Endoscopic Vacuum Therapy in Patients with Transmural Defects of the Upper Gastrointestinal Tract: A Systematic Review with Meta-analysis

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Abstract

A transmural defect of the upper gastrointestinal (UGI) tract is a life-threatening condition associated with high morbidity and mortality. Recently, endoscopic vacuum therapy (EVT) has shown rather excellent efficacy in managing UGI defects. We conducted a systematic review and meta-analysis to synthesise the available evidence on the efficacy of EVT in patients with transmural defects of the UGI tract. We searched the PubMed, Cochrane Library, and Embase databases for publications on the effect of EVT on successful closure, mortality, complications, and post-EVT stricture. Methodological quality was assessed using the Newcastle-Ottawa quality assessment scale. This meta-analysis included 29 studies involving 498 participants. The pooled estimate rate of EVT for successful closure was 0.85 (95% confidence interval [CI]: 0.81–0.88). The pooled estimate rate for mortality, complications, and post-EVT stricture was 0.11, 0.10, and 0.14, respectively. According to the aetiology of the transmural defect (perforation vs. leak and fistula), no significant difference was found in successful closure (odds ratio [OR]: 1.45, 95% CI: 0.45–4.67), mortality (OR: 0.77, 95% CI: 0.24–2.46), complications (OR: 0.94, 95% CI: 0.17–5.15), and post-EVT stricture (OR: 0.70, 95% CI: 0.12–4.24). The successful closure rate was significantly higher with EVT than with self-expanding metal stent (SEMS) placement (OR: 3.52, 95% CI: 1.79–6.91). In conclusion, EVT is an effective and safe treatment for treating leaks and fistulae as well as perforations in UGI defects. Moreover, EVT seems to be a better treatment option than SEMS placement in healing UGI defects.

Background

Transmural defects of the upper gastrointestinal (UGI) tract are categorised as perforations, leaks, or fistulae. A perforation is defined as an acute rupture of the gastrointestinal wall due to an endoscopic procedure, vomiting, foreign body, or peptic ulcer. A leak is a connection between the intraluminal and extraluminal spaces resulting from the disruption of the integrity of the wall, and the defect usually occurs after surgery. A fistula is defined as an abnormal communication between the gastrointestinal tract and other organs or the abscess cavity. Transmural defects of the UGI are life-threatening and associated with high morbidity and mortality. The optimal management of UGI transmural defects remains controversial. Surgery is one treatment strategy; however, the mortality rate has been known to be about 12–50%. Placement of a self-expanding metal stent (SEMS) has also proven to be an effective treatment strategy for UGI defects. However, SEMS treatment could also cause complications such as stent migration, stent ingrowth, perforation, bleeding, epidual abscess, and vascular fistula. Recently, endoscopic vacuum therapy (EVT) has shown rather excellent efficacy in managing UGI defects. This method applies continuous negative pressure to drain the infected fluid and accelerate wound healing. EVT is suitable for localised defects for which stent placement is not possible. Moreover, an external drainage is not necessary in most cases. However, the clinical success rate of EVT widely varies from 66.7–100%. In addition, corroborating evidence is needed because most studies are limited to case series and retrospective cohort studies with small sample sizes.

We performed a meta-analysis of the clinical outcomes of EVT in patients with transmural defects of the UGI tract. We aimed to assess the effect of EVT on successful closure, mortality, and postprocedural complications and stricture. In addition, we evaluated the efficacy of EVT according to the aetiology of the transmural defect (perforation vs. leak and fistula) and the treatment method (EVT vs. SEMS placement).

Material And Methods

2.1. Literature search strategy

We performed a systematic review and meta-analysis following the principles of the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement. The PubMed, Cochrane Library, and Embase databases (from inception to April 2020) were independently searched by three authors (DHJ, HRY, and CWH). We used the following search string: anastomotic leak OR anastomotic leakage OR postoperative leak OR postoperative leakage OR oesophageal leak OR oesophageal leakage OR oesophageal fistula OR leakage OR fistula OR leak OR perforation OR upper gastrointestinal tract OR oesophagus OR oesophageal OR gastric OR stomach OR oesophagectomy OR anastomosis AND endoscopic vacuum therapy OR endoscopic vacuum-assisted closure OR endoluminal vacuum therapy OR vacuum therapy OR vacuum-assisted closure OR negative pressure wound therapy OR endoscopic negative pressure therapy OR negative pressure therapy OR endovac therapy OR endo sponge. We manually and repetitively searched the cited references in published studies to identify other studies.

