Current treatment and outcome of esophageal perforation: A single-center experience and a pooled analysis

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Abstract

Background: Esophageal perforation has been one of the serious clinical emergencies, because of the high mortality and complication rates. However, the current prognosis of esophageal perforation and the outcomes of available treatment methods are not well defined. This study attempted to pool the immediate outcomes of esophageal perforation in the past 2 decades.

Methods: The clinical data of 22 consecutive adult patients with esophageal perforation in our center were analyzed. A pooled analysis was also conducted to summarize results from the literatures published between 1999 and 2020. Studies that met the inclusion criteria were assessed, and their methodological quality was examined.

Results: The mortality and complication rates in our center were 4.55% and 31.82%, separately. The pooled analysis included 45 studies published between 1999 and 2019, which highlighted an overall immediate mortality rate of 9.86%. Surgical treatments were associated with a pooled immediate mortality of 10.01%, and for conservative treatments of 6.49%. Besides, in the past decade, the mortality and complication rates decreased by 27.12% and 46.75%, respectively.

Conclusions: In the past 2 decades, the overall immediate mortality rate of esophageal perforation was about 10% in the worldwide, and the outcomes of esophageal perforation treatment are getting better in the last 10 years.

Ethics Registration Information: LW2020011.

Abbreviations: 95% CI = 95% confidence intervals, CT = computed tomography, EP = esophageal perforation, MeSH = Medical Subject Headings, PRISMA = preferred reporting items for systematic reviews and meta-analyses.

Keywords: complication rate, esophageal perforation, mortality rate, pooled analysis, retrospective study

1. Introduction

Esophageal perforation (EP) is a sudden, rare, and severe clinical event. It has been one of the serious clinical emergencies. Once perforation occurs, timely diagnosis and treatment must be made immediately. Otherwise, digestive juices may overfl ow through the perforation, which can result in a serious inflammation in the peritoneal cavity. It can even make death because of the systemic toxic symptoms caused by acute suppurative infection.[1,2]

Esophageal perforation can occur in the cervical, thoracic, or abdominal esophagus. There are many iatrogenic causes including endoscopic examinations, surgical procedures, placement of tubes and intubation, the non-iatrogenic causes may include spontaneous rupture (Boerhaave syndrome), thoracic trauma, swallowing foreign bodies, and penetrating wounds. Esophageal perforation presents high mortality rate ranging from 4% to 40%. It even has historically been associated with a mortality rate around 90% before the antibiotic era.[2]

Over the past 20 years, thanks to the continuous improvement of treatment, there is a signi cant improvement in treatment outcomes compared to those of the past.[3] In the present study, we planned to pool the immediate outcome of this emergency condition in the past 2 decades, and evaluate the ef cacy of current treatments following esophageal perforation. To achieve this goal, we analyzed the clinical data of consecutive adult patients with esophageal perforation in our center from 2010 to 2020, and then conducted a pooled analysis to summarize results from the literatures published between 1999 and 2020.

2. Methods

2.1. Retrospective study

The present study was approved by the Research Ethics Committee from Fourth Affiliated Hospital of Guangxi Medical...
University (LW2020011). We reviewed all cases of esophageal perforation treated in the Department of Cardiothoracic Surgery, Fourth Affiliated Hospital of Guangxi Medical University between 2010 and 2020. The diagnosis of esophageal perforation was established on the basis of clinical presentation, computed tomography (CT), contrast esophagram, and endoscopic evaluation. We analyzed and reviewed most of important clinical data, including cause, the site of the perforation, treatment, and outcome.

All patients were followed up until discharge or death. Mortality is defined as death within 30 days or during the same hospitalization, and morbidity is defined as nonfatal complications.

2.2. Pooled analysis

2.2.1. Search strategy. The guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA) were applied in the study.[4] We identified procurable studies published from 1999 up to 2020. An English-language literature review was performed through Web of Science, PubMed, and Cochrane Library databases for any study-evaluating outcome after treatment of esophageal perforation. The following combined text and Medical Subject Headings (MeSH) search strategy was used to search the databases mentioned above: ([Esophageal OR oesophageal] AND [rupture OR perforation]) AND (treatment OR management). We also examined conference proceedings and the references from retrieved articles for additional relevant publications.

