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Anti-reflux mucosectomy for refractory gastroesophageal reflux disease: a systematic review and meta-analysis *

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ABSTRACT

Background and study aims Anti-reflux mucosectomy (ARMS) is an emerging endoscopic treatment for refractory gastroesophageal reflux disease (GERD). We conducted a systematic review and meta-analysis to evaluate the safety and efficacy ARMS in refractory GERD.

Methods A comprehensive search of multiple databases (through March 2020) was performed to identify studies that reported outcomes of ARMS for refractory GERD. Outcomes assessed included technical success, clinical response, and adverse events (AEs). Clinical response was defined as discontinuation (complete) or reduction (partial) of proton pump inhibitors post-ARMS at follow up.

Results A total of 307 patients (mean age 46.9 [8.1] years, 41.5 % females) were included from 10 studies. The technical success and clinical response rates were 97.7 % (95 % confidence interval [CI], 94.6–99.0) and 80.1 % (95 % CI, 61.6–91.0), respectively. The pooled rate of complete and partial clinical response was 65.3 % (95 % CI, 51.4–77.0) and 21.5 % (95 % CI, 14.2–31.2), respectively. The rate of AEs was 17.2 % (95 % CI, 13.1–22.2) with most common AE being dysphagia/esophageal stricture followed by bleeding with rates of 11.4 % and 5.0 %, respectively. GERD health-related quality of life (GERD-HRQL) (mean difference [MD] = 14.9, $P<0.001$), GERD questionnaire (GERD-Q) (MD = 4.85, $P<0.001$) and mean acid exposure time (MD = 2.39, $P=0.01$) decreased significantly post-ARMS as compared to pre-procedure. There was no difference in terms of clinical response and AEs between ARMS and ARMS with banding on subgroup analysis.

Conclusions ARMS is a safe and effective procedure for treatment of refractory GERD with high rates of clinical response, acceptable safety profile and significant improvement in GERD-related quality of life. Prospective studies are needed to validate our findings.

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** These authors contributed equally.

Introduction

Gastroesophageal reflux disease (GERD) is a consequence of the failure of the normal anti-reflux barriers to protect against abnormal amounts of retrograde reflux of material from the stomach to the esophagus [1]. Longstanding GERD can predispose to esophagitis, esophageal ulcers, peptic esophageal strictures, Barrett's esophagus, and adenocarcinoma of the esophagus. Proton pump inhibitors (PPIs) are first-line treatment for GERD. They are antacid medications that inhibit meal-stimulated and nocturnal acid secretion [2]. About 30 % to 40 % of patients with GERD are refractory to treatment with PPIs [3]. Increased frequency or volume of reflux, ineffective PPI-induced control of gastric secretion, esophageal hypersensitivity, bile content of gastric juice, and other co-existing conditions such as obesity, hiatal hernia, and *Helicobacter pylori* infection are risk factors for refractory GERD [3].

Anti-reflux surgery such as laparoscopic fundoplication is beneficial in patients with refractory GERD but 25 % of patients have postoperative dysphagia, gas bloat syndrome, diarrhea, and increased flatus [4]. Moreover, 25 % to 62 % of patients require acid-suppressive medications 5 to 15 years after their anti-reflux surgery [5]. As a result, several novel surgical techniques that do not alter the anatomy of the cardia have been developed, but they, too, are associated with procedural limitations [6, 7]. A series of endoscopic treatments for treatment of GERD, such as transoral incisionless fundoplication (TIF) and magnetic sphincter augmentation (MSA), have also failed to show long-term efficacy [8]. As a result, the American Gastroenterological Association Institute, in their technical review on the use of endoscopic therapy for the treatment of GERD, reported that there were no definite indications for endoscopic therapy for GERD [9].

Anti-reflux mucosectomy (ARMS) is a new endoscopic technique for treatment of refractory GERD first reported by Inoue et al [10]. The aim of the procedure is to achieve fundoplication by submucosal fibrosis after mucosectomy at the esophagogastric junction (EGJ) and it has the advantage of an endoscopic approach. Since the introduction of ARMS, several prospective and retrospective studies have been performed to assess outcomes with it. We performed a systematic review and meta-analysis to assess the efficacy and safety of ARMS in treatment of refractory GERD.

Methods

Search strategy

We conducted a comprehensive search of several databases from inception to March 2021. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process and other non-indexed citations, Ovid Embase, Ovid Cochrane Central Register of Controlled trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. An experienced medical librarian using inputs from the study authors helped with the literature search. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The full search strategy is available in **Appendix 1**. The MOOSE and PRISMA checklist were followed and are provided in **Appendix 2** and **Appendix 3** [11, 12].

Study selection

In this meta-analysis, we included studies that evaluated outcomes of ARMS in patients with refractory GERD. Studies were included irrespective of the study sample size, inpatient/outpatient setting, and geography as long as they provided data needed for the analysis.

Studies done in pediatric populations (age < 18 years), and studies not published in English were our only exclusion criteria. In case of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted in a standardized form by at least two authors (RG, AM), and two authors (RG, AM) did the quality scoring independently. Primary study authors were contacted via email as needed for further information and/or clarification on data.

The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [13]. This quality score consisted of eight questions, the details of which are provided in **Supplementary Table 1**.

