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# Impact of Dissected Lymph Node Count and Positive Lymph Node Ratio Following Esophagectomy on Long-Term Outcomes in Esophageal Cancer

## *A Systematic Review and Meta-Analysis*

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**Objective:** This meta-analysis evaluated how the number of lymph nodes dissected (LND) and the positive lymph node ratio (LNR) following esophagectomy influence long-term outcomes in esophageal cancer.

**Background:** Esophagectomy is a critical treatment for esophageal cancer, but the optimal extent of lymphadenectomy remains debated, especially in the era of modern neoadjuvant protocols.

**Methods:** A systematic electronic search of Embase, Medline, and the Cochrane Library was performed for studies published between 2000 and 2024. Included studies assess overall survival (OS) in patients with esophageal cancer undergoing esophagectomy with lymphadenectomy, comparing groups with high and low LND and LNR. A subset analysis examined outcomes in patients receiving neoadjuvant therapy.

**Results:** In total, 18 and 19 articles were included in the LND and LNR meta-analyses, respectively. High LND and low LNR were associated with improved OS [LND: hazard ratio (HR) = 0.75, 95% confidence interval (CI) = 0.67–0.85, $P < 0.01$; LNR: HR = 0.39, 95% CI = 0.33–0.47, $P < 0.001$]. Subset analysis revealed that these survival benefits persisted in patients who received neoadjuvant therapy (LND: HR = 0.56, 95% CI = 0.34–0.93, $P = 0.01$; LNR: HR = 0.24, 95% CI = 0.15–0.39, $P < 0.001$).

**Conclusions:** These findings highlight the prognostic importance of high LND and low LNR in improving OS following esophagectomy, regardless of neoadjuvant therapy. Extensive lymphadenectomy may enhance survival, and LNR provides a valuable prognostic tool for guiding postoperative treatment decisions.

**Keywords:** esophageal cancer, esophagectomy, lymphadenectomy, overall survival, neoadjuvant therapy, lymph node dissection, lymph node ratio

## 1. INTRODUCTION

Esophageal cancer is among the leading causes of cancer-related deaths globally, with particularly high incidence rates in regions such as East Asia.[1] Although organ-preserving therapies are under investigation, the primary curative treatment for localized esophageal cancer remains surgical resection, often combined with neoadjuvant or adjuvant therapies.[2,3] The outcomes of esophagectomy depend on multiple factors, including tumor stage, patient condition, surgical margins, and the number of lymph nodes dissected (LND).[4]

Lymphadenectomy plays a pivotal role in esophageal cancer surgery by enabling accurate cancer staging and potentially improving outcomes through the removal of micrometastases.[5] The National Comprehensive Cancer Network guidelines recommend removing at least 15 lymph nodes to optimize staging and improve overall survival (OS).[6,7] However, the extent of LND varies owing to differences in surgical techniques, surgeon expertise and philosophy, and pathological examination thoroughness,[8] complicating the establishment of a definitive minimum number of LND for optimal prognosis.

The prognostic value of lymphadenectomy in esophageal cancer has been extensively studied.[9] Numerous reports have indicated that a higher number of LND is associated with better survival outcomes, likely due to improved staging accuracy and metastatic node removal.[7,10–21] Nevertheless, the ideal number of LND remains debated. Although some studies emphasize the benefits of extensive lymphadenectomy, others argue that aggressive lymph node dissection may increase postoperative complications without markedly improving survival rates, especially in high-risk patients or those receiving neoadjuvant therapy.[22] In addition to LND, the lymph node ratio (LNR), defined as the ratio of positive lymph nodes to total dissected lymph nodes, has emerged as a key prognostic factor in various

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**Table 1.**

**Characteristics of Studies Included in the Lymph Node Dissection Meta-Analysis**

| | | | | Neoadjuvant Therapy | | LND Groups (Counts) | | Patients in Groups | | 5-Year OS (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Year | Country | N | No | Yes | Low | High | Low | High | Low | High |
| Schwarz and Smith[17] | 2007 | USA | 3568 | 3568 (100) | 0 (0) | ≦4 | ≧30 | 1147 (29) | 158 (4) | 22 | 42 |
| Greenstein et al[10] | 2008 | USA | 972 | 972 (100) | 0 (0) | ≦10 | ≧18 | 685 (70) | 113 (12) | 55 | 75 |
| Peyre et al[7] | 2008 | USA | 2303 | 2303 (100) | 0 (0) | ≦22 | ≧23 | 1473 (64) | 830 (36) | 35 | 40 |
| Hsu et al[28] | 2009 | Taiwan | 488 | 488 (100) | 0 (0) | ≦14 | ≧15 | 183 (38) | 305 (63) | 31 | 38 |
| Groth et al[11] | 2010 | USA | 4882 | 3398 (70) | RT: 1484 (30) | 0 | ≧30 | 906 (19) | 158 (3) | 28 | 47 |
| Yang et al[20] | 2010 | China | 592 | 592 (100) | 0 (0) | ≦5 | ≧18 | 157 (27) | 90 (15) | 43 | 74 |
| Hu et al[29] | 2010 | China | 1098 | 1098 (100) | 0 (0) | ≦5 | ≧6 | 825 (75) | 301 (25) | 45 | 50 |
| Torgersen et al[18] | 2011 | USA | 84 | 0 (0) | NS: 84 (100) | ≦17 | ≧18 | 43 (51) | 41 (49) | 30 | 68 |
| Wong et al[30] | 2013 | USA | 246 | 246 (100) | 0 (0) | ≦19 | ≧20 | 207 (84) | 23 (9) | 50 | 52 |
| Hsu et al[14] | 2013 | Taiwan | 707 | 637 (90) | CRT: 70 (10) | ≦11 | ≧29 | 167 (24) | 185 (26) | 23 | 38 |
| Liu et al[15] | 2013 | China | 666 | 666 (100) | 0 (0) | ≦8 | ≧16 | 369 (55) | 87 (13) | 44 | 60 |
| Yuan et al[21] | 2015 | China | 312 | 294 (94) | CT: 17 (5), CRT: 1 (<1) | ≦16 | ≧29 | 68 (22) | 83 (27) | 31 | 60 |
| Almhanna et al[31] | 2016 | USA | 635 | 246 (39) | NS: 389 (61) | ≦7 | ≧21 | 318 (50) | 54 (9) | 43 | 35 |
| Lagergren et al[32] | 2016 | UK | 606 | 215 (35) | CT: 391 (65) | ≦10 | ≧21 | 166 (27) | 150 (25) | 48 | 46 |
| Samson et al[16] | 2017 | USA | 18777 | 7780 (41) | CRT: 10126 (54), CT: 871 (5) | ≦14 | ≧15 | 11816 (63) | 6961 (37) | 33 | 38 |
| Wu et al[19] | 2017 | China | 262 | 262 (100) | 0 (0) | ≦14 | ≧22 | 111 (42) | 64 (24) | 45 | 66 |
| Guo et al[12] | 2023 | China | 182 | 0 (0) | CRT: 182 (100) | ≦19 | ≧20 | 85 (47) | 97 (53) | 52 | 74 |
| Ho et al[13] | 2024 | Taiwan | 91 | 0 (0) | CRT: 91 (100) | ≦14 | ≧15 | 28 (31) | 63 (69) | 21 | 56 |

