



Association of the Preoperative Neutrophil-to-Lymphocyte Count Ratio and Platelet-to-Lymphocyte Count Ratio with Clinicopathological Characteristics in Patients with Papillary Thyroid Cancer

Sang Mi Kim^{1,*}, Eun Heui Kim^{2,*}, Bo Hyun Kim^{2,3}, Jong Ho Kim², Su Bin Park², Yoon Jeong Nam², Kang Hee Ahn², Min Young Oh¹, Won Jin Kim², Yun Kyung Jeon², Sang Soo Kim², Yong Ki Kim⁴, In Ju Kim²

¹Department of Internal Medicine, Donggeui Medical Center; ²Department of Internal Medicine, Pusan National University School of Medicine; ³Biomedical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine; ⁴Kim Yong Ki Internal Medicine Clinic, Busan, Korea

Background: Several inflammatory biomarkers, especially a high preoperative neutrophil-to-lymphocyte count ratio (NLR) and platelet-to-lymphocyte count ratio (PLR), are known to be indicator of poor prognosis in several cancers. However, very few studies have evaluated the significance of the NLR and PLR in papillary thyroid cancer (PTC). We evaluated the association of the preoperative NLR and PLR with clinicopathological characteristics in patients with PTC.

Methods: This study included 1,066 female patients who underwent total thyroidectomy for PTC. Patients were stratified into 4 quartiles by preoperative NLR and PLR. And the combination of preoperative NLR and PLR was calculated on the basis of data obtained value of tertile as follows: patients with both an elevated PLR and an elevated NLR were allocated a score of 2, and patients showing one or neither were allocated a score of 1 or 0, respectively.

Results: The preoperative NLR and PLR were significantly lower in patients aged ≥ 45 years and in patients with Hashimoto's thyroiditis. The PLR was significantly higher in patients with tumor size > 1 cm ($P=0.021$). When the patients were categorized into the aforementioned four groups, the group with the higher preoperative PLR was found to have a significantly increased incidence of lateral lymph node metastasis (LNM) ($P=0.018$). However, there are no significant association between the combination of preoperative NLR and PLR and prognostic factors in PTC patients.

Conclusion: These results suggest that a preoperative high PLR were significant associated with lateral LNM in female patients with PTC.

Keywords: Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Thyroid neoplasms; Prognosis

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Corresponding author: Bo Hyun Kim

Division of Endocrinology and Metabolism, Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea

Tel: +82-51-240-7678, **Fax:** +82-51-254-3237, **E-mail:** pons71@hanmail.net

*These authors contributed equally to this work.

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INTRODUCTION

In cancer patients, variations in clinical outcomes are associated with the oncological characteristics of the tumor and host responses to systemic inflammation. In particular, systemic inflammatory responses in malignancies may arise from nonspecific events that are altered by neuroendocrine metabolism, these may include hematopoietic changes, endocrine hormones, and changes secondary to tumor hypoxia, necrosis, or local tissue damage [1].

The tumor microenvironment and the inflammatory response in particular play several important roles in a variety of cancer, by promoting tumor cell proliferation, survival, angiogenesis, invasion, and metastasis. This is achieved through the release of T lymphocytes, chemokines, activated cytokines, interleukin-6 (IL-6), tumor necrosis factor α , and C-reactive protein (CRP), leading to neutrophilia. Such dysregulation of the immune system and the response to hormones may alter the effect of chemotherapy [2-4].

Recent studies have shown that several biomarkers associated with the inflammatory response, especially CRP, the neutrophil-to-lymphocyte count ratio (NLR), and the platelet-to-lymphocyte count ratio (PLR), are predictors of a poor prognosis [3]. A high preoperative NLR is a poor prognostic marker in some cancers, including cholangiocarcinoma as well as lung, gastric, pancreatic, colorectal, and ovarian cancers [5-11], and a high preoperative PLR is associated with a poor prognosis in pancreatic and operable colorectal cancers [11,12]. However, only a few studies have evaluated the significance of the NLR in thyroid cancer [13,14], and, to the best of our knowledge, there has been no studies investigating the PLR in patients with papillary thyroid cancer (PTC).

