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Review Article

Prognostic value of cervical lymph node metastasis ratio in Asian papillary thyroid carcinoma 5-year relapse-free survival: a meta-analysis

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Abstract: Cervical lymph node metastasis occurs frequently in papillary thyroid carcinoma. We aim to analyze the predictive value of cervical lymph node metastasis ratio (LNR) in papillary thyroid carcinoma 5-year relapse-free survival in Asian. Databases (Web of Science, PubMed, EMBASE, OVID, Elsevier Science Direct, and ProQuest) were searched to get the related articles. General data, cut-off ratio of LNR, five years of disease-free survival ratio and relapse-free survival ratio at different LNR cut-off values were obtained directly from included literatures and analyzed by diagnostic meta-analysis. Deeks' funnel plot asymmetry analysis was done to identify the publication bias. A total of 3880 Asian papillary thyroid carcinoma (PTC) patients from 7 articles were included. The sensitivity, specialty, and Diagnostic Odds Ratio combined values of LNR were 0.77 [0.67, 0.85], 0.76 [0.62, 0.87], and 10.85 [5.41, 21.77] respectively. The AUROC value of LNR was 0.83 [0.80, 0.86]. Compared with the fixed probability (20%) in preliminary experiments, the positive likelihood ratio (PLR) increased to 45%, and the negative likelihood ratio (NLR) reduced to 7%. No publication bias was found by Deeks' test. In conclusion, LNR can be used as a moderate predictor in PTC 5-years relapse-free survival for Asian.

Keywords: Lymph node metastasis ratio (LNR), papillary thyroid carcinoma (PTC), prognostic value, 5-year relapse-free survival (5-RFS), meta-analysis

Introduction

According to the GLOBALCAN data, about 2.1% of the diagnosed cancer worldwide is thyroid cancer [1]. As the main endocrine cancer, the incidence of thyroid cancer has continuously increased all over the world recent years [2, 3]. Usually, depending on the different pathological characteristics, thyroid carcinoma can be classified into four subtypes, papillary, follicular, medullary, and anaplastic thyroid cancer [4]. Papillary thyroid carcinoma (PTC), the most common kind of thyroid cancer, accounts for more than 80% of thyroid cancer [2, 5]. Though it has low malignancy and comparatively positive prognosis, the clinical manifestations of PTC is complex and diverse [2, 6]. Ten percent [7] of PTC patients may still be suffered with local recurrent and lymph node metastasis by which may even cause death [8]. Good predictor is indeed for providing appropriate suggestions to improve the PTC patients' postoperative relapse-free survival (RFS). Factors affecting PTC patients' postoperative relapse-free survival (RFS) varied, including TNM stage, infiltration depth, type of radical surgery, presence of cervical lymph node metastasis, isotope therapy after surgery, etc [9]. It was shown that the survival of patients with thyroid cancer was adversely affected by cervical lymph node metastases based on the Surveillance, Epidemiology, and End Results (SEER) database [10]. Furthermore, it was also reported by clinical studies that the postoperative survival of PTC patients was closely related with the metastasis cervical lymph node ratio (LNR). PTC patients with higher LNR always end up with a worse survival situation. By collecting the relevant data of LNR and postoperative relapse-free survival number for five years, then using diagnose Meta-analyses method, we aim to analyze the value of LNR in predicting

