



The role of preoperative complete blood count indices in the distinction of papillary thyroid cancer from nodular goiter

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Abstract

Aim: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (respectively, NLR and PLR) have been associated with poor prognosis in various cancers. This study was conducted to investigate PLR and NLR in patients with papillary thyroid cancer (PTC) and nodular goiter (NG).

Materials and Methods: Patients who had undergone thyroidectomy at our center were reviewed and the demographic, clinical and histopathological characteristics of patients with PTC or NG were recorded. Hemogram (complete blood count) results were used to calculate NLR and PLR.

Results: The groups were similar with respect to age, gender and thyroiditis characteristics. The NG group was found to have significantly larger gland size compared to the PTC group. NLR and PLR values were similar in the two groups ($p=0.556$ and $p=0.841$ respectively).

Conclusion: PLR and NLR appear to be exceedingly similar in PTC and NG, and therefore, they cannot be used to distinguish between PTC and NG. However, it may be valuable to conduct future studies that take into account lesion size when comparing these parameters in thyroid nodules.



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Introduction

Thyroid nodules are detected in 4% of individuals in physical examination and in more than half of individuals in ultrasonographic examination, even in societies with adequate iodine consumption [1]. Although the prevalence of thyroid nodules is increasing, malignancy is detected in only 5% to 10% [2]; nonetheless, thyroid cancer is the most common endocrine malignancy [3]. Thyroid surgery can be performed in cases of definite malignancy, suspected malignancy, and toxic nodular goiter (NG) [4]. Despite the relatively good prognosis of papillary thyroid cancer (PTC) in comparison to other thyroid cancers, invasion into surrounding tissues is observed in approximately 15% (5-34%) of patients at the time of first surgery. In addition, at the time of diagnosis, approximately one-third of

PTC cases demonstrate significant lymphadenopathy, and 1-7% have distant metastases [5,6].

In patients with thyroid nodules or suspicious lesions, malignant potential can be assessed by use of various methods, including ultrasonography and imaging-guided fine-needle aspiration biopsy (FNAB). Although FNAB is the recommended technique to differentiate malignant and benign lesions during preoperative evaluation [7], this minimally invasive procedure may lead to complications such as hematoma formation, needle tract seeding, and thyroid nodule infarction [8]. Therefore, determining methods that could enable non-invasive distinction of benign and malignant cases could be valuable to increase patient comfort.

It has been shown that inflammation may contribute to cancer development and progression [9]. Cancer-related inflammatory responses are known to influence the tumor microenvironment, and can lead to proliferation, angiogenesis and cancer progression [10]. Therefore, inflammation-

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related markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), may be associated with cancer prognosis [11]. NLR and PLR, which are calculated from widely-available hemogram results, have gained considerable interest as indicators of general immunoreactivity. In several studies, NLR and PLR have been shown to predict overall and disease-free survival in various types of solid tumors [12-14]. However, studies assessing NLR and PLR in thyroid nodules and thyroid cancers are few. Therefore, our aim was to evaluate possible relationships between patient characteristics and inflammatory markers, such as neutrophil count, lymphocyte count, platelet count, NLR and PLR in patients with PTC and NG.

Materials and Methods

Ethical approval was provided by the Non-Interventional Clinical Research Ethics Committee of Eskisehir Osmangazi University (Decision no: 18, date: November 24, 2020). According to descriptive statistics (effect size=0.307) in the study by Ozmen et al. [15], a total sample size of 336 achieve 80% power at the two-sided 0.05 significance level. Sample size was calculated by using two-sample t test power analysis via PASS 11 software (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.).

The medical files and histopathological examination reports of the patients who underwent thyroidectomy between June 2017 and December 2020 at the Eskişehir Osmangazi University Department of General Surgery. Department were reviewed retrospectively and those with a histopathologically confirmed diagnosis of either PTC or NG were evaluated for inclusion. Patients younger than 18 years old, smokers, alcohol abusers, those with hematological/oncological diseases, those with infectious disease history within the last three months, individuals with glucocorticoid use, coronary artery disease, diabetes mellitus, hypertension, connective tissue disease, autoimmune disease, and patients with renal or hepatic dysfunction were excluded from the study.

All data were obtained by retrospective review. Age, gender, hyperthyroidism status, FNAB status, Bethesda category (1 to 6) from FNAB assessment, type of surgery, histopathological features (gland size, largest nodule size, total nodule size, malignancy status, thyroiditis status, thyroiditis type), and the type of surgical intervention(s) applied (bilateral total thyroidectomy, BTT; central dissection, CD; unilateral modified radical neck dissection, UMRND; bilateral modified radical neck dissection, BM-RND) were recorded. Ultrasonography had been used to estimate each patient's gland size prior to surgery. In addition to clinical and pathological data, we recorded neutrophil, lymphocyte and platelet counts from hemograms obtained the day before surgery, and the NLR and PLR values were calculated.

