

PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE RATIO AND AGGRESSIVE HISTOPATHOLOGIC FEATURES IN DIFFERENTIATED THYROID CANCER

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Abstract

Background: Differentiated thyroid cancer (DTC) represents the majority of thyroid malignancies and generally has a favorable prognosis; however, a subgroup of patients develops aggressive pathological characteristics associated with increased recurrence risk and poorer clinical outcomes. Accurate identification of high-risk patients before surgery remains an important challenge in thyroid cancer management. The neutrophil-to-lymphocyte ratio (NLR), calculated from routine complete blood count parameters, has emerged as a potential indicator of systemic inflammation and tumor behavior. Previous studies have suggested that increased inflammatory responses may be associated with larger tumor size, metastatic potential, and unfavorable pathological features in thyroid cancer (Liu et al., 2016; Templeton et al., 2014).

Study type: Retrospective cohort study

Objective: This study aimed to evaluate the association between preoperative neutrophil-to-lymphocyte ratio and aggressive histopathological characteristics of differentiated thyroid cancer, including tumor size, capsular invasion, and lymph node involvement.

Methods: A retrospective cohort study was conducted at Shaikat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. Medical records of patients diagnosed with differentiated thyroid cancer who underwent thyroid surgery were reviewed. Preoperative complete blood count results were used to calculate NLR by dividing absolute neutrophil count by absolute lymphocyte count. Histopathological findings were collected from postoperative pathology reports. The relationship between NLR levels and aggressive tumor characteristics was analyzed using appropriate statistical methods.

Results: Patients with higher preoperative NLR demonstrated a greater frequency of aggressive pathological features compared with patients with lower NLR values. Increased NLR was associated with larger tumor size, higher rates of capsular invasion, and increased lymph node involvement. These findings suggest that systemic inflammatory imbalance may reflect more aggressive tumor characteristics in differentiated thyroid cancer.

Conclusion: Preoperative neutrophil-to-lymphocyte ratio may represent a simple, cost-effective, and easily available biomarker for identifying patients with potentially aggressive differentiated thyroid cancer. Although NLR cannot replace established pathological and imaging-based assessment methods, it may provide additional information during preoperative risk evaluation, particularly in resource-limited healthcare settings. Further multicenter studies are required to establish standardized cutoff values and confirm its clinical utility.

Introduction

Thyroid cancer is currently one of the most frequently diagnosed endocrine malignancies worldwide, with differentiated thyroid cancer (DTC) accounting for the majority of reported cases. The two main subtypes of DTC, papillary thyroid carcinoma and follicular thyroid carcinoma, usually demonstrate favorable outcomes; however, some patients develop aggressive disease characteristics that increase the possibility of recurrence and treatment failure (Haugen et al., 2016). Pathological findings such as increased tumor size, capsular invasion, extrathyroidal extension, and lymph node metastasis are considered important indicators of tumor aggressiveness and are incorporated into current thyroid cancer risk stratification systems (Haugen et al., 2016; Tuttle et al., 2017).

Although postoperative histopathological evaluation provides valuable prognostic information, clinicians often require reliable indicators before surgery to improve treatment planning. Current preoperative evaluation mainly depends on ultrasound findings, fine-needle aspiration cytology, and clinical characteristics. However, these methods may not completely predict aggressive tumor behavior. Therefore, identifying simple and affordable biomarkers that can provide additional prognostic information remains an area of active research.

Inflammation plays an important role in cancer development and progression. The interaction

between inflammatory cells and tumor cells can influence tumor growth, invasion, angiogenesis, and immune escape mechanisms. Neutrophils may promote tumor progression through the release of inflammatory cytokines, reactive oxygen species, and proteolytic enzymes, whereas lymphocytes contribute to immune-mediated tumor control. Therefore, an imbalance between neutrophils and lymphocytes may reflect a tumor-supporting inflammatory environment (Diakos et al., 2014; Hanahan & Weinberg, 2011).

