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The role of polyglycolic acid sheets in the management of post-endoscopic submucosal dissection gastrointestinal bleeding and esophageal stricture

A PRISMA compliant systematic review and meta-analysis

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Abstract

Background: As a relatively minimally invasive technique, endoscopic submucosal dissection (ESD) is widely used for the treatment of gastrointestinal lesions. However, it is associated with complications, such as postoperative bleeding, stricture, and perforation. A covering method using polyglycolic acid (PGA) sheets for ESD-induced ulcers has been reported to be effective in reducing the risk of post-ESD bleeding and esophageal stricture. Herein, we conducted a systematic review and meta-analysis to evaluate the role of PGA sheets in the prevention of gastrointestinal bleeding and esophageal stricture after ESD.

Methods: We searched PubMed, Web of Science, and the Cochrane Library databases on October 15, 2019. All eligible articles were selected based on the predefined inclusion and exclusion criteria. The main outcomes were the rates of post-ESD gastrointestinal bleeding and esophageal stricture. Cochrane's Q statistic and I^2 test were used to identify heterogeneity between the studies. When there was no obvious heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effect model was used. When there was obvious heterogeneity ($I^2 > 50\%$, $P < .1$), a random effect model was used. Funnel plots and the Egger regression test were used to assess publication bias.

Results: Fifteen articles were included in the meta-analysis, of which 7 were exclusively about the use of PGA sheets to prevent postoperative gastrointestinal bleeding, and the remaining reported the use of PGA sheets to prevent postoperative esophageal stenosis. Our analysis showed that preventive therapy with PGA sheets decreased the rates of post-ESD gastrointestinal bleeding (risk ratio [RR] = 0.35, 95% confidential interval [CI]: 0.19–0.64, $P < .001$) and esophageal stricture (RR = 0.46, 95% CI: 0.27–0.79, $P = .005$), and the gastrointestinal bleeding and esophageal stricture rates after preventive treatment with PGA sheets were 5.7% (95% CI: 3.6%–8.8%) and 20.6% (95% CI: 14.5%–28.4%), respectively.

Conclusion: The utilization of PGA sheets after ESD has an excellent outcome in reducing the risk of postoperative gastrointestinal bleeding and esophageal stricture.

Abbreviations: CI = confidential interval, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, PGA = polyglycolic acid, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trials, RR = risk ratio.

Keywords: endoscopic submucosal dissection, esophageal stricture, gastrointestinal bleeding, meta-analysis, polyglycolic acid sheets, systematic review

SP, SH, and HX contributed equally to this study.

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The authors have no conflicts of interest to disclose.

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1. Introduction

Endoscopic submucosal dissection (ESD) was first developed in the 1990s as an advanced technique to overcome the limitations of conventional endoscopic mucosal resection (EMR).[1] Compared with EMR, ESD can resect tumors en bloc regardless of tumor size and shape, leading to a more accurate histological diagnosis and reducing the risk of local recurrence.[2–4] Although ESD has advantages, it is associated with some potential complications, such as bleeding, perforation, and postoperative esophageal stricture. For gastrointestinal ESD, postoperative bleeding, one of the most serious complications, may lead to hemorrhagic shock and require transfusion therapy, interventional therapy, and even surgical treatment.[5,6] It was reported that the rate of bleeding after gastrointestinal ESD is 8.5%.[7] In addition, the post-ESD bleeding rate increases to approximately 21%–38% if patients are on antithrombotic therapy.[8–11] Regarding esophageal ESD, postprocedure stricture is a major concern. Some studies have reported that the incidence of esophageal stenosis in patients with post-ESD mucosal defects greater than three-quarters of the esophageal circumference is 70%–90%,[12–14] which seriously reduces the quality of life of these patients.

Recently, a novel endoscopic tissue covering method that using polyglycolic acid (PGA) sheets and fibrin glue has been found to have the potential to reduce the risk of post-ESD gastrointestinal bleeding,[15,16] and prevent esophageal stricture.[17,18] In 2014, Kengo et al first introduced polyglycolic acid sheets combined with fibrin glue to prevent duodenal perforation after ESD.[19] Subsequently, Toshiro and others reported the potential of PGA sheets to prevent esophageal stricture after ESD.[18,20] In 2015, a controlled study found that prophylactic use of PGA sheets reduced gastric bleeding after ESD.[16] After that, a number of papers about PGA sheets have been published. Herein, we conducted a meta-analysis to investigate the role of PGA sheets in preventing gastrointestinal bleeding and esophageal stricture after ESD, attempting to assess its comparative efficacy with regard to other preventive therapies.

2. Materials and methods

2.1. Search strategy

The systematic review was carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] To identify all relevant studies of the use of PGA sheets for preventing gastrointestinal bleeding or esophageal stricture, a systematic literature search was performed through the databases of PubMed, the Cochrane Library and Web of Science, with the language restricted to English, on October 15, 2019. The following search terms were used for these databases: "polyglycolic acid," "polyglycolide," "endoscopic submucosal dissection," "ESD," "esophageal stenosis," "esophageal stricture," and "bleeding."

2.2. Selection of studies

The studies were included according to the following criteria: (1) the enrolled patients, who were scheduled for ESD of early-stage esophageal or gastric adenoma or early gastric cancer or early gastrointestinal cancer; (2) the whole procedure was performed under endoscopy without any surgical intervention, with the ulcer covered with PGA sheets in a single-arm study, or a comparison of postoperative ulcers covered with PGA sheets and without PGA sheets in a controlled study; (3) the main endpoints were post-ESD gastrointestinal bleeding or esophageal stricture; (4) the sample size was >5; and (5) retrospective or prospective, case–control, or cohort studies and clinical trials (including randomized controlled trials). Any comments or review articles without original data were excluded. Studies of oral, hepatic, cardiac or laryngopharyngeal surgery, or esophageal perforation were also excluded. In the case of duplicated reports, only the most recent and comprehensive publication was included.

2.3. Date extraction and study quality assessment

The outcomes assessed were the rates of post-ESD gastrointestinal bleeding and esophageal stricture after preventive treatment with PGA sheets. Post-ESD gastrointestinal bleeding was defined as the occurrence of melena, hematemesis, or hematochezia during the postoperative follow-up period, and confirmed by endoscopy as postoperative ulcer bleeding. Postoperative esophageal stricture was defined as the presence of a stenosis of the esophageal lumen that prevented the passage of a 9.8-mm diameter upper gastrointestinal endoscope.

