



## Is there a predictive value of systemic inflammatory parameters and prognostic nutritional index in the detection of lymphatic metastases in papillary thyroid cancers?

Ali ÖZDEMİR<sup>1,\*</sup>, Osman BANDIRMALI<sup>2</sup>

<sup>1</sup>Department of General Surgery, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Türkiye

<sup>2</sup>Department of General Surgery, Training and Research Hospital, Recep Tayyip Erdoğan University, Rize, Türkiye

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### Abstract

This study aimed to assess the predictive value of systemic inflammatory parameters and the prognostic nutritional index (PNI) in identifying lymphatic metastases in papillary thyroid cancers (PTC). PTCs, characterized by their indolent nature and favorable prognosis, frequently disseminate to cervical lymph nodes, impacting recurrence and prognosis. However, the preoperative identification rate of cervical lymph node metastases ranges from 20% to 75%, necessitating supplemental examinations for precise detection and surgical planning. A retrospective analysis of 441 thyroidectomy cases, encompassing 272 PTC patients, was conducted. Patients were categorized into two cohorts: 221 lacked lymph node metastases, while 51 exhibited lymphatic metastases. Parameters including age, gender, systemic inflammatory markers derived from hemogram tests, serum albumin levels, and postoperative histopathology findings were scrutinized to evaluate the predictive potential of systemic inflammatory parameters and PNI in discerning between the two cohorts. The findings revealed that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) values bore statistically significant predictive capacity ( $p < 0.05$ ) in preoperatively detecting cervical lymph node metastases in PTC. Receiver operating characteristic (ROC) curves delineated the efficacy of NLR, PLR, and SII in prognostication. NLR exhibited an area under the curve (AUC) value of 0.932 (95% CI, 0.902-0.962;  $p < 0.001$ ), while PLR yielded an AUC value of 0.638 (95% CI, 0.555-0.721;  $p = 0.002$ ). SII analysis yielded an AUC value of 0.798 (95% CI, 0.736-0.861;  $p < 0.001$ ). Conversely, the prognostic nutritional index (PNI) demonstrated meager predictive utility, registering an AUC value of 0.192 (95% CI, 0.124-0.260;  $p < 0.001$ ), positioning below the reference line on the ROC curve. In conclusion, this study underscores NLR's utility in identifying cervical lymph node metastases in PTC. While PLR and SII evince some association with lymph node metastasis detection, their predictive efficacy remains constrained. Additionally, despite statistical significance, PNI exhibited inefficacy in forecasting lymph node metastases.

**Keywords:** papillary thyroid carcinomas, lymph node metastasis, prognostic nutritional index, inflammatory markers

### 1. Introduction

The incidence of thyroid cancers has significantly increased in the past decade, with papillary thyroid cancers (PTC) accounting for over 85% of all cases (1). PTC is characterized by slow growth and a favorable prognosis, but it can metastasize to the central or lateral neck lymph nodes in 30-80% of cases (2,3). The presence of lymph node metastasis has been associated with adverse effects on local recurrence and survival (3-4). Therefore, preoperative evaluation of cervical lymph node metastasis (CLNM) using imaging modalities, particularly ultrasonography (USG), is recommended for patients suspected or diagnosed with PTC. The 2015 American Thyroid Association guidelines recommend lymph node dissection for patients with CLNM (5). However, performing prophylactic dissection in patients without lymph node metastasis (cN0) remains controversial due to complications such as the good prognosis of PTCs, hypoparathyroidism,

increased risk of recurrent laryngeal nerve damage, and postoperative quality of life concerns (2,5).

Studies have reported a detection rate of cervical lymph node metastases ranging from 20-75% in the preoperative period using imaging methods, particularly for central lymph nodes with initial metastatic involvement (6,7). Additionally, the literature indicates that the rate of central CLNM detection after surgery in patients with preoperative cN0 ranges from 15-53% (8-10). Hence, there is a need for additional modalities to preoperatively assess metastatic involvement of neck lymphatics, and several studies have investigated this matter (11,12). Systemic inflammatory markers and the prognostic nutritional index are parameters that can be used to evaluate both the prognosis of PTC and the presence of preoperative lymphatic metastases (12).

\*Correspondence: paravoll@hotmail.com

This study aimed to investigate the predictive value of systemic inflammatory markers, specifically the systemic immune inflammation index (SII), and the prognostic nutritional index (PNI) obtained from routine preoperative tests, which are cost-effective and readily available, in the detection of cervical lymph node metastasis in patients with PTC.