Outcomes assessed

1. Pooled rate of technical success.
2. Pooled rate of clinical success based on discontinuation or reduction of PPI after ARMS. It was further categorized into complete if patients were able to discontinue PPIs post-ARMS and partial if ARMS led to reduction in PPI dose.
3. Pooled rate of adverse events (AEs) after ARMS. It was further classified into dysphagia and bleeding after ARMS.
4. Symptomatic improvement was further measured by validated pre-procedure and post-procedure questionnaire to assess typical and atypical GERD symptoms: GERD-Health-Related Quality of Life (HRQL) and Gastroesophageal Reflux Disease Questionnaire (GERD-Q).
5. Pre-and Post-ARMS DeMeester score and mean acid exposure time (AET) was also measured based on 24-hour pH study.

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model [14]. 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]. Mean difference between pre-procedure and post-procedure measures were calculated by inverse variance method. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity and the I^2 statistics.[16] In this, values of < 30 %, 30 % to 60 %, 61 % to 75 %, and > 75 % were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [17]. Publication bias was ascertained, qualitatively, by

visual inspection of funnel plot and quantitatively, by the Egger test [18]. $P \geq 0.05$ was used a priori to define significance of the difference between the groups compared as provided the statistical software. We conducted further subgroup analysis based on use of banding with ARMS.

The analysis was performed using Rstudio and Revman software.

Results

Search results and population characteristics

From an initial 909 studies, 560 records were screened, and 36 full-length articles were reviewed. Ten studies were included in the final analysis that reported outcomes of ARMS [19–28]. The schematic diagram of study selection is shown in ▶ **Fig. 1**.

A total of 307 patients with mean age 46.9 years (8.1) (range 37–56.8 years) were included in our study. Gender was reported in seven studies and among them, 41.5 % of patients were female. In six studies, ARMS-endoscopic mucosal resection (EMR) was performed and four studies, ARMS with banding was performed. All patients were on maximal PPI therapy before ARMS. The mean procedure duration was 40.3 minutes (8.5) (range 31.2–54.7 minutes) reported in six studies. Patient characteristics and data on assessed outcomes are shown in ▶ **Table 1**.

Characteristics and quality of included studies

Eight studies were prospective and two were retrospective in nature. Of the 10 observational studies, four studies were high quality, five were medium and one was low quality. Quality assessment is shown in **Supplementary Table 1**.

Meta-analysis outcomes

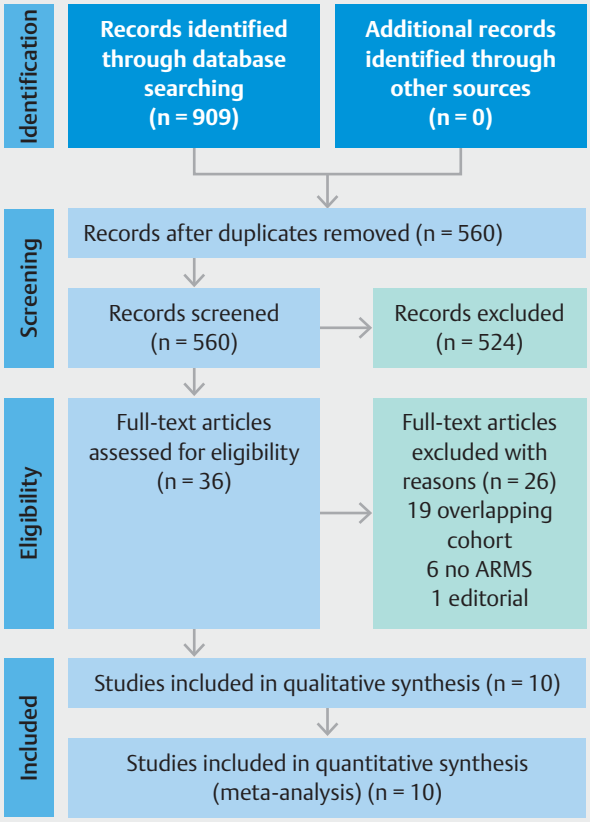
Technical and clinical success

The pooled rate of immediate technical success was 97.7 % (95 % confidence interval [CI] 94.6–99.0, $I^2 = 0$ %) (▶ **Fig. 2a**). ARMS was performed most using EMR in six studies and four studies utilized banding device with ARMS. Sumi et al also performed seven cases of ARMS with endoscopic mucosal dissection (ESD) [26].

Follow-up time ranged from 1 to 12 months. The pooled rate of clinical success was 80.1 % (95 % CI, 61.6–91.0, $I^2 = 84.9$ %) (▶ **Fig. 2b**). Rates of complete and partial clinical success were 65.3 % (95 % CI, 51.4–77.0, $I^2 = 73.1$) and 21.5 % (95 % CI, 14.2–31.2, $I^2 = 25.5$), respectively (▶ **Fig. 2c** and ▶ **Fig. 2 d**).

Adverse events

The pooled rate of overall AEs was 17.2 % (95 % CI, 13.1–22.2, $I^2 = 1.9$ %) (▶ **Fig. 3a**). There were a total of 49 AEs. The most common AE was dysphagia from esophageal stricture (n = 32) followed by bleeding (n = 8), three cases of perforation, muscle injury, and aspiration pneumonia each. Pooled rates of dysphagia and bleeding were 11.4 % (95 CI, 8.2–15.7, $I^2 = 0$) and 5 % (95 % CI, 1.9–12.3, $I^2 = 51.3$ %), respectively (▶ **Fig. 3b** and ▶ **Fig. 3c**).



