

Original Article

Transthoracic versus abdominal-transhiatal resection for treating Siewert type II/III adenocarcinoma of the esophagogastric junction: a meta-analysis

Zhi-Zheng, Jun-Cai, Jie Yin, Jun Zhang, Zhong-Tao Zhang, Kang-Li Wang

Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

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Abstract: Our study aimed to explore the differences in short and long-term outcomes about the transthoracic (TH) and abdominal-transhiatal (TA) approaches for treating esophagogastric junction (AEG). A systematic review of PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure and CBMdisc was performed. All original articles comparing TH with TA were included in the study. Meta-analysis was conducted using odd ratios (OR) and weighted mean differences (WMDs). Thirteen studies including 2489 patients with adenocarcinoma of the esophagogastric junction, with 1050 patients underwent TA and 1437 patients underwent TH were pooled for this study. There were no significant difference between two approaches concerning duration of operation, blood loss, anastomotic leakage and positive of proximal incisal margin. Lymph node excised also showed no significant differences between two procedures in RCTs while in TA group of Non-RCTs, the number of lymph node dissection is higher. TH approach was associated with a longer length of hospital stay and had higher incidence of respiratory and cardiovascular complications and early postoperative mortality. Overall analysis of 1, 3, 5-year survival showed no significant difference between two approaches. Based on the study, TA approach had a positive impact than TH for AEG with respect to respiratory and cardiovascular complications, hospital stay and early mortality rates. There were no significant differences between the two approaches for long-term survival. Therefore, two surgical approaches are acceptable, and the elders with poor cardiopulmonary function, we recommended TA approach for treating it.

Keywords: Gastric cancer, adenocarcinoma of the esophagogastric junction, Siewert type II/III, surgical resection, prognosis, meta-analysis

Introduction

Adenocarcinoma of the esophagogastric junction (AEG) was first described by Siewert in 1987. In contrast to the remarkably decreasing incidence of distal gastric cancer, it is evidently increasing in recently years, especially in the western countries [1-5]. AGE is a malignant tumor with early hematogenous and lymphatic dissemination. Though the use of chemotherapy, the 5-year survival rate was reported to be below 30% for AEG [6, 7]. Controversies exist in the literatures about the etiology and classification of AGE according to the borderline location, which is between the stomach and the esophagus. Consequently, the effectiveness of different surgical approaches have also been controversial, resulting in the different long-term survival rates that were reported in recent literatures [4, 8-12].

At present, en-bloc resection is still considered as the best way to treat the AEG type II/III. Due to the location of tumors' centers is different, the Siewert classification of AEG provide a variety of surgical approaches. Over the past few decades, two major surgical approaches have emerged to improve survival rates-the the transthoracic approach (TH) and the abdominal-transhiatal (TA). TH provides superior visualization of the operative field and allows complete dissection of the tumor and the mediastinal lymph nodes [13-15], sometimes in combination with a thoracoabdominal resection. It has often been associated to higher complications and mortality rates [16-18]. Some scholars have attempted to reduce the mortality rates by limiting the extent of the resection. It might be achieved by abdominal-transhiatal resection (TA), thus avoiding a formal thoracotomy and limiting the extent of surgical trauma.

TH versus TA resection for Siewert II/III AEG

Although three reviews have not revealed the superiority of TA to TH resection for AEG, Sasako M demonstrated the TA approach show better trend for survival of type II and III AEG than TH approach while some randomized controlled trials revealed opposite conclusion for type I and II AEG.

Although previous studies have sought to determine the most effective method, no conclusive evidence has been provided. This study aimed to compare the treatment effects and prognosis of the two operative approaches with respect to early postoperative mortality rate, postoperative complications and long-term survival rates. The pooled data of patients with Siewert type II/III adenocarcinoma of the esophagogastric junction were also evaluated in a systematic review of literature and examined by meta-analyses.

Materials and methods

This meta-analysis was conducted following the Cochrane Handbook (updated March 2011) and the Quality of Reporting Meta-analysis statement (QUOROM).

Methods used for literature search

We searched the electronic databases of PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, WeiPu, CBMdisc and WanFang systematically, using medical subject headings [(("Gastroesophageal Junction" [Mesh] AND "Carcinoma" [Mesh]) OR ("StomachNeoplasms" [Mesh] AND "Carcinoma" [Mesh]) OR ("Cardia" [Mesh] AND "Carcinoma" [Mesh]) OR ("Carcinoma" [Mesh] AND "Esophageal Neoplasms" [Mesh])) OR (((((((gastroesophageal junction) OR gastroesophageal junction) OR gastroesophageal junction) OR distal esophageal) OR lower third esophageal) OR cardia) OR subcardial) OR siewert)] AND (((transhiatal [Title/Abstract]) OR transabdominal [Title/Abstract]) OR transthoracic [Title/Abstract]) OR thoracoabdominal [Title/Abstract]) OR abdominothoracic [Title/Abstract]). Only those studies published in English and Chinese were included. The search was limited to the time between 1998 and 2015. To identify further relevant studies, the reference lists of articles identified were manually searched to find other related articles.

Inclusion criteria

Types of study: Randomized controlled trials (RCTs), clinical controlled trials, cohort studies, case-control studies and case series were all considered for inclusion.

Types of participants: 1) Patients with pathologically diagnosed primary adenocarcinoma of cardia or subcardia according to Siewert classification (type II and III). 2) Patients who received TA or TH approach. 3) The studies which have intention to performing curative operation were included.

Types of interventions: Surgical interventions assessed the difference in outcomes between TH resection and TA resection as management for Siewert type II/III adenocarcinoma of the esophagogastric junction.

Types of outcome measures: The outcomes of the studies were reviewed with attention to early postoperative complications and mortality rates and long-term survival. The following outcome variables analyzed were included: (1) lymph nodes excised; (2) duration of operation; (3) volume of blood loss; (4) positivity of proximal incisional margin; (5) postoperative complications; (6) in-hospital mortality rate; (7) hospital stay and (8) 1, 3, 5-year survival rates.

Exclusion criteria

a) Patients who had other type of carcinomas rather than adenocarcinoma, and who had undergone other surgical approaches rather than TH or TA were excluded. b) Patients with important complication (such as benign diseases) or with distant metastases were both excluded. c) Unpublished RCTs and abstracts of RCTs presented at national and international meetings were also excluded to prevent the duplication of data. d) Studies not published in English and Chinese were excluded. e) Uncertain trials or ones with inequality of characteristics on baselines between groups were excluded. f) The studies with many cases lost during the follow-up period were excluded.