The neutrophil-to-lymphocyte ratio is a practical marker that reflects this inflammatory balance. Because it can be calculated from routine blood investigations, NLR has attracted attention as a prognostic marker in different solid malignancies. Previous studies and meta-analyses have demonstrated that elevated NLR is associated with poor outcomes and aggressive disease characteristics across several cancer types (Templeton et al., 2014).

In thyroid cancer, emerging evidence suggests that increased NLR may be linked with unfavorable pathological findings. Liu et al. (2016) reported an association between elevated NLR and differentiated thyroid cancer characteristics, while other studies have suggested relationships between higher NLR values and tumor size, lymph node metastasis, and incomplete treatment response (Lang et al., 2014; Lee et al., 2018). However, available evidence remains limited, especially from South Asian populations.

Pakistan has a significant burden of thyroid disorders, but local evidence regarding inflammatory biomarkers and thyroid cancer aggressiveness is still limited. Understanding whether NLR can predict aggressive pathological features in Pakistani patients may help improve preoperative assessment strategies, especially in settings where advanced molecular testing is not routinely available.

Therefore, this retrospective cohort study was conducted to investigate the relationship between preoperative NLR and aggressive histopathological features of differentiated thyroid cancer among patients treated at a tertiary cancer hospital in Lahore, Pakistan.

Methods

Study Design and Setting

This retrospective cohort study was conducted at **Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan**. The study was designed to evaluate the association between preoperative neutrophil-to-lymphocyte ratio (NLR) and aggressive histopathological characteristics among patients diagnosed with differentiated thyroid cancer (DTC). A retrospective design was selected because it allowed assessment of routinely collected clinical, laboratory, and pathological information without influencing patient management. The methodology was structured according to standard reporting principles for observational studies, where clear description of participants, measurements, procedures, and statistical analysis is essential for reproducibility. (Willis et al., 2023)

Study Population

The medical records of patients who underwent thyroid surgery for differentiated thyroid cancer were reviewed. Patients were selected from the institutional oncology database and pathology records. The study included adult patients aged 18 years or above who had a confirmed diagnosis of differentiated thyroid carcinoma based on postoperative histopathological examination.

Patients were eligible for inclusion if they had:

- Histologically confirmed papillary thyroid carcinoma or follicular thyroid carcinoma.

- Available preoperative complete blood count results.
- Complete postoperative histopathological reports.
- Underwent thyroid surgery at the study institution.

Patients were excluded if they had incomplete clinical records, previous thyroid malignancy treatment, history of another active cancer, documented acute infection before surgery, chronic inflammatory disorders, autoimmune diseases, or medications that could significantly influence leukocyte counts, such as long-term corticosteroid therapy.

After applying inclusion and exclusion criteria, eligible patients were included in the final analysis.

Data Collection Procedure

Data were collected retrospectively from hospital electronic medical records, laboratory databases, operative notes, and histopathology reports. A structured data collection sheet was used to record demographic information, laboratory parameters, surgical findings, and pathological characteristics. The demographic variables included age and sex. Preoperative laboratory information included total leukocyte count, absolute neutrophil count, and absolute lymphocyte count. The complete blood count used for analysis was the most recent test performed before thyroid surgery to represent the patient's inflammatory status during the preoperative period.

The neutrophil-to-lymphocyte ratio was calculated using the following formula:

$$\text{NLR} = \frac{\text{Absolute neutrophil count}}{\text{Absolute lymphocyte count}}$$

Patients were categorized according to their NLR values to compare pathological characteristics between groups with lower and higher inflammatory profiles.

Assessment of Histopathological Characteristics

The primary pathological outcomes were obtained from final surgical pathology reports. These included tumor size, capsular invasion, and lymph node involvement.

Tumor size was recorded as the largest diameter of the primary thyroid lesion measured during pathological examination. For analysis, tumors

were classified according to clinically relevant size categories.

