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Prognostic value of lymph node ratio in cervical cancer

A meta-analysis

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Abstract:

Background: The role of the lymph node ratio (LNR) in the existing tumor node metastasis classification system should be verified as one of the prognosis prediction factors. This work evaluated LNR's performance in predicting cervical cancer (CC) prognosis through a meta-analysis.

Method: Related studies were retrieved from the Cochrane Library, EMBASE, and PubMed databases. The language was restricted to English. The combined hazard ratios (HRs) were utilized to analyze the prognostic value of LNR.

Results. Our study included 8 articles with 3325 subjects published after 2015. Based on our analysis, high LNR was the adverse prognostic factor for overall survival (OS, HR = 1.45; 95% CI = 1.23–1.73; *P* = .238) and disease-free survival (DFS, HR = 2.69; 95% CI = 1.98–3.66; *P* = .597) among the CC cases. Furthermore, as revealed by subgroup analysis, in CC patients, median LNR of about 0.0625 and 0.066 served as the prominent risk factor for DFS and OS.

Conclusions: The current work illustrates that elevated LNR is related to the dismal prognosis of CC. More well-designed clinical studies are warranted for assessing whether LNR is a factor independently predicting the prognosis of CC.

Abbreviations: CC = cervical cancer, CIs = confidence intervals, DFS = disease-free survival, HRs = hazard ratios, LNM = lymph node metastasis, LNR = lymph node ratio, OS = overall survival, P = prospective, ROC = receiver operating characteristic, R = retrospective.

Keywords: cervical cancer, lymph node ratio, meta-analysis, prognosis

1. Introduction

Cervical cancer (CC) ranks fourth among cancers in terms of morbidity. It also accounts for the fourth most frequent factor leading to cancer-associated mortality in females, causing 604,000 newly diagnosed cases and 342,000 death cases globally in 2020.[1] Surgical resection is the preferred treatment for patients based on the International Federation of Gynecology and Obstetrics stages ≤ IIA, whereas chemoradiation is recommended for patients belonging to higher stages.[2,3] The increased level of removed lymph nodes affects the metastatic lesion number in line with standardized pN classification. Lymph node metastasis (LNM) is an independent predictor of post-operative recurrence in CC patients and the detection lymph node involvement is crucial to define the extent of the irradiation field and to personalize specific treatment protocols.[4,5] It also possibly affects the altered tumor node metastasis classification stage of the tumor and impacts the accuracy of prognosis prediction.[6,7] LNM represents the most significant factor affecting the prognosis of CC.[8,9] In addition, the lymph node ratio (LNR), which indicates the ratio of LNM number to the overall dissected lymph node number, is a potent factor predicting the prognosis in some cancers.[10–12]

Nonetheless, the survival prediction of CC using LNR remains controversial. In some studies, a higher LNR is reported to predict poor CC prognosis,[13–15] but no such relation was detected in other studies like Giorgio et al(2019).[16] Therefore, this meta-analysis is carried out to evaluate the significance of LNR in predicting CC survival.

2. Material and Methods

2.1. Registration

The present study was reported in line with the preferred reporting items of the systematic review and meta-analysis guidelines.[17] The analysis was performed based on previous literature, so the patient consent and ethical approval were waived.

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2.2. Study search strategy and inclusion criteria

2.2.1. Search strategy PubMed, the Cochrane Library, and Embase databases were systemically searched (2015–2021) with keywords such as ("nodal ratio" OR "node ratio") AND ("cervical cancer" OR "cervical neoplasm." This search process was repeated till no novel related study was identified. Also, reference lists from selected studies were checked to determine possible eligible articles. Finally, 2 reviewers were responsible for evaluating studies according to our pre-determined criteria.

2.2.2. Study selection At first, keywords were utilized to search studies, the titles and abstracts were evaluated to eliminate the unrelated studies. Second, the remaining eligible studies were selected based on our study inclusion and exclusion criteria. The study inclusion criteria involved cases that had a pathological diagnosis of CC; the outcomes were overall survival (OS) and disease-free survival (DFS), and hazard ratios (HRs) together with appropriate 95% confidence intervals (CIs) were available or could be determined from the original data. Additionally, studies conforming to the following criteria were eliminated: meeting summaries, letters, posters, commentary articles, and those without available outcomes or results.