▶ **Fig. 1** Study selection flowchart.

Symptomatic improvement

Symptom improvement was measured by two validated GERD-associated scoring systems. Overall, mean GERD-HRQL (health-related quality of life) scores were reported in four studies, and they significantly improved after ARMS as compared to pre-procedure scores (mean difference [MD] = 14.9, [95 % CI, 9.30–20.6], $I^2 = 85$ %, $P < 0.001$). GERD-Q was reported in five studies and significantly improved after ARMS with MD of 4.85 [95 % CI, 2.7–7.03, $I^2 = 95$ %, $P < 0.001$]. These results are shown in ▶ **Fig. 4a** and ▶ **Fig. 4b**.

pH monitoring

Objective measures of GERD improvement were determined by esophageal pH monitoring. Three studies reported results of pre-ARMS and post-ARMS pH study. Mean AET (MD = 2.39, 95 % CI, 0.47–4.3, $I^2 = 74$ %, $P = 0.01$) decreased significantly post-ARMS as compared to pre-procedure (▶ **Fig. 4c**). Post-procedure DeMeester score was also reported in three studies. The mean difference between post- and pre-ARMS DeMeester score was 36.02 (95 % CI, −8.83 to 80.87, $I^2 = 99$, $P = 0.12$) (▶ **Fig. 4 d**).

Subgroup analysis

We performed subgroup analysis based on ARMS with banding (ARMS-B) and without banding. Among the 10 studies, six studies did not use banding with ARMS and four studies used ARMS-B. Compared to ARMS-B, ARMS did not have any statistical sig-

▶ **Table 1** Study and population characteristics.

Author, year	Technique	Age, mean years (SD)	Females	No. patients	GERD-HRQL score		GERD-Q score mean (SD)		DeMeester score mean (SD)		Mean esophageal acid exposure time (%) (SD)		Procedure time, mean, minutes (SD)	Technical success	Follow-up mean time (SD)	Clinical success	Partial clinical success	Complete clinical success	Adverse events	Dysphagia	Bleeding
					Pre-procedure	Post-procedure	Pre-procedure	Post-procedure	Pre-procedure	Post-procedure	Pre-procedure	Post-procedure									
Bapaye et al, 2017	ARMS	40.8 (19.2)	4	15	40.4	7.6	NR	NR	85.8	5.9	NR	NR		15	1 mo	15	4	11	3	1	0
Debourdeau et al, 2020	ARMS-B	44 (7.5)	5	6	30.6 (7.7)	6.8 (3.7)	13.3 (1.1)	6.2 (4.0)	NR	NR	NR	NR	<40 min	6	3 mo	3	2	1	2	1	1
Wong et al, 2020	ARMS-B	55 (17)	22	33	16.0 (12.0) (N = 24)	6.0 (7.1) (N = 15)	NR	NR	19.6 (10.1)	NR	NR	NR	36 (13)	33	6 mo	30	0	30	5	3	1
Kessler et al, 2013	ARMS-B	NR	NR	10	26.6 (0.4)	9 (1.6)	NR	NR	NR	NR	8.35 (0.04) (n = 9)	5.8 (1.19)	NR	10	6 mo	10	0	10	3	3	0
Prasad et al, 2019	ARMS	41–60	NR	11	NR	NR	NR	NR	NR	NR	NR	NR	NR	11	6 mo	8		8	0	0	0
Monino et al, 2020	ARMS-B	56.87 (14.47)	10	21	25.6 (8.8) (N = 18)	16.8 (6.4)	12.5 (1.5) (n = 18)	9 (2) (n = 18)	NR	NR	> 6 %	NR	35 (11)	21	10 (5) mo	16	4	12	4	3	1
Ortega et al, 2019	ARMS	41	NR	7	NR	NR	19	3	37.1	NR	NR	NR	45 min	7	3 mo	4		4	3	0	3

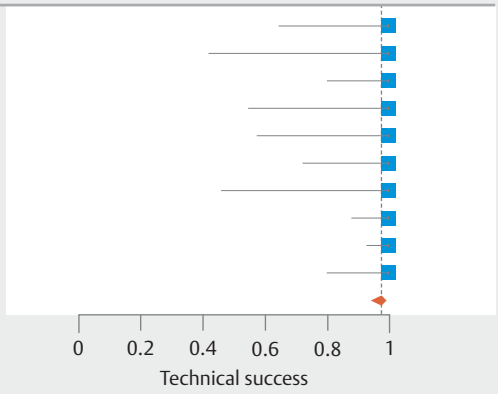
▶ **Table 1** (Continuation)

