Effect of Prophylactic Ligation of the Thoracic Duct on Long-Term Survival in Patients Undergoing Esophagectomy: A Meta-Analysis

Mei kun
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
Ce Chao
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
Long Xuanren
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
Ma Chao
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
Zhou Rui
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
Wang Bin (colin_iverson@163.com)
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital
DI Dongmei
Third Affiliated Hospital of Soochow University: Changzhou First People's Hospital

Research

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Abstract

Objective: To evaluate the existing literature by comparing long-term survival between patients who underwent prophylactic thoracic duct ligation (PLG) and non-prophylactic thoracic duct ligation (NPLG) during esophagectomy for esophageal cancer, a meta-analysis of relevant studies was conducted.

Background: The effect of PLG and NPLG on the long-term survival in patients undergoing esophagectomy for treatment of esophageal cancer has not been established.

Methods: All articles searches were performed in PubMed, Cochrane, Embase, and Web of Science, and the deadline is August 31, 2020. The search terms included esophagectomy AND thoracic duct. The selected articles compared the long-term survival of patients undergoing esophagectomy to treat esophageal cancer with prophylactic thoracic duct ligation (PLG) and non-prophylactic thoracic duct ligation (NPLG). The I^2 test and X^2 test were used to determine statistical heterogeneity. Publication bias was assessed using the Egger test. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All data analysis was performed using Stata12.0 software.

Result: A total of 4418 patients from eight studies were included in this meta-analysis. Pooled analysis revealed that a high overall survival (OS) was significantly associated with NPLG (HR=0.81, 95% CI: 0.74-0.88, P<.001), while the recurrence- free survival (RFS) and disease-free survival (DFS) were not significantly different (HR=1.02, 95% CI: 0.71-1.45, P<.001). There was no statistical difference in long-term survival among patients with different stages of esophageal cancer, while patients who underwent esophagectomy after 2019 had a better long-term prognosis (HR=0.57, 95% CI: 0.57-0.79). In addition, there was no significant difference in prognosis and survival between patients in Japan and China based on regional analysis.

Conclusions: Our meta-analysis showed that NPLG was associated with better long-term survival. Thus, we should preserve the thoracic duct during esophageal cancer surgery.

1. Introduction

Esophageal cancer is the seventh leading cause of cancer deaths worldwide (1). At present, esophagectomy is the most effective method to treat localized esophageal cancer (2-7). Prophylactic ligation of the thoracic duct (PLG) during esophageal cancer surgery is controversial. To reduce the morbidity associated with chylothorax, ligation of the thoracic duct should be performed prophylactically independent of intra-operative injury to the thoracic duct; however, PLG may result in post-operative intravenous volume loss, hemodynamic instability, and a delay in initiating enteral feeding (8, 9). Indeed, the effect of PLG on long-term survival in patients undergoing esophagectomy for esophageal cancer has not been established (9-13). Therefore, the purpose of our meta-analysis was to evaluate the long-term survival of PLG during esophagectomy for esophageal cancer.

2. Materials And Methods

2.1. Search strategy

PubMed, Cochrane, Embase, and Web of Science were searched for relevant studies that evaluated the long-term survival in esophageal cancer patients post-esophagectomy. The search terms included esophagectomy AND thoracic duct. In addition, references in the retrieved literature were manually reviewed. This study was a meta-analysis, so ethical approval was not required.

2.2. Inclusion and exclusion criteria

Inclusion criteria and methods of the analysis have been pre-defined and documented.

Studies were independently screened by two authors (Mei and Chao) according to the title, abstract, and type of article. The literature search had no language restrictions. The retrieved articles were included in the meta-analysis if all of the following criteria were met:

1. the article contained non-prophylactic thoracic duct ligation (NPLG) and PLG groups;
2. the article provided original data and sufficient information to estimate the hazard ratio (HR) for thoracic duct ligation;
3. Non-prophylactic thoracic duct ligation (NPLG) and PLG and prognosis of cancer patients were described. HR and 95 % CI are reported, or can be obtained indirectly through survival curve.

The exclusion criteria:

1. Without sufficient data;
2. Case reports, reviews, summaries of meetings or discussions.

2.3. Quality assessment

Two investigators (Mei and Chao) independently assessed the eligible studies in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS) (14). NOS scores of at least six were considered high-quality literature. Higher NOS scores showed higher literature quality.

2.4. Data extraction

One researcher extracted the data from the selected articles and the other researcher checked the extracted data. The following data were extracted:

1. first author, publication year, sample size, methods, duration of follow-up, and other relevant data; and

2. the overall survival rate (OS) and 95% confidence interval (CIs) were extracted if the data were clearly provided in the published study results; if survival data were not provided, survival data were extracted from the Kaplan-Meier curve for further processing (15).

Disagreements between reviewers were resolved by consensus.

