. Technical success. The pooled prevalence of technical success for peroral endoscopic myotomy in advanced achalasia cardia (overall) with subgroup analysis and pooled prevalence for sigmoid and megaesophagus.

All the 11 studied reported on technical and clinical success of POEM for advanced achalasia cardia with sigmoid and/or megaesophagus. Eight studies reported on sigmoid esophagus, 2 studies on megaesophagus (Ueda et al[14] and Qiu et al[22] while 1 study by Liu et al[5] reported on both sigmoid and megaesophagus. The pooled prevalence for technical success and clinical success was 98.27% (95% CI, 96.19-99.22; I^2 = 0%) and 89.38% (95% CI, 84.49-92.86; I^2 = 26%) respectively (Fig. 2 and 3). On subgroup analysis the pooled prevalence for technical success and clinical success for sigmoid and megaesophagus was 98.06% (95% CI, 95.41-99.19; I^2 = 0%), 98.47% (95% CI, 92.72-99.69; I^2 = 0%) and 87.92% (95% CI, 80.68-92.70; I^2 = 37%), 88.36% (95% CI, 62.62-97.17; I^2 = 77%), respectively (Fig. 2 and 3). On further subgroup analysis, the pooled prevalence for clinical success for studies with follow-up < 1 year (4 studies) was 89.37% (95% CI, 82.82-93.61; I^2 = 0%) and for those with follow-up between 1-3 years (7 studies) was 88.66% (95% CI, 81.65-91.22; I^2 = 46%) respectively (Fig. 2 and 3). Only 1 study by Nabi et al[16] had a follow-up of > 3 years with a clinical success of 72.7% (8/11). Three studies mentioned modified technique of POEM for advanced achalasia cardia, viz, (1) Lv et al[24]- described creation of a wider tunnel reaching up to half the esophageal circumference and start-

