

Efficacy of esophageal stents as a primary therapeutic option in spontaneous esophageal perforations: a systematic review and meta-analysis of observational studies

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Abstract

Background Spontaneous esophageal perforation traditionally mandates urgent surgical treatment. Lately, esophageal stents have been used to reduce the associated morbidity and mortality. The current systematic review aimed to assess the efficacy of stents as a primary treatment option in this scenario.

Methods A systematic search was conducted in PubMed/MEDLINE, Scopus and the Cochrane Library for studies published in the English language between 2000 and 2023. We included observational studies reporting on the use of stents, alongside conservative measures and drainage procedures, in patients with spontaneous esophageal perforations. Primary outcomes were sealing rate (persistent leak occlusion) and failure rate (mortality or conversion to a major surgical operation). Secondary outcomes included patients' presentation, sepsis, drainage procedures, and reinterventions. Results for primary outcomes were presented as pooled rates with 95% confidence intervals (CIs), using a random-effects model. Methodological quality was assessed using the MINORS score.

Results Eighteen studies involving 171 patients were included. Sealing rate was 86% (95%CI 77-93%) and failure rate was 14% (95%CI 7-22%). Weighted mortality rate was 6% (95%CI 2-13%), while conversion to surgical treatment was 2% (95%CI 0-9%). Late presentation was not related to a statistically significant increase in treatment failure (odds ratio 1.85, 95%CI 0.37-9.30; P=0.72). Drainage procedures were required for the majority of patients, with a high rate of surgical and endoscopic reinterventions.

Conclusions Our results imply that stents may offer an effective and safe alternative treatment for patients with spontaneous esophageal perforations. Additional endoscopic and surgical drainage procedures are frequently needed.

Keywords Boerhaave syndrome, spontaneous esophageal perforation, stent, esophagus, self-expanding metal stent

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Conflict of Interest: None

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Introduction

Spontaneous esophageal perforation, also called barogenic rupture or Boerhaave syndrome, is a rare nosologic entity, but one with serious clinical implications. It happens as a result of abrupt distal esophageal pressurization with a closed upper esophageal sphincter, or distal esophageal spasm. The ensuing rupture is usually on the left side of the lower intrathoracic portion of the esophagus [1]. If not promptly recognized and treated, it is often fatal, with contemporary series reporting a mortality rate between 15-42% [2-5]. Traditional treatment includes urgent surgical intervention in the form of primary repair, T-tube placement, or resection and diversion, with best results accomplished when patients are operated early after the insult [6-9].

During the last 2 decades there has been increasing interest in the use of prostheses for restoration of gastrointestinal continuity, alongside resuscitation and drainage of the infected cavities. It is thought that deployment of these devices to cover the esophageal gap can lead to better patient outcomes, reducing traditional operative time and allowing for resuscitation to be optimized. A recent systematic review on esophageal stents in the management of patients with anastomotic leaks and benign perforations included 66 studies and reported technical and clinical success rates of 96% and 87%, respectively [10].

Nonetheless, the existing literature on the use of stents in esophageal perforations frequently analyzes patients as a single population, without distinguishing between largely unequal clinical entities. Spontaneous perforations hold some clinically relevant particularities, including their intrathoracic position, the magnitude of the inflammatory response, associated comorbidities, and late presentation or treatment of patients. Hence, aggressive surgical treatment is usually warranted, while the use of stents is commonly regarded as a palliative measure or a last-resort option. Therefore, this systematic review and meta-analysis aimed to investigate the current evidence on the efficacy of esophageal stents, in terms of sealing the perforation, as well as treatment failure, in the subpopulation of patients with spontaneous perforations.

Materials and methods

Search strategy

A systematic search of PubMed/MEDLINE, Scopus and the Cochrane Library was conducted from inception to June 2023. We screened all the available medical literature published in the English language between 2000 and 2023, to identify articles reporting on the use of stents in patients with spontaneous esophageal perforations and their related outcomes. Text words and Medical Subject Heading (MeSH) terms were used, combined with Boolean operators (AND, OR). A detailed description of the complete search strategy is available in Supplementary Table 1. A manual search of the reference lists from the selected articles was also performed.

Eligibility criteria

Key questions were formulated according to the PIO framework: “How effective are stents in sealing the perforation in patients with spontaneous esophageal perforations?” and

“How effective are stents in preventing mortality and conversion to surgical treatment in patients with spontaneous esophageal perforations?”. We included observational studies, prospective and retrospective, providing raw data on the efficacy of stents, in terms of sealing the perforation or treatment failure, in adult patients with benign spontaneous esophageal perforations. Additional inclusion criteria were: a) original studies including at least 3 patients with spontaneous esophageal perforation primarily treated with stent implantation; and b) articles published in the English language. Exclusion criteria were: a) review articles, case reports, letters to the editor and conference abstracts; b) reports where stent placement was not used as a primary treatment option, but rather as complimentary or secondary to other endoscopic modalities (clips, endosuturing, endoscopic vacuum therapy) or surgical attempts to restore the esophageal continuity; c) publications with mixed populations, where the outcomes of patients with spontaneous esophageal perforations were not reported; and d) full articles unavailable.

The search protocol, article selection and data extraction were assessed by 2 independent authors. Any areas of disagreement were resolved through a case-by-case discussion involving all authors.

