Prognostic value of lymph node micrometastasis in esophageal cancer: A systematic review and meta-analysis

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Objective: Whether lymph node micrometastasis (LNM) increases the risk in esophageal cancer patients remains controversial. We conducted a systematic review and meta-analysis to explore the prognosis value of LNM in esophageal cancer patients.

Methods: Two reviewers independently searched electronic databases, including PubMed, Embase, and the Cochrane Library, for eligible citations until February 2022. We calculated pooled estimates of the hazards ratio with a random-effects model. The certainty of evidence was determined by the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) method. A sensitivity analysis was performed to assess the stability. Publication bias was assessed using funnel plots and Egger's test. We also performed subgroup analysis to explore the source of heterogeneity.

Results: A total of 16 studies, with 1,652 patients, were included. The overall survival (OS) was significantly increased with LNM negativity compared with LNM positivity (HR 1.95; 95% CI, 1.53−2.49; $P < 0.001$; $I^2 = 0.0\%$, $P = 0.930$; certainty of evidence: low). Relapse-free survival (RFS) was significantly increased with LNM negativity compared with LNM positivity (HR 3.39; 95% CI, 1.87−6.16; $P < 0.001$; $I^2 = 50.18\%$, $P = 0.060$; certainty of evidence: moderate). No significant difference was observed in recurrence between the two groups (certainty of evidence: low). Sensitivity analysis revealed a stable trend. In addition, the funnel plot and Egger's test did not show significant publication bias.

Conclusion: LNM positivity worsens the prognosis in esophageal cancer, and the evidence for RFS is moderate. Future relevant high-quality studies are warranted to validate our results further and provide a reference for guidelines.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier (CRD42022321768).

KEYWORDS

esophageal cancer, lymph node micrometastasis, prognosis, meta-analysis, systematic review

1 Introduction

The occurrence of esophageal cancer has increased in the Western world over the past few years and is expected to further rise (1, 2). Despite improvements in diagnostic methods and treatment, many patients are at the risk of recurrence post-surgery. Recurrence is likely to be associated with lymph node involvement as this is the strongest prognostic factor in esophageal cancer, with a 5-year survival rate in patients with pN3 ranging from 2% to 17% and that in patients with pN0 (no lymph node metastasis) being up to 83% (3). Lymph node micrometastasis (LNM) can be detected in the pN0 stage. In the presence of LNM, the 5-year survival rate for patients with esophageal cancer varies from less than 1% to 30% (4). Therefore, LNM may be a good survival predictor.

LNM is challenging to identify with certainty by routine Hematoxylin and Eosin (HE) staining. However, immunohistochemical (IHC) staining for cytokeratin can highlight small tumor cells, making them more easily detectable. A previous study (5) has reported that patients with LNM had significantly lower disease-free survival rates than those with negative lymph node metastasis in esophageal cancer. Another study (6) has reported that patients with LNM have a higher local recurrence rate than those without LNM. Another study (7) performed multivariate cox regression analysis, which showed that LNM was an independent prognostic factor for 5-year relapse-free survival (RFS) rate; however, no statistical differences were found in the 5-year overall survival (OS) rate between patients with LNM and those without LNM. It has been reported (8) that patients with LNM have significantly lower disease-free survival rates, indicating a worse prognosis. Although LNM has been evaluated in esophageal cancer, it is not included in TNM staging of esophageal cancer because there are no vital pieces of evidence indicating that LNM has a negative prognostic impact on esophageal cancer (9).

Nonetheless, Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) are watchful toward LNM (10, 11). Moreover, there is no meta-analysis quantifying the value of LNM in the prognosis of esophageal cancer. Therefore, we have performed this meta-analysis to assess the prognostic value of LNM in patients with esophageal cancer.

2 Methods

2.1 Data sources and search strategy

This meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (12). The study has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022321768) (13).

We searched for eligible studies in the electronic databases PubMed, Embase, and the Cochrane Library up to February 2022. We used the following combined text and MeSH terms: "Esophageal Neoplasms" and "Neoplasm Micrometastasis". The complete literature search strategy for PubMed is provided in Supplementary Appendices 1. We also conducted a manual search using the reference lists of critical articles published in English.

2.2 Study selection and data extraction

The articles included in the analysis were selected based on the following eligibility criteria: (1) all patients were diagnosed with esophageal cancer and (2) studies included information on the prognostic value of LNM in esophageal cancer. Articles were excluded from the analysis if (1) they were not presented in English or Chinese; (2) they were review articles, meta-analyses, or conference abstracts; and (3) they did not include the available data.

Two independent investigators (JY and QQL) reviewed all relevant and eligible literature using standardized data-

extraction forms. Disagreements were solved by consulting with a third investigator (MZ). The following data from each selected article: author names, year of publication, country/region, study design, total number of participants, age, sex, clinical outcomes, effect size with 95% CI, follow-up duration, and drop-out percentage were extracted.

2.3 Assessment of study quality

To assess the quality of each included study, two authors independently assessed the risk of bias using Quality In Prognosis Studies (QUIPS) tool (14). The studies were finally evaluated as "high risk of bias," "moderate risk of bias," and "low risk of bias". The QUIPS tool included six crucial areas to evaluate validity and bias in studies of prognostic factors, including participation, attrition, measurement of prognostic factors, outcomes, confounding factors, statistical analysis, and reporting.

