

The Potential of Preoperative Neutrophil-Lymphocyte Ratio in Predicting Papillary Thyroid Carcinoma Occult Nodal Metastasis: A Systematic Review

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ABSTRACT

Background: The trend of prophylactic neck dissection for clinically nodal-negative papillary thyroid carcinoma (PTC) is still a subject of controversy. Despite the risk of higher morbidities, a more selective approach based on risk factors has been proposed. Systemic inflammation highlights the potential of preoperative neutrophil-to-lymphocyte ratio (NLR) as a convenient biomarker in predicting nodal metastasis. This review aims to evaluate the potential of preoperative NLR in predicting occult nodal metastasis in PTC.

Methods: We conducted a systematic literature search across PubMed, ProQuest, Scopus, and Cochrane Library. The protocol of this systematic review had been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024516033.

Results: Eight cohort articles involving 3,434 patients across nations were included. All articles demonstrated an association between higher NLR and nodal metastasis. Four of these studies exhibited significant associations ($p < 0.05$), potentially explained by NLR cut-off values falling between 2 and 2.1.

Conclusion: NLR might serve as an excellent biomarker to predict occult nodal metastasis in patients with PTC. Moreover, this study could be a basis of utilizing NLR as an accessible, low-cost adjunct to refine preoperative risk stratification and to help prioritize intensified nodal evaluation in cN0 PTC.

Keywords: Neutrophil to lymphocyte ratio, nodal metastasis, papillary thyroid carcinoma

INTRODUCTION

Despite the generally favorable prognosis of Papillary Thyroid Carcinoma (PTC), with over 90% achieving a 10 year survival rate, locoregional recurrence remains an usual occurrence (1). Preoperative ultrasonography (USG) has

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limited effectiveness in identifying nodal metastasis, prompting some surgeons to advocate for routine prophylactic neck dissection during total thyroidectomy (2). Nonetheless, the trend of prophylactic neck dissection for cN0 papillary thyroid carcinoma (PTC) remains contentious. Despite the risk of higher morbidities, a selective approach considering risk factors for nodal metastasis has been proposed (3). Systemic inflammation is frequently observed in thyroid carcinoma progression (2,4). The tumor microenvironment, particularly the inflammatory response, plays a critical role in various malignancies by facilitating tumor cell proliferation, survival, angiogenesis, invasion, and metastasis (4). Consequently, the serum neutrophil-to-lymphocyte ratio (NLR) serves as an indicator of the dynamic interplay between antitumor immune activity and pro-tumor inflammatory processes. As an easily accessible inflammatory biomarker derived from routine blood tests, NLR has been widely studied for its prognostic value. For instance, Xu et al. demonstrated that an elevated NLR is an independent predictor of metastasis in patients with thyroid cancer (odds ratio = 5.918, 95% confidence interval: 1.147–30.541; $p = 0.034$), as determined through multivariate logistic regression analysis (5). Similarly, Manatakis et al. reported a significantly higher incidence of lymph node metastasis in patients with papillary thyroid carcinoma (PTC) when NLR exceeded 2.17 compared to those with an NLR below this threshold ($p=0.03$) (6). Preoperative neutrophil to lymphocyte ratio (NLR) might be predictive for nodal metastasis. However, its use is still limited and controversial. Moreover, wide variations in proposed cutoff values exacerbate this ongoing debate. Therefore, our study seeks to assess the predictive value of preoperative NLR for occult nodal metastasis in thyroid cancers.

MATERIALS AND METHODS

This study adheres to the guidelines stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (7). This systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024516033. As a systematic review, ethical approval or patient consent was not deemed necessary.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this study were as follows: all published RCT, cohort, cross-

sectional, case-control, and case series that documented the utilization of NLR to predict nodal metastasis of Papillary Thyroid Carcinoma patients were included. Duplicate studies, incomplete data, review articles, technical reports, editorials, commentaries, and letters were all excluded. In cases where multiple publications covered the same study or aspects of a study, data from a single study were used to avoid repetition. Articles not in English or Bahasa Indonesia were also excluded from the study.

