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Isabel Lopes Dias Azevedo

Endoscopic and surgical management of anastomotic leakages following gastroesophageal cancer surgery: a systematic review and meta-analysis

Tratamento endoscópico e cirúrgico de deiscências anastomóticas após cirurgia oncológica gastroesofágica: revisão sistemática e meta-análise

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TÍTULO DISSERTAÇÃO

Endoscopic and surgical management of anastomotic leakages following gastroesophageal cancer surgery: a systematic review and meta-analysis

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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I dedicate my dissertation work to my beloved parents, for their unconditional love and support.

Full title: Endoscopic and surgical management of anastomotic leakages following gastroesophageal cancer surgery: a systematic review and meta-analysis

Short title: Management of malignant anastomotic leaks

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Abstract

Background and objectives: Anastomotic leakage (AL) is one of the most feared postoperative complications of gastroesophageal surgery. AL can be managed by conservative, endoscopic (such as endoscopic vacuum therapy and stenting) or surgical methods, but optimal treatment remains controversial. The aim of our meta-analysis was to compare a) endoscopic and surgical interventions and b) different endoscopic treatments for AL following gastroesophageal cancer surgery.

Methods: Systematic review and meta-analysis, with search in three on-line databases (MEDLINE, ISI Web of Knowledge and Scopus) for studies evaluating surgical and endoscopic treatments for AL following gastroesophageal cancer surgery.

Results: A total of 32 studies comprising 1080 patients were included. Compared with surgical intervention, endoscopic treatment was associated with lower in-hospital mortality (6.4% [95% CI 3.8-9.6%] *versus* 35.8% [95% CI 23.9-48.5%]), although clinical success, hospital length of stay and intensive care unit (ICU) length of stay were similar in both groups. Compared with stenting, endoscopic vacuum therapy was associated with a lower rate of complications (OR 0.348 [95% CI 0.127-0.954]), shorter ICU length of stay (mean difference -14.77 days [95% CI -26.57 to -2.98]) and time until AL resolution (17.6 days [95% CI 14.1-21.2] *versus* 39.4 days [95% CI 27.0-51.8]). There were no significant differences in terms of clinical success, mortality, reinterventions, and hospital length of stay.

Conclusions: Endoscopic treatment (in comparison to surgical intervention) and endoscopic vacuum therapy (in comparison to stenting) are safer and more effective. However, more robust comparative studies are needed to confirm these benefits.

Keywords: anastomotic leak, esophageal neoplasms, stomach neoplasms, endoscopic treatment, surgical treatment, stent, endoscopic vacuum therapy.

Introduction

Surgical treatment of esophagogastric cancer is associated with significant mortality and morbidity rates. Esophagectomy's mortality and morbidity are reported to be as high as 3.8-4.5% and 24.0-44.9%, respectively [1-3]. Gastrectomy for gastric cancer carries a mortality of 4.1-4.7% and a morbidity of 23.6-36.0% [4,5].

Anastomotic leakage (AL) is one of the most feared postoperative complications of gastroesophageal surgery owing to its association with prolonged hospital stay, increased mortality and reduced quality of life [6-9]. In recent decades, improving of surgical techniques and better management of postoperative complications led to a decrease of those outcomes [10,11], although this adverse event is still frequent, with AL incidence rates ranging from 0 to 49% following esophagectomy [12] and from 2.1 to 14.6% after gastrectomy [13].

AL can be managed by conservative (which includes fasting, nutritional support, antibiotic therapy, and wound drainage), endoscopic (clips, stents, tissue adhesives or endoscopic vacuum therapy [EVT]) or surgical methods (primary closure of the leak, re-anastomosis, or resection of the conduit). Currently, treatment decision is usually based on the characteristics of the leakage and the patient's clinical condition, but optimal treatment remains controversial [13-15].

In the past, surgery was the treatment of choice, although it carries a higher mortality rate and nowadays is mostly used in cases of severe sepsis, large defects or when other treatments failed or are not available/indicated.

Conservative treatment, with or without percutaneous drainage, can be an option in clinically stable patients with small leakages [13,14]. More recently, endoscopic techniques for AL were developed and appear to be safer than surgical reintervention [13,14]. A recent systematic review compared stent placement with EVT and found that EVT was associated with higher rate of AL closure and lower mortality [16]. However, this systematic review focused only on esophageal leaks and included leaks after both malign and benign surgery. Other endoscopic methods have also been reported as safe

and effective, but most of this evidence results from small case series [13,16]. Thus, it is unclear which is the optimal strategy for endoscopic treatment of AL after oncological gastric or esophageal surgery. Moreover, the comparison of endoscopic and surgical treatments for AL is important to confirm if endoscopic treatment should be the first-line strategy.

The aims of this meta-analysis were to compare the outcomes of endoscopic and surgical treatments for AL following surgery for both esophageal and gastric cancer and to compare the outcomes of the different endoscopic methods.

Methods

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [17].

Search strategy

To identify published literature, a systematic search strategy was performed using 3 electronic databases (MEDLINE through PubMed, ISI Web of Knowledge, and Scopus), with last search performed on 2nd September 2020. No language or publication date restrictions were imposed. The search query for PubMed was (“anastomotic leak” OR “anastomotic dehiscence” OR “anastomosis dehiscence” OR “anastomotic fistula”) AND (gastric OR stomach OR esophag* OR oesophag* OR gastroesophageal OR “upper gastrointestinal tract”) AND (endoscopy OR “endoscopic management” OR “OTSC” OR stent OR sponge OR esophagectomy OR gastrectomy).

In addition, reference lists of review articles on the topic were searched to identify additional studies. We contacted all authors of studies that did not present the data as per inclusion criteria. Studies from authors that did not answer were not included in the quantitative analysis.

Study selection

Studies were reviewed initially based on title and abstract by two independent investigators (I.A. and R.O). The full text of the included studies was then independently screened by the same two investigators according to the criteria below. A third author (D.L.) intervened in case of disagreement. The reasons for excluding studies were recorded. This phase was performed with Rayyan online platform.

We included (1) randomized controlled trials, case-control or cohort studies (prospective or retrospective) and case series; (2) including patients who underwent endoscopic or surgical interventions as the first treatment for an AL following a gastroesophageal cancer surgery; (3) and evaluating the success of the endoscopic and surgical interventions in terms of at least one of the primary or secondary outcomes mentioned below.

Studies were excluded if they were (1) review articles, editorials, comments, letters, and surveys; (2) case reports; (3) animal studies; (4) if they included fewer than 10 patients who met the eligibility criteria; or (5) if there was population overlap between studies. In this last case, only the study with the largest sample or study period was included.

Outcomes

The primary outcomes were a) clinical success (defined as a complete closure of the AL, confirmed by upper endoscopy or imaging exam, with no need for re-intervention and no death occurring as a consequence of the AL or its treatment, during follow up); b) in-hospital mortality (overall and treatment-related mortality).

Secondary outcomes were rate of technical success (defined as a successful application of the chosen therapy), rate of endoscopic and surgical re-intervention, rate of complications, hospital and intensive care unit (ICU) length of stay, time until AL resolution and time until oral intake.

Data collection

Data was extracted and recorded on an electronic data extraction sheet by two independent investigators (I.A. and R.O). Disagreements were solved by consensus.

We retrieved information about: (1) study (title, first author, year of publication, country of origin, study period, study design, number of participants, number of patients with AL, and risk of bias); (2) participants (age, gender and comorbidities); (3) tumor characteristics (location, staging, neoadjuvant therapy and type of resection and reconstruction); (4) AL characteristics (time between surgery and AL diagnosis, modality of diagnosis, location and dimensions of AL); (5) interventions (number of patients treated with each endoscopic and surgical method, time between cancer surgery or AL diagnosis and treatment, characteristics of each treatment) and (6) the aforementioned outcomes.

Assessment of methodological quality

The risk of bias within studies was evaluated by I.A. using the Newcastle-Ottawa Scale for cohort studies, and independently checked by R.O.. Disagreements were solved by consensus. We also assessed the existence of publication bias by visual inspection of funnel plots and using the Egger's test for primary outcomes.