2.3. Data extraction

Two reviewers were responsible for data collection, and any disagreement was solved through negotiation or the opinion from a third reviewer. The data characteristics included first author, publication year, study design, study population origin, patient number, neoadjuvant treatment, tumor stage, threshold producing method, cancer-specific outcomes, thresholds of LNR, and HRs with 95% CIs. The present meta-analysis mainly explored the prognostic significance of LNR among CC cases.

2.4. Data processing and statistical analysis

We focused on analyzing the relation between LNR and survival time among CC cases. Combined HRs with 95% CIs were utilized for assessing CC survival based on the identical method adopted in our prior work.[18] DFS referred to the duration between initial therapy and disease progression dates, which indicated the duration following successful treatment without disease effect or symptom.[19] OS refers to the period between the original therapy date and the all-cause mortality date.[19,20] Data on multivariate HRs and 95% CIs were obtained from the enrolled studies, while for the unavailable multivariate HRs, the corresponding univariate HRs were retrieved. For unavailable univariate and multivariate HRs, the method by Parmar et al(2016)[21]was utilized for estimating HRs. The relevant variance was measured according to Kaplan–Meier survival curve analysis visualized through the Engauge Digitizer (version 9.4). High LNR combined with HR > 1 and < 1 indicated poor and favorable patient survival. The I^2 statistic and the Chi-square Q test were utilized to measure the statistical heterogeneity. $I^2 > 50\%$ and $P < .05$ indicated significant heterogeneity, so the random-effects model was used; otherwise, the fixed-effects model was adopted. Statistical analyses were undergone using STATA version 12.0 (STATA Corp., College Station, TX) and RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). The Egger's and Begg's tests were used to assess the bias using STATA version 12.0. A P value <.05 stood for statistical significance.

3. Results

3.1. Study retrieval results

After searching PubMed, Embase, and Cochrane Library databases, 995, 2274, and 0 studies with 3269 patients were obtained separately. Then, after removing duplicates and meeting summaries, 72 eligible studies were selected. Then, 48 studies were further removed because of undesirable study design (n = 28), case reports (n = 12), irrelevant to CC (n = 6), and unavailable reliable data (n = 13). At last, 8 eligible studies involving 3325 patients published during 2015 to 2021 were included in the meta-analysis[7,13–16,22–24] (Fig. 1).

3.2. Study features

The studies were retrospective (R) and published during 2015 to 2021, and the sample size ranged from 55 to 2269. There were 5 studies from Asia (2 from China, 1 from Turkey, 2 from Korea), 1 from Italy, 1 from Germany, and 1 from the USA. All the studies examined stage I to III CC patients. In addition, 6 studies analyzed DFS, and 7 examined OS. The follow-up period ranged from 13.2 to 68 months, with one or more histological features and treatments were reported. The LNR cutoff points used in the studies ranged from 0.01 to 0.2. Table 1 provides the information regarding the included articles, including histology and treatment.

3.3. Study quality assessment

The present analysis assessed the quality of the included studies using the CRITICAL APPRAISAL OF PROGNOSTIC STUDIES (https://www.cebm.net/wpcontent/uploads/2018/11/Prognosis.pdf; Fig. 2). All the included studies were evaluated with caution. The studies were R, and most of them were of high quality. One was a high-risk study, whereas 3 had unclear bias risk due to non-randomized or non-blinded study design. One study was at a high risk of bias due to the aspect of the prognostic factor (follow-up length measurement). At the same time, one had an unclear risk of bias, possibly due to the short median follow-up and the incomplete recurrence data. Many included studies were well-depicted and objectively reported adverse reactions.

