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Clinical and prognostic value of neutrophil-lymphocyte ratio for patients with thyroid cancer

A meta-analysis

Jidong Feng, MM[a], Yanyan Wang, MM[b], Guohui Shan, MM[b], Lei Gao, MD[c,*]

Abstract

Background: Although the malignant degree is relatively low and overall prognosis is excellent, some patients with thyroid cancer still experience metastasis during the follow-up, which leads to their possible death. Pretreatment neutrophil-to-lymphocyte ratio (NLR) has been recommended as a biomarker for the prediction of metastasis and prognosis in patients with cancers. However, its value in thyroid cancer remains inconclusive. This study aimed to comprehensively evaluate the prognostic and clinicopathological significance of NLR for thyroid cancer by a meta-analysis.

Methods: Eligible studies were identified by searching PubMed, EMBASE, and Cochrane Library databases. The associations between NLR level and disease-free survival (DFS) or clinicopathological parameters were estimated by calculating hazard ratio (HR) or effect size with 95% confidence interval (CI).

Results: Nine studies consisting of 3081 patients were enrolled. Results of meta-analysis showed that elevated NLR was not significantly associated with unfavorable DFS overall, but subgroup analysis of multivariate-adjusted studies demonstrated an elevation in pretreatment NLR predicted poor DFS (HR = 3.51, 95%CI = 1.42–8.70). Overall, a high level of NLR was significantly correlated with larger tumor size (standardized mean difference [SMD] = 0.49, 95%CI = 0.33–0.64), and metastasis status (risk ratio [RR] = 1.70, 95%CI = 1.10–2.64). The association with tumor size was still significant in the stratified analyses by country and histology type (Asian: SMD = 0.719, 95%CI = 0.44–0.98; non-Asian: SMD = 0.36, 95%CI = 0.17–0.56; medullary thyroid carcinoma: SMD = 0.57, 95%CI = 0.09–1.05; papillary thyroid carcinoma: SMD = 0.48, 95%CI = 0.31–0.64). The association between NLR and metastasis was only significant for papillary thyroid carcinoma subtype (RR = 1.82, 95%CI = 1.04–3.20).

Conclusion: Pretreatment NLR may serve as an excellent biomarker for prediction of tumor growth, metastasis, and prognosis in patients with thyroid cancer.

Abbreviations: CI = confidence interval, DFS = disease-free survival, ES = effect size, HR = hazard ratio, IL = interleukin, MTC = medullary thyroid carcinoma, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle-Ottawa Scale, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, ROS = reactive oxygen species, PTC = papillary thyroid carcinoma, RR = risk ratio, SMD = standardized mean difference.

Keywords: disease-free survival, medullary thyroid carcinoma, metastasis, neutrophil to lymphocyte ratio, papillary thyroid carcinoma, tumor size

1. Introduction

Thyroid cancer is the most common endocrine malignancy, accounting for about 96% of all endocrine cancers and 3% of all cancers.[1] It was estimated that there were 53,990 new cases in 2018 in the United States.[1] In China, the incidence rate of thyroid cancer was also increasing year by year, from 2.40 per 100,000 persons in 2003 to 13.75 per 100,000 persons in 2012.[2] Although the malignant degree of thyroid cancer is relatively low and the prognosis is excellent, especially for the differentiated histologic types, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma and medullary thyroid carcinoma (MTC) compared with anaplastic thyroid cancer. However, these differentiated histologic types were also reported to have potential risks of lymph node metastasis and distant metastasis,[3–5] which may ultimately induce the death of patients. Therefore, how to early identify patients at high risk of developing metastasis and poor prognosis may be clinically important.

Recently, numerous studies have suggested that activation of inflammation is a crucial mechanism for the initiation and progression of thyroid cancer.[6,7] The neutrophil-to-lymphocyte ratio (NLR) has been widely recognized as a biomarker to

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All data in this meta-analysis can be seen in previous published studies.