Basic data were extracted, including name of the first author, year of the publication, country of the study, type of study, location of lesion, procedure, the study duration, the number of patients and lesions, sex, and mean age. Clinical characteristics were extracted according to the assessed outcomes, bleeding or stricture, including the mean resection size, en bloc resection rate, antithrombotic agent therapy rate, technical success rate, bleeding rate, mean time of bleeding onset, rate of circumferential range ≥3/4, stricture rate, and adverse event rate.

2.4. Study quality assessment

We used the JADAD scale to evaluate the quality of the included randomized controlled trials (RCT)[22] and the Newcastle–Ottawa quality assessment scale to evaluate the quality of nonrandomized controlled trials and single-arm trials.[23] The specific components of the JADAD scale include: the generation of random sequences, hiding of randomization, blindness, and withdrawal or exit. The quality evaluation results were divided into high-quality (score 3–7) studies and low-quality (score 1–3) studies by quantitative evaluation. The Newcastle–Ottawa acale consists of 3 major categories: selection (a. representativeness of the exposure cohort; b. selection of the non-exposed cohort; c. determination of exposure; d. no outcome event occurred in the study participants before the study began), comparability (a. the study controlled the main influencing factors; b. the study controlled other confounding factors), and outcomes (a. assessment of outcome events; b. adequacy of follow-up time; c. completeness of follow-up). Each study included in the quality assessment was assessed as high-quality (score 7–9) research, medium-quality (score 5–6), and low-quality (score <5) research.

In addition, the work has been reported in line with PRISMA and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines.

2.5. Statistical analysis

Review Manager 5.3 (London, UK) and Comprehensive Meta-Analysis software version 3.0 were used to analyze the data. Given that the main purpose of this study was to evaluate whether preventive treatment with PGA sheets can reduce the incidence of outcome events, and to report the incidence of outcome events after prophylactic use, we used forest plots for statistical analysis. The risk ratio (RR) with 95% confidence interval (CI) was recommended for dichotomous variables, such as bleeding rate and stricture. In this study, we estimated heterogeneity with χ^2 and I^2 tests; $I^2 > 50\%$ or $P < .1$ were considered to indicate obvious heterogeneity.[24] When there was obvious heterogeneity, we used a random effect model, otherwise we used a fixed-effect model. Publication bias was detected by funnel plots and the Egger regression test. For the sensitivity analysis, we adopted the method of eliminating variables one by one and then combining the effect size. A 2-tailed P value <.05 was considered statistically significant.

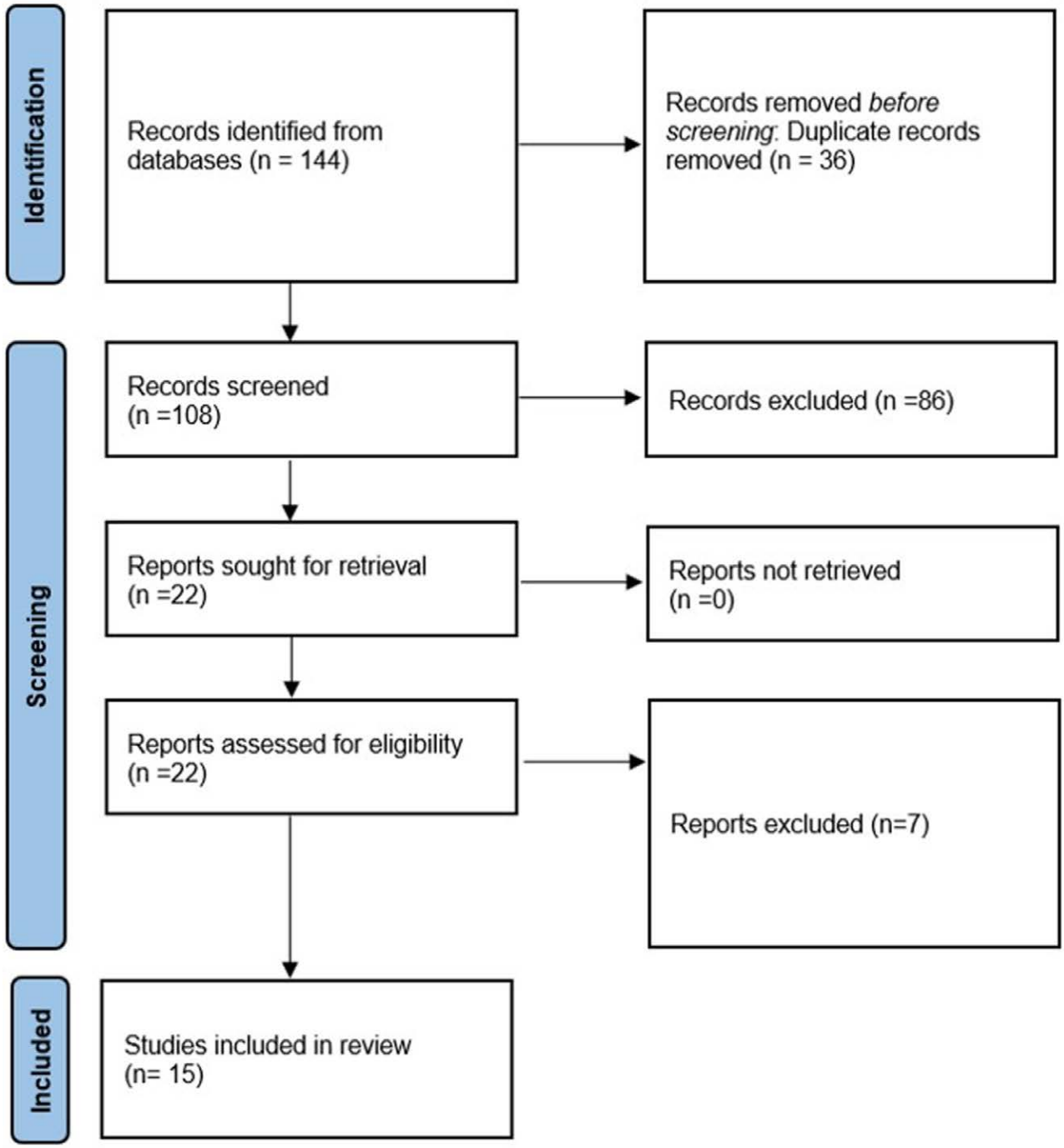

Figure 1. Screening flowchart for inclusion studies.