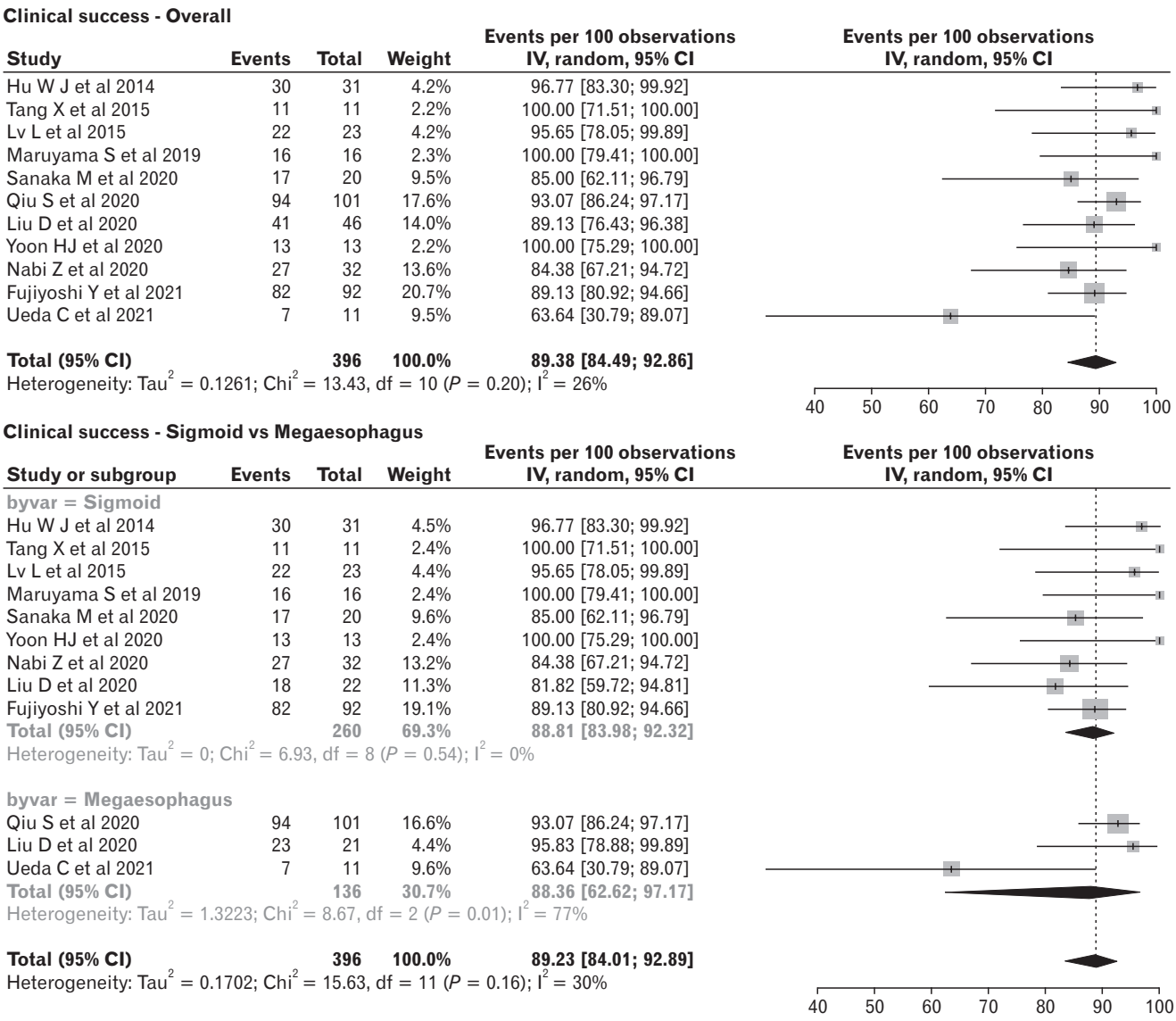

Figure 3. Clinical success. The pooled prevalence of clinical success for peroral endoscopic myotomy in advanced achalasia cardia (overall) with subgroup analysis and prevalence for sigmoid and megaesophagus and further subgroup analysis for follow-up < 1 year and between 1-3 years.

ing myotomy 0-1 cm from the incision to shorten the tunnel; (2) Qiu et al[22] described a reverse T incision for entry, a "short tunnel POEM"[25] with a tunnel of 6-8 cm and a myotomy of 3-6 cm and simultaneous submucosal and muscle dissection in case of submucosal fibrosis;[26] (3) Liu et al[27] described modified POEM with tunnelling and myotomy into a single step.

For assessing the efficacy of the procedure, 10 studies (excluding the study by Tang et al[17]) had pre- and post- values of ES for comparison. Seven studies had pre- and post-values of 4s-IRP and LESP for comparison. The SMD for ES, 4s-IRP, and LESP, when compared pre- and post-POEM were 4.81 ([95% CI, 3.09-6.62; I^2 = 97%] and for megaesophagus 5.8 [95% CI, −0.65-12.24; I^2 = 99%]), for 4s-IRP of 1.93 (95% CI, 1.09-2.76; I^2 = 83%) and for lower esophageal sphincter pressure of 2.06 (95% CI, 1.13-2.99; I^2 = 88%), and all were significant (Fig. 4). For the clinical success parameter which is our main outcome parameter, there is no heterogeneity seen as assessed by I^2 value of < 50%. But for the continuous outcome (ES, IRP, and LESP) compared pre- and post-, heterogeneity (I^2 value of > 50%) is seen. We conducted sensitivity analyses on these analyses, to detect the source of heterogeneity. For the ES, the Qiu et al[22] 2021 study was the study with the maximum contribution to heterogeneity, and excluding the

