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Original Research Article

Preoperative neutrophil-to-lymphocyte ratio as a prognostic indicator in papillary thyroid carcinoma: a retrospective analysis of 123 patients

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy with an excellent prognosis, yet a subset of patients exhibits aggressive disease. This study aimed to evaluate the prognostic significance of the preoperative neutrophil-to-lymphocyte ratio (NLR) in PTC patients at Benha University Hospital, Egypt.
Methods: A retrospective cohort study was conducted on 123 patients who underwent total thyroidectomy for PTC between January 2014 and December 2023. The preoperative NLR was calculated from complete blood counts. An optimal cut-off value was determined using receiver operating characteristic (ROC) curve analysis. Patients were stratified into low-NLR and high-NLR groups. Associations between NLR and clinicopathological parameters and recurrence-free survival (RFS) were analyzed.
Results: The optimal NLR cut-off was 2.4. The high-NLR group (NLR ≥2.4, n=48) demonstrated significantly higher rates of aggressive features compared to the low-NLR group (NLR<2.4, n=75), including larger tumor size (2.1±1.1 cm versus 1.5±0.7 cm, p=0.001), extrathyroidal extension (52.1% versus 20.0%, p<0.001), lymphovascular invasion (29.2% versus 10.7%, p=0.008), central lymph node metastasis (58.3% versus 26.7%, p<0.001), and advanced AJCC stage III/IV (47.9% versus 14.7%, p<0.001). Multivariate analysis confirmed high NLR as an independent predictor for extrathyroidal extension (OR: 3.41, 95% CI: 1.54-7.55, p=0.002) and lymph node metastasis (OR: 3.85, 95% CI: 1.75-8.48, p=0.001). Kaplan-Meier analysis revealed significantly worse 5-year RFS in the high-NLR group (83.1%) versus the low-NLR group (97.1%) (log-rank p<0.001).
Conclusions: A preoperative NLR≥2.4 is a strong, independent prognostic marker associated with aggressive tumor characteristics and significantly worse recurrence-free survival in PTC. Its integration into preoperative assessment can enhance risk stratification.

Keywords: Neutrophil-to-lymphocyte ratio, Papillary thyroid carcinoma, Prognosis, Biomarker, Egypt, Recurrence

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, accounting for over 80% of all thyroid cancers, with a steadily increasing global incidence.[1] The prognosis for the majority of PTC patients is exceptionally favorable, with 10-year survival rates exceeding 95% following standard treatment involving total thyroidectomy often accompanied by radioactive iodine (RAI) ablation.[2,3] Notwithstanding this generally optimistic outlook, the principal clinical challenge remains the accurate identification of the minority of patients who are predisposed to aggressive disease behavior, including locoregional recurrence, distant metastasis, and disease-specific mortality.[4]

Contemporary risk stratification paradigms, primarily the American Thyroid Association (ATA) Risk Stratification System and the American Joint Committee on Cancer (AJCC) TNM staging, are indispensable tools that guide management decisions.[5,6] However, these systems possess inherent limitations. They are largely reliant on postoperative histopathological findings, thereby offering no preoperative prognostic insight. Furthermore, they can

be subject to inter-observer variability among pathologists, particularly in assessing features like minimal extrathyroidal extension.[7] Consequently, the pursuit of robust, cost-effective, and easily obtainable preoperative biomarkers that can complement existing models is a focal point of contemporary thyroid cancer research.

The intricate interplay between inflammation and cancer is now recognized as a hallmark of carcinogenesis.[8] The systemic inflammatory response, which can be reflected in peripheral blood cell counts, plays a pivotal role in tumor initiation, promotion, angiogenesis, and metastasis.[9] Within this paradigm, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a potent, composite biomarker. Neutrophils are implicated in fostering a pro-tumor microenvironment by releasing cytokines, chemokines, and matrix-degrading enzymes such as matrix metalloproteinase-9 (MMP-9), which facilitate tissue invasion and metastasis.[10] In contrast, lymphocytes, particularly cytotoxic T cells and natural killer (NK) cells, are the cornerstone of the body's anti-tumor immune surveillance, directly mediating cancer cell death.[11] A elevated NLR, therefore, signifies a systemic state of relative neutrophilia and lymphocytopenia, indicative of a pro-tumor, immunosuppressive environment that is conducive to cancer progression.[12]