Date collection and analysis

Selection of studies: Three reviewers (J.Z, T.Z, K.W) screened the quality of the articles independently. To start with, they read through the

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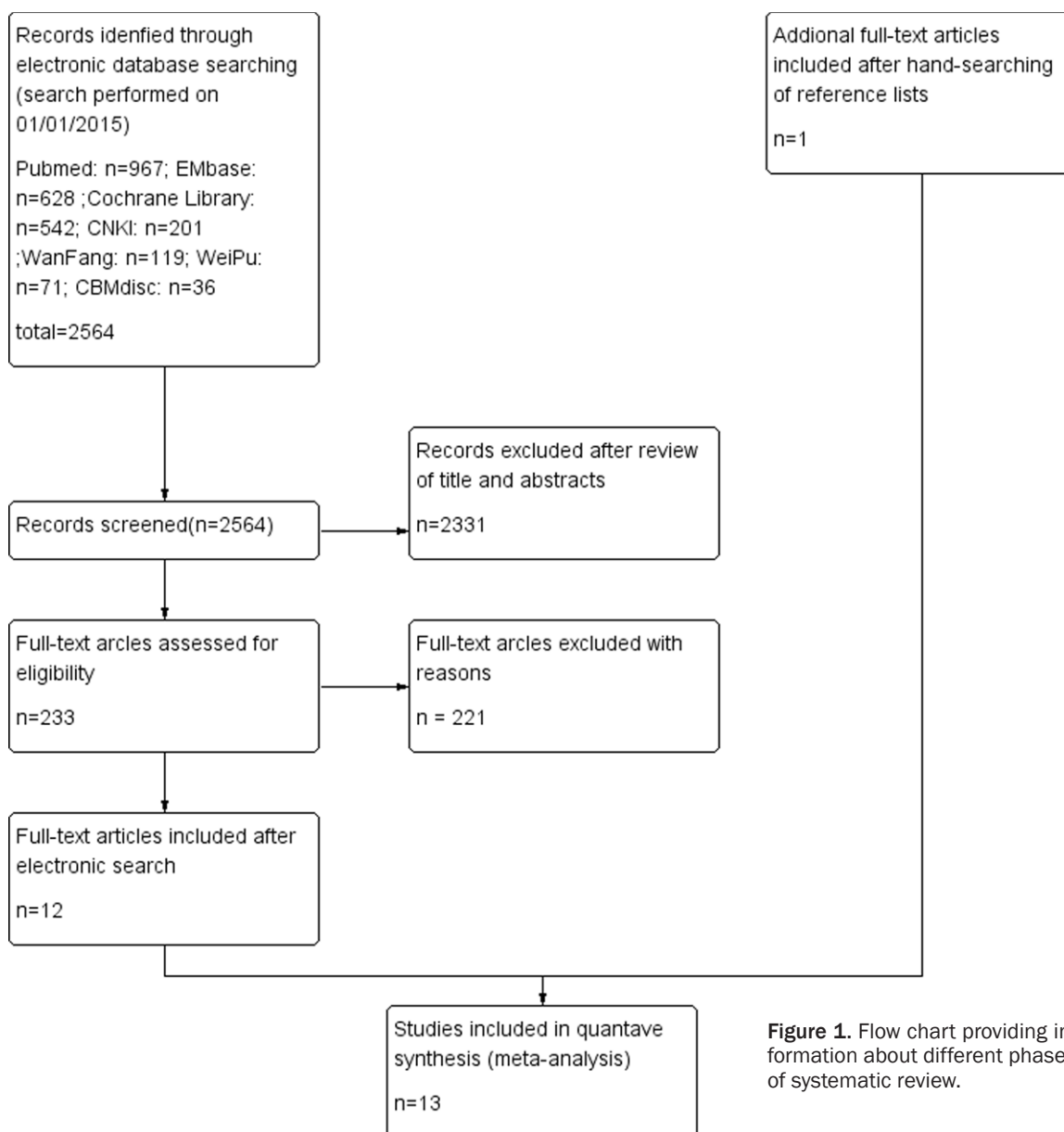


Figure 1. Flow chart providing information about different phases of systematic review.

title and abstract to eliminate unrelated studies, whereas, the related papers were retrieved for further identification. We managed disagreements through discussion and/or a deciding arbiter (MVD). All search results were put in Review Manager 5.2.

Data extraction and management: Three review authors (J.C, J.Y, Z.Z) designed a data extraction sheet for trial reports, which was a pilot study using the sample studies and revised by the other authors. The review authors (J.C, J.Y, Z.Z) then extracted data from the reports independently. We extracted data from each report

separately and then combined it in the event of multiple reports for the same study. The discrepancies were addressed with discussion until consensus was achieved. We used the Newcastle-Ottawa Scale (NOS) described by Wells et al, to assess the quality of all the non-randomized controlled studies [19]. The quality of each study was assessed in three parameters: Selection, comparability and exposure. The full score was considered 10 stars. If studies evaluated with more than 6 stars, we were inclined to consider it as high quality trials. The Cochrane Library Handbook was used to assess the quality of randomized controlled

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Table 1. Summary of included studies

First author	Year	country	Study period	Study type	No. of patients	No. of TH	No. of TA	Quality
Graham	1998	UK	1985-1997	Retrospective	153	32	119	7
Guan GX	2011	China	1990-2004	Retrospective	251	123	128	6
Omloo	2007	Netherlands	1994-2000	RCT	220	114	106	-
Hulscher	2002	Netherlands	1994-2000	RCT	220	114	106	-
Zhou JZ	2014	China	2007-2012	Retrospective	334	140	194	7
J. Wayman	1999	UK	1991-1995	prospective	40	20	20	6
Kikuo Koufuji	2005	Japan	1991-2000	Retrospective	49	24	25	6
Zhang XY	2014	China	2007-2012	Retrospective	135	57	78	6
Zhu ZJ	2006	China	2001-2005	Retrospective	273	175	98	5
Mitsuru Sasako	2006	Japan	1995-2003	RCT	167	85	82	-
Qin YS	2012	China	2000-2006	Retrospective	185	133	52	7
Wu ZY	2005	China	1994-2004	Retrospective	351	250	101	5
Zheng B	2010	China	1994-2003	Retrospective	331	284	47	7

Table 2. Quality assessment of the included RCTs

Study	Random allocation	Double-blind	Concealed allocation	Baseline features	Eligibility criteria	Loss to follow-up	Selection bias	Quality
Mitsuru Sasako	Yes	No	Yes	Yes	yes	Yes	No	Fair
Hulscher	Yes	No	Unknown	Yes	yes	Yes	No	Fair
Omloo	Yes	No	Unknown	Yes	yes	Yes	No	Fair

studies (RCTs), which contained seven items: randomization, allocation concealment, baseline features, eligibility criteria, blinding, loss to follow-up and selection bias. Studies valued with six or seven “yes” were recognized as high quality, while four or five “yes” as moderate quality and not more than three “yes” as low quality.

All related data including the primary author, the year of publication, origin country, the type and period of study, the number of patients who performed operation by two approaches (TA and TH) and their characteristics were extracted by the reviewers independently.