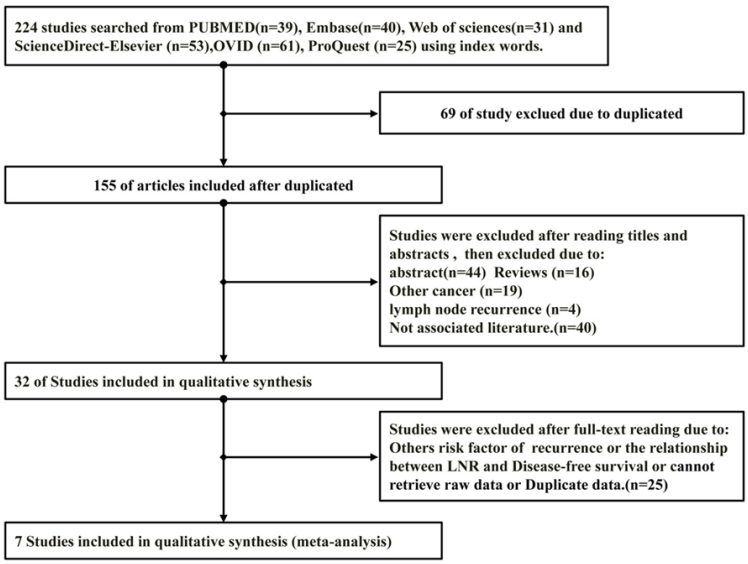

Figure 1. The process of study selection for the meta-analysis.

PTC patients' postoperative 5-year relapse-free survival (5-RFS).

Materials and methods

Search strategy and literatures selection

Databases (Web of Science, PubMed, EMBASE, OVID, Elsevier Science Direct, and ProQuest) were searched using the terms ("thyroid neoplasms" OR "thyroid cancer" OR "thyroid carcinoma" OR "carcinoma of thyroid), ("lymph nodes ratio" OR "lymph node ratio" OR "ratio of metastatic LN" OR "ratio of metastatic LNs" OR "LN ratio" OR "lymph nodes (LN) ratio" OR "lymph node (LN) ratio" OR LNR), and ("replase free survival" OR RFS OR "5-RFS" OR "Prognostic or Recurrence or survival" OR DFS). Manual searches were also conducted by reviewing the references of publications. The publications included were from inception to July 26th 2016. A total of 224 articles were searched using medical subject headings (MeSH) combined with text words mentioned above.

The retrieved articles were screened according to include and exclude criteria. Include criteria: (1) well designed random research or case-control study; (2) the object was about papillary thyroid carcinoma; (2) the primary treatment was studies about Asian. Exclude criteria: (1) published duplicate data; (2) abstract, comment, review and editorial reviews, guidelines, or case reports; (3) no sufficient data were reported, or in which relevant raw data could not be abstracted; (4) cell, animal or simulations experiments studies. The selection of retrieved studies was finished by two investigators according to the inclusion criteria listed above. Disagreements were resolved by discussion with the third investigator.

Data extraction and quality assessment

The quality assessment and data extraction were also done by two independent researchers and discussed with the third people when there were disagreements.

The following characteristics were extracted from each study: first author, year of publication, general data of the patients (country, enrolled year, total number, average age, and gender ratio), and the cut-off ratio of LNR. The five years of disease-free survival ratio and relapse-free survival ratio at different LNR cut-off values were obtained directly from included literatures. Engauge Digitizer V4.1 software was used to get these data from the survival curves when no actual numerical was given or could not contact the authors of included articles for study data by e-mail.

To assess the quality of each included study, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [11, 12]. Four domains, including patient selection, index test, reference test flow of patients through the study, and the timing of the index and reference tests (flow and timing), were used to assess applicability and evaluate the risk of bias. A standardized table and figure, recommended by the QUADAS-2 official website, were used to display the summarized results of the QUADAS-2, with numbers of studies observed with "high risk", "high risk", or "unclear risk" of bias or applicability concerns for each domain.

Table 1. Characteristics of the included studies and patients' baseline demographics

The first mane	Published year	Study design	Country	The patient collect year	Disease	Cut-off value	Underwent therapy	Patients	Male	Age	Follow-up
Jeon [14]	2013	retrospective	Korea	1995-2005	PTC	0.4	TT + rCND	295	10%	44.4	8 (5.8-10.0) years
Cho [15]	2014	retrospective	Korea	2005-2006	PTC	0.2	TT or less than TT	336	8%	48	5.3 ± 2.1 years
Ryu [16]	2014	retrospective	Korea	2000-2006	PTC	0.65	TT + bilateral pCND	283	24%	44.8	78 (63-137) months
Lee [17]	2015	retrospective	China	2006-2011	PTC	0.26	TT + pCND	136	29.40%	51	62 (33-90) months
Park [18]	2016	retrospective	Korea	2004-2009	PTC	0.22	TT + bCND	212	19%	46	80 (6-134) months
Lee [19]	2016	retrospective	China	1985-2009	PTC	0.4	TT + CCND	1654	12.50%	44.6	107.1 (72-286) months
						0.5	TT + MRND	640			
Lee [20]	2016	retrospective	China	1996-2010	PTC	0.42	TT + pCND	324	23.50%	46.3	63 (14-181) months