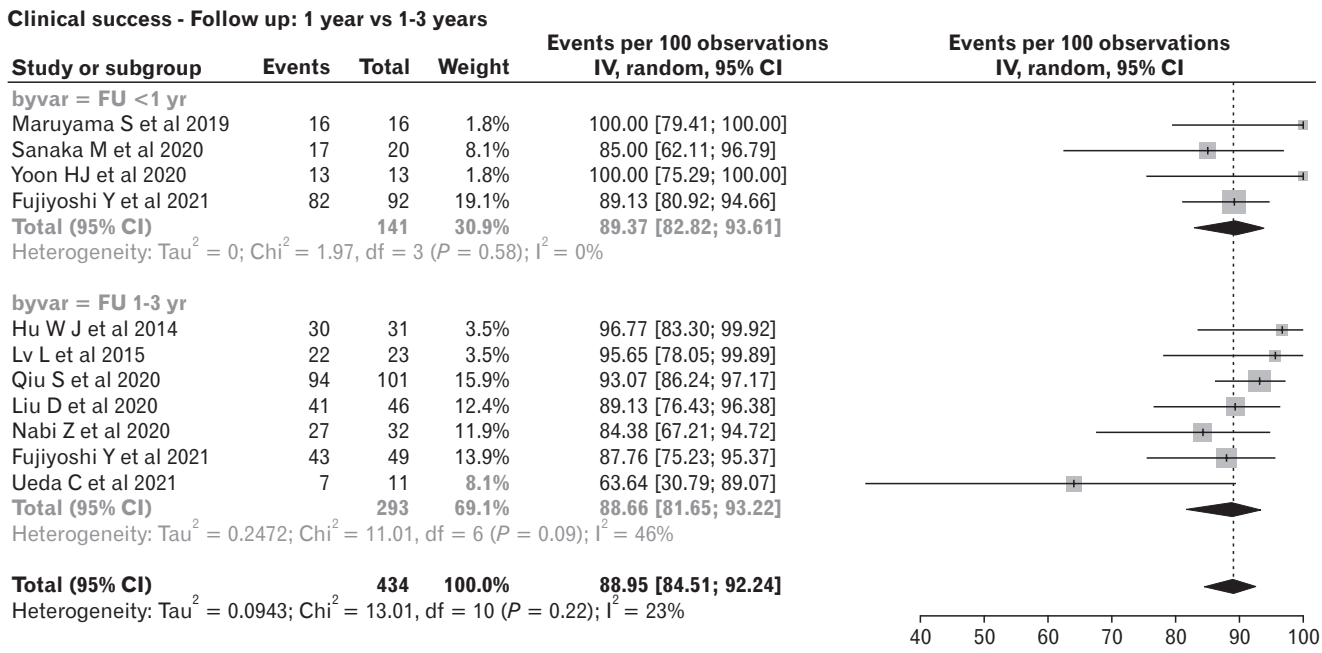

Figure 3. Continued.

study changed the pooled effect size to 3.54 (2.62-4.46) with I^2 = 90%. (Supplementary Fig. 1). For the 4s-IRP, the Lv et al[24] 2016 was the study with maximum contribution to heterogeneity, and excluding the study changed the heterogeneity to 7% with pooled effect size of 1.22 (0.89-1.54) (Supplementary Fig. 2). For the LESP, Lv et al[24] 2016 was the study with maximum contribution to heterogeneity, and excluding the study changed the heterogeneity to 80% with pooled effect size of 1.53 (0.83-2.24) (Supplementary Fig. 3).

Out of the 11 studies, 2 studies mentioned adverse events as per the ASGE lexicon (Qiu et al[22] and Lv et al[24]) while 2 studies used other criteria (Ueda et al[14] [IPOEMS] and Maruyama et al[20] [Clinical practice guidelines for POEM and JCOG PC] criteria). Five studies mentioned the adverse events as observations without using any criteria (Nabi et al,[16] Hu et al,[18] Fujiyoshi et al,[19] Sanaka et al,[21] and Lv et al[24]). Two studies (Yoon et al[15] and Tang et al[17]) did not mention adverse events in their results. We conducted analysis for adverse events, however, there was marked heterogeneity among the studies, hence, it was decided to exclude adverse event rate from analysis and to only mention the details of adverse events from individual studies in Tables 1 and 2 (Table 1 provides the adverse event rate of individual studies while Table 2 discusses in details the various adverse events that were encountered in each study). The adverse event rate was found between 0.0-46.8%. Of particular mention are the 2 studies by Hu et al[18] and Lv et al[24] which reported very high rates of adverse events (Table 1). However, they included expected inconsequential intraoperative events like subcutaneous emphysema and capnoperitoneum/capnothorax as adverse event which lead to false impression of high adverse event rate.

Quality Assessment (See Table 3)

Nine of the 11 studies fulfilled all the criteria of the Joanna Briggs critical appraisal tool for case series and cohort studies.[5,14-16,18,20-22,24] Two of the abstracts that were included were unclear regarding the statistical methods used for analysis[17,19] while 1 abstract was unclear regarding demographics of the participants and did not report the outcomes and follow-up results clearly.[5] The funnel plot for publication bias assessed for prevalence for clinical success showed no bias. Also, on quantitative analysis, Egger's test performed on the clinical success data does not indicate the presence of funnel plot asymmetry (intercept 0.835 [95% CI, −0.69 to −2.36; P = 0.311]) (Fig. 5).