3.3.1. Primary outcome: DFS Five articles examined DFS and LNR. The study by Peter et al(2020).[22] was regarded as 2 separate works because it utilized 2 data sets relating DFS with LNR. After combining HRs, a high LNR was indicative of dismal DFS. The fixed-effects model did not show any significant difference (HR = 2.69; 95% CI = 1.98–3.66; $P = .597$; $I^2 = 0.0\%$) (Fig. 3A), or between-study heterogeneity. A sensitivity analysis was performed to predict the influence of each study on the combined HRs. There was no significant alteration after omitting each study (Fig. S1A, http://links.lww.com/MD/H391), indicating that the significance of the results was maintained. The Funnel plots did not reveal any distinct publication bias (Fig. 4A). The potential publication bias was examined by Begg's and Egger's tests, which depicted obvious publication bias ($P = .016$, $P = .012$) (Fig. S2A, http://links.lww.com/MD/H392).Trimming and filling analysis was performed to ensure that the combined HRs were reliable and obtain funnel plots subsequently. Funnel plots revealed the symmetry, with no distinct alteration of effect size before and after adding the hypothesis study (HR = 2.264; 95% CI 1.932–3.563) (Fig. 4B), which suggested that LNR was significantly associated with DFS. Further, subgroup analyses were performed through stratification based on region, cutoff, and threshold methods (Table 2). According to the subgroup analysis stratified based on region, the HR of 4 Asian studies was 2.75 (95% CI: 1.82–4.15; $P = .230$), the 2 European studies exhibited significant associations (HR = 2.48; 95% CI = 1.43–4.32), and the single American study also demonstrated distinct associations (HR = 2.97; 95% CI = 1.26–7.01). For the 2 studies that adopted the threshold method based on the ROC curve, their HR was 6.55 (95%CI: 2.55–16.81; $P = .643$), while the 5 studies that adopted the method-based thresholds,

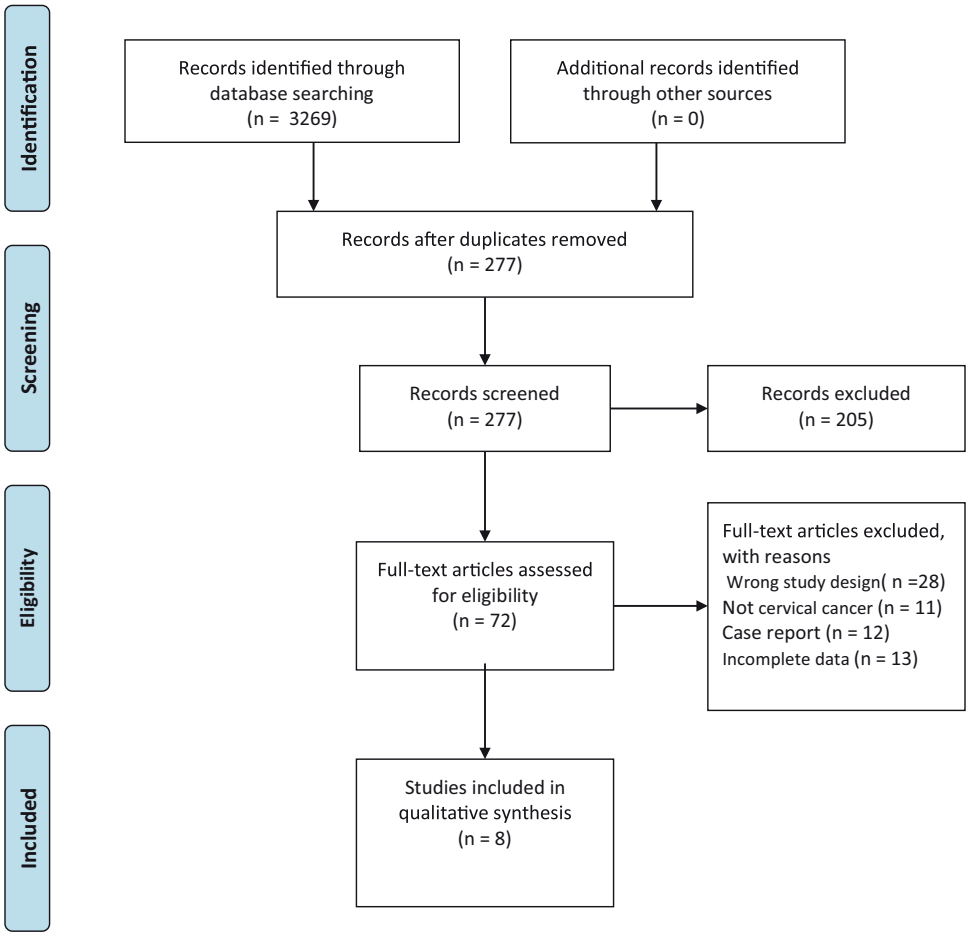

Figure 1. Flow diagram of study selection.

Table 1

Enrolled study features.