Statistical analysis

We performed a meta-analysis including all studies (single-arm or double arm) presenting data allowing the calculation of pooled prevalence (for categorical variables) and weighted mean (for continuous variables), using random-effects model with MetaXL 5.3. Double-arm comparative studies were analysed through calculation of odds ratio (OR) and weighted mean differences (WMD). Heterogeneity between studies was tested using I^2 statistic and Cochran's Q test. Significant heterogeneity was defined as $I^2>40\%$ and/or $p<0.05$. Subgroup analysis was conducted to explore potential sources of heterogeneity according to a) tumor location (esophageal *versus* gastric) and b) mortality

definition (overall mortality *versus* treatment-related mortality). Sensitivity analyses were also conducted in case of important definition and/or technical differences between studies and presence of outliers.

Results

a) Study selection, study characteristics and quality evaluation

After removing 2382 duplicates, 2733 titles and abstracts were screened, and 126 articles underwent full-text assessment, of which 32 were included in the systematic review (Figure 1) [18-49]. We also checked the reference list of previous systematic reviews on the topic but found no further relevant studies.

General characteristics of the included studies (29 retrospective and 3 prospective) are shown in Table 1. Details regarding demographic and clinical characteristics of the patients are presented in Supplementary Table 1. Twenty-one of the included studies (65.6%) evaluated endoscopic treatment [18-22,25-27,29-33,38-41,43,46,47,49], 3 (9.4%) focused on surgical intervention [34,35,44], and 8 (25.0%) evaluated both types of intervention [23,24,28,36,37,42,45,48].

Overall, 936 patients were treated with endoscopic methods, including 533 with stent placement (22 studies) [18-20,22-28,30,31,33,37-40,42,45,47-49], 133 with EVT (6 studies) [19,30,41,43,45,46], 70 with clips (3 studies) [18,40,42,47], 14 with fibrin glue (2 studies) [31,47], 86 with argon plasma coagulation (1 study) [40], and 45 with multimodal interventions (3 studies) [21,36,38]. In 75 patients across 4 studies, the outcomes of different endoscopic treatments were evaluated together [28,29,32,47]. Regarding stent placement, most studies used self-expanded metal stents (SEMS), which were fully covered in the majority of the patients. Meta-analysis comparing partially and fully covered metal stents was not performed due to the low number of studies evaluating outcomes separately. Details about the endoscopic treatment are summarized in Table 2.

A total of 144 patients were treated with surgical interventions, including 13 with anastomosis disassembly and ostomy (3 studies) [24,28,44], 17 with suture of anastomosis (3 studies) [34,35,37], 20 with re-anastomosis (3 studies) [28,42,44], and 19 with other surgical interventions (3 studies) [28,35,44]. In 75 patients across 4 studies, the outcomes of different surgical treatments were evaluated together [23,36,45,48].

Methodological quality of the included studies is described in Table 1. The median Newcastle-Ottawa score was 6 (IQR 5-6). Funnel plots and Egger's test did not show evidence of publication bias when evaluating in-hospital mortality after endoscopic (p=0.410) and surgical treatment (p=0.169) and clinical success after endoscopic treatment (p=0.053).

b) Surgical *versus* endoscopic treatment

Technical success was presented in 6 endoscopic studies, with 5 of them reporting a technical success of 100% [22,24,25,29,49] and the other presenting a rate of 92.9% [26].

Clinical success (leak closure rate) was similar in endoscopic and surgical studies (83.2% [95% CI 77.0-88.6%] *versus* 82.2% [95% CI 67.7-93.3%]) (Figure 2 and Table 3). However, overall in-hospital mortality was significantly higher in surgical studies than in endoscopic studies (35.8% [95% CI 23.9-48.5%) *versus* 6.4% [95% CI 3.8-9.6%]) (Figure 3 and Table 3). Death directly due to adverse events of endoscopic treatment was described in 8 endoscopic studies, and the pooled treatment related mortality was 1.4% (95% CI 0.0-3.8%). Clinical success and mortality were similar when stratifying by lesion location (Table 3).

After surgical treatment, there were no surgical reinterventions (0% [95% CI 0-4.8%]) [23,24,28,35-37,42,44]. After endoscopic treatment, the rate of surgical reintervention was 4.9% (95% CI 2.7-7.6%) (Supplementary figure 1) [18-33,36-39,41-43,46,47,49].

Surgical complications were presented in 3 studies, which reported development of stenosis, fistulae, and severe bleeding in 17.6% [44], 30.0% [35] and 2.9% [36] of the

patients, respectively. Overall adverse events occurred in 26.6% of the patients treated with EVT or stenting (95% CI 20.7-33.0%; detailed below).

There were no significant differences in terms of hospital or ICU length of stay (Table 4). Most studies defined hospital length of stay as time between cancer surgery and discharge. Sensitivity analysis excluding two studies with slightly different definitions of this outcome [27,36] did not significantly affect the estimates.

Time until AL resolution was only presented in 1 surgical study (50.1 ± 60.0 days) [35]. In endoscopic studies, mean time until AL resolution ranged from 12.0 to 63.4 days [19-23,26,27,29,30,38,39,41,43,46,47,49].

c) EVT *versus* stent

c1) Single-arm meta-analysis

EVT, in comparison to stent, was associated with a non-significantly higher clinical success rate (91.3% [95% CI 79.2-99.6%] *versus* 81.5% [95% CI 73.6-88.3%]) (Table 3) and a non-significantly lower in-hospital mortality rate (6.0% [95% CI 1.8-11.4%] *versus* 8.6% [95% CI 4.6-13.4%]) (Table 3).

EVT was associated with a non-significantly lower rate of surgical reinterventions (1.8% [95% CI 0-5.2.0%] *versus* 5.7% [95% CI 2.6-9.6%]), but a non-significantly higher rate of endoscopic reinterventions (8.3% [95% CI 0-21.4%] *versus* 4.0% [95% CI 2.2-6.4%])[18-20,22-27,30,31,33,37-39,41-43,46,47,49]. Moreover, EVT required 1 to 18 sponges, while the number of stents ranged from 1 to 7 (Table 2).

EVT and stenting complications are shown on Table 5. The overall complications rate, considering the occurrence of migration of endoscopic device, stenosis, severe bleeding, perforation or fistulization, was non-significantly lower in the EVT group (14.0% [95% CI 3.2-27.7%] *versus* 32.6% [95% CI 24.0-41.9%]) [18-20,22,23,25-27,30,31,33,37-43,46-49]. Sensitivity analysis, excluding an outlier (Feith, M. *et al.,* 67.0% of overall complications after stenting[25]), did not significantly affect the estimates. EVT was associated with a non-significantly lower migration rate compared to stenting. Sensitivity analysis

excluding an outlier (Feith, M. *et al*., 53% migration after stent placement[25]) did not significantly affect the estimates. Stenosis rate was non-significantly higher in the EVT group. Sensitivity analysis excluding two outliers (Min, Y. W. *et al*., 35% stenosis after EVT [43]; Ma, H. *et al.,* 43% stenosis after stent placement [40]) found that stenosis rate was similar in EVT and stent studies. Other adverse events (severe bleeding, perforation and fistulization) were infrequent (<3.5%) and were similar in EVT and stent groups.

There were no significant differences in terms of hospital or ICU length of stay (Table 4). Freeman, R. K. *et al* [27], which included patients who underwent stent placement before being transferred from other facilities, reported a shorter hospital length of stay (9.0 days [95% CI 7.2-10.8]); sensitivity analysis excluding this study did not significantly affect the estimates.

EVT was associated with a significantly shorter time until AL resolution compared with stenting (17.6 days [95% CI 14.1-21.2] *versus* 39.4 days [95% CI 27.0-51.8]) (Figure 4) [19,20,25,26,30,38,39,41,43,46,47,49]. Sensitivity analysis excluding an outlier (Freeman, R. K. *et al*., 12 days until AL resolution after stent placement [27]) did not significantly affect the estimates.

