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Impact of negative lymph node removal on survival in esophageal cancer: a systematic review and meta-analysis

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Abstract

Background Recent studies have reported that a high number of negative lymph nodes (NLNs) removed can be associated with improved survival in esophageal cancer(EC) after surgery; however, the effect size of a high number of removed NLNs on survival rates has been reported to vary, which may be due to the small sample size of early studies. This meta-analysis aimed to evaluate the effect of the high number of NLNs removed on the survival rate of patients with EC after surgery.

Methods We searched PubMed, Embase, Scopus, Web of Science, and Google Scholar databases with relevant Mesh terms to find studies that investigated the effect of the number of NLNs resected on the survival of EC patients after surgery until February 17, 2025. This systematic review was conducted based on the PRISMA 2020 checklist. Cochran's I^2 was used to evaluate heterogeneity between studies. Publication bias was evaluated using the Egger test. Heterogeneity between studies was controlled by meta-regression. Finally, eight studies involving 5,521 EC patients were included.

Results The survival rate in patients whose number of removed NLNs ≥ 19 was significantly better than those with removed NLNs < 19 (HR: 0.88, 95% CI: 0.81, 0.95, I^2 = 84.4). Subgroup analysis of 8 studies showed that the protective effect of the high number of removed NLNs) ≥ 19 (was greater in adenocarcinoma patients than in SCC (Pooled HR: 0.63 vs. 0.88).

Conclusion The high number of NLNs removed (≥ 19) during surgery was associated with improved survival after surgery, especially in patients with adenocarcinoma. Removing ≥ 19 NLNs significantly improves survival in EC patients, particularly those with adenocarcinoma. This threshold should be incorporated into surgical guidelines.

Keywords Five- survival rate, Surgery, Esophageal cancer, Lymph node, Esophagostomy

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Introduction

Esophageal cancer (EC) is one of the most common (9th leading cancer) and deadliest (6th leading cause of cancer death) cancers worldwide [1, 2]. In 2020, according to the Global Cancer Observatory (Globocan), 604,100 patients with EC were reported worldwide [2]. More than 500,000 deaths from EC occur worldwide each year [1, 3, 4]. In terms of histology (EC) includes two subgroups of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), the two main histological subgroups of EC with distinct epidemiological and clinical characteristics [5].

Despite the improvement in the survival rate of EC in recent decades, the prognosis of EC is still poor. The 5-year survival rate of patients is reported to be less than 20% [6, 7]. The 5-year survival rate of EC patients is reported to be between 10% and 30% [8].

The standard treatment of tumors in the early stages is surgery, and the role of adjuvant treatments is still one of the challenges surgeons face for patients with these tumors. In advanced stages of tumors, there is a consensus on the importance of volume reduction surgery and chemotherapy [9].

The survival rate of patients after treatment varies depending on various factors, including tumor characteristics (tumor stage, presence of metastasis, tumor histology, tumor pathology, number of involved lymph nodes), the number of negative lymph nodes (NLNs) and positive lymph nodes (PLNs) removed, adjuvant treatment, and demographic characteristics of patients [10–15]. The role of the number of PLNs in N-stage classification has been confirmed by the American Joint Committee on Cancer (AJCC, 7th edition). However, the role of the number of NLNs is still debated [16].

Recent studies have shown that, as with other cancers [17, 18], the number of NLNs removed during surgery can be related to the survival of EC after surgery [14, 19]. Most studies have reported that a high number of NLNs can be associated with improved patient survival [6, 19]. However, the effect size of a high number of removed NLNs on survival rate has been reported differently based on several studies [6, 14, 20, 21], which may be due to the small sample size of the initial studies. Based on our knowledge, a systematic review has investigated the relationship between the number of lymph nodes removed and the survival of patients after surgery. Therefore, considering the importance of the subject, this meta-analysis was conducted to evaluate the effect of the number of NLNs removed on the survival rate of patients with EC after surgery for the first time.

Methods

Literature search

First, surgical oncologists and epidemiologists determined the research question and search strategy based on the PICO formula (population, interventions, comparators, and outcomes). PubMed, Scopus, Google Scholar, Embase, and Web of Sciences databases, as well as study references, were searched by two independent researchers to find relevant articles that investigated the effect of the number of NLNs removed on the survival of EC patients after surgery from September until 24, 2014. The general search strategy was defined using mesh terms and research questions. The last search was updated on February 17, 2025. This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22].