2.2.2. Inclusion criteria. The included studies in the pooled analysis met the following criteria:

1) a full article published in English language;
2) physician-confirmed esophageal perforation;
3) prospective or retrospective observational studies that included at least 20 perforation cases with more than 1 type of etiology;
4) included adult patients;
5) reporting on in-hospital or 30-days mortality after any kind of treatment;
6) presentation of original data;
7) published after January 1999.

If the results of a study had been published in more than 1 publication, only the one with the most complete information was included.

2.2.3. Data extraction and assessment of the methodological quality. The primary outcome of this review was inhospital or 30-days mortality, which can be defined as death during the hospital stay or the 30-day postoperative period. The complication rate was considered a secondary outcome measure.

Two investigators independently extracted information from the included studies, including first author, year of publication, study period, number of patients, main treatment modality, in-hospital/30-day mortality, and complication rate. Any disagreements were resolved through discussion.

The main treatment modality included surgical treatment and conservative treatment. The surgical treatment was defined as modalities that had directly accessed to the perforation, such as primary suture repair with or without tissue reinforcement or esophagectomy. The conservative treatment included nonsurgical treatment or endoscopic treatment that did not repair the fistula, but used an invasive procedure. The fasting, prolonged parenteral nutrition, use of broad-spectrum antibiotics, and percutaneous drainage under CT or ultrasound guidance were also considered as conservative treatments.

All studies included in the pooled analysis were evaluated regarding their quality according to GRADE classification of Cochrane handbook.[5]

2.2.4. Statistical analysis. A pooled proportion estimate and its 95% confidence intervals (95% CI) were obtained by weighting those of specific studies. To examine the heterogeneity, we performed the Higgins $I^2$ test.[6-8] The $I^2$ value describes the percentage of total variation across studies due to heterogeneity rather than chance. The value of $I^2$ ranged from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). We calculated the summary proportion and its 95% CI based on the fixed-effect model if a substantial heterogeneity was not found ($I^2 \leq 50\%$). Conversely, we calculated the pooled proportion and its 95% CI based on the random-effect model, if the substantial heterogeneity was found ($I^2 > 50\%$). Statistical analyses were performed using the freely downloadable software package META (version 4.11-0) for R (version 3.6.3).[9-11]

3. Results

3.1. Retrospective study

During the investigational period, a total of 22 consecutive patients with esophageal perforation were treated at our center. The patient characteristics and univariate predictors of mortality, morbidity, are shown in Table 1.

The 22 patients comprised 14 (63.64%) men and 8 (36.36%) women, with a mean age of 64.18 years (ranged from 41 to 85 years). The treatment for most of the patients started within

| Variable                  | No. of patients | Mortality | Morbidity |
|---------------------------|-----------------|-----------|-----------|
| Sex                       |                 |           |           |
| Male                      | 14              | 1         | 6         |
| Female                    | 8               | 0         | 1         |
| Cause of perforation      |                 |           |           |
| Spontaneous               | 5               | 1         | 3         |
| Foreign body              | 16              | 0         | 4         |
| Iatrogenic                | 1               | 0         | 0         |
| Location of perforation   |                 |           |           |
| Cervical                  | 6               | 0         | 0         |
| Thoracic                  | 16              | 1         | 7         |
| Age (yr)                  |                 |           |           |
| <60                       | 7               | 0         | 1         |
| >60                       | 15              | 1         | 6         |
| Treatment                 |                 |           |           |
| Surgical                  | 18              | 1         | 5         |
| Conservative              | 4               | 0         | 0         |
| Diagnosis/treatment delay time |         |           |           |
| <24h                      | 20              | 1         | 6         |
| >24h                      | 2               | 0         | 1         |
| Thoracic infection        |                 |           |           |
| Yes                       | 8               | 1         | 6         |
| No                        | 14              | 0         | 1         |
| Total                     | 22              | 1         | 7         |
24 hours after the event, only 2 patients treated later than 24 hours (3 and 4 days, respectively). The perforation was spontaneous in 5 patients, foreign body-related in 16 patients, and 1 patient caused by iatrogenic rupture. Perforation was localized to the thoracic esophagus in 16 patients, and in the cervical area in 6 patients. Fourteen patients were mild cases without thoracic infection, the other 8 patients with thoracic infection. Eighteen patients were treated surgically and 4 patients were treated with a conservative approach.