3. Results

3.1. Baseline characteristics of enrolled studies

A total of 144 records were identified from the 3 electronic databases; 15 articles were included in the final analysis based on the inclusion and exclusion criteria (Fig. 1). The basic characteristics of the included studies were shown in Table 1. All of the studies were performed between 2014 and 2019. Most of the studies (n = 12) were conducted in Japan, and the others (n = 3) were performed in China. They included randomized controlled trials (n = 3), nonrandomized controlled trials (n = 5), and single-armed trials (n = 7). Some of them (n = 7) focused exclusively on gastrointestinal bleeding and the remainder (n = 8) exclusively on esophageal stricture. The location of lesions in the study included the esophagus (n = 8), stomach (n = 5), colorectum (n = 1), and the whole gastrointestinal tract (n = 1). Most of the studies (n = 13) included >10 cases. A total of 814 patients were included, and the majority of patients were male (n = 513, 63.0%). The mean age ranged from 59.9 to 78.5 years.

The clinical characteristics and outcomes of using PGA sheets to prevent post-ESD gastrointestinal bleeding were summarized in Table 2. Most patients (n = 419, 74.7%) included in our analysis took long-term antithrombotic drugs. The mean size of ESD resection was >20 mm in most of the studies. The time of bleeding onset post-ESD in patients undergoing preventive treatments with PGA sheets and fibrin glue varied from 7 to 17 days. The adverse event rates ranged from 0% to 3%.

Table 1

Basic characteristics of included studies.

Author	Year	Country	Type of study	Type of end	Location of lesion	Procedure	Duration	No.of lesions	No.of patients	Sex (M/F)	Age, mean (yr)
Kawata et al[25]	2018	Japan	CT	Bleeding	Gastric	MCFP	April 2014–September 2015	52	38	33/5	78.5
						Blank	April 2014–September 2015	53	46	37/9	78.0
Mori et al[26]	2017	Japan	CT	Bleeding	Gastric	C-PGA	NA	19	19	11/8	76
						DDSS-PGA	NA	20	20	12/8	77
Tsuji et al[16]	2015	Japan	CT	Bleeding	Gastric	MCFP	July 2013–February 2014	45	45	41/4	73.6
						Blank	Before July 2013	41	41	34/7	74.8
Tsuji et al[27]	2014	Japan	SAT	Bleeding	colorectal	MCFP	September 2012–November 2012	10	10	8/2	68.0
Kataoka et al[28]	2019	Japan	CT	Bleeding	Gastric	MCFP	September 2014–September 2016	67	67	NA	72.9
						Blank	September 2014–September 2016	70	70	NA	73.0
Fukuda et al[15]	2016	Japan	CT	Bleeding	All	MCFP	July 2012–December 2015	104	104	76/28	74.8
						Blank	July 2012–December 2015	70	70	52/18	75.2
Kikuchi et al[29]	2018	Japan	SAT	Bleeding	Gastric	MCFP	July 2014–November 2015	22	20	17/3	75.5
Li et al[30]	2018	China	SAT	Stricture	Esophagus	TS-PGA+FCMS	June 2016–May 2017	9	9	8/1	61.4
Chai et al[31]	2018	China	CT	Stricture	Esophagus	TS-PGA+FCMS	July 2016–May 2017	34	34	22/12	62.74
						Stent	July 2016–May 2017	32	32	18/14	59.91
Iizuka et al[20]	2017	Japan	CT	Stricture	Esophagus	TS-PGA+FCMS	January 2012–July 2016	39	39	30/9	68.7
						Steroid injection	January 2012–July 2016	31	31	25/6	67.1
Iizuka et al[18]	2015	Japan	SAT	Stricture	Esophagus	MCFP	May 2012–August 2013	15	15	13/2	63.8
Nagami et al[32]	2016	Japan	SAT	Stricture	Esophagus	hybrid therapy	November 2013–June 2015	10	10	9/1	68.9
Sakaguchi et al[17]	2015	Japan	SAT	Stricture	Esophagus	MCFP	September 2013–March 2014	8	8	7/1	69.1
Sakaguchi et al[33]	2016	Japan	SAT	Stricture	Esophagus	Hybrid therapy	December 2014–July 2015	11	11	10/1	75.4
Yang et al[34]	2019	China	CT	Stricture	Esophagus	PGA+stent	January 2016–May 2017	38	38	27/11	64.53
						Stent	January 2016–May 2017	37	37	23/14	60.97

All = esophageal, gastric, and colorectal, C-PGA = conventional polyglycolic acid, CT = controlled trial, DDSS-PGA = device delivery station system polyglycolic acid, Hybrid therapy = locoregional steroid injection and polyglycolic acid sheets with fibrin glue, M/F = male/female, MCFP = mucosal defect covered with fibrin glue and polyglycolic acid sheet, SAT = single-arm trial, TS-PGA+FCMS = triamcinolone-soaked polyglycolic acid sheet plus fully covered metal stent.

Table 3 showed the clinical characteristic and outcomes of the use of PGA sheets for preventing esophageal stricture. In these studies, most patients (n = 233, 88.3%) had a circular resection of the esophageal mucosa of more than three-quarters of the circumference. The resected lesions were located in the upper (n = 20, 7.6%), middle (n = 126, 47.7%), and lower (n = 118, 44.7%) thirds of the esophagus. The technical success rate of PGA was 100%. Postoperative follow-up time varied from 6 to 131 weeks. The rate of adverse events ranged from 0% to 9.1%.

3.2. Risk of bias within studies

The quality scores of each included study according to the JADAD scale or the Newcastle–Ottawa quality assessment scale were shown in Table 4. The 3 RCTs[26,28,31] were all high-quality trials (scores ranged from 6 to 7). The final methodological quality evaluation revealed that 1 study was of low quality, 8 of medium quality, and 6 of high quality.

3.3. Clinical outcomes

3.3.1. Bleeding

As shown in Table 2, the rate of bleeding varied from 0% to 22.0%. Seven studies[15,16,25–29] were composed of 323 patients who underwent preventive treatment with PGA sheets after ESD. The estimated pooled bleeding rate was 5.7% (95% CI: 3.6%–8.8%) (Fig. 2). There was no obvious heterogeneity among the studies ($Q = 2.805$, $I^2 < 0.001$, $P = .833$). No significant publication bias was detected by the funnel plot (Fig. 3A) and the Egger test ($P = .46$). Based on the study quality, the subgroup analysis showed that the rate of bleeding was 6.7% (95% CI: 3.6%–12.0%, $I^2 < 0.001$) in high-quality studies (n = 3), 4.6% (95% CI: 2.3%–9.2%, $I^2 \leq 0.001$) in moderate-quality studies (n = 3), and 4.5% (95% CI: 0.3%–44.8%, $I^2 \leq 0.001$) in the low-quality study (n = 1), respectively (Fig. 4A). Based on the study type, the subgroup analysis showed that the rate of bleeding was 5.0% (95%

Table 2

Clinical outcomes of studies on bleeding rates after ESD.