Discussion

The present metanalysis shows that POEM is an effective modality of treatment for both groups of sigmoid and megaesophagus in advanced achalasia cardia with a pooled technical success of 98.27% and clinical success of 89.38%. The clinical success was

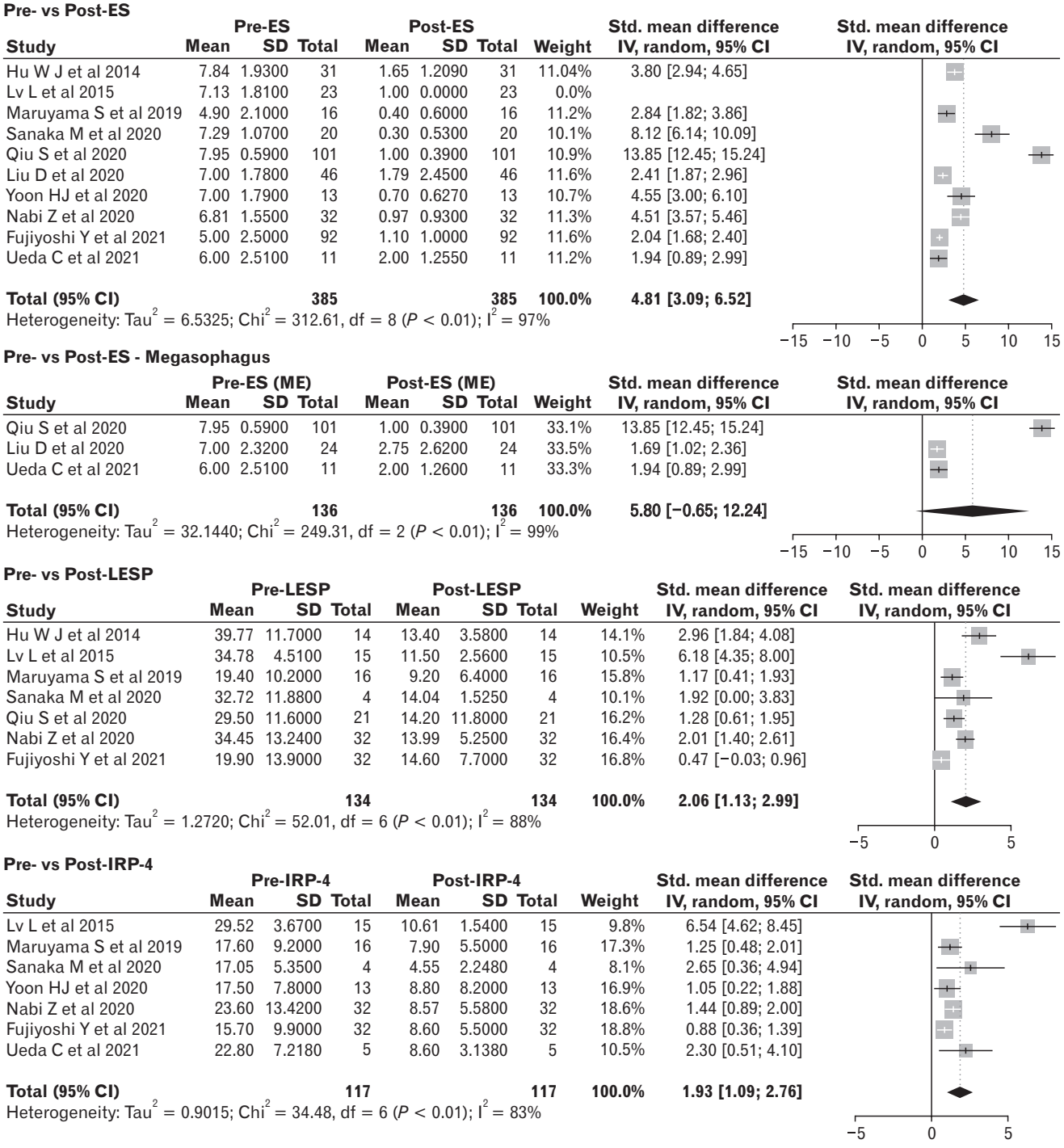

Figure 4. Standardized mean difference of pre and post-peroral endoscopic myotomy-Eckardt score (ES), 4-second integrated relaxation pressure (4s-IRP) and lower esophageal sphincter pressure (LESP) are shown.

comparable between both the sigmoid (87.92%) and the megaesophagus (88.36%) groups with sustained rate until 3 years of follow-up (88.66%). The post-POEM scores showed a significant reduction with SMD for ES of 4.81, for 4s-IRP of 1.93, and for LESP of 2.06 respectively. Thus, not only subjective scores (ES) but also objective scores (4s-IRP and LESP) have shown significant improvement post-POEM in advanced achalasia cardia with sigmoid and/or megaesophagus.