The sources were searched using the following mesh terms: Esophageal cancer, esophageal neoplasms, esophagus Neoplasm, cancer of the esophagus, esophageal cancers, esophagus Cancer, thoracic cancer, negative lymph nodes, lymph nodes, esophagostomy, surgery, surgical resection, resection, cervical esophagostomy, thoracic surgical procedures, thoracic surgical procedure, thoracotomy, thoracoscopic, trans-thoracic esophagectomy, two-field lymphadenectomy, Trans-thoracic esophagectomy and lymphadenectomy, lymph node excision, lymph node dissection, lymphadenectomy, survival rate, survival, overall survival, cumulative survival rate and mean survival time)

Eligibility criteria

The inclusion criteria for this meta-analysis included original observational studies (cohort, cross-sectional, and case-control) that evaluated the effect of the number of NLNs harvested on the survival rate of EC patients after surgery, Studies that reported the number of negative lymph nodes removed and differentiated between negative and positive lymph nodes and studies with a minimum follow-up of 6 months. Studies that examined the relationship between the number of NLNs removed and survival, but the number of NLNs removed were not classified, case reports letters to the editor, interventional studies, review articles, and meta-analysis, and lack of access to the full text of the article as exclusion criteria were defined.

The number of NLNs in the studies included in this meta-analysis was classified into two groups, including < 19, and ≥ 19. In a study, classification was done in two groups, < 3 and ≥ 3 NLNs, which were included in the histology subgroup analysis but excluded from the overall effect estimation analysis. The number of harvested NLNs ≥ 19 was defined as the high number of NLNs.

Screening and data extraction

In the initial search of the databases by two independent researchers, 1,307 articles were found. Two independent researchers initially searched the databases. Using Endnote version 22 software, common and repeated studies between databases were identified and removed. A total of 276 articles remained for evaluation. Two independent researchers evaluated the remaining articles regarding the relevance of the titles, objectives, and abstracts to the research question. The full text of 91 studies was fully reviewed. Finally, eight observational studies were included. (Fig. 1).

To extract data, first, the variables were designed based on a literature review and by a committee consisting of oncology surgeons, oncologists, and epidemiologists. Excel software was used for data extraction. Two independent researchers extracted the variables from the primary studies. If there was a conflict in the time of the variable, this difference was resolved by the third researcher. The variables of this systematic review