Mean time until oral intake, only reported in 4 stent studies, ranged between 1.7 and 28.8 days [22,33,37,40].

c2) Double-arm meta-analysis

Meta-analysis of the studies directly comparing EVT with stent placement revealed that EVT was associated with non-significantly higher clinical success (OR 1.91 [95% CI 0.47-7.79]) [19,30], lower in-hospital mortality (OR 0.39 [95% CI 0.13-1.18]) [19,45], and lower endoscopic (OR 0.21 [95% CI 0.02-1.88]) (Supplementary figure 2) and surgical (OR 0.45 [95% CI 0.04-5.61]) reintervention rates [19,30]. There were also non-significantly lower rates of migration of endoscopic device (OR 0.51 [95% CI 0.17-1.55]) and stenosis (OR 0.58 [95% CI 0.09-3.97]), but a significantly lower rate of overall complications in the EVT group (OR 0.35 [95% CI 0.13-0.95]) (Figure 5) [19,30].

EVT was associated with non-significantly shorter time until AL resolution (WMD -8.67 days [95% CI -22.54 to 5.20]) [19,30] and shorter hospital length of stay (WMD -12.98 days [- 31.27 to 7.98]) (Supplementary figure 3) [19,30,45]. There was a significantly shorter ICU length of stay in the EVT group compared to the stent group (WMD -14.77 days [95% CI -26.57 to -2.98]) (Supplementary figure 4) [19,45].

d) Other endoscopic treatments

Some of the included studies focused on other endoscopic treatments besides stents and EVT, namely clips, fibrin glue, argon plasma coagulation, and multimodal modalities, that were not included in meta-analysis due to the reduced number of studies on these treatments. There were no deaths directly related to any of these treatments. Clipping and fibrin glue had clinical success in 66.7% and 78.6% of the patients, respectively. Multimodal modalities had higher rates of clinical success ranging from 80.0% to 96.0%. Details on the outcomes of these treatments are shown in Table 6.

Discussion

This systematic review and meta-analysis evaluated the efficacy of endoscopic and surgical interventions in the management of AL after gastroesophageal cancer surgery. To our knowledge, this is the first meta-analysis simultaneously comparing 1) endoscopic *versus* surgical interventions and 2) EVT *versus* stent placement in this specific context.

Our results demonstrated that endoscopic treatment, in comparison to surgical intervention, was associated with a significantly lower in-hospital mortality rate. However, no significant differences were found between these treatments in terms of clinical success, surgical reinterventions, hospital length of stay and ICU length of stay. The decreased mortality found in the endoscopic therapy group may be related with the lesser invasiveness of these therapies, although it is also possible that there are

differences in the clinical status and/or dehiscence characteristics of the patients between the two groups that may contribute to this difference in mortality. For instance, Schweigert, M. *et al* found that patients in the surgical group were generally in worse condition, being more frequently septic [48]. However, most studies did not present data on the clinical status at presentation.

We found a non-significantly higher clinical success rate and a non-significantly lower in-hospital mortality rate for EVT compared to stent placement. As EVT is a relatively new technique, it is possible that the first studies evaluating this method included patients in which a favorable outcome was expected (selection bias), thus influencing the results [16].

Our single-arm meta-analysis revealed no significant differences between EVT and stent placement in terms of reinterventions or complications. However, there was a significantly lower rate of overall complications in the EVT group, although this difference is mainly explained by a single study, which had a weight of 89.6% [19].

We found that EVT was associated with a significantly shorter time until AL resolution compared with stent placement. This might be due to the fact that, in EVT, sponges were changed frequently, usually every 72-120h, until successful healing of the AL [19,30,41,43,46]. In contrast, the stents usually remain in place for 4-8 weeks until follow-up endoscopy with stent change or stent removal [24,25]. Therefore, we cannot exactly ascertain the moment when AL closure was achieved in the case of stent placement. As pointed out by Scognamiglio *et al.*, a more adequate outcome parameter to measure the success of therapy would be the time until resolution of AL-associated symptoms or the time until start of oral nutrition [16]. However, none of the studies reported time until resolution of AL-associated symptoms, but 4 stent studies presented the mean time until oral intake, which ranged from 1.7 to 28.8 days (lower than the reported time until to AL resolution).

As sponge changes are much more frequent than stent replacement, EVT requires a higher number of endoscopic devices and procedures. This offers the possibility to

assess the wound regularly, which might help in detecting complications before their progression, which might contribute to the lower rate of overall complications in EVT studies. In addition, it allows endoscopic lavage and debridement at each sponge exchange, which has been shown to reduce pleural inflammation and leakage-associated mortality [50]. However, the higher number of endoscopic procedures and devices increases the cost of EVT, which has been shown to be twice the cost of stent placement [51].

Regarding hospital and ICU length of stay, there were no significant differences between EVT and stent placement in single-arm studies, although in comparative studies EVT was associated with a significantly shorter ICU length of stay compared to stenting.

Our study has some limitations. Included studies are mostly retrospective, single-arm and/or include a small sample size. In addition, one problem that led to limited comparability of several outcomes was the fact that their definitions were heterogenous or absent in many studies. Another limitation was the heterogeneity found on most analysis, that did not decrease when stratifying by tumour location. Variables such as presence of comorbidities, dimensions and location of AL, time until diagnosis or time until treatment have differences between studies and may also contribute for heterogeneity. Moreover, whereas stent placement is quite standardized and reproducible, EVT procedure may differ between institutions in terms of the magnitude of negative pressure, interval between sponge changes and placement of the sponge (extra- or intraluminal). A fourth limitation refers to the relatively low number of EVT studies and patients, which may have led to underpowerment to detect existent differences.

In conclusion, we found that endoscopic treatment was associated with a lower in-hospital mortality compared to surgical intervention. EVT is associated with a lower rate of overall complications and a shorter ICU length of stay compared to stenting. Other differences, although not significant, seemed to point to a greater efficacy and safety profile of endoscopic treatment, in comparison to surgical intervention, and of EVT

compared to stenting. These findings can help in the definition of standardized treatment algorithms.

Although EVT seems like a promising treatment, the lack of comparative studies poses a challenge in making definite conclusions. Therefore, it is essential to develop more robust prospective randomized comparative studies with standardized interventions and outcomes in order to compare EVT with other modalities such as stents and clips.

Tables

Table 1 – General characteristics and quality evaluation of the included studies

Author, year	Country	Study period	Tumor location	Esophagectomy – n (%)	Neoadjuvant therapy – n (%)	AL – n (%)	Time until AL diagnosis (#) – mean ± SD	Quality (*)	M-A
Prospective studies									
Endoscopic treatment									
Feith, M. 2011	DE	2003-2009	E	87 (75.7)	89 (77.4)	-	8.4 ± 3.5	6	Yes
Kucukay, F. 2012	TR	-	G	0 (0)	-	-	5.4 ± 1.8	4	Yes
Fernandez, A. 2015	ES	2011-2013	E, G	4 (28.6)	-	-	-	6	Yes
Retrospective studies									
Endoscopic treatment									
Freeman, R. K. 2015	USA	7-year period	E	45 (100)	38 (84.4)	-	-	5	Yes
Gonzalez, J.M. 2016	FR	2010-2014	E	34 (97.1)	25 (71.4)	-	8.2 ± 5.6	4	Yes
Kauer, W. K. 2007	DE	1998-2005	E	12 (100)	-	12 (4.5)	-	4	Yes
Leenders, B. J. M. 2013	NL	2007-2010	E	15 (100)	-	19 (16.0)	-	6	Yes
Mennigen, R. 2015	DE	2009-2015	E	15 (100)	11 (73.3)	-	11.8 ± 11.5	6	Yes
Min, Y. W. 2019	KR	2015-2017	E	20 (100)	10 (50.0)	-	14.7 ± 8.0	6	Yes
Wu, G. 2017	CN	-	E	27 (100)	-	-	-	5	Yes
Kim, Y. J. 2012	KR	2003-2011	G	0 (0)	-	66 (12.6)	8.6 ± 5.4	6	Yes
Al-issa, M. A 2013	DK	2007-2010	E, G	-	-	20 (9.6)	-	6	Yes