2.2. Study selection

In the first stage of the study selection, the title and abstract of articles that our keyword search returned were scrutinised to rule out irrelevant articles. Later, the full texts of all selected studies were screened according to our inclusion and exclusion criteria. The inclusion criteria were as follows: (1) a diagnosis of perforation, leak, or fistula of the UGI tract; (2) EVT as a primary or rescue treatment; and (3) investigations of adults aged ≥ 18 years. The exclusion criteria were as follows: (1) article types other than original articles; (2) case reports including fewer than two patients; (3) abstract-only publications; and (4) publications in a language other than English. If several publications covering the same study population existed, only the most recent study was selected.

2.3. Data extraction

Three review authors (DHJ, HRY, and CWH) independently extracted data from the included studies using a pre-data extraction form. Further, we reviewed the titles and abstracts of all included studies to exclude irrelevant publications. Any discrepancies in data interpretation were resolved through a discussion, review of studies, and consultation with one other author (SJJ). We extracted the following information: year of publication, first author, study design, patient age and sex, sample size, study region, follow-up duration, transmural defect size, time to diagnosis, time to treatment, EVT type, successful closure rate, mortality rate, complication rate, post-EVT stricture rate, hospital length of stay, intensive care unit length of stay, treatment duration, and number of sponge changes.
2.4. Primary and secondary outcomes

The primary outcome was the successful closure rate. Successful closure was defined as no evidence of leak under direct endoscopic visualisation and the absence of contrast extravasation on either a computed tomography scan with oral contrast, an oesophagography, or a UGI study. The secondary outcomes were mortality rate, complication rate (Clavien-Dindo ≥ 3), and stricture rate after EVT.

2.5. Methodological quality

The Newcastle-Ottawa quality assessment scale for cohort studies was used to evaluate the risk of bias. This scale rates studies on three sources of bias (selection, comparability, and outcome) based on eight criteria. Each criterion is rated with 1 star except comparability, which is rated a maximum of 2 stars. For this systematic review, studies scoring 7–9 stars were defined to be of high methodological quality, studies scoring 4–6 stars were defined to be of moderate methodological quality, and studies scoring 1–3 stars were defined to be of poor methodological quality. Three authors (CWH, HRY, and DHJ) independently evaluated the methodological quality of the selected studies. Any disagreement between the three authors was resolved by discussion.

2.6. Statistical analysis

A meta-analysis was performed using the statistical software R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria). The Mantel-Haenszel random-effect model was applied for binary end points. The random-effect model was selected because it could consider the possibility of heterogeneity. In addition, we performed subgroup analyses according to the following criteria: closure rate, mortality rate, complication rate, post-EVT stricture rate according to the aetiology of the transmural defect (perforation vs. leak and fistula), closure rate of EVT and SEMS.

The $I^2$ test developed by Higgins was used for determining heterogeneity. This test measures the percentage of total variation across studies. In cases of significant heterogeneity ($I^2 > 25\%$), the methodological section of each publication was re-evaluated for deciding whether any discrepancy could be checked. We used the Egger test to assess the extent of publication bias. A $p$ value of < 0.05 was considered statistically significant.

2.7. Institutional review board

Approval by an internal review board was not applicable since only data which were already published was used for this study.

Results

3.1. Study selection

Overall, 2585 studies were identified. Duplicated articles ($n = 392$) were excluded. Further, 2144 articles were rejected based on the title and abstract. Forty-nine articles were fully reviewed. After the eligibility assessment, 20 articles were additionally excluded (Supplementary Fig. 1). A total of 29 articles were included involving 498 participants.[11, 12, 16, 20–45]