TT + pCND, total thyroidectomy with prophylactic central neck dissection; TT + rCND, total thyroidectomy with routine central neck dissection; TT + bCND, total thyroidectomy with bilateral central neck dissection; TT + cCND, total thyroidectomy with central compartment node dissection; TT + mRND, total thyroidectomy and CCND with modified radical neck dissection.

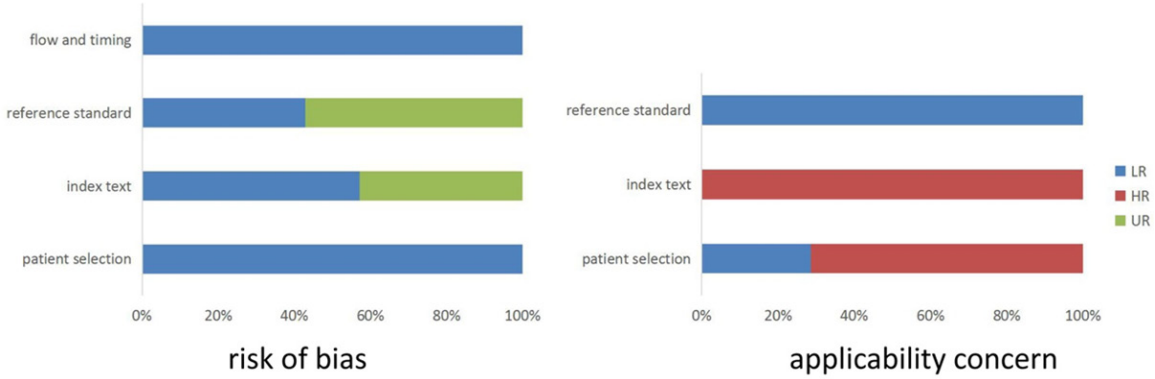

Figure 2. The quality evaluation results LC: low concern; HC: high concern; UC: unclear concern.

Table 2. Summary of review authors' ratings of bias risk and applicability concerns for each study

Study	Risk of bias				Applicability concern		
	Patient selection	Index text	Reference standard	Flow and timing	Patient selection	Index text	Reference standard
Cho (2014) [15]	LC	LC	UC	LC	HC	HC	LC
Jeon (2013) [14]	LC	LC	UC	LC	LC	HC	LC
Lee (2015) [17]	LC	LC	UC	LC	HC	HC	LC
Park (2016) [18]	LC	LC	UC	LC	HC	HC	LC
Lee (2016) [19]	LC	UC	LC	LC	HC	HC	LC
Ryu (2014) [16]	LC	UC	LC	LC	HC	HC	LC
Lee (2016) [20]	LC	UC	LC	LC	LC	HC	LC

LC, low concern; HC, high concern; UC, unclear concern.

Table 3. Summary of the pooled estimates of NLR in the Predicting of 5-RFS in PTC patient

	Estimates (95% CI)
No. of study	8
No. of PTC	3880
Sensitivity	0.77 [0.666, 0.848]
Specificity	0.765 [0.616, 0.868]
Positive Likelihood Ratio	3.27 [1.971, 5.425]
Negative Likelihood Ratio	0.301 [0.209, 0.435]
Diagnostic Score	2.384 [1.688, 3.08]
Diagnostic Odds Ratio	10.852 [5.411, 21.765]
NPV	0.69 [0.62, 0.76]
PPV	0.69 [0.62, 0.75]

NPV, negative predictive value; PPV, positive predictive value.