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

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represent the systemic inflammatory condition.[8,9] Thus, it may serve as a potential predictive marker for metastasis and poor prognosis for thyroid cancer patients like other cancers.[8–11] This hypothesis has been demonstrated by several studies. For example, Xu et al demonstrated that NLR was an independent predictor of metastasis (odds ratio = 5.918, 95% confidence intervals [CI]: 1.147–30.541; $P = .034$) for patients with MTC after multivariate logistic regression analysis.[12] Manatakis et al also proved that the incidence rate of lymph node metastasis was significantly higher in PTC patients with NLR > 2.17 than those with NLR < 2.17 ($P = .03$).[13] Kaplan–Meier curve and univariate analyses in the study of Kim et al revealed that a high level of NLR was significantly correlated with poor 5-year disease-free survival (DFS) rate for PTC patients.[14] Lee et al also identified high NLR as an independent predictor of DFS in PTC patients aged ≥ 45 years (hazard ratio [HR] = 2.96; 95%CI = 1.08–8.09; $P = .035$).[15] However, inconsistent results were also present: Jiang et al reported no significant associations between the NLR and lymph node metastasis ($P = .461$)[16] and DFS ($P = .124$) for MTC patients.[17] The negative correlation with DFS was also verified in the study of Lang et al ($P = .447$).[18] Accordingly, the predictive potential of NLR for metastasis and poor prognosis remains inconclusive.

In this study, we aimed to perform a meta-analysis to comprehensively evaluate the prognostic and clinicopathological significance of NLR in patients with thyroid cancer. Analysis of all related articles may enhance the statistical power and thus may achieve a more convincing conclusion.

2. Materials and methods

2.1. Search strategies

This analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. No ethical approval was required because this meta-analysis only used the published studies.

The electronic databases of PubMed, EMBASE, and Cochrane Library were comprehensively searched to screen articles that evaluated the associations between NLR and prognosis or clinicopathological characteristics for patients with thyroid cancer. The combinations of the following keywords were used: ("neutrophil to lymphocyte ratio" OR "neutrophil-to-lymphocyte ratio" OR "neutrophil lymphocyte ratio" or "NLR") and ("thyroid carcinoma" OR "thyroid cancer"). The search was confined to articles that were published in English before October 1, 2019. Furthermore, the reference lists of retrieved publications were manually searched to further screen potential eligible articles.

2.2. Inclusion and exclusion criteria

Eligible studies were identified if they met the following inclusion criteria:

1) patients were pathologically diagnosed as thyroid cancer;
2) pretreatment NLR was measured;
3) the influence of NLR on prognostic outcomes (such as DFS) or clinicopathological characteristics of patients was evaluated;
4) HR or effect size (ES) with its 95%CI could be directly obtained or calculated according to the data or figures provided by the articles; and
5) a cut-off value for NLR was reported.

The exclusion criteria were:

1) duplicate publication;
2) conference abstracts, reviews, letters, case reports, comments, cell line, or animal studies; and
3) studies in which necessary data could not be extracted.

2.3. Data extraction

The following data were extracted from each included article: author name, publication year, country, sample size, histology type, cut-off value of NLR, follow-up, statistical methods, direct HRs/ES, and 95%CIs or data used for calculation of HRs/ES and 95%CIs to evaluate prognosis (DFS) or patients' clinicopathological characteristics (such as sex, age, tumor size, stage, metastasis, focality, capsule invasion, coexisting disease, follicular-variant, and extrathyroidal invasion). The survival data in the Kaplan–Meier curves were estimated via a digitizing software – Engauge Digitizer (version 4.1; http://digitizer.sourceforge.net/). Univariate (or Kaplan–Meier curve) and multivariate results were both extracted. The quality of included studies was assessed according to the Newcastle–Ottawa Scale (NOS) criteria,[19] with NOS scores ≥ 6 graded as high quality. Data extraction and quality assessment processes were performed by 2 independent investigators. Any disagreement was resolved by consensus agreement or with the input of a third review researcher.

2.4. Statistical analysis

The pooled HR and its 95%CI were calculated to assess the relationship between NLR and DFS. The pooled risk ratio (RR, binary data) or standardized mean difference (SMD, continuous data) and its corresponding 95%CI were calculated to determine the associations between NLR and clinicopathological characteristics. Statistical heterogeneity was determined by using Cochrane's Q and I^2 statistic tests. A random-effects model was applied to pool the study results if $P < .10$ and $I^2 > 50\%$ (obvious heterogeneity); otherwise, a fixed-effects model was selected. Egger linear regression test was used to test the publication bias among articles.[20] Sensitivity analysis was performed by excluding single studies in turn. Furthermore, a subgroup analysis was also performed according to country, histology type and statistical analysis methods. All statistical analyses were conducted using STATA 13.0 (STATA Corporation, College Station, TX). $P < .05$ was considered to be statistically significant.