Author	Procedure	Resection size, mean (mm)	Antithrombotic agent therapy [%, (n/N)]	Technical success [%, (n/N)]	Bleeding [%, (n/N)]	Adverse events [%, (n/N)]
Kawata et al[25]	Covering	43	100 (38/38)	100 (52/52)	5.8 (3/52)	0
	Blank	38	100 (46/46)	100 (53/53)	20.8 (11/53)	0
Mori et al[26]	C-PGA	16.9	36.8 (7/19)	100 (19/19)	21 (4/19)	0
	DDSS-PGA	15.3	45.0 (9/20)	100 (20/20)	0	0
Tsuji et al[16]	Covering	40.1	64.4 (29/45)	100 (45/45)	6.7 (3/45)	2.4 (1/45)
	Blank	43.9	56.1 (23/41)	100 (45/45)	22.0 (9/41)	0
Tsuji et al[27]	Covering	39.7	NA	100 (10/10)	0	0
Kataoka et al[28]	Covering	47.5	35.8 (24/67)	100 (67/67)	4.5 (3/67)	3.0 (2/67)
	Blank	51.3	40.0 (28/70)	100 (70/70)	5.7 (4/70)	1.4 (1/70)
Fukuda et al[15]	MCFP	43.4	100 (104/104)	100 (104/104)	3.8 (4/104)	1.0 (1/104)
	Blank	45.3	100 (70/70)	100 (70/70)	12.9 (9/70)	2.9 (2/70)
Kikuchi et al[29]	MCFP	31.5	100 (20/20)	100 (20/20)	0	0

C-PGA = conventional polyglycolic acid, DDSS-PGA = device delivery station system polyglycolic acid, ESD = endoscopic submucosal dissection, MCFP = mucosal defect covered with fibrin glue and PGA sheets.

CI: 2.9%–8.4%, $I^2 < 0.001$) in controlled studies (n = 4) and 8.1% (95% CI: 3.4%–18.1%, $I^2 < 0.001$) in single-arm studies (n = 3) (Fig. 4B). Four studies[15,16,25,28] compared the bleeding rate between patients with and without PGA sheets: the RR was 0.35 (95% CI: 0.19–0.64, $I^2 = 0\%$, $\chi^2 = 1.43$, $P < .001$), indicating that the preventive therapy with PGA sheets decreased the risk of gastrointestinal bleeding after ESD (Fig. 5), and there was no obvious heterogeneity. For the sensitivity analysis, no single study significantly changed the outcome or the heterogeneity. No significant publication bias was detected by the funnel plot (Fig. 3B) and the Egger test ($P = .24$).

3.3.2. Esophageal stricture

The rate of esophageal stricture after ESD ranged from 7.7% to 46.9% (Table 3). Eight studies[17,18,20,30–34] with a total of 164 patients who underwent preventive treatment with PGA sheets after ESD were included. The estimated pooled esophageal stricture rate was 20.6% (95% CI: 14.5%–28.4%) (Fig. 6). In the sensitivity analysis, the largest change in the rate of esophageal stricture occurred when the study by Nagami et al[32] was removed, which reduced the heterogeneity level from high to low and changed the effect size from 20.6% to 17.9% ($Q = 6.552$, $P = .364$, $I^2 = 8.430$). However, overall, there was no obvious heterogeneity. No significant publication bias was detected by the funnel plot (Fig. 3C) and the Egger test ($P = .84$). Based on the study quality, the subgroup analysis showed that the rate of esophageal stricture was 14.9% (95% CI: 9.2%–23.3%, $I^2 < 0.001$) in high-quality studies (n = 3) and 31.1% (95% CI: 19.9%–46.5%, $I^2 = 23.241$) in medium-quality studies (n = 5) (Fig. 7A). Based on the study type, the subgroup analysis showed that the rate of esophageal stricture was 14.9% (95% CI: 9.2%–23.3%, $I^2 < 0.001$) in controlled studies (n = 3) and 31.1% (95% CI: 19.9%–46.5%, $I^2 = 23.241$) in single-arm studies (n = 5) (Fig. 7B). Three studies[20,31,34] compared the stricture rate between patients with and without PGA sheets. The RR was 0.46 (95% CI: 0.27–0.79, $I^2 = 0\%$, $\chi^2 = 0.90$, $P = .005$) (Fig. 8), which demonstrated that preventive therapy with PGA sheets decreased the risk of esophageal stricture after ESD, and there was no obvious heterogeneity. In the sensitivity analysis, no single study significantly changed the outcome or the heterogeneity. No significant publication bias was detected by the funnel plot (Fig. 3D) and the Egger test ($P = .13$).

4. Discussion

Although ESD has many advantages over other treatments in cases of upper gastrointestinal lesions, and some guidelines have

Table 3

Clinical outcomes of studies on stricture rates after esophageal ESD.

Author	Year	Procedure	Circumferential range ≥3/4 rate (%) (n/N)	Location of lesion (U/M/L)	Technical success rate (%) (n/N)	Stricture rate (%) (n/N)	Follow-up time (wk)	Adverse event (n/N)
Li et al[30]	2018	TS-PGA+FCMS	100 (9/9)	0/8/1	100 (9/9)	33.3 (3/9)	Dec-22	0
Chai et al[31]	2018	TS-PGA+FCMS	100 (34/34)	0/12/22	100 (34/34)	20.5 (7/34)	6	0
		Stent	100 (32/32)	0/17/15	100 (32/32)	46.9 (15/32)	6	0
Iizuka et al[20]	2017	TS-PGA+FCMS	74.4 (29/39)	5/23/11	100 (33/33)	9.1 (3/33)	6	Jan-33
		Steroid injection	64.5 (20/31)	6/14/11	100 (29/29)	10.3 (3/29)	6	0
Iizuka et al[18]	2015	MCFP	33.3 (5/15)	0/10/5	100 (13/13)	7.7 (1/13)	6	Jan-13
Nagami et al[32]	2016	Hybrid therapy	100 (10/10)	05-03-02	100 (10/10)	50 (5/10)	10-131	0
Sakaguchi et al[17]	2015	MCFP	100 (8/8)	02-04-02	100 (8/8)	37.5 (3/8)	8	0
Sakaguchi et al et al[33]	2016	Hybrid therapy	100 (11/11)	0/9/2	100 (11/11)	18.2 (2/11)	12	01 November
Yang et al[34]	2019	PGA+stent	100 (38/38)	01-11-26	100 (38/38)	13.2 (5/38)	NA	NA
		Stent	100 (37/37)	1/15/21	100 (37/37)	35.1 (13/37)	NA	NA

EBD = endoscopic balloon dilatation, ESD = endoscopic submucosal dissection, Hybrid therapy = locoregional steroid injection and polyglycolic acid sheets with fibrin glue, MCFP = mucosal defect covered with fibrin glue and polyglycolic acid sheets, TS-PGA+FCMS = triamcinolone-soaked polyglycolic acid sheet plus fully covered metal stent, U/M/L = upper/middle/lower.