Study	Yr	Country	Study design	Sample size	Neoadjuvant therapy	Tumor stage	Cutoff generating approach	Cancer-specific outcomes	Cut off value of outcomes
Yoon Hee Leeet al.	2021	Korea	R	260	radical hysterectomy.	IB1 IB2 IIB IIA1 IIA2	ROC	DFS, OS	0.0625
Se Ik Kimet al.	2021	Korea	R	55	CCRT followed by chemotherapy	IB1-IIA2	ROC	DFS	0.0831
Koray Aslanet al.	2020	Turkey	R	185	systematic pelvic and para-aortic lymphadenectomy Adjuvant treatment	IIIC	Others	DFS,OS	0.05
Peter Widschwendter et al	2019	Germany	R	86	surgery Chemotherapy Radiotherapy Chemoradiation	IB1–IIB	Others	DFS, OS	0.010(DFS),0.066(OS)
Giorgio Boganiet al.	2019	Italy	R	177	adjuvant radiation and chemotherapy	IIIC	Others	OS	-
chen liet al.	2016	China	R	198	Surgery radiotherapy; chemotherapy;, chemoradiotherapy.	IB1–IIB	Others	DFS,OS	0.20
Juan Zhouet al.	2016	China	R	2269	Surgery radiotherapy	I -II	ROC	OS	0.12
Nicole D. Fleming et al	2015	USA	R	95	Surgery radiotherapy	IA -IIB	Others	DFS,OS	0.066(DFS),0.076(OS)

CCRT = concurrent chemoradiation therapy, DFS = disease-free survival, OS = overall survival, R = retrospective, ROC = receiver operating characteristic.

their HR was 2.42 (95%CI: 1.74–3.35; $P = .968$). Depending on the threshold, patients were classified as 2 subgroups based on median LNR, involving high (≥0.0625) or low (<0.0625) LNR groups. As revealed by the analysis, the HRs of high and low LNR threshold subgroups were 3.28 (95% CI: 2.05–5.23, $P = .376$) and 2.31 (95% CI: 1.53–3.48, $P = .868$), respectively.

3.3.2. Primary outcome: OS. Five articles examined OS and LNR. The study by Peter et al[22] had 2 individual parts because it enrolled 2 data sets associating OS with LNR. After combining the HRs, a higher LNR indicated a dismal OS. The fixed-effects model did not observe any significant difference (HR = 1.45; 95% CI = 1.23–1.73; $P = .238$; $I^2 = 24.0\%$) (Fig. 3B), without

Figure 2. (A) Graph exhibiting bias risk judgments on bias risk items through reviewers displayed percentage among all included studies. (B) Risk of bias summarization: Risk of bias item judgment by reviewers for all the included studies.

any between-study heterogeneity. A sensitivity analysis was conducted for predicting the impact of individual studies on the combined HRs. However, the results remained unchanged after successively eliminating individual studies (Fig. S1B, http://links.lww.com/MD/H391), indicating the reliability of our results. The funnel plots did not reveal any distinct publication bias (Fig. 4C). Begg's and Egger's tests were also performed for evaluating potential publication bias. A distinct publication bias was detected by the Egger's test (P = .016) (Fig. S2B, http://links.lww.com/MD/H392) but not by Begg's test (P = .386). Consequently, this work carried out trimming and filling analysis to ensure the reliability of combined HRs and the acquisition of symmetry in

