



Outcome of treatment modalities for spontaneous esophageal rupture: a meta-analysis and case series

Jiajian Pan, MM^{a,b}, Yong Ge, MM^{a,b}, Tianci Feng, MM^{a,b}, Chengwen Zheng, MM^{a,b}, Xueqiu Zhang, MM^{a,b}, Shoujie Feng, PhD^{a,b}, Teng Sun, MD^{a,b}, Feng Zhao, MD^{c,*}, Zhengbu Sha, MD^{c,*}, Hao Zhang, MD, PhD^{a,b,*}

Background: Current treatment modalities for spontaneous esophageal perforation remain controversial because of their rarity.

Objective: To describe our institution's experience in managing patients with spontaneous esophageal rupture and conduct a meta-analysis of existing studies to determine the best evidence-based treatment options.

Methods: The authors enrolled patients with spontaneous esophageal rupture who underwent their first treatment at our institution. The authors also identified studies through a systematic search of the MEDLINE, EMBASE, and Cochrane Library databases before 1 April 2024, for inclusion in the meta-analysis.

Results: This case series included data from 17 patients with delayed diagnosis who were treated with esophageal stents, with an immediate mortality rate of 5.9%. In addition to the cases from our institution, the authors obtained 944 patients from 46 studies in the final analysis. The combined immediate mortality rate was 11% (95% CI: 0.08–0.15). The combined reintervention rate was 11% (95% CI: 0.05–0.19). The combined immediate mortality was 6% (95% CI: 0.04–0.09) after primary closure, 14% (95% CI: 0.02–0.32) after T-tube drain repair, 2% (95% CI: 0.00–0.15) after esophagectomy, 8% (95% CI: 0.03–0.15) after stent placement, and 22% (95% CI: 0.03–0.47) after conservative treatment. The subgroup analysis based on the timing of the intervention showed that the immediate mortality rate in patients initiating treatment within 24 h of rupture was 3% (95% CI: 0.01–0.08), whereas that in patients initiating treatment > 24 h later was 12% (95% CI: 0.08–0.18).

Conclusion: Outcomes are best after esophagectomy, and primary closure or esophageal stenting is a good option compared with other treatment modalities. Prognosis is related to the timing of intervention, and accurate diagnosis and treatment within 24 h significantly reduces the risk of death in patients. Patients with delayed diagnosis may have a better prognosis with stent placement.

Keywords: Boerhaave syndrome, spontaneous esophageal rupture, treatment, meta-analysis

Introduction

Spontaneous esophageal rupture, also known as Boerhaave syndrome, is a longitudinal transmural tear of the esophagus caused by a sudden increase in pressure in the distal lumen of the esophagus, accounting for ~10–15% of all cases of esophageal rupture^[1,2]. An epidemiologic survey conducted in Iceland in 2010 revealed an incidence of 3.1 cases of spontaneous esophageal rupture per million people per year^[3].

Spontaneous esophageal rupture is difficult to differentiate from myocardial infarction, entrapment aneurysm, peptic ulcer, or pancreatitis because of the lack of specific clinical symptoms, often leading to delayed diagnosis and serious complications. Spontaneous esophageal rupture also has a higher mortality rate than other causes of esophageal perforation^[4–6]. Since Barrett *et al.* first reported successful surgical treatment of spontaneous esophageal rupture in 1947, surgery has been the mainstay of treatment, including primary closure with or without tissue

^aThoracic Surgery Laboratory, Xuzhou Medical University, ^bDepartment of Thoracic Surgery, The Affiliated Hospital of Xuzhou Medical University and ^cDepartment of Thoracic Surgery, The Third Affiliated Hospital of Xuzhou Medical University, Xuzhou, People's Republic of China

J.P. and Y.G. are co-first authors.

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*Corresponding authors. Address: Department of Thoracic Surgery, Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou 221003, Jiangsu, People's Republic of China. Tel: +86 516 858 063 10. E-mail: zhanghao@xzhmu.edu.cn (H. Zhang); Department of Thoracic Surgery, The Third Affiliated Hospital of Xuzhou Medical University, 388 South Fuxing Road, Xuzhou 221010, Jiangsu, China. Tel: +86 516 836 385 40. E-mail: shazhengbu@126.com (Z. Sha), and Tel: +86 516 836 385 50. E-mail: zxx76@163.com (F. Zhao).