Berlth, F. 2018 - EVT - SEMS	DE	2007-2016	E, G	93 (83.8)	68 (61.3) 18 (52.9) 50 (64.9)	-	10.2 ± 11.4 12.6 ± 13.7 8.5 ± 4.6	6	Yes
Bohle, W. 2020	DE	2009-2015	E, G	27 (79.4)	22 (64.7)	-	9.3 ± 6.5	6	Yes
Böhm, G. 2010	DE	2000-2007	E, G	-	-	81 (25.9)	11 ± 8	6	Yes
Dai, Y. Y.2009	DE	2001-2007	E, G	17 (77.3)	-	-	6.5 ± NA	6	Yes
Hwang, J.J. 2016	KR	2008-2014	E, G	9 (50.0)	-	-	-	6	Yes
Licht, E. 2015	USA	2003-2012	E, G	-	-	-	8.9 ± 5.8	4	Yes
Ma, H. 2018	CN	2008- 2016	E, G	-	-	263 (10.1)	-	6	Yes
Schorsch, T. 2014	DE	2006-2013	E, G	9 (45.0)	10 (50.0)	-	9.9 ± 5.4	6	Yes
Schubert, D. 2006	DE	2000-2004	E, G	19 (73.1)	-	-	6.7 ± 2.8	6	Yes
Surgical treatment									
Lee, D. H. 2012	KR	2000-2010	E	10 (100)	-	23 (3.5)	12.0 ± 8.6	5	Yes
Page, R.D. 2004	UK	9 year period	E	17 (100)	-	-	9.3 ± 5.6	6	Yes
Lang, H. 2000	DE	1968-1998	G	0 (0)	-	83 (7.5)	-	4	Yes
Endoscopic and surgical treatment									
Angulo, D.R. 2018	ES	2011-2016	E	10 (100)	6 (60.0)	10 (11.8)	-	6	Yes
Etxaniz, S. L. 2013	ES	2003-2011	E	10 (100)	-	18 (23.4)	-	6	Yes
Fumagali, U. 2018	IT	2014-2017	E	40 (100)	-	59 (11.8)	-	4	Yes
Schniewind, B. 2013	DE	1995-2012	E	47 (100)	-	62 (16.9)	-	8	Yes
Schweigert, M. 2014	DE	2004-2013	E	49 (100)	14 (28.6)	49 (13.8)	-	6	Yes

Lee, S. 2015 - Endoscopy - Surgery	KR	2000-2013	G	0 (0)	-	133 (0.7)	 9.8 ± 5.5 17.9 ± 24.0	7	Yes
Lee, S. R. 2018	KR	2002-2016	G	0 (0)	-	13 (3.1)	3.9 ± 1.7	6	Yes
Milek, T. 2016	PL	1996-2014	G	0 (0)	-	23 (4.7)	7 ± NA	6	Yes

(#) Defined as time between cancer surgery and AL detection. (*) Quality evaluation using Newcastle Ottawa Quality Assessment Scale for cohort studies. NA: not available; DE: Germany; TR: Turkey; ES: Spain; DK: Denmark; USA: United States of America; IT: Italy; FR: France; KR: South Korea; NL: The Netherlands; CN: China; PL: Poland; UK: United Kingdom; E: esophageal and/or esophagogastric junction; G: gastric; M-A: included in meta-analysis.

Table 2 – Characteristics of endoscopic treatment

Author, year	Number of patients treated with EVT or stent	Type of stent			Number of endoscopic devices – median (range) OR mean ± SD
		Plastic stent – n (%)	Metal stent – n (%)		
			Partially covered – n (%)	Fully covered – n (%)	
EVT studies					
Mennigen, R. 2015	15				6.5 (1-18)
Min, Y. W. 2019	20				5 (2-12)
Schorsch, T. 2014	20				3 (1-15)
Stent studies					
Angulo, D.R. 2018	8	0 (0)	0 (0)	8 (100)	1.5 (1-2)
Etxaniz, S. L. 2013	9	0 (0)	0 (0)	9 (100)	-
Feith, M. 2011	115	0 (0)	0 (0)	115 (100)	-
Freeman, R. K. 2015	45	26 (57.8)	0 (0)	19 (42.2)	-
Fumagali, U. 2018	12	12 (100)			-
Kauer, W. K. 2007	10	0 (0)	0 (0)	10 (100)	1.4 ± NA
Leenders, B. J. M. 2013	10	0 (0)	10 (100)		1 ± 0
Schweigert, M. 2014	29	29 (100)			-
Wu, G. 2017	27	0 (0)	0 (0)	27 (100)	-
Kucukay, F. 2012	14	0 (0)	2 (14.3)	12 (85.7)	-
Lee, S. R. []	8	0 (0)	0 (0)	8 (100)	2 ± NA
Milek, T. 2016	12	0 (0)	12 (100)		-
Al-issa, M. A []	15	0 (0)	0 (0)	15 (100)	1.1 ± NA
Bohle, W. []	34	0 (0)	34 (100)		2 (1-7)
Dai, Y. Y. []	22	22 (100)			2 (NA)
Fernandez, A. 2015	14	0 (0)	0 (0)	14 (100)	1 (1-2)*
Licht, E. 2015	31	0 (0)	31 (100)		-
Ma, H. 2018	7	0 (0)	7 (100)		-
Schubert, D. 2006	11	9 (81.8)	0 (0)	2 (18.2)	1 ± 0
Double arm studies					
Berlth, F. 2018 - EVT - Stent	 34 77	 - 0 (0)	 - 0 (0)	 - 77 (100)	 3 (1-9) 1 (1-3)
Hwang, J.J. 2016 - EVT - Stent	 7 11	 - 0 (0)	 - 11 (100)		 4 (2-10) 2 (1-4)

Schniewind, B. 2013				
- EVT	17	-	-	-
- Stent	12	4 (33.3)	8 (66.7)	-

* Data regarding 1 patient was not available

Table 3 – Primary outcomes according to treatment and tumor location

Mortality	Pooled mortality (95% CI)	I^2
Endoscopic studies		
Overall	6.4 (3.8-9.6) [18-29,31-33,36-38,41-43,45-49]	57%
AL after esophageal tumor	6.2 (2.2-11.3) [23-25,27-29,31,38,41,43,45,48,49]	66%
AL after gastric tumor	6.3 (0.3-0.14.8) [32,33,36,37,42]	53%
EVT	6.0 (1.8-11.4) [19,41,43,45,46]	10%
Stent placement	8.6 (4.6-13.4) [18-20,22-28,31,33,37,38,42,45,47-49]	61%
Surgical studies		
Overall	35.8 (23.9-48.5) [23,24,28,34-37,42,44,45,48]	52%
AL after esophageal tumor	33.3 (18.3-49.6) [23,24,28,35,44,45,48]	55%
AL after gastric tumor	42.3 (17.4-68.6) [34,36,37,42]	61%
Clinical success	**Pooled clinical success rate (95% CI)**	**I^2**
Endoscopic studies		
Overall	83.2 (77.0-88.6) [18-27,30-33,36-39,41-43,46,47,49]	72%
AL after esophageal tumor	86.6 (76.4-95.0) [23-25,27,31,38,39,41,43,49]	78%
AL after gastric tumor	80.0 (61.3-95.5) [32,33,36,37,42]	76%
EVT	91.3 (79.2-99.6) [19,30,41,43,46]	77%
Stent placement	81.5 (73.6-88.3) [18-20,22-27,30,31,33,37-39,42,47,49]	72%
Surgical studies with > 5 patients		
Overall	82.2 (67.7-93.3) [35,36,42,44]	41%
AL after esophageal tumor	75.8 (45.4-98.7) [35,44]	61%
AL after gastric tumor	87.8 (64.8-100) [36,42]	53%

Table 4 – Hospital and ICU length of stay according to treatment

	Hospital length of stay, days - Weighted mean (95% CI)	I^2
Endoscopic treatment	45.9 (35.9-55.9) [19,23,27,30,32,36-38,40,41,43,45,48]	97%
- EVT	51.4 (45.1-57.7) [19,30,41,43,45]	32%
- Stent placement	44.6 (31.8-57.4) [19,23,27,30,37,38,40,45,48]	97%
Surgical treatment	41.9 (30.9-52.9) [36,44,45,48]	72%
	ICU length of stay, days - Weighted mean (95% CI)	I^2
Endoscopic treatment	19.5 (13.0 - 26.0) [19,45,47]	69%
- EVT	18.1 (3.8-32.5) [19,45]	87%
- Stent placement	21.1 (12.7-29.5) [19,45,47]	41%
Surgical treatment	21.7 (3.4 - 40.1) [44,45]	86%