Overall mortality for the entire group was 4.55% (1 death in 22 patients). The univariate analysis was done for the influences on mortality of independent variables sex, age, cause of perforation, perforation location, and treatment approach. There was no variable found to be associated with increased mortality.

The complications developed in 7 patients (31.82%). The univariate analysis was also done for the influences on morbidity of independent variables. There was a statistically significant difference between morbidity and the thoracic infection. The morbidity was higher in patients with thoracic infection than those without thoracic infection (75.00% vs 7.14%, \( P = .002 \)). The perforation location was also found to be associated with morbidity. The morbidity rate according to perforation location was higher in thoracic perforation (43.75%), with statistically significant difference (\( P = .049 \)) between cervical perforation (0%).

### 3.2. Pooled analysis

The flow diagram of the identification of relevant studies is shown in Figure 1. A total of 3154 references were identified through the main electronic databases and the bibliographies of relevant articles. After the exclusion of duplicates and criteria screening, 53 studies published between 1999 and 2019 met all the inclusion criteria, and were included in the final analysis.\(^{[12-64]}\)

All articles included were retrospective studies. There was no prospective study or randomized controlled trial detected. According to GRADE classification, the quality of studies can be evaluated as high, moderate, low, or very low. Table 2 shows the main characteristics of the included studies in the final pooled analysis. Throughout the 53 included studies, 3009 patients were evaluated. Besides, most of the studies (38/53) were of very low or low quality included.

### 3.3. Analysis of mortality

The mortality rate is a primary outcome for treatment of esophageal perforation. All the included studies reported immediate mortality (shown in Table 3). As shown in Figure 2, the overall immediate mortality was 9.86% (95% CI 7.73–12.20; \( I^2 = 73\% \)).

In all, 26 and 37 studies reported patients and deaths received conservative treatments and surgical treatments, respectively.

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**Figure 1.** Selection of studies for inclusion in this pooled analysis.
Table 3

Characteristics of studies included in the final analysis.