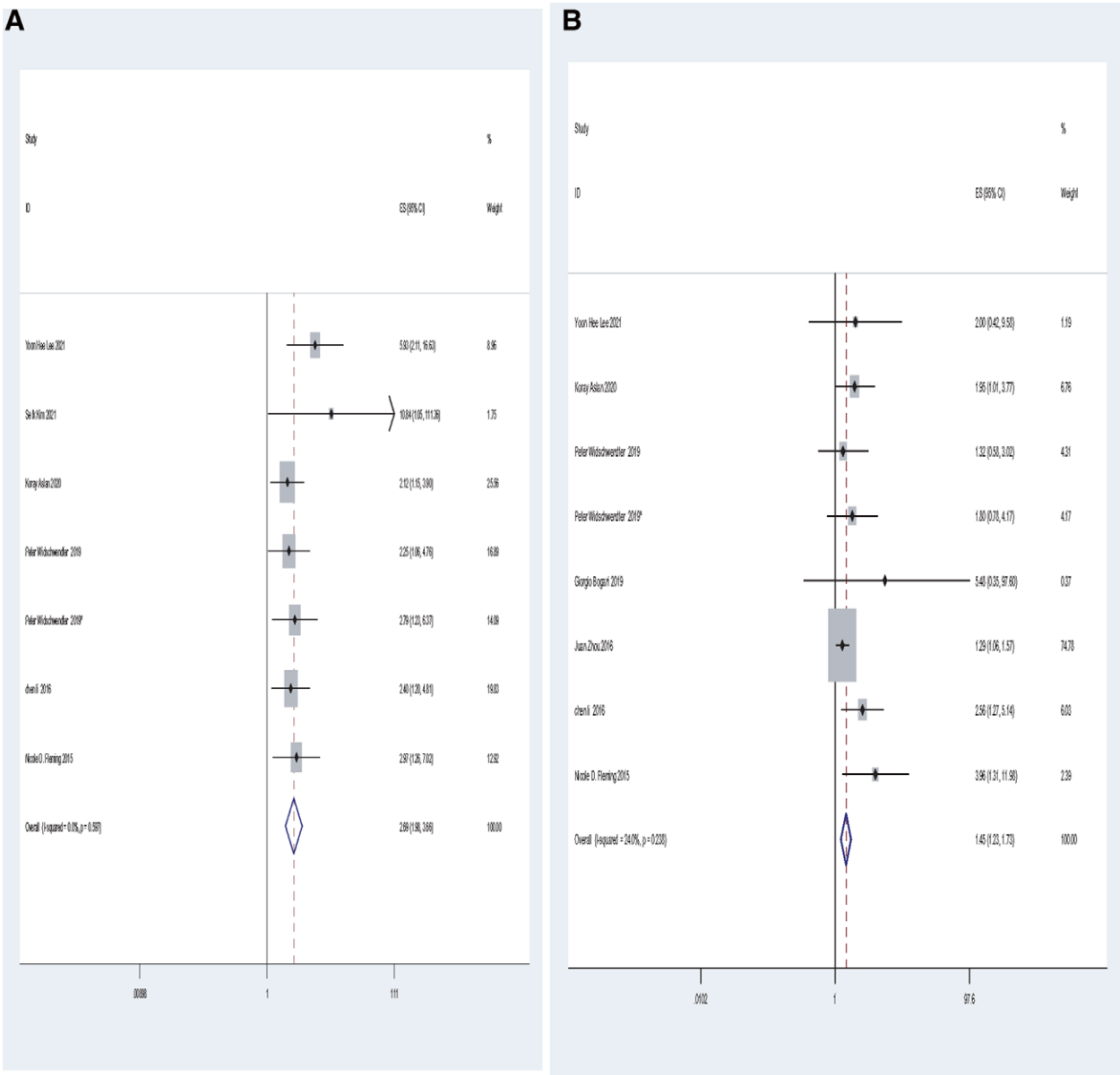

Figure 3. Forest plots showing HRs of DFS and OS as a function of LNR (A, DFS; B, OS). Heterogeneity was detected using the Chi-square test, where $P < .05$ indicated distinct heterogeneity between studies. Horizontal lines = 95% CI (Fixed: fixed-effects model; Horizontal lines = 95% CI. Rhombus = estimates with corresponding 95% CI. Squares = individual study point estimates). DFS = disease-free survival, LNR = lymph node ratio, OS = overall survival.

funnel plots. Afterward, funnel plots revealed symmetry, without any distinct alteration of results before or after the hypothesis study (HR = 1.350; 95% CI 1.147–1.590) (Fig. 4D), indicating that LNR was significantly related to DFS. Furthermore, a subgroup analysis was conducted through stratification based on region, cutoff, and threshold methods (Table 2). As revealed by subgroup analysis stratified based on region, the HR of 4 Asian studies was 1.40 (95% CI: 1.17–1.68; $P = .191$), and the single American study also demonstrated distinct associations (HR = 3.96; 95% CI = 1.31–11.98). However, the 2 European studies did not exhibit significant correlations (HR = 1.62; 95% CI = 0.91–2.88). The HR of the 2 studies that adopted the threshold method based on the ROC curve analysis was 1.30 (95%CI: 1.06–1.58; $P = .583$), while the 6 studies that adopted other method-based thresholds were 2.09 (95%CI: 1.48–2.97; $P = .637$). Depending on the threshold, patients were classified as high (≥0.066) or low (<0.066) LNR subgroups based on the median LNR value. After subgroup analysis, HRs of high and low LNR threshold subgroups were 1.41 (95% CI: 1.18–1.69, $P = .120$) and 1.96 (95% CI: 1.07–3.59, $P = .975$), respectively. The study of Giorgio et al[16] did not give the cutoff value of LNR, and HR was 5.48 (95%CI: 1.18–1.69).