Study outcomes and definitions

Primary outcomes were final sealing rate and failure rate. Final sealing was defined as successful and persistent occlusion or healing of the perforation site with the use of stents, even after multiple endoscopic attempts and drainage procedures (in the form of laparoscopic/open abdominal drainage, video-assisted thoracoscopic surgery drainage and decortication, mediastinotomy and drainage, thoracotomy and drainage, percutaneous chest tube insertion or endoscopic cavity drainage). Technically successful stent deployment and coverage of the leak at the time of the initial insertion did not qualify as a successful sealing of the perforation. Furthermore, utilization of other endoscopic or surgical techniques to cover the leak did not qualify as a successful leak occlusion by means of stent therapy.

Failure of stent therapy was defined as either conversion to surgical therapy (i.e., patient underwent major surgical procedure in the form of esophagectomy/diversion/primary repair) or death (in-hospital or otherwise disease-related mortality).

Data were also collected for secondary outcomes, including late presentation and treatment (>24 h) of patients, presence or development of sepsis or septic shock, initial drainage procedures performed, additional (late) drainage procedures performed and endoscopic reinterventions (re-stenting due to migration or persistent leakage or repositioning of the stent).

Statistical analysis

Dichotomous variables were expressed as counts and percentages and an initial unweighted pooling was performed,

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whenever possible. Associations between variables were assessed using Fisher's exact test. A P-value <0.05 was considered significant. For the consistently reported primary study outcomes a proportional meta-analysis was undertaken. A random-effects model was employed for all measures, using the inverse variance method and the Freeman-Tukey double arcsine transformation. Heterogeneity was assessed using Cochran's Q test and I^2 statistics, although the latter measure tends to be relatively high in this context [11]. Variables were expressed as percentages and a cumulative point estimate with 95% confidence intervals (CI) was presented. To evaluate for publication bias, Egger's test of asymmetry was used, along with the respective funnel plots. For the purposes of data management, analysis and statistical synthesis, we used the R Foundation Statistical software version 4.2.1 (2022-06-23).

Quality assessment and certainty of evidence

Methodological quality for the selected studies was evaluated by 2 independent authors, using the methodological index for non-randomized studies (MINORS) [12]. A list of 8 items in the case of non-comparative studies, and 12 items in comparative studies, were scored from 0-2. The cumulative score provided an overall estimate of the quality of the individual study. The certainty of the provided evidence was qualitatively evaluated, taking into consideration the risk of bias from the included studies, inconsistency, imprecision, indirectness and possible publication bias.

This review was reported according to the PRISMA 2020 guidelines (Supplementary Table 2). The study was registered in the Research Registry (UIN reviewregistry 1655).

Results

After the removal of duplicates, 541 records were identified and screened. Eventually, 18 studies [13-30] were included and are analyzed in this review, reporting on the use of stents as a primary treatment in cases of spontaneous esophageal perforations and their related outcomes in 171 patients. The study selection process is presented in Fig. 1.

Baseline characteristics

Details of the studies included, their characteristics and outcomes are summarized in Table 1. Most of them were small, retrospective, single-cohort studies including 3-23 patients with Boerhaave syndrome, with only 2 prospective observational studies included. There was only a single comparative study, which compared the results between endoscopic stent insertion and primary surgical treatment in patients with spontaneous esophageal perforations [21]. Eleven of the studies were designed to include only patients with the aforementioned pathology. The rest included patients suffering from benign

esophageal disruptions due to trauma (iatrogenic or not), anastomotic leaks, inflammatory pathologies, ingestion of foreign bodies and other; hence, a subpopulation analysis was necessary. Most of the chosen studies were small, retrospective, single-cohort studies that suffered from methodological flaws (mean MINORS score of 10). A detailed assessment of the methodological quality of the included studies can be found in Supplementary Table 3.

In general, both fully covered and partially covered metal stents and plastic esophageal stents were used. Metal stents were used in 13 studies. In 3 studies both plastic and metal stents were used, while 1 study reported on the use of plastic Polyflex™ stents and another investigated the use of Montgomery salivary bypass stents™ in patients with a leaking esophagus.

Sealing rate

Final sealing was reported in 13 studies, representing a total of 110 patients. Sealing was achieved in 90/110 (82%) of those patients. From the weighted pooled analysis, the sealing rate was 86% (95%CI 77-93%) with a low between-study heterogeneity ($Q=14.74$; $df=12$; $P=0.26$; $I^2=19\%$) (Fig. 2). Five studies did not report the sealing rate and were excluded from the analysis. Patients with a persistent esophageal leakage, despite receiving stent and drainage treatment, were considered as failures of leak sealing. Moreover, when appropriate according to individual study protocols, patients who died or were lost to follow up before stent extraction were also considered unsuccessful in achieving sealing of the perforation. In one study, the reported "primary" sealing rate was 50% (8/16), but eventually 3 more patients achieved sealing with a drainage procedure and a second stent [17].

Failure rate

Sixteen studies, including a total of 160 patients, presented data on failure of stent therapy. Stent failure was reported for 27/160 (17%) of the included patients. The pooled failure rate was 14% (95%CI 7-22%) with a low between-study heterogeneity ($Q=22.14$; $df=15$; $P=0.10$; $I^2=32\%$) (Fig. 3). Two studies did not report on the failure rate and were therefore excluded from analysis. Failure is a composite of mortality and conversion to surgical repair; one particular study did not specify mortality and conversion rates, but reported failure rate as previously defined.