3. Results

3.1. Characteristics of the included studies

A flow chart of the literature retrieval is presented in Figure 1. A total of 312 studies were initially obtained after searching the databases. Among them, 64 were left by the removal of duplicates. Subsequently, 54 articles were excluded by reading the title or abstract because they did not meet our inclusion criteria: other cancer (n = 22), meta-analysis study (n = 5), without prognosis or clinical information (n = 16), not related with NLR (n = 7), and descriptive study (n = 4). Ten full-text articles were then downloaded and read, after which 1 was further eliminated because of lack of relevant data. Finally, 9 studies consisting of 3081 patients were available for this meta-analysis.[12–18,21,22] The characteristics of these 9 eligible studies

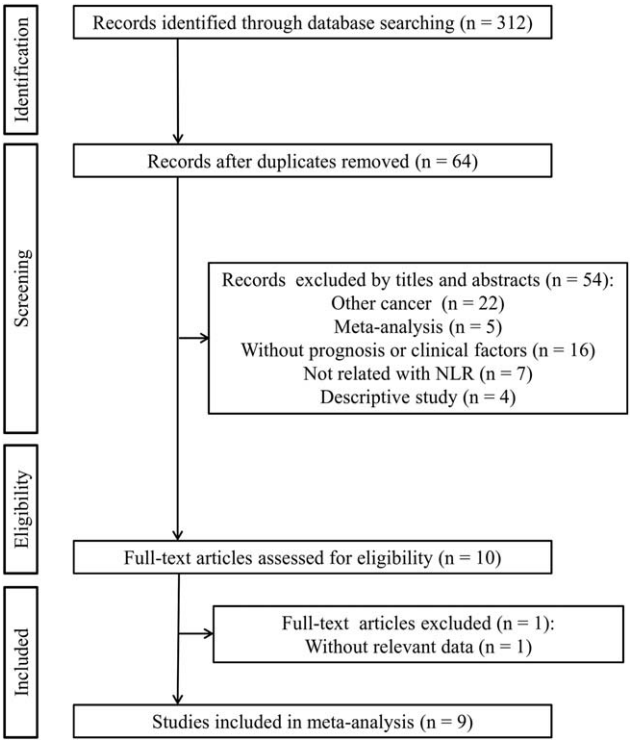

Figure 1. Flow diagram of studies selection procedure. NLR = neutrophil-to-lymphocyte ratio.

are listed in Table 1. Four studies with 5 datasets because the study of Lee et al[15] divided the patients into 2 cohorts (≥ 45 years and < 45 years) reported the association between NLR and DFS, while 6 investigated the link between NLR and clinicopathological data. Univariate analysis was used for most of the studies on DFS (excluding Lee et al[15] and Kim et al,[14] in which univariate and multivariate were both included) and all studies on clinicopathological data. Thus, univariate and multivariate results were both extracted and meta-analysis was performed using only the univariate (Kaplan–Meier)/multivariate (5) or combined results (7) for DFS. Three studies analyzed the MTC subtype, while the other 6 described PTC subtype. Most of the studies were performed in Asia (7/9, 77.8%), including China (n = 5) and Korea (n = 2); and the other 2 were about the population of Greece (n = 1) and Turkey (n = 1). The quality of all eligible studies varied from 7 to 9, indicating all studies were considered to be in high-quality (Table 1).

3.2. Association between NLR and prognosis

A significant heterogeneity was present among 5 (or 7) studies and thus a random-effects model was chosen to pool the study results. Meta-analysis showed that elevated NLR was not significantly associated with unfavorable DFS (Table 2). In order to further explore the source of heterogeneity, subgroup analyses based on country, histology type, and statistical methods were carried out. The results demonstrated an elevation in pretreatment NLR was significantly correlated with poor DFS (HR = 3.51, 95%CI = 1.42–8.70; $P = .007$) when the studies with multivariate analysis were integrated (Fig. 2; Table 3). Also, no heterogeneity was present in this subgroup meta-analysis, indicating the result was credible.

3.3. Association between NLR and clinicopathological characteristics

Overall, a high level of NLR was significantly associated with larger tumor size (SMD = 0.49, 95%CI = 0.33–0.64; $P < .001$) (Fig. 3; Table 2) and metastasis situation (RR = 1.70, 95%CI = 1.10–2.64; $P = .018$) (Fig. 4; Table 2). The associations between NLR and other clinicopathological features (sex, age, stage, focality, capsule invasion, coexisting disease, follicular-variant, and extrathyroidal invasion) was not significant (Table 2).

Table 1

Characteristics of the studies included in the meta-analysis.