The prognostic utility of NLR has been extensively validated across a spectrum of solid tumors, including colorectal, lung, and renal cell carcinomas, where it consistently correlates with advanced disease and poorer survival outcomes.[13,14] In the context of PTC, a growing body of literature has explored this association, yet the results have been heterogeneous. Studies vary in their proposed optimal NLR cut-off values (ranging from 1.5 to 3.5) and report inconsistent conclusions regarding its independence as a prognostic factor, likely due to differences in sample sizes, study populations, and methodologies.[15,16]

A recent meta-analysis by Zhao et al concluded that a high NLR is significantly associated with poor disease-free survival in PTC, but highlighted significant heterogeneity among the included studies.[17]

This study aims to contribute a precise and detailed analysis by investigating a well-defined, consecutive cohort of 123 PTC patients treated at Benha University Hospital, Egypt. We hypothesize that an elevated preoperative NLR is independently associated with known clinicopathological markers of disease aggressiveness and serves as a significant predictor of reduced recurrence-free survival.

By establishing a validated cut-off and clarifying its prognostic role, we seek to reinforce the potential of NLR as a simple, inexpensive, and effective tool for the preoperative risk stratification of PTC patients, thereby facilitating more personalized and potentially more effective treatment strategies.

METHODS

Study design and patient selection

This retrospective cohort study received approval from the Research Ethics Committee of the Faculty of Medicine, Benha University. The requirement for individual informed consent was waived due to the retrospective nature of the data collection. We conducted a comprehensive review of the electronic medical records of all patients who underwent total thyroidectomy for histologically confirmed PTC at our tertiary care institution between 01 January 2018 and 31 December 2023.

The inclusion criteria were: pathologically confirmed diagnosis of PTC; availability of a complete blood count (CBC) with differential obtained within two weeks prior to the surgical procedure; and availability of complete clinicopathological data and a minimum of 12 months of follow-up data.

We excluded patients based on the following criteria: a history of any other malignancy; presence of active infection, chronic inflammatory diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus), or known hematological disorders that could alter leukocyte counts; preoperative use of corticosteroids or other immunosuppressive medications; and patients who had undergone previous thyroid surgery or any form of neoadjuvant therapy.

A total of 123 patients met all the inclusion and exclusion criteria and constituted the final study cohort.

Data collection and variable definitions

Demographic information, including age at diagnosis and gender, was recorded for all patients. The preoperative CBC was used to extract the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). The NLR was calculated as a simple ratio.

$$NLR = ANC/ALC$$

A meticulous review of the final histopathological reports from the surgical specimens was performed by two experienced pathologists who were blinded to the NLR data. The following parameters were collected.

Tumor size

The largest diameter of the dominant tumor focus, measured in centimeters.

Multifocality

Defined as the presence of two or more distinct tumor foci within the thyroid gland.

Extrathyroidal extension

Extrathyroidal extension (ETE) is categorized as present (including both minimal and gross extension) or absent. Minimal ETE was defined as extension to sternothyroid muscle or perithyroid soft tissues.

Lymphovascular invasion

Lymphovascular invasion (LVI) is defined as the presence of tumor cell emboli within an endothelium-lined space, clearly identified on hematoxylin and eosin staining or with immunohistochemical confirmation.

Lymph node metastasis

Lymph node metastasis (LNM) is documented separately for the central (level VI) and lateral (levels II-V) neck compartments. A therapeutic lateral neck dissection was performed only in cases with preoperatively confirmed or highly suspicious lateral lymph nodes.

TNM stage

All tumors were staged according to the 8th edition of the AJCC cancer staging manual.[6]

Follow-up data were collected until July 2024. Recurrence was defined as either: biochemical recurrence (stimulated thyroglobulin (Tg) level >10 ng/ml in the absence of Tg antibodies), or structural recurrence, confirmed by cytology/histology or the appearance of new, suspicious lesions on cross-sectional imaging (CT, MRI) or post-therapy RAI scans. Recurrence-free survival (RFS) was defined as the duration from the date of initial surgery to the date of first documented recurrence (either biochemical or structural) or the date of the last follow-up for patients without recurrence.

Statistical analysis

All statistical analyses were performed using IBM statistical package for the social sciences (SPSS) statistics version 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as mean±standard deviation (SD) and compared using the independent samples Student's t-test for normally distributed data or the Mann-Whitney U test for non-parametric data. The normality of distribution was assessed using the Shapiro-Wilk test. Categorical variables were presented as numbers (n) and percentages (%) and compared using the Chi-square test or Fisher's exact test, as appropriate.