Mortality and conversion to surgical repair

Patients failing stent therapy included 14 deaths and 10 patients who underwent a major surgical operation in the form of esophagectomy, diversion or esophageal repair. The mortality rate was 6% (95%CI 2-13%) with insignificant heterogeneity ($Q=12.87$; $df=14$; $P=0.54$; $I^2=0\%$) (Fig. 4). The rate of conversion

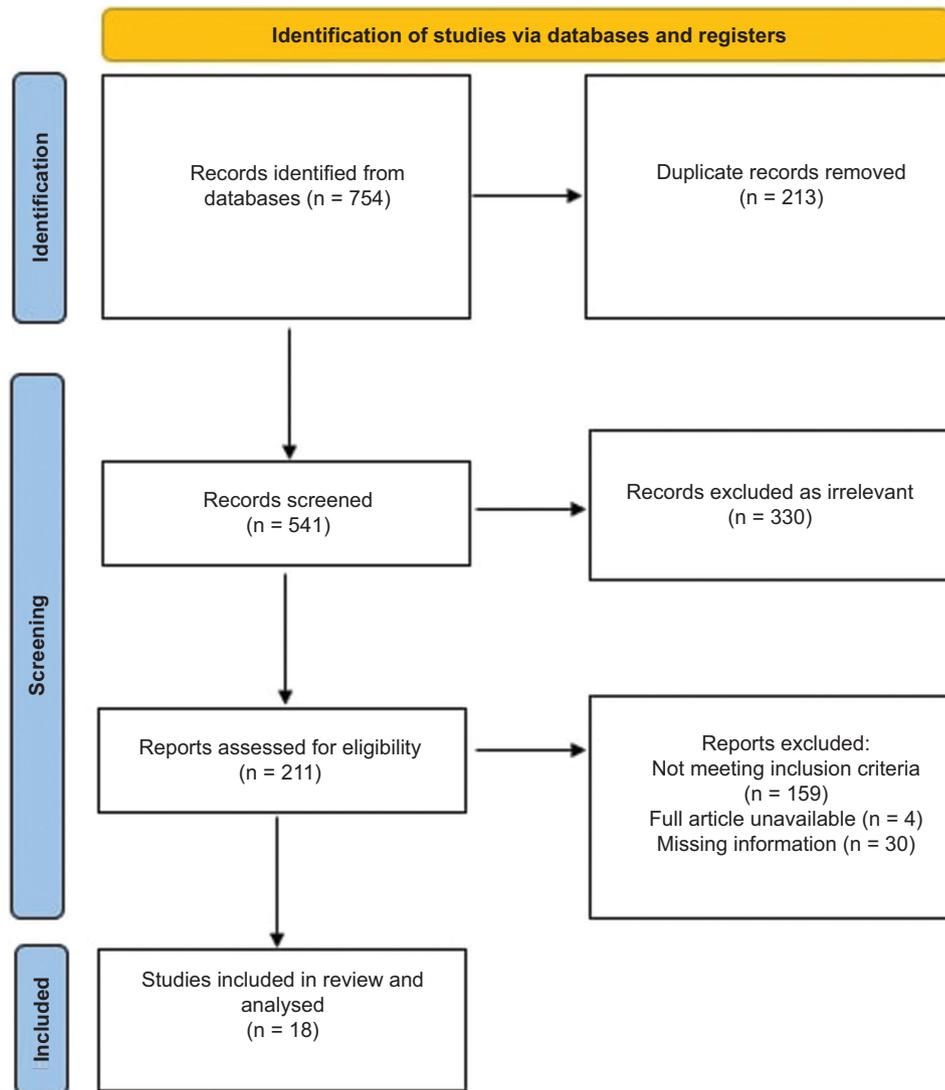


Figure 1 PRISMA flow diagram

to surgical repair was 2% (95%CI 0-9%) with low between-study heterogeneity ($Q=18.66$; $df=14$; $P=0.18$; $I^2=25\%$) (Fig. 5).

Presentation of patients

Delayed presentation or treatment of patients was reported in 13 studies. Overall, 64% (67/105) of patients were treated after at least 24 hours from the presumed time of esophageal rupture. Data on late presentation/treatment and related clinical outcomes were provided by 11 studies, including 75 patients in total [13-15,18,22,25-30]. The failure rate was 18% for late presenters (10/56) and 11% for early presenters (2/19). Even though the odds for failing stent therapy were 1.8 times greater in late-presenting patients compared to patients with presentation and treatment in less than 24 h, the difference was not statistically significant (odds ratio [OR] 1.85, 95%CI 0.37-9.30; $P=0.72$).

Development of sepsis or septic shock at presentation or during the treatment course was reported in 10 studies, including 106 patients, and the cumulative rate was 49% (52/106).

Other procedures

Concomitant drainage procedures were reported in 13 studies, including 129 patients, with a rate of 88% (114/129). These included percutaneous chest tube insertions or other surgical modalities utilized to drain pleural or mediastinal fluid collections or decorticate the lung.

The endoscopic reintervention rate was reported in 8 studies including 99 patients. From the available data, 27% of patients (27/99) required an additional stent deployment or repositioning of the initial stent, most commonly because of persistent leakage or migration.