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reinforcement, T-tube drainage, surgical debridement and drainage, esophagectomy with or without primary reconstruction, and esophageal exclusion^[7–9]. A potential advantage of surgical treatment is its ability to extensively decontaminate and drain the mediastinal and pleural cavities to control infection, thus permitting early closure of the fissure and achieving lung expansion. However, the surgical procedures may be associated with serious complications. Recently, with improvements in intensive care management, the discovery of stronger antibiotics, and the emergence of endoscopic techniques, nonsurgical treatments have been increasingly used as less invasive approaches. These include the use of conservative treatments, esophageal stents, fibrin glue, and endoscopic clips, which may provide a better quality of life for less well-conditioned patients and greatly reduce the need for high-risk open-heart or open-abdominal surgery^[10–12]. Guidelines for the management of spontaneous esophageal rupture are currently lacking, and the efficacy of different treatment strategies and the optimal timing of the intervention remain controversial^[13–15].

Thus, to systematically assess the outcome of currently available treatment strategies and clarify the timing of interventions, we weighted and ranked the results of several independent studies by a meta-analysis, in conjunction with our center's experience in treating cases of spontaneous esophageal rupture. Our findings will serve as a reference for guiding clinical decisions in the future.

Materials and methods

Institutional case series

This retrospective study included patients with spontaneous esophageal ruptures who were treated at our institution. Patients with esophageal perforations caused by instruments, foreign bodies, external trauma, or underlying diseases (e.g. malignancy) were excluded. Demographic and clinical data (sex, age, treatment modalities, complications, reinterventions, length of hospitalization, and outcomes) were collected. This study was approved by the local Ethics Committee (approval number: XYFY2023-KL369-01).

Meta-analysis

Search strategy and selection criteria

This study was prospectively registered in the PROSPERO. A comprehensive literature search guided in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Digital Content 1, <http://links.lww.com/JS9/D193>) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) (Supplemental Digital Content 2, <http://links.lww.com/JS9/D194>) guidelines was conducted to identify scientific publications reporting the treatment of patients with spontaneous esophageal rupture^[16,17]. The literature search was conducted using three databases, namely MEDLINE, EMBASE, and the Cochrane Library, on 1 April 2024. The literature search strategy comprised MeSH terms and free words, such as 'Boerhaave syndrome' and 'therapeutics'. In addition, we manually searched the reference lists of eligible studies for potentially missing studies. The full search strategy is presented in Supplementary File 1 (Supplemental Digital Content 3, <http://links.lww.com/JS9/D195>). The search was conducted by two independent researchers, and a third researcher was consulted in

HIGHLIGHTS

- This study summarizes the outcomes of interventions for spontaneous esophageal rupture.
- Outcomes are best after esophagectomy treatment, and primary closure or esophageal stenting is also a good option compared with other interventions.
- Patients with delayed diagnosis may have a better prognosis with stent placement.
- Accurate diagnosis and treatment within 24 h significantly reduces the risk of death.

case of disagreements regarding study inclusion. This meta-analysis did not require approval from the ethics committee or informed consent from participants.

The titles and abstracts of the articles were skimmed, and the full texts of the relevant articles were reviewed to assess their inclusion in the analysis. The inclusion criteria were as follows: studies including patients with spontaneous esophageal rupture who received treatment (of any type), and studies that reported a clear sample size or mortality rate, or in which the immediate mortality rate could be calculated indirectly based on the information provided in the study. Case series, comparative cohort studies, nonrandomized prospective and retrospective studies, and randomized controlled trials were included, whereas letters, case reports, narrative reviews, editorials, conference proceedings, duplicate literature, and publications in languages other than English were excluded.

Data extraction and quality assessment

The following data were retrieved from the included publications: author names, year of publication, study design, sample size, country of study, baseline demographics of patients, type of therapeutic intervention, hospitalization/30-day mortality rate, reintervention, and delayed treatment. All data were entered independently by two researchers in predesigned Excel sheets (Microsoft Corporation), which were compared only at the end of the review process to reduce selection bias. Differences were resolved by consensus after consultation with a third researcher. The Newcastle–Ottawa scale was used to evaluate the quality of the noncontrolled trials^[18]. Case series studies were assessed using the JBI Critical Appraisal Checklist for Case Series^[19].

Definitions

The primary outcome in this study was mortality; however, different studies have reported different definitions of mortality, preventing precise comparisons of pooled data and affecting comparative analyses. Therefore, we redefined mortality and calculated the immediate mortality rate for each treatment modality, defined as death during hospitalization or within 30 days after surgery, based on the reported data. The secondary outcome was the reintervention rate.

Statistical analysis

A database was created using Microsoft Excel (Microsoft Corporation) and the data were statistically analyzed using Stata 15.0 (Stata Corporation LLC). The heterogeneity of the studies was assessed using the I^2 index and Cochran χ^2 test (Q test).

Significant heterogeneity was determined when the I^2 value was $> 50\%$ or the P -value was < 0.1 and was analyzed using a random-effects model; otherwise, a fixed-effects model was used. Proportions are expressed as combined proportions (%) and 95% CIs, and continuous variables are summarized with mean differences and 95% CIs. Sensitivity analysis was conducted to analyze the stability and reliability of the pooled results. Finally, potential publication bias was identified using funnel plots, Begg's test, and Egger's test.