Study	Year	Country	No. of patients	Tumor type	Cut-off	Analysis parameters	Statistical method	Follow (mo)		NOS score
Xu N	2018	China	61	MTC	1.784	Metastasis	MV	Unclear	R	7
Manatakis DK	2017	Greece	205	PTC	2.17	Metastasis/tumor size/ multifocality/ bilaterality/extrathyroidal invasion/ stage/follicular-variant/thyroiditis/sex/ age	NV	Unclear	R	8
Jiang K	2017	China	78	MTC	2.7	DFS	KM	39.3	R	7
Jiang K	2016	China	70	MTC	1.9	Metastasis/tumor size/multifocality/ bilaterality/capsule invasion/autoimmune thyroid disease / stage/age/sex	NV	39.4	R	9
Gong W	2016	China	161	PTC	2	Metastasis/tumor size/ multifocality/ age/sex	NV	Unclear	R	8
Lang BH	2014	China	191	PTC	1.93	DFS/multifocality/ bilaterality/ extrathyroidal extension / follicular-variant/ thyroiditis/sex/stage	KM/NV	41.3	R	7
Kim JY	2014	South Korea	268	PTC	1.5	DFS	KM/NV/MV	41.2	R	8
Lee KH	2019	Korea	1846	PTC	2.1	DFS	KM/NV/MV	75	R	7
Ceylan Y	2019	Turkey	201	PTC	1.92	Metastasis/tumor size/multifocality/ bilaterality/capsule invasion/ extrathyroidal spread/age/sex	NV	Unclear	R	8

DFS = disease-free survival, KM = Kaplan–Meier, MTC = medullary thyroid carcinoma, MV = multivariate, NOS = Newcastle-Ottawa Scale, NV = univariate, PTC = papillary thyroid carcinoma, R = retrospective.

Table 2

Meta-analysis of the association between NLR and prognosis or clinicopathological features of thyroid cancer.

Comparison	Studies	ES (95%CI)	*P*-value	I^2	P_H-value	Model
DFS	7[a]	1.79 (0.97,3.33)	.064	65.9	.007	R
	5[b]	1.40 (0.73,2.70)	.311	63.4	.027	R
Age	2	-0.09 (-0.33,0.15)	.448	0.0	.787	F
Age (45 > vs <45)	3	1.02 (0.86,1.20)	.842	0.0	.894	F
Sex (male vs female)	5	1.14 (0.90,1.44)	.292	0.0	.675	F
Tumor size	4	0.49 (0.33,0.64)	**<.001**	39.8	.173	R
Bilaterality	4	0.98 (0.78,1.24)	.889	0.0	.801	F
Multifocality	5	1.26 (0.90,1.78)	.182	68.4	.013	R
Stage (III/IV vs I/II)	3	1.24 (0.81,1.90)	.319	62.5	.069	R
Thyroiditis	3	1.13 (0.90,1.41)	.297	0.0	.502	F
Follicular-variant	2	0.99 (0.81,1.21)	.951	0.0	.980	F
Extra-thyroidal extension	2	1.71 (0.52,5.69)	.380	71.0	.063	R
Capsule invasion	2	0.99 (0.73,1.34)	.963	0.0	.800	F
Metastasis	5	1.70 (1.10,2.64)	**.018**	61.9	.033	R

CI = confidence interval, DFS = disease-free survival, ES = effect size, F = fixed, NLR = neutrophil-to-lymphocyte ratio, P_H = *P*-value for heterogeneity, R = random.

[a]Univariate and multivariate results were both used.

[b]Only the univariate (Kaplan–Meier) or multivariate results were used.

Furthermore, the association was also stratified by country and histology type. The results were still significant for tumor size, irrespective of ethnicity (Asian: SMD = 0.719, 95%CI = 0.44–0.98; $P < .001$; or non-Asian: SMD = 0.36, 95%CI = 0.17–0.56; $P < .001$) or the presence of PTC (MTC: SMD = 0.57, 95%CI = 0.09–1.05; $P = .020$; or PTC: SMD = 0.48, 95%CI = 0.31–0.64; $P < .001$) (Fig. 3, Table 3). The association between NLR and metastasis was only significant in PTC subtype (RR = 1.82, 95% CI = 1.04–3.20; $P = .037$) (Fig. 4; Table 3).

3.4. Publication bias and sensitivity analyses

Because a significant heterogeneity was found in studies to evaluate the association between NLR and tumor size/metastasis; thus, the publication bias was estimated for these 2 characteristics. Egger test showed that no significant publication bias was observed for tumor size ($P = .558$) and metastasis status ($P = .131$), respectively. The sensitivity analysis also confirmed the stability of the association after the removal of any single study (Fig. 5).