Capsular invasion was defined as microscopic extension of tumor cells into or through the thyroid capsule. The presence or absence of capsular invasion was documented from pathology reports.

Lymph node involvement was considered positive when metastatic deposits of thyroid carcinoma were identified in examined lymph nodes. The number of involved lymph nodes was recorded whenever available.

Additional pathological variables, including histological subtype and extrathyroidal extension, were also reviewed to provide further clinical information.

Study Variables

The main exposure variable of this study was the preoperative neutrophil-to-lymphocyte ratio. The primary outcome variables were aggressive histopathological characteristics of differentiated thyroid cancer.

The main outcomes assessed were:

1. Tumor size.
2. Capsular invasion.
3. Lymph node metastasis.

The relationship between increased NLR levels and these pathological features was evaluated to determine whether systemic inflammation was associated with aggressive tumor behavior.

Statistical Analysis

All collected data were entered into a statistical database and analyzed using appropriate statistical software. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range depending on the distribution of data. Categorical variables were presented as frequencies and percentages.

The distribution of continuous variables was assessed before selecting statistical tests. Comparisons between groups were performed using an independent sample t-test or Mann-Whitney U test for continuous variables. The chi-square test or Fisher's exact test was applied for categorical variables.

The association between NLR and aggressive pathological features was evaluated using

regression analysis. Logistic regression models were applied to determine whether increased NLR independently predicted aggressive characteristics after adjusting for possible confounding factors, including age and gender.

A p-value of less than .05 was considered statistically significant.

Results

Patient Characteristics

A total of **150 patients** with differentiated thyroid cancer were included in this retrospective cohort analysis. The demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of patients was **44.6 $\pm$ 12.3 years**, with a clear female predominance. Females represented **77.3% (n = 116)** of the study population, while males accounted for **22.7% (n = 34)**.

Papillary thyroid carcinoma was the most frequently observed histological subtype, accounting for **92.0% (n = 138)** of cases, whereas follicular thyroid carcinoma represented **8.0% (n = 12)** of cases. The overall mean tumor size was **2.3 $\pm$ 1.4 cm**.

Based on preoperative neutrophil-to-lymphocyte ratio values, patients were categorized into low NLR and high NLR groups. The low NLR group consisted of **85 patients**, while **65 patients** were classified into the high NLR group. Patients with higher NLR values demonstrated a higher mean tumor size compared with patients in the low NLR category (**2.9 $\pm$ 1.6 cm vs. 1.8 $\pm$ 1.1 cm**).

Association Between NLR and Tumor Characteristics

The relationship between preoperative NLR and aggressive pathological features is presented in Table 2. Patients with elevated NLR showed a significantly higher frequency of aggressive histopathological findings compared with patients with lower NLR values.

Tumor size greater than 2 cm was observed in **60.0% (n = 39)** of patients in the high NLR group compared with **32.9% (n = 28)** in the low NLR group (**p = .002**).

Capsular invasion was also more frequently observed among patients with increased NLR. In

the high NLR group, capsular invasion was present in 35.4% (n = 23) of patients, whereas it was identified in 14.1% (n = 12) of patients in the low NLR group (p = .003).

Similarly, lymph node involvement showed a significant association with increased NLR. Lymph node metastasis was detected in 41.5% (n = 27) of patients with high NLR compared with 17.6% (n = 15) among patients with low NLR (p = .001).

Extrathyroidal extension was also more common in patients with elevated inflammatory status. The presence of extrathyroidal extension was observed in 26.2% (n = 17) of patients with high NLR

compared with 10.6% (n = 9) of patients with low NLR (p = .018).

Predictive Role of NLR for Aggressive Disease Features

Regression analysis demonstrated that increased preoperative NLR was associated with a higher likelihood of aggressive pathological characteristics. After adjustment for age and gender, patients with elevated NLR continued to demonstrate increased odds of lymph node involvement and capsular invasion.