Table 4

Quality of included studies—JADAD scale, Newcastle–Ottawa scale.

Studies	JADAD	Newcastle	Quality
Kawata et al[25]	—	8	High
Mori et al[26]	6	—	High
Tsuji et al[16]	—	6	Medium
Tsuji et al[27]	—	3	Low
Kataoka et al[28]	6	—	High
Fukuda et al[15]	—	6	Medium
Kikuchi et al[29]	—	6	Medium
Li et al[30]	—	6	Medium
Chai et al[31]	7	—	High
Iizuka et al[20]	—	7	High
Iizuka et al[18]	—	5	Medium
Nagami et al[32]	—	6	Medium
Sakaguchi et al[17]	—	5	Medium
Sakaguchi et al[33]	—	5	Medium
Yang et al[34]	—	8	High

adopted it as a standard treatment for upper gastrointestinal tumors, we cannot ignore its intraoperative or postoperative complications, such as bleeding, perforation, and stricture.[35] Recently, a novel endoscopic shielding method using PGA sheets and fibrin glue has been reported be effective in reducing the post-ESD bleeding and stricture rates.[15,16] However, some studies have suggested that prophylactic use of PGA sheets was not effective in reducing the rates of bleeding or esophageal stricture after ESD.[20,28] Therefore, we performed this meta-analysis to evaluate the effect of PGA sheets in prevention of post-ESD gastrointestinal bleeding and esophageal stricture.

In this study, our results showed that the rates of gastrointestinal bleeding and stricture in the PGA sheets group were significantly lower than in the control group. Regarding the complication of bleeding, this finding was consistent with a recent study,[36] which demonstrated that the rate of delayed bleeding was much lower in the shielding group (2.6 %, 1/38) than that in the conventional group (14.1%, 12/85). Mori et al[26] pointed out that in the healing process of artificial ulcers after ESD, PGA sheets played an anti-inflammatory role and promote the production of rich granulation tissue. At the same time, PGA sheets promoted the migration of epidermal cells on rich granulation tissue, accelerated the activity of fibroblasts, and formed collagen scar tissue. Such a coating method can also protect surfaces from physical and chemical factors such as ulcer stimulants in food, gastric acid, bile, and pancreatic juice.[15]

However, our result is not consistent with Kataoka et als' report.[28] They suggested that the possible reasons for the different findings were: (a) patient inclusion criteria not ideal, resulting in a low overall rate of bleeding after ESD; (b) technological advances in ESD have led to reduced rates of postoperative bleeding; and (c) small sample size—increasing the sample size may produce different results.

In 2017, Mori et al[26] used RCTs to evaluate the effect of different delivery systems on the use of PGA sheets to prevent bleeding after ESD. The results showed that a new delivery system can reduce bleeding after ESD when compared with traditional delivery methods. However, because all patients received treatment with PGA sheets, this RCT was regarded as a single-armed trial and we included it in our pooled analysis, which may have produced heterogeneity. As PGA sheets have been widely used as an absorbable biomaterial in the surgical field, the incidence of adverse events related to PGA sheets is close to zero, so we did not analyze the incidence of adverse events in our study.

ESD has been widely used for resection of esophageal lesions, especially esophageal squamous cell carcinoma.[37] However, esophageal stricture is a major complication that can occur following ESD in patients left with large mucosal defects, and leads to a poor quality of life.[18] Our meta-analysis showed that prophylactic use of PGA sheets can effectively reduce the rate of esophageal stricture after ESD. By pooled analysis, the results showed that the esophageal stricture rate after prophylactic use of PGA sheets is 17.1%. This is consistent with the results of a randomized controlled trial in 2018,[31] which reported that the postoperative stricture rate (20.5%) of ulcers covered with PGA sheets was lower than in the non-covered group (46.9%; P = .024). The development of esophageal stricture after ESD mainly involves 3 overlapping pathological processes: inflammatory response, epidermal cell proliferation, and tissue reconstruction.[38] The mechanism of action of PGA sheets in preventing esophageal stricture after ESD may involve: (a) PGA sheets protect the ulcer