Results

Institutional case series

Table 1 presents the details of the retrospective institutional case series. This study included 17 patients (13 males and 4 females) treated between 2010 and 2022, with a median age of 55 years (interquartile range: 48–63.5) years at diagnosis. The perforation sites in all the patients were located in the distal esophagus. The interval between esophageal rupture and treatment was 3–10 (5.5 ± 2.0) days. The primary interventions were endoscopic esophageal stents and percutaneous chest drainage. The median length of hospitalization was 32.5 days. The postoperative follow-up outcomes showed that one patient had a persistent fistula at the perforation site and resumed normal life after a second surgical suture; one developed rib necrosis that required rib resection and surgical debridement; one died 82 days after stent placement because of severe sepsis secondary to multiorgan failure; and one died of myocardial infarction 5 months after discharge.

Meta-analysis

A total of 2216 potentially relevant records were initially generated from the MEDLINE, EMBASE, and Cochrane Library databases. After removing 480 duplicate records, the titles and abstracts of each record were screened. Finally, we exclude 1690 ineligible studies, and 46 studies (944 patients) were ultimately eligible for analysis (Fig. 1).

The inclusion of studies in the combined analysis resulted in a combined immediate mortality rate of 11% ($n = 944$, 46 studies; 95% CI: 0.08–0.15) (Fig. 2, Table 2). Subgroup analyses based on different treatment modalities revealed a combined immediate mortality rate of 6% after primary closure ($n = 496$, 29 studies; 95% CI: 0.04–0.09), 6% after T-tube drain repair ($n = 91$, nine studies; 95% CI: 0.02–0.32), 2% after esophagectomy ($n = 38$, nine studies; 95% CI: 0–0.15), 8% after stent placement ($n = 129$, 12 studies; 95% CI: 0.03–0.15), and 22% after conservative management procedures ($n = 102$, 15 studies; 95% CI: 0.03–0.47). The combined reintervention rate was 11% ($n = 445$, 28 studies; 95% CI: 0.05–0.19), whereas that after esophagectomy was 0% ($n = 23$, three studies; 95% CI: 0–0.11) (Table 3).

The immediate mortality rates of patients treated within or after 24 h of spontaneous esophageal rupture were reported in 28 studies. The combined immediate mortality rate was 3% for treatment initiation within 24 h of esophageal perforation ($n = 205$, 28 studies; 95% CI: 0.01–0.08) and 12% for treatment initiation after 24 h ($n = 292$, 28 studies; 95% CI: 0.08–0.18) (Table 4).

Table 1
Characteristics of patients in our case series.

No.	Sex/age (year)	Interval to treatment (days)	Perforation site/ size(cm)	Empyema (+/-)	Intervention	Length of stay (days)	Morbidity	Subsequent procedures	Survival
1	M/62	5	lower/6	+	Stent	50	None		Yes
2	M/62	7	lower/2	+	Stent	34	Stent migration		Yes
3	M/58	10	lower/7	+	Stent	59	None		Yes
4	M/46	8	lower/4	+	Stent	53	None		Yes
5	M/41	3	lower/3	+	Stent	34	Rib necrosis	Partial rib resection + Surgical debridement	Yes
6	F/78	7	lower/3	+	Stent	None	Sepsis		No, died of multiple organ failure 82 days after stent implantation
7	F/77	5	lower/2	+	Stent	33	None		No, died of myocardial infarction 3 months after stent removal
8	M/51	4	lower/4	+	Stent	32	None		Yes
9	M/63	6	lower/4	+	Stent	30	Gastroesophageal reflux		Yes
10	M/48	8	lower/2	+	Stent	56	Persistent leak	Primary closure	Yes
11	M/44	3	lower/5	+	Stent	32	None		Yes
12	M/64	4	lower/4	+	Stent	2	None		Yes
13	F/55	5	lower/5	+	Stent	23	None		Yes
14	M/68	7	lower/2	+	Stent	5	None		Yes
15	M/53	6	lower/3	+	Stent	17	None		Yes
16	M/48	3	lower/4	+	Stent	57	None		Yes
17	F/51	3	lower/2	+	Stent	12	Gastroesophageal reflux		Yes