Table 1 Related outcomes from included studies

Year	Study [ref.]	Study type	MINORS	Stents used	No patients	Late(>24h) pres/Tx	Sepsis
2023	Chiu [13]	Retrospective	10	Wallflex	5	5/5 (100%)	3/5 (60%)
2018	Hauge [14]	Retrospective	8	Ultraflex, Wallflex, SX-ELLA, Niti-S, Polyflex	15	9/15 (60%)	-
2018	Aloreidi [15]	Retrospective	9	Wallflex	6	4/6 (67%)	6/6 (100%)
2018	Huh [16]	Retrospective	10	Hanarostent, Choo stent	4	-	-
2016	Glatz [17]	Prospective Observational	11	Ultraflex, Leufen	16	4/16 (25%) ^a	6/16 (38%)
2016	Wu [18]	Retrospective	10	Nanjing	19	16/19 (84%)	5/19 (26%)
2014	Gubler [19]	Retrospective	10	Niti S, Rusch, Ultraflex, Hanarostent	7	-	-
2014	Persson [20]	Retrospective	10	CSEMS	23	-	-
2013	Schweigert [21]	Retrospective Comparative	14	Polyflex, Ultraflex	13	-	9/13 (69%)
2013	Darrien [22]	Retrospective	10	Ultraflex, Polyflex	5	2/5 (40%)	5/5 (100%)
2012	Koivukangas [23]	Retrospective	9	Hanarostent, Nanjing	14	7/14 (50%)	7/14 (50%)
2009	Freeman [24]	Prospective Observational	12	Polyflex	19	-	3/19 (16%) ^f
2009	Salminen [25]	Retrospective	8	Hanarostent	3	3/3 (100%)	-
2008	Kim [26]	Retrospective	9	Montgomery salivary bypass stent	4	4/4 (100%)	4/4 (100%)
2006	Fischer [27]	Retrospective	8	Ultraflex	5	1/5 (20%)	4/5 (80%)
2006	Prichard [28]	Retrospective	7	CSEMS	5	5/5 (100%)	-
2003	Siersema [29]	Retrospective	10	Fleming, Ultraflex	5	4/5 (80%)	-
2001	Chung [30]	Retrospective	8	Song, Niti S	3	3/3 (100%)	-
Pooled data					171	67/105 (64%)	52/106 (49%)
Year	Concomitant drainage	Additional Drainage	Endoscopic reintervention	Final Sealing	Failure	Conversion to surgical repair	Mortality
2023	5/5 (100%)	1/5 (20%)	0 (0)	5/5 (100%)	0 (0)	0 (0)	0 (0)
2018	14/15 (93%)	4/15 (27%)	5/15 (33%)	13/15 (87%)	2/15 (13%)	0(0)	2/15 (13%)
2018	6/6 (100%)	0(0)	3/6 (50%)	-	0(0)	0(0)	0(0)
2018	-	-	-	4/4 (100%)	-	-	-
2016	15/16 (94%)	11/16 (69%)	5/16 (31%)	11/16 (69%) b	6/16 (38%)	4/16 (25%)	2/16 (13%)
2016	19/19 (100%)	-	0(0)	16/19 (84%)	1/19 (5%) ^c	0(0)	1/19 (5%)
2014	-	-	-	5/7 (71%)	-	-	-
2014	-	-	-	-	3/23 (13%) ^d	-	-
2013	13/13 (100%)	11/13 (85%)	-	-	2/13 (15%)	0(0)	2/13 (15%)
2013	5/5 (100%)	4/5 (80%)	4/5 (80%)	2/5 (40%) ^e	1/5 (20%)	0(0)	1/5 (20%)

(Contd...)

Table 1 (Continued)

Year	Concomitant drainage	Additional drainage	Endoscopic reintervention	Final sealing	Failure	Conversion to surgical repair	Mortality
2012	12/14 (86%)	-	6/14 (43%)	-	2/14 (14%)	0(0)	2/14 (14%)
2009	12/14 (86%)	0(0)	4/19 (21%)	17/19 (89%)	2/19 (11%)	2/19 (11%)	0 (0)
2009	9/19 (47%)	-	-	1/3 (33%)	2/3 (67%)	1/3 (33%)	1/3 (33%)
2008	3/3 (100%)	-	-	4/4 (100%)	0 (0)	0 (0)	0 (0)
2006	4/4 (100%)	2/5 (40%)	-	4/5 (80%)	1/5 (20%)	0 (0)	1/5 (20%)
2006	4/5 (80%)	-	-	-	4/5 (80%)	2/5 (40%)	2/5 (40%)
2003	5/5 (100%)	-	-	5/5 (100%)	1/5 (20%)	1/5 (20%)	0 (0)
2001	-	-	-	3/3 (100%)	0 (0)	0 (0)	0 (0)
Pooled data	114/129 (88%)	33/84 (39%)	27/99 (27%)	90/110 (82%)	27/160 (17%)	10/137 (7%)	14/137 (10%)

a: >48 h delay in treatment

b: 8 patients achieved “primary” sealing, and 3 more after repeat stenting and drainage

c: massive hematemesis in a patient with retained stent

d: 1 more patient (not included in the analysis) was stented only for palliation and died three days later

e: three patients with esophagocutaneous fistula after stent removal. Eventually all healed with anal plug placement

f: 13 other patients were diagnosed with mediastinitis at the initial evaluation

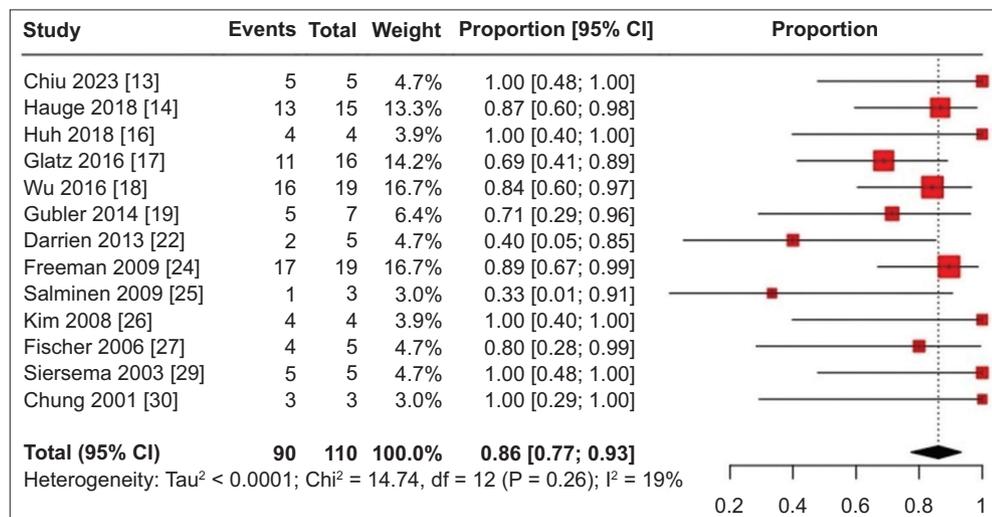


Figure 2 Sealing forest plot
CI, confidence interval

In 8 studies data on additional drainage procedures were provided. The rate of surgical reinterventions was 39% (33/84).

