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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 overflow 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 significant 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 efficacy 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

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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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 in-hospital 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

Table 1

The patient characteristics and univariate predictors of mortality, morbidity.

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	2
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.

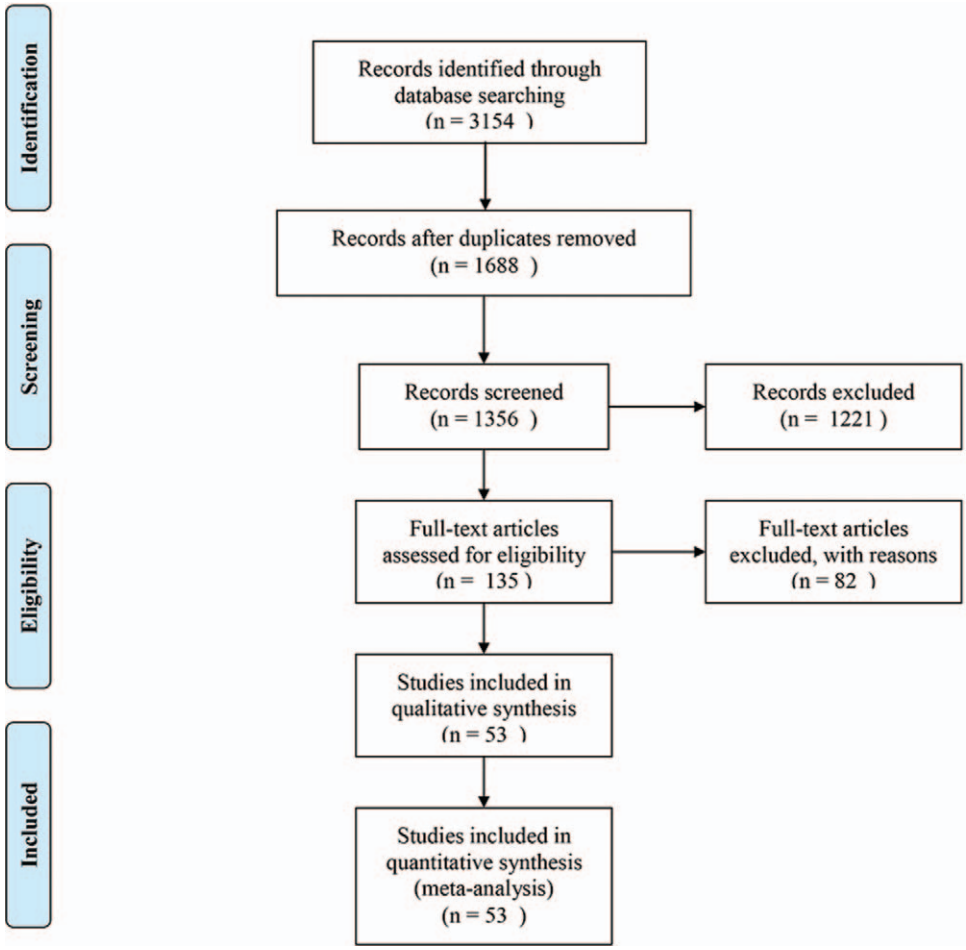

Figure 1. Selection of studies for inclusion in this pooled analysis.