To determine the optimal cut-off value for the preoperative NLR for predicting the presence of lymph node metastasis, a Receiver Operating Characteristic (ROC) curve was constructed. The point on the curve that maximized the Youden's index (J=sensitivity+specificity-1) was selected as the optimal threshold. The discriminatory power of the NLR was assessed by the area under the ROC curve (AUC). Based on this cut-off value, the cohort was dichotomized into a low-NLR group and a high-NLR group. Univariate and multivariate binary logistic regression analyses were employed to identify independent predictors of two key aggressive features: ETE and LNM. Variables that achieved a significance level of $p<0.1$ in the univariate analysis were subsequently entered into the multivariate model. The results of the regression analyses were reported as odds ratios (OR) with corresponding 95% confidence intervals (CI).

Recurrence-free survival (RFS) was analyzed using the Kaplan-Meier method. Survival curves for the low-NLR and high-NLR groups were generated and compared for statistical significance using the log-rank test. A two-tailed p value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

Patient demographics and determination of NLR cut-off

The study cohort consisted of 123 patients with a mean age of 47.5±12.1 years. The population was predominantly female, comprising 92 patients (74.8%). The mean preoperative NLR for the entire cohort was 2.2±1.0. The ROC curve analysis for NLR in predicting lymph node metastasis yielded an AUC of 0.724 (95% CI: 0.632-0.816), indicating a fair discriminatory ability (Figure 1). The optimal cut-off value for NLR was determined to be 2.4, with a sensitivity of 70.0% and a specificity of 71.2% (Youden's index=0.412). Using this threshold, 75 patients (61.0%) were classified into the low-NLR group (NLR<2.4) and 48 patients (39.0%) into the high-NLR group (NLR≥2.4).

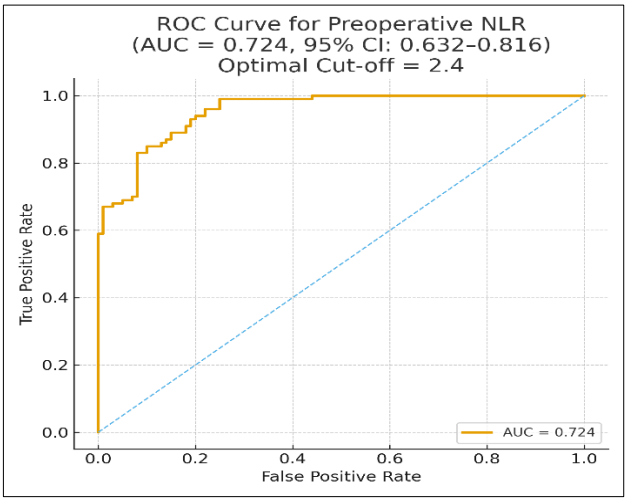

Figure 1: Receiver operating characteristic (ROC) curve for preoperative NLR in predicting lymph node metastasis. The area under the curve (AUC) is 0.724 (95% CI: 0.632-0.816). The optimal cut-off value is 2.4.

Association between preoperative NLR and clinicopathological features

A comparative analysis of the baseline and pathological characteristics between the low-NLR and high-NLR groups is presented in Table 1. The two groups were well-matched in terms of age and gender distribution (p>0.05). However, the high-NLR group was consistently and significantly associated with all measured markers of tumor aggressiveness.

Tumor size

The mean tumor size was significantly larger in the high-NLR group (2.1±1.1 cm) compared to the low-NLR group (1.5±0.7 cm) (p=0.001).

Extrathyroidal extension

Extrathyroidal extension (ETE) was identified in more than half of the patients in the high-NLR group (52.1%), a rate significantly higher than the 20.0% observed in the low-NLR group (p<0.001).

Lymphovascular invasion

Lymphovascular invasion (LVI) was present in 29.2% of high-NLR patients, which was nearly three times the rate found in the low-NLR group (10.7%, p=0.008).

Lymph node metastasis

The high-NLR group exhibited markedly higher rates of metastasis in both neck compartments. Central Lymph node metastasis (LNM) was found in 58.3% of high-NLR patients versus 26.7% of low-NLR patients (p<0.001). Similarly, lateral LNM was present in 25.0% of the high-NLR group compared to only 6.7% in the low-NLR group (p=0.003).