Values in parentheses indicate percentages within each study. The total number of patients in low and high LND groups may not sum to 100% due to exclusion of intermediate groups or variations in study-specific definitions.
CRT indicates chemoradiotherapy; CT, chemotherapy; LND, lymph nodes dissected; NS, not specified; OS, overall survival; RT, radiotherapy.

cancers, including esophageal cancer.[23,24] Therefore, determining both LND and LNR is crucial for improving the prognosis of patients with esophageal cancer; however, LNR depends on LND and cannot be evaluated independently. It also remains unclear whether LND or LNR is more predictive of prognosis.

To address these uncertainties, we conducted meta-analyses to evaluate the associations of LND and LNR with OS in patients with esophageal cancer undergoing esophagectomy. Given the variability in LND and LNR across institutions and the influence of neoadjuvant therapy on surgical outcomes, our analysis stratified the data based on these 3 factors. By comparing the hazard ratios (HRs) from LND and LNR meta-analyses, we assessed which metric is a stronger prognostic indicator.

## METHODS

### Registration

The meta-analyses were registered *a priori* in the International Prospective Register of Systematic Reviews, "PROSPERO," under special identifiers CRD42024607008 and CRD42024612713. This study did not involve any new individual patient data collection and is based entirely on previously published literature. Therefore, institutional review board approval was not required.

### Literature Search

The meta-analyses followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses, "PRISMA," guidelines[25] and the Cochrane Handbook for Systematic Reviews of Interventions.[26] A comprehensive literature search was performed to identify studies evaluating the impact of LND and LNR during esophagectomy on long-term outcomes in esophageal cancer cases. Two authors (E.B. and H.T.) independently conducted literature searches. Electronic databases, including PubMed and Cochrane Central Register of Controlled Trials, were queried for published and ahead-of-publication studies from the inception of each database to September 2024. The search strategy involved using the following terms: for LND, ((("2000"[Date - Publication]:"2024"[Date - Publication])) AND (("controlled clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]))) AND (esophageal neoplasm OR esophageal cancer) AND (lymph node excision OR lymph node dissection); for LNR, ((("2000"[Date - Publication]:"2024"[Date - Publication])) AND (("controlled clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]))) AND (esophageal neoplasm OR esophageal cancer) AND (lymph node ratio).

### Study Selection and Eligibility

Based on the literature search, 2 independent authors (E.B. and H.T.) screened studies evaluating OS in patients with esophageal cancer undergoing esophagectomy. Only studies comparing outcomes between groups with high versus low numbers of LND and high versus low positive LNR were eligible for inclusion.

Studies were selected according to the following criteria[27]: (1) population: patients diagnosed with esophageal cancer who underwent esophagectomy; (2) intervention: lymphadenectomy, with a comparison between high and low LND groups or high and low LNR groups; (3) outcome: OS reported as the primary outcome; (4) study design: randomized controlled trials (RCTs), systematic reviews, cohort studies, and retrospective analyses published in peer-reviewed journals. Articles that did not provide data comparing LND or LNR groups or did not focus on OS were excluded. Study selection involved an initial screening of titles and abstracts, followed by a full-text review to confirm study eligibility. Any disagreements between the 2 reviewing authors (E.B. and H.T.) were resolved through discussion and consensus.

### Data Extraction

For data extraction, 2 authors (E.B. and H.T.) independently assessed and reviewed the abstracts of the selected articles, resolving any discrepancies through consensus. Extracted data included the first author, publication year, study design, number of patients, (neo)adjuvant treatment, LND thresholds, LND groups, LNR cutoffs, LNR groups, and outcome measures. Extracted data are presented in Tables 1 and 2, separating patients treated with and without neoadjuvant therapy. When studies reported more than 2