Table 5 – Complications according to treatment

	Overall complications - Pooled prevalence (95% CI)	I^2
EVT	14.0 (3.2-27.7) [19,30,41,43,46]	65%
Stent placement	32.6 (24.0-41.9) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	75%
	Migration – Pooled prevalence (95% CI)	I^2
EVT	6.1 (0.8-13.9) [19,30,41,43,46]	80%
Stent placement	21.5 (13.5-30.8) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	41%
	Stenosis - Pooled prevalence (95% CI)	I^2
EVT	8.1 (0-20.2) [19,30,41,43,46]	32%
Stent placement	4.9 (2.6-7.7) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	69%
	Severe bleeding - Pooled prevalence (95% CI)	I^2
EVT	1.1 (0-3.8) [19,30,41,43,46]	0%
Stent placement	2.0 (0.8-3.6) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	10%
	Perforation - Pooled prevalence (95% CI)	I^2
EVT	1.1 (0-3.8) [19,30,41,43,46]	0%
Stent placement	1.7 (0.7-3.0) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	0%
	Fistulisation - Pooled prevalence (95% CI)	I^2
EVT	1.1 (0-3.8) [19,30,41,43,46]	0%
Stent placement	3.2 (1.9-5.0) [18-20,22,23,25-27,30,31,33,37-40,42,47-49]	0%

Table 6 – Outcomes of endoscopic treatments besides EVT and stenting

	Mortality – n (%)	Clinical success – n (%)	Endoscopic reintervention – n (%)	Surgical reintervention – n (%)	Migration – n (%)	Stenosis – n (%)	Severe bleeding – n (%)	Fistulae – n (%)	Perforation – n (%)	Hospital length of stay, days - mean ± SD	ICU length of stay, days - mean ± SD	Time until AL resolution, days - mean ± SD	Time until oral intake, days - mean ± SD
Clips													
Ma, H. 2018	-	-	-	-	-	22 (34.4)	0 (0)	0 (0)	0 (0)	15.6 ± 2.8	-	-	13.1 ± 2.6
Milek, T. 2016	0 (0)	2 (50.0)	2 (50.0)	0 (0)	-	-	-	-	-	19 ± NA	-	-	-
Schubert, D. 2006	0 (0)	2 (100)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	-	5 ± 3	-	-
Fibrin glue													
Kauer, W. K. 2007	0 (0)	2 (100)	0 (0)	0 (0)	-	-	-	-	-	-	-	-	-
Schubert, D. 2006	0 (0)	9 (75.0)	3 (25.0)	0 (0)	-	3 (25.0)	0 (0)	0 (0)	0 (0)	-	11.7 ± 7.7	-	-
Fibrin glue + vycril mesh													
Bohm, G. 2010	0 (0)	13 (93.3)	1 (6.7)	0 (0)	-	NA	0 (0)	1 (6,7)	0 (0)	-	-	44 ± 9	-
Fibrin glue and/or clip													
Lee, S. 2015	0 (0)	24 (96.0)	0 (0)	1 (4.0)	-	0 (0)	1 (4.0)	0 (0)	0 (0)	16.2 ± 10.8	-	-	8.4 ± 6.3

Argon plasma coagulation													
Ma, H. 2018	-	-	-	-	-	2 (2.3)	0 (0)	0 (0)	0 (0)	9.5 ± 0.7	-	-	7.6 ± 0.6
Stent + clip													
Leenders, B. J. M. 2013	0 (0)	4 (80.0)	0 (0)	0 (0)	2 (40.0)	0 (0)	0 (0)	1 (20.0)	0 (0)	19.8 ± 9.8	-	9.7 ± 2.9*	-

* Time until AL resolution was measured in weeks; NA: not available or unclear information

Supplementary table 1 – Demographic and clinical characteristics of the patients

Author, year	Age, years – mean ± SD	Male gender – n (%)	Obesity – n (%)	Diabetes mellitus – n (%)	Tumor stage III or IV – n (%)	Time of AL diagnosis[#], days - mean ± SD	Method of diagnosis	AL location			AL circunference > 25% - n (%)	AL size, cm - mean ± SD and/or median (range)
								Cervical – n (%)	Intrathoracic – n (%)	Abdominal – n (%)		
Endoscopic treatment												
Al-issa, M. A 2013	-	-	-	-	-	-	CS, CT, E	-	-	-	-	-
Berlth, F. 2018 - EVT - SEMS	 64.7 ± 9.8 64.2 ± 9.4	 29 (85.3) 63 (81.8)	-	-	-	 12.6 ± 13.7 8.5 ± 4.6	CS, CT, E	 0 (0) 1 (1.3)	 29 (85.3) 72 (93.5)	 5 (14.7) 4 (5.2)	 8 (26.7)[†] 12 (16.0)[‡]	-
Bohle, W. 2020	65.4 ± 8.1	26 (76.5)	-	8 (23.5)	-	9.3 ± 6.5	E	-	-	-	[Ł]	-
Böhm, G. 2010	-	-	-	-	-	11 ± 8	E	-	-	-	-	-
Dai, Y. Y. 2009	63 ± NA	18 (81.8)	-	-	-	6.5 ± NA	CS, E	-	-	-	-	-
Feith, M. 2011	60.4 ± 13.0	-	-	-	-	8.4 ± 3.5	E	-	-	-	-	-
Fernandez, A. 2015	63.8 ± 9.1	11 (78.6)	-	-	-	-	CS	-	-	-	-	-
Freeman, R. K. 2015	61 ± 19	-	-	-	-	-	CS	0 (0)	45 (100)	0 (0)	-	-
Gonzalez, J.M. 2016	61.7 ± 8.9	31 (88.6)	-	-	-	8.2 ± 5.6	CS, CT, E	16 (48.5)*	17 (51.5)*	0 (0)*	-	-

Hwang, J.J. 2016 - EVT - Stent	71,1 ± 4.7 67.4 ± 8.1	5 (71.4) 9 (81.8)	-	-	-	-	-	-	-	-	-	0.81 (0.3 – 2.0) 0,66 (0,2 – 2.0)
Kauer, W. K. 2007	-	-	-	-	-	-	CS, E	0 (0)	12 (100)	0 (0)	-	-
Kim, Y. J. 2012	62.8 ± 10.7	24 (72.7)	-	-	12 (36.4)	8.6 ± 5.4	CS, CT, E	0 (0)	0 (0)	33 (100)	-	1.7 (0.5-4)
Kucukay, F. 2012	47.4 ± 7.9	-	-	-	10 (71.4)	5.4 ± 1.8	CS, E	-	-	-	14 (100)	-
Leenders, B. J. M. 2013	60.4 ± 11.1	9 (60.0)	-	-	-	-	-	12 (80.0)	3 (20.0)	0 (0)	-	-
Licht, E. 2015	-	-	-	-	-	8.9 ± 5.8	CS, CT	-	-	-	-	-
Ma, H. 2018 - APC - Clips - Stents	63.2 ± 6.97	127 (80.9)	-	-	-	-	CS, E	2 (1.3)	155 (98.7)	0 (0)	-	0.7 ± 0.4 1.0 ± 0.2 1.7 ± 0.1
Mennigen, R. 2015	57.0 ± 9.8	14 (93.3)	-	-	-	11.8 ± 11.5	E	0 (0)	15 (100)	0 (0)	-	-
Min, Y. W. 2019	66.1 ± 6.4	20 (100)	-	-	-	14.7 ± 8.0	CS, E	7 (35.0)	13 (65.0)	0 (0)	-	1.75 (0.5-3)
Schorsch, T. 2014	69.4 ± 10.1	14 (70.0)	-	-	-	9.9 ± 5.4[§]	CT, E	-	-	-	-	1.75 ± 1.2 1,25 (0.5-4)
Schubert, D. 2006	61.2 ± 12.4	17 (65.4)	-	-	-	6.7 ± 2.8	CS, E	0 (0)	26 (100)	0 (0)	18 (69.2)	-
Wu, G. 2017	60.8 ± 7.0	19 (70.4)	-	-		-	CS, CT	27 (100)	0 (0)	0 (0)	-	-
Surgical treatment												
Lang, H. 2000	-	-	-	-	-	-	CS	-	-	-	-	-