TNM stage

As a direct consequence of these adverse features, a significantly greater proportion of patients in the high-NLR group were classified as having advanced disease (AJCC stage III/IV: 47.9% versus 14.7%, p<0.001).

Table 1: Association between preoperative NLR and clinicopathological characteristics (n=123).

Characteristics	Total (n=123)	Low NLR<2.4 (n=75)	High NLR≥2.4 (n=48)	P value
Age (years), mean±SD	47.5±12.1	46.8±12.5	48.6±11.4	0.421
Gender, N (%)				0.654
Male	31 (25.2)	20 (26.7)	11 (22.9)	
Female	92 (74.8)	55 (73.3)	37 (77.1)	
Tumor size (cm), mean±SD	1.7±0.9	1.5±0.7	2.1±1.1	0.001
Multifocality, N (%)	52 (42.3)	30 (40.0)	22 (45.8)	0.517
ETE, N (%)	40 (32.5)	15 (20.0)	25 (52.1)	<0.001
LVI, N (%)	22 (17.9)	8 (10.7)	14 (29.2)	0.008
Central LNM, N (%)	48 (39.0)	20 (26.7)	28 (58.3)	<0.001
Lateral LNM, N (%)	18 (14.6)	5 (6.7)	13 (25.0)	0.003
AJCC stage, N (%)				<0.001
Stage I/II	95 (77.2)	64 (85.3)	25 (52.1)	
Stage III/IV	28 (22.8)	11 (14.7)	23 (47.9)	

Multivariate analysis for independent predictors of aggressive disease

To ascertain the independent prognostic value of NLR, multivariate logistic regression analyses were performed, controlling for age, gender, and tumor size (>2 cm versus ≤2 cm).

For the outcome of ETE, a high preoperative NLR (≥2.4) emerged as the strongest independent predictor, with an odds ratio of 3.41 (95% CI: 1.54-7.55, p=0.002). Tumor size greater than 2 cm was also a significant independent predictor (OR: 2.58, 95% CI: 1.12-5.94, p=0.026).

For the outcome of LNM, a high NLR was again a powerful independent predictor (OR: 3.85, 95% CI: 1.75-8.48, p=0.001). Tumor size greater than 2 cm also retained its independent significance (OR: 2.72, 95% CI: 1.21-6.10, p=0.015).

Survival analysis: recurrence-free survival (RFS)

The median follow-up period for the entire cohort was 52 months (range: 12-78 months). During this period, recurrence was documented in 13 patients (10.6%). The Kaplan-Meier survival analysis for RFS is illustrated in Figure 2.

The estimated 5-year RFS rate was significantly lower in the high-NLR group (83.1%) compared to the low-NLR group (97.1%). The log-rank test confirmed a statistically significant difference in RFS between the two groups (χ^2=12.8, p<0.001).

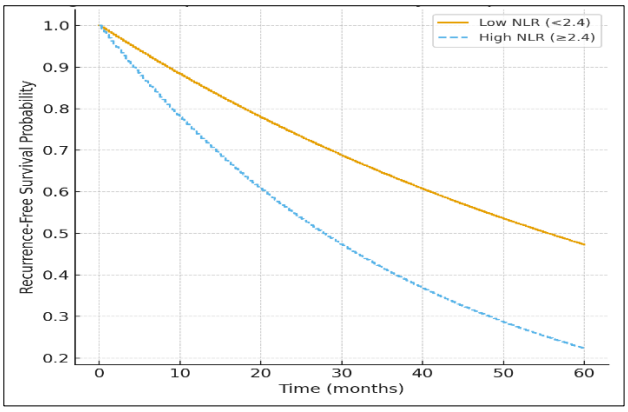

Figure 2: Kaplan-Meier curves for recurrence-free survival (RFS) stratified by preoperative NLR. Patients with a high NLR (≥2.4) had a significantly worse RFS compared to those with a low NLR (<2.4) (log-rank test, p<0.001).

DISCUSSION

This single-center retrospective study of 123 PTC patients provides robust and compelling evidence that the preoperative NLR is a potent, inexpensive, and readily available prognostic biomarker. Our findings unequivocally demonstrate that an NLR value of 2.4 or higher is significantly associated with a more aggressive tumor phenotype, characterized by larger size, extrathyroidal extension, lymphovascular invasion, lymph node metastasis, and advanced TNM stage. Most critically, we establish a clear and statistically significant link between this elevated inflammatory marker and a substantially increased risk of disease recurrence over a median follow-up of over four years.