**Table 2.**

**Characteristics of Studies Included in the Lymph Node Ratio Meta-Analysis**

| Reference | Year | Country | N | Neoadjuvant Therapy | Adjuvant Therapy | LNR Cutoff | HR | LL | UL | HR Type | *P* Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tachibana et al[33] | 2000 | Japan | 266 | NA | NA | 0.105 | 0.297 | 0.096 | 0.916 | MA | 0.0345 |
| He et al[34] | 2013 | China | 353 | None | None | 0.3 | 0.666 | 0.465 | 0.955 | MA | 0.027 |
| Sisic et al[35] | 2013 | Germany | 316 | NA | NA | 0.2 | 0.25 | 0.15 | 0.41 | MA | <0.001 |
| Wang et al[36] | 2015 | China | 209 | None | None | 0.2 | 0.585 | 0.366 | 0.936 | MA | <0.05 |
| Melis et al[37] | 2015 | Italy | 233 | NA | NA | 0.6 | 0.39 | 0.25 | 0.63 | MA | <0.001 |
| Huang et al[38] | 2015 | China | 167 | None | None | 0.15 | 0.48 | 0.29 | 0.79 | MA | 0.004 |
| Xu et al[39] | 2015 | China | 688 | None | None | 0.15 | 0.69 | 0.54 | 0.87 | MA | 0.002 |
| Wei et al[40] | 2015 | USA | 496 | None | None | 0.3 | 0.425 | 0.123 | 0.995 | MA | 0.011 |
| Shao et al[41] | 2016 | China | 916 | None | None | 0.35 | 0.29 | 0.22 | 0.37 | MA | <0.001 |
| Wang et al[42] | 2017 | China | 446 | NA | NA | 0.2 | 0.544 | 0.345 | 0.856 | MA | 0.009 |
| Yukawa et al[43] | 2020 | Japan | 120 | NA | NA | 0.1 | 0.233 | 0.124 | 0.436 | MA | <0.001 |
| Jang et al[44] | 2020 | Korea | 270 | Received | Received | 0.1 | 0.123 | 0.063 | 0.238 | MA | <0.001 |
| Ye et al[45] | 2020 | China | 2239 | Received | Received | 0.3 | 0.281 | 0.237 | 0.334 | UA | <0.001 |
| Kano et al[46] | 2021 | Japan | 199 | Received | Received | 0.13 | 0.200 | 0.117 | 0.341 | MA | <0.001 |
| Zhang et al[47] | 2021 | USA | 1144 | None | None | 0.16 | 0.499 | 0.407 | 0.612 | MA | <0.001 |
| Zhang et al[47] | 2021 | China | 930 | None | None | 0.16 | 0.413 | 0.328 | 0.520 | MA | <0.001 |
| Liang et al[48] | 2023 | China | 2165 | Received | Received | 0.23 | 0.50 | 0.44 | 0.53 | MA | <0.001 |
| Hou et al[49] | 2023 | China | 272 | NA | NA | 0.15 | 0.743 | 0.57 | 1.15 | MA | 0.0001 |
| Chen et al[23] | 2024 | China | 212 | Received | Received | 0.1 | 0.168 | 0.081 | 0.345 | MA | <0.001 |

HR indicates hazard ratio; LL, lower limit of 95% confidence interval; LNR, lymph node ratio; MA, multivariate analysis; NA, not available; UA, univariate analysis.; UL, upper limit of 95% confidence interval.

categories for LND or LNR, only the lowest and highest categories were extracted to improve comparability.

### Study Outcome

The primary outcome for the LND meta-analysis was 5-year OS in patients undergoing esophagectomy for esophageal cancer, stratified by LND. HRs were also investigated for comparison with LNR. Studies were categorized into 2 groups based on lymphadenectomy extent, that is, high versus low LND. High LND was defined based on thresholds established in each study, focusing on those that differentiated survival outcomes. The thresholds for high and low LND varied across studies. For analysis, the highest and lowest LND groups from each study were compared. The primary outcome for the LNR meta-analysis was HR in patients undergoing esophagectomy for esophageal cancer, stratified by the positive LNR cutoff.

For each study in the LND meta-analysis, HRs for 5-year OS were extracted or calculated, comparing high versus low LND patient groups. When HRs were not directly reported, survival data were extracted from Kaplan–Meier curves. Studies that did not report 5-year OS or did not clearly stratify by LND were excluded.

### Assessment of Methodological Quality and Risk of Bias

Two authors (E.B. and H.T.) independently assessed the risk of bias in the reviewed studies. The revised tool for assessing risk of bias in randomized trials, "RoB 2,"[50] was used for RCTs, whereas the Risk of Bias In Nonrandomized Studies of Interventions, "ROBINS-I,"[51] was used for nonrandomized studies. The quality of evidence for the primary outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach, which scores each endpoint from "very low to "high."[52] Additionally, funnel plots were used to assess publication bias for the primary outcome.

### Statistical Analysis

Statistical analyses were performed using Review Manager Web (The Cochrane Collaboration, Oxford, UK). Pooled analysis was conducted using a Mantel–Haenszel model, with odds ratios (ORs) and 95% confidence intervals (CIs) reported for the LND analysis. For LND and LNR analysis, pooled analysis was also performed using an inverse variance model, with HRs and 95% CIs reported. The significance of pooled ORs and HRs was assessed using the $Z$-test, with $P < 0.05$ considered statistically significant. Statistical heterogeneity for each pooled estimate was determined using Cochran's chi-square statistic and quantified via the $I^2$ statistic, with $I^2 > 50\%$ indicating heterogeneity. If heterogeneity was present, a random-effects model was used; if heterogeneity was absent, a fixed-effects model was applied.

## RESULTS

### Search Results

The systematic search for LND identified 125 articles from Embase, Medline, and the Cochrane Library through primary screening (Fig. 1A). A secondary screening led to the retrieval of 6 articles,[9,12,13,53–55] which were subjected to a qualitative systematic review. Among these articles, one high-quality systematic review was included.[9] This review covered 25 articles up to September 2017,[7,10,11,14–22,28–32,56–63] prompting a new qualitative systematic review of these 25 articles and those published from October 2017 onward. From this new review, 16 articles from the previous review and 2 articles published from October 2017 onward[7,10–21,28–32] were included in a quantitative systematic review (Table 1). The 18 included studies, published between 2007 and 2024, had sample sizes ranging from 84 to 18,777 patients. When categorized by treatment, 9 studies included patients undergoing primary esophagectomy,[7,10,15,17,19,20,28–30] 3 studies included patients receiving neoadjuvant therapy followed by esophagectomy,[12,13,18] and 6 studies involved both gro ups.[11,14,16,21,31,32] The thresholds used to define low and high LND groups are summarized in Table 1.