Author, year	Technique	Age, mean years (SD)	Females	No. patients	GERD-HRQL score		GERD-Q score mean (SD)		DeMeester score mean (SD)		Mean esophageal acid exposure time (%) (SD)		Procedure time, mean, minutes (SD)	Technical success	Follow-up mean time (SD)	Clinical success	Partial clinical success	Complete clinical success	Adverse events	Dysphagia	Bleeding
Patil et al, 2020	ARMS	37 (9.9)	18	62	NR	NR	10.6 (1.9) (n = 44)	3.4 (1.5) (n = 44)	76.8 (18.3) (n = 45)	14.3 (6.1) (n = 45)	NR	NR	NR	62	12 mo	55	12	43	10	5	0
Sumi et al, 2020	ARMS	54.0 (15.7)	46	109	NR	NR	9.4 (2.7) (n = 88)	6.6 (2.5)	64.4 (75.7) (n = 27)	24.9 (36.0) (n = 27)	20.8 (24.3) (n = 27)	6.9 (10.4)	54.7 (27.0).	109	2–6 mo	42		42	17	14	2
Yoo et al, 2020	ARMS	51.3 (16.3)	11	33	NR	NR	11.1 (3.1) (n = 33)	6.8 (3.1)	14.3 (10.9)	7.7 (9.4)	3.1 (3.1)	1.8 (2.4)	33.5 (12.7)	33	6 mo	31	10	21	2	2	0

ARMS, anti-reflux mucosectomy; GERD, gastroesophageal reflux disease; GERD-HRQL, GERD health-related quality of life; GERD-Q, GERD questionnaire; NR, not reported; SD, standard deviation.

Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	15	15	1.000	[0.650; 0.998]
Debourdeau et al. 2020	6	6	1.000	[0.423; 0.996]
Wong et al. 2020	33	33	1.000	[0.804; 0.999]
Kessler et al. 2013	10	10	1.000	[0.552; 0.997]
Prasad et al. 2019	11	11	1.000	[0.575; 0.997]
Monino et al. 2020	21	21	1.000	[0.723; 0.999]
Ortega et al. 2019	7	7	1.000	[0.461; 0.996]
Patil et al. 2020	62	62	1.000	[0.885; 1.000]
Sumi et al. 2020	109	109	1.000	[0.932; 1.000]
Yoo et al. 2020	33	33	1.000	[0.804; 0.999]
Random effects model			**0.997**	**[0.946; 0.990]**

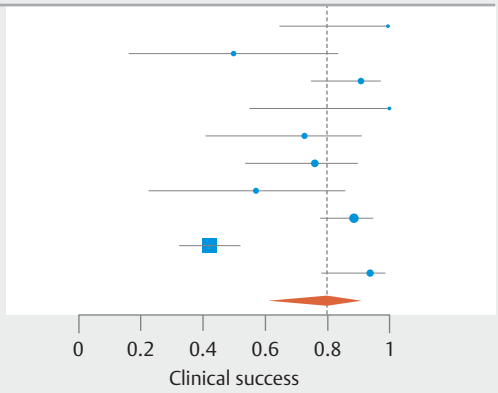
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.5221$, $\chi^2_9 = 33.46$ ($P < 0.01$)



a

Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	15	15	1.000	[0.650; 0.998]
Debourdeau et al. 2020	3	6	0.500	[0.168; 0.832]
Wong et al. 2020	30	33	0.909	[0.753; 0.970]
Kessler et al. 2013	10	10	1.000	[0.552; 0.997]
Prasad et al. 2019	8	11	0.727	[0.414; 0.910]
Monino et al. 2020	16	21	0.762	[0.540; 0.897]
Ortega et al. 2019	4	7	0.571	[0.230; 0.856]
Patil et al. 2020	55	62	0.887	[0.782; 0.945]
Sumi et al. 2020	42	100	0.420	[0.327; 0.519]
Yoo et al. 2020	31	33	0.939	[0.788; 0.985]
Random effects model			**0.801**	**[0.616; 0.910]**

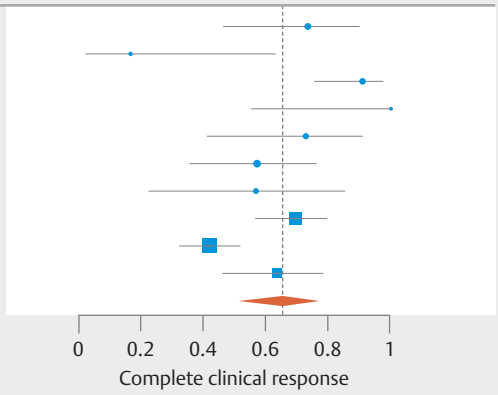
Heterogeneity: $I^2 = 85\%$, $\tau^2 = 1.6491$, $\chi^2_9 = 59.49$ ($P < 0.01$)



b

Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	11	15	0.733	[0.467; 0.896]
Debourdeau et al. 2020	1	6	0.167	[0.023; 0.631]
Wong et al. 2020	30	33	0.909	[0.753; 0.970]
Kessler et al. 2013	10	10	1.000	[0.552; 0.997]
Prasad et al. 2019	8	11	0.727	[0.414; 0.910]
Monino et al. 2020	12	21	0.571	[0.360; 0.760]
Ortega et al. 2019	4	7	0.571	[0.230; 0.856]
Patil et al. 2020	43	62	0.694	[0.569; 0.795]
Sumi et al. 2020	42	100	0.420	[0.327; 0.519]
Yoo et al. 2020	21	33	0.636	[0.463; 0.781]
Random effects model			**0.653**	**[0.514; 0.770]**

Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.5221$, $\chi^2_9 = 33.46$ ($P < 0.01$)