3.2. Study characteristics and methodological quality

The baseline characteristics of the included studies are listed in Table 1. Nineteen articles were retrospective cohort studies and 10 studies were case series studies. Eight studies included only patients with postoperative leak.[11, 21, 23, 24, 31, 40, 41, 44] and two studies included only patients with perforation.[22, 25] Eleven studies included patients with both postoperative leak and perforation.[12, 16, 27, 29, 30, 32, 33, 36, 38, 39, 42] Four studies included patients with fistula.[34, 35, 43, 45] Four studies compared EVT with SEMS.[20, 26, 28, 37] A total of 24 studies were conducted in Western countries (Germany 14, United States 4, Switzerland 2, United Kingdom 2, Portugal 1, and Australia 1), whereas 5 studies were conducted in Asia (Korea 4 and China 1).
| Authors        | Study design | N | Male (n) | Age (median, years) | BMI (median) | Region of study | Follow-up (median, months) | Method of diagnosis | Defect size (median, mm) | Time to diagnosis (median, days) | T tr (d) |
|----------------|--------------|---|----------|---------------------|--------------|-----------------|--------------------------|----------------------|-------------------------|-------------------------------|---------|
| Palmes 2020    | Case series  | Fistula: 4 | NA | NA | NA | Western (Germany) | MA | Endoscopy | NA | NA | N |
| Jung 2019      | Retrospective | Leak: 23  | 20 | 65.1† | NA | Western (Germany) | 11.8† | NA | NA | Leak: 8.5 | N |
| Jeon 2019      | Retrospective | Leak: 22 | 17 | 68 | NA | Eastern (Korea) | 29.8 | Endoscopy | NA | 11 | N |
| Watson 2019    | Case series  | Leak: 2  | 2  | 69.6† | NA | Western (USA) | 2.7 | Endoscopy | NA | NA | N |
| Pinto 2019     | Case series  | Leak: 2 | 1 | 44.0† | NA | Western (Portugal) | NA | Endoscopy | NA | NA | N |
| Morell 2019    | Case series  | Leak: 6  | 2 | 49.0† | 44.2 | Western (Switzerland) | NA | Endoscopy | 20† | 4.5† | 3 |
| Min 2019       | Retrospective | Leak: 20 | 20 | 66.5 | NA | Eastern (Korea) | 7.1 | Endoscopy | 17.5 | 12.5 | 3 |
| Loske 2019     | Case series  | Leak: 1  | 4 | 65.7† | NA | Western (Germany) | NA | Endoscopy | NA | NA | N |
| Leeds 2019     | Retrospective | Leak: 54 | NA | NA | NA | Western (USA) | NA | NA | NA | NA | N |
| Walsh 2019     | Case series  | Leak: 1  | 1 | 69.5 | NA | Western (USA) | NA | NA | 20 | 21 | N |
| Alakkari 2019  | Case series  | Leak: 1  | 0 | 67† | NA | Western (UK) | NA | NA | NA | NA | 1 |
| Berth 2018     | Retrospective | Leak: 111 | 92 | EVT: 65 | SEMS: 64 | Western (Germany) | NA | Endoscopy | NA | EVT: 8 | E |
| Valli 2018     | Retrospective | Leak: 11 | 9 | Leak: 57.5 | Fistula: 80 | Western (Switzerland) | NA | Endoscopy | NA | NA | L |
| Still 2018     | Retrospective | Leak: 2 | 6 | 63 | 23 | Western (USA) | NA | Endoscopy | NA | NA | N |
| Pournaras 2018 | Retrospective | Leak: 14 | NA | NA | NA | Western (UK) | NA | NA | NA | NA | N |