2.5. Statistical analysis

The HR and 95% CI were used to assess the long-term effects of thoracic duct ligation and a test for heterogeneity was also performed using I^2 tests (16). If a X^2 test had a P<0.05 or I^2>50%, we considered the heterogeneity to be significant, and a random-effect model was adopted; otherwise, a fixed-effects model was adopted. A Begg funnel plot was used to detect publication bias. Data management and analysis were performed with STATA 12.0 software (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Search results

As shown in the following flow chart, a total of 1292 studies were retrieved from PubMed, Cochrane, Embase, and Web of Science according to the search strategy. Of the 1292 studies, 615 were duplicates and deleted. A total of 643 studies were excluded based on abstract screening, including 568 unrelated studies, 60 cases, 12 reviews, and two letters. After reading through the entire study, 26 studies lacking data were excluded. Finally, eight studies were analyzed（FIG. 1） (10, 17-23).

3.2. Study characteristics

Detailed information about the eight studies is available in Table 1. The eight studies were published between 2006 and 2020, including four each conducted in Japan and China. A total of 4418 patients (2128 and 2290 underwent NPLG and PLG, respectively) were included. Kaplan-Meier curves were provided in all studies. The HR and 95% CI were provided in the Chen study (18), and the corresponding HR and 95% CI were extracted by Kaplan-Meier curve for the other studies that did not provide direct data. The NOS scores ranged from 7-8.

3.3. Correlation between NPLG and HR of cancer patients

Due to the low heterogeneity of the study, the fixed-effect model was used (I^2=14.5%, p=0.306). The following forest map (Fig. 2) shows the correlation between NPLG and long-term patient survival （HR=0.81, 95% CI:0.74-0.88, P<0.001). In addition, the RFS was not statistically significant （HR=1.02, 95%CI:0.71-1.45, p=0.293）

The OS for different esophageal cancer stages were not statistically significant (Figs. 3).

Compared with patients undergoing esophagectomy before and after 2019, Patients who underwent esophagectomy after 2019 had a better prognosis (HR=0.67, 95% CI: 0.57-0.79, p=0.689) than patients who underwent esophagectomy before 2019, which may have reflected the improvement in surgical techniques (Figs. 4).

A comparison of esophageal cancer patients in different geographic regions revealed statistical significance in both groups, but there was no significant difference (Figs. 5).

3.4. Publication bias

The Begg funnel plot showed similar symmetry, suggesting no publication bias (Begg test: P=0.815 and Egger test: P=0.705; Fig. 6 Moreover, the Egger test was performed to assess the publication bias of the included studies (10, 17-23).

4. Discussion

The thoracic duct, the largest lymphatic vessel in the body, originates from hemangioblastic stem cells and generally develops at the end of the 6^{th} week of gestation. In an adult, the thoracic duct is located at T12 – L2 to the right of the midline. The thoracic duct courses cranially to enter the thorax through the aortic hiatus. The posterior thoracic duct is often damaged during esophagectomy because of adhesions of the esophagus to adjacent soft tissues. In addition, this finding may be due to variations in the thoracic duct due to embryonic developmental deviations, which can occur in any part of the duct circuit. So, there are a number of studies involving routine ligation of the thoracic duct (24-29).

In the past decade, the majority of studies have focused on PLG for reducing the incidence of post-operative chylothorax, but few studies have addressed long-term survival. Tao (23) reported that PLG is a safe and effective method to reduce post-operative chylothorax. Both Satoru (22) and Matsuda (17) concluded that ligation has a superior effect on long-term prognosis.

A number of studies, however, have shown that PLG may have adverse outcomes. For example, PLG has been shown to increase the incidence of post-operative chylothorax and left recurrent laryngeal nerve (RLN) palsy (21). In addition, it has also been clarified that routine PLG is not necessary (19, 20). Furthermore, Hou (10) and Chen (18) investigated the effect of PLG on long-term survival, and reported that the PLG group had a lower 5-year survival rate than the NPLG group (48.2% vs. 61.6%, P < 0.001).

Therefore, we performed this meta-analysis to obtain more definitive conclusions on the effects of NPLG and PLG on long-term survival in patients undergoing esophagectomy for esophageal cancer. In fact, more and more researchers have shown that NPLG has a better prognosis. This is the first meta-analysis to determine the effect of PLG and NPLG on long-term survival of esophageal cancer patients.

Specifically, our findings suggested that NPLG has a higher long-term survival rate in patients with esophageal cancer. Eight studies and 4418 patients were included, indicating good reliability of the results. The pooled HR value was 0.81 (95% CI: 0.74-0.88, $P < 0.001$).

Furthermore, because the thoracic duct has immune and nutrition functions, injury to the thoracic duct leads to chylothorax, which in turn leads to weakened immune function, malnutrition, impaired respiratory function, and decreased plasma proteins, fat-soluble vitamins, triglycerides, lymphocytes, electrolytes, and endovascular volume. Therefore, the difference in RFS between the PLG and NPLG groups in this study was not significant, while the OS was statistically significant (24-27, 29).