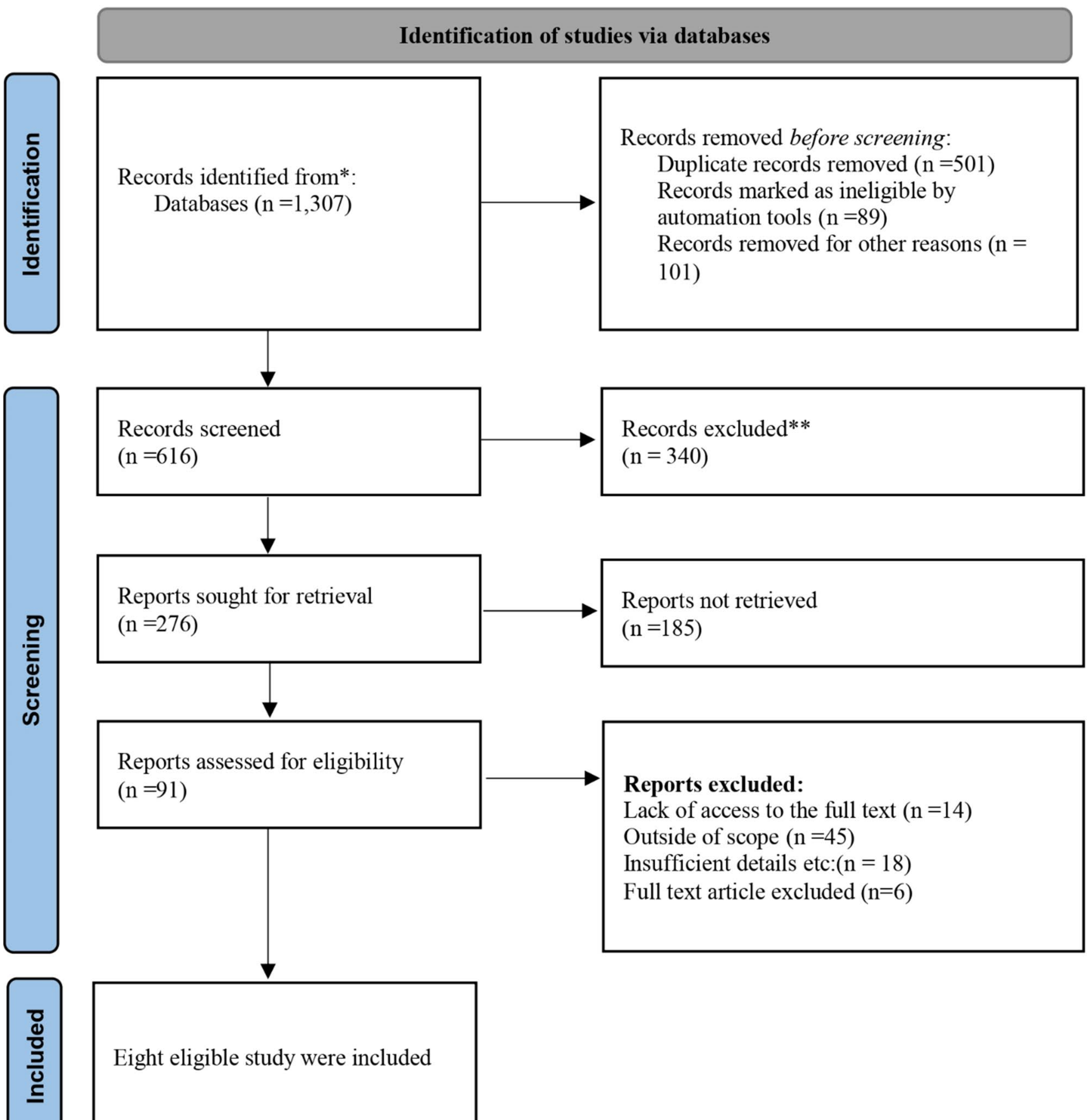

Fig. 1 Flowchart page of studies based on PRISMA 2020

include the first author, the year and country of the study, the study design, the total number of patients with EC, the number of NLNs removed, the number of patients examined for each group of removed NLNs, the mean age, tumor histology (EC and AD), gender, average follow-up period, 5-year survival rate based on the number of NLNs removed, type of surgical procedure, history of preoperative CRT, the effect size of the overall relationship between the number of NLNs removed and Survival after surgery, effect size of high number of resected NLNs with survival according to tumor histology (Hazard ratio (HR) and 95% confidence interval (CI)).

Quality assessment

The quality of cohort studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies checklist [23]. These checklists assess the quality of studies in three primary areas: selection, comparability, and outcome/introduction, and assign points for each area. The GRADE (Grade for Assessment, Development, and Evaluation of Recommendations) approach was used to evidence level for the research finding [24].

Statistical analysis

Data analysis was performed using STATA version 17 statistical software. To estimate the size of the effect of the number of NLNs removed on survival after surgery, the Hazard ratio (HR) in the 95% confidence interval (95% CI) was used using the random effects method. Heterogeneity and inconsistency between studies were evaluated with Cochran's Q and I^2 tests. The publication bias of the studies was assessed using Egger's test, and the results were presented with funnel plots. We used the trim-fill method to address potential publication bias and its impact on the combined estimation of the influence of the number of harvested NLNs on survival. Considering the high heterogeneity between studies, subgroups of harvested NLNs and tumor histology were used to control heterogeneity between studies with meta-regression based on the quality of studies. Sensitivity analysis was performed to estimate each study's effect size and weight on the overall result.

Results

Eight observational studies [14, 15, 19–21, 25–27], including 5,521 EC patients, were included in this meta-analysis. The mean age of the patients in this study was 63.4 ± 4.1 years. 80% of patients were male. The mean follow-up of patients after surgery was 25.6 months. Thoracotomy was the most common surgical procedure. The overall 5-year survival rate of patients after surgery was 38.8%. Most of the studies were conducted in China. In terms of tumor histology, SCC was the most common tumor type. The majority of studies were of good or moderate quality. Based on GRADE, the level of certainty of the evidence for the results of this systematic review was moderate to high. The characteristics of the studies included in this meta-analysis are reported separately in Table 1.