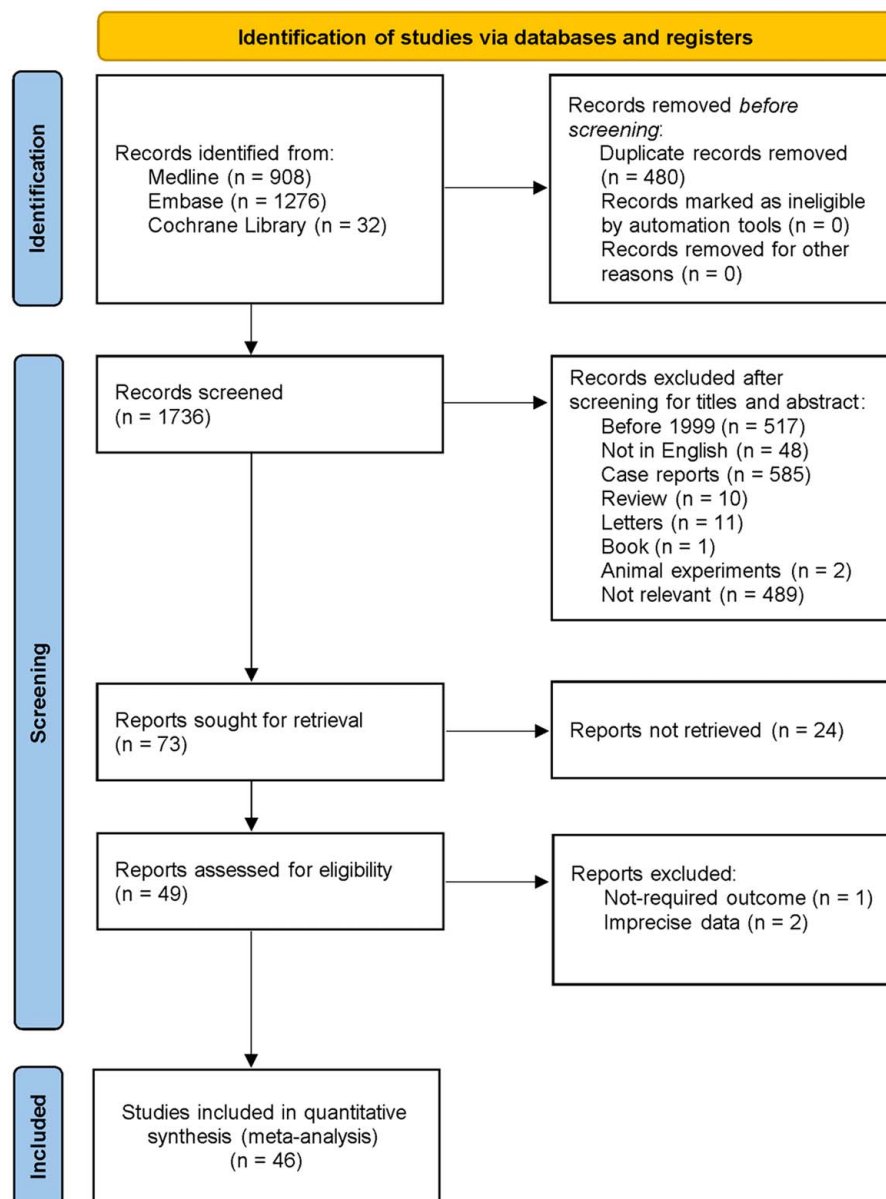


Figure 1. PRISMA flow diagram of the search strategy. In total, 2216 potentially relevant records were initially generated from MEDLINE, EMBASE, and Cochrane Library databases. After removing 480 duplicate records, the title and abstract of each record were screened. Finally, 1690 ineligible studies were excluded, and 46 studies (944 patients) were ultimately eligible for the analysis.

Most studies were conducted in Europe or Asia, with few studies conducted in South America and Oceania and none in Africa or Antarctica. The combined immediate mortality rate was 20% in studies conducted in Europe ($n=446$, 23 studies; 95% CI: 0.16–0.24), 1% in North America ($n=46$, 4 studies; 95% CI: 0.01–0.09), and 4% in Asia ($n=434$, 17 studies; 95% CI: 0.02–0.07). The Supplementary File 3 (Supplemental Digital Content 4, <http://links.lww.com/JS9/D196>) provides detailed information of each study.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the 15 nonrandomized studies. The JBI Critical Appraisal Checklist for

Case Series was used to appraise the 31 case series. The details of each study are presented in Supplementary File 2 (Supplemental Digital Content 5, <http://links.lww.com/JS9/D197>).

Sensitivity analysis

The results of the sensitivity analysis are shown in Figure 3. Sensitivity analysis was conducted by omitting one study at a time to examine the influence of the combined effect size, and test the stability of the quantitative synthesis results. The results of the meta-analysis showed that none of the combined results were not significantly influenced by any of the individual studies and were generally relatively reliable.