Publication bias

Funnel plots for the primary outcomes of sealing and stent failure are depicted in Supplementary Fig. 1 and 2, respectively. Egger's test to assess funnel plot asymmetry did not reveal statistically significant publication bias in any of the included measures.

Certainty of evidence

Confidence for the body of evidence presented herein remains low to very low. The reasons for that are mainly the high risk of bias from the included studies and indirectness, which may occur as a result of underreporting of other co-interventions performed. We tried to combat indirectness, in relation to population and outcomes, by adhering to our inclusion criteria and primary outcome definitions and avoiding the use of surrogate outcomes. One could also consider downgrading due to the small sample size and small number of events. Nevertheless, we consider we included a relatively large number of patients with spontaneous

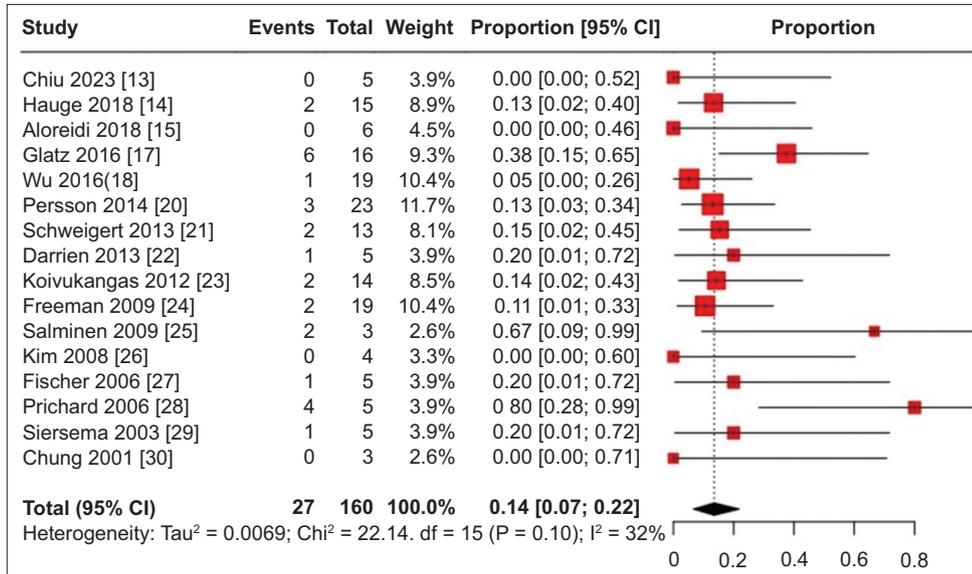


Figure 3 Failure of stent therapy forest plot
CI, confidence interval

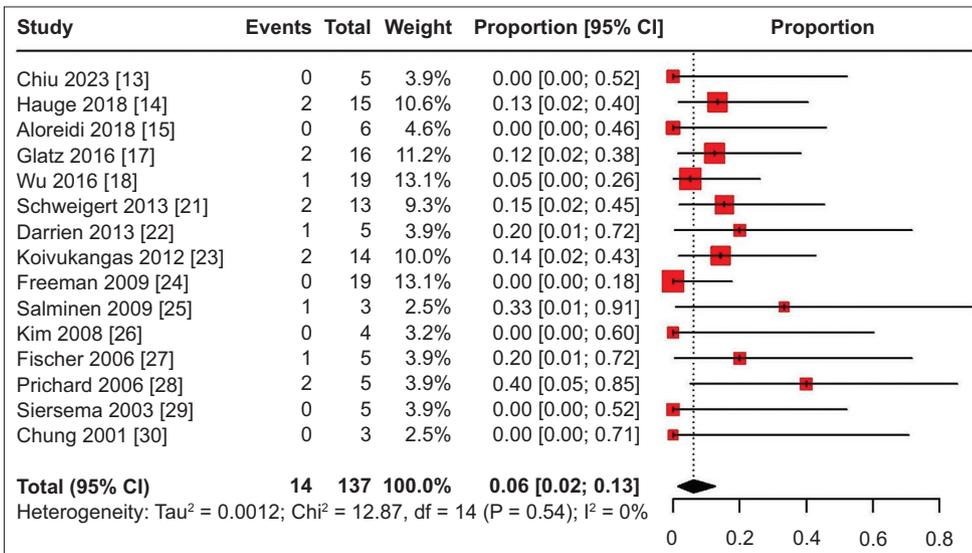


Figure 4 Mortality forest plot
CI, confidence interval

esophageal perforations treated primarily by means of stent therapy. On the other hand, our study did not suffer from inconsistency or significant publication bias, indicated by the measures of heterogeneity and Egger’s test of asymmetry, respectively. Moreover, the clinical success of the stent therapy was high, even though a significant number of patients presented late for treatment, were septic, severely debilitated and were therefore considered unfit for surgery [13,18,22,25-26,28,30].