The effect of removed NLNs on the survival rate

Based on the pooled estimate of 8 studies, the 5-year survival rate in patients with the number of removed NLNs ≥ 19, NLNs 10 to 19, and NLNs < 10 was 62%, 56%, and 42%, respectively. The pooled estimate of 7 studies showed that regardless of the histology of cancer, the survival rate in patients whose number of removed NLNs ≥ 19 was significantly better than the patients with removed NLNs < 19 (HR: 0.88, 95% CI: 0.81, 0.95, I^2 = 84.4). Fig. 2.

Subgroups analysis

Subgroup analysis showed that the protective effect of removed NLNs on survival rates varied with an increasing number of removed NLNs and tumor histology.

- The protective effect of removed NLNs on patient survival was greater in patients who had ≥ 19 NLNs removed compared to patients who had < 19 NLNs removed (HR = 0.53 vs. 0.71). (Fig. 3)
- The protective effect of the high number of removed NLNs) ≥ 19 (was higher in patients whose tumor histology was adenoma-carcinoma. Then, in patients with SCC tumor histology (Pooled HR: 0.63 vs. 0.88). (Fig. 4)

Meta-regression and sensitivity analysis

A sensitivity analysis was performed based on each study's results, and each study's effect on the overall estimate was determined. Due to the high heterogeneity between the studies, adjusted meta-regression was performed based on the quality of the studies, tumor histology, and the number of NLNs. In line with the primary results, The number of removed NLNs ≥ 19 compared to NLNs < 19 was associated with an improved patient survival rate (HR: 0.90, 95% CI: 0.84, 0.96, I^2 = 24.1).

Publication bias

The analysis revealed that biased publication impacts the generation of negative results, leading to asymmetry in the funnel plot. Furthermore, evidence of publication bias was identified through Egger's test (Egger's test t = -2.67, P = 0.041, 95% CI: -4.8, -0.5) (Fig. 5). As significant publication bias was detected, we utilized the Trim & Fill method to account for the impact of censored studies on our combined estimate. Based on our assessment, four studies were censored due to publication bias. Upon incorporating their effect on the overall estimate, it was

Table 1 The characteristics of the studies included in this meta-analysis

Author	Study design	Country	Sample size	Mean follow-up (Month)	Mean Age	Sex (Male %)	Histology	Surgical Procedure	Preoperative CRT(yes)	Quality of studies
AJ Greenstein(2008)[14]	Prospective	USA	972	NA	66.1	770	Adenoma: 612 SCC: 313	Surgical resection	112	Good
HX Yang(2010)[19]	Retrospective	China	592	29.5	65.7	431	Adenoma: 585 SCC: 7	Surgical resection and LN dissection (thoracotomy, the Ivor-Lewis approach, and the cervico-thoraco-abdominal).	NA	Moderate
PK Hsu(2013)[25]	Retrospective	Taiwan	707	28.4	62.2	660	Adenoma: 44 SCC: 663	Open & Thoracoscopic	637	Good
Z Zhu (2014)[20]	Retrospective	China	332	30.5	58	269	SCC: 332	Three-field lymphadenectomy	170	Moderate
M Ma(2016)[21]	Retrospective	China	381	29.1	62	281	SCC: 381	Trans-thoracic esophagectomy, and two-field lymphadenectomy	NA	Moderate
HR Wu(2018)[26]	Retrospective	China	429	32.2	65	282	Adenoma: 429	Two-field lymphadenectomy	165	Good
L Yu(2020)[27]	Retrospective	China	344	NA	NA	271	SCC: 344	Trans-thoracic esophagectomy and lymphadenectomy	NA	Moderate
L Zhou(2020)[15]	Retrospective	China	1764	48.1	64.6	1451	Adenoma: 1121 SCC: 470	Thoracotomy, laparotomy, and a collar neck incision	1028	Good

evident that the pooled effect would increase to 0.94 when accounting for unpublished papers. Also, the overall survival rate decreased to 26.4%.

Discussion

In this systematic review and meta-analysis, we evaluated the effect of the number of negative lymph nodes harvested on the survival of 5552 EC patients after surgery. We also investigated the effect size of a high number of removed NLNs based on tumor histology.

According to the results of our study, the median age of the patients was 63 years, and most of the patients were men (male to female ratio was 4:1). SCC was the most common tumor type. Most of the studies were conducted in China. The pooled evaluation of 8 studies showed that patients' survival rates differed based on the number of lymph nodes removed. Patients with ≥ 19 removed NLNs had the highest survival rates, while those with < 10 had the lowest.