In this study, we evaluated the association between the preoperative NLR and PLR and the clinicopathological characteristics of patients with PTC.

METHODS

We performed a retrospective chart review of 1,194 patients who underwent total thyroidectomy for PTC at Pusan National University Hospital between February 1, 2011 and May 31, 2013 to collect their clinical characteristics and demographic data.

Laboratory data were obtained from screening blood samples collected up to 2 weeks prior to total thyroidectomy, while thyroid-stimulating hormone (TSH) levels were measured before surgery. Complete blood counts, and automated differen-

tial counts were obtained 1 day before surgery. The NLR was calculated by dividing neutrophil count by the lymphocyte count; similarly, the PLR was calculated by dividing the platelet count by the lymphocyte count. Fasting morning blood samples were collected for these analyses.

Some earlier studies revealed that women in an immunocompromised state have higher neutrophil counts than men, probably because of sex hormones [15,16]. Accordingly, we surmised that there would be a gender-based difference in neutrophil counts in some pathologic conditions such as thyroid cancer. Additionally, it has been reported that gender influences clinicopathological features that predict the prognosis of PTC [17]. Therefore, we excluded male patients from the study ($n=128$), and investigated the association between the preoperative NLR and PLR and the clinicopathological features of 1,066 female patients with PTC. These female patients were reassigned into quartiles based on the preoperative NLR and PLR.

A previous study showed that the combined evaluation of the NLR and PLR was superior to the evaluation of the NLR or PLR alone as a predictive factor in patients with esophageal cancer [18]. Thus, we assumed that the combination of NLR and PLR was more likely to predict poor clinicopathological factors than the NLR or PLR alone in patients with PTC.

The patients were stratified into tertile groups based on the preoperative NLR and PLR. Then the combination of NLR and PLR was calculated on the basis of data obtained value of 3rd tertile as follows: patients with both an elevated PLR (>144.07) and an elevated NLR (>1.88) were allocated a score of 2, and patients showing one or neither were allocated a score of 1 or 0, respectively.

Central compartment neck dissections were routinely performed during total thyroidectomy; selective neck dissections were performed when node metastasis was suspected by ultrasonography or computed tomography findings, or upon positive cytological findings in samples obtained by preoperative fine needle aspiration from suspicious cervical neck lymph nodes.

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Tumor size was determined according to the greatest diameter of the lesion, based on postoperative biopsy results. Patients were staged according to the TNM classification system of the American Joint Committee on Cancer [19]. The T stage was classified as 1/2 or 3/4, while the N stage was classified according to lymph node metastasis (LNM) (N0 vs. N1) and lateral LNM (N0+N1a vs. N1b).

We tested for Hashimoto's thyroiditis, which was identified

by diffuse lymphocyte infiltration, and lymphoid follicular formation in postoperative biopsy samples. We used the Seeplex BRAF ACE detection kit (Seegene, Seoul, Korea) to detect the *BRAF V600E* mutation in tumor tissues after thyroidectomy.

Informed consent was obtained from all patients, prior to thyroidectomy. The study was approved by the Institutional Review Board at Pusan National University Hospital, Busan, Korea.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Co., Armonk, NY, USA). The Student *t* test was used to evaluate the relationship between the preoperative NLR and

PLR and the other clinicopathological characteristics of PTC. One-way analysis of variance and Pearson chi-square test were used to compare different quartiles. Among the continuous variables, NLR, PLR, TSH, and tumor size are expressed as the median and interquartile range (IQR) age, BMI, and the number of tumors are expressed as mean±standard deviation. A *P*<0.05 was considered statistically significant.