Statistical analyses

A Cochrane-Q test of heterogeneity was performed using inconsistency index, I^2, as a measure to illustrate the percentage of the total variability in effect estimates among trials that is caused by heterogeneity instead of chance [13]. A value of I^2 more than 50% was defined as heterogeneity. A two-sided p value < 0.05 indicated statistical significance.

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), diagnostic score, and area under the summary receiver operating curve (AUSROC) with the corresponding 95% confidence interval (CI) were obtained by a bivariate binomial mixed model. The sensitivity, specificity, DOR, and AUSROC were considered as the major outcomes in this study. Since the cut-off values were different among the included studies, diagnostic threshold effects were inspected. The summary receiver operating curve (SROC) was visually evaluated. A Spearman correlation analysis was used to assess the heterogeneity derived from diagnostic threshold effects.

Meta-regression analysis was carried out to identify the sources of heterogeneity among studies. Possible sources of heterogeneity in-

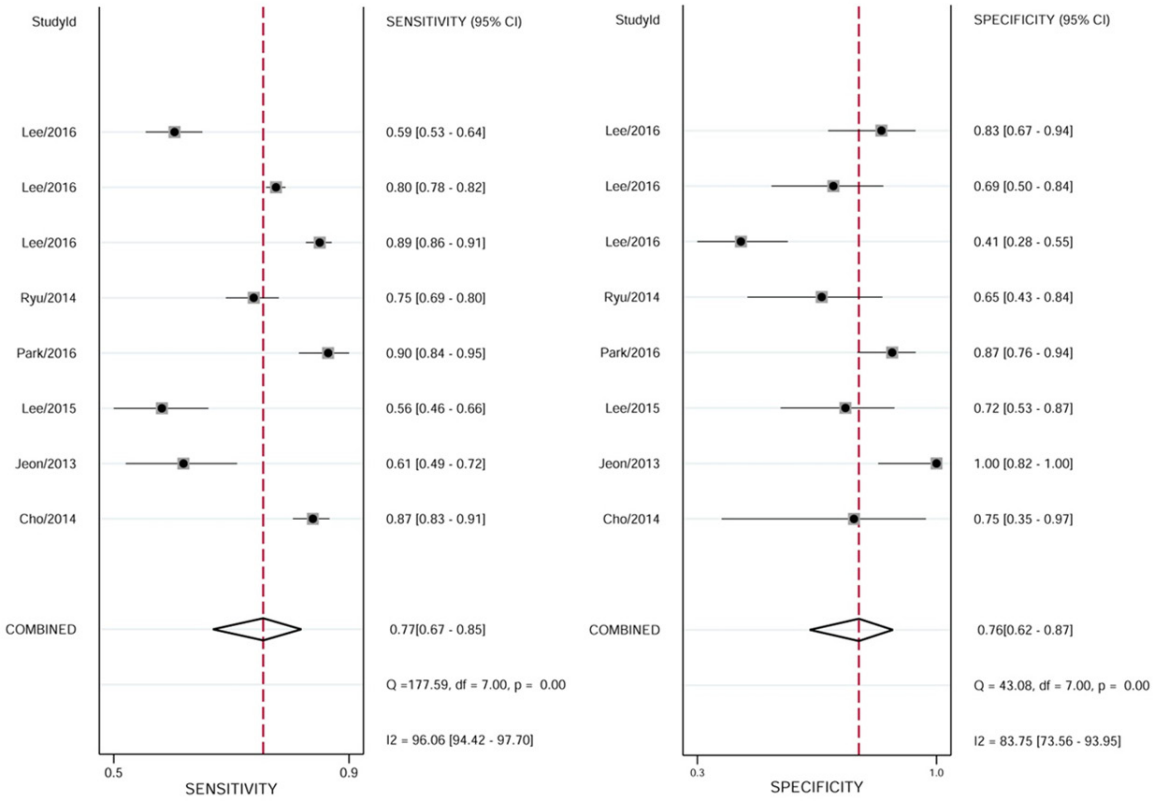

Figure 3. Sensitivity and specificity of LNR to predict PTC 5-years RFS.