The systematic search for LNR yielded 122 articles from Embase, Medline, and the Cochrane Library through primary screening (Fig. 1B). A secondary screening retrieved 23 articles, which were subjected to a qualitative systematic rev iew.[23,24,33–49,64–67] Among these articles, one high-quality systematic review was included.[24] This review covered 21 articles published up to December 2022, prompting a new qualitative systematic review of these articles and those published from January 2023 onward. Based on this new review, 16 articles from the previous review and 3 articles published from January 2023 onward[23,33–49] were included in a quantitative systematic review (Table 2). The 19 included studies, published

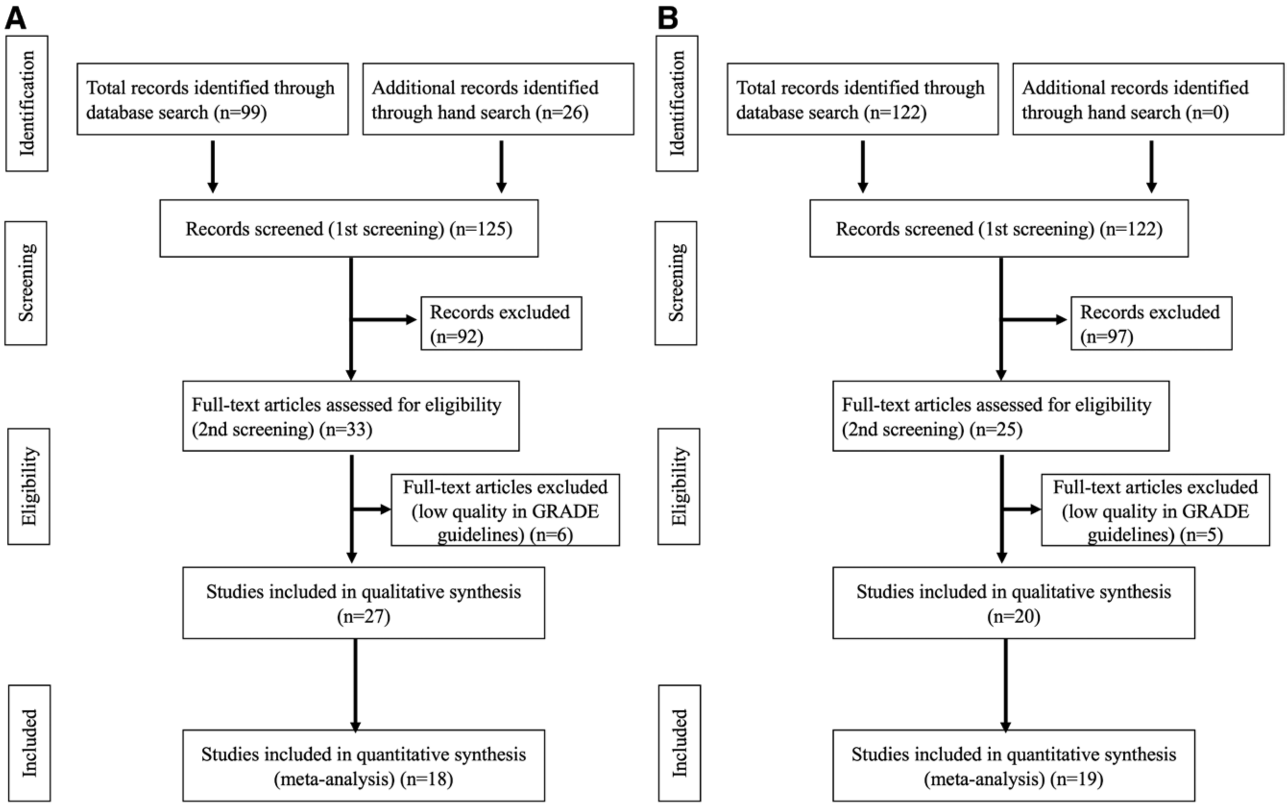



**FIGURE 1.** Flow diagrams outlining the inclusion and exclusion criteria for studies evaluating (A) the number of lymph nodes dissected and (B) the positive lymph node ratio.

between 2000 and 2024, had sample sizes ranging from 167 to 2239 patients. When categorized by treatment, 5 studies included patients undergoing neoadjuvant therapy followed by esophagectomy.[23,44–46,48] The LNR cutoffs for the low and high groups are summarized in Table 2.

## LND and OS Across All Studies

A pooled analysis of 18 articles[7,10–21,28–32] compared 5-year OS between the low and high LND groups (Fig. 2A). The low group ranged from 0 to ≤22 lymph nodes, whereas the high group ranged from ≥6 to ≥30, except for one study that subdivided the high group into groups comprising ≤5 and ≥6,[29] with all groups having ≥15 lymph nodes. The meta-analysis, including 28,517 patients (18,754 and 9763 in the high and low LND groups, respectively), revealed that high LND was associated with significantly improved OS (OR = 0.55, 95% CI = 0.45–0.66, $P$ < 0.01). Another pooled analysis of the same 18 articles[7,10–21,28–32] compared HRs between the low and high LND groups (Fig. 3A). This meta-analysis also demonstrated that high LND was associated with better OS (HR = 0.75, 95% CI = 0.67–0.85, $P$ < 0.001).

## LND and OS in Cases With Neoadjuvant Therapy Followed by Esophagectomy

A pooled analysis of 4 articles[12,13,16,18] compared 5-year OS between the low and high LND groups in patients receiving neoadjuvant therapy followed by esophagectomy (Fig. 2B). The low group ranged from ≤14 to ≤19 lymph nodes, whereas the high group ranged from ≥15 to ≥20. The meta-analysis, including 19,134 patients (7162 and 11,972 in the high and low LND groups, respectively), demonstrated that high LND was significantly associated with improved OS (OR = 0.37, 95% CI = 0.17–0.81, $P$ = 0.01). A pooled analysis of the same 4 articles[12,13,16,18] also compared HRs between the low and high LND groups in this cohort (Fig. 3B), with this meta-analysis showing that high LND was associated with better OS (HR = 0.56, 95% CI = 0.34–0.93, $P$ = 0.03).