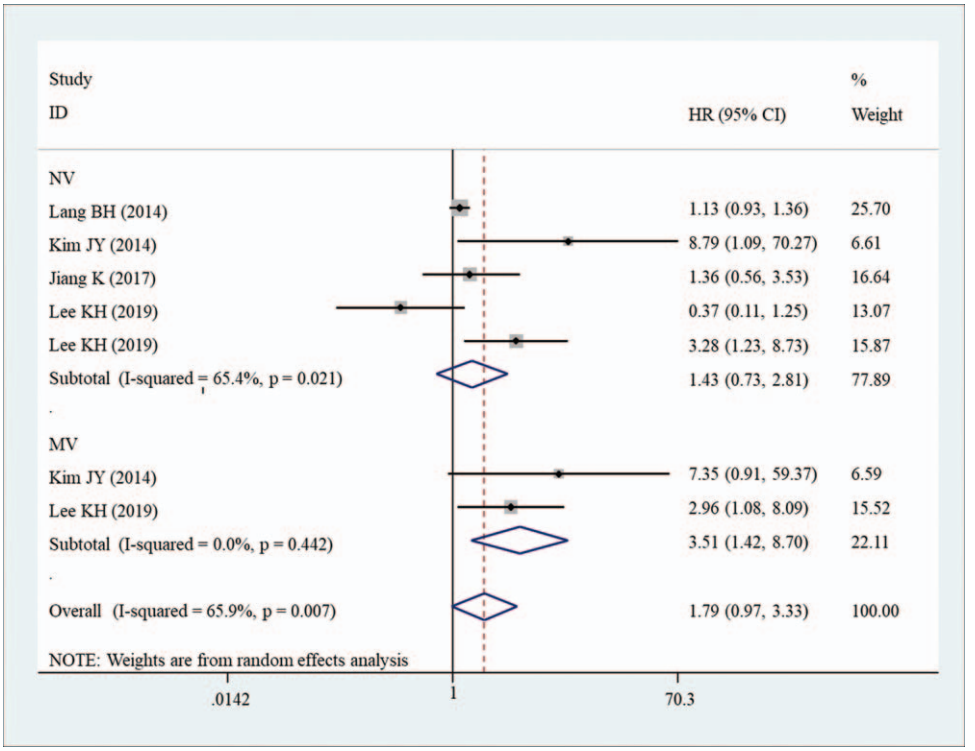

Figure 2. Forest plots for the association of neutrophil to lymphocyte ratio with disease-free survival. CI = confidence interval, HR = hazard ratio, MV = multivariate, NV = univariate.

Table 3

Subgroup analysis.

Comparison		Qualified studies	HR or ES (95%CI)	*P*-value	I^2	P_H-value	Model
DFS	Ethnicity						
	Asian	5	1.40 (0.73,2.70)	.311	63.4	.027	R
	Non-Asian	–	–	–	–	–	–
	Tumor type						
	MTC	1	1.36 (0.54,3.42)	.513	–	–	–
	PTC	4	1.47 (0.60,3.63)	.401	72.2	.013	R
	Statistical methods						
	NV	5	1.43 (0.73,2.81)	.298	65.4	.021	R
	MV	2	3.51 (1.42,8.70)	**.007**	0.00	.442	F
Sex	Ethnicity						
	Asian	2	1.23 (0.88,1.73)	.231	0.0	.480	F
	Non-Asian	2	1.05 (0.75,1.47)	.774	0.0	.438	F
	Tumor type						
	MTC	1	1.15 (0.65,2.05)	.626	–	–	–
	PTC	4	1.14 (0.87,1.47)	.344	0.0	.508	F
Tumor size	Ethnicity						
	Asian	2	0.71 (0.44,0.98)	<**.001**	0.0	.596	F
	Non-Asian	2	0.36 (0.17,0.56)	<**.001**	0.0	.484	F
	Tumor type						
	MTC	1	0.57 (0.09,1.05)	**.020**	–	–	–
	PTC	4	0.48 (0.31,0.64)	<**.001**	58.8	.088	F
Bilaterality	Ethnicity						
	Asian	2	0.95 (0.65,1.38)	.774	0.0	.951	F
	Non-Asian	2	1.01 (0.75,1.35)	.967	0.0	.336	F
	Tumor type						
	MTC	1	0.93 (0.53,1.63)	.808	–	–	–
	PTC	4	0.99 (0.77,1.28)	.954	0.0	.619	F
Multifocality	Ethnicity						
	Asian	3	1.70 (0.80,3.61)	.167	81.1	.005	R
	Non-Asian	2	1.03 (0.82,1.29)	.828	0.0	.493	F
	Tumor type						
	MTC	1	3.80 (1.60,9.04)	.003	–	–	–
	PTC	4	1.09 (0.91,1.31)	.369	33.6	.210	F
Metastasis	Ethnicity						
	Asian	3	1.82 (0.96,3.44)	.068	71.3	.031	R
	Non-Asian	2	1.87 (0.59,5.93)	.285	69.4	.071	R
	Tumor type						
	MTC	2	2.13 (0.45,10.09)	.341	72.5	.056	R
	PTC	3	1.82 (1.04,3.20)	**.037**	62.9	.068	R