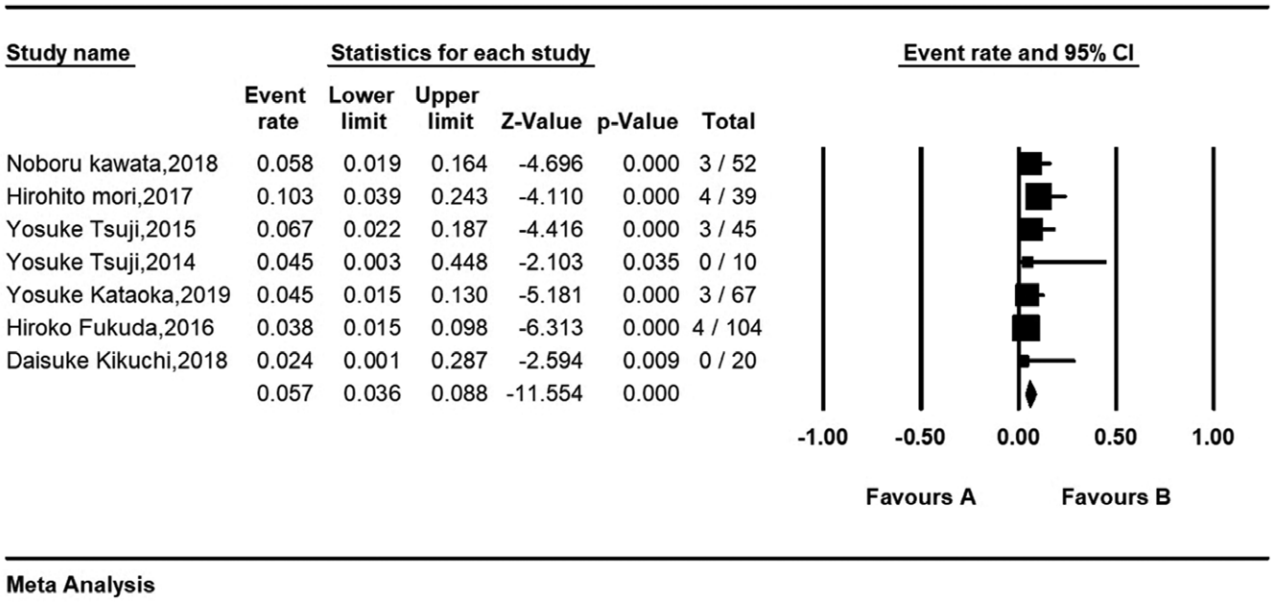

Figure 2. Forest plot of gastrointestinal bleeding rate after endoscopic submucosal dissection using polyglycolic acid sheets. CI = confidence interval.

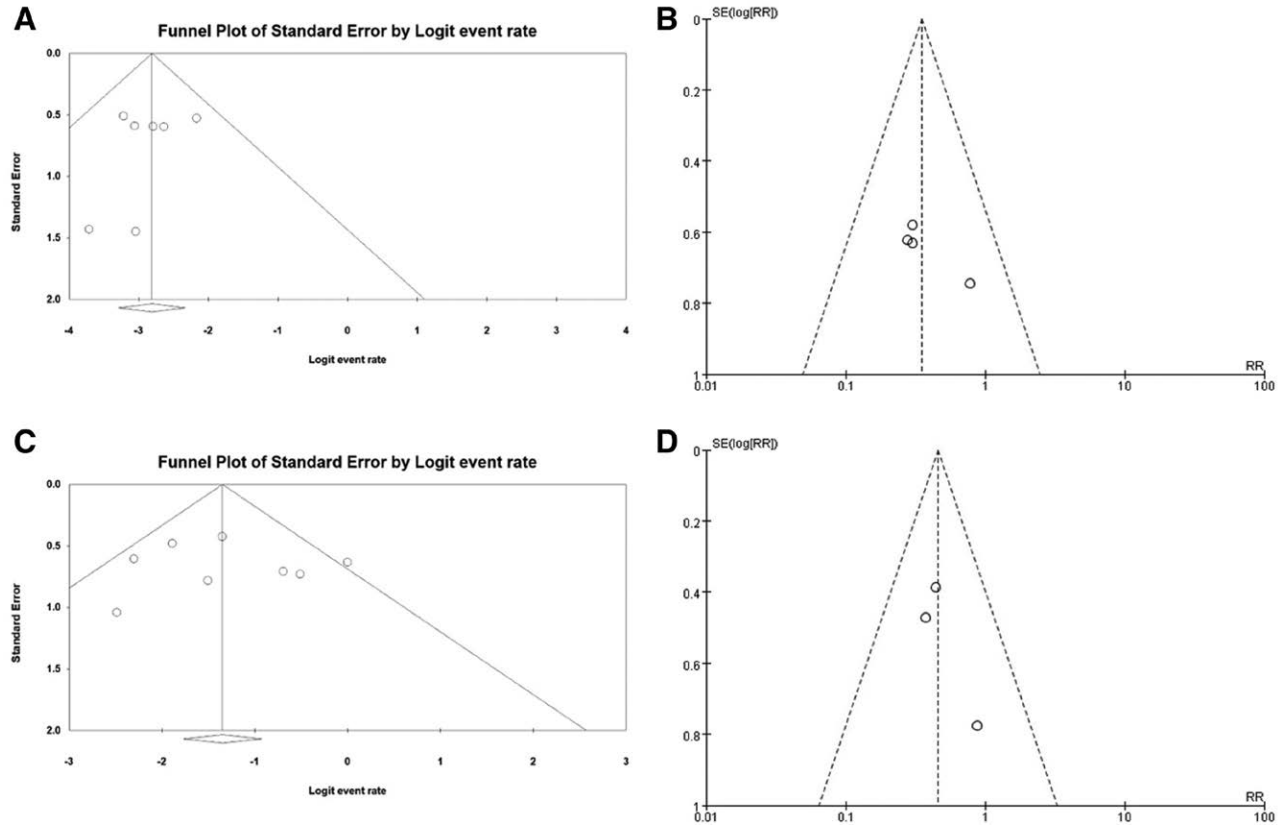

Figure 3. (A) Funnel plot on the study of gastrointestinal bleeding rate after endoscopic submucosal dissection using polyglycolic acid sheets; (B) Funnel plot for 4 studies comparing gastrointestinal bleeding rates with or without polyglycolic acid sheets after endoscopic submucosal dissection; (C) Funnel plot for stricture rate after esophageal endoscopic submucosal dissection using polyglycolic acid sheets; (D) Funnel plot of controlled studies on whether polyglycolic acid sheets prophylactic use can reduce esophageal stricture after endoscopic submucosal dissection.