In addition, some limitations to this study should be discussed and studied. The results of this meta-analysis showed some heterogeneity (I^2=14.5%). The lack of standardized ligation techniques may be one reason for the heterogeneity. For example, Chen (18) performed PLG by ligation of lymphoid adipose tissue between the aorta and the singular artery, whereas Hou (10) performed direct ligation near the diaphragmatic hiatus. The HR was obtained using Engauge Digitizer 10.0 software from the Kaplan–Meier curve, which may have been a source of error. In addition, the articles collected in this study only included studies conducted in China and Japan, which may be representative of Asia, thus additional data should be collected, especially for patient groups in Europe and the United States. The selected articles in this study were all retrospective studies, with no prospective studies. Therefore, a large prospective study should be conducted to verify our results.

Drinking milk before surgery can help with thoracic duct imaging and reduce intra-operative injury. In addition, contrast-enhanced multi-row computed tomography with axial and coronal multi-plane reconstruction may also be used to display the thoracic duct.

5. Conclusion

This meta-analysis showed that NPLG has a better long-term survival rate for patients with esophageal cancer. Therefore, PLG should be avoided during esophagectomy

6. Abbreviations

PLG prophylactic thoracic duct ligation

NPLG non-prophylactic thoracic duct ligation

HRs hazard ratios

CIs confidence intervals

OS overall survival

RFS recurrence- free survival

DFS disease-free survival

NOS Newcastle-Ottawa Quality Assessment Scale

RLN recurrent laryngeal nerve

SE standard error

CSS cause-specific survival

Declarations

7. **Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8. **Author Contributions**

MK, CC, and BW conceived and designed the study. MK drafted the original paper. MK, CC, and XRL extracted all data and performed the analyses. CM, RZ, and DMD supervised the project and provided direction and guidance throughout the preparation of this manuscript. BW revised the final manuscript. All authors contributed to the article and approved the submitted version.

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10. **Availability of date and materials**

All the date analyzed in this study are obtained from the original articles.

11. **Ethics approval and consent to participate**

This study was a meta-analysis, so ethical approval was not required.

12. **Consent for publication**

Not applicable.

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Tables

Table 1. Basic characteristics of the included studies

OS=overall survival, DFS=disease-free survival, CSS=cause-specific survival, RFS=recurrence-free survival, HR=hazard ratio, CI=confidence interval

Auther	Year	TDP	TDS	Study type	OS/CSS/DFS/RFS	NOS	Follow-up Time	HR	95%CI
T.Oshikiri,	2019	122	122	retrospective cohort study	OS、DFS、CSS	7	median follow-up 4.5 years	HR(OS) 0.68 HR(DFS) 0.83	CI(OS):0.45-1.03 CI(DFS):0.55-1.24
Tao Bao	2019	40	133	retrospective cohort	OS	7	-	1.07	0.58-1.97
Satoru Matsuda	2016	cStage I=36 cStage II-IV=45	cStage I=34 cStage II-IV=36	retrospective cohort study	OS	7	-	HR(cStage I)0.8 HR(cStage II-IV)0.85	CI(cStage I);0.06-9.89 CI(cStage II-
Fu	2006	218	171	retrospective cohort	OS	8	3-156month	0.94	0.76-1.15
S.Matsuda	2020	CT1N0=14 CT1N1=8 Stage II=14 Stage III or IV=8	CT1N0=79 CT1N1=15 Stage II=42 Stage III or IV=55	retrospective cohort study	RFS	7	6-60month	HR(CT1N0)6.16 HR(CT1N1)1.86 HR(Stage II)1.78 HR(Stage III or IV)1.66	CI(CT1N0):0.88-43.11 CI(CT1N1):0.11-32.57 CI(Stage II):0.53-
X.Hou	2014	815	989	retrospective cohort	OS	7	3-120month	0.85	0.75-0.96
Naoya Yoshida	2019	cStage I=190 cStage II=62 cStage	cStage I=25 cStage II=24 cStage III=79 cStage IV=13	retrospective cohort study	OS	7	3-60month	HR(cStage I)0.38 HR(cStage II)0.53 HR(cStage III)0.74 HR(cStage IV)1.73	CI(cStage I):0.03-4.97 CI(cStage II):0.21-1.33 CI(cStage
Jun-Ying Chen MD,PhD	2020	462	473	retrospective cohort study	OS	7	3-60month	0.63	0.52-0.63