RESULTS

A total of 1,066 female PTC patients were included in this analysis. Table 1 shows the relationships between the preopera-

Table 1. The Association between Preoperative NLR and PLR Values and the Clinicopathological Characteristics of Papillary Thyroid Cancer

Characteristic	Patients, <i>n</i> (%)	NLR		PLR	
		Median (IQR)	<i>P</i> value	Median (IQR)	<i>P</i> value
Age, yr			0.001		<0.001
<45	324 (30.4)	1.75 (1.03–2.31)		135.60 (91.00–163.06)	
≥45	742 (69.6)	1.52 (1.16–2.00)		123.60 (99.32–151.42)	
Tumor size, cm			0.522		0.021
≤1	774 (75.6)	1.59 (1.20–2.06)		124.41 (103.13–155.09)	
>1	292 (27.4)	1.53 (1.22–2.12)		129.17 (106.24–162.44)	
T stage			0.370		0.801
1/2	944 (88.6)	1.57 (1.21–2.08)		125.62 (104.05–156.11)	
3/4	122 (11.4)	1.63 (1.20–2.13)		127.70 (97.84–156.75)	
LNM			0.634		0.765
N0	432 (40.5)	1.57 (1.19–2.07)		125.59 (103.28–156.72)	
N1	634 (59.5)	1.68 (1.34–2.24)		132.10 (114.12–149.81)	
Multifocality			0.483		0.526
Negative	746 (70)	1.60 (1.23–2.11)		126.06 (105.58–156.75)	
Positive	320 (30)	1.53 (1.16–2.04)		126.50 (99.35–154.50)	
Hashimoto's thyroiditis			0.005		0.039
Negative	940 (88.2)	1.58 (1.21–2.11)		127.61 (104.89–157.38)	
Positive	126 (11.8)	1.52 (1.18–1.89)		119.48 (94.02–147.48)	
ETE			0.185		0.805
Negative	654 (61.4)	1.59 (1.20–2.08)		124.31 (103.27–157.95)	
Positive	412 (38.6)	1.57 (1.22–2.10)		128.09 (106.15–154.26)	
Lateral LNM			0.101		0.316
Negative	1,001 (93.9)	1.57 (1.19–2.07)		125.59 (103.28–156.72)	
Positive	65 (6.1)	1.68 (1.34–2.24)		132.10 (114.38–148.46)	
LVI			0.155		0.400
Negative	524/715 (73.3)	1.58 (1.21–2.04)		126.96 (103.58–157.59)	
Positive	191/715 (26.7)	1.52 (1.13–2.22)		130.18 (104.77–158.92)	
<i>BRAF V600E</i> mutation			0.896		0.658
Negative	383/1,003 (38.2)	1.58 (1.17–2.08)		125.96 (101.57–154.28)	
Positive	620/1,003 (61.8)	1.57 (1.23–2.10)		125.68 (103.93–156.72)	

Statistical significance was tested by the Student *t* test.

NLR, neutrophil-to-lymphocyte count ratio; PLR, platelet-to-lymphocyte count ratio; IQR, interquartile range; LNM, lymph node metastasis; ETE, extrathyroidal extension; LVI, lymphovascular invasion.

tive NLR and PLR values, and the clinicopathological characteristics of PTC. The preoperative NLR and PLR were significantly lower in patients aged ≥ 45 years and in patients with

Hashimoto's thyroiditis. The PLR was significantly higher in patients with tumor size > 1 cm; the median PLR was 139.89, with an IQR of 129.17 (vs. 132.41 with an IQR of 124.41 in

Table 2. Comparisons of the Prevalence of Prognostic Factors between Preoperative NLR Quartile Groups

Variable	Group 1	Group 2	Group 3	Group 4	P value
No. in quartile	266	266	266	268	
NLR, range	0.25–1.21	1.21–1.57	1.57–2.07	2.08–10.20	
Age, yr	51.99 \pm 10.64	50.72 \pm 11.09	48.96 \pm 11.17 ^a	49.16 \pm 11.78 ^a	0.005
BMI, kg/m ²	23.55 \pm 3.04	23.37 \pm 2.96	24.17 \pm 13.33	23.30 \pm 3.13	0.482
Tumor size, cm	0.86 \pm 0.58	0.92 \pm 0.61	0.80 \pm 0.53	0.88 \pm 0.61	0.131
TSH, mIU/L	1.45 (0.92–2.39)	1.38 (0.84–2.26)	1.33 (0.90–2.13)	1.27 (0.84–2.04)	0.245
T stage 3/4, %	31 (11.7)	25 (9.4)	34 (12.8)	32 (11.9)	0.649
LNM, %	166 (62.4)	157 (59.0)	153 (57.5)	158 (59.0)	0.700
Lateral LNM, %	11 (4.1)	20 (7.5)	15 (5.6)	19 (7.1)	0.350
Multifocality, %	90 (33.8)	81 (30.5)	76 (28.6)	73 (27.2)	0.374
ETE, %	101 (38.0)	110 (41.4)	98 (36.8)	103 (38.4)	0.743
LVI, %	57/187 (30.5)	43/171 (25.1)	32/179 (17.9)	59/178 (33.1)	0.006
<i>BRAF V600E</i> mutation, %	147/252 (58.3)	163/248 (65.7)	153/249 (61.4)	157/254 (61.8)	0.405