2.4 Assessment of quality of evidence

The certainty of evidence was determined following the Grade of Recommendations Assessment, Development and Evaluation (GRADE) method (15, 16). The assessment of evidence quality was based on five aspects: limitations, inconsistencies, indirectness, inaccuracies, and publication bias. The evidence quality of each outcome was rated as "high," "moderate," "low," and "very low".

2.5 Study outcomes

We assessed the effect of the prognostic value of LNM in esophageal cancer on three outcomes: OS, RFS, and recurrence. In five of the included studies (5, 8, 17–19), disease-free survival was regarded as RFS because they have the same definition.

2.6 Statistical analyses

All statistical analyses were performed using Stata (version 16.0). We calculated pooled estimates of the hazards ratio (HR) and odds ratio (OR) with a random-effects model (Dersimonian-Laird method). In the included articles (6, 20, 21), the HR of OS was transformed by a survival curve (22). The I^2 statistic and P-value of Cochrane's Q test were used to assess the heterogeneity of effects, with I^2 = 25%–50% indicating mild, 50%–75% indicating moderate, and >75% indicating severe heterogeneity (23, 24).

We specified subgroups to explore the source of heterogeneity. Several subgroups were also analyzed, including study design, which was divided into retrospective, prospective,

and RCT; region, which was divided into Asia and non-Asia; antibody type, which was divided into Ber-EP4 and AE1/AE3; follow-up duration, which was divided into less than five years and more than five years; tumor type, which was divided into squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC); pN status, which was divided into pN + (studies including LNM in pN+ patients) and pN0 (studies restricted to LNM in pN0 patients); single-center/multicenter studies; and univariate/multivariate analysis.

A P-value < 0.05 indicated statistical significance. In addition, we assessed asymmetry using funnel plots and Egger's test and defined significant publication bias if P value is <0.05. Finally, we conducted sensitivity analyses to evaluate the stability of the results. Sensitivity analysis was conducted for all studies except three wherein the HRs were transformed by a survival curve to verify the stability of our results (6, 20, 21).

3 Results

3.1 Study selection and baseline characteristics

Of the 540 studies identified in our analysis, and 495 abstracts were retrieved and reviewed for possible inclusion after removing duplicates. Subsequently, 45 full-text manuscripts were assessed for eligibility, from which 29 did not meet the inclusion criteria and were excluded. Accordingly, only 16 studies including 1,652 patients were included (5–7, 17–21, 25–32) (Figure 1). The study characteristics and baseline
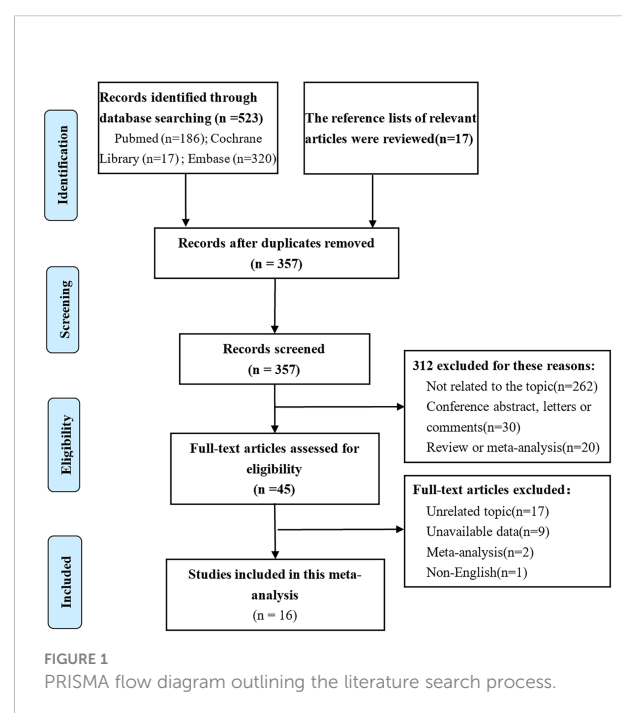

FIGURE 1
PRISMA flow diagram outlining the literature search process.

demographics are shown (Table 1). The majority of studies were based in Asia. The study designs were randomized, retrospective, or prospective studies. LNM evaluation was performed *via* IHC staining with different antibody types that were classified as AE1/AE3 and Ber-EP4. Follow-up durations ranged from 1 month to 174 months. The basic features of esophageal cancer are shown in Supplementary Appendices 2.

3.2 Quality assessment

Observational studies had low-to-moderate bias using the QUIPS tool (14) (Supplementary Appendices 3). Furthermore, confounding factors were not assessed in three studies (18, 27, 29); the drop-out time was not assessed in two studies (7, 26).