Table 2

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
Gaudinez	2000	1975–1999	US	44	2		Moderate
Ökten	2000	1986–1998	Turkey	31	9		Low
Sung	2002	1986–1999	Korea	20	1	9	Low
Tomaselli	2002	1990–1999	Austria	38	6		Low
Muir	2003	1985–2000	UK	75	12		Moderate
Port	2003	1990–2001	US	26	1		Moderate
Amir	2004	1985–2001	Netherlands	38	0	23	Moderate
Gupta	2004	1986–2001	India	57	8		Low
Jougon	2004	1980–2003	France	24	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		Low
Vogel	2005	1992–2004	US	47	2		Moderate
Kiernan	2006	1988–2005	US	48	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		Low
Griffiths	2008	1995–2008	UK	34	8	24	Low
Abbas	2009	1998–2008	US	119	15	75	Moderate
Amudhan	2009	1999–2007	India	48	3	18	Low
Eroglu	2009	1989–2008	Turkey	44	5	12	Low
Udelnow	2009	2001–2008	Germany	41	9		Low
Hermansson	2010	1970–2006	Sweden	125	24	54	Moderate
Keeling	2010	1997–2008	US	97	8	57	Moderate
Onat	2010	1980–2008	Turkey	30	5	13	Low
Schmidt	2010	1998–2006	Germany	62	9		Low
Shaker	2010	2002–2008	UK	27	5		Low
Vallböhmer	2010	1996–2008	Germany	44	3		Low
Vidarsdottir	2010	1980–2007	Iceland	24	0		Low
Haveman	2011	1985–2009	Netherlands	24	2	20	Low
Jiang	2011	1980–2010	China	42	0		Low
Kuppusamy	2011	1989–2009	US	81	3	31	Moderate
Minnich	2011	1998–2009	US	81	9		Moderate
Peng	2012	1985–2010	China	121	1	10	Low
Lin	2013	1997–2013	China	66	8		Low
Troja	2014	2004–2012	Germany	39	8		Low
Persson	2014	2003–2013	Sweden	48	8		Low
Aghajanzadeh	2014	2001–2011	Iran	26	2		Low
Ben-David	2014	2007–2013	US	76	1		Low
Biancari	2014	2000–2013	EU	194	34		Moderate
Navaneethan	2014	2007–2012	US	20	2	2	Low
Wahed	2014	2002–2012	UK	96	22		Moderate
Dziedzic	2016	2010–2015	Poland	102	10	10	Moderate
Ali	2017	2009–2013	US; Canada; EU	199	30		Moderate
Biancari	2017	2006–2015	Finland	43	4		Low
Law	2017	1997–2013	Hong Kong	43	10		Low
Fattahi Masoom	2018	1996–2015	Iran	27	1	4	Low
Han	2018	1993–2012	China	21	0		Low
Wigley	2018	2003–2017	UK	87	11	40	Low
Hauge	2019	2007–2014	Norway	21	1	3	Low
Vinh	2019	2009–2017	Vietnam	65	0		Low
Kang	2019	2008–2018	South Korea	28	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					.021
Surgical treatment	37	10.01% (95% CI 7.18–13.17%)	68	Random-effect model	
Conservative treatment	26	6.49% (95% CI 2.82–11.11%)	52	Random-effect model	
Published year					.006
Before 2010	30	11.32% (95% CI 8.64–14.28%)	61	Random-effect model	
After 2010	23	8.25% (95% CI 5.11–11.97%)	80	Random-effect model	
Hospital volume					.449
≥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	