Patients were also categorized with respect to the type of surgery applied and Bethesda score. Surgery types were cross-tabulated with Bethesda categories, and descriptive results were provided with respect to diagnosis (PTC or NG).

Statistical analysis

The SPSS v22.0 (IBM corp, released 2013, Armonk, NY) software was used for statistical analysis. Shapiro-Wilk's test was used to investigate the compliance of continuous variables with normal distribution. For comparisons between groups, we used the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Chi-square analyses were used in the analysis of cross tables (distribution of categorical variables). Categorical data were summarized as number (percentage) and continuous data as mean \pm standard deviation (SD) and median (minimum- maximum). P values of <0.05 were defined to demonstrate statistical significance.

Results

In total, 333 individuals who had undergone thyroid surgery and met the inclusion/exclusion criteria were included. Of the patients, 255 (76.6%) were female and 78 (23.4%) were male. As a result of histopathological examination, 172 (51.7%) of the patients were found to have PTC, and 161 (48.3%) had NG. The age distributions of the PTC and NG groups were similar ($p = 0.150$). FNAB was performed in 170 patients (51.1%) in the pre-operative period, whereas 163 patients (48.9%) had undergone thyroid surgery without prior FNAB application. When the groups were compared, FNAB was found to have been applied significantly more frequently in the PTC group ($p < 0.005$). Thyroiditis was reported in 88 patients (26.4%). Of these, lymphocytic thyroiditis was observed in 64 patients (19.2%), Hashimoto's thyroiditis in 22 patients (6.6%), and subacute granulomatous thyroiditis in 2 patients (0.6%). The vertical and transverse dimensions of the glands were found to be significantly greater in patients with NG ($p < 0.001$). Additionally, the largest and total nodule sizes were significantly greater in the NG group ($p = 0.002$ and $p = 0.003$, respectively) (Table 1).

The groups were similar in terms of neutrophil count, lymphocyte count, platelet count, NLR and PLR (Table 2).

Discussion

In recent years, inflammatory markers have come to be used for uncustomary purposes. The NLR and PLR values are an important example and they appear to have value in the assessment of various disease scenarios and related characteristics, including diagnostic roles and prognostic predictions. The current study focused on evaluating whether NLR and PLR values could be used to differentiate patients with PTC from those with NG; however, the results indicate that these inflammatory parameters do not have such a role.

Inflammation, cytokines, chemokines and CRP are known to induce proliferation and angiogenesis in tumors, primarily via neutrophil induction and also by limiting treatment response [9]. Tumor-related stress increases neutrophil count while decreasing lymphocyte count [16]. Also, cytokines, leukocytes and phagocytic mediators may lead to DNA damage, apoptosis inhibition and increased angiogenesis; thereby resulting in tumor growth and disease progression. It is also established that lymphocytes may

Table 1. Comparison of study groups with respect to demographic, clinical and pathological characteristics.

		PTC n = 172 (51.7%)	NG n = 161 (48.3%)	P value
Age, mean ± SD, median (min-max)		52.12 ± 13.39, 51.5 (22-85)	54.23 ± 13.35, 55 (26-80)	0.150
Gender, number (percentage)	Female	136 (53.3%)	119 (46.7%)	0.260
	Male	36 (46.2%)	42 (53.8%)	
Thyroiditis, number (percentage)	Yes	51 (58%)	37 (42%)	0.168
	No	121 (49.4%)	124 (50.6%)	
Type of thyroiditis, number (percentage)	Lymphocytic	39 (60.9%)	25 (39.1%)	0.178
	Hashimoto's	12 (54.5%)	10 (45.5%)	
	Subacute granulomatosis	0	2 (100%)	
Vertical gland size (mm), mean ± SD, median (min-max)		5.74 ± 1.87, 5.5 (2-16)	7.06 ± 2.28, 6.5 (3.5-15.5)	<0.001
Transverse gland size (mm), mean ± SD, median (min-max)		5.22 ± 1.73, 5 (1.1-13.5)	6.25 ± 2.26, 6 (2.5-19)	<0.001
Largest nodule size (mm), mean ± SD, median (min-max)		2.30 ± 1.62, 2 (0.2-10)	2.76 ± 1.79, 2.5 (1-14.5)	0.002
Total nodule size (mm), mean ± SD, median (min-max)		3.98 ± 2.86, 3.25 (0.3-20)	4.90 ± 3.01, 4.3 (0.3-14.5)	0.003

Categorical data were summarized as number (percentage) and continuous data as mean ± standard deviation and median (minimum-maximum). PTC: Papillary thyroid cancer, NG: Nodular goiter, SD: Standard deviation, P values in bold denote statistical significance.