Values are expressed as mean \pm SD, median (interquartile range), or number (%). Statistical significance was tested by one-way analysis of variance, or the chi-square test.

NLR, neutrophil-to-lymphocyte count ratio; BMI, body mass index; TSH, thyroid-stimulating hormone; LNM, lymph node metastasis; ETE, extra-thyroidal extension; LVI, lymphovascular invasion.

^aThe differences were only between quartile group 1 and quartile group 3 and 4 in *post hoc* analysis.

Table 3. Comparisons of the Prevalence of Prognostic Factors between Preoperative PLR Quartile Groups

Variable	Group 1	Group 2	Group 3	Group 4	P value
No. in quartile	266	266	266	268	
PLR, range	13.32–103.85	104.01–125.96	126.0–155.97	156.25–407.81	
Age, yr	52.93 \pm 10.62	49.56 \pm 11.26 ^a	49.72 \pm 11.36 ^a	48.62 \pm 11.25 ^a	<0.001
BMI, kg/m ²	23.87 \pm 3.26	23.51 \pm 3.23	23.85 \pm 13.27	23.16 \pm 2.91	0.631
Tumor size, cm	0.87 \pm 0.60	0.86 \pm 0.60	0.88 \pm 0.59	0.84 \pm 0.55	0.914
TSH, mIU/L	1.37 (0.90–2.33)	1.32 (0.78–2.10)	1.42 (0.93–2.24)	1.32 (0.87–2.18)	0.212
T stage 3/4, %	33 (12.4)	24 (9.0)	33 (12.4)	32 (11.9)	0.554
LNM, %	159 (59.8)	154 (57.9)	166 (62.4)	155 (57.8)	0.675
Lateral LNM, %	8 (3.0)	18 (6.8)	25 (9.4)	14 (5.2)	0.018
Multifocality, %	90 (33.8)	70 (26.3)	82 (30.8)	78 (29.1)	0.287
ETE, %	96 (36.1)	100 (37.6)	120 (45.1)	96 (35.8)	0.092
LVI, %	46/177 (26.0)	43/168 (25.6)	52/182 (29.1)	49/188 (26.1)	0.865
<i>BRAF V600E</i> mutation, %	155/254 (61.0)	156/249 (62.7)	152/248 (61.3)	157/252 (62.3)	0.978

Values are expressed as mean \pm SD, median (interquartile range), or number (%). Statistical significance was tested by one-way analysis of variance, or the chi-square test.

PLR, platelet-to-lymphocyte count ratio; BMI, body mass index; TSH, thyroid-stimulating hormone; LNM, lymph node metastasis; ETE, extra-thyroidal extension; LVI, lymphovascular invasion.

^aThe differences were significant only between quartile group 1 and quartile group 2, 3, and 4 in *post hoc* analysis.

Table 4. Relationships between Clinicopathological Characteristics and the Combination of Preoperative NLR and PLR in Papillary Thyroid Cancer Patients