Figures

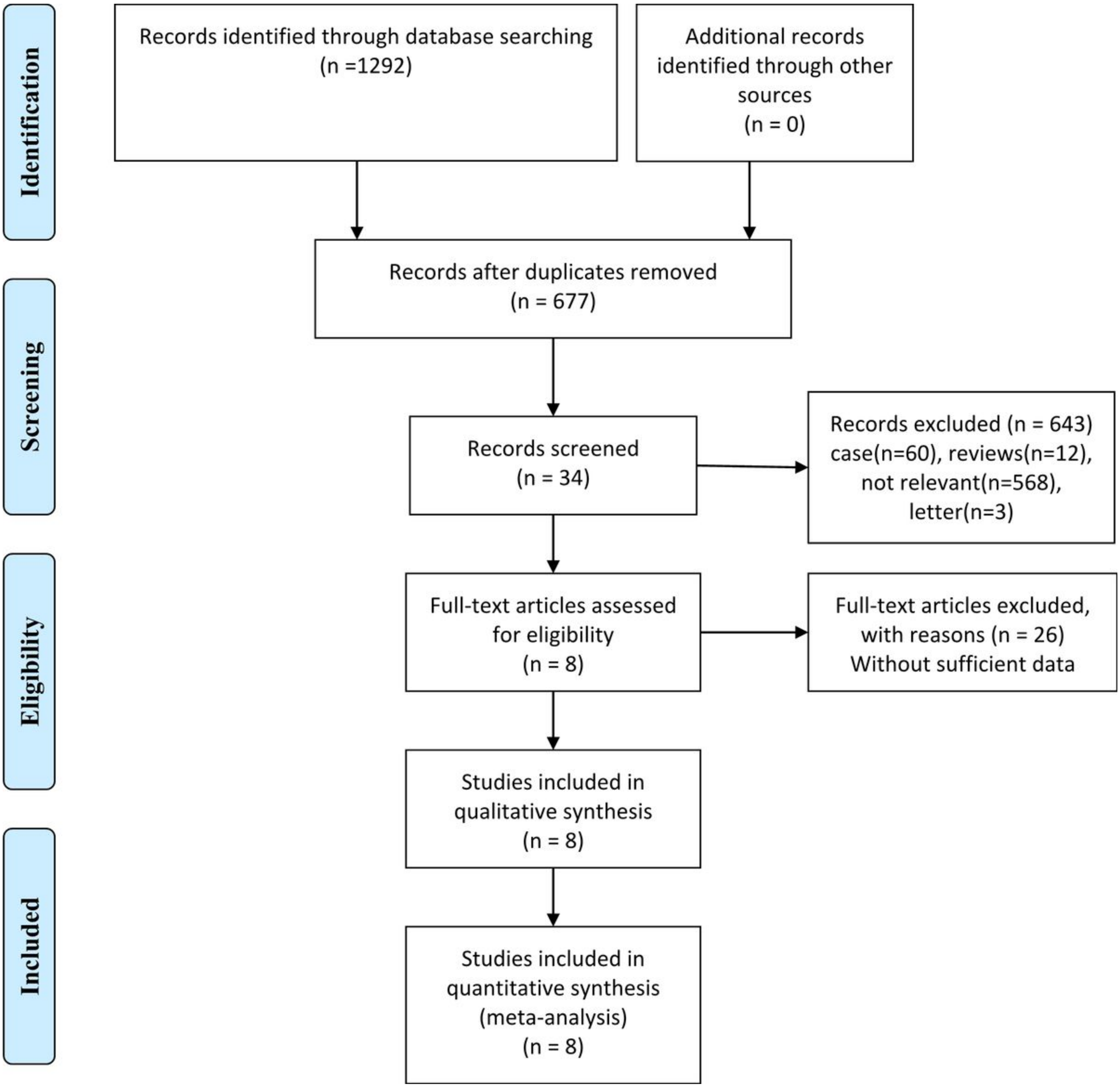

Figure 1

Flowchart of meta-analysis.