Table 2. Details of Adverse Events From Each Study Along With Gastroesophageal Reflux Disease Rate[a]

Study and year	Adverse events reported	GERD rate
Fujiyoshi et al,[19] 2020	Mucosal perforation-3, mucosal hematoma/bleeding-3	GERD 2 mo post-POEM--symptoms: 10/88 (11.3%) RE[b]: N/A/B/C/D-37 (42.5%), 29 (33.3%), 13 (14.9%), 7 (8.0%), 1 (1.1%) PPI usage rate-16.1% (13/81)
Ueda et al,[14] 2021	Failed mucosal entry closure-2 (needing clip and loop and fibrin glue) (18.2%)	GERD symptoms-1 (9.0%)
Sanaka et al,[21] 2021	None	GERD symptoms-1 (5.5%)
Qiu et al,[22] 2021	Mucosal injury-4 (3.6%), delayed haemorrhage-2 (1.8%), gas-related complications-4 (3.6%), pneumoperitoneum only, n = 1, pneumomediastinum only, n = 3, overall-10 (8.9%)	GERD symptoms-27 (26.7%) RE: LA-B-5 (83.3%), LA-C-1 (16.6%)
Liu et al,[5] 2021	Mucosal injury-2 (4.0%), bleeding -3 (6.0%), subcutaneous emphysema-3 (6.0%), perforation-1 (2.0%), overall-9 (18.0%)	GERD symptoms-13/46 (28.2%) RE: LA-A-7 (87.5%), LA-C-1 (12.5%)
Tang et al,[17] 2016	Not available	GERD symptoms-2/11 (18.1%)
Yoon et al,[15] 2020	None	Not available
Nabi et al,[16] 2021	Delayed mucosal barrier failure-1, symptomatic pleural effusion needing drainage-1	Abnormal acid exposure on 24 hour pH study-3 RE: LA-A-7/18 (38.8%), LA-B- 11/18 (6.1%)
Maruyama et al,[20] 2020	Mucosal injury-1 (25.0%), incomplete clipping-2 (50.0%), pneumoperitoneum-1 (25.0%) overall-4 (25.0%)	RE: LA-N/A/B-9 (56.2%), 5 (31.2%), 2 (12.5%)
Lv et al,[24] 2016	SCE-7 (30.4%), MSCE-1 (4.3%), Mucosal injury 1 (4.3%), Overall-9 (39.1%)	RE: LA-A-3/23 (13.0%)
Hu et al,[18] 2015	Mucosal injury-12 (37.5%), pneumoperitoneum needing needle aspiration-2 (5.8%), pneumothorax needing ICTD under water seal-1 (3.1%)	GERD symptoms-7/31 (22.5%) RE: LA-A-5 (71.4%), LA-C- 1 (14.2%)

[a]Major adverse events occurred in 3 studies.
Ueda et al[14]: failed mucosal entry closure-2 (needing clip and loop and fibrin glue) (18.2%).
Liu et al[5]: 2 patients needed Sengstaken- Blakemore tube for hemostasis-2/50 (4.0%).
Nabi et al[16]: delayed mucosal barrier failure-1, symptomatic pleural effusion needing drainage-1 (2/32 [6.3%]).
[b]N/A/B/C/D- Los Angeles (LA) grading of reflux esophagitis.
GERD, gastroesophageal reflux disease; POEM, peroral endoscopic myotomy; RE, reflux esophagitis; PPI, proton pump inhibitor; SCE, subcutaneous emphysema; MSCE, mediastinal + subcutaneous emphysema; ICTD, intercostal drain.

During the initial years of introduction of POEM, it was believed that the anatomical distortion because of the sigmoid shape in advanced achalasia cardia would render it difficult to perform POEM in this subset of patients, however, as more and more experience was gained, data have now emerged where POEM has shown good efficacy even in this subset of patients.