Characteristic	Score 0	Score 1	Score 2	P value
No. in quartile	334	517	215	
NLR	1.23 (0.25–1.87)	1.57 (0.57–5.09)	2.50 (1.88–10.20)	
PLR	103.95 (13.32–143.82)	125.43 (47.99–294.70)	181.01 (144.07–407.81)	
Age, yr	51.58±11.36	50.09±10.95	48.33±11.47 ^a	0.004
BMI, kg/m ²	24.20±11.91	23.34±3.17	23.28±3.07	0.178
Tumor size, cm	0.85±0.57	0.86±0.59	0.88±0.60	0.876
TSH, mIU/L	1.32 (0.79–2.33)	1.43 (0.91–2.24)	1.29 (0.86–2.12)	0.507
T stage 3/4, %	43 (12.9)	52 (10.1)	27 (12.6)	0.383
LNM, %	214 (64.1)	296 (57.3)	124 (57.7)	0.118
Lateral LNM, %	19 (5.7)	34 (6.6)	12 (5.6)	0.817
Multifocality, %	107 (32.0)	153 (29.6)	60 (27.9)	0.563
ETE, %	126 (37.7)	203 (39.3)	83 (38.6)	0.903
LVI, %	65/218 (29.8)	82/343 (23.9)	44/154 (28.6)	0.256
<i>BRAF V600E</i> mutation, %	191/312 (61.2)	305/488 (62.5)	124/203 (61.1)	0.909

Values are expressed as median (interquartile range), mean±SD, or number (%). Statistical significance was tested by one-way analysis of variance, or the chi-square test.

NLR, neutrophil-to-lymphocyte count ratio; PLR, platelet-to-lymphocyte count ratio; BMI, body mass index; TSH, thyroid-stimulating hormone; LNM, lymph node metastasis; ETE, extrathyroidal extension; LVI, lymphovascular invasion.

^aThe differences were significant only between the score 0 and the score 2.

patients with tumor size ≤1 cm; $P=0.021$). The preoperative NLR and PLR were not associated with multifocality, extrathyroidal extension (ETE), lateral LNM, lymphovascular invasion (LVI), the *BRAF V600E* mutation, tumor size, T stage, or LNM.

Patients were stratified by quartiles according to the preoperative NLR and PLR, and the prevalence of prognostic factors was compared between preoperative NLR and PLR quartiles (Tables 2, 3). Table 2 shows the relationships between clinicopathologic factors and NLR quartiles. The older patients had significant lower LNR values, but the differences were only between quartile 1 and quartile 3 and 4 in *post hoc* analysis. Significant differences were found between the NLR and LVI ($P=0.006$), but, there was not a meaningful correlation between NLR and LVI.

Table 3 showed that increasing preoperative PLR values from quartile 1 to quartile 3 were associated with increasing incidences of lateral LNM ($P=0.018$), with a positive correlation between the preoperative PLR from quartile 1 to quartile 3 ($r=0.032$, $P=0.003$, data not shown) and lateral LNM. However, patients in quartile 4 had a lower incidence of lateral LNM than patients in quartile 2 and 3. The older patients had

significant lower PLR values, but the differences were significant only between quartile 1 and quartile 2, 3, and 4 in *post hoc* analysis. The preoperative PLR were not significantly associated with other clinicopathological factors (e.g., BMI, tumor size, TSH, T stage, LNM, multifocality, ETE, LVI, and the *BRAF V600E* mutation).

The higher value of combination of preoperative NLR and PLR were significantly associated with younger age in one way analysis of variance ($P=0.004$), but the differences were significant only between the score 0 and the score 2 (Table 4). There are no correlation between the combination of preoperative NLR and PLR and other prognostic factors (e.g., BMI, tumor size, TSH, T stage, LNM, lateral LNM, multifocality, ETE, LVI, and the *BRAF V600E* mutation).

DISCUSSION

Systemic inflammation has been reported to contribute to cancer development and progression, through the promotion of proliferation, survival, migration, and angiogenesis, as well as the suppression of antitumor immunity through the release of chemokines, especially regulatory T cells [20,21].

The mechanism underlying the association of a high NLR with a poor cancer prognosis remains unknown. Cancers have been shown to secrete myeloid growth factors, such as granulocyte colony-stimulating factor, IL-1, IL-6, and tumor necrosis factor- α , which may result in tumor-related leukocytosis and neutrophilia [12]. Accordingly, neutrophils promote cancer progression and stimulate the tumor microenvironment by releasing tumor growth promoting factors, such as vascular endothelial growth factor [22,23], hepatocyte growth factor [24], IL-6 [25], IL-8 [26], matrix metalloproteinases [27], and elastases [28].