EVT, endoscopic vacuum therapy; CT, computed tomography; IC, intracavitary; IL, intraluminary; NA, not available; SEMS, self-expanding metal stent †Data ex
| Authors          | Study design  | N          | Male (n) | Age (median, years) | BMI (median) | Region of study | Follow-up (median, months) | Method of diagnosis | Defect size (median, mm) | Time to diagnosis (median, days) | T (m/d) |
|------------------|---------------|------------|----------|---------------------|--------------|-----------------|---------------------------|---------------------|--------------------------|-------------------------------|---------|
| Ooi 2018         | Retrospective | Leak: 6    | NA       | 56.7†               | NA           | Western (Australia) | NA                       | NA                  | 18.3                     | NA                            | 3       |
| Noh 2018         | Retrospective | Leak: 12   | 12       | 57.0                | NA           | Eastern (Korea)   | 12.9                     | CT                  | 13                       | 13.5                           | 1       |
| Loske 2018       | Case series   | Leak: 3    | NA       | NA                  | NA           | Western (Germany) | NA                       | NA                  | NA                       | NA                            | N       |
| Laukoetter 2017  | Retrospective | Leak: 39   | 31       | 65                  | NA           | Western (Germany) | 5.4                      | Endoscopy CT          | NA                       | NA                            | 8       |
| Kuehn 2016       | Retrospective | Leak: 11   | 15       | 72                  | NA           | Western (Germany) | 17                       | Endoscopy CT          | NA                       | NA                            | N       |
| Hwang 2016       | Retrospective | Leak: 18   | 14       | EVT: 7 SEMS: 11     | NA           | Eastern (Korea)   | NA                       | EVT: 8.1 SEMS: 6.6    | NA                       | NA                            | N       |
| Möschler 2015    | Retrospective | Leak: 5    | 5        | 73.9†               | NA           | Western (Germany) | 4                        | NA                  | NA                       | NA                            | N       |
| Mennigen 2015    | Retrospective | Leak: 45   | 35       | EVT: 56 SEMS: 65.5  | NA           | Western (Germany) | EVT: 8.3 SEMS: 16.8     | Endoscopy CT          | NA                       | EVT: 7                           | N       |
| Loske 2015       | Case series   | Perforation: 10 | NA | NA                  | NA           | Western (Germany) | 2.8                      | Endoscopy CT          | 19                       | <1                             | N       |
| Heits 2014       | Retrospective | Perforation: 10 | 5       | 66†                | NA           | Western (Germany) | 9                        | Endoscopy CT          | 4.2                      | NA                            | N       |
| Liu 2014         | Case series   | Leak: 5    | NA       | 61.8†               | NA           | Eastern (China)   | NA                       | Endoscopy CT          | NA                       | 9.2                           | N       |
| Schorsch 2013    | Retrospective | Leak: 17   | NA       | NA                  | NA           | Western (Germany) | NA                       | NA                  | 14.7                     | 10                             | N       |
| Schniewind 2013  | Retrospective | Leak: 47   | NA       | NA                  | NA           | Western (Germany) | NA                       | NA                  | NA                       | NA                            | N       |
| Brangewitz 2013  | Retrospective | EVT: 32 SEMS: 39 | 58 | EVT: 63 SEMS: 62 | EVT: 25.2 SEMS: 26.4 | Western (Germany) | NA                       | NA                  | NA                       | NA                            | N       |

EVT, endoscopic vacuum therapy; CT, computed tomography; IC, intracavitary; IL, intraluminary; NA, not available; SEMS, self-expanding metal stent †Data ex