Lee, D. H. 2012	61.3 ± 5.9	10 (100)	-	-	-	12.0 ± 8.6	CS	9 (90.0)	1 (10.0)	0 (0)	-	-
Page, R.D. 2004	-	-	-	-	-	9.3 ± 5.6	CS, E	-	-	-	-	-
Endoscopic and surgical treatment												
Angulo, D.R. 2018	64.5 ± 9.8	10 (100)	-	-	6 (60.0)	-	-	0 (0)	10 (100)	0 (0)	-	-
Etxaniz, S. L. 2013	-	-	-	-	-	-	CS, CT, E	10 (100)	0 (0)	0 (0)	-	-
Fumagali, U. 2018	-	-	-	-	-	-	-	0 (0)	40 (100)	0 (0)	-	-
Lee, S. 2015 - Endoscopy - Surgery	 62.7 ± 9.0 66.3 ± 7.7	 16 (64.0) 27 (77.1)	-	-	-	 9.8 ± 5.5 17.9 ± 24.0	CS, CT	-	-	-	-	-
Lee, S. R. 2018	58.9 ± 10.7	5 (50.0)	2 (20.0)	1 (10)	4 (40.0)	3.9 ± 1.7	CS, CT, E	-	-	-	1 (10.0)	-
Milek, T. 2016	64 ± NA	17 (73.9)	-	0 (0)	-	-	CS, CT	-	-	-	-	-
Schniewind, B. 2013	-	-	-	-	-	-	CS, E	7 (14,9)	40 (85.1)	0 (0)	-	-
Schweigert, M. 2014	64.8 ± NA	-	-	-	-	-	CT, E	0 (0)	49 (100)	0 (0)	-	-

(#) Defined as time between surgery and leak detection. (§) Data about 1 patient was not available. (*) Data about 2 patients was not available. (†) Data about 4 patients was not available. (‡) Data about 2 patients was not available. (Ł) In 28 patients (82%), leak size was smaller than 1/3 of anastomotic circumference; 6 patients (18%) presented with a leak size between 1/3 and 2/3 of esophageal circumference. APC: argon plasma coagulation; CS: contrast study; CT: computed tomography scan; E: upper endoscopy.

Figures

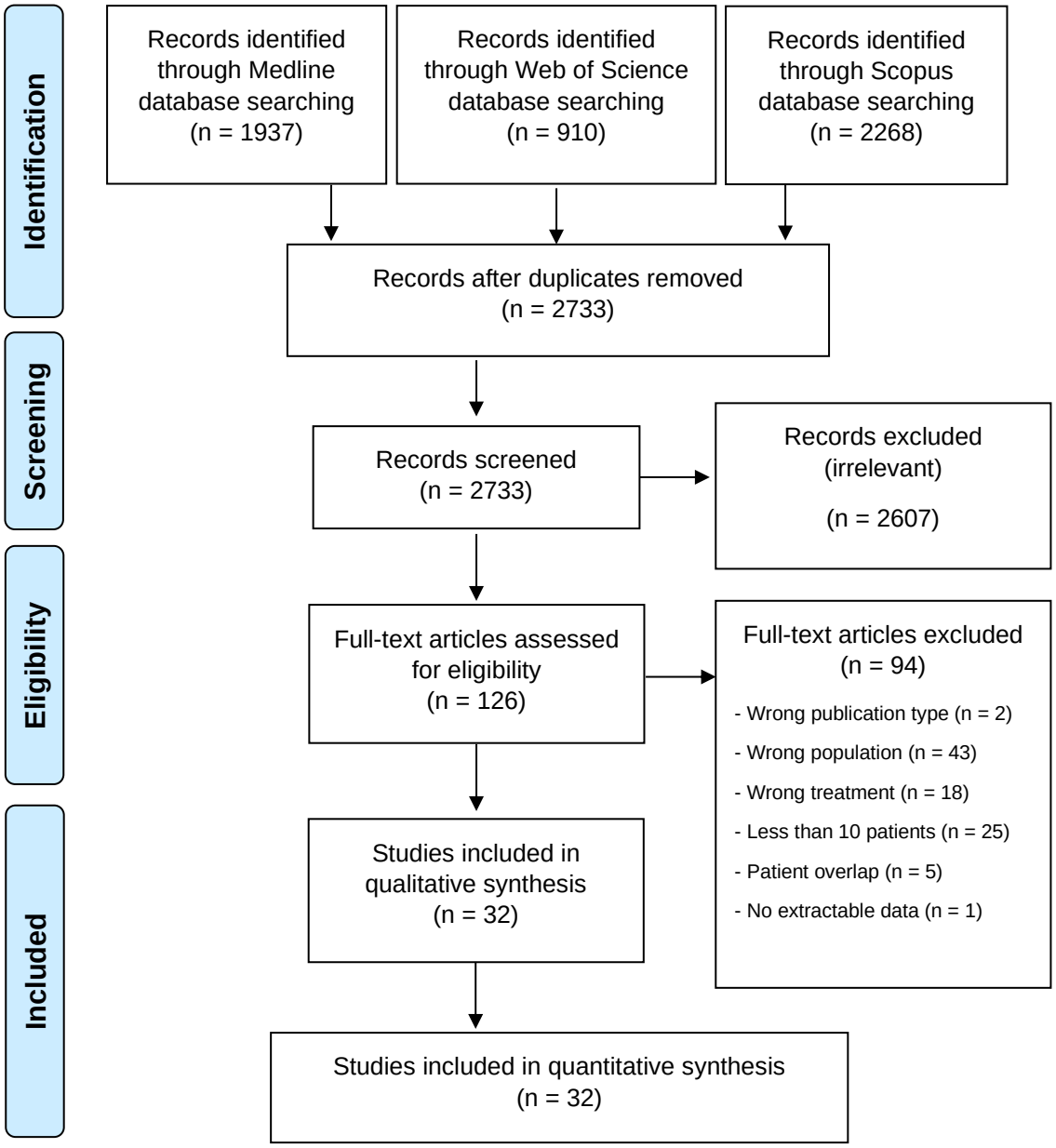


Figure 1 – Flow diagram of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses