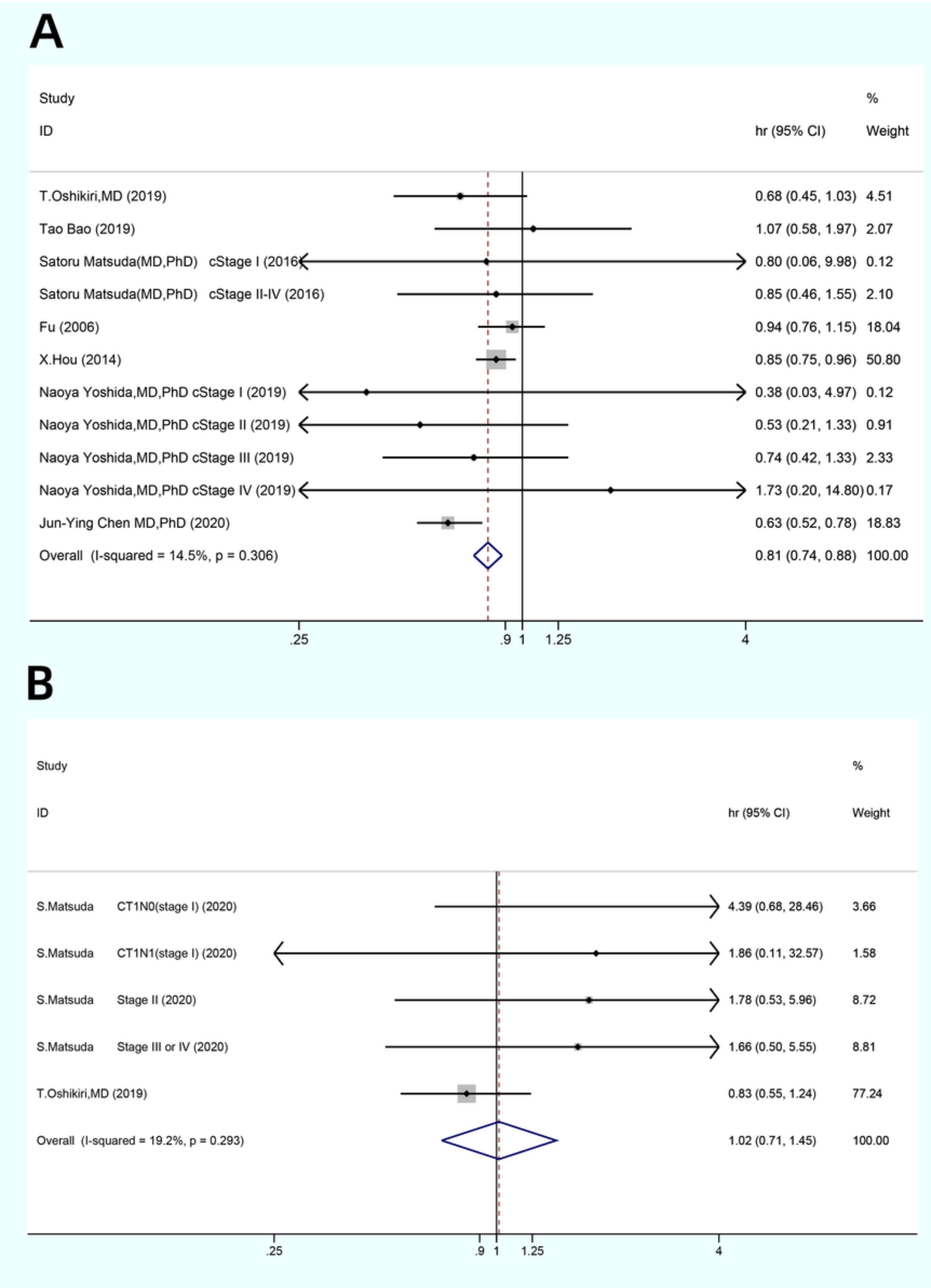

Figure 2

Forest plot of the association between NPLG and overall survival in esophageal cancer. HR=hazard ratio, CI=confidence interval