Table 2 summarises the clinical outcomes of the included studies. All studies except two [21, 34] reported the successful closure rate. Mortality was reported in all studies except one [38]. The complication and post-EVT stricture rates were reported in 21 and 16 studies, respectively. Hospital stay, intensive care unit stay, duration of therapy, and number of sponge changes were reported in 14, 5, 23, and 22 studies, respectively.
| Authors     | N       | Successful closure rate (n, %) | Mortality rate (n, %) | Complication rate (n, %) | Stricture rate (n, %) | Hospital stay (median, days) | ICU stay (median, days) | Duration of therapy (median, days) | Sponge changes |
|------------|---------|--------------------------------|----------------------|-------------------------|----------------------|-----------------------------|------------------------|-----------------------------------|----------------|
| Palms 2020 | Fistula: 4 | 2/4 (50) | 2/4 (50) | NA | NA | NA | NA | 88.5 | NA |
| Jung 2019  | Leak: 23 | 20/23 (87.0) | 1/23 (4.3) | 0/23 (0) | 3/13 (23.1) | 54.4 | NA | 15.7 | 3.4 |
| Perforation: 7 | 5/7 (71.4) | 1/7 (14.3) | 0/7 (0) | 1/2 (50.0) | 33.7 | NA | 27.0 | 6.4 |
| Jeon 2019  | Leak: 22 | 19/22 (86.4) | 0/22 (0) | NA | 3/15 (23.1) | 54.4 | NA | 15.7 | 3.4 |
| Watson 2019 | Leak: 2 | 2/2 (100.0) | 0/2 (0) | NA | 2/2 (100.0) | 54.4 | NA | 15.7 | 3.4 |
| Perforation: 7 | 1/1 (100.0) | 0/1 (0) | 0/1 (0) | NA | 1/1 (100.0) | 54.4 | NA | 15.7 | 3.4 |
| Pinto 2019  | Leak: 2 | 1/2 (50.0) | 0/2 (0) | NA | 0/2 (0) | 24 | NA | 13 | 3 |
| Morell 2019 | Leak: 6 | 6/6 (100.0) | 0/6 (0) | NA | 0/6 (0) | 39.8† | 10.2† | 32.3† | 4 |
| Min 2019    | Leak: 20 | 19/20 | 1/20 | NA | 6/19 | NA | 11.0 | 1.8 |
| Loske 2019  | Leak: 1 | 1/1 (100.0) | 0/1 (0) | NA | 0/1 (0) | 24 | NA | 11.0 | 1.8 |
| Perforation: 10 | 1/1 (100.0) | 0/1 (0) | 0/1 (0) | NA | 0/1 (0) | 24 | NA | 11.0 | 1.8 |
| Leeds 2019  | Leak: 54 | 44/54 (81.5) | 1/54 (0.9) | NA | 1/54 (0.9) | 24 | NA | 11.0 | 1.8 |
| Perforation: 20 | 19/20 (95.0) | 1/20 (0.5) | 1/20 (0.5) | NA | 1/20 (0.5) | 24 | NA | 11.0 | 1.8 |
| Walsh 2019  | Leak: 1 | 2/2 (100.0) | 1/2 (50.0) | NA | 0/2 (0) | 24 | NA | 11.0 | 1.8 |
| Perforation: 1 | 1/1 (100.0) | 0/1 (0) | 0/1 (0) | NA | 0/1 (0) | 24 | NA | 11.0 | 1.8 |
| Alakkari 2019 | Leak: 1 | 1/1 (100.0) | 0/1 (0) | NA | 0/1 (0) | 24 | NA | 11.0 | 1.8 |
| Perforation: 1 | 1/1 (100.0) | 0/1 (0) | 0/1 (0) | NA | 0/1 (0) | 24 | NA | 11.0 | 1.8 |
| Berth 2018  | Leak: 111 | 30/35 (85.7) | 4/35 (11.4) | 0/27 (0) | 1/27 (3.7) | 39 | 8 | 12 | 3 |
| EVT: 35 | 55/76 (72.4) | 10/76 (13.2) | 13/69 (18.8) | 5/69 (7.2) | 37 | 7 | 28 | 1 |
| SEMS 76    | 4/35 (11.4) | 13/69 (18.8) | 5/69 (7.2) | 37 | 7 | 28 | 1 |
| Valli 2018  | Leak: 1 | 9/11 (81.8) | 0/11 (0) | NA | 2/11 (18.1) | NA | 20.8 | 5 |
| Fistula: 1 | 0/1 (0) | 1/1 (100.0) | 0/1 (0) | NA | 1/1 (100.0) | NA | 20.8 | 5 |
| Still 2018  | Leak: 2 | NA | 1/13† | 1/13† | NA | NA | 11.0 | 1.8 |
| Perforation: 9 | 1/13† | 1/13† | NA | NA | 11.0 | 1.8 |
| Fistula: 2 | 1/13† | 1/13† | NA | NA | 11.0 | 1.8 |
| Poumaras 2018 | Leak: 14 | 14/14 (100.0) | 0/14 (0) | NA | 1/14 (7.1) | NA | 11.0 | 1.8 |
| Perforation: 7 | 6/7 (85.7) | 1/7 (14.3) | 1/7 (14.3) | NA | 1/7 (14.3) | NA | 11.0 | 1.8 |
| Ooi 2018    | Leak: 6 | 4/6 (66.7) | 1/6 (16.7) | NA | 2/6 (33.3) | NA | 11.0 | 1.8 |
| Perforation: 4 | 2/4 (50.0) | 1/4 (25.0) | 1/4 (25.0) | NA | 1/4 (25.0) | NA | 11.0 | 1.8 |
| Noh 2018    | Leak: 12 | 10/12 (83.3) | 1/12 (8.3) | NA | 1/12 (8.3) | NA | 11.0 | 1.8 |