| First author | Year of publication | Study period | Study region | Cases | Mortality | Morbidity | GRADE quality |
|--------------|---------------------|--------------|--------------|-------|-----------|------------|---------------|
| Lawrence     | 1999                | 1987–1996    | UK           | 21    | 3         | 2          | Low           |
| Gaudzina     | 2000                | 1975–1999    | US           | 44    | 2         | 2          | Moderate      |
| Öktten       | 2000                | 1986–1998    | Turkey       | 31    | 9         | 9          | Low           |
| Sung         | 2002                | 1986–1999    | Korea        | 20    | 1         | 9          | Low           |
| Tomaselli    | 2002                | 1990–1999    | Austria      | 38    | 6         | 6          | Low           |
| Muir         | 2003                | 1985–2000    | UK           | 75    | 12        | 12         | Moderate      |
| Port         | 2003                | 1990–2001    | US           | 26    | 1         | 1          | Moderate      |
| Amir         | 2004                | 1985–2001    | Netherlands  | 38    | 0         | 23         | Moderate      |
| Gupta        | 2004                | 1986–2001    | India        | 57    | 8         | 8          | Low           |
| Jougon       | 2004                | 1980–2003    | France       | 24    | 5         | 5          | Low           |
| Rubikas      | 2004                | 1987–2001    | Lithuania    | 84    | 16        | 36         | Low           |
| Chao         | 2005                | 1995–2002    | Taiwan       | 28    | 3         | 13         | Low           |
| Richardson   | 2005                | 1985–2004    | US           | 64    | 1         | 1          | Low           |
| Vogel        | 2005                | 1992–2004    | US           | 47    | 2         | 2          | Moderate      |
| Kiernan      | 2006                | 1988–2005    | US           | 48    | 6         | 6          | Low           |
| Erdogan      | 2007                | 1990–2006    | Turkey       | 28    | 3         | 12         | Low           |
| Linden       | 2007                | 1989–2003    | US           | 43    | 3         | 20         | Moderate      |
| Griffin      | 2008                | 1993–2007    | UK           | 48    | 11        | 11         | Low           |
| Griffiths    | 2008                | 1995–2008    | UK           | 34    | 8         | 24         | Low           |
| Abbas        | 2008                | 1998–2008    | US           | 119   | 15        | 75         | Moderate      |
| Arnuethan    | 2009                | 1999–2007    | India        | 48    | 3         | 18         | Low           |
| Ergolu       | 2009                | 1989–2008    | Turkey       | 44    | 5         | 12         | Low           |
| Udelrow      | 2009                | 2001–2008    | Germany      | 41    | 9         | 9          | Low           |
| Heremansion  | 2010                | 1970–2006    | Sweden       | 125   | 24        | 54         | Moderate      |
| Keeling      | 2010                | 1997–2008    | US           | 97    | 8         | 57         | Moderate      |
| Onat         | 2010                | 1989–2008    | Turkey       | 30    | 5         | 13         | Low           |
| Schmidt      | 2010                | 1998–2006    | Germany      | 62    | 9         | 9          | Low           |
| Shaker       | 2010                | 2002–2008    | UK           | 27    | 5         | 5          | Low           |
| Vallbohrer   | 2010                | 1996–2008    | Germany      | 44    | 3         | 3          | Low           |
| Vidarsoffter | 2010                | 1980–2007    | Iceland      | 24    | 0         | 0          | Low           |
| Havenman     | 2011                | 1985–2009    | Netherlands  | 24    | 2         | 2          | Low           |
| Jiang        | 2011                | 1989–2010    | China        | 42    | 0         | 0          | Low           |
| Kuppusamy    | 2011                | 1989–2008    | US           | 81    | 3         | 31         | Moderate      |
| Minnich      | 2011                | 1998–2009    | US           | 81    | 9         | 9          | Moderate      |
| Peng         | 2012                | 1985–2010    | China        | 121   | 1         | 10         | Low           |
| Lin          | 2013                | 1997–2013    | China        | 66    | 8         | 8          | Low           |
| Troja        | 2014                | 2004–2012    | Germany      | 39    | 8         | 8          | Low           |
| Persson      | 2014                | 2003–2013    | Sweden       | 48    | 8         | 8          | Low           |
| Aghajanzadeh | 2014                | 2001–2011    | Iran         | 26    | 2         | 2          | Low           |
| Ben-David    | 2014                | 2007–2013    | US           | 76    | 1         | 1          | Low           |
| Biancari     | 2014                | 2000–2013    | EU           | 194   | 34        | 34         | Moderate      |
| Navaneethan  | 2014                | 2007–2012    | US           | 20    | 2         | 2          | Low           |
| Wahed        | 2014                | 2002–2012    | UK           | 96    | 22        | 22         | Moderate      |
| Dolezic      | 2016                | 2010–2015    | Poland       | 102   | 10        | 10         | Moderate      |
| Ali          | 2017                | 2009–2013    | US; Canada; EU| 199  | 30        | 30         | Moderate      |
| Giancari     | 2017                | 2006–2015    | Finland      | 43    | 4         | 4          | Low           |
| Law          | 2017                | 1997–2013    | Hong Kong    | 43    | 10        | 10         | Low           |
| Fattahi Masoom| 2018              | 1996–2015    | Iran         | 27    | 1         | 1          | Low           |
| Han          | 2018                | 1993–2012    | China        | 21    | 0         | 0          | Low           |
| Wigley       | 2018                | 2003–2017    | UK           | 87    | 11        | 40         | Low           |
| Haugue       | 2018                | 2007–2014    | Norway       | 21    | 1         | 3          | Low           |
| Virh         | 2019                | 2009–2017    | Vietnam      | 65    | 0         | 0          | Low           |
| Kang         | 2019                | 2008–2018    | South Korea  | 28    | 3         | 3          | Low           |