## 2. Materials and Methods

A retrospective analysis was conducted on 441 cases of thyroidectomy performed at the General Surgery Clinic of Recep Tayyip Erdoğan University Training and Research Hospital between January 2018 and June 2022. Among the patients operated on, 276 were diagnosed with papillary thyroid cancer. Excluding 151 patients with benign thyroid disease and 14 patients with other thyroid malignancies, the study included 272 patients with PTC. Four patients with PTC who had a history of systemic lupus erythematosus, lymphoma, and gastrointestinal system malignancy were also excluded.

The study evaluated the 272 patients with PTC and classified them into two groups based on the presence or

**Table 1.** Systemic inflammatory markers, SII and PNI formulas

Parameters	Formulas
Systemic inflammatory markers	Neutrophil-to-lymphocyte ratio (NLR)
	Platelet-to-lymphocyte ratio (PLR)
Systemic immune-inflammation index (SII)	[Platelet x (Neutrophil / lymphocyte)]
Prognostic nutritional index (PNI)	[10 × serum albumin (g/dl) + 0.005 × total lymphocyte count/mm <sup>3</sup> ]

## 2.3. Statistical Analysis

The data obtained in this study were analyzed using IBM SPSS Statistics software for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as mean and standard deviation, were used to present numerical data, while categorical data were expressed as numbers and percentages. The relationships between categorical data were assessed using the chi-square test and Fisher's exact test. The distribution characteristics of continuous data were determined through the Kolmogorov-Smirnov and Shapiro-Wilk tests, and differences between groups were evaluated using the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was conducted for the PNI and SII variables to investigate their predictive ability for metastasis. A significance level of  $p < 0.05$  was considered for all statistical analyses.

## 3. Results

The retrospective analysis included 441 cases of thyroidectomy performed at the General Surgery Clinic of Recep Tayyip Erdoğan University Training and Research Hospital between January 2018 and June 2022. Among the 272 patients included in the study, cervical lymph node metastasis (CLNM) was not detected in 221 cases. However, 51 patients either had cN0 status with incidentally detected metastases in pathology specimens or were diagnosed with preoperative

absence of CLNM, considering both preoperative and postoperative pathology results. The patients' age, gender, systemic inflammatory markers derived from hemogram tests, serum albumin values, and postoperative pathology results were analyzed.

### 2.1. Ethics Committee Decision

This study received approval from the Recep Tayyip Erdoğan University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee, dated 19/01/2023, with reference number 2023/21.

### 2.2. Definitions

The definitions of systemic inflammatory markers, including the systemic immune inflammation index (SII) and the prognostic nutritional index (PNI), were established based on the formulas provided in Table 1, which considered the levels of neutrophils (N), lymphocytes (L), platelets (P), as well as serum albumin values derived from the hemogram analysis (13,14). In our study, we utilized these markers to calculate the values of systemic inflammatory markers, SII, and PNI, using the specified formulas presented in Table 1.

lymph node metastasis and underwent neck dissection. Thus, the prevalence of papillary thyroid cancer (PTC) was found to be 95.1% among all thyroidal cancers, with lymph node metastasis observed in 18.8% of PTC cases. These findings align with existing literature (1,8,9).

The mean age of CLNM-negative patients in the study was  $48.8 \pm 11.4$  years, while CLNM-positive patients had a mean age of  $43.9 \pm 17.3$  years. It was noted that patients with lymphatic metastases were significantly younger ( $p = 0.015$ ) (Table 2).

192 (70.6%) of the patients diagnosed with papillary thyroid cancer were female, and metastasis was detected in 37 (19.3%) of them. (Although PTC is more common in female patients, no statistically significant difference was found in terms of gender when examining the groups with or without lymph node metastasis ( $p = 0.073$ ) (Table 3).

In the postoperative pathology assessments, the tumor diameter was determined to be  $18.5 (\pm 13.7)$  mm in CLNM-positive patients, which was significantly larger than the group without metastasis (Mann-Whitney U test,  $p = 0.017$ ) (Table 2).

**Table 2.** Age, tumor size, PNI ve systemic inflammatory markers

	Lymph node metastasis negative	Lymph node metastasis positive	p
The average age (± SD)	48.8 (±11.4)	43.9 (±17.3)	<b>p=0.015*</b>
Tumor size (cm) (± SD)	13.4(±13.1)	18.5(±13.7)	<b>p=0.017*</b>
NLR (± SD)	1.5 (±0.3)	2.1(±0.4)	<b>p&lt;0.001*</b>
PLR (± SD)	121.7(±31.7)	138.5(±35.4)	<b>p=0.002*</b>
SII (± SD)	424.2(±121.2)	554.8(±125.6)	<b>p&lt;0.001*</b>
PNI (± SD)	56.9(±3.3)	52.9(±3.1)	<b>p&lt;0.001*</b>

SD: Standard deviation. \*: Mann Whitney U test

Furthermore, the pathology reports also examined the presence of vascular, lymphatic, and capsular invasion, as well as the presence of multicentricity in the tumor. The incidence of lymphatic and capsular invasion was found to be significantly higher in the CLNM-positive patient group

( $p<0.001$  for both, Fisher's exact test). However, there was no significant difference between the groups with or without lymphatic metastatic vascular invasion or multicentricity (Table 3).