Discussion

The intention of the current review was to investigate the role of esophageal stents, alongside conservative measures and

drainage procedures, in the subpopulation of patients with Boerhaave syndrome. Our results indicate that stents provided sustained and successful leak occlusion in 86% of the patients, while the pooled failure rate was 14%. The mortality rate was low and comparable to reported rates for surgically treated patients with iatrogenic or spontaneous esophageal perforations [4,31]. These encouraging results may be explained by the fact that stents temporarily bridge the esophageal gap, allowing for epithelization to occur, while preventing further mediastinal and pleural contamination. Further theoretical advantages of stent therapy in such severely ill patients are: (i) the avoidance of a potentially hazardous and physiologically stressful major operation; and (ii) organ preservation with potentially better functional outcomes. Surgical interventions to drain

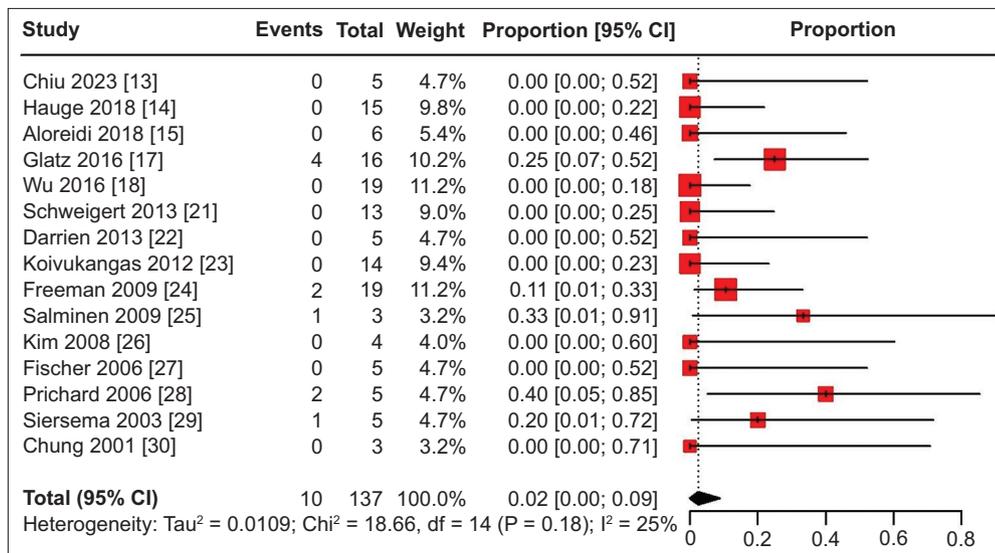


Figure 5 Conversion to surgical repair forest plot
CI, confidence interval

the infected cavities were necessary for the vast majority of patients in our study. Indeed, it seems that one should not disregard drainage procedures as an integral part of their treatment strategy, along with supportive care, including fluid resuscitation, antimicrobial therapy and nutritional support.

Spontaneous esophageal perforation or Boerhaave syndrome is a rare but often fatal condition. The condition has frequently been associated with forceful emesis and alcohol abuse [32]. Gastric juice, food and air accumulate in the mediastinum and pleura leading to rapid and sustained toxicity and sepsis. Furthermore, the rarity of the disease can result in a significant delay in recognizing it and providing treatment. It has been reported that half of the cases of Boerhaave syndrome are misdiagnosed as peptic ulcers, pneumothoraces, myocardial infarctions, and other pathologies [6,25,33-34].

Traditionally, the treatment of esophageal perforations has been surgical. Recently, Elliott *et al* investigated the role of minimally invasive surgical management in the context of spontaneous esophageal perforations [35]. Patients were managed with a combination of thoracoscopic debridement, primary repair and laparoscopic feeding jejunostomy, and the authors reported a low mortality rate of 10%. However, primary repair of inflamed and fragile tissues during surgical exploration, especially in cases of late-presenting patients with severe mediastinal inflammation, has historically been associated with poor outcomes, and an esophagectomy or exclusion and diversion may be unavoidable [4].

Esophageal stents have previously been used as palliative measures in tumor stenoses, for benign esophageal leaks and for anastomotic post-esophagectomy leaks [36,37]. We investigated their efficacy in the setting of benign spontaneous esophageal perforations, in which they provided high sealing rates. Sealing was generally assessed by a combination of contrast studies and endoscopic examination. However, 5 studies did not provide data on the specific modality used to assess sealing. Another possible limitation is the different

definitions of successful sealing used by the investigators. Some studies evaluated patients for ongoing leakage during the initial hospitalization and active treatment, while others used more strict criteria, encompassing sustained leak occlusion after stent extraction. The follow-up period also varied among studies.

Treatment failure in our study was evaluated as a composite of mortality and conversion to a major surgical operation. Mortality was mostly attributed to the magnitude of systematic toxicity, meaning ongoing sepsis and development of multiple organ failure. Stent-related complications, such as bleeding, fistula formation or bowel obstruction from migrated stents, can occasionally lead to fatal events. Early removal of the indwelling esophageal stents within 28 days for acute perforations has been shown to reduce stent-related complications [38]. In our review, the conversion rate was only 2%. In 10 studies none of the patients converted to surgical treatment. In the remaining 5 studies, conversion rates were between 11% and 40%. Another study, not included in this review, reported on 19 patients with spontaneous esophageal perforation, in 4 of whom (i.e., 21%) it was not possible to salvage the esophagus, and esophagectomy with diversion was required [39]. The variability among studies may reflect differences in management strategies, cutoff limits for conversion or just the physicians' clinical judgment.