The pooled risk ratio (binary data) or standardized mean difference (continuous data) and its corresponding 95%CI were calculated to determine the associations between NLR and clinicopathological characteristics. HR was used for DFS. Bold indicates the statistical significance after analysis of 2 or more studies.

CI = confidence interval, DFS = disease-free survival, ES = effect size, F = fixed, HR = hazard ratio, MTC = medullary thyroid carcinoma, MV = multivariate, NLR = neutrophil-to-lymphocyte ratio, NV = univariate, P_H = *P*-value for heterogeneity, PTC = papillary thyroid carcinoma, R = random.

4. Discussion

Although a previous study in 2016 had attempted to use the meta-analysis to explore the association between NLR and differentiated thyroid cancer, its included literatures focused on distinguishing patients of differentiated thyroid cancer from benign nodules, not involving its prognostic and clinical importance.[23] The present study, for the first time, integrated all the updated evidence to re-assess the correlation between pretreatment NLR and prognosis or clinicopathological features in thyroid cancer patients. The results supported that high NLR was significantly associated with unfavorable DFS and survival-related factors such as larger tumor size and positive lymph node and/or distant metastasis. Our study seemed to be in line with the previous meta-analyses of other cancers, such as soft tissue sarcoma (tumor size, DFS),[8] breast cancer (DFS),[24] esophageal squamous cell carcinoma (lymph node metastasis),[25] gastrointestinal stromal tumors (tumor size, DFS),[26] and cervical cancer (tumor size, lymph node metastasis).[27]

The association with tumor size and metastasis status highlighted the possible roles of NLR in promoting tumor cell proliferation and metastasis. This hypothesis had been confirmed by previous in vitro and in vivo experiments. High NLR means more count of neutrophils or less count of lymphocytes. It was reported that neutrophils (e.g., upregulation of CD11b and CD66b and shedding of CD62L) were activated in thyroid cancer and its levels correlated with larger tumor size.[28] Neutrophils were indicated as escorts for circulating tumor cells to drive their cell cycle progression within the bloodstream and expand their metastatic potential.[29] Pro-inflammatory factors including interleukin (IL)-6, IL-8, IL-1β, and tumor necrosis factor-α were also found to be significantly released in cancer-activated neutrophil-like cells, which subsequently activated the ERK pathway and epithelial-mesenchymal transition, ultimately