**Table 3.** Gender and medical characteristics of patients

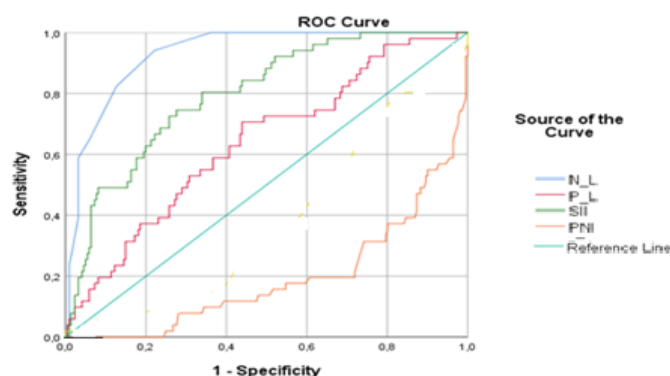
		Lymph node metastasis						p
		Negative		Positive		Total		
		n	%	n	%	n	%	
Gender	Male	66	82.5	14	17.5	80	29.4	<b>p=0.073*</b>
	Female	155	80.7	37	19.3	192	70.6	
Vascular invasion	Yes	8	66.7	4	33.7	12	4.4	<b>p=0.186**</b>
	No	213	81.9	47	18.1	260	95.6	
Lymphatic invasion	Yes	16	30.2	37	69.8	53	19.5	<b>p&lt;0.001**</b>
	No	205	93.6	14	6.4	219	80.5	
Multicentricity	Yes	117	77.5	34	22.5	151	55.5	<b>p=0.075*</b>
	No	104	86	17	14	121	45.5	
Capsular invasion	Yes	119	72.1	46	27.9	165	60.7	<b>p&lt;0.001**</b>
	No	102	95.3	5	4.7	107	39.3	

\* : Chi-square test \*\* : Fisher's exact test

Analyses were conducted to investigate the predictive value of systemic inflammatory markers, including NLR, PLR, SII, and PNI, in the patient group with CLNM (Table 2). In the CLNM-positive group, the mean NLR value was  $2.1\pm 0.4$ , and the PLR value was  $138.5\pm 35.4$ , both of which were significantly higher ( $p<0.001$  and  $p=0.002$ , respectively, Mann-Whitney U test) (Table 2). Similarly, the mean SII index was determined as  $554.8\pm 125.6$ , and it was found to be statistically significant, consistent with the previous two parameters ( $p<0.001$ , Mann-Whitney U test) (Table 2).

Receiver operating characteristic (ROC) curves were constructed for NLR, PLR, and SII to demonstrate their predictive capability for CLNM (Fig.1.), and the corresponding area under the curve (AUC) values, cut-off values, as well as sensitivity and specificity data, were calculated for these parameters (Table 4). The AUC value for NLR was 0.932 (95% CI, 0.902-0.962;  $p<0.001$ ), whereas the AUC value for PLR was 0.638 (95% CI, 0.555-0.721;  $p=0.002$ ). In the ROC analysis for SII, the AUC value was 0.798 (95% CI, 0.736-

0.861;  $p<0.001$ ) (Table 4). Additionally, the cut-off values determined from the ROC analysis were as follows: NLR: 1.75, PLR: 23.4, and SII: 475.4. For PNI, the AUC value was found to be 0.192 (95% CI, 0.124-0.260 ( $p<0.001$ )), but a cut-off value could not be calculated (Table 4).



**Fig.1.** Roc Curve for NLR, PLR, SII

**Table 4.** Data of ROC curve for NLR, PLR and SII

Test Result Variable(s)	AUC	Cut off	Sensitivite (%)	Spesifite (%)	p	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
NLR	0.932	1.75	82.4	87.3	<0.001	0.902	0.962
PLR	0.638	123.4	62.7	59.3	0.002	0.555	0.721
SII	0.798	475.4	72.5	74.2	<0.001	0.736	0.861
PNI	0.192	-	-	-	<0.001	0.124	0.260

#### 4. Discussion

The occurrence of central lymph node metastasis (CLNM) in papillary thyroid cancer (PTC) has been reported in various studies, ranging from 15% to 53%, and is known to be directly associated with both recurrence and overall survival (8-10). Identifying CLNM in cN0 patients after surgery requires secondary operations, which can lead to high complication rates and reduced quality of life. Therefore, additional modalities are being explored considering the limitations of preoperative imaging methods in detecting CLNM (12). In recent years, systemic inflammatory markers and the prognostic nutritional index (PNI) have been used in the literature to assess prognosis, recurrence, and lymphatic metastasis, particularly in solid tumors (15, 16). In our study, we aimed to evaluate inflammatory markers for the detection of CLNM in cN0 patients.