The pooled estimate of 7 studies showed that a high number of lymph nodes removed during surgery was associated with improved survival of patients after surgery. Based on subgroup analysis, the effect of the number of NLNs removed during the operation had a positive relationship with the survival of the patients after the surgery, and with the increase in the number of NLNs removed during surgery, the protective effect of the number of NLNs removed on the survival of patients increased. Also, the effect of a high number of removed NLNs differed according to tumor histology, and the protective effect of a high number of removed NLNs (≥ 19) was greater in patients whose tumor histology was adenocarcinoma than in patients whose tumor histology was SCC. Previous research has demonstrated that patients with esophageal squamous cell carcinoma generally have a poorer overall prognosis than those with adenocarcinoma. This is partly due to a higher incidence of comorbidities. Additionally, they tend to exhibit a distinct pattern of lymphatic involvement and a greater inclination for the disease to spread locally rather than systemically [28–31]. The higher survival rate in adenocarcinoma patients compared to SCC patients can be explained by the clinical, histological, and oncological differences between SCC and adenocarcinoma. Studies have shown that the average age of diagnosis of SCC is higher than that of adenocarcinoma. Also, these tumors are diagnosed later and at more advanced stages than adenocarcinoma, which usually has more limited effects on treatment in these patients. The time to recurrence in this type of tumor is shorter, and the recurrence rate is higher in these patients, which is associated with a lower survival rate of this type of tumor [32, 33].