Some relative contraindications exist to the use of esophageal stents. Large defects (>6 cm), those traversing the gastroesophageal junction, or proximal cervical injuries are related to increased failure rates [40]. In addition, patients with circumferential esophageal necrosis are not ideal candidates for placement of an esophageal stent and might therefore benefit from a surgical approach instead. Late presentation or treatment of esophageal perforations by any cause has long been considered to relate to inferior outcomes [16-17,20-21,23,41]. Diagnostic delay of the condition for more than 24 hours has also been incorporated in the Pittsburgh Perforation Severity score, which has been validated as a predictor of complications

in patients with spontaneous esophageal perforations [42]. From our analysis, the odds for failing stent therapy were 1.8 times higher in late-presenting patients compared to patients with presentation and treatment in less than 24 h (OR 1.85, 95%CI 0.37-9.30), although the difference was not statistically significant ($P=0.72$). However, we only analyzed studies providing raw data on early and late-presenting patients and their related outcomes. Given the small sample size, it is possible that our study was underpowered to reveal a statistically significant correlation. Persson *et al*, in their 10-year retrospective study including 40 patients receiving stent treatment, the majority of whom suffered from spontaneous perforations, identified the time elapsed between perforation and stent placement as the only significant predictor of clinical failure [20]. However, other authors consider stent placement in their practice, irrespective of the duration of the perforation [43].

A possible caveat of stent therapy is the high rates of endoscopic and surgical reinterventions reported by other authors [2,44]. In our study, 39% of patients needed supplementary surgical reinterventions, because of undrained pleural effusions or empyemas. Drainage procedures varied from percutaneous chest tube insertion to thoracoscopic or open debridement, decortication and drainage. Moreover, 27% of patients needed at least a second endoscopic reintervention, usually for ongoing leakage or migration. Stent migration appears to be a common problem in benign distal perforations, possibly due to the lack of a stricture or significant stenosis. Plastic and fully covered self-expandable metal stents are also at greater risk for stent migration [45]. This condition requires repeat endoscopy in an effort to re-establish right positioning. Depending on the unit's preferences, clipping or suturing the stent in place may be an additional step during the initial endoscopy.

Alternative endoscopic modalities to treat esophageal perforations are through or over-the-scope clips, endoscopic suturing devices and the novel endoluminal vacuum therapy, although the literature is limited to case reports and small case series. Clips may be sufficient for small to moderate sized perforations up to 2 cm, while endoscopic suturing can be applied for larger defects [46-48]. Endoscopic vacuum treatment has been evaluated in small trials, including patients with Boerhaave syndrome, and seems to be a safe and feasible option, with the limitation of the need for frequent sponge changes [49,50].

Even though our study included a relatively large number of patients with spontaneous esophageal perforations, it had some obvious weaknesses. Most of the included studies were small observational studies with methodological flaws. As a result, confounding, non-blinding, selective reporting and loss to follow up may have biased our results. Furthermore, additional variables or important patient outcomes were not evaluated, mainly because of a lack of data, making it difficult to draw any meaningful conclusions. Analysis and synthesis of observational studies may be problematic, since it involves summing up data on patients with variable comparability and stemming from different institutions or study periods. However, since high quality prospective controlled studies

with larger number of patients are not to be expected, given the rarity of the disease and the urgency of the decisions made, we believe our results may be useful in guiding decision making.

In conclusion, despite recent advances in critical care and surgical technique, spontaneous esophageal perforation is a life-threatening condition and its appropriate treatment still remains in question. Stents, instead of strictly palliative or futile approaches, may offer an invaluable tool in the hands of the treating physician. Our results imply that in select patients with spontaneous perforations, especially in poor surgical candidates, they may offer an effective alternative treatment strategy. Nonetheless, drainage procedures and aggressive resuscitation should not be neglected. A high proportion are likely to need additional endoscopic or surgical reinterventions to achieve source control and lead to final healing.

Summary Box

What is already known:

- Spontaneous esophageal perforation, or Boerhaave syndrome, is a rare but life-threatening condition
- Esophageal stents have been used in an effort to reduce associated morbidity and mortality in benign esophageal perforations

What the new findings are:

- Available low-evidence data from observational studies indicate that stents may offer an effective alternative treatment strategy, in terms of sealing of the perforation and treatment success, in patients with spontaneous esophageal perforations
- Drainage procedures and aggressive resuscitation are invaluable
- Endoscopic and surgical reinterventions are frequently needed to achieve source control