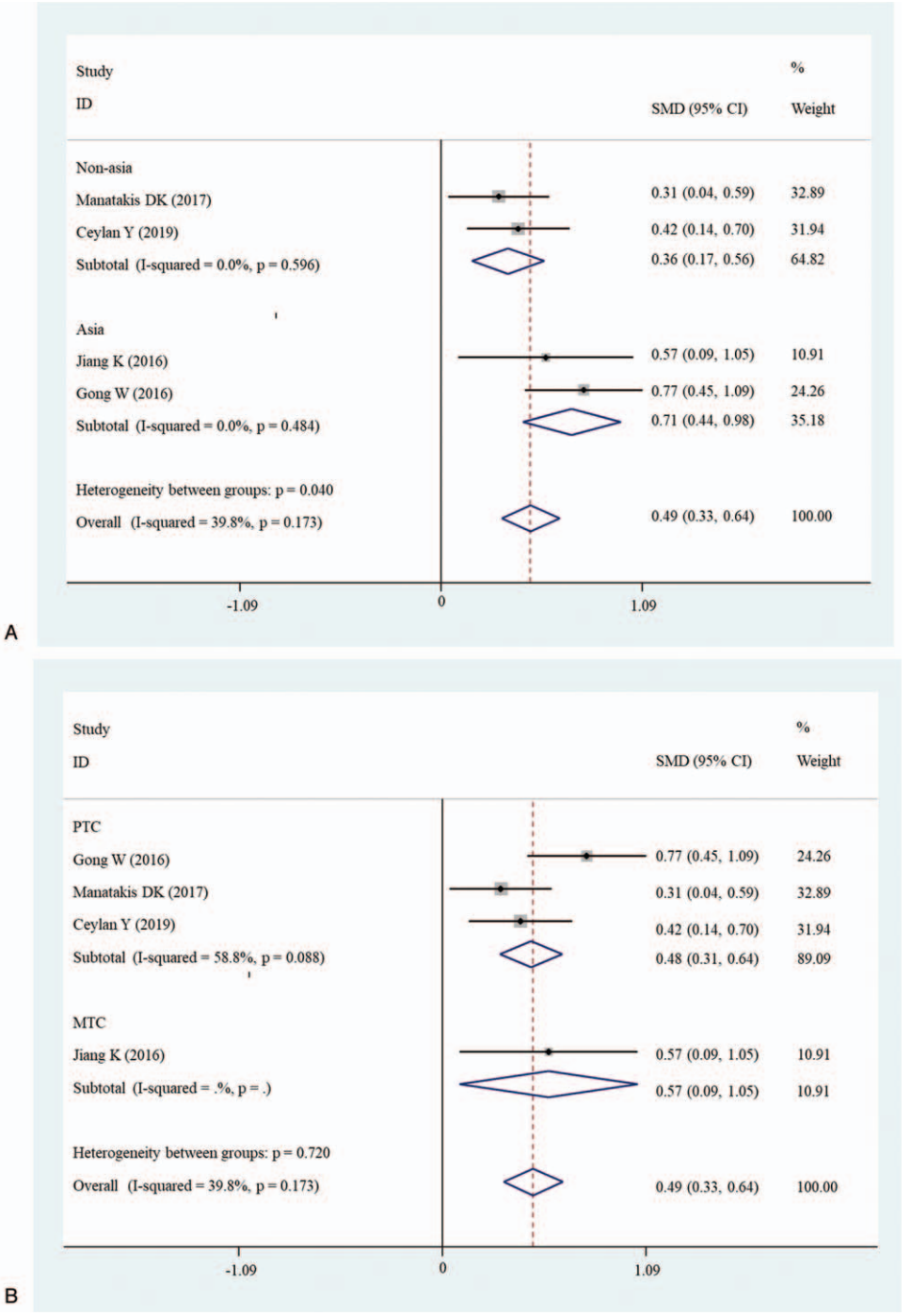

Figure 3. Forest plots for the association of neutrophil-to-lymphocyte ratio with tumor size. CI = confidence interval, MTC = medullary thyroid carcinoma, PTC = papillary thyroid carcinoma, SMD = standardized mean difference.

triggering cancer cell migration and invasion.[30] Co-incubation with neutrophils was also demonstrated to induce proliferation of cancer cells in a dose-dependent manner, the mechanism of which was related to its secretion of elastase and cyclooxygenase 2.[31] Inhibition of neutrophil elastase activity and cyclooxygenase 2 in vitro or constructing the model mice with neutrophil elastase knockout were shown to significantly exert anti-tumor effects.[31,32] Furthermore, the study of Domínguez-Luis et al revealed in response to the chemokine receptor CXCR2 ligand CXCL8, neutrophils initiated the generation of intracellular reactive oxygen species (ROS) (oxidative stress indicator) which subsequently induced the shedding of L-selectin in neutrophils and further promoted the inflammatory response and tumorigenesis.[33] This conclusion was also observed by Manukyan et al who found neutrophils from chronic lymphocytic leukemia patients produced more ROS and pro-inflammatory IL-1β and tumor necrosis factor-a compared to controls in both resting and activated conditions.[34] It was also reported that activation of