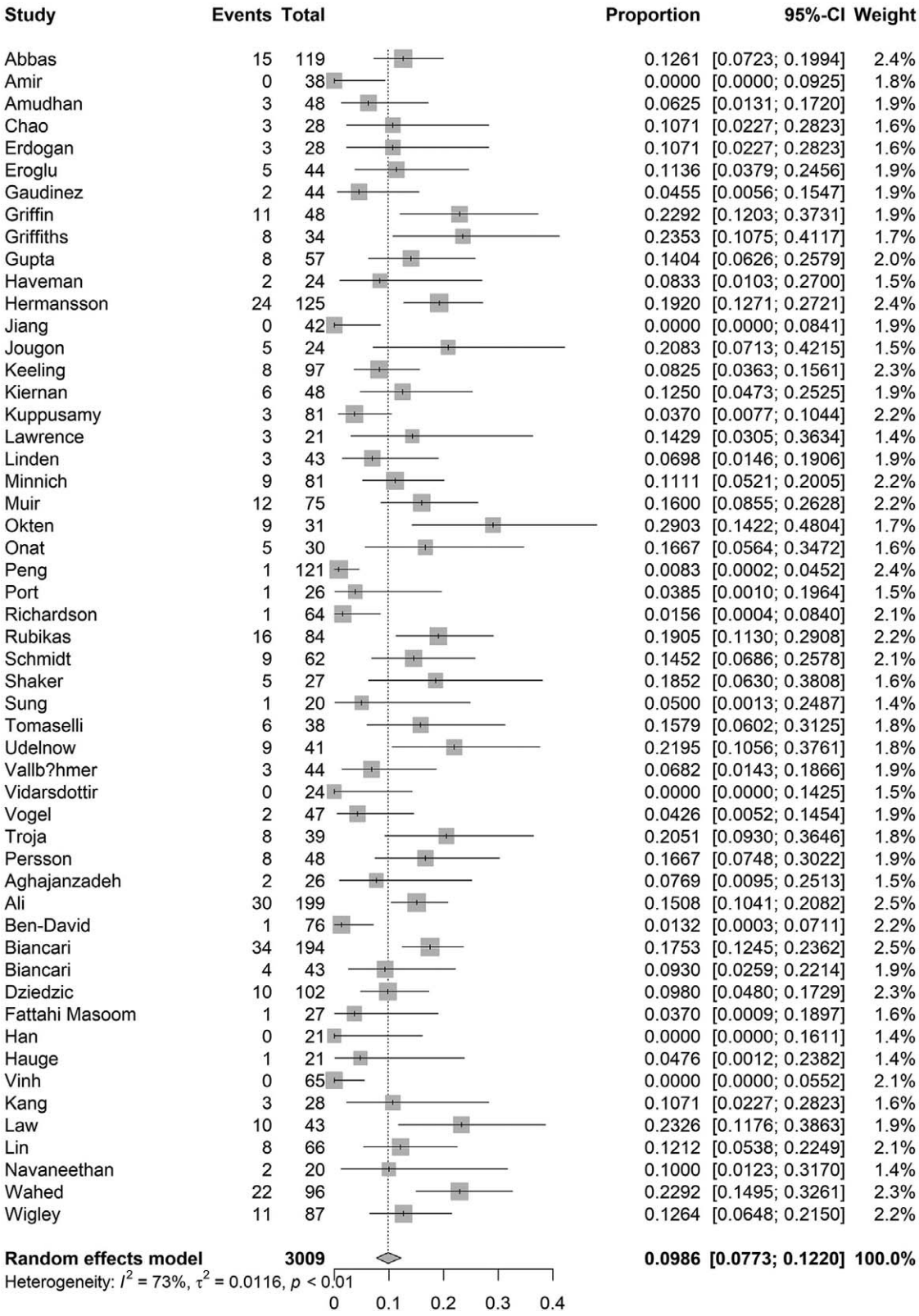

Figure 2. Forest plot summarizing pooled immediate mortality rate after esophageal perforation.

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

Table 4

Stratified analyses of complication rate.

Stratified analysis	No. of studies	Overall complication rate and 95% CI	I^2 (%)	Analysis model	*P*
Treatment approach					.004
Surgical treatment	8	48.72% (95% CI 38.02–59.87%)	74	Random-effect model	
Conservative treatment	5	37.29% (95% CI 28.22–46.78%)	0	Fixed-effect model	
Published year					<.001
Before 2010	13	48.62% (95% CI 41.92–55.35%)	67	Random-effect model	
After 2010	8	25.89% (95% CI 11.45–43.45%)	93	Random-effect model	
Hospital volume					.060
≥5 cases per year	7	36.20% (95% CI 18.45–56.10%)	96	Random-effect model	
<5 cases per year	14	41.61% (95% CI 31.98–51.55%)	81	Random-effect model	

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%; $I^2 = 91\%$, as shown in Fig. 3).

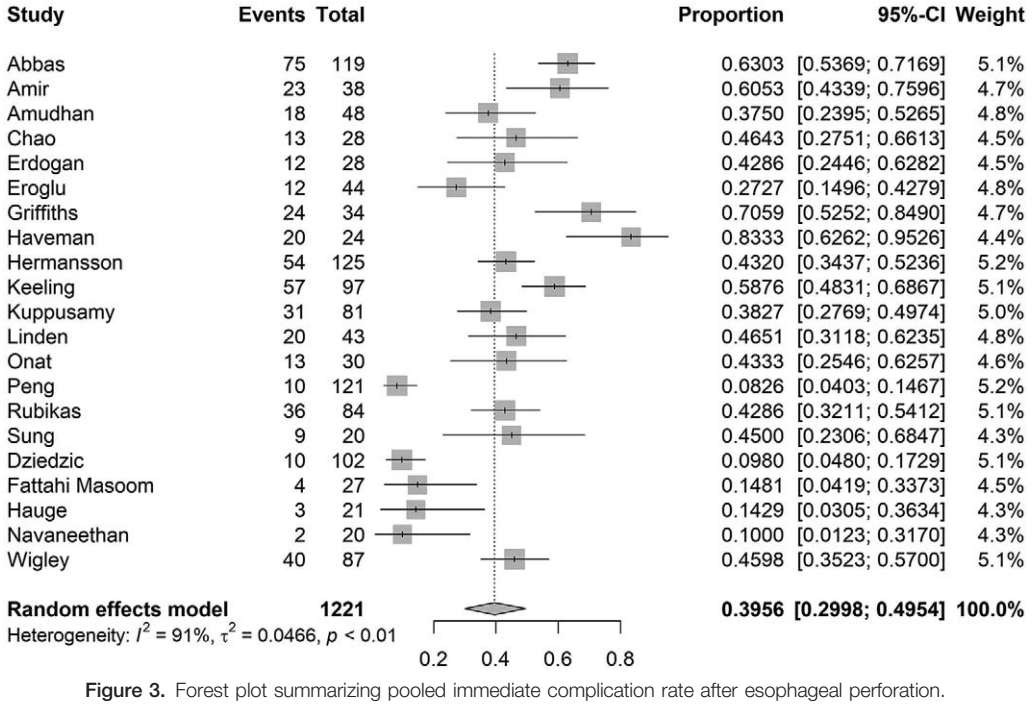

Figure 3. Forest plot summarizing pooled immediate complication rate after esophageal perforation.

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 ≥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 (≥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 ≥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.

Several 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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Writing – review & editing: Yufeng Deng, Tianzhu Yuan.

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