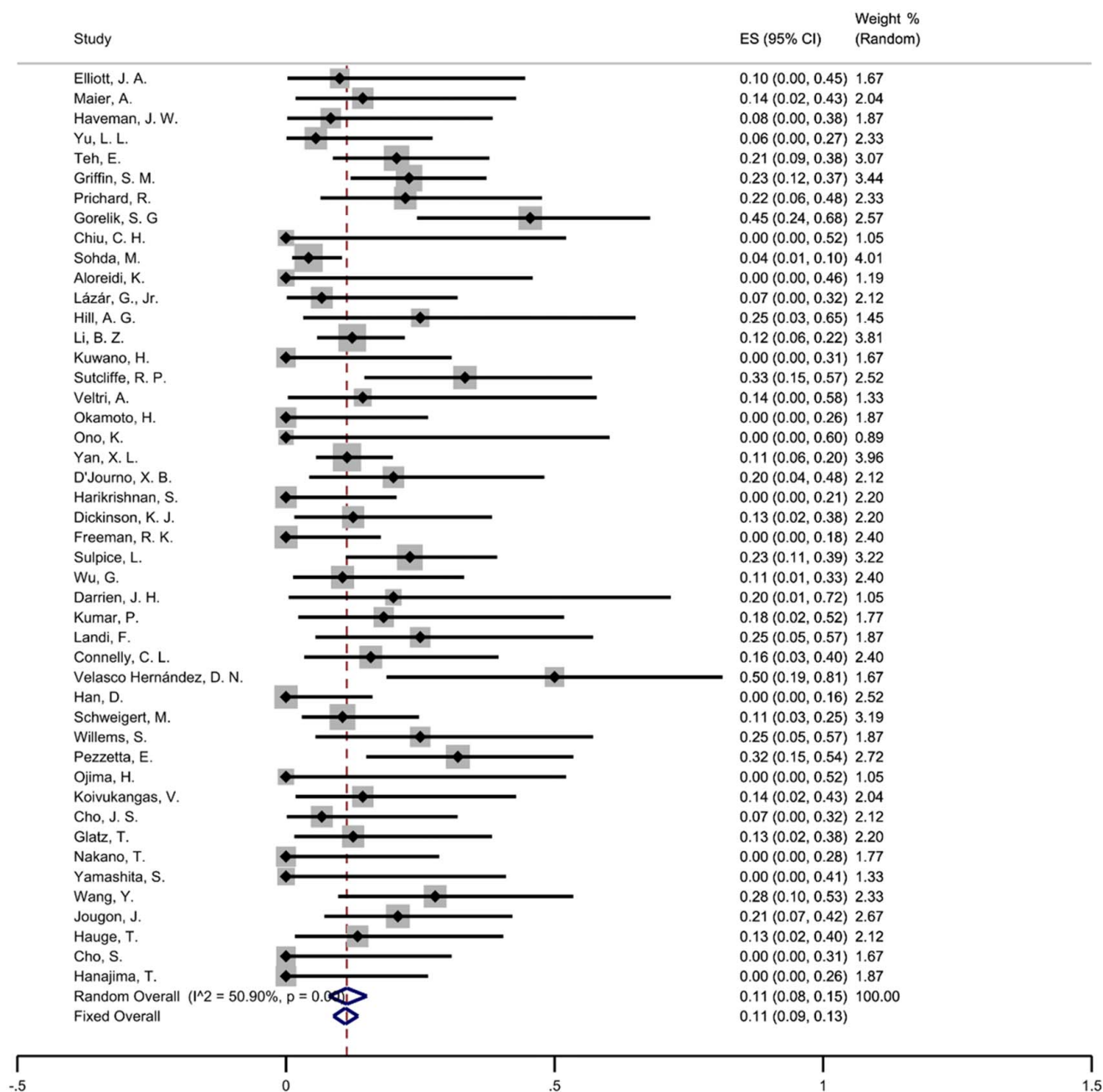


Figure 2. Forest plot summarizing immediate mortality after spontaneous esophageal rupture. We included 46 studies screened for inclusion in the pooled analysis, resulting in a combined immediate mortality rate of 11% ($N = 944$, 46 studies; 95% CI: 0.08–0.15) for spontaneous esophageal rupture.

Publication bias

To ensure the validity of the meta-analysis results, funnel plots, Begg's test, and Egger's test were used to estimate the publication bias. Figure 4 shows that the funnel plot showed no significant asymmetry, indicating that publication bias was not found in the studies, as suggested by the Begg's test (test results for the immediate mortality rate: $P = 0.232$; test results for the reintervention rate: $P = 0.593$) and Egger's test (test results for the immediate mortality rate: $P = 0.921$; test results for the reintervention rate: $P = 0.672$).