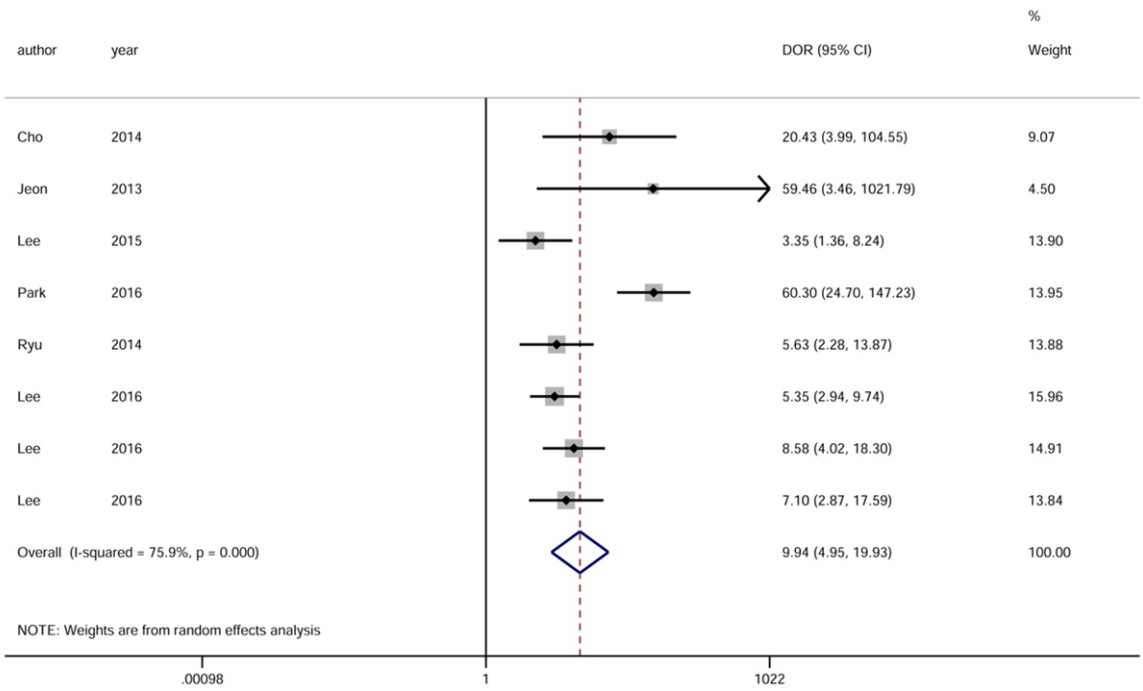

Figure 4. Diagnostic Odds Ratio of LNR to predict PTC 5-years RFS.

cluding published year, country, study design, number of study subjects, and cut-off value of LNR in each study were included in the analysis. Publication Bias was identified by Deeks'