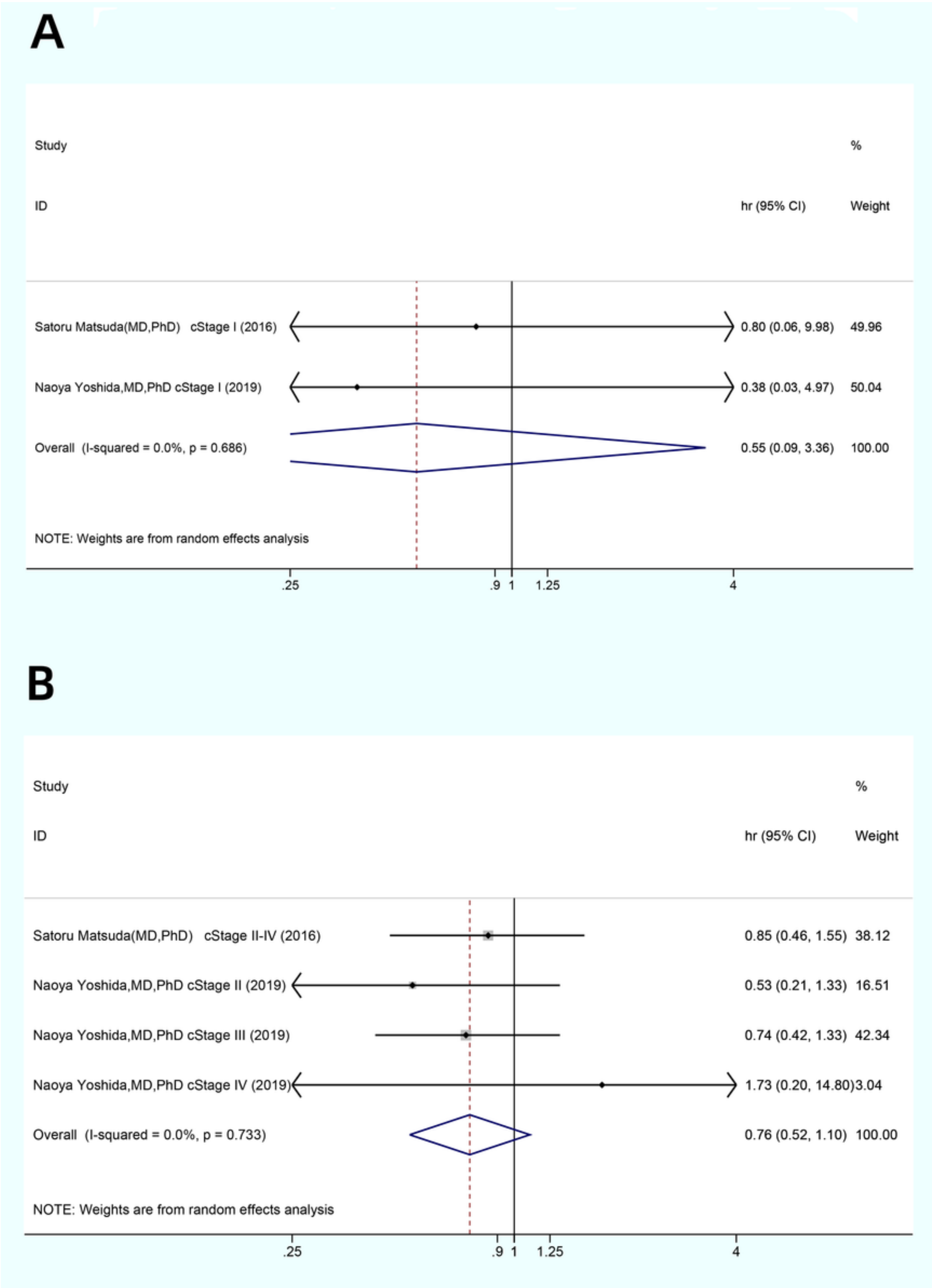

Figure 3

A: Forest plot of stage I esophageal cancer. B: Forest plot of stage II-IV esophageal cancer. HR=hazard ratio, CI=confidence interval