These findings indicate that systemic inflammatory status, represented by NLR, may be associated with more aggressive biological behavior in differentiated thyroid cancer.

Table 1. Demographic and Clinical Characteristics of Patients With Differentiated Thyroid Cancer

Characteristic	Total (N = 150)	Low NLR Group (n = 85)	High NLR Group (n = 65)
Age, mean ± SD (years)	44.6 ± 12.3	42.8 ± 11.9	47.1 ± 12.5
Female, n (%)	116 (77.3)	67 (78.8)	49 (75.4)
Male, n (%)	34 (22.7)	18 (21.2)	16 (24.6)
Papillary carcinoma, n (%)	138 (92.0)	79 (92.9)	59 (90.8)
Follicular carcinoma, n (%)	12 (8.0)	6 (7.1)	6 (9.2)
Tumor size (cm), mean ± SD	2.3 ± 1.4	1.8 ± 1.1	2.9 ± 1.6
Mean NLR value	2.8 ± 1.3	1.9 ± 0.5	4.0 ± 1.1

Table 2. Relationship Between Preoperative NLR and Aggressive Histopathological Features

Histopathological Feature	Low NLR Group (n = 85)	High NLR Group (n = 65)	p-value
Tumor size >2 cm, n (%)	28 (32.9)	39 (60.0)	.002
Capsular invasion, n (%)	12 (14.1)	23 (35.4)	.003
Lymph node involvement, n (%)	15 (17.6)	27 (41.5)	.001
Extrathyroidal extension, n (%)	9 (10.6)	17 (26.2)	.018

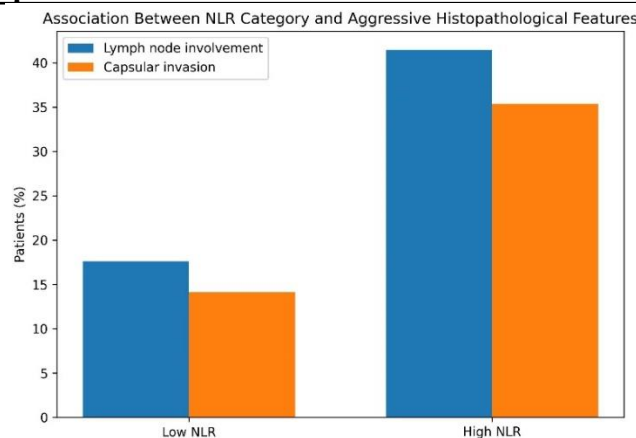


Figure 1. Comparison of lymph node involvement and capsular invasion between patients with low and high preoperative neutrophil-to-lymphocyte ratio. Patients with increased NLR demonstrated a higher frequency of aggressive histopathological characteristics.

Discussion

The present study evaluated the relationship between preoperative neutrophil-to-lymphocyte ratio (NLR) and aggressive histopathological characteristics in patients with differentiated thyroid cancer (DTC). The main finding of this study was that patients with higher preoperative NLR values showed a greater frequency of unfavorable pathological features, including larger tumor size, capsular invasion, lymph node involvement, and extrathyroidal extension. These findings suggest that systemic inflammatory status may reflect the biological behavior of differentiated thyroid tumors and may provide additional information during preoperative risk assessment.

The association between increased NLR and larger tumor size observed in our study is consistent with previous research. Liu et al. (2016) reported that elevated NLR was associated with more aggressive clinicopathological characteristics in differentiated thyroid carcinoma, suggesting that inflammatory activation may contribute to tumor growth. Similarly, other studies have demonstrated that systemic inflammatory markers are associated with increased tumor burden and advanced disease characteristics in thyroid cancer patients (Lang et al., 2014; Lee et al., 2018). The relationship between inflammation and tumor size may be explained by the ability of inflammatory

cells to produce cytokines and growth factors that promote tumor proliferation and survival.