3.3 LNM and prognosis of esophageal cancer

A total of 1,169 patients were identified in nine studies (5–7, 20, 21, 25, 26, 28, 31). The OS was significantly increased with LNM negativity compared with LNM positivity in esophageal cancer patients (HR 1.95; 95% CI, 1.53–2.49; $P < 0.001$; $I^2 =$ 0.0%, $P = 0.930$; Figure 2; certainty of evidence, low). The results of subgroup analysis showed that there was a trend for OS in Asians (HR 1.82, 95% CI, 1.34–2.47; $I^2 = 0.0\%$, $P = 0.840$) to be lower than in non-Asians (HR 2.20, 95% CI, 1.47–3.28; $I^2 =$ 0.0%, $P = 0.780$), although no significant difference was observed between these subgroups ($P=0.47$) (Table 2) (Supplementary Appendices 4). Similarly, no significant differences were observed in outcomes between subgroups of study design, antibody types, follow-up duration, pN status, single-center/ multicenter, univariate/multivariate analysis and tumor type (Table 2) (Supplementary Appendices 5-11).

A total of 944 patients were identified in seven studies (5, 7, 19, 25, 26, 28, 30). The RFS was significantly increased with LNM negativity compared with LNM positivity in esophageal cancer patients (HR 3.39; 95% CI, 1.87–6.16; $P < 0.001$; $I^2 =$ 50.18%, $P = 0.060$; Figure 3; certainty of evidence, moderate). The results of subgroup analysis showed that there was a trend for RFS in Asians (HR 3.18, 95% CI, 1.43–7.05; $I^2 = 54.53\%$, $P =$ 0.070) to be lower than in non-Asians (HR 4.25, 95% CI, 1.93– 9.37; $I^2 = 0.0\%$, $P = 0.680$), although no significant difference was seen between these subgroups ($P = 0.610$) (Table 2) (Supplementary Appendices 12). Further, no significant differences were observed between subgroups of study design, region, antibody types, follow-up duration, pN status, single-center/multicenter, univariate/multivariate analysis, and tumor types (Table 2) (Supplementary Appendices 13-19).

A total of 184 patients were identified in three studies (18, 27, 29). No significant difference was observed in recurrence

between LNM positivity and LNM negativity groups (HR 1.74; 95% CI, 0.85–3.56; $P = 0.130$; $I^2 = 0\%$, $P = 0.810$; Figure 4; certainty of evidence, low). Further, no significant differences were observed between subgroups of follow-up duration (Supplementary Appendices 20).

3.4 Sensitivity analysis and publication bias

Sensitivity analysis with the exclusion of one trial at a time revealed a stable trend (Supplementary Appendices 21-23). In addition, after excluding three articles (6, 20, 21) for which the HR was transformed by a survival curve, it was observed that OS was significantly increased with LNM negativity compared with LNM positivity (HR 1.93; 95% CI, 1.47–2.52; $P < 0.001$; $I^2 =$ 0.0%, $P = 0.820$), and the trend was still stable.

Moreover, no significant asymmetry was observed by visual inspection of the funnel plot of studies reporting OS (Figure 5). The Egger's test did not show significant publication bias ($P = 0.445$).

3.5 Evidence quality

The original studies were observational studies that provided low-quality evidence. The OS and recurrence data showed low certainty, indicating that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect (33, 34). The outcome of RFS was upgraded because of the large effect size; therefore, it shows moderate certainty, indicating that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (33, 34). Further details are provided in Table 3.

4 Discussion

In this meta-analysis, moderate-quality evidence showed that RFS was significantly increased with LNM negativity compared with LNM positivity in esophageal cancer patients. The OS was significantly increased with LNM negativity compared with LNM positivity in esophageal cancer patients, although the quality of evidence was low. However, no significant difference was observed in recurrence. Regretfully, several subgroups were not found to be a source of heterogeneity.

According to the UICC Tumor, Node, Metastasis-classification, eighth editions guidelines on lymph node involvement in esophageal cancer, the presence of tumor cells exceeding 0.2 mm in greatest extent is categorized as metastasis (9). LNM is a tumor lesion in a lymph node between 0.2 and

TABLE 1 Study characteristics and baseline demographics.