Search Strategy

To identify relevant articles, a systematic literature search was conducted in electronic databases, including PubMed, ProQuest, Scopus, and Cochrane Library. Articles published from 2014 until the current year were considered, and proper English-language keywords combined with Boolean logical operators were used to search. No limitations were set on the search. The identified studies were recorded in Microsoft Excel 2020 along with their relevant details.

Data Extraction and Study Appraisal

The authors conducted independent data extraction for this study. The following information was extracted from the included studies: duration of the study, country of study, study design, duration of follow-up, number of subjects, sex, age, primary diagnosis, treatment received, neutrophil-lymphocyte ratio, nodal metastases, and any other relevant outcomes. The level of evidence of each article was decided based on the criteria outlined by the Oxford Centre for Evidence-Based Medicine (8).

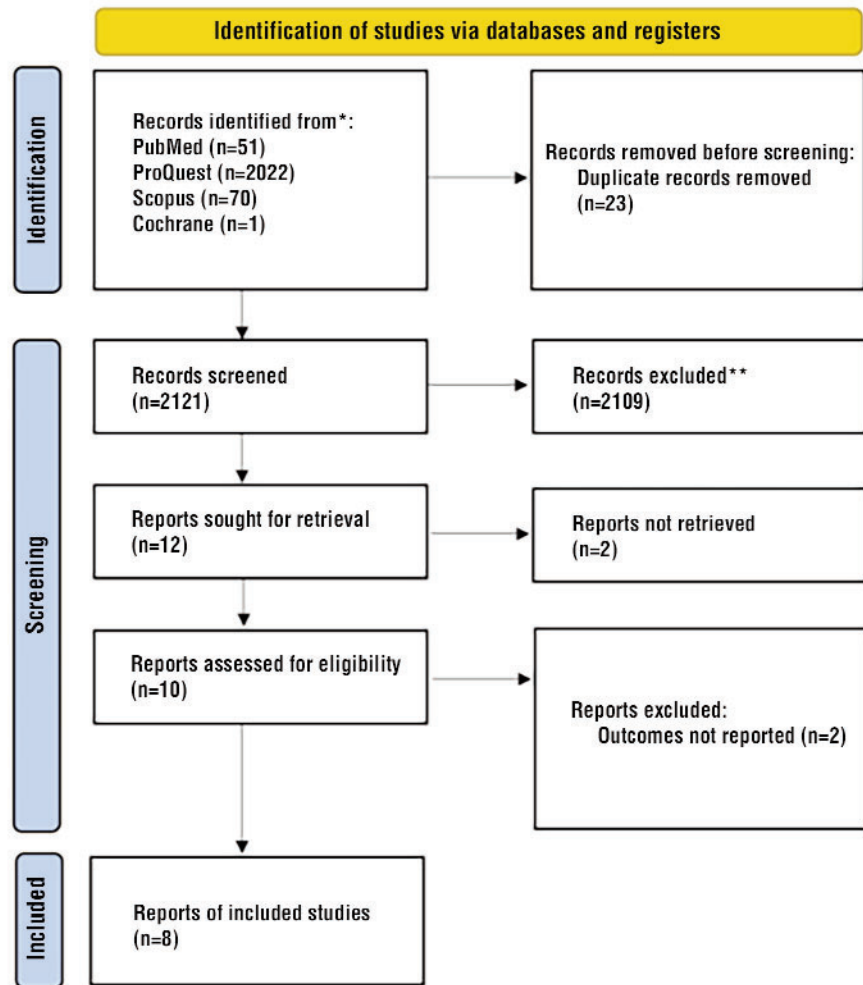
To appraise each study, the proper tool for each study design was used. The Newcastle Ottawa Scale was used for cohort studies, examining studies from its selection of cohorts, comparability of cohorts, and validity of outcomes (9).