Statistical analysis

Review Manager Version 5.2 supplied by the Cochrane Collaboration was employed for the analysis. Meta-analyses were conducted using odds ratios (ORs) for dichotomous data, which corresponds to the odds of adverse events appearing in the treatment group (TA), compared to the control group (TH). The OR >1 indicates the probability of a result to most likely occur in the treatment group, P<0.05 and 95%

CI does was considered statistically significance. The Mantel-Haenszel method was used to combine the ORs for the results of interest. If the heterogeneity of results had significance, we would use a random effects model. On the contrary, a fixed effect was used. For continuous variables, we used the random effects weighted mean difference (WMD) as summary statistic. P<0.05 was considered statistically significant. Statistical heterogeneity in each meta-analysis was assessed using τ^2 (tau-squared), χ^2 and I^2 statistics [20]. For the computations, CI estimates and standard deviation are required. However, some published clinical trials only reported the size, median and range of the trial, rather than reporting the mean and standard deviation. For these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo et al [21]. For survival analysis, if trials reported survival curves only, the 1, 3, 5-year survival rates were extracted from the figures [22]. If the data which extracted could not be used for meta-analysis, we would like to present the conclusion in a descriptive and qualitative method [23]. Heterogeneity was consid-

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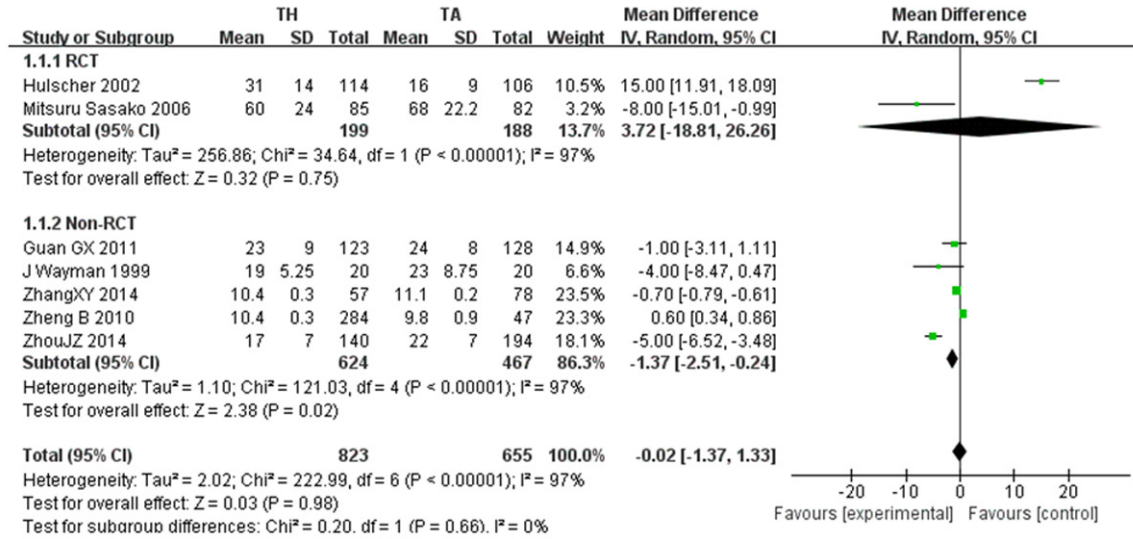


Figure 2. Extent of lymphadenectomy.

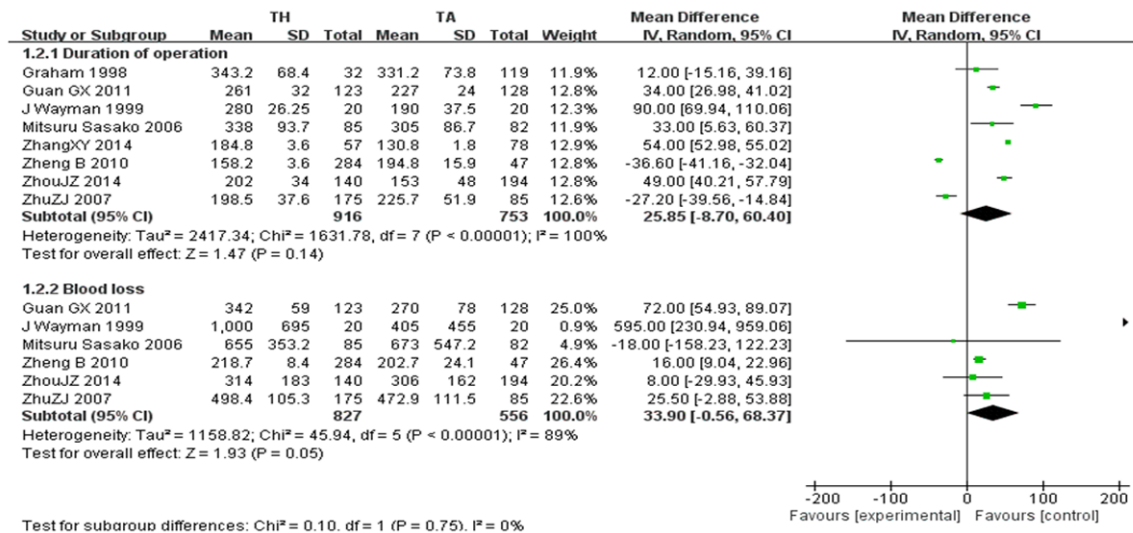


Figure 3. Duration of operation and Blood loss.

ered as significant if either the *P* value of χ^2 analysis was <0.10 or $I^2 > 50\%$.

Subgroup analyses included randomized controlled trials. Sensitivity analyses included studies which considered as high quality trials. Funnel plots were performed to determine the presence of publication bias in the meta-analysis.

Results

Selected studies: There were 2564 studies selected in the preliminary research, including

967 from Pubmed, 628 from EMBASE, 542 from Cochrane Library, 201 from CNKI, 119 from Wan Fang, 71 from WeiPu and 36 from CBMDisc. After cross-browsing the title and abstracts by the reviewers, 233 potential studies were included and after reading the full-text, only 12 articles were selected. Meanwhile, by further searching the potential trials, only 1 study were in accordance with the inclusion criteria. Finally, there were 13 trials included in the meta-analysis [24-26, 27-36] the flow chart containing selection information has been summarized in **Figure 1**. As a whole, selected

TH versus TA resection for Siewert II/III AEG

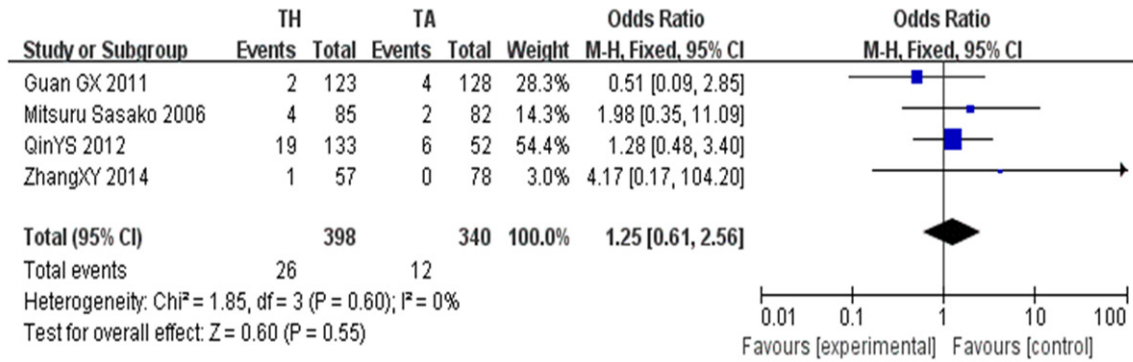


Figure 4. Positive of proximal incisal margin.