4. Discussion

Lymph node involvement within CC could have an important role. Some studies suggest that positive lymph node involvement negatively affects patient prognosis, irrespective of the stage the patient is diagnosed.[25,26] For illustrating the importance of nodal status, the latest Federation of Gynecology and Obstetrics 2018 classification system has listed nodal disease (pathological or radiological) into the classification, which significantly upstages CC confined to uterine cervix from stage I to stage III.[27] LNM is an independent predictor and post-operative recurrence in CC patients.[28–30] Furthermore, relevant meta-analyses suggest the feasibility of using LNR in predicting cancer survival among oral squamous cell carcinomas, rectal carcinoma, and non-small cell lung carcinoma.[31–33]

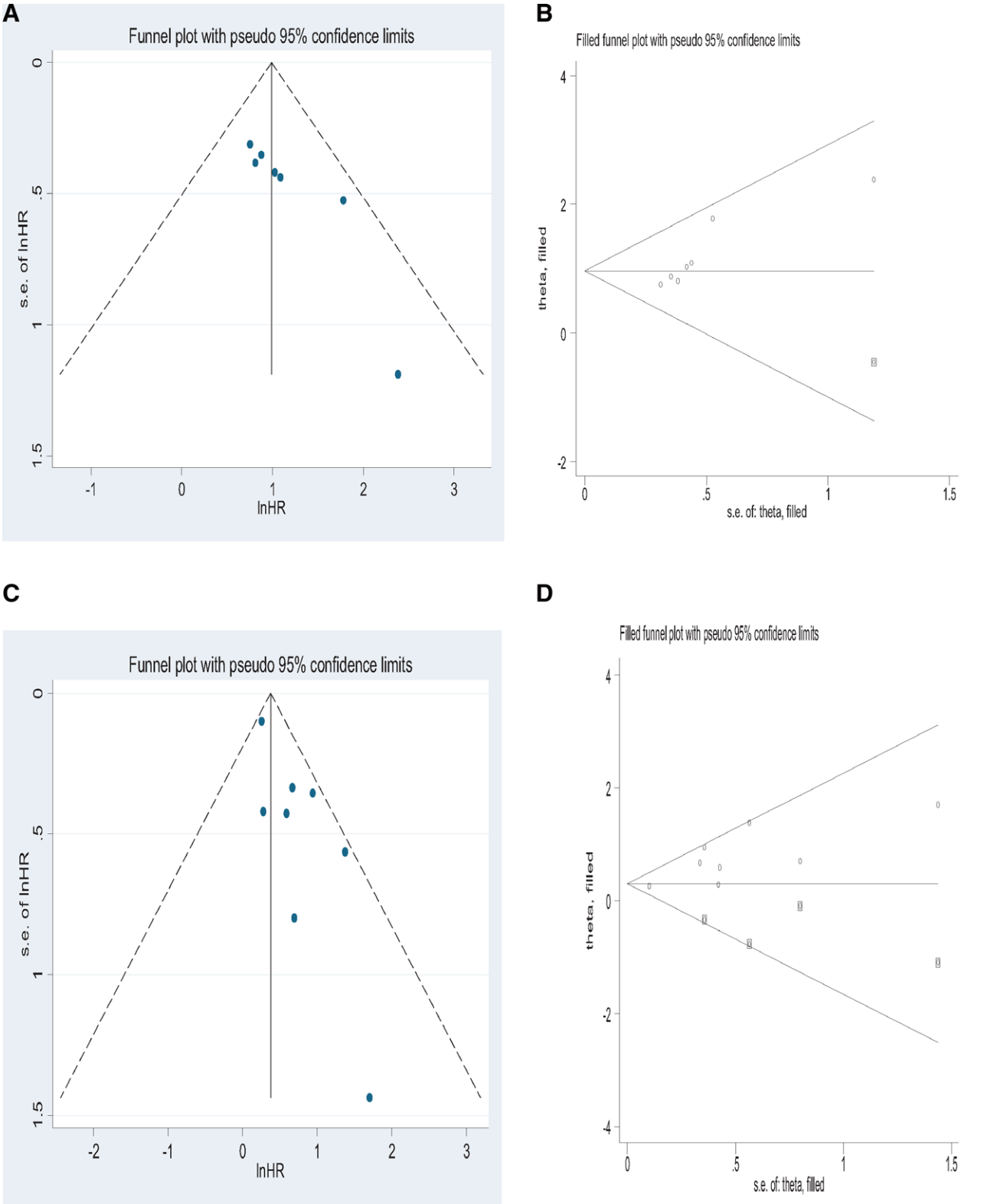

Figure 4. Funnel plots with no (A) or with (B) trimming and filling analysis on DFS; Funnel plots with no (C) or with (D) trimming and filling analysis on OS. Pseudo, 95% CI, was also determined for producing funnel plots and the relevant 95%CI for the specific standard error (SE). DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

There is little information regarding the burden of LNR within CC. CC cases may benefit when LNR values can predict their DFS and OS. LNR is a superior measuring tool for prognosis since it combines information regarding neck dissection type with the burden of locoregional metastasis, thereby integrating the merits of the 2 parameters and overcoming the demerits.[11] To the best of our knowledge, the present meta-analysis has first illustrated the significance of LNR in predicting CC prognosis. The current meta-analysis involving 8 eligible studies described the relation of CC with LNR. Based on our combined analyses,

Table 2

The subgroup of DFS and OS of LNR.

Endpoint	Factor	No. of studies	Heterogeneity test (I^2, P)	Effect model	HR	95%CI of HR	Conclusion
DFS	region						
	Asian	4	30.3, .230	fixed	2.75	1.82,4.15	significant
	Europen	2	0.0, .705	fixed	2.48	1.43,4.32	significant
	American	1	-,-	-	2.97	1.26,7.01	significant
	Cutoff method						
	ROC	2	0.0, .643	fixed	6.55	2.55,16.81	significant
	Others	5	0.0, .968	fixed	2.42	1.74,3.35	significant
	Threshold						
	≥0.0625	4	3.2, .376	fixed	3.28	2.05,5.23	significant
	<0.0625	3	0.0, .868	fixed	2.31	1.53,3.48	significant
OS	region						
	Asian	4	36.8, .191	fixed	1.40	1.17,1.68	significant