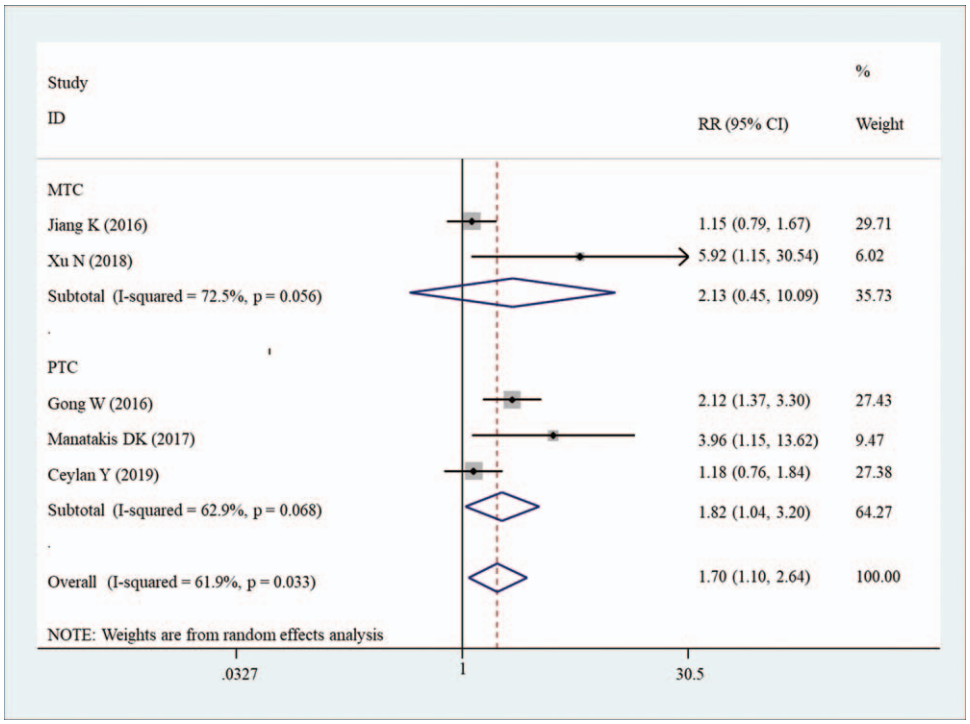

Figure 4. Forest plots for the association of neutrophil-to-lymphocyte ratio with metastasis. CI = confidence interval, MTC = medullary thyroid carcinoma, PTC = papillary thyroid carcinoma, RR = risk ratio.

oxidative stress may play a key role in thyroid carcinogenesis by directly triggering DNA damage and contributing to the genomic instability in thyroid cells.[35] Conversely, infiltrating lymphocytes were revealed to be markedly reduced or absent in thyroid cancer.[36] Also, the cases with low CD8+ lymphocyte infiltration were shown to have a significantly increased incidence of lymph node metastasis and poor DFS.[37] The low lymphocyte count may be attributed to the activation of the ROS-mediated apoptosis pathway.[38,39] These findings indicated the protective roles of lymphocyte infiltration against the development of thyroid tumors. Thus, high NLR may represent an imbalance between the tumor-promoting and tumor-suppressing function.

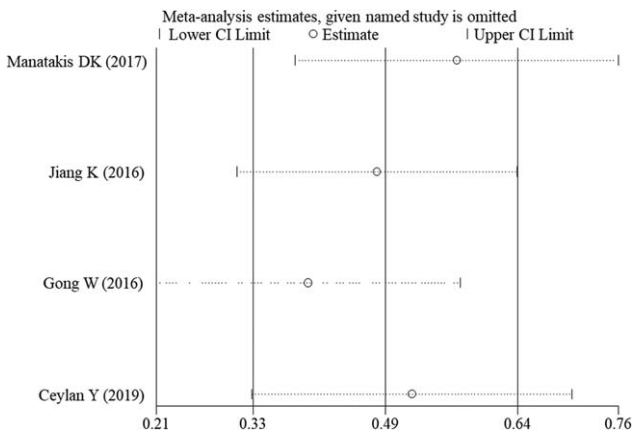

Figure 5. Sensitivity analysis for tumor size. CI = confidence interval.

There were some limitations that should be acknowledged. First, all included studies were retrospectively designed, which inevitably caused some biases. Second, the number of enrolled articles was relatively less and sample size in them was also not large. These may influence the accuracy and unavailability (e.g., subgroup analysis for other clinicopathological features, such as stage, invasion, etc) of the results. Third, most of the studies to investigate the association with DFS or clinicopathological features were based on the univariate analysis. Whether NLR was an independent prognostic marker for thyroid cancer required additional confirmation. Fourth, the application of NLR for prediction of DFS needed further verification because of the lack of unified cut-off value.

5. Conclusion

Our findings demonstrate pretreatment NLR may serve as an excellent biomarker for prediction of tumor growth, metastasis and prognosis in patients with thyroid cancer. For the patients with a risk of shorter DFS and metastasis (above the cut-off of NLR), more treatment options should be used to prevent possible unfavorable outcomes.

Author contributions

Conceptualization: Jidong Feng, Lei Gao.
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Supervision: Lei Gao.
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Writing – review & editing: Lei Gao.

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