EVT, endoscopic vacuum therapy; ICU, intensive care unit; NA, not available; SEMS, self-expanding metal stent †Data expressed as mean. ‡Only total rate was available. §Two patients died due to fatal hemorrhage during EVT.
| Authors       | N       | Successful closure rate (n, %) | Mortality rate (n, %) | Complication rate (n, %) | Stricture rate (n, %) | Hospital stay (median, days) | ICU stay (median, days) | Duration of therapy (median, days) | Sponge changes |
|---------------|---------|--------------------------------|-----------------------|--------------------------|-----------------------|-----------------------------|--------------------------|-------------------------------|----------------|
| Loske 2018    | Leak: 3 | 3/3 (100.0)                   | 0/3 (0)               | 0/3 (0)                  | 0/3 (0)               | NA                         | NA                       | NA                           | NA             |
|               | Perforation: 1 | 1/1 (100.0)            | 0/1 (0)               | 0/1 (0)                  | 0/1 (0)               | NA                         | NA                       | NA                           | NA             |
| Laukoetter 2017 | Leak: 39 | 36/39 (92.3)               | 5/39 (12.8)           | 2/39 (5.1)§             | 4/39 (10.2)           | 60                         | NA                       | 20                           | 6              |
|               | Perforation: 13 | 13/13 (100.0)         | 0/13 (0)              | 0/13 (0)                 | 0/13 (0)              | NA                         | NA                       | NA                           | NA             |
| Kuehn 2016    | Leak: 11 | 9/11 (81.8)                 | 1/11 (18.2)           | NA                       | 1/11 (18.2)           | NA                         | NA                       | NA                           | 4              |
|               | Perforation: 10 | 10/10 (100.0)         | 0/10 (0)              | NA                       | 0/10 (0)              | NA                         | NA                       | 12                           | 5              |
| Hwang 2016    | Leak: 18 | 7/7 (100.0)                 | 0/7 (0)               | 0/7 (0)                  | NA                    | 37.1                       | NA                       | 19.5                          | 4.3            |
|               | EVT: 7   | 7/11 (63.6)                 | 2/11 (18.2)           | 6/11 (54.5)              | 87.3                  | NA                         | NA                       | 27.0                          | 1.6            |
|               | SEMS 11  |                                |                       |                          |                       | NA                         | NA                       | NA                           | NA             |
| Möschler 2015 | Leak: 5  | 2/5 (40.0)                  | 2/5 (40.0)            | 0/5 (0)                  | 1/10 (10.0)§           | NA                         | NA                       | 34.2                          | 8.4            |
|               | Perforation: 5 | 5/5 (100.0)             | 0/5 (0)               | 0/5 (0)                  | NA                    | 13.0                       | NA                       | 13.0                          | 2.0            |
| Menningen 2015| Leak: 45 | 19/22 (86.4)                | 3/22 (13.6)           | 0/22 (0)                 | NA                    | 58                         | NA                       | 26.5                          | 6.5            |
|               | EVT: 22  | 14/23 (60.9)                | 6/23 (26.1)           | 0/23 (0)                 | NA                    | 53                         | NA                       | 36.0                          | 2.0            |
|               | SEMS 23  |                                |                       |                          |                       | NA                         | NA                       | NA                           | NA             |
| Loske 2015    | Perforation: 10 | 10/10 (100.0)         | 0/10 (0)              | 0/10 (0)                 | 0/10 (0)              | NA                         | NA                       | 5                             | 2              |
| Heits 2014    | Perforation: 10 | 9/10 (90.0)              | 1/10 (10.0)           | NA                       | NA                    | 48†                        | 22†                      | NA                           | 5.4†           |
| Liu 2014      | Leak: 5  | 5/5 (100.0)                 | 0/5 (0)               | 0/5 (0)                  | NA                    | NA                         | NA                       | 34.2                          | NA             |
| Schorsch 2013 | Leak: 17 | 16/17 (94.1)                | 1/17 (5.9)            | NA                       | 1/17 (5.9)            | NA                         | NA                       | 12.0                          | NA             |
| Schniewind 2013 | Leak: 29 | NA                           | 2/17 (11.8)           | NA                       | NA                    | 57†                        | 26†                      | NA                           | NA             |
|               | EVT: 17  |                                | 5/12 (41.7)           | NA                       | NA                    | 62†                        | 38†                      | NA                           | NA             |
|               | SEMS 12  |                                |                       |                          |                       | NA                         | NA                       | NA                           | NA             |
| Brangelwitz 2013 | EVT:32  | 27/32 (84.4)                | 9/32 (28.1)           | 3/32 (9.4)               | 48.5                  | NA                         | 23                       | 7                             | 3              |
|               | SEMS: 39 | 21/39 (53.8)                | 3/39 (7.6)            | 11/39 (28.2)            | 41                    | NA                         | 33                       | 3                             |                |

EVT, endoscopic vacuum therapy; ICU, intensive care unit; NA, not available; SEMS, self-expanding metal stent †Data expressed as mean. § Two patients died due to fatal hemorrhage during EVT.