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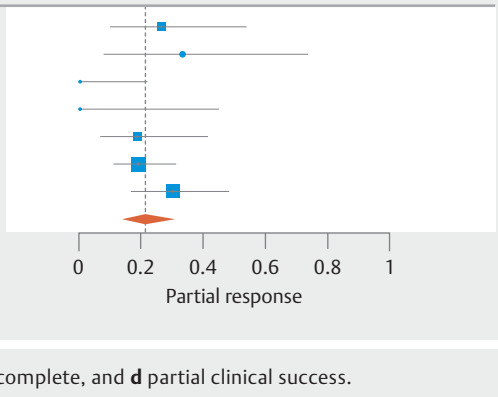
Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	4	15	0.267	[0.104; 0.533]
Debourdeau et al. 2020	2	6	0.333	[0.084; 0.732]
Wong et al. 2020	0	33	0.000	[0.001; 0.196]
Kessler et al. 2013	0	10	0.000	[0.003; 0.448]
Monino et al. 2020	4	21	0.190	[0.073; 0.412]
Patil et al. 2020	12	62	0.194	[0.113; 0.311]
Yoo et al. 2020	10	33	0.303	[0.171; 0.477]
Random effects model			**0.215**	**[0.142; 0.312]**

Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.1105$, $\chi^2_6 = 8.06$ ($P = 0.23$)

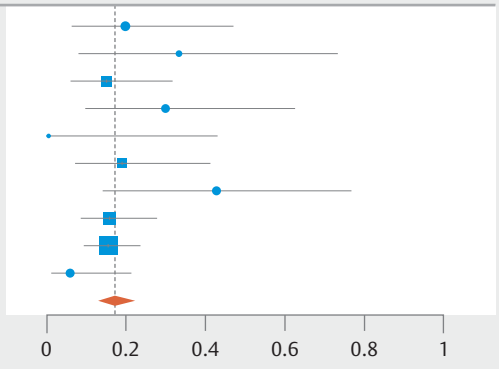


d

▶ **Fig. 2** Forest plots showing **a** pooled rate of technical success, **b** clinical success, **c** complete, and **d** partial clinical success.

Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	3	15	0.200	[0.066; 0.470]
Debourdeau et al. 2020	2	6	0.333	[0.084; 0.732]
Wong et al. 2020	5	33	0.152	[0.065; 0.316]
Kessler et al. 2013	3	10	0.300	[0.100; 0.624]
Prasad et al. 2019	0	11	0.000	[0.003; 0.425]
Monino et al. 2020	4	21	0.190	[0.073; 0.412]
Ortega et al. 2019	3	7	0.429	[0.144; 0.770]
Patil et al. 2020	10	62	0.161	[0.089; 0.275]
Sumi et al. 2020	17	109	0.156	[0.099; 0.237]
Yoo et al. 2020	2	33	0.061	[0.015; 0.212]
Random effects model			**0.172**	**[0.131; 0.222]**

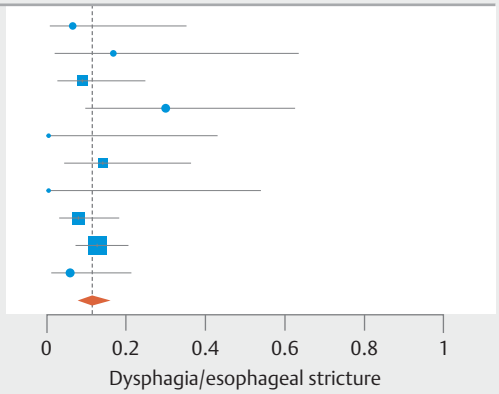
Heterogeneity: $I^2 = 1\%$, $\tau^2 = 0.0054$, $\chi^2_9 = 9.17$ ($P < 0.42$)



a

Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	1	15	0.067	[0.009; 0.352]
Debourdeau et al. 2020	1	6	0.167	[0.023; 0.631]
Wong et al. 2020	3	33	0.091	[0.030; 0.247]
Kessler et al. 2013	3	10	0.300	[0.100; 0.624]
Prasad et al. 2019	0	11	0.000	[0.003; 0.425]
Monino et al. 2020	3	21	0.143	[0.047; 0.361]
Ortega et al. 2019	0	7	0.000	[0.004; 0.539]
Patil et al. 2020	5	62	0.081	[0.034; 0.180]
Sumi et al. 2020	14	109	0.128	[0.078; 0.205]
Yoo et al. 2020	2	33	0.061	[0.015; 0.212]
Random effects model			**0.114**	**[0.082; 0.157]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_9 = 6.43$ ($P = 0.70$)



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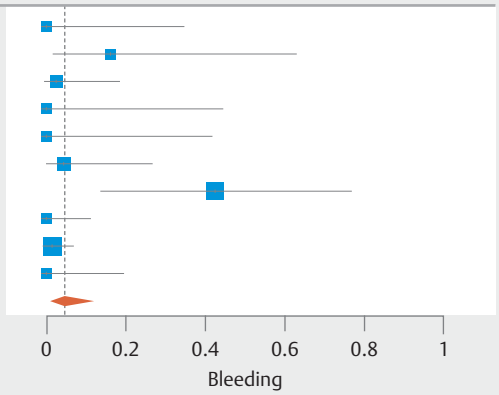
Study	Cases	Total	Proportion	95% CI
Bapaye et al. 2017	0	15	0.000	[0.002; 0.350]
Debourdeau et al. 2020	1	6	0.167	[0.023; 0.631]
Wong et al. 2020	1	33	0.030	[0.004; 0.186]
Kessler et al. 2013	0	10	0.000	[0.003; 0.448]
Prasad et al. 2019	0	11	0.000	[0.003; 0.425]
Monino et al. 2020	1	21	0.048	[0.007; 0.271]
Ortega et al. 2019	3	7	0.429	[0.144; 0.770]
Patil et al. 2020	0	62	0.000	[0.000; 0.115]
Sumi et al. 2020	2	109	0.018	[0.005; 0.070]
Yoo et al. 2020	0	33	0.000	[0.001; 0.196]
Random effects model			**0.050**	**[0.019; 0.123]**