	Europen	3	0.0, .601	fixed	1.62	0.91,2.88	insignificant,-
	American	1	-,-	-	3.96	1.31,11.98	significant
	Cutoff method						
	ROC	2	0.0, .583	fixed	1.30	1.06,1.58	significant
	Others	6	0.0, .637	fixed	2.09	1.48,2.97	significant
	Threshold						
	≥0.066	5	45.4, .120	fixed	1.41	1.18,1.69	significant
	<0.066	2	0.0, .975	fixed	1.96	1.07,3.59	significant
	-	1	-,-	-	5.48	1.18,1.69	significant

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LNR = lymph node ratio, OS = overall survival, *P* = prospective, R = retrospective, ROC = receiver operating characteristic.

a high LNR was indicative of dismal DFS (HR = 2.69; 95% CI = 1.98–3.66; $P = .597$; $I^2 = 0.0\%$) and OS (HR = 1.45; 95% CI = 1.23–1.73; $P = .238$; $I^2 = 24.0\%$) in CC. Additionally, there was low inter-study heterogeneity, thus, enhancing the robustness of the results. Although there might be potential publication bias among our enrolled articles, we found that the bias did not affect our final analysis after trimming and filling analysis. Sensitivity analysis also strengthened results.

No distinct heterogeneity was observed in LNR while predicting DFS ($I^2 = 0.0\%$; $P = .597$). Though Begg's and Egger's tests detected publication bias of LNR, the funnel plots showed symmetry following trimming and filling, with no distinct variation of results (HR = 2.264; 95% CI 1.932–3.563). However, certain confounding factors affected the relationship between LNR and DFS. Therefore, this work conducted subgroup analysis through stratification according to region, cutoff, and threshold method. Based on the subgroup analysis stratified according to region, Asian and European groups showed statistical significance, with the absence of heterogeneity. The single American study examined DFS and LNR and found that DFS was significantly related to LNR. Secondly, this study was divided into 2 subgroups by the threshold method, including ROC ($I^2 = 0.0\%$, $P = .643$) and other ($I^2 = 0.0\%$, $P = .968$) groups, which revealed statistical significance without any heterogeneity. Additionally, there were different threshold values among different studies. Therefore, all the studies were classified into 2 groups according to the median of 0.0625. There was statistical significance between the threshold above 0.0625 ($I^2 = 3.2\%$, $P = .376$) and the threshold less than 0.0625 ($I^2 = 0\%$, $P = .868$), without any heterogeneity.