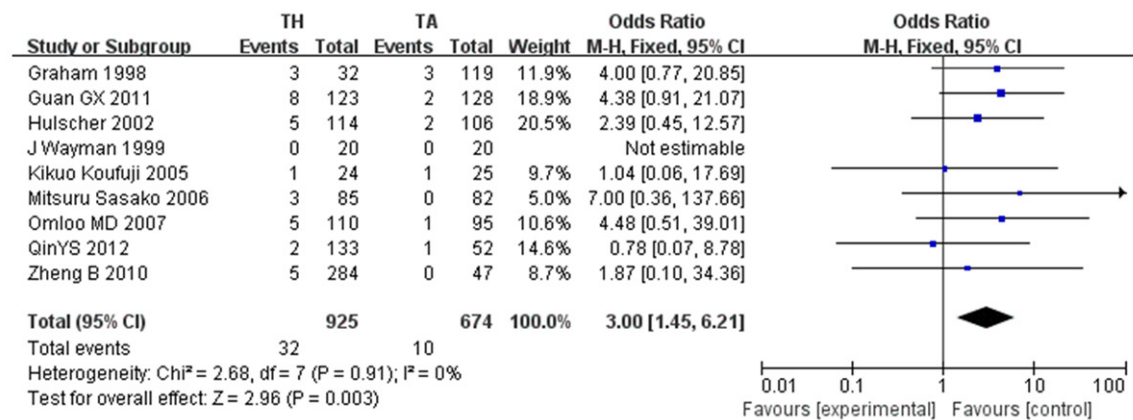


Figure 5. Early mortality.

studies included 3 randomized controlled trials, 1 prospective study and 9 retrospective studies. There were two studies which reported on the same patients with AEG, so we integrated with the pooled data from the two studies [28, 34]. Among a total of 2489 patients, 1050 (42.2%) patients underwent TA and 1437 (57.7%) patients who underwent TH were compared. The detailed information of included studies and patient demographics are presented in (Tables 1 and 2).

Surgical outcomes

Extent of lymphadenectomy: The number of lymph node dissection was sufficiently reported in 7 studies, which included 2 RCTs [25, 34] and 5 Non-RCTs articles [27, 29, 31-33]. No significant difference between TH and TA group was found in RCTs (WMD=3.72, 95 CI: -18.81~26.26, P=0.75). While in Non-RCTs (WMD=-1.37, 95 CI: -2.51~-0.24, P=0.02) stud-

ies, TA a mean of 2 more lymph nodes were retrieved compared to the TH. However, heterogeneity was significant (P<0.001, I²=97%) (Figure 2).

Duration of operation and blood loss: Eight articles [24, 25, 27, 29, 31-33, 36] offered the data about the duration of operation. However, analysis of the data showed no significance between the two approaches (WMD=25.85, 95 CI: -8.70~60.40, P=0.14). Although six studies [25, 27, 29, 31, 32, 36] provided the data on blood loss, there were no significance between the two approaches (WMD=33.90, 95 CI: -0.56~68.37, P=0.05) (Figure 3).

Positive of proximal incisal margin: The incidence of positive of proximal incisal margin [25, 26, 31, 33] between the TH group (26 of 398, 6.5%) and the TA group (12 of 340, 3.5%; OR, 1.25; CI, 0.61~2.56; P=0.55) were no significance. Heterogeneity between the