Table 3

Stratified analyses of mortality rate.

| Stratified analysis       | No. of studies | Overall mortality rate and 95% CI | $I^2$ (%) | Analysis model | $P$   |
|---------------------------|----------------|----------------------------------|-----------|----------------|------|
| Treatment approach        |                |                                   |           |                |      |
| Surgical treatment        | 37             | 10.01% (95% CI 7.18–13.17%)       | 68        | Random-effect model | .021 |
| Conservative treatment    | 26             | 6.49% (95% CI 2.82–11.11%)        | 52        | Random-effect model | .006 |
| Published year            |                |                                   |           |                |      |
| Before 2010               | 30             | 11.32% (95% CI 8.64–14.28%)       | 61        | Random-effect model | .449 |
| After 2010                | 23             | 8.25% (95% CI 5.11–11.97%)        | 80        | Random-effect model |      |
| Hospital volume           |                |                                   |           |                |      |
| ≥5 cases per year         | 16             | 10.48% (95% CI 6.84–14.75%)       | 84        | Random-effect model |      |
| <5 cases per year         | 37             | 9.58% (95% CI 7.02–12.43%)        | 63        | Random-effect model |      |
Surgical treatments were associated with a pooled immediate mortality of 10.01% (95% CI 7.18–13.17%), and for conservative treatments of 6.49% (95% CI 2.82–11.11%).

For different surgical treatment modalities, the immediate mortality was also pooled. The mortality after T-tube or any other tube repair was higher than others at 18.3% (95% CI 9.5–27.1%). The values of mortality after esophagectomy, primary

![Forest plot summarizing pooled immediate mortality rate after esophageal perforation.](Deng et al. Medicine (2021) 100:16 www.md-journal.com 5)
repair, and stent-grafting were 11.6% (95% CI 8.5–20.1%), 8.5% (95% CI 6.3–12.2%), and 6.9% (95% CI 3.5–11.5%), respectively. Studies published before 2010 had a pooled mortality of 11.32% (95% CI 8.64–14.28%), which is significantly lower than those published after 2010 had a pooled mortality of 8.25% (95% CI 5.11–11.97%) (P = .006).

In 15 studies, cervical perforations were associated with a pooled mortality of 6.2% (95% CI 3.5–8.8%). The pooled mortality was 10.5% (95% CI 7.5–14.2%) for thoracic perforations in 20 studies, and 13.2% (95% CI 4.6–25.2%) for intraabdominal perforations in 8 studies.

For different causes of perforation, the pooled immediate mortality for esophageal perforation after iatrogenic perforation was 12.8% (95% CI 8.3–18.9%) in 19 studies, it was 2.1% (95% CI 0.6–4.4%) caused by foreign bodies in 11 studies, and 15.2% (95% CI 12.3–19.9%) with spontaneous perforation in 21 studies.

Comparative analysis was performed for the effect of hospital volume on clinical outcomes. In 16 studies, the hospitals treated ≥5 cases per year. The hospitals treated <5 cases per year in 37 studies. Mortality was not significantly different in those hospitals (10.48%, 95% CI 6.84–14.75% for hospitals treated ≥5 cases and 9.58%, 95% CI 7.02–12.43% for hospitals treated <5 cases) (P = .449).

In the included studies, 26 reported the timing of the esophageal perforation to treatment and the relationships to outcome. The pooled immediate mortality was 7.4% (95% CI 0.6–10.8%) for the patients received treatment was started within 24 hours after the occurrence of perforation, and it was 20.3% (95% CI 16.1–24.7%) for those treated later than 24 hours after the occurrence. The immediate mortality for treatments later than 24 hours after the occurrence was significantly higher than within 24 hours (P < .001).