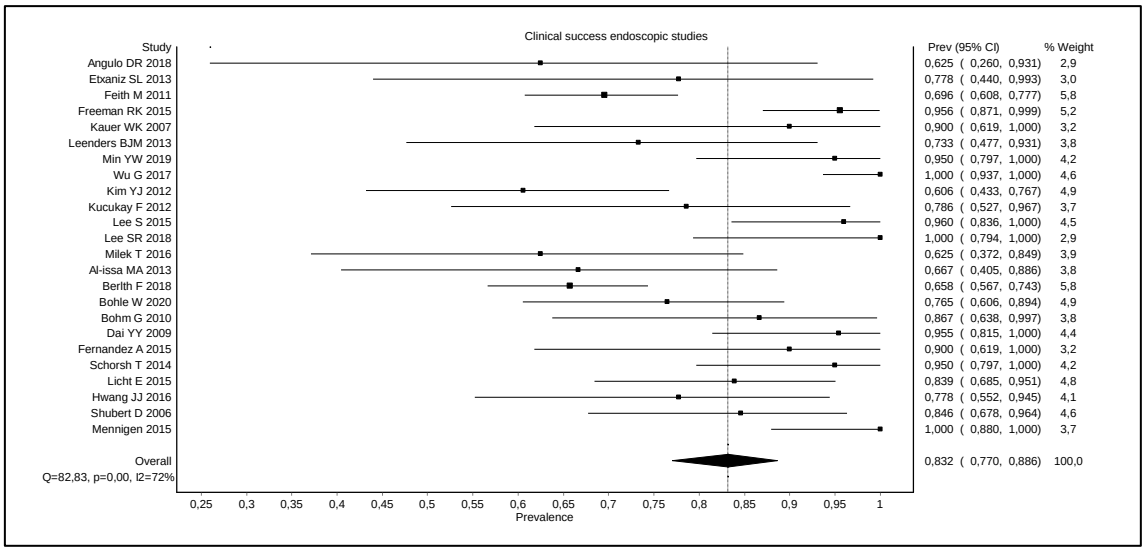


Figure 2 – Forest plot of clinical success after endoscopic treatment

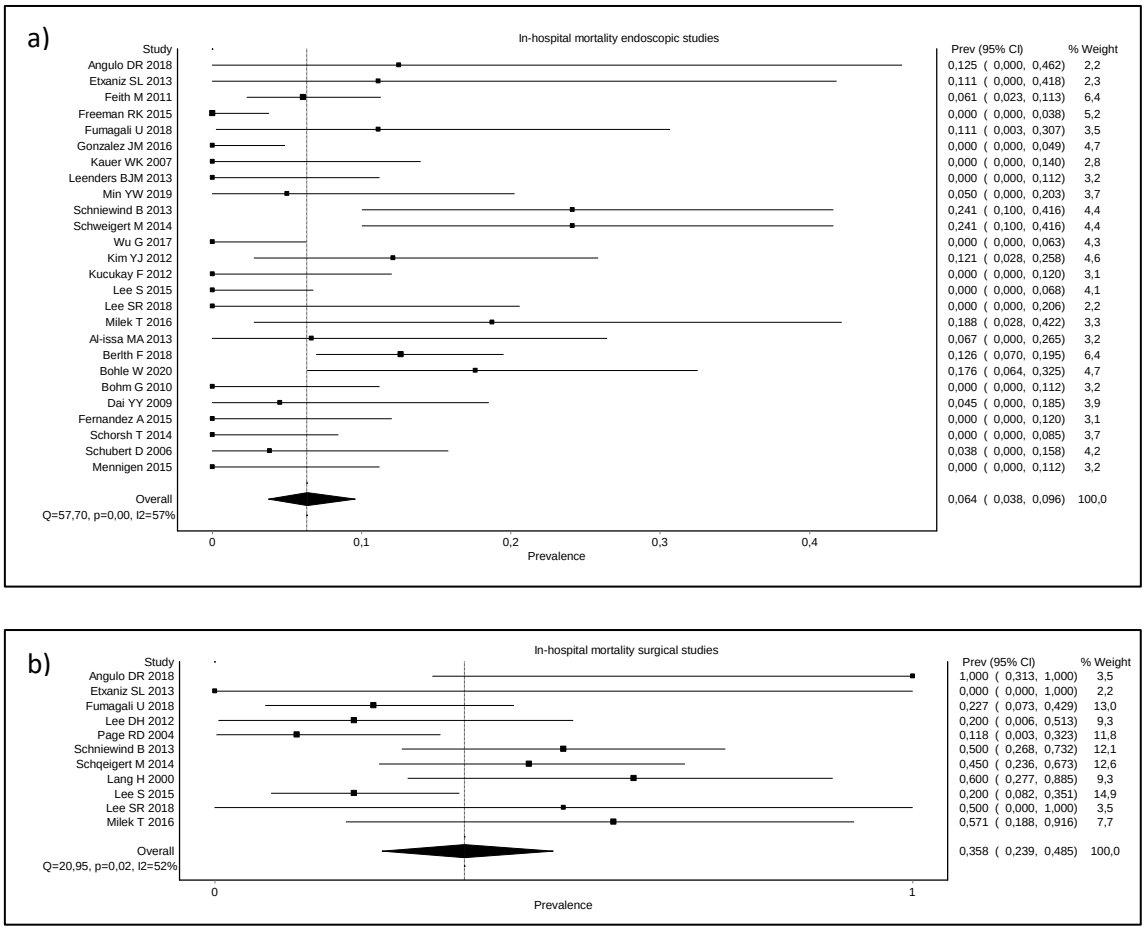


Figure 3 - Forest plot of in-hospital mortality according to treatment: a) endoscopic treatment; b) surgical treatment.

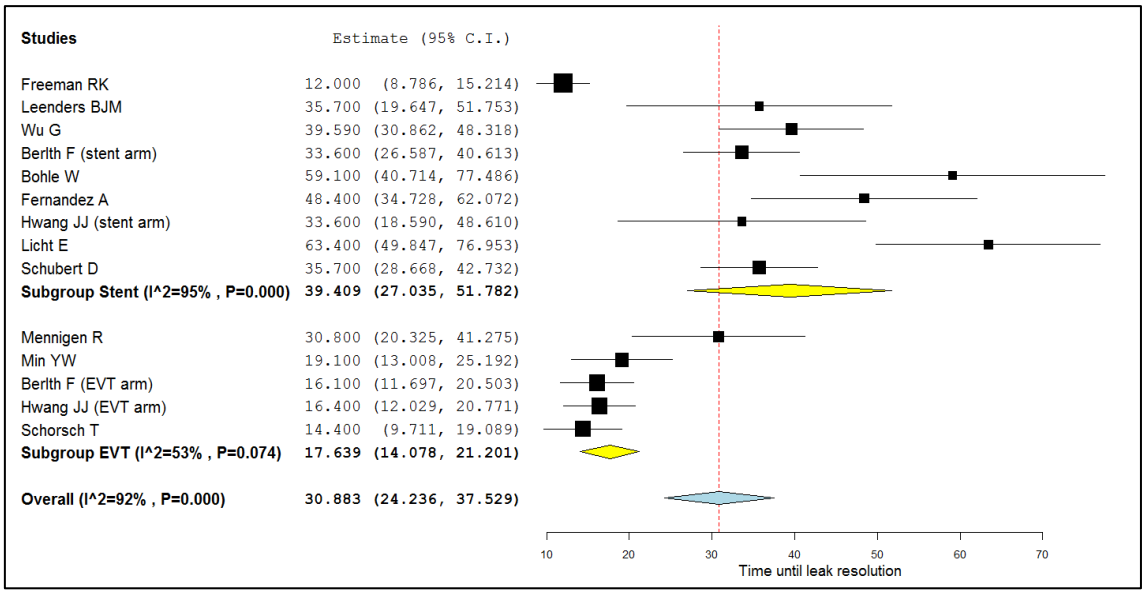


Fig. 4 – Forest plot of time until AL resolution according to treatment (EVT *versus* stent placement)