First author	Year	Country	Study design	S/M	AgeMean ± SD/range, years	Patients, nP/N	Male, nP/N	LNs, n	Average LNs, n	Definition of LNM	Antibody types	Median follow-up, (range), month	Drop-out (n, %)
Izbicki,J.R. (25).	1997	Germany	POS	S	57.0(34.0-76.0)	42/26	33/21	1308	NA	conventional histopathological negative and IHC positive	Ber-EP4	21.0(2.0-51.0)	5, 7.4
Komukai,S., (26)	2000	Japan	POS	S	60.8 ± 7.3	14/23	12/20	2845	75(38-127)	pN0 and IHC positive	AE1/AE3	60.0	NA
Matsumoto, M., (27)	2000	Japan	POS	S	64.1(37.0-85.0)	33/26	27/24	2714	46(14-103) *	pN0 and IHC positive	AE1/AE3	60.0	0
Sato,F., (28)	2001	Japan	ROS	S	64.7 ± 9.0	20/30	15/21	1840	37(6-136)	pN0 and IHC positive	AE1/AE3	67.0(7.0-136.0)	0
Doki,Y., (20)	2002	Japan	ROS	M	NA	11/30	NA	2168	53	pN0 and IHC positive	AE1/AE3	120.0	0
Nakamura, T., (29)	2002	Japan	ROS	S	62.5(41.0-76.0)	14/39	NA	2511	49	pN0 and IHC positive	AE1/AE3	53.5(2.0-92.0)	0
Xiao,X.W. (30)	2002	China	ROS	S	55.0(38.0-75.0)	61/25	48/20	1500	NA	conventional histopathological negative and IHC positive	Ber-EP4	25.0(1.0-67.0)	6, 7.0
Tanabe,T., (17)	2003	Japan	POS	S	63.0(40.0-78.0)	12/34	NA	3494	44(4-153) *	pN0 and IHC positive	AE1/AE3	54.0(7.0-136.0)	0
Shiozaki,H., (21)	2007	Japan	POS	M	NA	25/139	NA	NA	NA	pN0 and IHC positive	AE1/AE3	20.0	0
Chao,Y.K., (18)	2009	China	POS	S	57.2(39.0-68.0)	6/46	6/46	510	10(5–32)	pN0 and IHC positive	AE1/AE3	62.3(10.4-137.0)	0
Koenig, A.M., (6)	2009	Germany	ROS	S	60.0(39.0-83.0)	25/48	21/37	2174	25(6–74) *	conventional histopathological negative and IHC positive	AE1/AE3	38.5 (3.0-101.0)	4, 5.5
Zingg,U., (19)	2009	Switzerland	POS	S	61.0(36.0-85.0)	24/62	71/15	1204	NA	pN0 and IHC positive	AE1/AE3	47.4 (14.0-159.0)	3, 3.5
Thompson, S.K., (31)	2010	Australia	POS	S	61.3 ± 9.3	31/88	27/66	661	5*	pN0 and IHC positive	AE1/AE3	68.5	0
Prenzel, K.L., (32)	2012	Germany	POS	S	NA	7/41	NA	1344	28(15-52)	pN0 and IHC positive	AE1/AE3	99.6(58.8-160.8)	0

(Continued)

TABLE 1 Continued

First author	Year	Country	Study design	S/M	AgeMean ± SD/range, years	Patients, nP/N	Male, nP/N	LNs, n	Average LNs, n	Definition of LNM	Antibody types	Median follow-up, (range), month	Drop-out (n, %)
Chen,S.B., (5)	2020	China	POS	S	58.0(36.0-78.0)	88/428	65/301	11578	20 (10-69)*	pN0 and IHC positive	AE1/AE3	69.9 (1.0-174.0)	14, 2.7
Hiraki,Y. (7)	2021	Japan	RCT	M	67.0(46.0-78.0)	24/77	19/68	NA	67(16-139)*	conventional histopathological negative and IHC positive	AE1/AE3	60.0	NA

S/M, single-center/multicenter; RCT, Randomized study; ROS, Retrospective observational study; POS, Prospective observational study; P/N, lymph node micrometastasis positive/lymph node micrometastasis negative; LNs, lymph nodes; IHC, Immunohistochemical; pN0, Node-negative; * median; pN0 and IHC positive: lymph node micrometastasis was defined as the presence in lymph nodes of tumor cells that were immunohistochemically positive for IHC staining. NA, Not available.

2 mm in diameter and/or a microscopic collection of more than 200 tumor cells in a lymph node (35–37).

Although most studies (19, 31, 32) have found that LNM positivity indicates a worse prognosis than LNM negativity, studies (7, 28) have found no statistically significant difference between prognosis between the two. Further, these studies (27, 29, 38) have found that recurrence with LNM positivity has a different clinical significance in esophageal cancer. Most of the included observational trials had small statistical power in this meta-analysis. Meta-analysis is an ideal statistical tool that increases the statistical power and the precision of comparisons and offers more powerful evidence for clinical decision-making. Thus, this meta-analysis was conducted to assess the clinical significance of LNM in esophageal cancer. Our meta-analysis showed that LNM is a strong prognostic factor in esophageal cancer.

We also conducted subgroup analyses in this meta-analysis including subgroups of study design, region, antibody type, follow-up duration, pN status, single-center/multicenter study, univariate/ultivariate analysis, and tumor type to explore heterogeneity. However, we could not identify the source of heterogeneity. Among the subgroups, it found that OS and RFS may be a worse trend for non-Asians compared with Asians. The incidence of esophageal cancer has increased over the past years in the Western world and is predicted to increase further given a rise in alcohol consumption and lack of physical exercise (39). Compared with Eastern patients, Western patients have a larger BMI, making it relatively difficult to achieve the minimal number of harvested lymph nodes. This is associated with a worse prognosis for esophageal cancer in Western patients (40, 41).