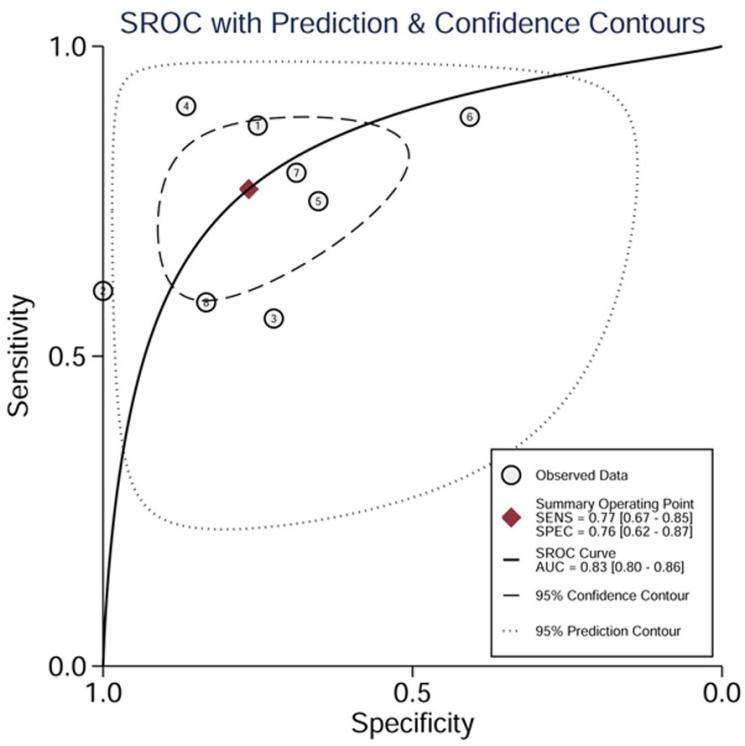

Figure 5. Summary ROC curve with confidence and prediction regions around mean operating sensitivity and specificity point.

funnel plot asymmetry analysis. Briefly, the Deeks' funnel plot was a scatter plot of the inverse of the square root of effective sample size [1/root (ESS)] against the ln (DOR). The Fagan nomogram plot was used to determine the post-test probabilities. A bivariate box plot was applied to assess the distributional properties of sensitivity against specificity and investigate possible outliers.

All data synthesis and most statistical analyses were undertaken by STATA software version 12.0 (College Station, TX, USA).

Results

Eligible studies

Total of 224 articles were recruited by searching terms, of which about 31 studies were included after preliminary screening. Non-English written articles or studies inconsistent with the inclusive criteria were excluded. Due to the data deficiencies of 5-DFS, only 3880 PTC patients from 7 articles were included for the meta-analysis finally [14-20]. The literature selection process and patients' baseline demographics were shown in **Figure 1**. Study characteristics were summarized in **Table 1**. All the studies included were retrospective researches about patients from China or Korea from 1985 to 2011. The majority of the patients had total thyroidectomy with neck dissection.

Quality evaluation

As the newest standard of assessment tool, QUADAS-2 was used to evaluate the qualities of the recruited studies by two in depended researchers. The results were shown in **Figure 2** and **Table 2**. No study fulfilled all QUADAS-2 criteria for low risk of bias. All 7 studies were assessed to have a low risk of bias in two domains, Patient Selection, and Flow and Timing. Three studies [16, 19, 20] were assessed with unclear risk in the index test and four studies [14, 15, 17, 18] with unclear risk in the reference standard.

Diagnostic accuracy evaluation

A total of 3880 Asian PTC patients from 8 studies in these 7 articles were analyzed in this system evaluation and meta-analysis. By bivariate model, we collected the predictive value of metastatic LNR in PTC 5-RFS and concluded in **Table 3**. The combined values of sensitivity, specialty, and Diagnostic Odds Ratio (DOR) were 0.77 [0.67, 0.85] (**Figure 3**), 0.76 [0.62, 0.87] (**Figure 3**), and 10.85 [5.41, 21.77] respectively (**Figure 4**). The AUROC value was 0.83 [0.80, 0.86] (**Figure 5**). The Spearman correlation coefficient was 0.21, no significant threshold effect was shown, which suggested that these articles could be merged (**Table 3**). The Fagan's nomogram analysis in **Figure 6** showed that compared with the fixed probability (20%) in preliminary experiments, the positive likelihood ratio (PLR) increased to 45%, while the negative likelihood ratio (NLR) reduced to 7%. All these results indicated that LNR can be effective to predict the Asian PTC patients' postoperative RFS.