Numerous studies in the literature have reported that inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) serve as independent prognostic factors in solid tumors (14-16). An increased proportion of neutrophils is associated with tumor progression and invasion, while decreased proportions of lymphocytes and monocytes are associated with reduced antineoplastic effects. Platelets have also been shown to influence tumor progression and metastasis development (15, 17). For instance, Ceylan et al. found that patients with papillary thyroid cancer who had a high NLR before surgery exhibited larger tumor sizes and a higher rate of extrathyroidal spread (18). Wen et al., in a study involving 558 patients, found that NLR values were higher in patients with advanced papillary thyroid cancer (19). Similarly, Offi et al. reported higher recurrence rates in patients with elevated NLR values (14). Deng et al., in a meta-analysis comprising 4621 patients with esophageal cancer, demonstrated that high PLR levels were associated with advanced tumor stage, degree of invasion, and lymphatic involvement (20). High PLR levels have also been linked to advanced disease and increased frequency of lymphatic involvement in various other solid tumors (18). In a meta-analysis by Zhong et al., it was observed that high SII levels were associated with worse overall survival in most solid tumors (21). Zhang et al., in a study conducted on PTC patients, found that those with cervical lymph node metastases

had higher SII levels compared to those without metastasis (22).

In our study, when examining NLR, PLR, and SII values for predicting the presence of CLNM in the preoperative period for PTC, all three parameters yielded p-values below 0.05, indicating statistical significance. ROC analyses were also performed to evaluate the predictive capability of these parameters. Based on the AUC value of 0.932 and the significant p-value, we believe that NLR is a suitable marker for predicting the presence of metastasis. Although PLR and SII demonstrated statistically significant p-values, their discriminative power in predicting lymphatic metastasis appeared relatively lower based on the AUC values.

The prognostic nutritional index (PNI) provides information about both the nutritional and immune system status of patients (13). It has been recognized as an independent prognostic score in various solid tumors, including gastrointestinal system tumors, hepatocellular carcinoma, and breast cancer, where a low PNI value is associated with worse prognosis and more frequent metastasis (15, 16, 23).

In a multicenter study involving 1873 patients with differentiated thyroid cancer, Chen et al. demonstrated that low PNI values were associated with a higher incidence of lymph node metastases and increased recurrence rates (11). Although the PNI value was statistically significant ( $p < 0.001$ ) in detecting CLNM in our study, its ability to predict the presence of metastasis was deemed inappropriate due to the AUC values being below 80%.

Furthermore, our study examined the pathological data of patients, revealing a statistically significant increase in the incidence of lymphatic metastases among those with lymphatic and capsular invasion. Existing literature also supports the notion that cases involving capsule and lymphatic invasion are associated with an elevated risk of lymph node metastasis (19, 24). However, it is important to note that these factors are determined postoperatively.

Nevertheless, this study has certain limitations. The retrospective nature of our study and the limited number of patients are major limitations. The determination of neutrophil, lymphocyte, platelet counts, and albumin values based on a single preoperative test may introduce bias. Additionally, the

lack of a standardized cut-off value for these parameters in the reviewed literature during the study is noteworthy. Therefore, further studies are needed.

In conclusion, this study suggests that the NLR value may serve as an active marker in detecting CLNM. Although PLR and SII demonstrate some correlation with CLNM detection, their predictive capabilities are limited. Despite the statistical significance of the PNI value, its effectiveness in predicting CLNM was deemed inadequate. Additionally, our study revealed high rates of lymphatic metastasis in cases involving larger tumor size and lymphatic and capsular invasion. However, it is crucial to consider that these parameters can only be evaluated postoperatively.

### Conflict of Interest

The authors declared no conflict of interest.

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None to declare.

### Authors' contributions

Concept: A.Ö, O.B., Design: A.Ö, O.B., Data Collection or Processing: A.Ö, O.B., Analysis or Interpretation: A.Ö, O.B., Literature Search: A.Ö, O.B., Writing: A.Ö, O.B.

### Ethical Statement

This study received approval from the Recep Tayyip Erdoğan University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee, dated 19/01/2023, with reference number 2023/21.

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