The results of this study are of clinical significance. Here we provide a more objective appraisal of the evidence than traditional narrative reviews and a more precise estimate of the prognostic value of LNM than that currently available. The data presented here may help plan future clinical trials and may help determine whether LNM can be used as a prognostic factor in esophageal cancer. For example, LNM was included in the current AJCC staging system for breast cancer (35); however, LNM in esophageal cancer is not designated as a staging parameter. The data from observational studies suggest that LNM has a clinically significant detrimental effect on OS and RFS in esophageal cancer. It has been shown that control of LNM by neoadjuvant chemotherapy (NAC) in esophageal squamous cell carcinoma (ESCC) is significantly associated with improved RFS at pN0 stage (7). Patients with ESCC who underwent surgery after receiving NAC with Adriamycin + cisplatin + 5-fluorouracil (ACF) or docetaxel + cisplatin + 5-fluorouracil (DCF) have shown a better RFS in the DCF group, and DCF controlled LNM better than ACF (7, 42). In addition to controlling distant metastasis recurrence, LNM control is an important requirement in NAC regimens, and DCF is effective for LNM control (42, 43). We ventured to speculate whether
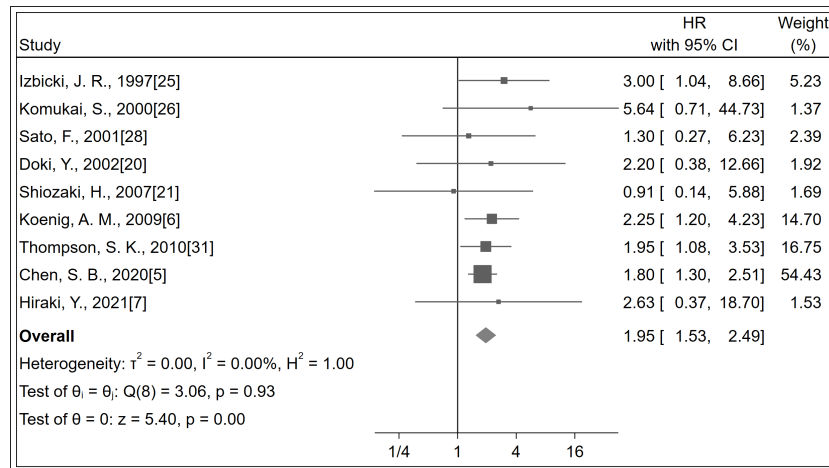
FIGURE 2
Forest plot of OS.

TABLE 2 Subgroup analysis of clinical outcomes.

Subgroup	No. studies	No. patients	Effect size	Heterogeneity		Test of group differences
			HR (95%CI)	I^2(%)	P value	P value
Region						
Asia	6	909	1.82(1.34,2.47)	0	0.84	0.47
Non-Asia	3	260	2.20(1.47,3.28)	0	0.78	
Study design						
RCT	1	101	2.63(0.37,18.70)	0	–	0.91
Prospective	5	164	1.91(1.45,2.50)	0	0.65	
Retrospective	3	904	2.10(1.20,3.65)	0	0.82	
Antibody types						
AE1/AE3	8	1101	1.91(1.49,2.44)	0	0.93	0.41
Ber-EP4	1	68	3.00(1.04,8.66)	0	–	
Follow-up duration						
Less than 5 years	2	232	2.14(0.74,6.14)	15.78	0.28	0.85
More than 5 years	7	937	1.93(1.50,2.49)	0	0.94	
Single-center/multicenter						
Single-center	6	863	1.96(1.53,2.52)	0	0.81	0.83
Multicenter	3	306	1.74(0.60,5.06)	0	0.70	
Tumor types						
SCC+EAC	3	260	2.20(1.47,3.28)	0	0.78	0.47
SCC	6	909	1.82(1.34,2.47)	0	0.84	
						(Continued)

TABLE 2 Continued

Subgroup	No. studies	No. patients	Effect size	Heterogeneity		Test of group differences
			HR (95%CI)	I^2(%)	*P* value	*P* value
Univariate/multivariate analysis						
Multivariate analysis	5	790	1.91(1.46,2.51)	0	0.72	0.76
Univariate analysis	4	379	2.10(1.22,3.63)	0	0.83	
pN status						
pN+	3	242	2.44(1.45,4.12)	0	0.90	0.34
pN0	6	927	1.83(1.40,2.41)	0	0.86	
Relapse-free survival						
Region						
Asia	5	803	3.18(1.43,7.05)	54.53	0.07	0.61
Non-Asia	2	141	4.25(1.93,9.37)	0	0.68	
Study design						
RCT	1	101	4.75(1.13,19.90)	–	–	0.85
Prospective	4	707	2.99(1.50,5.98)	52.34	0.10	
Retrospective	2	136	3.50(0.53,23.06)	59.03	0.12	
Antibody types						
AE1/AE3	5	790	2.73(1.41,5.29)	37.66	0.17	0.25
Ber-EP4	2	154	4.94(2.28,10.73)	0	0.38	
Follow-up duration						
Less than 5 years	2	154	4.94(2.28,10.73)	0	0.38	0.25
More than 5 years	5	790	2.73(1.41,5.29)	37.66	0.17	
Single-center/multicenter						
Single-center	6	843	3.29(1.71,6.33)	54.03	0.05	0.65
Multicenter	1	101	4.75(1.13,19.90)	–	–	
Tumor types						
SCC+EAC	3	240	5.03(2.58,9.82)	0	0.68	0.10
SCC	4	704	2.28(1.19,4.37)	26.96	0.25	
Univariate/multivariate analysis						
Multivariate analysis	6	843	3.29(1.71,6.33)	54.03	0.05	0.65
Univariate analysis	1	101	4.75(1.13,19.90)	0	0.06	
pN status						
pN+	3	255	4.90(2.48,9.69)	0	0.68	0.19
pN0	4	689	2.49(1.19,5.22)	38.41	0.18	