3.4. Comparison of complication rates

The incidence of medical complications following esophageal perforation is another important parameter for treatment. The summarized complication rates were shown in Table 4. A total of 21 included studies (1221 patients) reported complication rates. The overall complication rate was 39.56% (95% CI 29.98–49.54%; I² = 91%, as shown in Fig. 3).
Pooled complication rate of patients with conservative treatments was significantly lower than those with surgical treatments (37.29%, 95% CI 28.22–46.78% vs 48.72%, 95% CI 38.02–59.87%, \( P < .004 \)). The complication rate of studies published before 2010 was 48.62% (95% CI 41.92–55.35%), while that of studies published after 2010 was 25.89% (95% CI 11.45–43.45%). The difference was also significant (\( P < .001 \)).

For the effect of hospital volume, the complication rate for hospitals treated \( \geq 5 \) cases per year was 36.20% (95% CI 18.45–56.10%), and that for hospitals treated <\( 5 \) cases per year was 41.61% (95% CI 31.98–51.55%). There was no significant difference (\( P = .060 \)).

### 4. Discussion

In spite of the low incidence of esophageal perforation, it has always been a serious medical emergency, prone to serious consequences. Because of these characteristics, the feasibility of conducting clinical trials has been compromised, especially the randomized processes seem so difficult to carry out in such populations. To date, the current evidence about the efficacy of treatment for perforations is based only in retrospective case series studies.

The present pooled analysis highlighted an overall immediate mortality rate of 9.86%. In the retrospective study of our center, the immediate mortality rate was 4.55%, which is rather lower than the pooled analysis of previous studies. For the morbidity rate, our center was also much lower than the pooled analysis (31.82% vs 39.56%). This may be related to the characteristics of the patients we treated. Most of the patients we treated were mild patients, and most of them are diagnosed in time (less than 24 hours).

This study showed that markedly increased mortality rate can be expected in patients undergoing surgical treatments than conservative treatments. This result is consistent with Biancari’s study, but contrary to Hasimoto’s. There was also a significant higher complication rate in patients with surgical treatments than conservative treatments. This may also be due to the choice of conservative treatment in the majority of mild cases, there was less chest contamination.

Comparing studies published at different decades, we found a significant decrease in both mortality and complication rates. The mortality rate decreased by 27.12% (from 11.32% before 2010 to 8.25% after 2010, \( P = .006 \)), and the complication rate decreased by 46.75% (from 48.62% before 2010 to 25.89% after 2010, \( P < .001 \)). This may be attributed to the more mature diagnosis and treatment technology, better surgical environment, and the application of new instruments and drugs in the last decade. Markar\(^{[3]}\) reported the reduction in mortality associated with increasing hospital volume. In their study, the volume–outcome relationship seen appears to be continuous in nature, with a threshold of 3 cases per year (\( \geq 36 \) cases over the study period) this translates to approximately a 30% reduction in 30- and 90-day mortality in multivariate analysis. The patients in the center with more cases are likely to be managed by multidisciplinary teams with access to high-quality services capable of better treatment in these complex patients.\(^{[3]}\) However, in our present study, the difference in mortality was not significant, with the threshold of 5 cases per year. The complication rates were slightly lower in centers with \( \geq 5 \) cases per year, but the difference was not significant, too. In the last decade, the treatment of esophageal perforation has been gradually standardized, and the gap of outcomes in various centers has been gradually narrowed. In addition, due to the implementation of hierarchical diagnosis and treatment, worst-off patients are often referred to large hospitals, which also result in that the large hospitals received relatively high mortality rate.

Severai limitations of this pooled analysis should be mentioned here. There was no prospective study or randomized controlled trial detected, so all articles included were retrospective studies. The quality of individual studies included in the pooled analysis was not always optimal. Besides, there is heterogeneity and possibility of publication bias across some stratified analysis. Finally, only the studies in English language were considered. This may cause omission of relevant studies published in other languages. However, the results of this pooled analysis effectively summarize the immediate outcomes (mortality and complication rates) with current treatment modalities and provide a background for further studies on this severe emergency condition.

### 5. Conclusions

In summary, we investigated the treatment outcomes of esophageal perforation in our center and conducted a pooled analysis of results from other relevant published studies. In the past 2 decades, the overall immediate mortality rate was 9.86%. In addition, we found a significant decrease in both mortality and complication rates of studies published after 2010 compared with those before 2010, which suggested the outcomes of esophageal perforation treatment are getting better.

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