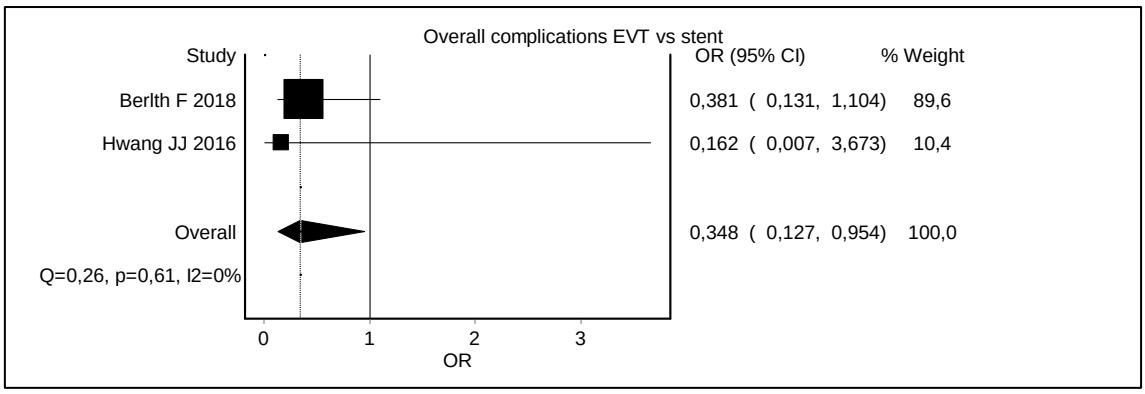
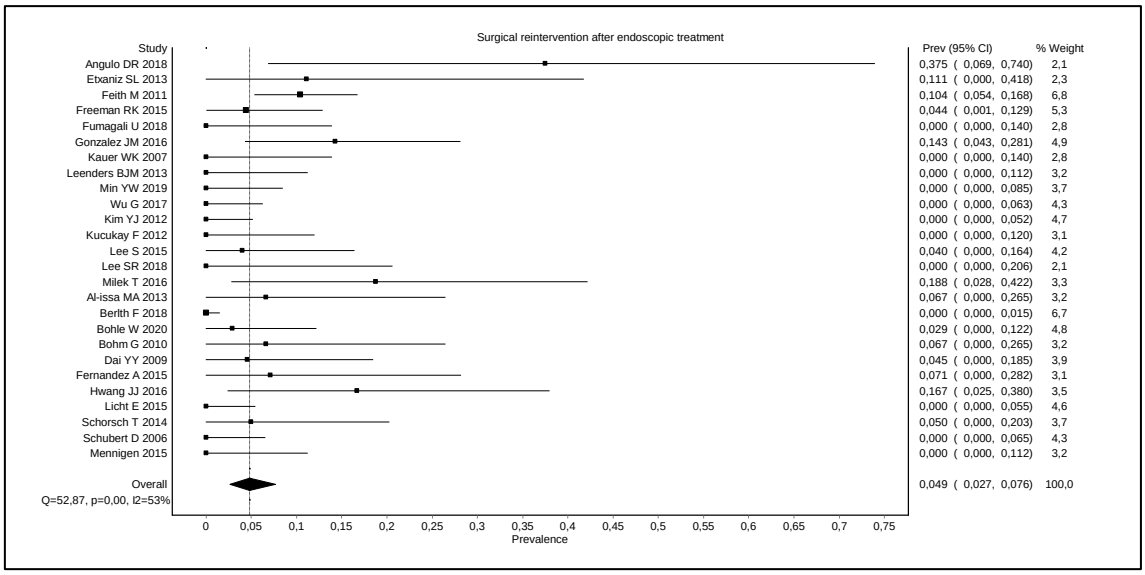
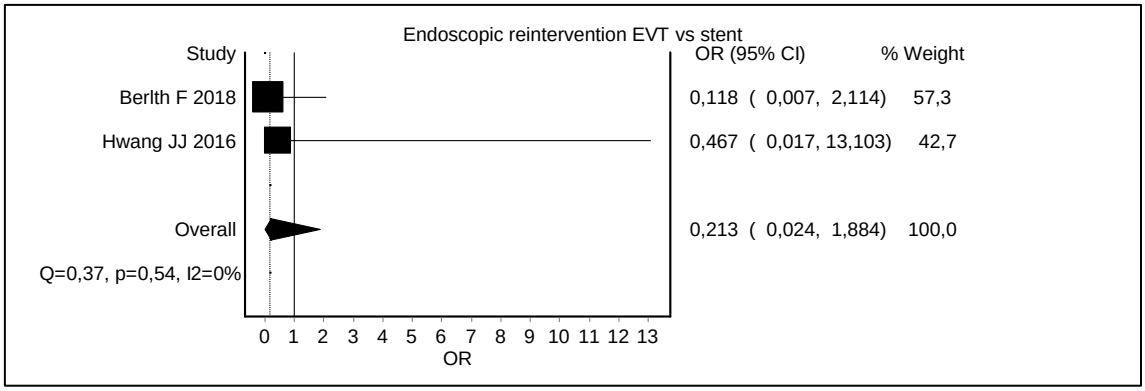


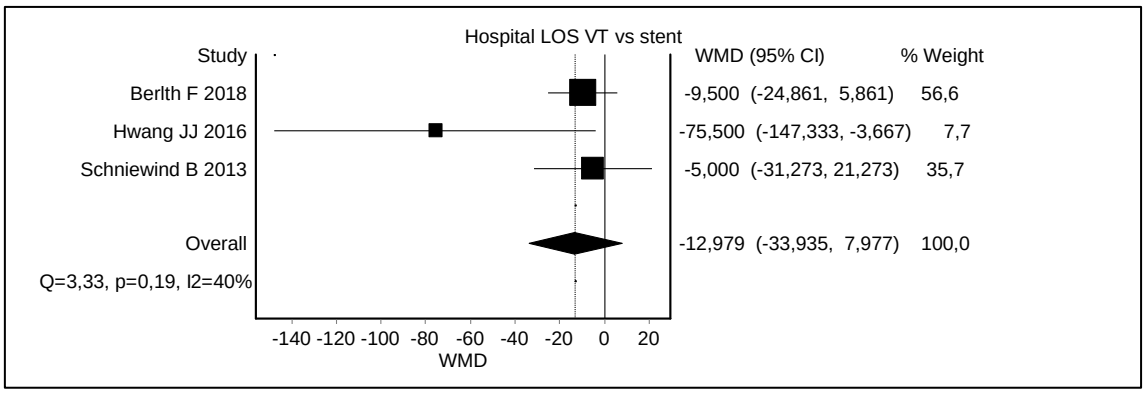
Figure 5 - Forest plot of overall complications according to treatment (EVT *versus* stent placement)



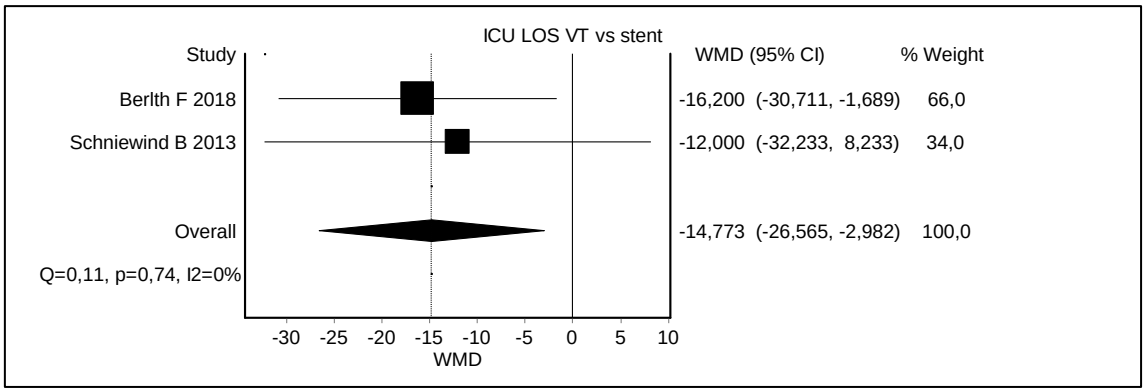
Supplementary figure 1 – Forest plot of surgical reintervention after endoscopic treatment



Supplementary figure 2 – Forest plot of endoscopic reintervention according to treatment (EVT *versus* stent placement)



Supplementary figure 3 - Forest plot of hospital length of stay according to treatment (EVT *versus* stent placement)



Supplementary figure 4 - Forest plot of ICU length of stay according to treatment (EVT *versus* stent placement)

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Anexos

1. Guidance for author on the preparation and submission of manuscripts to the European Journal of Gastroenterology & Hepatology

Aims and scope

The *European Journal of Gastroenterology & Hepatology* publishes papers reporting original clinical and scientific research which are of a high standard and which contribute to the advancement of knowledge in the field of gastroenterology and hepatology.

The journal publishes five types of manuscripts: reviews, original papers, short articles (word limit 2,500), case reports and letters to the Editor.

Letters commenting on papers in the Journal will be considered for publication. They should be submitted within 4 weeks of the appearance of the original item and be 300 words, or shorter. Such letters will be passed to the authors of the original paper, who will be offered an opportunity to reply.

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Acknowledgements

Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions.

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More than six authors:

Cardoso AC, Cravo C, Calçado FL, Rezende G, Campos CFF, Neto JMA, et al. The performance of M and XL probes of FibroScan for the diagnosis of steatosis and fibrosis on a Brazilian nonalcoholic fatty liver disease cohort. *Eur J Gastroentrol Hepatol* 2020;**32**: 231-238.

Supplements:

McColl KEL. Pathophysiology of duodenal ulcer disease. Eur J Gastroenterol Hepatol

2012; 9 (Suppl 1): S9-S12. McColl KEL. Pathophysiology of duodenal ulcer disease. *Eur J Gastroenterol Hepatol* 2012;**9**(Suppl 1): S9-S12.

Books

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Avanduk C. *Manual of Gastroentrology: Diagnosis and Therapy*. 4th ed. 2008 Philadelphia: Lippincott Williams & Wilkins.

Chapter in a book:

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Online

Snyder CL, Young DO, Green PHR, Taylor AKPagon RA, Bird TC, Dolan CR, Stephens K. Celiac disease GeneReviews [Online, 03 July 2008]. 1993 Seattle University of Washington.

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TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search strategy	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Effect measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section and Topic	Item #	Checklist item	Reported on page # / figure # / table #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, Tables 1-2, Supplementary Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	8-11, Figures 2-5, Supplementary figures 1-4, Tables 3-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10, Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
OTHER INFORMATION			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1