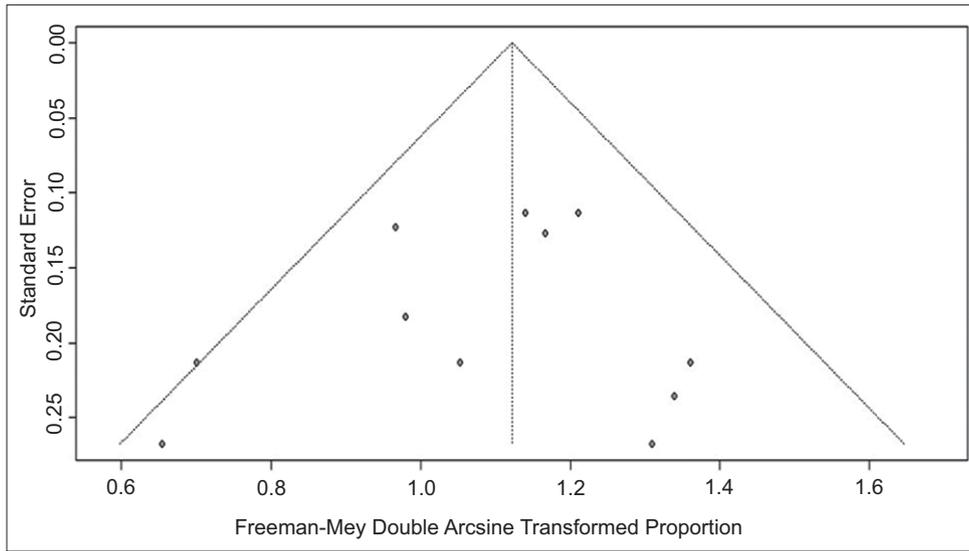
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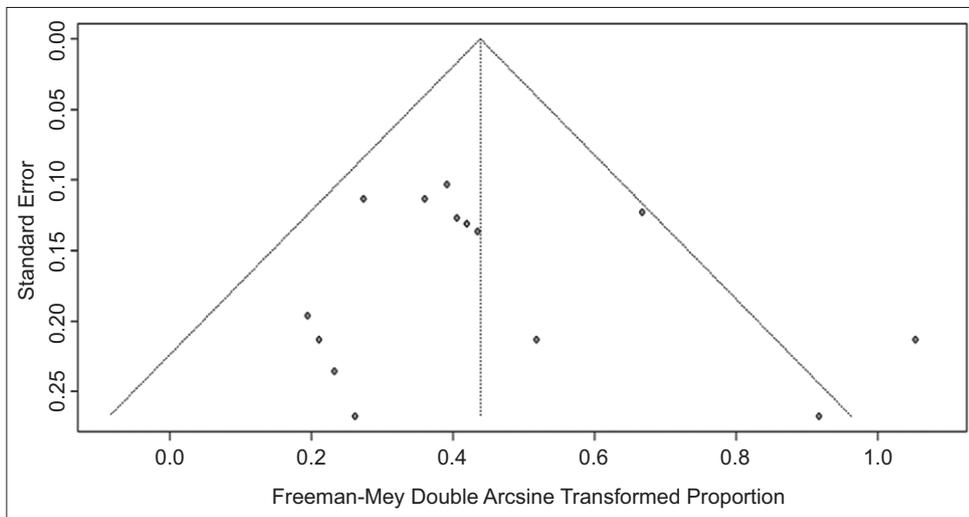
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Supplementary material



Supplementary Figure 1 Sealing funnel plot



Supplementary Figure 2 Failure of stent therapy funnel plot

Supplementary Table 1 Complete search strategy

PubMed/Medline
#1 (Textwords): “Boerhaave’s”, “Spontaneous esophageal perforation”, “Spontaneous esophageal rupture”, “Esophageal rupture”, “Stent”, “Esophageal stent”
(“Boerhaave’s” OR “Spontaneous esophageal perforation” OR “Spontaneous esophageal rupture” OR “Esophageal rupture”) AND (Stent OR “Esophageal stent”) Filters: English, from 2000 - 2023
Results: 270
#2 (MeSH terms): “Esophageal Perforation”, “Boerhaave syndrome”, “Stents”, “Self Expandable
Metallic Stents”
((“Esophageal Perforation”[MeSH Terms] OR “Boerhaave syndrome”[Supplementary Concept])AND (“Stents”[MeSH Terms] OR “Self Expandable Metallic Stents”[MeSH Terms])) AND ((english[Filter]) AND (2000:2023[pdat]))
Results: 273
Scopus
TITLE-ABS-KEY (“esophageal perforation” OR “esophageal rupture” OR “spontaneous perforation esophagus” OR boerhaave) AND stent Filters: English, from 2000-2023
Results: 174
Cochrane Library
((“esophageal perforation” OR “esophageal rupture” OR “spontaneous perforation esophagus”
OR Boerhaave) AND stent):ti,ab,kw Filters: English, from 2000-2023
Results: 37

Supplementary Table 2 PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	Page 1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 2-3
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5, Supplementary Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A (raw data were included)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A

(Contd...)

Supplementary Table 2 (Continued)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Page 8, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Table 1, Figures 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 8-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 8-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 10, Supplementary Fig. 2-3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 10
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11
	23b	Discuss any limitations of the evidence included in the review.	Page 14
	23c	Discuss any limitations of the review processes used.	Page 14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Supplementary Table 3 MINORS scores of included studies

Study [ref.]	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Score
Chiu 2023 [13]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Hauge 2018 [14]	2	2	0	2	0	1	1	0	N/A	N/A	N/A	N/A	8
Aloreidi 2018 [15]	2	2	0	1	0	2	2	0	N/A	N/A	N/A	N/A	9
Huh 2018 [16]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Glatz 2016 [17]	2	2	1	2	0	2	2	0	N/A	N/A	N/A	N/A	11
Wu 2016 [18]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Gubler 2014 [19]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Persson 2014 [20]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Schweigert 2013 [21]	2	2	0	2	0	1	2	0	1	1	1	2	14
Darrien 2013 [22]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Koivukangas 2012 [23]	2	2	0	1	0	2	2	0	N/A	N/A	N/A	N/A	9
Freeman 2009 [24]	2	2	2	2	0	2	2	0	N/A	N/A	N/A	N/A	12
Salminen 2009 [25]	2	2	0	2	0	1	1	0	N/A	N/A	N/A	N/A	8
Kim 2008 [26]	2	2	0	2	0	2	1	0	N/A	N/A	N/A	N/A	9
Fischer 2006 [27]	2	2	0	1	0	2	1	0	N/A	N/A	N/A	N/A	8
Prichard 2006 [28]	2	2	0	1	0	1	1	0	N/A	N/A	N/A	N/A	7
Siersema 2003 [29]	2	2	0	2	0	2	2	0	N/A	N/A	N/A	N/A	10
Chung 2001 [30]	2	0	0	2	0	2	2	0	N/A	N/A	N/A	N/A	8