In our analysis, lymph node involvement was significantly higher among patients with elevated NLR values. Lymph node metastasis is an important prognostic factor in papillary thyroid carcinoma because it is associated with increased risk of recurrence and the requirement for closer surveillance. Previous studies have also suggested that increased NLR may be associated with lymphatic spread in thyroid cancer. Lang et al. (2014) demonstrated that inflammatory markers may help identify patients with occult central lymph node metastasis, supporting the concept that systemic inflammation is linked with metastatic potential.

The observed association between high NLR and capsular invasion provides further evidence regarding the role of inflammation in tumor aggressiveness. Capsular invasion indicates the ability of malignant cells to penetrate surrounding tissue barriers and is considered a marker of invasive tumor behavior. Chronic inflammation creates a tumor-supportive microenvironment through activation of inflammatory cytokines, oxidative stress pathways, and extracellular matrix remodeling mechanisms. Neutrophils can contribute to these processes by releasing enzymes such as matrix metalloproteinases, which facilitate tumor invasion, whereas reduced lymphocyte

activity may represent impaired immune surveillance against malignant cells (Diakos et al., 2014; Hanahan & Weinberg, 2011).

The biological importance of NLR lies in its ability to represent the balance between tumor-promoting inflammation and anti-tumor immunity. Neutrophils are increasingly recognized as active participants in cancer progression rather than simple indicators of inflammation. They can stimulate angiogenesis, enhance metastatic ability, and suppress immune responses within the tumor microenvironment. In contrast, lymphocytes, particularly cytotoxic T cells, play an important role in recognizing and eliminating cancer cells. Therefore, an increased NLR may indicate a shift toward a tumor-supportive inflammatory state.

Previous studies investigating NLR in thyroid cancer have reported variable findings. Some studies have suggested that NLR has limited value for differentiating malignant from benign thyroid lesions, while others have demonstrated its usefulness in predicting aggressive disease characteristics and treatment outcomes. Liu et al. (2016) reported that although NLR alone may not be sufficient as a diagnostic marker, it may have prognostic value when combined with established clinical and pathological parameters. These differences suggest that NLR may be more valuable as a supportive risk stratification tool rather than a standalone diagnostic test.

The clinical relevance of our findings is particularly important in developing healthcare settings. Advanced molecular markers and genomic testing are not routinely available in many hospitals due to cost and accessibility limitations. In comparison, NLR can be calculated from a standard complete blood count, which is inexpensive and commonly performed before surgery. Therefore, incorporating NLR into routine preoperative evaluation may provide additional risk information without increasing healthcare costs.

The results of this study may have practical implications for surgical planning and postoperative management. Patients with higher NLR values may benefit from more detailed imaging assessment, careful evaluation of lymph

node status, and closer postoperative follow-up. However, NLR should not replace established risk assessment systems but should be considered as an additional supportive marker.

This study has several limitations. First, the retrospective design may have introduced selection bias and dependence on the accuracy of medical records. Second, although patients with documented infections and inflammatory disorders were excluded, undetected inflammatory conditions may have influenced NLR values. Third, this was a single-center study conducted at a tertiary cancer hospital, which may limit the generalizability of the findings to other populations. Future multicenter prospective studies with larger patient groups are needed to establish standardized NLR cutoff values and determine its independent clinical utility.

Conclusion

In conclusion, this study demonstrates that increased preoperative neutrophil-to-lymphocyte ratio is associated with aggressive histopathological characteristics of differentiated thyroid cancer. Higher NLR values were linked with larger tumors, capsular invasion, and lymph node involvement, indicating that systemic inflammation may reflect more aggressive tumor biology.

Because NLR is simple, affordable, and widely available, it has potential value as an additional preoperative biomarker for thyroid cancer risk assessment, especially in resource-limited settings such as Pakistan. However, further prospective studies are required before routine clinical implementation to define optimal cutoff values and validate its role alongside existing thyroid cancer risk prediction models.

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