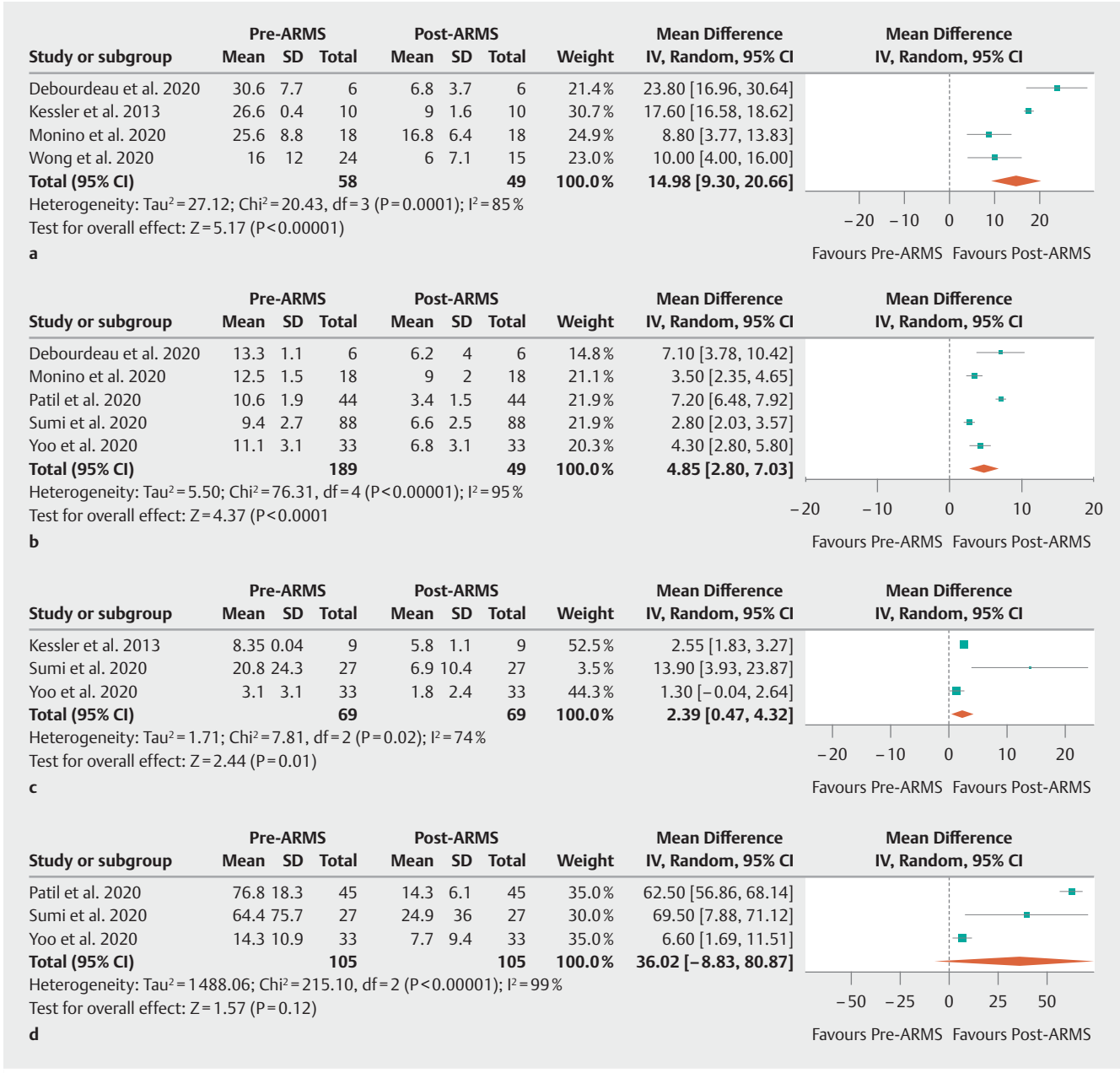
Heterogeneity: $I^2 = 51\%$, $\tau^2 = 1.2360$, $\chi^2_9 = 18.49$ ($P = 0.03$)



c

▶ **Fig. 3** Forest plot showing **a** pooled rate of overall adverse events, **b** dysphagia, and **c** bleeding after ARMS.