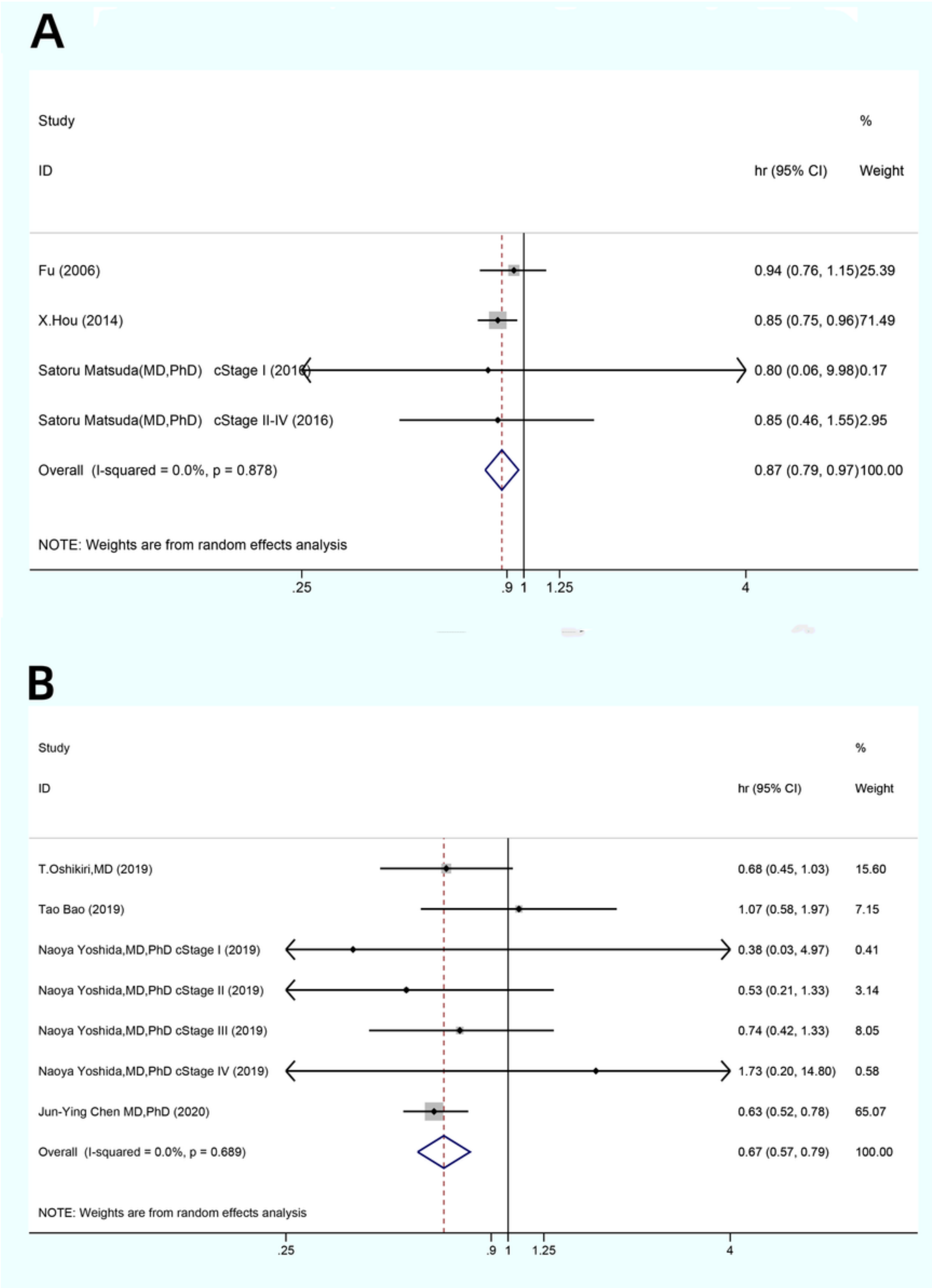

Figure 4

A: Forest plot of esophagectomy for esophageal cancer before 2019. B: Forest plot of esophageal cancer surgery after 2019. HR=hazard ratio, CI=confidence interval