HR, hazard Ratio; RCT, randomized controlled trial; SCC, Squamous cell carcinoma; EAC, Esophageal adenocarcinoma.
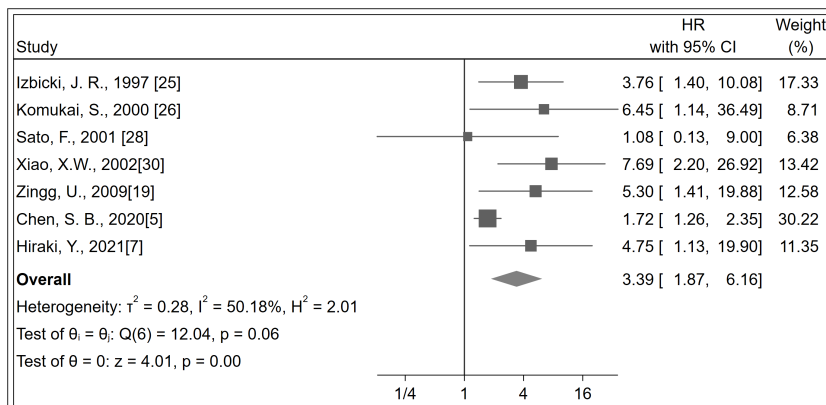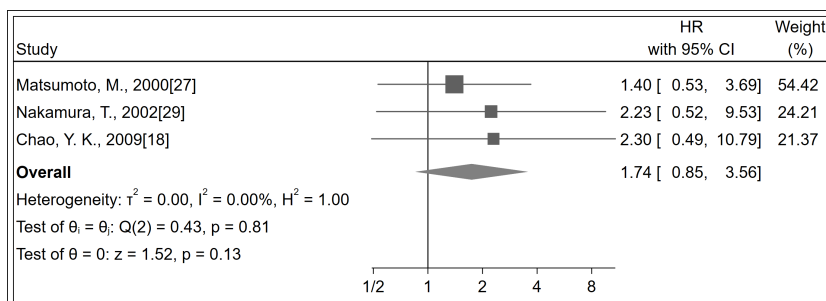
FIGURE 3
Forest plot of RFS.
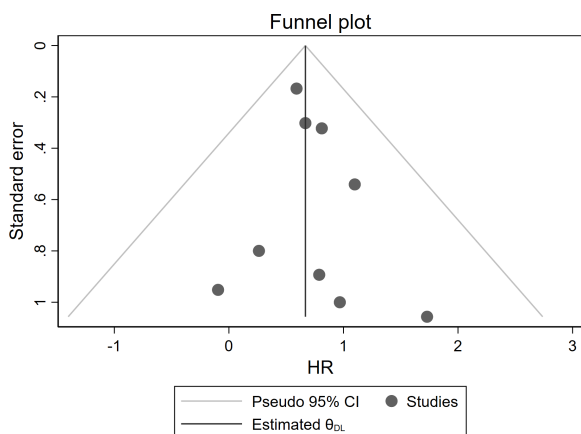

FIGURE 4
Forest plot of recurrence.

FIGURE 5
Funnel plot to assess publication bias of OS.

LNM can be included in the staging of N in esophageal cancer. At the same time, LNM was a poor prognostic factor in esophageal cancer, which provided a reference for the treatment and prognostic value of LNM in other gastrointestinal cancers.

There were some limitations to this meta-analysis. First, because the definition of LNM itself has not been standardized, the original research reported some differences in the definition of LNM, which may be the source of heterogeneity. However, further exploration could not be carried out because of the limitation of the original data. Second, an estimated moderate degree of heterogeneity was found for RFS among studies. However, secondary analyses including subgroup analysis and sensitivity analysis were performed to partly explore this limitation. Third, the results of this study needed to be interpreted with caution because a majority of studies were Asian, although there were no restrictions on the study population in this study. Lastly, the evidence is low-to-

TABLE 3 Summary of the results of GRADE.

Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNM positive	LNM negative	Relative (95% CI)	Absolute(95% CI)	Certainty
			Certainty assessment				Nº of patients		Effect		
Overall survival (follow-up: range 1 months to 174 months)											
9	observational studies	not serious	not serious	not serious	not serious	none	279/1169 (23.9%)	890/1169 (76.1%)	HR 1.95 (1.53 to 2.49)	177 more per 1,000 (from 127 more to 210 more)	⊕⊕◯◯ Low
Relapse-free survival (follow-up: range 1 months to 174 months)											
7	observational studies	not serious	not serious	not serious	not serious	strong association	272/944 (28.8%)	672/944 (71.2%)	HR 3.39 (1.87 to 6.16)	273 more per 1,000 (from 191 more to 288 more)	⊕⊕⊕◯ Moderate
Recurrence (follow-up: range 10.4 months to 137 months)											
3	observational studies	not serious	not serious	not serious	not serious	none	53/194 (27.3%)	141/194 (72.7%)	OR 1.74 (0.85 to 3.56)	96 more per 1,000 (from 33 fewer to 178 more)	⊕⊕◯◯ Low

LNM positive: lymph node micrometastasis positive; LNM negative: lymph node micrometastasis negative; The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; HR, hazard Ratio; OR, odds ratio CI, confidence interval; HR, hazard Ratio; OR, odds ratio.

moderate quality because most studies included in the analysis were observational in nature. Therefore, future relevant high-quality studies with a large sample size are needed to confirm the prognostic value of LNM.