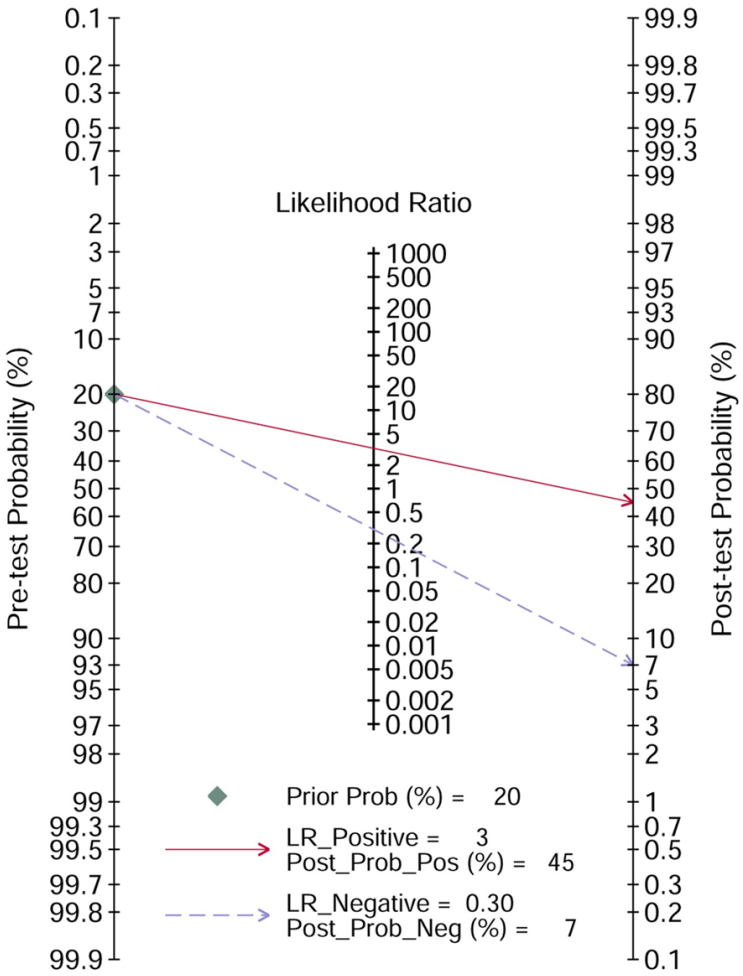

Figure 6. Fagan plot analysis to evaluate the predictive of LNR.

Table 4. Sources of heterogeneity analyze

Parameter	*I*-squared (95% CI)	LRT Chi	*p* value
Country	62.69 [15.95, 100.00]	5.36	0.07
Cutoff value	0.00 [0.00, 100.00]	1.58	0.45
Size	4.88 [0.00, 100.00]	2.1	0.35

Heterogeneity and publication bias analysis

As shown in the forest graphs (**Figures 3** and **4**), great heterogeneity exited in the analysis of sensitivity, specialty, and DOR. No significant threshold effect was shown by the spearman correlation coefficient analysis suggests that the heterogeneity wasn't caused by correlation coefficient. The studies recruited in this paper were all retrospective analysis, no heterogeneity was caused by experiment design. After the meta-regression analysis on countries, sample size, and the threshold, we found that these factors all could decrease the heterogeneity, suggesting that the heterogeneity might be cause by these figures (**Table 4**). However, no significant difference was shown among each subgroup.

We used Bivariate Box Plot method to access the distribution of sensitivity and specificity of this analysis and determine the possible diagnosis outliers. Even though the data from Jeno and Lee showed abnormal value, the shape of Bivariate Box Plot graph was bilateral symmetrical (**Figure 7**), which also suggested the tightness data of normal distribution. The publication bias was evaluated by Deeks' test. The graphical funnel plots of included studies appeared to be almost symmetrical. The *p* value of Deeks' test was 0.230 indicated no publication bias in this study (**Figure 8**).

Discussion

PTC is the most common malignant tumor in thyroid, of which the 5-RFS rate is above 50% [21]. PTC usually accompanies with lymphoid nodes metastasis. Though lots of scholars consider that cervical lymph node metastasis has little influence on PTC survival, more and more studies start to pay attention to it. White et al. reported that LNR may impact PTC recurrence [22]. Smith et al. identified 11453 PTC cases in the SEER database and 40.1% were lymphoid nodes metastasis positive. A case-control study from Lundgren et al. [23] indicated that cervical lymph node metastasis is one of the primary characteristics associated with high morbidity of PTC. All these suggested that cervical lymph node metastasis may play an important role in PTC survival.