TH versus TA resection for Siewert II/III AEG

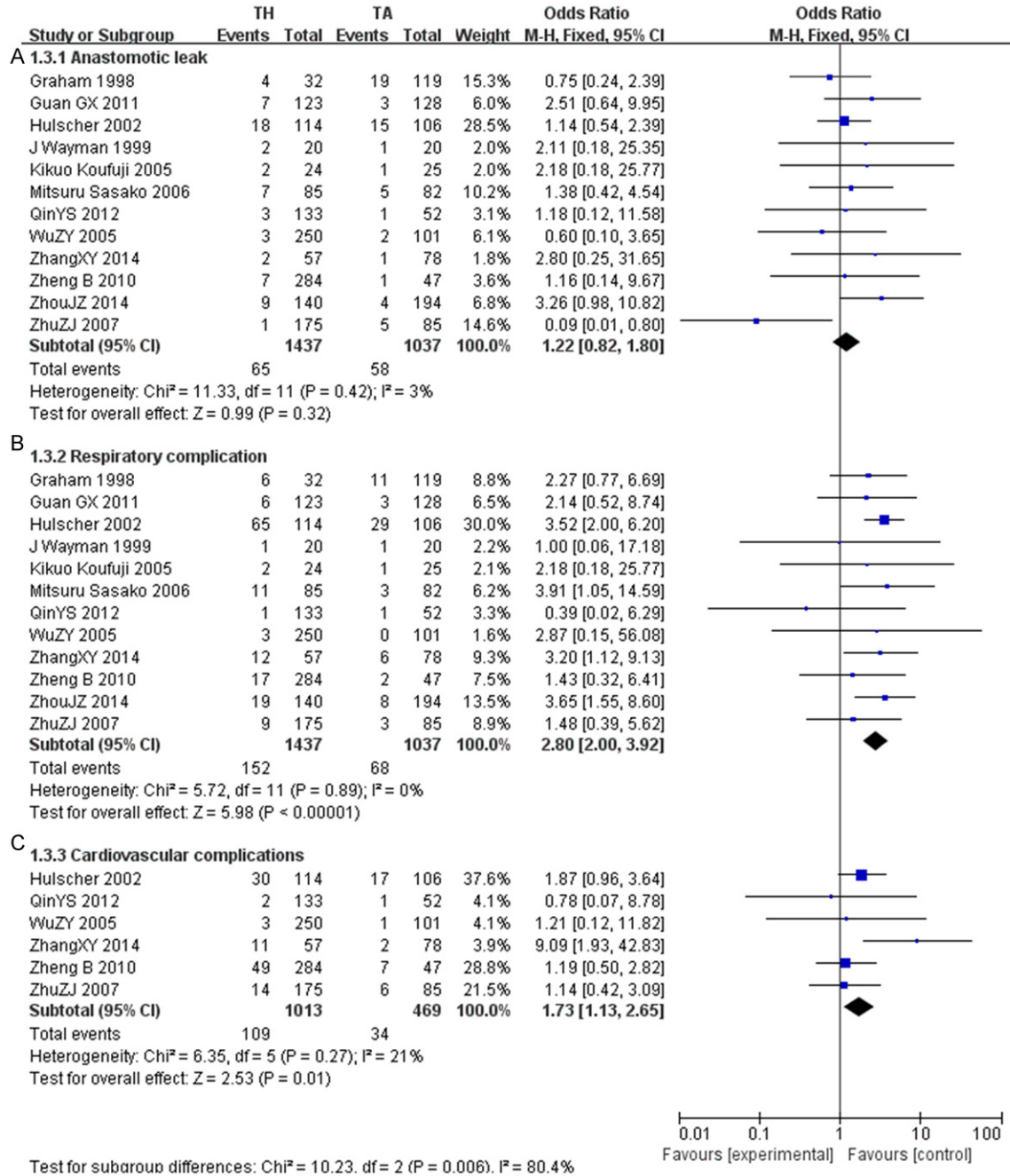


Figure 6. Postoperative complications (A. Anastomotic leak; B. Respiratory complications; C. Cardiovascular complications).

studies was not significant (P=0.60; I²=0%) (Figure 4).

Perioperative safety and short-term outcome

Early mortality: Early mortality [24-31, 34], reported as either <30 day or in-hospital mortality, was greater for TH approach (32 of 925,

3.5%) as compared to the TA approach (10 of 674, 1.5%; OR, 3.00; CI, 1.45~6.21; P=0.003). Studies did not show any significant heterogeneity (P=0.91; I²=0%) (Figure 5).

Anastomotic leak: 12 studies [24-27, 29-36] reported no significant difference between two approaches (OR, 1.22; CI, 0.82~1.80).

TH versus TA resection for Siewert II/III AEG

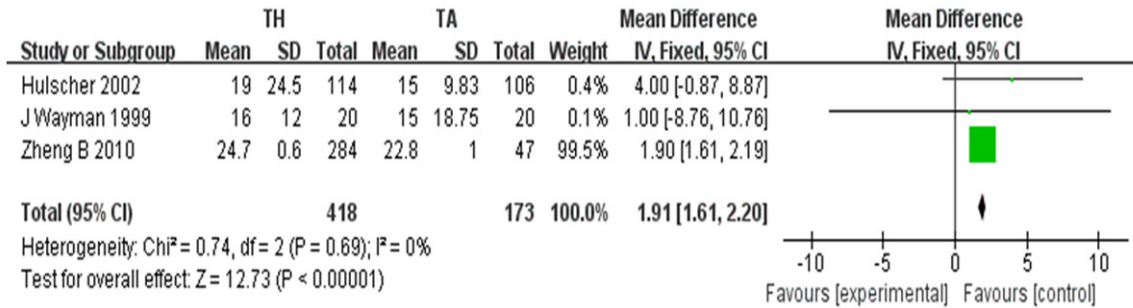


Figure 7. Hospital stay.

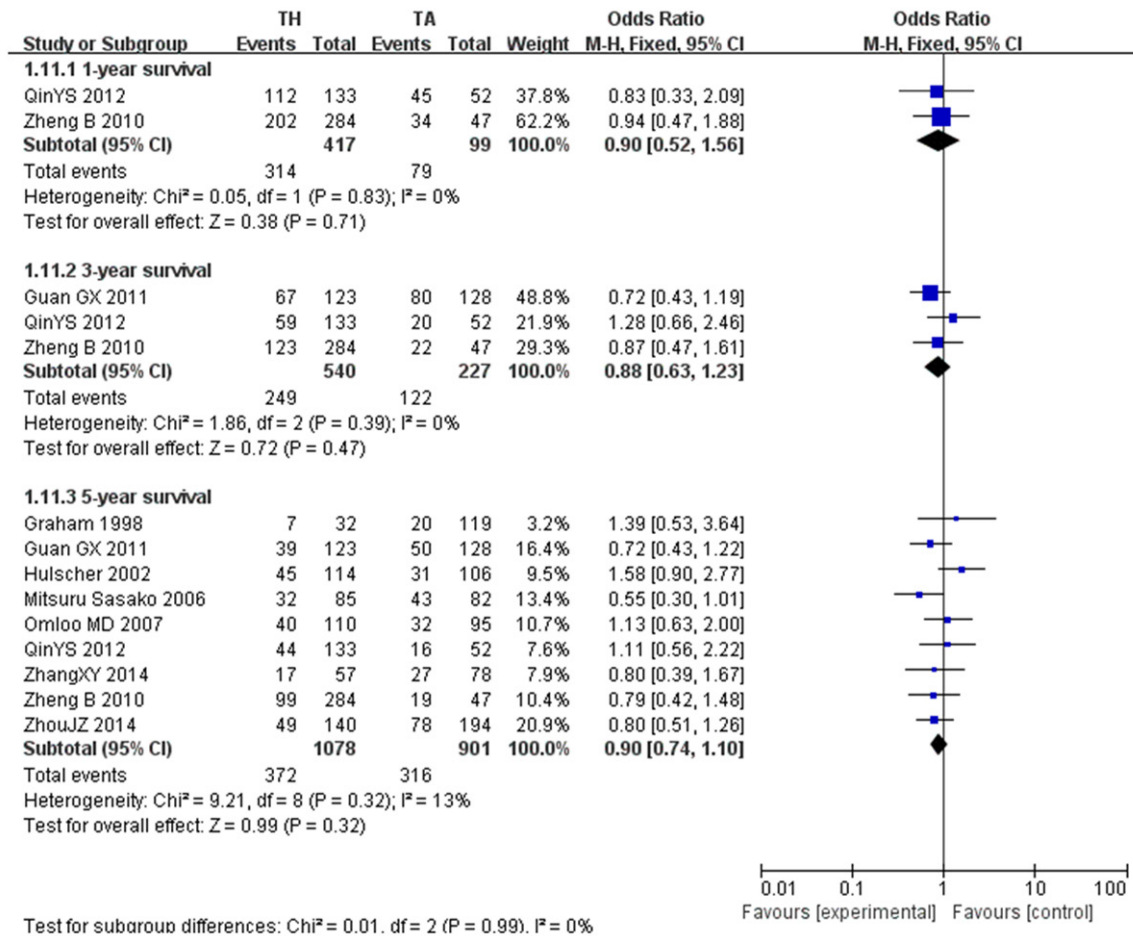


Figure 8. 1, 3, 5-year survival.

Heterogeneity was not significant ($P=0.42$; $I^2=3\%$) (Figure 6).