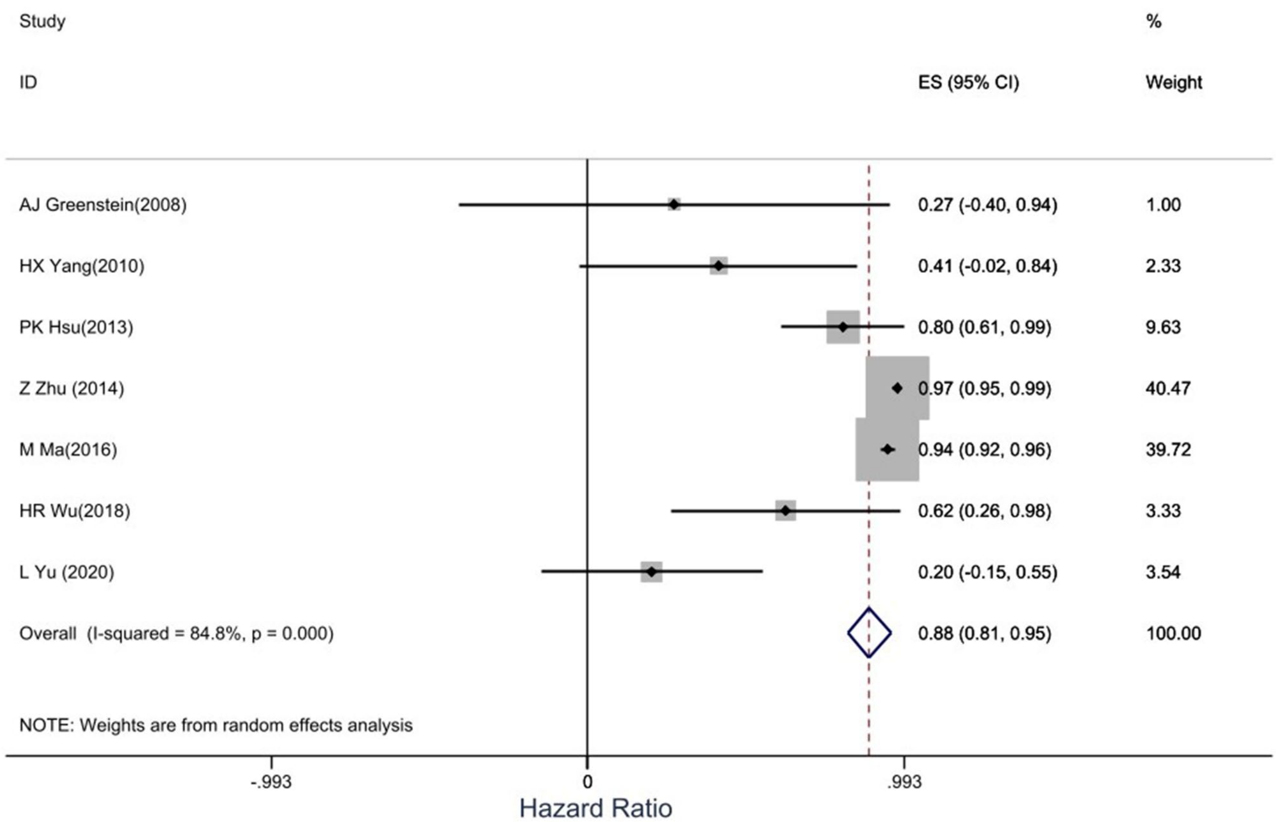

Fig. 2 The effect of the high number of removed NLNs on the survival rate

The majority of studies included in this meta-analysis were of good or moderate quality. Sensitivity analysis evaluated the individual effect of each study on the overall estimate of the study. Meta-regression analysis showed that the majority of the heterogeneity between studies was due to differences in the quality of the studies, tumor histology, and the number of NLNs. Also, differences in surgical techniques and populations studied in different geographical regions could explain the heterogeneity between studies.

In a meta-analysis, E Visser et al., [34]evaluated the effect of increasing the number of negative lymph nodes harvested on the survival of EC patients in 26 studies. They showed that the overall survival was significantly improved by increasing the number of harvested lymph nodes. Their meta-analysis showed the benefit of increasing lymph node efficiency on overall and disease-free survival. In a review study, M Elshaer et al., [35] showed that the lymph nodes ratio and the number of positive nodes removed during surgery were significantly related to the overall survival of pancreatic ductal adenocarcinoma. In another meta-analysis, T Chiyoda et al., [36]showed that lymphadenectomy was associated with improved overall survival of patients after surgery in patients with advanced and early stages of epithelial ovarian cancer.

While the exact mechanism behind the influence of the number of NLNs on survival prediction in patients with AC remains unclear, various theories have been suggested regarding the beneficial effects of excising a larger number of them. The correlation between the higher number of NLN removed and enhanced survival and decreased tumor recurrence can be explained by eliminating a greater quantity of lymph nodes and expanding the safety margin for removing all affected lymph nodes. The association between an increasing number of NLNs and improved survival is most likely due to the misclassification of patients in the primary studies included in this meta-analysis. Insufficient lymph node dissection could result in imprecise lymph node staging, and the removal of additional lymph nodes might provide a more accurate assessment of lymph node status. Consequently, research has introduced the stage migration hypothesis, which posits that obtaining precise lymph node data and assessing the lymph node stage by removing extra lymph nodes diminishes the chances of errors in nodal staging [37].

Some patients diagnosed as having NLNs disease may probably have had cancer spread to regional LNs. As the number of LNs removed during surgery increases, the likelihood of missing a positive LN decreases, leading to fewer patients with higher-stage disease being incorrectly classified as having stage I or stage IIA cancer. This