## LNR and OS Across All Studies

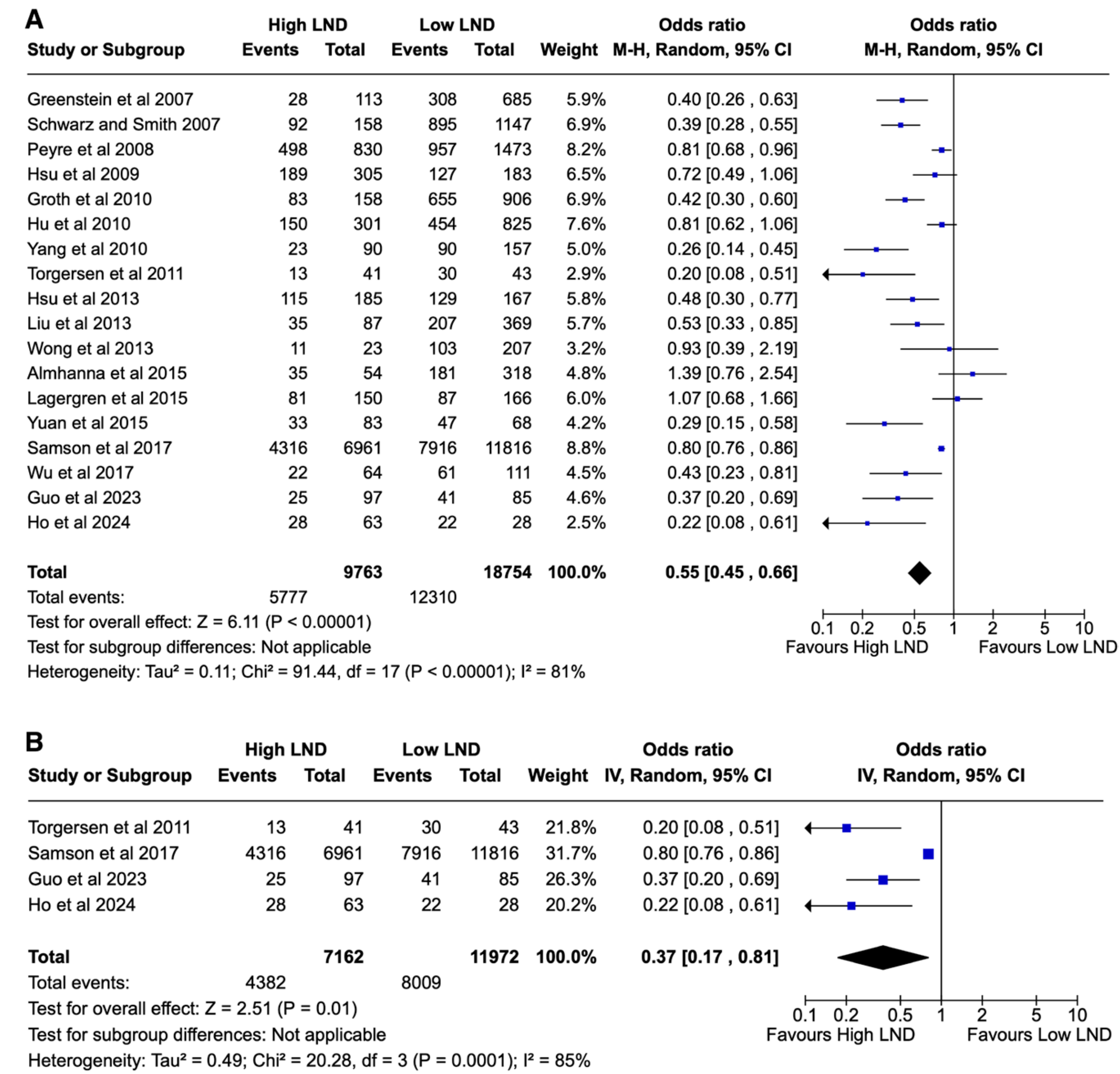
A pooled analysis of 19 articles[23,33–49] compared HRs between the low and high LNR groups (Fig. 4A). The LNR cutoff ranged from 0.1 to 0.6, with this meta-analysis showing that low LNR was associated with better OS (HR = 0.39, 95% CI = 0.33–0.47, $P$ < 0.001).

## LNR and OS in Cases With Neoadjuvant Therapy Followed by Esophagectomy

A pooled analysis of 5 articles[23,44–46,48] compared HR between the low and high LNR groups in patients receiving neoadjuvant therapy followed by esophagectomy (Fig. 4B). The LNR cutoff ranged from 0.1 to 0.3, and the meta-analysis demonstrated that low LNR was associated with better OS (HR = 0.24, 95% CI = 0.15–0.39, $P$ < 0.001).

## Risk of Bias

In these meta-analyses, based on Grading of Recommendations Assessment, Development, and Evaluation, the risk of bias, inconsistency, indirectness, imprecision, and publication bias were not significant.[52] The $I^2$ statistic indicated heterogeneity (Figs. 2–4); however, forest plots showed that the point estimates' directions were generally consistent. Given that heterogeneity was not significant, a random-effect analysis was used to resolve any unexplained heterogeneity, leading to reliable results.