RESULTS

Search Selection and Characteristics

In this study, a literature search was conducted using the keyword “(neutrophil to lymphocyte ratio OR neutrophil-to-lymphocyte ratio OR neutrophil lymphocyte ratio OR NLR) AND (papillary thyroid carcinoma OR papillary thyroid cancer)”. 2144 records were identified from the databases, as shown in *fig. 1*, and the number of hits acquired using the respective keywords used on each database is presented in *table 1*. After removing

Figure 1 - PRISMA flow diagram of the literature search



23 duplicate studies and excluding 2109 studies that did not meet the inclusion criteria, 8 articles were downloaded and read. After further assessment, 6 retrospective cohort studies were included in the study as 2 articles didn't report the relevant outcomes. Detailed characteristics of each study are described in *table 2* and *table 3*.

A total of 3,434 patients from 8 retrospective cohorts were included. Most included studies were conducted in Asia and two others (Manatakis et al and Cevlan et al) were conducted in Europe. The population

across studies were mostly female, ranging from 20 - to 68-year-old. All studies revealed a connection between higher NLR values and nodal metastasis progression. However, only four of these studies showed significant associations ($p < 0.05$) which can be attributed to NLR cut-off values falling between 2 and 2.1. Despite this, one study conducted by Shrestha, et al, which used 2.37 as the NLR cut-off, failed to produce a significant association ($p = 0.262$). Three studies (Lang et al, Gong et al, and Ceylan et al) reported that higher NLR value was significantly correlated with larger tumor size, which may explain the correlation of node metastasis. Further details can be found in *table 2*.

Table 1 - Number of hits of each database.

Database	Hits
PubMed	51
ProQuest	2022 (Scholarly Journal)
Scopus	70
Cochrane	1

Critical Appraisal

The eligible studies were subjected to a process of critical appraisal based on their respective study designs. Given that all of the studies were retrospective cohort studies, we employed The Newcastle Ottawa Scale to

Table 2 - Baseline Characteristics of Included Studies.

No	Author (Year)	LoE*	Duration of study	Country	Design	Follow-up duration	Population		
							Subject (n)	Sex (n(%))	Age (years)
1.	Lang et al. (2014)	2b	Jan 2004 – Oct 2012	China	Retrospective Cohort	41.3 months	191	Female (151 (79.1%))	47.9 ± 15.8
2.	Kim et al. (2014)	2b	Mar 2005 – Sep 2012	Korea	Retrospective Cohort	6 – 99 months	542	Female (451 (83.2%))	48.8 ± 12.3
3.	Gong et al. (2016)	2b	April 2014 – Sep 2015	China	Retrospective Cohort	Not mentioned	161	Female (119 (74%))	Median 47 (23-66)
4.	Manatakis et al. (2017)	2b	Jan 2006 – Dec 2015	Greece	Retrospective Cohort	Not mentioned	205	Female (150 (73.2%))	51.2 ± 14.7
5.	Lee et al. (2019)	2b	Jan 2008 – Jan 2012	Korea	Retrospective Cohort	75 months	1846	Female (1465 (79.4%))	Age <45 years (914) Age >45 years (932)
6.	Ceylan et al. (2019)	2b	Jan 2015 – Dec 2016	Turkey	Retrospective Cohort	Not mentioned	201	Female (155 (77.1%))	47.1 ± 14.3
7.	Cheong et al. (2021)	2b	Jan 2009 – Sep 2019	Korea	Retrospective cohort	Not mentioned	531	Female (404 (76.1%))	50.5 ± 13.6
8.	Shrestha et al. (2021)	2b	April 2015 - Oct 2018	Nepal	Retrospective cohort	Not mentioned	31	Female (18 (58.1%))	Age <45 years (26) Age >45 years (5)