5 Conclusion

LNM positivity has a worse prognosis in esophageal cancer, although the evidence for this is low to moderate. Future relevant high-quality studies are needed to further validate our results and provide a reference for guidelines.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JY and QL: literature search, screening, data extraction, data analysis and results visualization. The manuscript was written with the contributions of all authors. MZ: fund acquirement. All authors have approved the final version of the manuscript.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1025855/full#supplementary-material

References

1. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2019) 17 (7):855–83. doi: 10.6004/jnccn.2019.0033

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654

3. Okholm C, Svendsen LB, Achiam MP. Status and prognosis of lymph node metastasis in patients with cardia cancer - a systematic review. *Surg Oncol* (2014) 23 (3):140–6. doi: 10.1016/j.suronc.2014.06.001

4. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* (2003) 349 (23):2241–52. doi: 10.1056/NEJMra035010

5. Chen SB, Liu DT, Huang SJ, Weng HR, Wang G, Li H, et al. Prognostic value of occult lymph node metastases in patients with completely resected esophageal squamous cell carcinoma. *Sci Rep* (2020) 10(1):22007. doi: 10.1038/s41598-020-79073-9

6. Koenig AM, Prenzel KL, Bogoevski D, Yekebas EF, Bubenheim M, Faithova L, et al. Strong impact of micrometastatic tumor cell load in patients with esophageal carcinoma. *Ann Surg Oncol* (2009) 16(2):454–62. doi: 10.1245/s10434-008-0169-7

7. Hiraki Y, Kimura Y, Imano M, Kato H, Iwama M, Shiraishi O, et al. Controlling lymph node micrometastases by neoadjuvant chemotherapy affects the prognosis in advanced esophageal squamous cell carcinoma. *Surg Today* (2021) 51(1):118–26. doi: 10.1007/s00595-020-02059-7

8. Heeren PAM, Kelder W, Blondeel I, van Westreenen HL, Hollema H, Plukker JT. Prognostic value of nodal micrometastases in patients with cancer of the gastro-oesophageal junction. *Eur J Surg Oncol* (2005) 31(3):270–6. doi: 10.1016/j.ejso.2004.12.001

9. Brierley JDGM, Wittekind C eds. *The TNM classification of malignant tumours. 8th edn*. Oxford: Wiley Blackwell (2017).

10. Rice TW DTP, Blackstone EH. AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice, 8th edition, Ann Cardiothorac. *Surg* (2017) 6:119–30. doi: 10.21037/acs.2017.03.14

11. Odze RD LA, Ochiai A, Washington MK. *WHO classification of tumors of the oesophagus. 5th*. WHO Classification of Tumours Editorial Board (2019).

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed)* (2021) 74(9):790–9. doi: 10.1016/j.rec.2021.07.010

13. PROSPERO. *International prospective register of systematic reviews* (Accessed 25 July 2018).

14. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* (2013) 158(4):280–6. doi: 10.7326/0003-4819-158-4-201302190-00009

15. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. *J Clin Epidemiol* (2016) 70:106–10. doi: 10.1016/j.jclinepi.2015.08.013

16. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. *Considering resource Use rating Qual economic evidence. J Clin Epidemiol* (2013) 66(2):140–50. doi: 10.1016/j.jclinepi.2012.04.012

17. Tanabe T, Nishimaki T, Watanabe H, Ajioka Y, Akazawa K, Komukai S, et al. Immunohistochemically detected micrometastasis in lymph nodes from superficial esophageal squamous cell carcinoma. *J Surg Oncol* (2003) 82(3):153–9. doi: 10.1002/jso.10207

18. Chao YK, Yeh CJ, Chuang WY, Fan KH, Hsieh MJ, Chu Y, et al. Prognostic significance of immunohistochemically detected lymph node micrometastases in pT0N0 esophageal squamous cell carcinoma. *J Surg Oncol* (2009) 100(7):559–62. doi: 10.1002/jso.21362

19. Zingg U, Montani M, Busch M, Metzger U, Went P, Oertli D. Prognostic influence of immunohistochemically detected lymph node micrometastasis and histological subtype in pN0 oesophageal cancer. *Eur J Surg Oncol* (2009) 35(6):593–9. doi: 10.1016/j.ejso.2008.12.001

20. Doki Y, Ishikawa O, Mano M, Hiratsuka M, Sasaki Y, Kameyama M, et al. Cytokeratin deposits in lymph nodes show distinct clinical significance from lymph node micrometastasis in human esophageal cancers. *J Surg Res* (2002) 107(1):75–81. doi: 10.1006/jsre.2002.6506

21. Shiozaki H, Fujiwara Y, Hirai T, Matsubara H, Mori M, Nakamura T, et al. Clinical significance of immunohistochemically detected lymph node micrometastasis in patients with histologically node-negative esophageal carcinoma: A multi-institutional study. *Esophagus* (2007) 4(1):35–9. doi: 10.1007/s10388-006-0098-0

22. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* (2007) 8:16. doi: 10.1186/1745-6215-8-16

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj* (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

24. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract* (2008) 14(5):951–7. doi: 10.1111/j.1365-2753.2008.00986.x

25. Izbicki JR, Hosch SB, Pichlmeier U, Rehders A, Busch C, Niendorf A, et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. *N Engl J Med* (1997) 337(17):1188–94. doi: 10.1056/NEJM199710233371702

26. Komukai S, Nishimaki T, Watanabe H, Ajioka Y, Suzuki T, Hatakeyama K. Significance of immunohistochemically demonstrated micrometastases to lymph nodes in esophageal cancer with histologically negative nodes. *Surgery* (2000) 127 (1):40–6. doi: 10.1067/msy.2000.102754

27. Matsumoto M, Natsugoe S, Nakashima S, Sakamoto F, Okumura H, Sakita H, et al. Clinical significance of lymph node micrometastasis of pN0 esophageal squamous cell carcinoma. *Cancer Lett* (2000) 153(1-2):189–97. doi: 10.1016/s0304-3835(00)00374-8

28. Sato F, Shimada Y, Li Z, Watanabe G, Maeda M, Imamura M. Lymph node micrometastasis and prognosis in patients with oesophageal squamous cell carcinoma. *Br J Surg* (2001) 88(3):426–32. doi: 10.1046/j.1365-2168.2001.01687.x

29. Nakamura T, Ide H, Eguchi R, Hayashi K, Ota M, Takasaki K. Clinical implications of lymph node micrometastasis in patients with histologically node-negative (pN0) esophageal carcinoma. *J Surg Oncol* (2002) 79(4):224–9. doi: 10.1002/jso.10080

30. Xiao XW. Relationship between lymph node metastases in esophageal carcinoma and its prognosis. *Chi J Cancer Res* (2002) 14(4):297–301. doi: 10.1007/s11670-002-0065-9

31. Thompson SK, Ruszkiewicz AR, Jamieson GG, Sullivan TR, Devitt PG. Isolated tumor cells in esophageal cancer: implications for the surgeon and the pathologist. *Ann Surg* (2010) 252(2):299–306. doi: 10.1097/SLA.0b013e3181e61e15

32. Prenzel KL, Hölscher AH, Drebber U, Agavonova M, Gutschow CA, Bollschweiler E. Prognostic impact of nodal micrometastasis in early esophageal cancer. *Eur J Surg Oncol* (2012) 38(4):314–8. doi: 10.1016/j.ejso.2012.01.007

33. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* (2011) 64(4):383–94. doi: 10.1016/j.jclinepi.2010.04.026

34. Schunemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol* (2019) 111:105–14. doi: 10.1016/j.jclinepi.2018.01.012

35. MB AAmerican Joint Committee on Cancer. *AJCC Cancer Staging Manual. 8th edn.* New York: Springer-Verlag (2017).

36. Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer* (1999) 86(12):2668–73.

37. Xu X, Zheng G, Zhang T, Zhao Y, Zheng Z. Clinical Significance of Metastasis or Micrometastasis to the Lymph Node Along the Superior Mesenteric Vein in Gastric Carcinoma: A Retrospective Analysis. *Front Oncol* (2021) 11:707249. doi: 10.3389/fonc.2021.707249

38. Buskens CJ, Ten Kate FJ, Obertop H, Izbicki JR, van Lanschot JJ. Analysis of micrometastatic disease in histologically negative lymph nodes of patients with adenocarcinoma of the distal esophagus or gastric cardia. *Dis Esophagus* (2008) 21 (6):488–95. doi: 10.1111/j.1442-2050.2007.00805.x

39. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. *World J Gastrointest Oncol* (2014) 6(5):112–20. doi: 10.4251/wjgo.v6.i5.112

40. Zhang H, Yan X, Yang YS, Yang H, Yuan Y, Tian D, et al. The Least Nodal Disease Burden Defines the Minimum Number of Nodes Retrieved for Esophageal Squamous Cell Carcinoma. *Front Oncol* (2022) 12:764227. doi: 10.3389/fonc.2022.764227

41. Wu LL, Zhong JD, Zhu JL, Kang L, Huang YY, Lin P, et al. Postoperative survival effect of the number of examined lymph nodes on esophageal squamous cell carcinoma with pathological stage T1-3N0M0. *BMC Cancer* (2022) 22(1):118. doi: 10.1186/s12885-022-09207-x

42. Yamasaki M, Yasuda T, Yano M, Hirao M, Kobayashi K, Fujitani K, et al. Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). *Ann Oncol* (2017) 28(1):116–20. doi: 10.1093/annonc/mdw439

43. Shiraishi O, Yamasaki M, Makino T, Motoori M, Miyata H, Shinkai M, et al. Feasibility of Preoperative Chemotherapy with Docetaxel, Cisplatin, and 5-Fluorouracil versus Adriamycin, Cisplatin, and 5-Fluorouracil for Resectable Advanced Esophageal Cancer. *Oncology* (2017) 92(2):101–8. doi: 10.1159/000452765