**A**

| Study or Subgroup | High LND Events | High LND Total | Low LND Events | Low LND Total | Weight | Odds ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Greenstein et al 2007 | 28 | 113 | 308 | 685 | 5.9% | 0.40 [0.26 , 0.63] |
| Schwarz and Smith 2007 | 92 | 158 | 895 | 1147 | 6.9% | 0.39 [0.28 , 0.55] |
| Peyre et al 2008 | 498 | 830 | 957 | 1473 | 8.2% | 0.81 [0.68 , 0.96] |
| Hsu et al 2009 | 189 | 305 | 127 | 183 | 6.5% | 0.72 [0.49 , 1.06] |
| Groth et al 2010 | 83 | 158 | 655 | 906 | 6.9% | 0.42 [0.30 , 0.60] |
| Hu et al 2010 | 150 | 301 | 454 | 825 | 7.6% | 0.81 [0.62 , 1.06] |
| Yang et al 2010 | 23 | 90 | 90 | 157 | 5.0% | 0.26 [0.14 , 0.45] |
| Torgersen et al 2011 | 13 | 41 | 30 | 43 | 2.9% | 0.20 [0.08 , 0.51] |
| Hsu et al 2013 | 115 | 185 | 129 | 167 | 5.8% | 0.48 [0.30 , 0.77] |
| Liu et al 2013 | 35 | 87 | 207 | 369 | 5.7% | 0.53 [0.33 , 0.85] |
| Wong et al 2013 | 11 | 23 | 103 | 207 | 3.2% | 0.93 [0.39 , 2.19] |
| Almhanna et al 2015 | 35 | 54 | 181 | 318 | 4.8% | 1.39 [0.76 , 2.54] |
| Lagergren et al 2015 | 81 | 150 | 87 | 166 | 6.0% | 1.07 [0.68 , 1.66] |
| Yuan et al 2015 | 33 | 83 | 47 | 68 | 4.2% | 0.29 [0.15 , 0.58] |
| Samson et al 2017 | 4316 | 6961 | 7916 | 11816 | 8.8% | 0.80 [0.76 , 0.86] |
| Wu et al 2017 | 22 | 64 | 61 | 111 | 4.5% | 0.43 [0.23 , 0.81] |
| Guo et al 2023 | 25 | 97 | 41 | 85 | 4.6% | 0.37 [0.20 , 0.69] |
| Ho et al 2024 | 28 | 63 | 22 | 28 | 2.5% | 0.22 [0.08 , 0.61] |
| **Total** | | **9763** | | **18754** | **100.0%** | **0.55 [0.45 , 0.66]** |
| Total events: | 5777 | | 12310 | | | |

Test for overall effect: Z = 6.11 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.11; Chi² = 91.44, df = 17 (P < 0.00001); I² = 81%

**B**

| Study or Subgroup | High LND Events | High LND Total | Low LND Events | Low LND Total | Weight | Odds ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Torgersen et al 2011 | 13 | 41 | 30 | 43 | 21.8% | 0.20 [0.08 , 0.51] |
| Samson et al 2017 | 4316 | 6961 | 7916 | 11816 | 31.7% | 0.80 [0.76 , 0.86] |
| Guo et al 2023 | 25 | 97 | 41 | 85 | 26.3% | 0.37 [0.20 , 0.69] |
| Ho et al 2024 | 28 | 63 | 22 | 28 | 20.2% | 0.22 [0.08 , 0.61] |
| **Total** | | **7162** | | **11972** | **100.0%** | **0.37 [0.17 , 0.81]** |
| Total events: | 4382 | | 8009 | | | |

Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.49; Chi² = 20.28, df = 3 (P = 0.0001); I² = 85%

FIGURE 2. Forest plots showing the improved odds ratios associated with (A) a high number of lymph nodes dissected and (B) a high number of lymph nodes dissected in patients receiving neoadjuvant therapy followed by esophagectomy.

## DISCUSSION

LND and LNR are influenced by several factors, including variations in surgical techniques, specimen handling (eg, en-bloc vs separate submission),[68] and the methods used by pathologists to retrieve lymph nodes.[69] Although LNR, determined postoperatively, depends on LND and cannot be modified during surgery, LND can be adjusted intraoperatively, making it essential for surgical strategy and postoperative treatment planning. In contrast, LNR serves only as a valuable postoperative prognostic tool.[70] In our meta-analyses, LND showed HRs of 0.75 for all patients and 0.56 for those receiving neoadjuvant therapy, whereas LNR showed lower HRs of 0.39 and 0.24, respectively. Although direct statistical comparisons are not feasible, the lower HRs for LNR suggest that it may be a more robust prognostic predictor of postoperative outcomes, regardless of neoadjuvant therapy.

Previous systematic reviews have explored the impact of LND and LNR on esophageal cancer prognosis independently.[9,24] However, to the best of our knowledge, our study is the first meta-analysis to simultaneously assess and compare the prognostic value of LND and LNR. A key strength of our analysis is the inclusion of the NEOCRETEC5010 trial,[12] which demonstrated the association between high LND and improved outcomes following neoadjuvant chemoradiotherapy. This addition provides insights into the relative importance of LND and LNR in predicting long-term survival outcomes following esophagectomy.

For advanced esophageal cancer treatment, regional differences in neoadjuvant therapies exist, such as the use of chemoradiotherapy (41.4 Gy + carboplatin + paclitaxel) followed by esophagectomy in North America (eg, the CROSS and ESOPEC trials), and FLOT therapy (5-FU + leucovorin + oxaliplatin + docetaxel) followed by esophagectomy in Europe,[71,72] whereas Japan prefers the DCF regimen (docetaxel + cisplatin + 5-fluorouracil) followed by esophagectomy, based on the JCOG1109 trial.[73] Despite these regional differences, our