Discussion

In this study, we conducted a meta-analysis of the outcomes of treatment modalities for spontaneous esophageal rupture to provide clinicians with valuable baseline data. This study reports the clinical characteristics and outcomes of patients with spontaneous esophageal ruptures treated at a single institution and includes a meta-analysis of the existing literature on spontaneous esophageal ruptures. We found that the outcomes varied across treatment modalities, with esophagectomy presenting a better prognosis than other modalities after treatment. Esophageal stent

Table 2
Combined immediate mortality with each treatment for spontaneous esophageal rupture.

Treatment	Number of studies	Sample size	Events	Combined immediate mortality	95% CI	Heterogeneity	
						$I^2/\%$	P
Primary closure	29	496	52	0.06	0.04–0.09	39.11	0.02
T-tube drainage	9	91	20	0.14	0.02–0.32	70.54	0.00
Esophagectomy	9	38	5	0.02	0.00–0.15	27.42	0.20
Stent implantation	12	129	17	0.08	0.03–0.15	31.18	0.14
Conservative treatment	15	102	24	0.22	0.03–0.47	70.54	0.00
Total	46	944	133	0.11	0.08–0.15	50.90	0.00

placement may have some advantages in treating patients with delayed diagnosis.

In 1968, Hendren and Henderson successfully demonstrated that esophagectomy and digestive tract reconstruction for thoracic segmental esophageal perforation allowed direct removal of the diseased segments of the esophagus and was considered the most invasive form of therapy^[20,21]. This is a promising option for patients with spontaneous esophageal perforation with severe necrosis of the esophageal wall, severe localized contamination, and concomitant systemic sepsis. In our study, the patients who underwent esophagectomy had the lowest combined immediate mortality rate (2%). The main limitations of this treatment modality include the complexity of the surgical procedure, severe operative trauma, and several postoperative complications. Hence, it is not the recommended first choice in clinical practice. However, this result suggests that less conservative surgical approaches may lead to better outcomes, and this radical technique should be considered in the future. Conservative treatment, including broad-spectrum antibiotics and/or percutaneous chest drainage, remains a controversial therapeutic measure and is generally only used in patients with small perforations in the early stages of the disease, who show mild clinical symptoms and no obvious signs of toxicity, or in those with a poor general condition, who are considered a high-risk group for surgery^[22–24]. The results of this meta-analysis revealed that the combined immediate mortality rate for conservative treatment was 22%, which was the highest among the five treatment modalities. The immediate mortality rate of primary closure and esophageal stent placement was ranked second to that of esophagectomy (6 vs. 8%), which was consistent with the immediate mortality rate of stenting for spontaneous esophageal rupture reported at our center (5.88%). Therefore, primary closure or esophageal stenting is recommended as first-line treatment for first-time patients.

Our subgroup analysis of the timing of interventional therapy showed that patients treated beyond 24 h after spontaneous esophageal rupture had a higher immediate mortality rate than those treated within 24 h (12 vs. 3%). This suggests that the interval between esophageal rupture and treatment initiation may be an important factor contributing to the increased mortality rate, corroborating the results of national and international studies^[25,26]. The results of a case-series study by Schmidt *et al.* revealed a mortality rate of 11% when treated within 6 h of rupture, 13.3% when treated within 6–24 h, and 22.2% when treated after 24 h^[25]. The high mortality rate of spontaneous esophageal rupture associated with treatment after 24 h could be attributed to the degree of thoracic or mediastinal infection. In our case series, all patients were first examined in other departments and were not diagnosed immediately; instead, they were referred to the Thoracic Surgery Department for definitive treatment after developing pyothorax. Delayed diagnosis and treatment greatly increase the risk of mortality; therefore, it is crucial to identify the risk factors for spontaneous esophageal rupture and perform early diagnostic interventions.

The secondary outcome of this study was the reintervention rate after treatment. Because the esophagus lacks mesentery or mesothelial cell encapsulation, its wall is highly susceptible to severe inflammation and edema, or even necrosis, after rupture, thus increasing the difficulty of treating laceration and suturing the rupture, as well as increasing the risk of infection and continuous leakage^[13,27–29]. Our findings showed that T-tube drainage and stent placement were associated with the highest reintervention rate (23%). However, T-tube drainage is generally used in high-risk groups with serious conditions that cannot be treated surgically, such as patients with spontaneous esophageal rupture with mediastinitis or severe edema of the esophageal wall^[9,13]. Thus, the patients included in the study may have had poorer esophageal localization, and the increased difficulty in

Table 3
Combined reintervention rate of each treatment for spontaneous esophageal rupture.