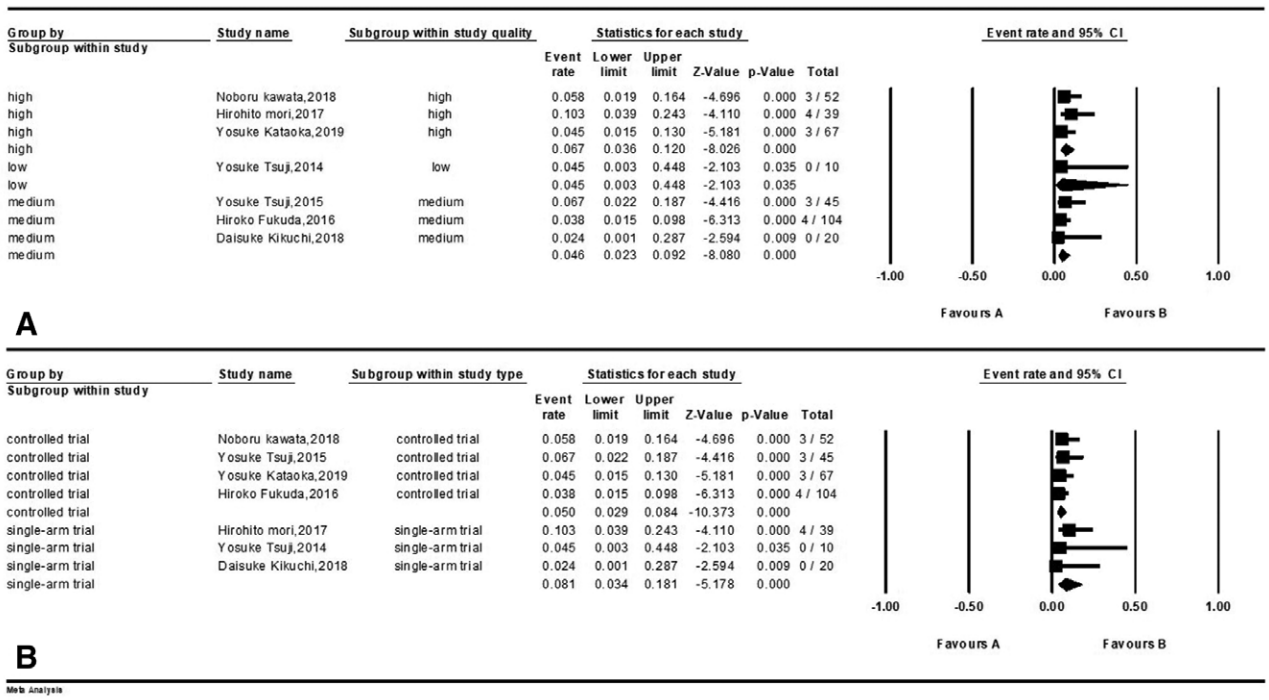

Figure 4. (A) Forest plot of the postesophageal endoscopic submucosal gastrointestinal bleeding rate based on study quality; (B) Forest plot of the postesophageal endoscopic submucosal gastrointestinal bleeding rate based on study type. CI = confidence interval.

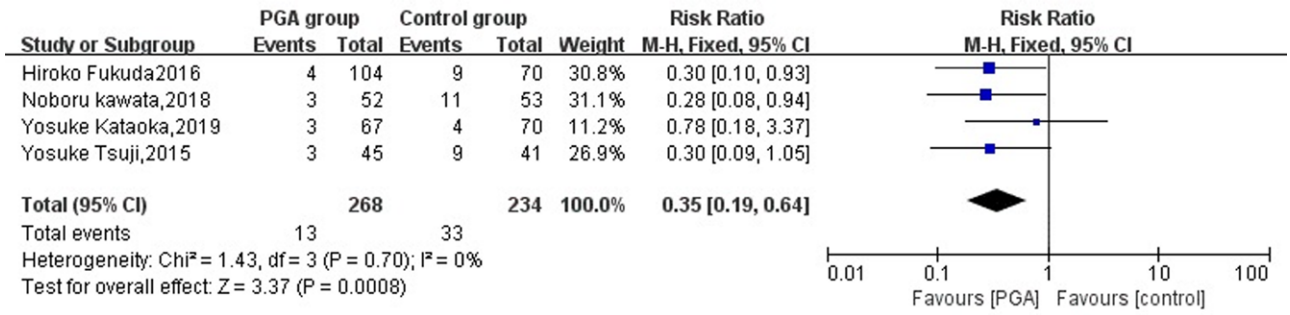

Figure 5. Forest plot comparing gastrointestinal bleeding rates with or without polyglycolic acid sheets after endoscopic submucosal dissection. CI = confidence interval, PGA = polyglycolic acid.

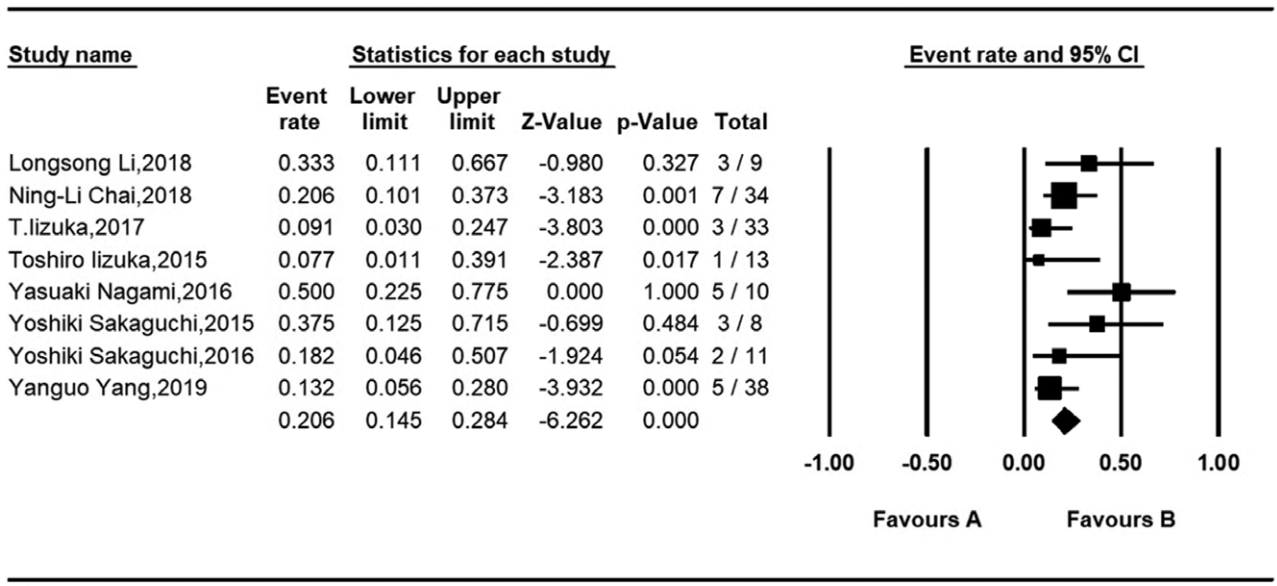

Figure 6. Forest plot of stricture rate after esophageal endoscopic submucosal dissection using polyglycolic acid sheets. CI = confidence interval.

surface resulting from ESD from exogenous materials, reducing the local inflammatory response; (b) acting as a scaffold for cell adhesion and promoting tissue regeneration; and (c) strengthening adhesions and reducing scar contracture.[17,18,20,27,30–32,39,40] However, a controlled study by Iizuka et al[20] demonstrated that PGA sheets cannot reduce the rate of esophageal stricture after ESD. The study also suggested that possible reasons may be the premature detachment of PGA sheets and insufficient study follow-up time. It should be noted that the control group in this study received topical steroid injection to prevent esophageal stricture. Local injection of glucocorticoids prevents esophageal stricture after ESD by inhibiting inflammation, inhibiting collagen synthesis, and promoting collagen degradation[14,41]; however, it can cause complications such as perforation, bleeding, and mediastinal abscess.[13,14] PGA sheets not only avoid these complications caused by local steroid injections but also can be safely applied to patients with contraindications to steroid use such as latent tuberculosis infection.[42] Stent implantation is considered to be a safe and effective method to prevent esophageal strictures after ESD, but we cannot ignore its complications, such as esophageal perforation, severe bleeding, stent displacement, and fractures.[43–46] Some studies[31,34] have overcome these shortcomings by using stents combined with PGA sheets, or a combination of stents, steroids, and PGA sheets. There has been no controlled study of the effectiveness of each method of prevention, so we cannot determine which method is associated with a lower incidence of esophageal stenosis after ESD. Furthermore, there were few complications and no adverse reactions related to PGA sheets in any study. In other words, PGA sheets are safe when used to prevent esophageal stricture after ESD.