The methodological quality of the studies is shown in Supplementary Table 1. The quality was poor in 15 of the included studies[22, 23, 25, 27, 30, 32, 34–36, 39–43, 45] and moderate in 14 studies.[11, 12, 16, 20, 21, 24, 26, 28, 29, 31, 33, 37, 38, 44]

### 3.3. Primary and secondary outcomes

#### 3.3.1. Primary outcome – successful closure rate

Twenty-seven studies reported data on successful closure for 456 patients. The pooled estimate rate for successful closure was 0.85 (95% confidence interval [CI]: 0.81–0.88, Fig. 1). No heterogeneity was found among the studies ($I^2 = 0\%$, $p = 0.68$). No publication bias was detected by the Egger test ($p = 0.33$).

#### 3.3.2. Secondary outcomes – mortality, complication, and post-EVT stricture rates
Data on mortality were reported in 28 studies that showed the information of 412 patients. The pooled estimate rate for mortality was 0.11 (95% CI: 0.09–0.15, Fig. 2, A). No heterogeneity was found among these studies ($I^2 = 0\%$, $p = 0.96$). No publication bias was detected by the Egger test ($p = 0.38$). Twenty-one studies reported data on complications for 304 patients. The pooled estimate rate for complications was 0.10 (95% CI: 0.06–0.15, Fig. 2, B). A low heterogeneity was found among the studies ($I^2 = 13.8\%$, $p = 0.28$). Publication bias was detected by the Egger test ($p < 0.05$). Sixteen studies reported data on post-EVT stricture for 240 patients. The pooled estimate rate for post-EVT stricture was 0.14 (95% CI: 0.10–0.20, Fig. 2, C). No heterogeneity was found among these studies ($I^2 = 0\%$, $p = 0.45$). No publication bias was detected by the Egger test ($p = 0.06$).

### 3.4. Subgroup analysis

#### 3.4.1. Perforation vs. leak and fistula – successful closure, mortality, complication, and post-EVT stricture rates

Evaluation of the successful closure rate according to the aetiology of the transmural defect was performed in 11 studies. The pooled analysis showed that the successful closure rate was similar between the perforation and leak groups (odds ratio [OR]: 1.45, 95% CI: 0.45–4.67, $p = 0.53$, Fig. 3, A). A low heterogeneity was detected among the studies ($I^2 = 24.1\%$, $p = 0.24$). Data on mortality according to the aetiology of the transmural defect were available for 10 studies. The analysis revealed no significant difference between the two groups in mortality rate (OR: 0.77, 95% CI: 0.24–2.46, $p = 0.66$, Fig. 3, B), with no heterogeneity ($I^2 = 0\%$, $p = 0.58$). Eight studies reported data on complications according to the aetiology of the transmural defect. The pooled analysis showed that the complication rate was similar between the perforation and leak groups (OR: 0.94, 95% CI: 0.17–5.15, $p = 0.94$, Fig. 3, C). No heterogeneity was detected among the studies ($I^2 = 0\%$, $p = 0.79$). Data of post-EVT stricture rate according to the aetiology of the transmural defect were available for five studies. No significant difference between the two groups was observed in the post-EVT stricture rate (OR: 0.70, 95% CI: 0.12–4.24, $p = 0.70$, Fig. 3, D), with no heterogeneity ($I^2 = 0\%$, $p = 0.47$).

#### 3.4.2. Successful closure rate (EVT vs. SEMS)

The analysis of four studies involving 245 participants (96 in the EVT group and 149 in the SEMS group) showed a significant high successful closure rate in the EVT group (OR: 3.52, 95% CI: 1.79–6.91, $p < 0.05$, Fig. 4), with no heterogeneity ($I^2 = 0\%$, $p = 0.75$).

### Discussion

To date, many studies have shown promising outcomes in patients with transmural defects of the UGI tract with EVT as a definitive treatment. However, those previous studies included only a limited number of patients. Recently, several systematic reviews were reported on the usefulness of EVT in transmural defects of the UGI tract,[17, 46–48] However, those previous reviews were only descriptive and did not show any statistical analysis with a summary estimate. Therefore, a meta-analysis was needed to synthesise the available data on the efficacy of EVT in transmural defects of the UGI tract. Our meta-analysis contained case series in which a single group was assessed with no within-study comparisons. Nevertheless, this meta-analysis has an advantage over a narrative review because it assessed effect sizes and integrated all of them in a single statistical analysis.