Treatment	Number of studies	Sample size	Events	Combined reintervention rate	95% CI	Heterogeneity	
						$I^2/\%$	P
Primary closure	15	166	19	0.05	0.00–0.14	55.08	0.01
T-tube drainage	3	46	9	0.23	0.00–0.69	84.75	0.00
Esophagectomy	3	23	1	0.00	0.00–0.11	0.00	0.81
Stent implantation	10	111	32	0.23	0.06–0.45	74.75	0.00
Conservative treatment	8	53	6	0.01	0.00–0.11	19.93	0.27
Total	28	445	78	0.11	0.05–0.19	76.89	0.00

Table 4
Combined immediate mortality at different treatment intervals.

Interval to treatment	Number of studies	Sample size	Events	Combined immediate mortality	95% CI	Heterogeneity	
						$I^2/\%$	P
< 24 H	28	205	17	0.03	0.01–0.08	0.00	0.97
> 24 H	28	292	54	0.12	0.08–0.18	28.50	0.09

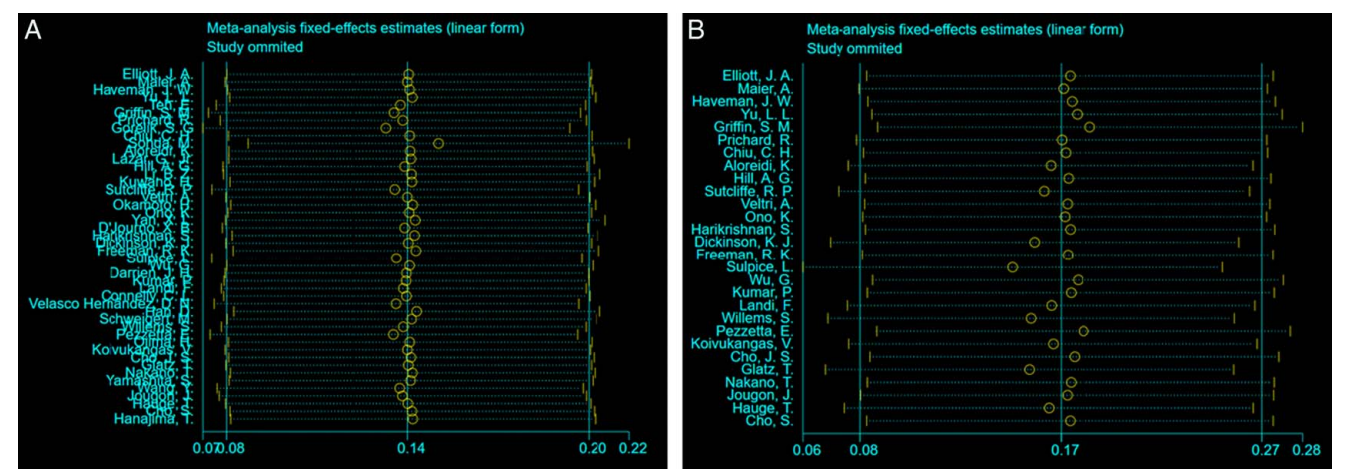


Figure 3. Sensitivity analysis. (A) Sensitivity analysis for immediate mortality rate; (B) Sensitivity analysis for reintervention rate. Sensitivity analysis was conducted by omitting one study at a time to examine the influence on the combined effect size, and test the stability of the quantitative synthesis results. The results showed that neither combined mortality nor reintervention rates were significantly influenced by any of the individual studies and were generally relatively reliable.