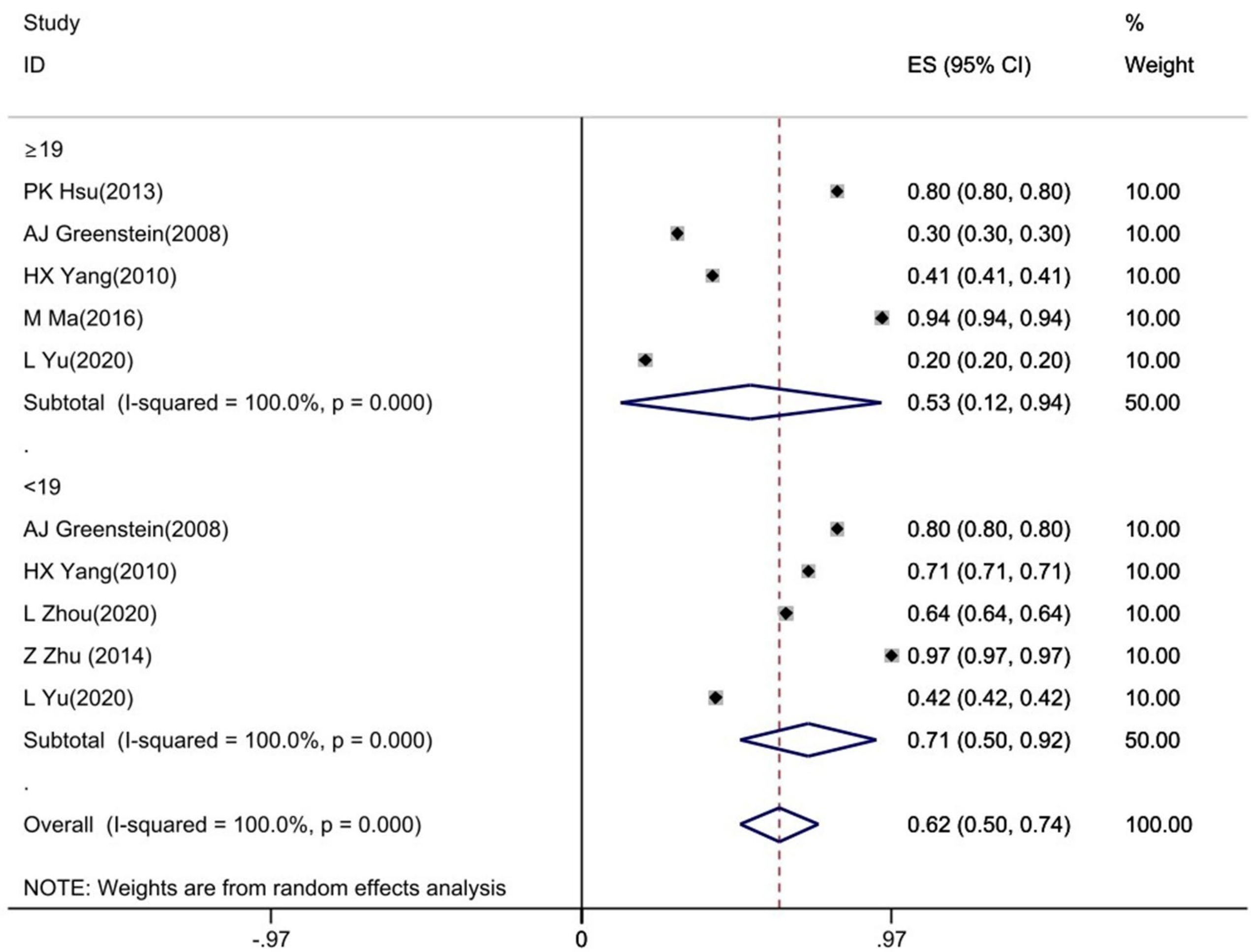

Fig. 3 The protective effect of removed NLNs on patient survival was greater in patients with more NLNs removed

phenomenon, known as stage migration, may result in poor survival rates associated with a low LN harvest [14, 38–42]. An alternative explanation for the current findings is that removing more LNs leads to higher cure rates.

Limitations

Our study was about the strengths and weaknesses that should be pointed out. First, due to the design of the primary studies included in this meta-analysis, we could not assess the association of a higher number of NLN removal with survival rate in EC patients based on a number of important variables, such as sex and age of the patients. Second, most primary studies were conducted in china and developed countries, and their results should be generalized to other countries with caution. Thirdly, The studies conducted in this meta-analysis were conducted in different study environments, periods, places, and populations, which can affect the results of the study to some extent. Evaluating the effect of the number of negative lymph nodes removed on the survival of EC patients after surgery and also evaluating the effect size of the high number of removed NLNs based on tumor histology for the first time in a meta-analysis was the most important strength of this study.

Conclusion

This meta-analysis showed that a high number of NLNs removed during surgery was associated with improved patient survival after surgery. Removing ≥ 19 NLNs significantly improves survival in EC patients, particularly those with adenocarcinoma. The level of certainty of the evidence for the findings was moderate to high. This threshold should be incorporated into surgical guidelines. Future studies with large sample sizes in several populations with different characteristics could help to estimate the results more accurately. It is also recommended to evaluate the results in different populations that have undergone lymph node dissection with different strategies.