This metanalysis shows technical and clinical success of POEM for advanced achalasia cardia with sigmoid and/or megaesophagus of 98% and 89%, respectively, which is similar to the efficacy of POEM seen in routine cases of achalasia cardia.[1,28] There was marked heterogeneity in the reporting rate of adverse events among the included studies (0-47%) due to the usage of various definitions and inclusion of inconsequential intraoperative events as adverse events. Hence, we decided not to include adverse events as our outcome measure and to only provide details of the same in tabular form (Tables 1 and 2). In routine cases of achalasia cardia the adverse event rate for mild events is seen in up to 5%, moderate up to 8% and severe up to 3%.[28] The majority of the included studies reported adverse event rate < 10% with 2 studies reporting 0% rate (Table 1). Also, most studies reported mild events except for 3 studies which reported major events requiring intervention (Liu et al,[5] Ueda et al,[14] and Nabi et al[16]). Thus, from this data POEM appears to be a safe procedure in this technically difficult subset as well.

As advanced achalasia cardia with sigmoid and/or megaesophagus is considered an end stage burnt out disease one would expect the morphological alterations that take place to be permanent and non-modifiable even with treatment. However, POEM has shown promising results even in this parameter with morphological restoration by reducing the diameter of the esophageal body and increas-

Table 3. Quality Assessment of Included Studies by Joanna Briggs Critical Appraisal Tool

A. Joanna Briggs Index for Critical Appraisal of Case Series

Criteria	Hu et al,[18] 2015	Tang X et al,[20] 2015	Lv et al,[24] 2016	Qiu et al,[22] 2021	Liu et al,[5] 2021	Yoon et al,[15] 2020	Nabi et al,[16] 2021	Fujiyoshi et al,[19] 2020
Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow-up results of cases clearly reported?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was statistical analysis appropriate?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear

B. Joanna Briggs Index for Critical Appraisal of Cohort Studies

Criteria	Maruyama et al[20]	Sanaka et al[21]	Ueda et al[14]
Were the 2 groups similar and recruited from the same population?	Yes	Yes	Yes
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	Yes	Yes	Yes
Were strategies to address incomplete follow-up utilized?	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes

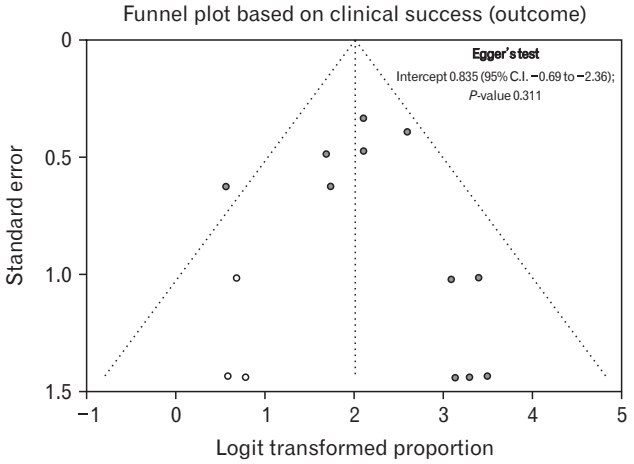

Figure 5. Funnel plot showing no publication bias with quantitative analysis by Egger's test showing no asymmetry in the plot.

ing the diameter of esophagogastric junction opening, and also widening the angulations from acute to more obtuse angles as shown in 3 of the included studies.[14,15,20] However, the study by Nabi et al[16] involving 32 patients has shown that there is deterioration of both symptom score (ES) and free flow of barium at > 1 year of follow-up, suggesting the need of close watch in this subset of patients.

The strengths of this metanalysis are good number of studies (n = 11) and sample (n = 428) given the uncommon presentation of this subset. Also, the main outcomes, viz, clinical and technical success did not show any heterogeneity. We also conducted subgroup analysis for sigmoid and megaesophagus along with the analysis of the clinical success with follow-up < 1 year and between 1-3 years, thereby reducing the heterogeneity. We also performed sensitivity analysis for data showing marked heterogeneity. The limitations of the metanalysis are retrospective study design of majority of the included studies with the associated confounding factors. The parameters (both subjective and objective) to assess the clinical efficacy post-POEM showed significant heterogeneity. The possible reasons could be variation in the study design, outcome parameter measurement as well as sample size between the different included studies. Apart from these, the other important limitations include variation in definition of sigmoid achalasia in different studies, variability in the reporting of adverse events, and variable follow-up periods as low as 2 months in some studies.

Conclusion

Based on the results of this metanalysis, POEM appears to be an effective modality of treatment for advanced achalasia cardia with sigmoid and megaesophagus. We need appropriately powered randomized trials and long-term data to confirm the above findings.

Supplementary Materials

Note: To access the supplementary table and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm21122.

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