* Level of evidence

Table 3 - Study Results

No.	Author (Year)	Analysis Parameters	NLR Cut-off	Results
1.	Lang et al. (2014)	Disease-free survival, multifocality, bilaterality, extra-thyroidal extension	1.93	- Age at surgery ($p = 0.001$) and tumor size ($p = 0.037$) increased significantly with higher NLR. - No significant association was found between NLR and disease-free survival or occult central nodal metastasis.
2.	Kim et al. (2014)	Disease-free survival, presence of node metastasis, multifocality, extrathyroidal extension	Divided into four quartiles	No significant difference was in the occurrence of lymph node metastasis among the quartiles.
3.	Gong et al. (2016)	Metastasis, tumor size, multifocality	2	- In multivariate analysis: Patients with high NLR significantly have a larger tumor, present with lymph node metastasis, and have multifocality. - Lymph node metastasis (Standard regression coefficient (95%CI) = 0.295(0.245-0.739), $p=0.000$).
4.	Manatakis et al. (2017)	Metastasis, multifocality, bilaterality, extra-thyroidal invasion, follicular variant, stage	2.17	High NLR patients had a significantly higher rate of lymph node metastasis compared to low NLR patients. (11.7% vs. 2.9%, $p = 0.03$)
5.	Lee et al. (2019)	Disease-free survival	2.1	In the ≥ 45 age group, lymphovascular invasion (Hazard Ratio (95% CI) = 3.99 (1.08–14.73), $p = 0.038$)
6.	Ceylan et al. (2019)	Metastasis, tumor size, multifocality, bilaterality, capsule invasion, extra-thyroidal spread	1.92	- Larger tumor size and extra-thyroidal spread were correlated with higher NLR values with significant relationship - No significant relationship was found between NLR and age, multifocality, bilaterality, presence of thyroid capsule invasion, surgical margin positivity, and lymph node metastasis.
7.	Cheong et al. (2021)	Metastasis, multifocality/extra-thyroidal, extension/stage	Not mentioned	Patients with central nodal metastases had a non-significantly higher NLR value compared to those without (1.56 (1.3-2.04) vs 1.53 (1.17-1.97), $p = 0.197$).
8.	Shrestha et al. (2021)	Metastasis, multifocality, tumor size, extra-thyroidal extension, bilaterality	2.37	- Higher NLR value was non-significantly higher in patients with nodal metastasis compared to those without ($p = 0.262$). - No significant correlation was found between NLR and age, thyroid capsule invasion, multifocality, and lymph node metastasis.

Table 4 - Critical appraisal of included cohort studies

Study	S1	S2	S3	S4	C1	O1	O2	O3	Total	Quality
Lang et al. (2014)									10	Good
Kim et al. (2014)									8	Good
Gong et al. (2016)									7	Poor
Manatakis et al. (2017)									7	Poor
Lee et al. (2019)									10	Good
Ceylan et al. (2019)									7	Poor
Cheong et al. (2021)									6	Poor
Shrestha et al. (2021)									6	Poor

S: selection, C: comparability, O: outcome

Conversion to Agency for Healthcare Research and Quality (AHRQ) standards:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

perform a thorough evaluation of the studies. The critical appraisal of these cohort studies is presented in *table 4*, which provides a detailed assessment of the studies' selection, comparability of cohorts, and validity of outcomes. The present analysis concerns eight studies, of which three, namely Lang (2014), Kim (2014), and Lee (2019), exhibit characteristics of good quality as they satisfy all appraisal criteria. Conversely, the remaining studies are considered to be of inferior quality as they do not explicitly mention the follow-up period in the article, despite satisfying the selection and comparability domains.

DISCUSSION

The studies included are all retrospective cohort. Based on Oxford Centre for Evidence-Based Medicine criteria, these studies are designated as level 2B evidence (8). Upon conducting a thorough critical appraisal, the cohort studies were found to be good in quality. Most studies have included all participants with consecutive sampling and clearly reported the demographics and outcomes. However, some studies did not clearly state the inclusion criteria. In several studies, it was not stated whether the condition was measured in a standard and reliable manner for all participants, and whether valid methods were utilized for identifying the condition. The study included in this study was doubtful in validity as it was a non-randomized study. Although no randomization was done, follow-up was still completely done in more than 40 months in studies by Lang, et al, Kim et al, and Lee, et al. However, other studies did not mention clearly the follow up period.