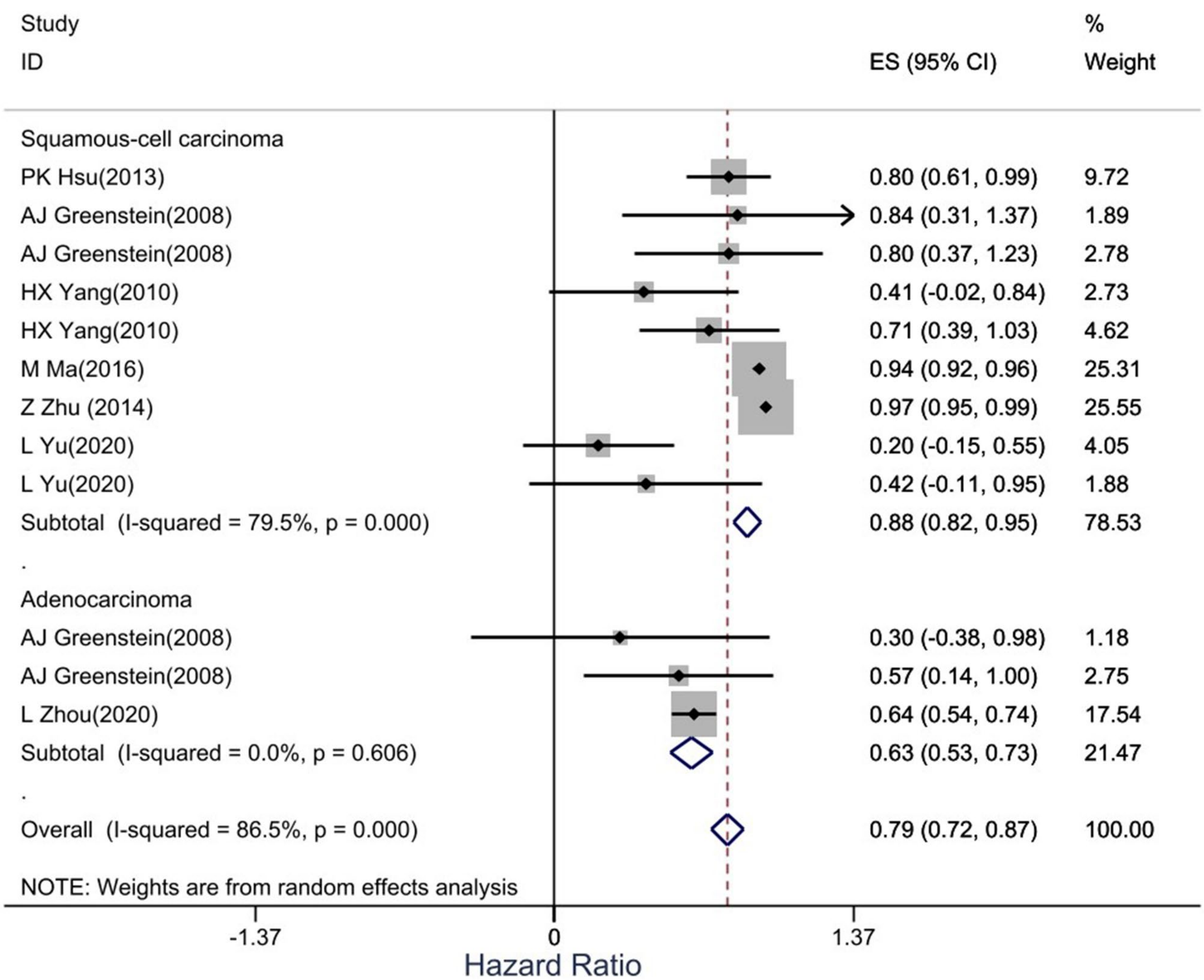

Fig. 4 The protective effect of a higher number of removed NLNs was greater in patients with adenocarcinoma tumor histology than SCC

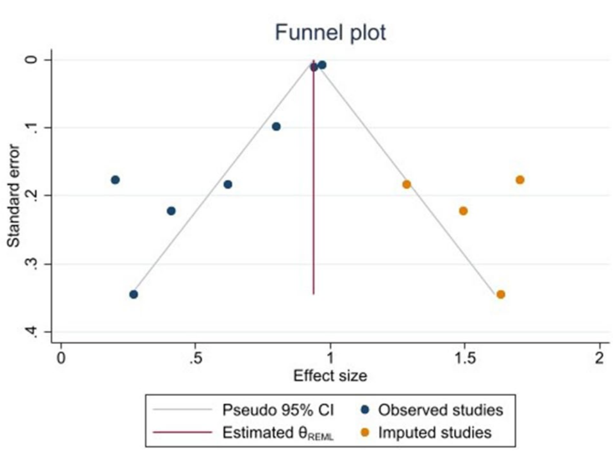

Fig. 5 Bias publication assessment in the funnel plot

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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NA.

Author contributions

Conception and design: AT, MB and FA - Analysis and interpretation of data: M B and BG - Data collection: MB, MS, AT and MMK - Participation in drafting or revising the article: AT, MB, BG, FA, ST,MH.

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Data availability

The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was registered with PROSPERO.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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