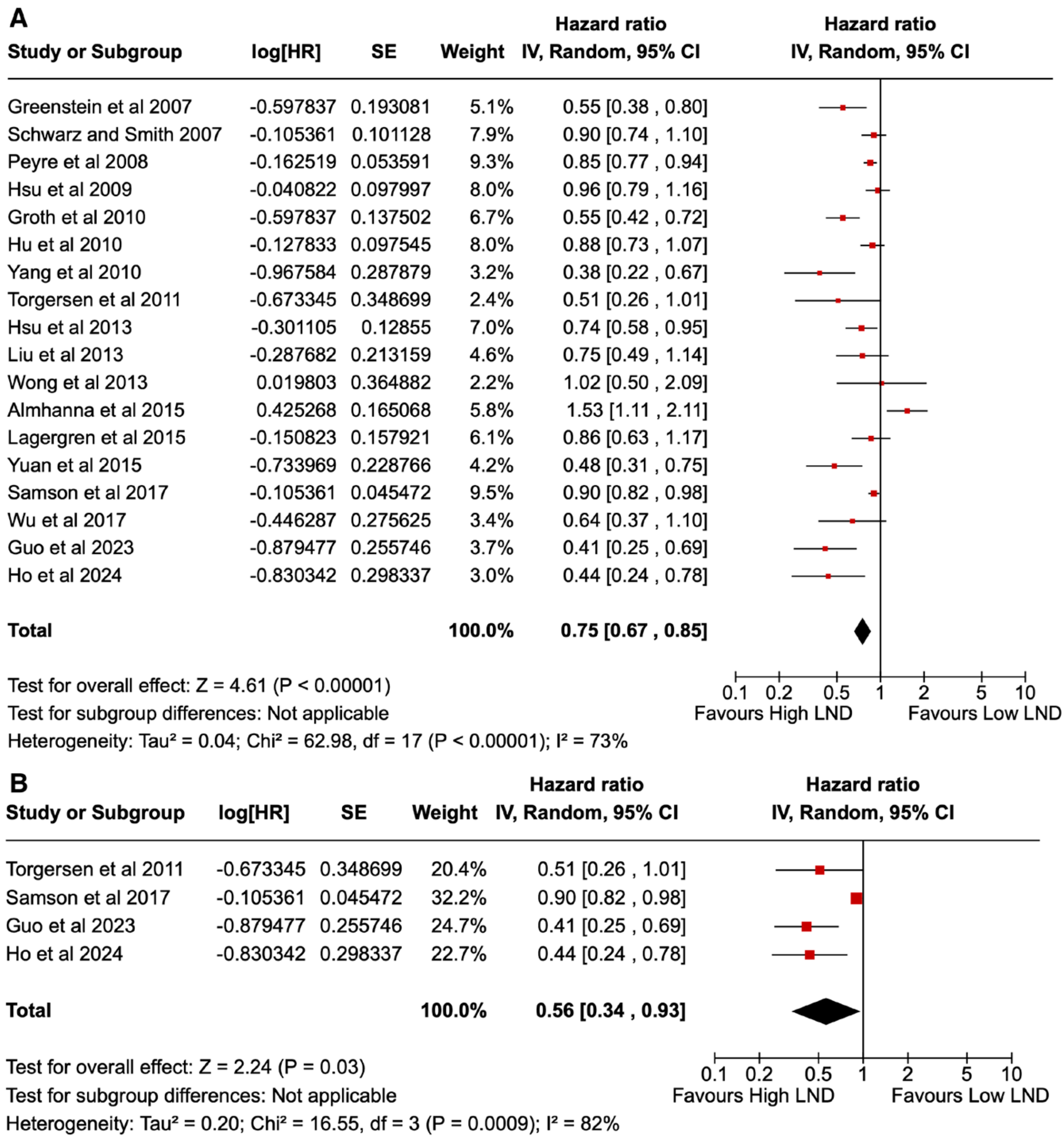



**FIGURE 3.** Forest plots showing the improved hazard ratios associated with (A) a high number of lymph nodes dissected and (B) a high number of lymph nodes dissected in patients receiving neoadjuvant therapy followed by esophagectomy.

analysis shows that high LND and low LNR are associated with improved survival. Although increasing the number of LND remains a cornerstone of surgical treatment, LNR is emerging as a critical prognostic indicator, providing additional insights into long-term outcomes and guiding postoperative treatment across diverse clinical settings. Even in patients with clinical or pathological complete response in lymph nodes following neoadjuvant therapy, viable tumor cells may persist in the primary site. Thus, comprehensive lymphadenectomy remains critical not only for accurate pathological staging but also for therapeutic removal of potential residual disease. This supports the ongoing relevance of adequate nodal retrieval regardless of apparent nodal response to induction treatment.

Although our meta-analysis did not stratify outcomes based on tumor location, it is important to note that the optimal extent and anatomical regions of lymphadenectomy differ depending on tumor location. For instance, in upper third esophageal cancers—particularly squamous cell carcinoma—cervical lymphadenectomy is often considered essential in surgical protocols, especially in East Asian countries such as Japan. The prognostic implications of high LND shown in this meta-analysis should thus be interpreted in the context of anatomical tumor distribution and institutional strategies.

Traditionally, guidelines have recommended a minimum of 15 lymph nodes for adequate staging and improved long-term prognosis.[6,7] In our meta-analysis, all high LND groups