Respiratory and cardiovascular complications:
 The incidence of overall respiratory complications [24-27, 29-36] increased significantly in the TH group (152 of 1437, 10.58%) as com-

pared to the TA group (68 of 1037, 6.55%; OR, 2.80; CI, 2.00~3.92; $P<0.001$). Heterogeneity between studies was not significant ($P=0.89$; $I^2=0\%$). In addition, rates of cardiovascular complications [26, 27, 33-36] were significantly lower in TA (34/469, 7.25%) than in TH (109 of 1013, 10.76%; OR, 1.73; CI, 1.13-2.65;

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Table 3. Sensitivity analysis performed for studies comparing TA and TH: high quality studies

	No. of studies	No. of patients	OR/WMD	95% CI	P-value	HG χ^2 P-value	HG I ²
Surgical outcomes							
Extent of Lymphadenectomy	7	1478	-0.57	-0.65, -0.48	<0.00001	<0.00001	97
Duration of Operation	7	1409	33.53	-3.03, 70.09	0.07	<0.00001	100
Blood Loss	5	1123	37.07	-6.94, 81.07	0.10	<0.00001	91
Positive of Proximal margin	4	738	1.25	0.61, 2.56	0.55	0.60	0
Perioperative Safety and Short-term Outcome							
Early Mortality	9	1599	3.00	1.45, 6.21	0.003	0.91	0
Anastomotic Leak	10	1863	1.47	0.97, 2.24	0.07	0.87	0
Respiratory complication	10	1863	2.93	2.06, 4.15	<0.0001	0.85	0
Cardiovascular Complications	4	871	1.93	1.19, 3.13	0.008	0.13	46
Hospital Stay	3	591	1.91	1.61, 2.20	<0.00001	0.69	0
Long-term outcomes							
1-Year Survival	2	516	0.90	0.52, 1.56	0.71	0.83	0
3-Year Survival	3	767	0.88	0.63, 1.23	0.47	0.39	0
5-Year Survival	9	1979	0.90	0.74, 1.10	0.32	0.32	13

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; HG, heterogeneity; χ^2 , Chi squared.

P=0.01). Studies did not show significant heterogeneity (P=0.27; I²=21%) (**Figure 6**).

Hospital stay: The postoperative duration of the hospital stay [27, 29, 34] for patients who underwent TH was on an average 2 days longer than that for the TA patients (P<0.001; CI, 1.00~3.00). Heterogeneity was not significant for hospital stay (P=0.69; I²=0%) (**Figure 7**).

Long-term outcomes

1, 3-Year survival: Overall analysis of 1-year survival [26, 27] showed no significant difference between the TH group (314 of 417, 75.3%) and TA group (79 of 99, 79.8%; OR, 0.90; CI, 0.52~1.56; P=0.71). No heterogeneity was detected for any other assessed outcomes (P=0.83; I²=0%). Meanwhile, three articles reported a 3-year survival rate [26, 27, 31], with an overall OR of 0.88, with 95% CI of 0.63-1.23. The study did not show significant difference in 3-year survival rate (P=0.39; I²=0%) (**Figure 8**).

5-Year survival: The most important outcome after any cancer treatment is the actual 5-year survival rate [24, 31, 34]. Interestingly this meta-analysis did not show any significant differences in the 5-year survival rate between the TH groups and TA groups (OR, 0.90; CI, 0.74~1.10; P=0.32), and was not subjected to heterogeneity (P=0.32; I²=13%) (**Figure 8**).

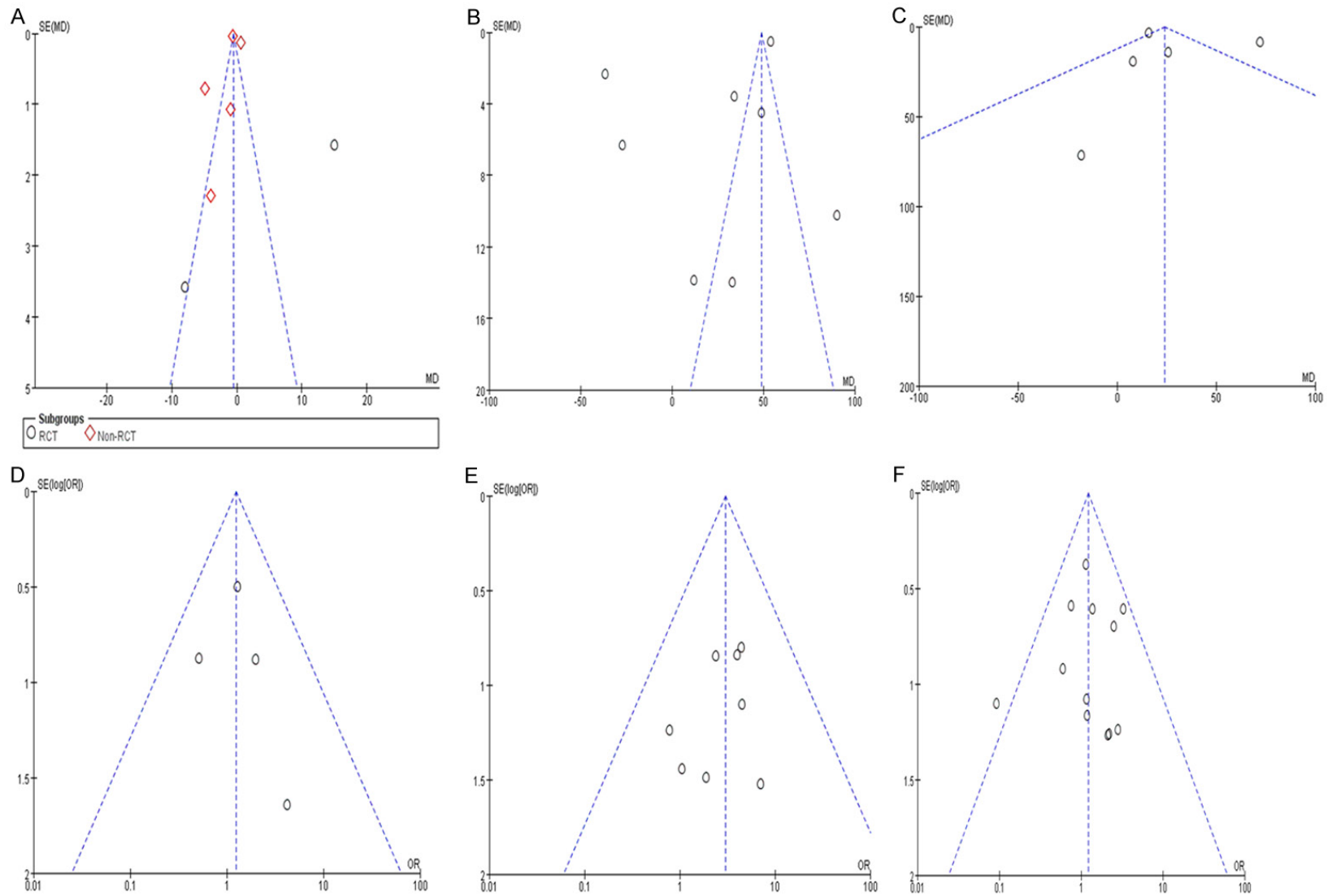
Sensitivity analyses

8 Non-RCTs studies [24, 26, 27, 29-33] received ≥ 6 points for methodological quality and 3 RCTs studies [25, 28, 34] of Fair level in sensitivity analysis. Duration of operation, blood loss, positive of proximal incisal margin, anastomotic leak, early mortality, respiratory complication, cardiovascular complications, hospital stay and 1, 3, 5-year survival showed the same outcomes as in the overall analysis. Significant findings specific to high quality sensitivity analysis were: In TA, more lymph nodes were retrieved as compared with TH (OR: -0.57; 95% CI: -0.65~-0.48), although heterogeneity was significant (P<0.00001, I²=97%) (**Table 3**).