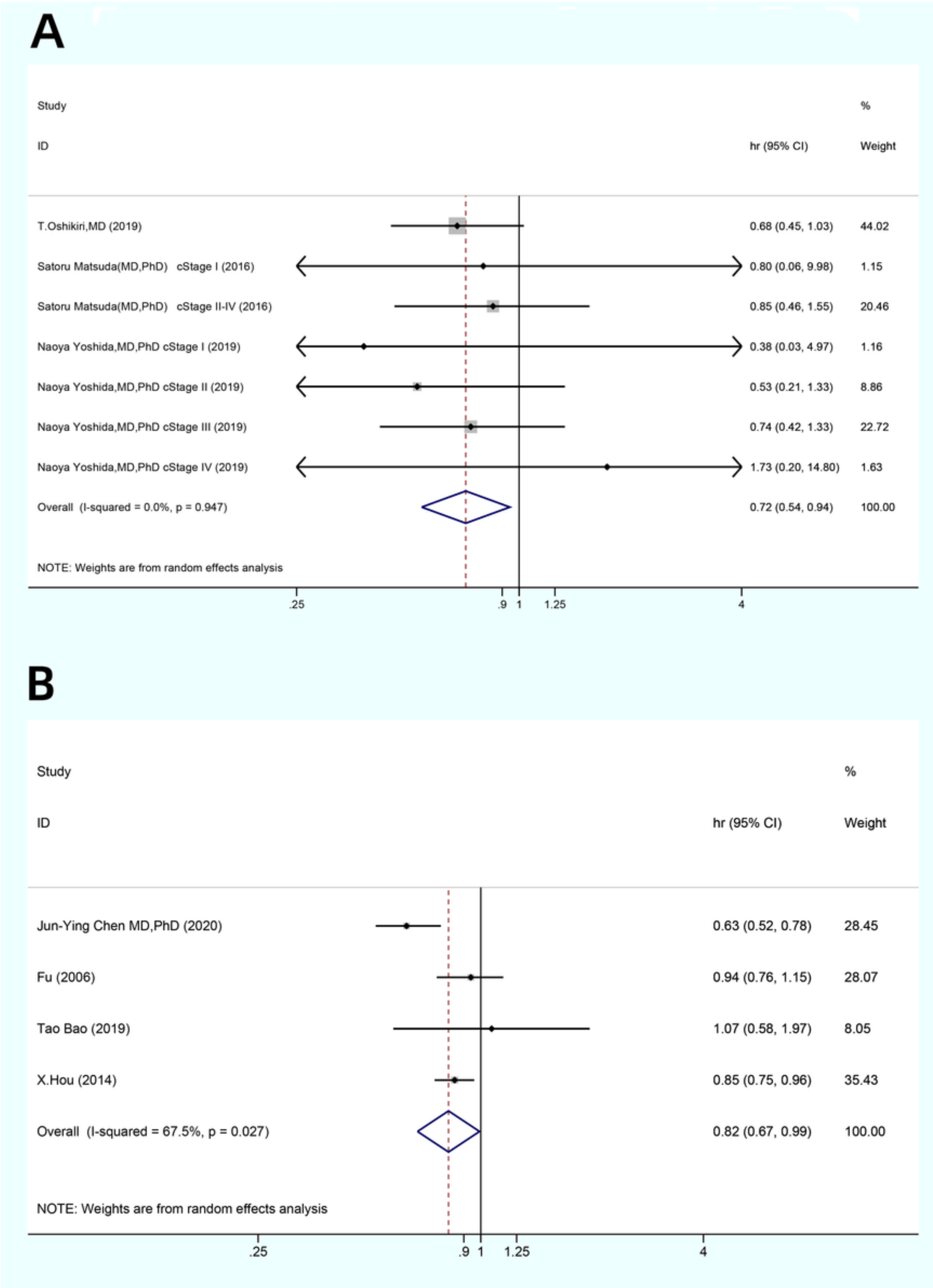

Figure 5

A: Forest plot of esophageal cancer surgery in Japan. B: Forest plot of esophageal cancer surgery in China. HR=hazard ratio, CI=confidence interval

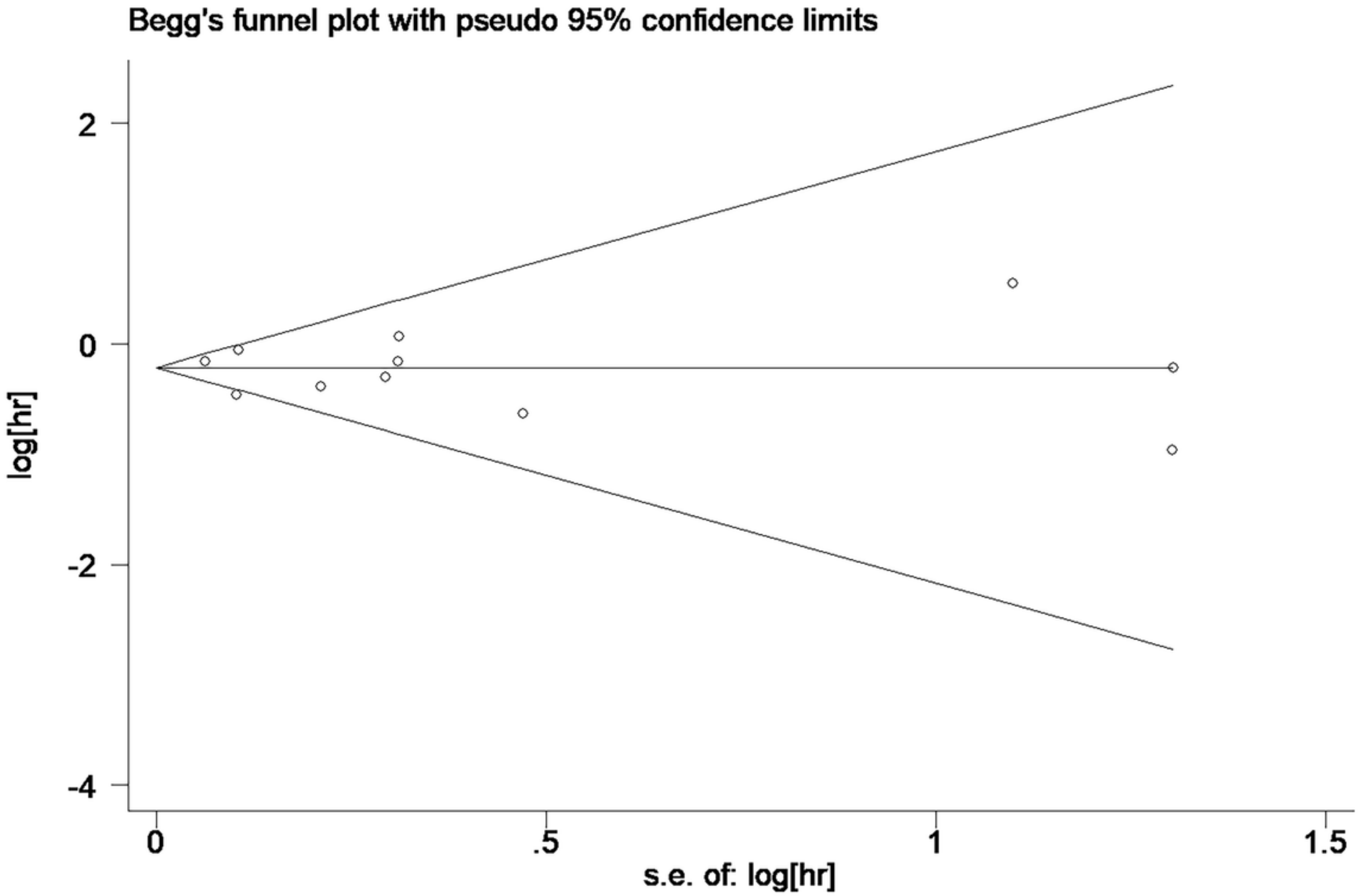

Figure 6

Begg funnel plot indicator test for publication bias of NPLG and overall survival. HR=hazard ratio, SE=standard error