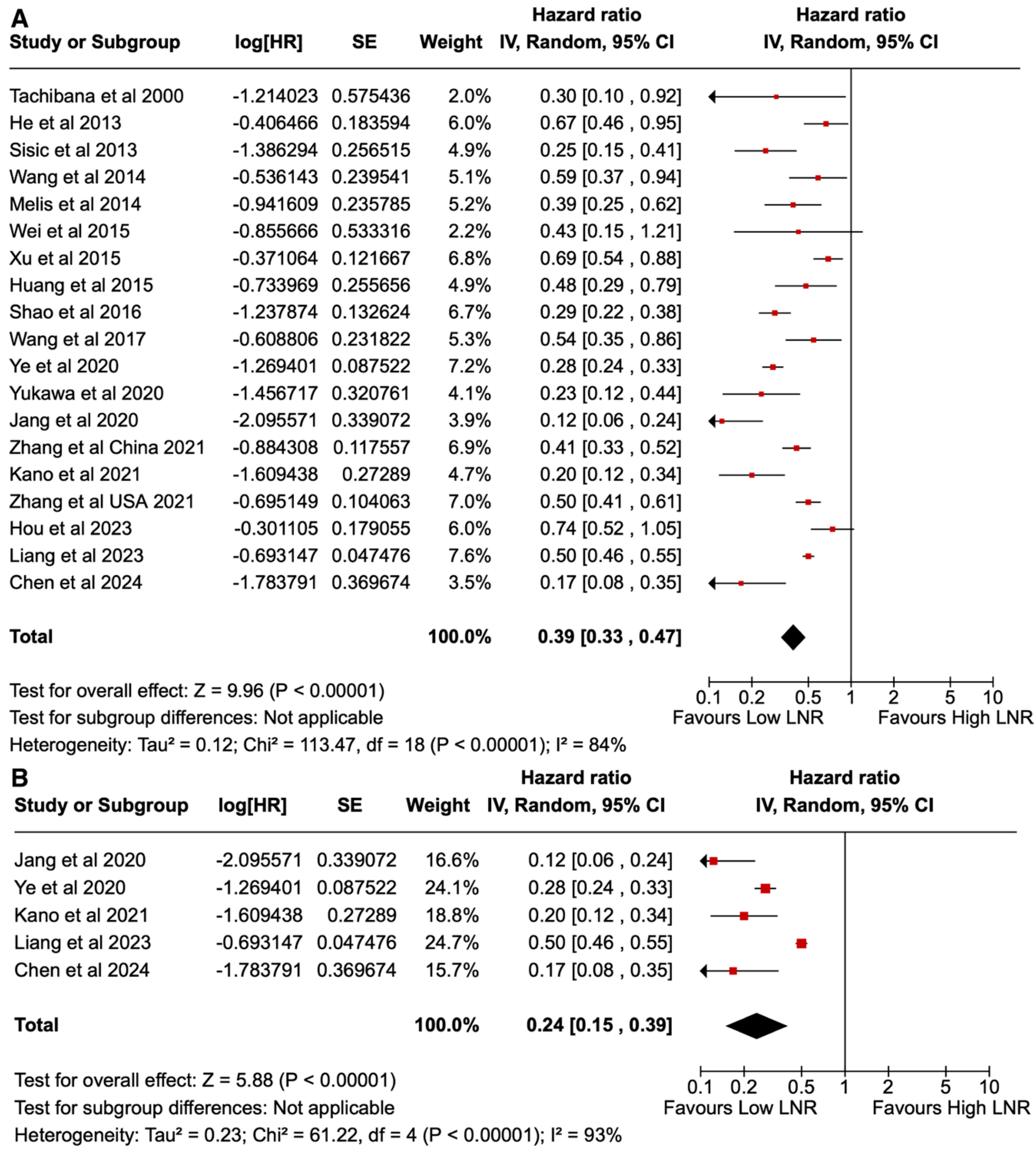



FIGURE 4. Forest plots showing the improved hazard ratio associated with (A) a low lymph node ratio and (B) a low lymph node ratio in patients receiving neoadjuvant therapy followed by esophagectomy.

included ≥15 dissected lymph nodes, except for one study that divided the groups at ≤5 nodes.[29] The consistent association between high LND (≥15) and improved survival suggests that aiming for at least 15 lymph nodes remains crucial for optimal staging and prognosis, even in patients receiving neoadjuvant therapy. Achieving this threshold maximizes the therapeutic benefit of esophagectomy while minimizing the risk of residual disease.

In addition to high LND, low LNR has been shown to independently predict a favorable prognosis. Our meta-analysis revealed that LNR cutoffs ranged from 0.10 to 0.35, with only 1 study using a higher cutoff of 0.6.[37] Although it remains challenging to establish a definitive LNR cutoff, our findings suggest that an LNR of ≤0.10 is consistently associated with improved prognosis across all studies, emphasizing the utility of targeting this LNR value as an effective prognostic marker to guide postoperative therapeutic decisions. Patients with a high LNR, indicative of a larger residual disease burden, may benefit from adjuvant treatments, such as intensified chemotherapy or immune checkpoint inhibitors. For example, the CheckMate 577 trial demonstrated that patients with a high LNR could benefit from nivolumab therapy to enhance survival outcomes.[74] The emergence of adjuvant therapies, particularly immune checkpoint inhibitors such as nivolumab, has reshaped the treatment paradigm. In this context, LNR may serve not only as a prognostic marker but also as a stratification tool to identify candidates who could benefit most from adjuvant interventions.

The complementary roles of LND and LNR highlight the importance of collaboration among surgeons, pathologists, and oncologists. Surgeons should aim to maximize lymph node retrieval, pathologists must ensure thorough examination of the lymph nodes for accurate LNR calculation, and oncologists can use LNR to identify patients who may benefit from adjuvant therapies. Future research should focus on standardizing LND thresholds and LNR cutoffs to enhance their clinical applicability. Prospective studies assessing the combined use of LND and LNR to guide treatment strategies would provide further evidence for their role in esophageal cancer management. Additionally, exploring the impact of emerging treatments, such as immunotherapy, on LND and LNR may further refine therapeutic approaches. Importantly, our recommendation to aim for an LNR <0.1 assumes that lymph nodes are retrieved from anatomically relevant regions. Dissecting lymph nodes from nonregional areas, such as the omentum in thoracic esophageal cancer, solely to artificially reduce the LNR is not oncologically appropriate.

Several limitations must be considered when interpreting the findings of this meta-analysis. First, unmeasured prognostic factors, such as patient comorbidities, surgical technique variations, and differences in postoperative care, may have influenced survival outcomes. Second, the heterogeneity in LND thresholds across studies, driven by differences in surgical and pathological practices, also introduces variability.[54,68,69,75] Finally, differences in neoadjuvant treatment regimens and follow-up protocols across studies contribute to inconsistencies. These limitations underscore the need for standardized criteria and larger, multicenter studies to clarify the prognostic importance of lymph node yield in esophageal cancer.

In conclusion, this meta-analysis highlights the importance of maximizing LND as a surgical strategy to improve staging and survival outcomes in esophageal cancer cases. It also shows that LNR can serve as a valuable prognostic tool for guiding postoperative therapy decisions. By integrating efforts to optimize LND and leveraging LNR to inform adjuvant therapies, clinicians can improve survival outcomes for patients undergoing esophagectomy.

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