Publication bias

Funnel plots (precision vs. WMD or log OR) demonstrated asymmetry for the extent of lymphadenectomy, blood loss, anastomotic leak and length of hospital stay suggesting presence of publication bias for these outcomes. No points were outside the 95% confidence interval limits for early mortality, duration of operation, respiratory and cardiovascular complications, positive of proximal incisal margin, and 1, 3, 5-year survival suggesting the absence of publication bias for these outcomes (**Figure 9**).

TH versus TA resection for Siewert II/III AEG



TH versus TA resection for Siewert II/III AEG

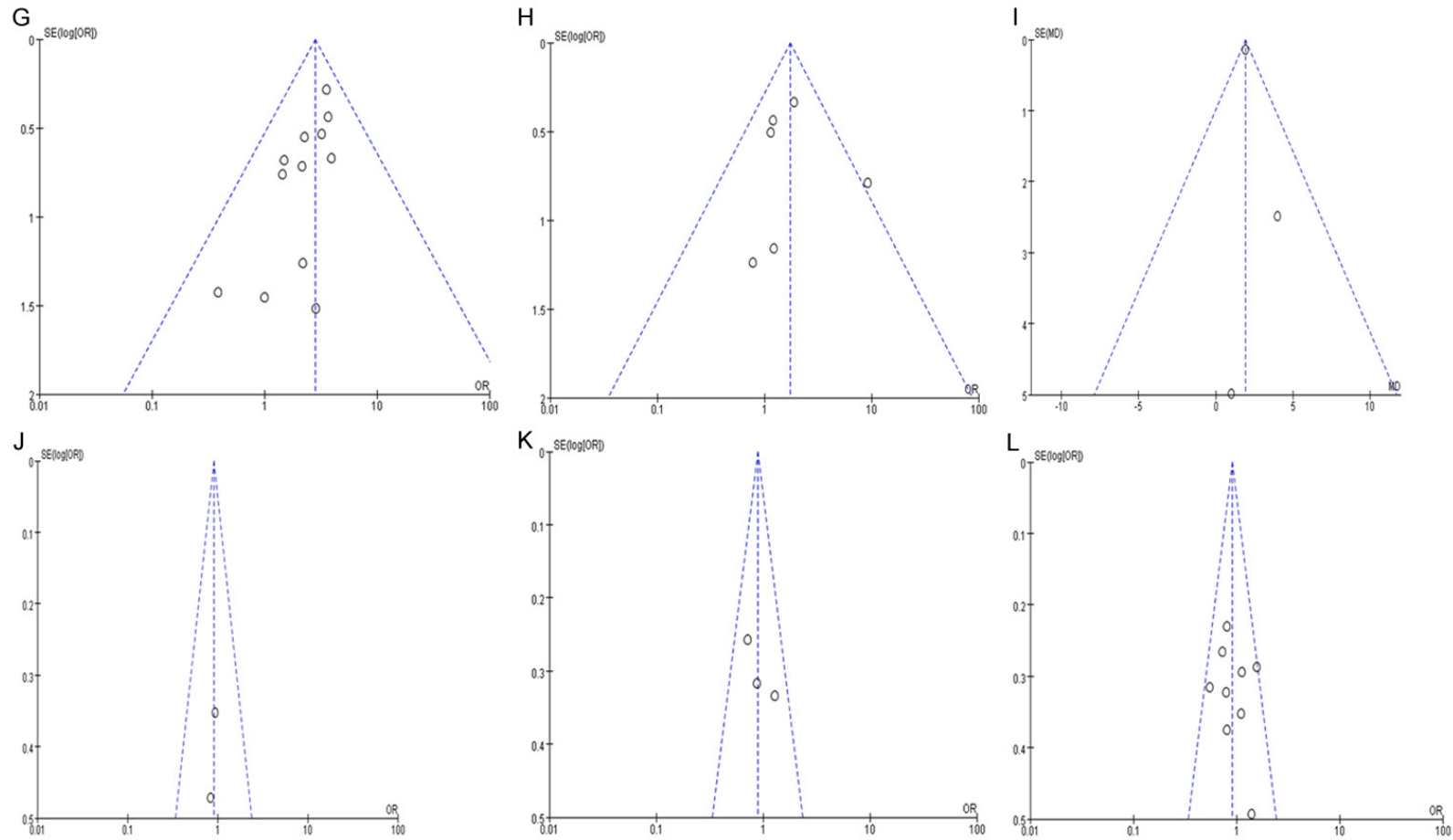


Figure 9. Funnel plots demonstrate asymmetry for extent of lymphadenectomy. (A) Blood loss; (C) Anastomotic leak (F) and length of hospital stay (I) suggesting the presence of publication bias. No points fall outside the 95% CI limits for any variables suggesting the absence of publication bias. (A) Extent of lymphadenectomy; (B) Duration of Operation; (C) Blood loss; (D) Positive of proximal margin; (E) Early mortality; (F) Anastomotic leak; (G) Respiratory complication; (H) Cardiovascular complication; (I) Hospital stay; (J) 1-Year survival; (K) 3-Year survival; (L) 5-Year survival.

Discussion

The two major surgical approaches in treating Type II/III AEG are transthoracic (TH) and abdominal-transhiatal (TA) approach and it has been controversial as to which approach is reasonable. Both approaches have their advantages and disadvantages. Our study aimed to evaluate the differences in short and long-term results about the two approaches for providing evidence-based study basis on the treatment of AEG. In this study, we compared the two approaches and the outcomes of the meta-analysis has demonstrated TA to be associated with significantly reduced duration of hospital stays, early mortality and lower rate of postoperative respiratory and cardiovascular complications. Meanwhile, the incidence of proximal positive incisional margin was not increase after TA. Our results showed that there were no significant differences between the two approaches for anastomotic leak, blood loss, duration of operation, the number of lymph node dissection and 1, 3, 5-year survival.