In this meta-analysis, the closure rate of EVT for transmural UGI defects was rather excellent (85%), with low mortality (11%), complication (10%), and post-EVT stricture (14%) rates. And, no significant difference was found in successful closure (OR: 1.45, 95% CI: 0.45–4.67), mortality (OR: 0.77, 95% CI: 0.24–2.46), complications (OR: 0.94, 95% CI: 0.17–5.15, $p = 0.94$), and post-EVT stricture (OR: 0.70, 95% CI: 0.12–4.24, $p = 0.70$) according to the aetiology of the transmural defect (perforation vs. leak and fistula). Although the aetiology of transmural UGI defects was different, the efficacy of EVT was similar between the groups. In addition, the successful closure rate was significantly higher with EVT than with SEMS (OR: 3.52, 95% CI: 1.79–6.91). To date, only one meta-analysis has reported studies comparing EVT and SEMS for the treatment of oesophageal defects.[49] In this previous study, the closure rate of oesophageal leak was also significantly higher with EVT than with SEMS, similar to our results. However, the number of included patients was smaller than that in our meta-analysis.

The principle of EVT is similar to the classical vacuum-assisted closure treatment, which is a well-established therapy for chronic superficial wounds.[50] In EVT, a polyurethane sponge is placed into the defect to treat it with the application of negative pressure. Defect healing is achieved through the continuous drainage of dirty fluid, thus decreasing bacterial colonisation, enhancing vascularity, and promoting tissue granulation.[50, 51] An internal vacuum sponge (endo-SPONGE) device was first successfully introduced for UGI anastomosis leak in 2008.[13] Since then, EVT has been used for the management of UGI defects and has shown good short-term and long-term clinical outcomes. Meanwhile, SEMS placement has also shown effective results for UGI defects.[5, 6] However, stent therapy may be accompanied by additional abscess drainage, local pressure necrosis of the mucosa, stent migration, stent ingrowth, bleeding, and perforation. Surgery is also one of the strategies for transmural defects of the UGI; however, it has been known to be associated with a high mortality rate.[3, 4] To date, comparative studies between different treatment modalities for UGI defects are rare.[52] Therefore, the clinical evidence on EVT for UGI defects is still insufficient for directing treatment modalities. According to our meta-analysis, EVT is an effective and safe treatment method for treating leaks and fistulae as well as perforations. In addition, EVT seems to have a significantly higher success rate in healing UGI defects than SEMS placement.

Usually, transmural defects of the UGI tract are classified as perforations, leaks, or fistulae. Of these, fistulae have been known to be the most difficult to close because the epithelial tract is often fibrotic and they arise in unhealthy tissue, which is inflamed, damaged, or ischaemic. Although the included cases were too
few (n = 6), this meta-analysis showed a successful closure rate of 50% in patients with fistula. Given the poor response to other treatments such as SEMS placement, EVT would be promising option for treating patients with fistula.

The major disadvantages of EVT are the necessity for repetitive endoscopic procedures, nasogastric tube-related discomfort, and sponge dislocation. The main and most dreadful event associated with EVT is massive bleeding. [17, 46] It can occur from a fistula between the cavity and the main vessels and from rupture of a pseudoaneurysm from circumjacent vessels or heart chambers. More frequent changes of the sponge may be helpful to prevent or reduce the risk of severe bleeding. Moreover, massive bleeding can occur in cases of intracavitary therapy in which direct contact to blood vessels is possible. Therefore, intraluminary EVT may be safer than intracavitary EVT. Additionally, computed tomography scans should be reviewed before starting intracavitary EVT to exclude vascular issues. In our review, post-EVT stricture occurred in 14% cases. However, all strictures were easily resolved through endoscopic dilatations (26 cases).

**Limitations**

Although this is the first meta-analysis to assess the effect of EVT in patients with UGI defects, it had several limitations. All included studies were retrospective in nature without randomisation. This could have resulted in a selection bias in this study. Although randomised controlled trials are considered the best method for evaluating a treatment effect, performing such trials would be difficult owing to ethical concerns and methodological difficulty. Second, the included studies had a limited quality. Third, the sample size of each study was insufficient. Therefore, additional data would be needed to define the role of EVT in patients with UGI defects. Finally, most of the included studies were from Western countries, especially Germany. Large-scale studies from additional regions are required to validate the usefulness of EVT for the treatment of UGI defects. Despite these limitations, this meta-analysis, to our knowledge, showed the most comprehensive results on EVT for UGI defects thus far.

**Conclusions**

This meta-analysis found that EVT is an effective and safe treatment for leaks and fistulae as well as perforations in UGI defects. In addition, EVT seems to be a better treatment option in healing UGI defects than SEMS placement.

**Declarations**

**Conflict of Interest Disclosure:**

None.

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