nificant difference in pooled rater of technical succss (98.1% [95% CI, 94.3–99.4, $I^2 = 0\%$] vs. 96.8% [95% CI, 88–99.2, $I^2 = 0\%$], $P = 0.55$), clinical success (79.2% [95% CI, 53.3–92.7, $I^2 = 89\%$] vs. 81.7% [95% CI, 49.0–95.4, $I^2 = 54.9\%$], $P = 0.87$), complete clinical (63.4% [95% CI, 45.0–77.1, $I^2 = 68.5\%$] vs. 71.6% [95% CI, 46.4–88, $I^2 = 79.6\%$], $P = 0.41$) and partial clinical response (24.5% [95% CI, 14.9–37.7, $I^2 = 0\%$] vs. 15.3% [95% CI, 6.6–31.7, $I^2 = 45.4\%$], $P = 0.3$). The rates of AEs (16.5% [95% CI, 11.8–22.5, $I^2 = 24.7\%$] vs. 20.7% [95% CI, 12.5–32.4, $I^2 = 0\%$], $P = 0.44$), dysphagia (10.5% [95% CI, 7.1–15.3, $I^2 = 0\%$] vs. 15.4% [95% CI, 8.4–26.5, $I^2 = 0\%$], $P = 0.28$) and bleeding (4.4% [95% CI, 1.2–15.1, $I^2 = 69.9\%$] vs. 5.9% [95% CI, 1.2–24.4, $I^2 = 0\%$], $P = 0.77$) with ARMS were not significantly different than with ARMS-B. Results of subgroup analysis are summarized in ▶ **Table 2**.



▶ **Fig. 4** Forest plot showing mean difference of **a** GERD-HRQL, **b** GERD-Q, **c** mean acid exposure time, and **d** DeMeester score pre-and post-ARMS.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed dispersion of the calculated rates using the I^2 percentage values. I^2 provides information about what proportion of the dispersion was true vs a chance [29]. There was low heterogeneity in technical success and high heterogeneity in clinical success outcome. Calculated I^2 values are reported with pooled results.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was no evidence of publication bias for technical (**Supplementary Fig. 2a**, Eggers 2-tailed $P = 0.07$) and clinical success outcomes (**Supplementary Fig. 2b**, Eggers 2-talied $P = 0.09$).

▶ **Table 2** Summary of pooled rates with subgroup analysis.

Outcome	ARMS	ARMS without banding (A)	ARMS with banding (B)	*P* value (A vs B)
Technical success	97.7 (94.6–99.0), $I^2 = 0$, 10 studies	98.1 (94.3–99.4), $I^2 = 0$, 6 studies	96.8 (88.0–99.2), 4 studies, $I^2 = 0$, 4 studies	0.55
Clinical success (reduction or discontinuation of PPI)	80.1 (61.6–91.0), $I^2 = 84.9$, 10 studies	79.2 (53.3–92.7), $I^2 = 89\%$, 6 studies	81.7 (49.0– 95.4), $I^2 = 54.9\%$, 4 studies	0.87
Complete clinal response	65.3 (51.4–77.0), $I^2 = 73.1$, 10 studies	63.4 (45.0–77.1), $I^2 = 68.5$, 6 studies	71.6 (46.4–88), $I^2 = 79.6\%$, 4 studies	0.41
Partial/reduction PPI	21.5 (14.2–31.2), $I^2 = 25.5$, 7 studies	24.5 (14.9–37.7), $I^2 = 0$, 3 studies	15.3 (6.6–31.7), $I^2 = 45.4\%$, 4 studies	0.3
Adverse events	17.2 (13.1 to 22.2), $I^2 = 1.9$, 10 studies	16.5 (11.8–22.5), $I^2 = 24.7$, 6 studies	20.7 (12.5–32.4), $I^2 = 0$, 4 studies	0.44
Dysphagia	11.4 (8.2 to 15.7), $I^2 = 0$, 10 studies	10.5 (7.1–15.3), $I^2 = 0$, 6 studies	15.4 (8.4–26.5), $I^2 = 0$, 4 studies	0.28
Bleeding	5.0 (1.9 to 12.3), $I^2 = 51.3$, 10 studies	4.4 (1.2 –15.1), $I^2 = 69.7$, 6 studies	5.9 (1.2–24.4), $I^2 = 0$, 4 studies	0.77

Values are shown as rate, 95% confidence interval, I^2, number of studies. ARMS, anti-reflux mucosectomy; PPI, proton pump inhibitor.

Discussion

Our study demonstrates that ARMS is a technically feasible and effective procedure for treatment of refractory GERD. It has a very high technical success rate of 97.7%. ARMS led to a significant discontinuation (65.3%) and reduction (21.5%) of PPI usage after the procedure. ARMS is also a relatively safe and well tolerated procedure. The rate of AEs is 17.2%, with dysphagia and bleeding being the most common complications. To our knowledge, this is the first systematic review and meta-analysis to assess the technical success, clinical response, and AEs of ARMS in refractory GERD.

We also report that ARMS significantly improves GERD-related symptoms. The GERD-HRQL scale is a disease-specific instrument, developed to help overcome variability in evaluating response to treatments for GERD and has been validated as a significant predictor of patient satisfaction. A reduction in the score by 50% or more is considered a successful intervention [30].

GERD-Q is a self-administered survey for GERD. It has a sensitivity of 65% and a specificity of 71% for diagnosis of GERD [31]. In our analysis, in post-ARMS, there was a significant decrease in GERD-HRQL (14.9) and GERD-Q (4.8) scores. While subjective scoring systems are biased by placebo effect of undergoing treatment, objective measures of AET and DeMeester scores do not have this limitation [32, 33]. In our analysis, post-ARMS, the mean AET decreased significantly by 2.39% and there was a trend toward improved DeMeester score but it did not reach statistical significance. Subgroup analysis was performed to compare ARMS with and without banding. It is important to note that both procedures were associated with similar technical success (98.1% vs 96.8%) without any significant difference. The addition of banding to EMR was not associated with a higher rate of AEs. The pooled rate of clinical success was not significantly different in patients undergoing ARMS (79.2%) when compared to ARMS-B (81.7%).