The exact mechanisms underlying the association between an elevated PLR values and the biological behavior of cancer cells remain unclear. One hypothesis is that megakaryocyte-mediated thrombocytosis may result from the release of proinflammatory mediators such as IL-1, IL-2, and IL-6 [29]. Moreover, a high PLR value may be considered an indicator of inflammation [20].

Several studies have reported that a high NLR may be associated with a poor prognosis of solid tumor cancers, including lung, gastric, pancreatic, ovarian, and colorectal cancers, in addition to colorectal liver metastases, and cholangiocarcinomas [5-10,30,31]. Moreover, the PLR has recently been identified as an independent prognostic factor in patients undergoing potentially curative resections for pancreatic and operable colorectal cancers [3,11]; the PLR is also associated with a poor prognosis in breast cancer patients [32]. The combination of preoperative NLR and PLR has been shown to be significantly associated with the risk of cervical stromal involvement in patients with endometrial cancer [33]. Thus, the preoperative NLR and/or PLR are independent prognostic factors for several malignancies.

Previous studies have demonstrated that neutrophil viability and counts were significantly higher in women than in men because of the effect of sex hormones [14]. Furthermore, another study showed that female patients had higher circulating neutrophil counts, lower lymphocyte counts, and consequently higher NLR, indicating a more immunocompromised state than in male patients during the days immediately following surgery for stomach cancer [15]. Based on these results, we hypothesized that female patients have a higher white blood cell count than male patients under similar circumstances, which is why male patients were excluded in this study.

Liu et al. [34] previously showed that a high preoperative NLR was associated with increased tumor size and a high risk of recurrence in differentiated thyroid cancers. In this study, the NLR did not have significant association with the clinicopatho-

logical characteristics in PTC patients. But an elevated PLR values (especially in the first to third quartiles) were associated with an increased risk of lateral LNM (Table 3). However, patients in the fourth quartiles (PLR >156.25) had a lower incidence of lateral LNM than those belonging to the second and third quartiles. Seretis et al. [13] have reported similar results, showing a significant association of between a high NLR and thyroid cancer, especially for NLR >2.5, although the third (NLR >2.5 to 3.0) and fourth (NLR >3 to 6.9) quartiles showed lower incidences of thyroid cancer than the first and second. Although further large multicenter studies are required to confirm this association in thyroid cancer patients, our results suggest that there is a weak association between the NLR or PLR and prognosis in thyroid cancer once the NLR or PLR exceeds a certain value. Previous study showed that combination of NLR and PLR value was found to be much more applicable for predicting postoperative survival than patient stratification according to either the NLR or PLR alone in an esophageal squamous cell carcinoma [18]. Therefore we evaluated the usefulness of combination of NLR and PLR for predicting prognostic factor in patients with PTC. Unfortunately, our result showed no significant correlation with prognostic factors in PTC patients.

There were several limitations to our study. First, our study design was retrospective and only Asian patients in single institution were included; hence, our study did not represent the general population. Second, some studies have reported that chemotherapy can normalize an elevated NLR, and that patients with a normalized NLR may have improved outcomes [35,36]. However, our study did not evaluate the changes in NLR and PLR after thyroidectomy, or radioactive iodine therapy. Third, serum CRP levels are not evaluated during routine preoperative laboratory examinations of thyroid cancer patients. Neutrophil and lymphocyte counts may be influenced by infections, inflammation, medication, and other noncancerous conditions [37,38]. As we did not evaluate other medical conditions or medications, our results might be influenced by these confounding factors. Fourth, this study included only female patients with PTC.

Despite these limitations, this study offers some insight on our understanding of the link between preoperative inflammatory marker such as NLR, PLR and clinicopathological characteristics in patients with PTC. To the best of our knowledge, this study was the first study for association between PLR and prognostic factors in patients with PTC.

In conclusion, higher preoperative PLR were associated with

lateral LNM in patients with PTC. Measurement of the PLR is cost-effective, safe, and readily available. Thus, preoperative PLR may be valuable for predicting adverse clinicopathological outcomes in PTC. More large-scale prospective studies are required to validate our results, before the preoperative NLR or PLR can be used as biomarkers for risk stratification.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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