Across all studies, there was a total of 3434 subjects. In each of study, the majority gender is female. Central

tendency of the age was reported with mean or median. The majority of subjects in all studies consists of >45 years old patients, indicating the older age to be a risk factor of malignancy incidence and its worse progression.

It is widely acknowledged that systemic inflammation frequently accompanies various human cancers, including thyroid carcinoma, while NLR emerging as a robust biomarker depicting systemic inflammation levels. Studies have revealed a positive correlation between increased NLR and increased levels of circulating pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-7, IL-8, IL-2, IL-17, interleukin-1 receptor alpha (IL-1R α), and monocyte chemotactic protein-1 (16). These mediators foster a micro-environment conducive to cancer invasion. Furthermore, neutrophils have been implicated in inhibiting tumor necrosis factor-alpha (TNF- α) secretion while promoting the generation of vascular endothelial growth factor (VEGF), thereby playing a significant role in tumor angiogenesis and progressions (17). Moreover, inflammatory cells also mediate biological processes such as lymphangiogenesis. Lymphangiogenesis plays an important role in the process of lymph node metastasis, as evidenced by studies demonstrating a clear association between heightened lymphangiogenesis and the occurrence of lymph node metastasis (18). VEGF stands out as the principal driver of lymphangiogenesis, underscoring its pivotal role in this biological process (17,18).

Besides, elevated NLR levels may stem from diminished lymphocyte proliferation, consequently fostering tumorigenesis and metastatic spread through attenuated antitumor mechanisms. Metastatic sites often show an abundance of leukocytes, potentially

fueling cancer growth and progression. Additionally, malignancies possess mechanisms to induce anergic tolerance in lymphocytes or suppress immune responses through various cytokines (19). Notably, cancers commonly depress innate immune responses, notably evidenced by decreased helper T-cell lymphocyte levels (20). Lymphocytes play a crucial role in both cellular and humoral immunity in humans, exerting a notable inhibitory influence on cancer cell proliferation and impeding cancer cell metastasis (16,19).

While the utility of Neutrophil-to-Lymphocyte Ratio (NLR) as a prognostic biomarker has been extensively validated in numerous non-thyroidal cancers, its role in predicting prognosis in Papillary Thyroid Carcinoma (PTC) remains relatively underexplored. Moreover, there is no established threshold values defining elevated Neutrophil-to-Lymphocyte Ratio (NLR) predictive in occult nodal metastasis of PTC. In this review, four of studies exhibited significant associations ($p < 0.05$) with potentially NLR cut-off values falling between 2 and 2.1.

The main limitation of this review lies in the limited variety of study types included. The majority of studies incorporated were in the form of retrospective cohort study. Due to the fact that studies were retrospective, it was prone to selection biases. Inclusion of other study involving prospective data extraction might enhance the analysis and provide a more comprehensive perspective. Besides, Neutrophil and lymphocyte levels might be affected by other infections, medication, and other comorbidities. Nevertheless, as they were not evaluated, this might act as a confounding factor in this study. By addressing these limitations and incorporating a wider range of study types regions, future research can aid in the strengthening of evidence on NLR utilisation in predicting nodal metastasis. By addressing these limitations and incorporating a wider range of study types of regions, future research can aid in the strengthening of evidence on NLR utilisation in predicting nodal metastasis. Despite these limitations, this study offers insight of the preoperative NLR to predict nodal metastasis in PTC cases. To the best of our knowledge, this study was the first systematic review on latest studies, hence offering high grade of scientific evidence in this topic.

CONCLUSION

Preoperative neutrophil-to-lymphocyte ratio (NLR) shows a consistent, directionally positive association with occult nodal metastasis in clinically node-negative papillary thyroid carcinoma (PTC). Taken together,

these data support the use of NLR as an accessible, low-cost adjunct to refine preoperative risk stratification and to help prioritize intensified nodal evaluation in cN0 PTC, particularly when other clinicopathologic risk features co-exist.

Conflict of Interest

The authors declare that there is no competing interest regarding the making and the publication of this article.

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