Our study had several limitations. First, some studies had small sample sizes[17,27,30,33] and smaller total sample sizes (n = 837), so our results may be less clinically relevant. Second, some factors such as resection area and resection circumference may affect the assessed endpoints, and subgroup analysis was not performed due to incomplete data, which may affect its clinical application subdivision criteria. Third, only 3 RCTs[26,28,31] were included in the analysis. Fourth, in the study of PGA sheets to prevent esophageal stricture after ESD, other interventions such as stents, steroid injection, steroid-soaked PGA sheets, and fibrin glue were also included, which can cause great heterogeneity in our meta-analysis.

5. Conclusion

In conclusion, the utilization of PGA sheets after ESD has an excellent outcome in reducing the risk of postoperative

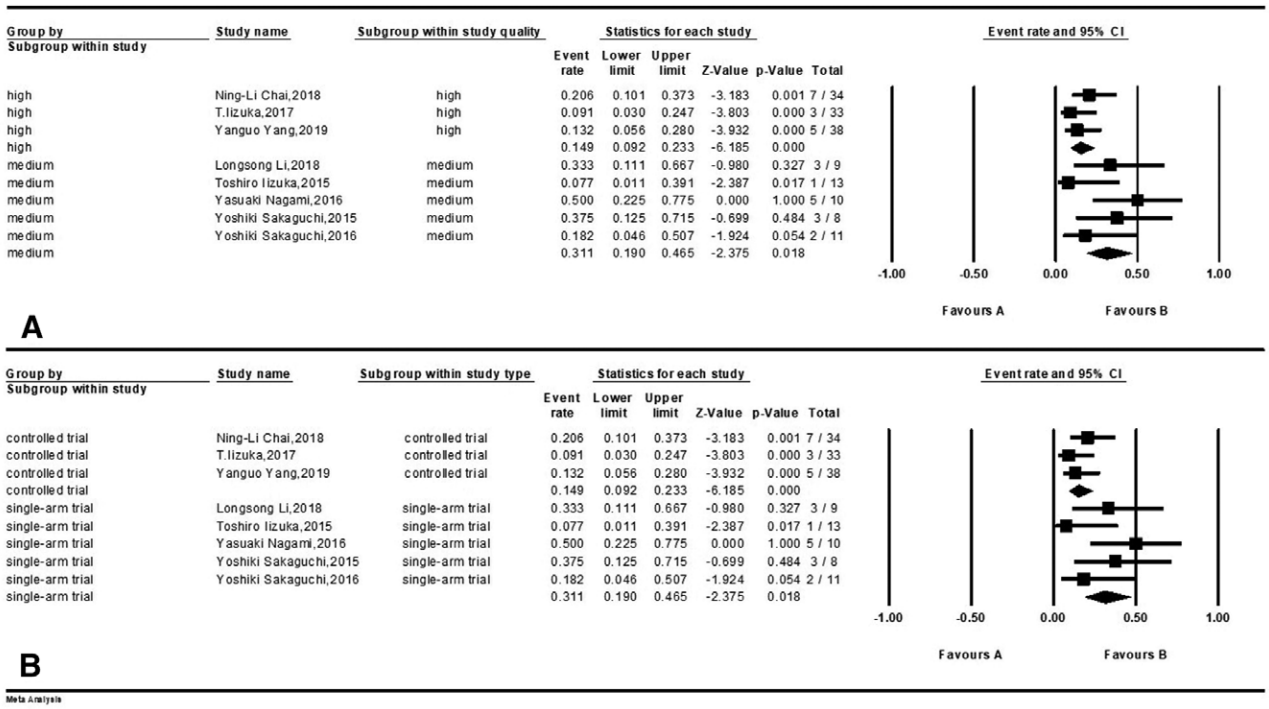

Figure 7. A. Forest plot of the rate of esophageal stricture based on study quality; (B) Forest plot of the rate of esophageal stricture based on study type. CI = confidence interval.

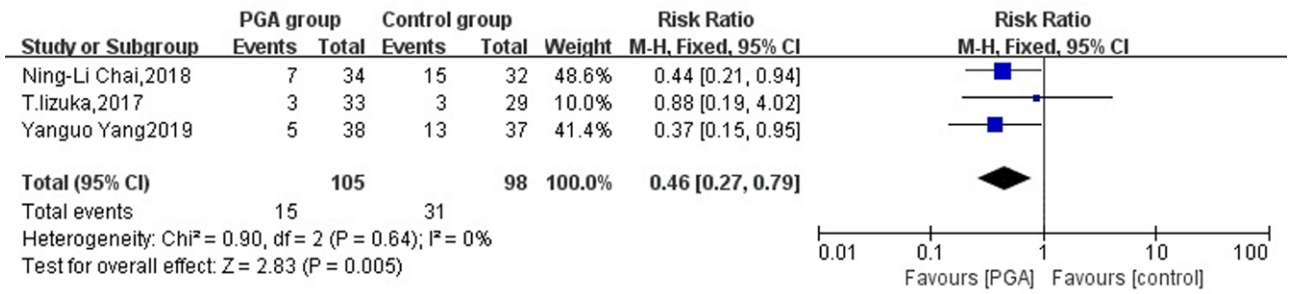

Figure 8. Effect of polyglycolic acid sheets on stricture rate after esophageal endoscopic submucosal dissection. CI = confidence interval, PGA = polyglycolic acid.

gastrointestinal bleeding and esophageal stricture. More high-quality clinical trials are warranted in the future.

Author contributions

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Acquisition of data and critical revision: Shali Tan, Chunyu Zhong and Yan Peng.

Revision of manuscript, and final approval of manuscript: Muhan Lü and Xiaowei Tang

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