The potential of LNR (metastasis lymph node ratio) has already been reported as prognosti-

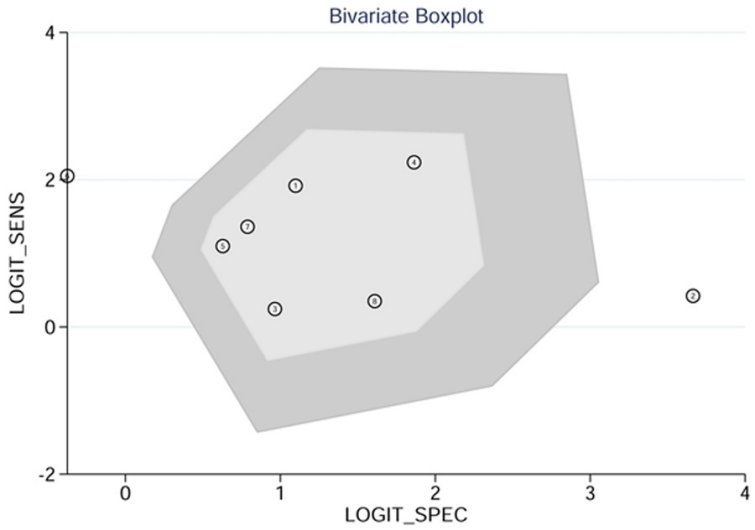

Figure 7. Bivariate box plot result.

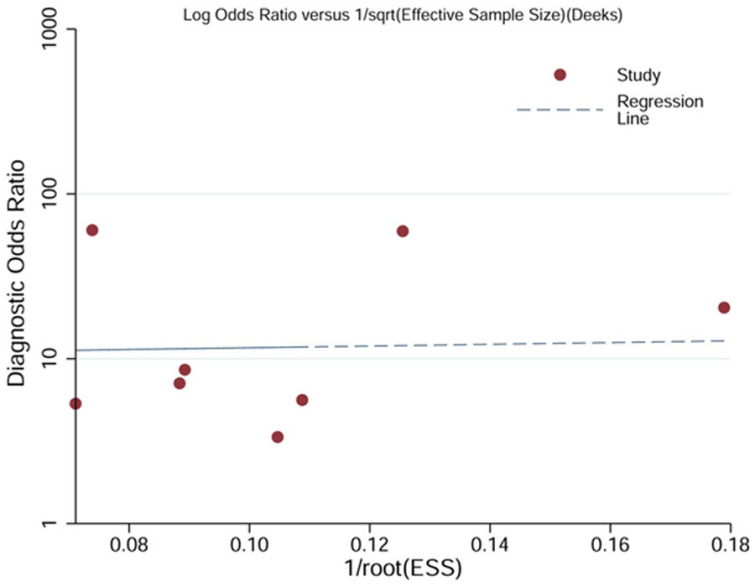

Figure 8. Deeks' funnel plot asymmetry analysis.

cator for other cancer treatment and survive. Studies from Sun [24] and Masaya [25] reported that LNR is a prognostic factor for non-small cell lung cancer. Depend on the analysis from 1101 patients, Chen et al. [26] declared that LNR has prognostic value for gastric cancer. Parnaby [27] and colleagues found that LNR has prognosticevalue on survival for patients undergoing curative colon cancer resection. Our study focused on the prognostic value of LNR in papillary thyroid carcinoma 5-year relapse-free survival. Seven studies about Asian were recruited in this systematic review. The results from diagnostic accuracy evaluation show that LNR is effective to predict the 5-RFS of PTC. Though high heterogeneity exists among these studies, no statistical difference has been shown in possible heterogeneity source. Along with the tightness data and low publication bias make our study a quality meta-analysis.

However, some limitations should be mentioned. First, because of the language restriction, we cannot include all the related research. Second, all the data were extracted from retrospective studies, the adjuvant chemotherapy or some other potential cofounders may affect the results. Last, the source of heterogeneity among these studies recruited in this study needs more deeply analysis.

In conclusion, our study demonstrated that LNR can be used as a moderate predictor in PTC 5- RFS for Asian.

Disclosure of conflict of interest

None.

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