Likewise, no evident heterogeneity was measured in OS to predict LNR ($I^2 = 24.0\%$; $P = .238$). Moreover, the Egger's ($P = .016$) test revealed significant publication bias, which was not detected by Begg's test ($P = .386$). Consequently, trimming and filling analysis was performed to ensure the reliability of combined HRs and the symmetry of funnel plots (Fig. 4), without any significant alteration of results (HR = 1.350; 95% CI 1.147–1.590) (Fig. 4). We also performed subgroup analysis through stratification according to region, threshold, and cutoff method. As revealed by subgroup analysis based on region, the American and Asian locations showed significance, indicating that OS was significantly related to LNR. However, the European location (HR = 1.62; 95% CI 0.91–2.88) did not reveal any statistical significance because it was affected by the small sample size, thereby inducing low statistical efficiency. In addition, it had poor statistical power because 3 articles examined DFS and LNR. Therefore, more studies are warranted for investigating the significance of LNR in predicting OS in CC cases. Secondly, studies were divided based on threshold into 2 subgroups, ROC ($I^2 = 0.0\%$, $P = .583$) and Other ($I^2 = 0.0\%$, $P = .637$) groups exhibited statistical significance, without any heterogeneity. Thirdly, different studies had various optimal thresholds. Therefore, studies were classified into 2 groups based on the median of 0.066. Fourthly, multiple thresholds for our included studies were divided into 2 groups, threshold above 0.066 ($I^2 = 45.4\%$, $P = .120$) and threshold less than 0.0625 ($I^2 = 0\%$, $P = .975$) exhibited statistical significance without any heterogeneity.

LNR was also the factor predicting DFS among CC cases with a threshold higher than 0.0625. Nonetheless, our study failed to determine the best threshold for LNR. The differences in thresholds, histological approaches, and delineation strategies among the various studies could impact the event occurrence and patient prognosis. More investigations with information derived from single patients are warranted for determining the best threshold and delineation strategies to assess the prognostic significance of LNR.

Moreover, enrolled study quality should be considered because it accounted for one of the limitations in this study. First, the Cochrane risk bias tool assessed those enrolled studies, and high-quality works were enrolled, but some did not include detailed patient information. Furthermore, all the studies were R. Therefore, more prospective research combining CC survival and LNR should be conducted. Second, due to CC heterogeneity, the present study enrolled cases at diverse stages, histological grades, and those receiving different treatments, which could have impacted event occurrence and patient survival. Third, only English language-based studies were enrolled, possibly leading to language bias. Fourth, published literature was enrolled in database searching, which could induce publication bias. Nonetheless, publication bias assessment revealed the reliability of the results.

5. Conclusion

Although diverse approaches were adopted for CC cases of various subtypes, this meta-analysis indicates that an elevated LNR was related to the poor prognosis in CC patients. Meanwhile, the cutoff values 0.0625 and 0.066 could be suitable to predict DFS and OS of CC. However, further high-quality research with a larger sample size should be performed to verify the reliability of our results.

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All authors have contributed significantly. All authors are in agreement with the content of the manuscript.

Author contributions

Conceptualization: Haixia Cui, Weibo Wen, Lan Liu.
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Formal analysis: Haixia Cui, Lan Liu.
Funding acquisition: Weibo Wen.
Investigation: Weibo Wen, Xiangdan Li, Lan Liu.
Methodology: Weibo Wen, Xiangdan Li, Lan Liu.
Project administration: Yuan Huang, Weibo Wen, Xiangdan Li, Lan Liu.
Resources: Yuan Huang, Weibo Wen, Xiangdan Li, Dongyuan Xu.
Software: Yuan Huang, Weibo Wen, Xiangdan Li, Dongyuan Xu.
Supervision: Yuan Huang, Xiangdan Li, Dongyuan Xu.
Validation: Yuan Huang, Dongyuan Xu.
Visualization: Yuan Huang, Dongyuan Xu.
Writing – original draft: Yuan Huang, Dongyuan Xu.
Writing – review & editing: Yuan Huang, Dongyuan Xu.

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