When all data were combined, the number of lymph node dissection did not differ significantly between TH and TA procedures, but the pooled data from Non-RCTs were showed a trend of increasing lymph node accumulation in the TA approach. That may be due to Siewert II/III AEG mainly transfers downward to abdominal lymph node, TA method can be provide direct visualization of the lymph nodes of the abdominal cavity. Because of the location of the tumor between the esophagus and stomach, it is important to determine the complexity of lymph node metastasis, as in the surgery it may be need to clean up the abdominal and thoracic lymph nodes at the same time. Lymph node clearance is regarded as a prognostic factors for the adenocarcinoma of the esophagogastric junction [37]. According to a recent study, the metastasis of posterior mediastinal lymph nodes, paraesophageal lymph nodes and superior phrenic lymph node of AEG accounted for 10%-20% in overall lymph node metastasis. With the change in the tumor location towards the distal, the incidence of pleural metastasis gradually declines. However, we should still adopt the radical operation in order to reduce the postoperative recurrence rate [6, 38]. Different subtypes of AEGs mainly transfers downward to abdominal lymph node and may

also transfer upward to mediastinal lymph node. The transfer rate of mediastinal lymph node of Siewert type I was the highest, while Type II/III it was lowest and mainly metastasis to posterior and inferior mediastinum. It is reported by Siewert [25] et al that the transfer rate of mediastinum lymph node of II/III AEG were 12% and 6% respectively, of which superior mediastinum rate was only 1%. This shows that the lymph node metastasis of Siewert II/III was more transferred to the abdominal cavity. Our meta-analysis results are similar with the Siewert's outcomes. In addition, the transfer rate of mediastinal lymph node was associated with the esophagus infiltrating depth and range. The more of the tumor infiltration, the higher of mediastinal lymph node rate and vice versa [39]. Considering the same reason, following consensus has been formed: a) Lymph node dissection of radical resection of II/III AEG should focus on the abdominal cavity. The mediastinal lymph node dissection should be executed based on AEG types, stage, and the esophagus infiltrating degree. b) In principle, Siewert II/III AEG should be in accordance with the operation specification about the upper stomach cancer determined the scope of lymph node cleaning. In case of tumor infiltration, the distal esophagus, resection of the inferior mediastinum lymph node, hiatal lymph nodes and inferior phrenic lymph nodes should be taken into consideration. We did not remove the superior mediastinal lymph nodes in theory. Although, abdominal lymph node metastasis is the major route of Siewert II/III AEG and thoroughly dissection abdominal lymph node is the key way, there is no long-term survival benefit about extended lymph nodes of inferior mediastinum resection [25].

Transthoracic resections resulted in worse postoperative complications than transhiatal resections in our meta-analysis, especially respiratory and cardiovascular complication, but some scholars reported that there was no significantly difference of respiratory complication between TH and TA approaches. Theoretically, TA resections had the deficiency in formal thoracotomy, resulting in a higher frequency of pulmonary and cardiovascular complications [40]. This was confirmed by the present data. The pain after thoracotomy restrained diaphragmatic movement and difficulty to expectorate could interpret why respiratory

complications were lower in TA procedure. While cardiovascular complications might be related to myocardial ischemia from pain, hypoxemia, electrolyte disturbance after thoracotomy. However, there was no significant difference about the incidence of anastomotic leakage. In terms of anastomotic leakage, several articles have reported various results [18, 41, 42] That is probably due to cough from pulmonary complication that increases the tension of anastomosis; on the other hand, pleural effusion drainage was inadequate and infection persisted, resulting in anastomosis disunion. In addition, after pooling the data, the early morbidity (which is defined as hospital deaths related to special diseases within 30 days after surgery) rates was higher in TH (OR, 3.00; CI, 1.45-6.21). Consequently, TA approach helped patients to recover more quickly and significantly decreased the duration of hospital stay [43].

Meta-analysis on included studies showed that TA had no significant difference from TH on 1, 3, 5-year overall survival rates. This outcome is supported by previously literature [40]. However, a recent article predicted a superior 5-year survival for transhiatal resections, which is consistent with that in one included studies that reported potential higher overall survival rate in TA approach compared with the TH approach in type II tumors [25]. For type III tumor [25], one studies showed potential 5-year survival benefits in the TA approach. Therefore some researchers recommend the TA approach for type II/III AEG. Meanwhile, Mariette [17] et al reported overall 3 or 5 year survival rates were not affected by the choice of surgical approach. The difference in survival rates was associated with R0 resection, pathological node-positive category and tumor differentiation. Some scholars [44] also underlined age as a risk factor for long-term survival. Thus, the long-term survival of patients with Siewert type II/III AEG may also be influenced by tumor stage, complication and completely resection.

There are still some limitations associated with this meta-analysis, though the study was executed according to the Quality of Reporting Meta-Analyses (QUOROM) statements and the Cochrane Handbook (updated March 2011). First of all, the quality of meta-analysis lies on original trials included. In this analysis, 9 original articles were retrospective studies and 1 article was prospective studies. Although they

all are the best evidences available to date, the outcomes are less compelling compare to randomized controlled trials (RCT). And there was a potential heterogeneity in several aspects. Meanwhile, RCTs, prospective studies and retrospective studies were assessed using different standards and then pooled together, which may decrease the power of the results. Secondly, the exclusion of original articles published in languages other than English and Chinese is also another potential limitation to this meta-analysis. Thirdly, publication bias was detected on funnel plot analysis for results of extent of lymphadenectomy, blood loss, anastomotic leak and length of hospital stay. This is of concern as the selective publication studies may result in pooled effect sizes obtained from studies exclusively located from the published scientific literature revealing a more significant result in terms of the magnitude of harm or benefit of an intervention than in actual [45, 46]. However, it should be noted there are number of limitation to the assessment of publication bias in the meta-analysis. First, the number of articles was inadequate to sensitively detect such a bias [47]. Second, a random effects model of meta-analysis was utilized for this analysis, and this model is known to exaggerate the presence of publication bias due to attributing heavier weighting to smaller studies than the fixed effects model of meta-analysis. Finally, funnel plots are not an ideal method for assessing publication bias due to their inability to differentiate between forms of bias, however they remain the accepted method for assessment of publication bias [48, 49]. Then, we used the median to estimate the mean and standard deviation, because the ranges are unstable and unlike other measures of variation, it increase when the sample size increases. They describe the extremes of observed outcomes rather than the average variation. Therefore, ranges have not been recommended to estimate standard deviations, and it may lead to unpersuasive outcomes.

In conclusion, this analysis has shown the TH group has higher incidence of respiratory and cardiovascular complications and early postoperative mortality, so that TH method increased the duration of hospital stay. Furthermore, our results failed to show TA approach bring more advantages to the patients who underwent TH resection on 1, 3, 5-year survival rates. Although two surgical approaches are accept-

able, for the elders with poor cardiopulmonary function, we recommended TA approach for treating Siewert II/III AEG in order to achieve better quality of life and reduce early mortality.

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Disclosure of conflict of interest

None.

Address correspondence to: Jun Zhang, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, 95 Yongan Road District, Beijing 100050, China. E-mail: z.z1003@163.com

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