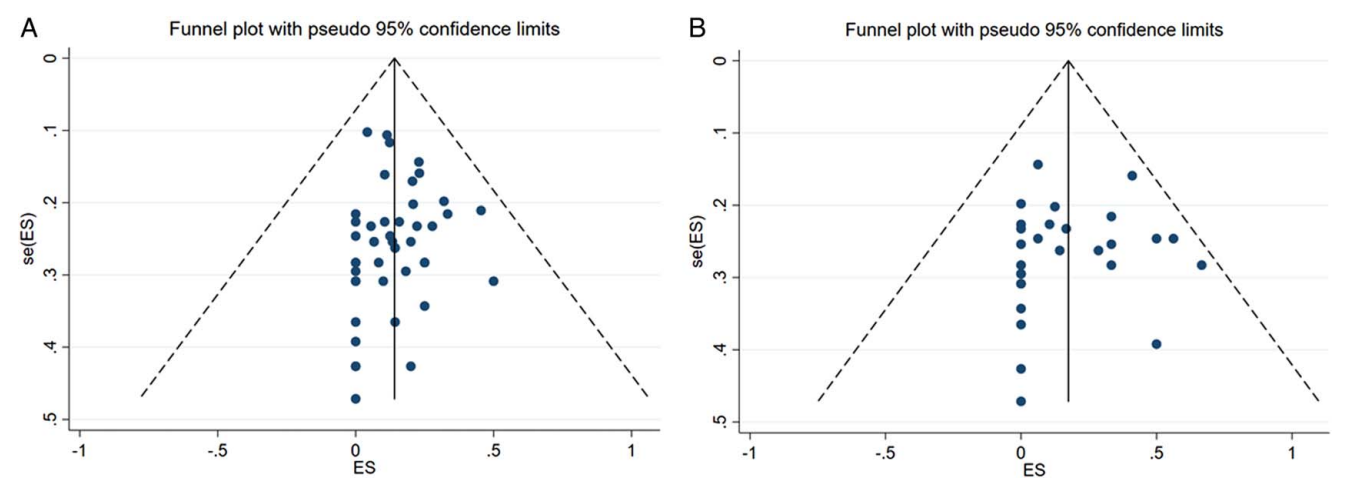


Figure 4. Funnel plot with pseudo 95% confidence limits. The horizontal line represents the summary effect estimates, and the dotted lines are pseudo 95% CIs. (A) Funnel plot for immediate mortality rate; (B) Funnel plot for reintervention rate. To ensure the validity of the meta-analysis results, funnel plots was used to estimate the publication bias. The result shows the funnel plot has no significant asymmetry, indicating that publication bias was not found in the studies.

healing may have contributed to the higher reintervention rate. The use of esophageal stents is associated with an increased rate of complications such as stent displacement, bleeding, and increased perforation, often requiring endoscopic repositioning or replacement of the stent, which is a major contributor to the high reintervention rate^[30,31]. Surprisingly, the reintervention rate for esophagectomy was 0%; however, these data were obtained from nine small studies that included only 38 patients.

Given the low mortality rate associated with esophagectomy, it is an acceptable option when initial nonesophagectomy treatment has failed.

In our cases, where the interval between esophageal rupture and treatment was much longer than 24 h and was combined with severe thoracic or mediastinal infections, the immediate mortality rate of spontaneous esophageal rupture treated with a stent was 5.88%, second only to that of esophagectomy.

Moreover, the reintervention rate was lower than the results of the meta-analysis (11.8 vs. 23%), which may also be associated with a lower complication rate. We have summarized our experience of using stents to treat patients with spontaneous esophageal rupture. Gastroscopy is performed before surgery to identify factors that may affect stent placement therapy and to select a model that will generate sufficient radial force on the adjacent structures to completely seal the stent. The lower section of the esophageal stent is then extended to an appropriate location within the gastric lumen to reduce the incidence of dislocation. The placement of a decompression tube in the gastrointestinal tract was essential to minimize the potential for reflux of gastrointestinal fluid into the cleft.

This study had several limitations that warrant discussion. First, this institutional case series was a retrospective observational study. Such studies have some limitations owing to their design, which may affect the internal validity and generalizability of the results. Second, the studies included in this meta-analysis had different study designs, populations, and treatments, and the pooled results may be biased. Third, most of the included data were derived from moderate-quality studies and the evidence remains limited. Therefore, it is necessary to conduct multicenter studies or prospective trials with larger sample sizes for further validation. Finally, although we tried our best to retrieve the full texts of the articles, complete data from some ongoing studies are not yet available. Further follow-up studies will be conducted to validate our results.

Conclusions

Our findings suggest that esophagectomy for spontaneous esophageal rupture has the best outcomes, with primary closure or esophageal stenting being a good option. Moreover, prognosis correlates with the timing of intervention, and accurate diagnosis and treatment within 24 h significantly reduces the risk of death in patients. Patients with delayed diagnosis may have a better prognosis with stent placement.

Ethical approval

The case series included in our study were approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval number: XYFY2023-KL369-01).

Consent

Our study did not involve images of patients or volunteers, and written and signed consent was obtained from patients.

Source of funding

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Conflicts of interest disclosure

The authors declare that they have no conflict of interest.

Author contribution

J.P. and Y.G.: study concept and design; J.P., Y.G., and C.Z.: acquisition, analysis, and interpretation of data; J.P.: drafting of the manuscript; H.Z., Z.S., and F.Z.: critical revision of the manuscript and approving the submitted draft. All authors gave critical revision comments and agreed to the final version of the manuscript.

Research registration unique identifying number (UIN)

The study was prospectively registered in PROSPERO (CRD42023459385).

Guarantor

Hao Zhang, Department of Thoracic Surgery, Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou 221003, Jiangsu, China. E-mail: zhanghao@xzhmu.edu.cn

Data availability statement

Data will be available upon reasonable request. Any datasets generated and/or analyzed during this study are publicly available, accessible upon reasonable request, or data shared. Eligible and interested researchers can contact Prof. Hao Zhang (E-mail: zhanghao@xzhmu.edu.cn), Department of Thoracic Surgery, Affiliated Hospital of Xuzhou Medical University to request access to the data.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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