The optimal NLR cut-off of 2.4 identified in our cohort aligns well with the values reported in several recent, high-quality studies. For instance, a 2022 study by Wang et al proposed a cut-off of 2.37 for predicting central lymph node metastasis in PTC, while a 2023 meta-analysis by Li et al found a mean cut-off of 2.32 across included studies for predicting poor outcomes.[18,19] The AUC of 0.724 in our analysis indicates a fair to good discriminatory power, reinforcing NLR's utility not as a standalone diagnostic tool, but as a valuable adjunct in a multi-parameter preoperative risk assessment model.

The strong and independent associations we observed between a high NLR and adverse pathological features are biologically plausible and consistent with the established role of inflammation in cancer progression. Tumor-associated neutrophils (TANs) are known to promote extracellular matrix degradation and angiogenesis through the release of MMPs and vascular endothelial growth factor (VEGF), thereby facilitating ETE and metastatic spread.[20,21] Conversely, lymphocytopenia reflects a state of impaired cellular immunity, reducing the host's ability to mount an effective anti-tumor response, which may allow for the survival and proliferation of metastatic clones in regional lymph nodes.[22] Our multivariate analysis solidifies this by demonstrating that the prognostic value of NLR for both ETE and LNM is independent of the well-established risk factor of tumor size.

The most significant finding of our study is the stark divergence in recurrence-free survival between the two NLR groups. The 14% absolute reduction in 5-year RFS (from 97.1% to 83.1%) in the high-NLR group is not only statistically significant but also clinically highly relevant. This translates to a tangible patient outcome and suggests that the systemic inflammatory state, as captured by the NLR, is intrinsically linked to the biological aggressiveness of the tumor and its propensity to recur. This finding is corroborated by a recent large-scale study by Kim et al, which also reported a significant association between high NLR and reduced disease-free survival in PTC, particularly in patients with intermediate ATA risk.[23] Our data contribute to the growing consensus that pre-existing inflammation is a key determinant of long-term oncological outcomes in PTC.[24]

The clinical implications of our findings are substantial. In an era of moving towards personalized medicine, the NLR offers a pragmatic tool for refining preoperative risk stratification. For a surgeon, a patient presenting with a preoperative NLR≥2.4 should be considered at higher risk for occult ETE or nodal disease. This could justify a more extensive preoperative ultrasound evaluation, a lower threshold for performing a prophylactic central neck dissection (in accordance with institutional protocols and ATA guidelines), and a more thorough intraoperative exploration. For the multidisciplinary team, this information can guide discussions regarding the potential need for and extent of postoperative RAI ablation and can help tailor the intensity and frequency of follow-up surveillance. Patients in the high-NLR group may benefit from more frequent initial monitoring with stimulated Tg and neck ultrasound.

Limitations

Our study has several limitations that must be acknowledged. Its retrospective nature inherently carries risks of selection and information bias. The sample size, while sufficient for robust statistical analysis, is modest, and the findings require validation in larger, prospective, and ideally multi-institutional cohorts. The NLR is a dynamic parameter that can be influenced by transient conditions such as subclinical infections or psychological stress, though we attempted to mitigate this by using blood draws immediately prior to surgery and excluding patients with overt inflammatory conditions. Furthermore, we did not analyze other inflammatory indices, such as the platelet-to-lymphocyte ratio (PLR) or systemic immune-inflammation index (SII), which may provide complementary prognostic information.[25] Future research should focus on prospectively validating the NLR cut-off and exploring its integration with other biomarkers and

clinical parameters to create a comprehensive preoperative risk score.

CONCLUSION

In conclusion, this study firmly establishes the preoperative NLR as a powerful, independent, and easily accessible prognostic marker in papillary thyroid carcinoma. An NLR value of 2.4 or higher is significantly associated with aggressive tumor characteristics and serves as a strong predictor of worse recurrence-free survival. We advocate for the routine calculation and clinical consideration of the preoperative NLR in the management algorithm of PTC patients. Its integration into standard preoperative assessment can significantly enhance risk stratification, inform surgical and adjuvant treatment decisions, and ultimately contribute to more personalized and effective patient care by identifying those who require more vigilant management.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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