The most common AE was dysphagia from strictures. We reported a 11.4% risk of dysphagia in our analysis. Patil et al hypothesized that resection on more than two-thirds of the distal squamous esophageal mucosa is the cause of stricture formation [25]. Another hypothesis is that involvement of squamous mucosa in the resected area leads to a high occurrence of strictures [34]. Further, Sumi et al reported that patients undergoing crescentic resection had a higher risk of dysphagia when compared to those who had butterfly-shaped resection. Twelve of 81 patients had stenosis after crescentic resection while only one of 21 had stenosis after butterfly-shaped mucosal resection [26]. Although the strictures can be easily treated with endoscopic balloon dilation, there is a need to standardize the ARMS technique to prevent these AEs.

Approximately 40% of patients with GERD fail to respond to aggressive acid-suppressive therapy. Moreover, there are concerns about the long-term effects of PPI therapy as well. Because fewer than 5% of patients with refractory GERD undergo laparoscopic fundoplication, there is a treatment gap [3]. Newer, less invasive techniques have been developed to fill this gap, but with little success. The LINX reflux management system that augments the lower esophageal sphincter (LES) function using a small expandable ring of linked magnetic beads, Enodstim LES stimulating system, and LES electrical stimulation therapy that use electrical energy to stimulate closure of LES are some of the alternative surgical approaches to refractory GERD treatment [8, 35, 36]. Several endoscopic models have also evolved to treat refractory GERD. Stretta utilizes a radiofrequency generator and a specialized balloon/catheter system that is used to remodel the EGJ and LES [37]. Medigus is an endoscopic stapling system that is capable of creating a partial fundoplication [38]. The newest approach is the TIF, which uses

endoscopically placed polypropylene fasteners to create a 200– to 270– degree fundoplication. Although there is initial improvement in symptoms, over time, the fasteners tend to dislodge [39,40]. However, because of unclear long-term data, high economic burden, and inability to mitigate acid reflux, these procedures have not yet gained widespread acceptance.

Based on current literature, ARMS appears to be effective and well tolerated. The success of ARMS is likely related to its ability to cause submucosal fibrosis at LES. Relaxation of the crura and LES is a normal physiological process that occurs while swallowing. Transient lower esophageal relaxation (TLESR) is relaxation of the LES that is not initiated by swallowing. TLESRs contribute to 90 % of reflux episodes [41]. ARMS prevents the frequent occurrence of TLESRs. Recently, the ARMS technique has been further refined using a technique of anti-reflex mucosal ablation that causes similar scarring [42]. Proper patient selection was always performed for all the studies. Patients with hiatal hernia > 3 cm, esophageal motility disorders, major psychiatric illness, and extremely obese were excluded. All patients underwent upper gastrointestinal endoscopy, high-resolution manometry, and multichannel intraluminal impedance and pH monitoring prior to the procedure.

ARMS is usually performed using a cap-fitted EMR device. A variation of this technique, EMR with band ligation (ARMS-B) has been utilized in some studies. ARMS is performed by mucosal resection of more than two-thirds of the mucosa on the lesser curvature of the cardia below the gastroesophageal junction during retroflexed view in the stomach [34]. A small amount of mucosa is left in the lesser curvature in a butterfly shape to avoid transient stenosis. Rates of transient stenoses are significantly lower when a butterfly-shaped resection is performed when compared to the original crescent-shaped resection [26]. Care should be taken to avoid resection of squamous mucosa of the esophagus, which is associated with high rates of stricture formation. ESD is another method to achieve mucosal resection, but is associated with a higher rate of AEs [26]. After ARMS, a repeat endoscopic evaluation is performed in 2 to 3 weeks to assess for stenosis. Patients are then assessed periodically after 2 months.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data, low heterogeneity, studies from throughout the world, and rigorous evaluation of study quality. In addition, because we used both subjective and objective measures to quantify efficacy of clinical outcome, the results are generalizable. However, there are some limitations in this study, most of which are inherent to any meta-analysis. The included studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. The cost associated with the procedure was not evaluated in our analysis. We were also unable to compare ARMS with the current standard of care for refractory GERD and laparoscopic fundoplication. Further, the endoscopic procedure is highly operator-dependent. The success and safety profile are dependent on the expertise of the person performing the procedure. We also could not compare procedure time between the two techniques. In addition, follow-up was quite variable in included studies, which added to heterogeneity for clinical success along with small sample size. There is limited precision in our estimates as evidenced by wide confidence intervals. We also could not directly compare outcomes of ARMS with other endoscopic techniques such as TIF and MSA as data are not available. Additional subgroup analyses were also not possible due to lack of data. Nevertheless, our study is the first meta-analysis evaluating the feasibility, effectiveness, and tolerability of ARMS.

Conclusions

In conclusion, ARMS seems to be an effective and well-tolerated endoscopic treatment strategy for refractory GERD. It is a less invasive technique that can fill the treatment gap between PPI therapy and laparoscopic fundoplication for treatment of refractory GERD. Future prospective studies with long-term follow up are needed to validate our findings.

Competing interests

The authors declare that they have no conflict of interest.

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