Table 2. Comparison of hemogram values and NLR and PLR between the two groups.

	PTC (n = 172)	NG (n = 161)	P value
Neutrophil count ($\times 10^3$ /ml), mean ±SD, Median (min-max)	4.52 ± 1.76, 4.14 (1.51-12.30)	4.46 ± 1.68, 4.21 (1.32-13.80)	0.942
Lymphocyte count ($\times 10^3$ /ml), mean ±SD, Median (min-max)	2.16 ± 0.65, 2.07 (0.95-4.74)	2.11 ± 0.70, 2.03 (0.43-5.22)	0.508
Platelet count ($\times 10^3$ /ml), mean ±SD, Median (min-max)	272.46 ± 65.61, 264.5 (75-490)	263.96 ± 73.58, 251 (102-593)	0.081
NLR, mean ±SD, Median (min-max)	2.21 ± 0.99, 1.93 (0.50-6.44)	2.36 ± 1.51, 2.02 (0.49-14.37)	0.556
PLR, mean ±SD, Median (min-max)	133.80 ± 43.77, 128.6 (62.5-342.7)	141.09 ± 92.45, 127.7 (45.2-997.7)	0.841

Categorical data were summarized as number (percentage) and continuous data as mean ± standard deviation and median (minimum-maximum). PTC: Papillary thyroid cancer, NG: Nodular goiter, SD: Standard deviation, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

influence tumor growth and immune response [17]. Recent studies have shown that NLR elevation in various cancers can predict aggressive features [12-14].

Seretis et al. reported that NLR was significantly increased in cases of incidentally detected papillary microcarcinoma and in patients with thyroid cancer [18]. Lang et al. evaluated preoperative NLR values in PTC. They found that, although a higher NLR may mean a worse tumor profile, it was not associated with shorter disease-free survival or a higher risk of central lymph node metastasis in PTC [19]. Prior studies have also reported a significant relationship between high levels of preoperative NLR and the size and extrathyroidal spread of PTC [20,21]. In their study, Kim et al. reported a prognostic role for NLR in PTC. They used different cut-off values for NLR and found that higher NLR was associated with more advanced disease stage and more aggressive tumor behavior, despite describing heterogeneous cut-off values. The same study showed significantly increased NLR in subjects with PTC relative to individuals without thyroid nodules, and in those with solid lesions compared to those with cystic lesions; however, there were no significant differences between patients with benign and malignant thyroid nodules [22]. In contrast, in the study by Liu et al., NLR was reportedly similar in patients with thyroid cancer and those with follicular adenoma [13]. As a result of our study, we determined that NLR is not meaningful in distinguishing

between PTC and NG. In fact, while we expected higher NLR and PLR values in the PTC group, we observed that the groups were exceedingly similar. Considering the significant increase in gland and nodule sizes in the NG group, we predict that the size of the lesion(s) could have contributed to increased inflammatory activation. Therefore, it would not be unfeasible to suggest that, if a healthy control group had been included in the study, NLR values would likely be higher in all patients with nodules when compared to controls, which would have resulted in similar results to Kim et al.'s study.

Costantini et al. [23] suggested that inflammation-dependent production of cytokines in cancer may be associated with platelet count [24]. Platelets are among the group of cells that release vascular endothelial growth factor (VEGF) which is a factor contributing to angiogenesis and tumor cell extravasation [25]. Previous studies have established that VEGF and various other growth factors can increase tumor growth rate by inducing angiogenesis and neovascularization [26]. IL-1 and IL-6 may also induce thrombocytosis by causing megakaryocyte proliferation [25,26]. Owing to these relationships, PLR has been investigated in many studies and is described as a valuable inflammatory indicator [27]. For instance, patients who demonstrated poor prognosis after surgery for colorectal or pancreatic cancer were found to have high PLR value in the preoperative period [28]. Similarly, elevated

preoperative NLR is also suggested to be a poor prognostic marker in cancers of the stomach, pancreas, colorectal region, gall bladder, lung and ovaries [13].

Turkmen et al. showed that PLR could predict inflammation better than NLR in end-stage renal disease [29]. In another study conducted in patients with PTC, the authors reported significantly higher PLR among those with a tumor diameter of >1 cm. As a result of subgroup analysis, high preoperative PLR was found to be associated with the development of lateral lymph node metastasis [30]. Ari and his colleagues also reported elevated PLR and NLR in patients with papillary carcinoma when compared to healthy individuals, albeit the difference was significant only for PLR [31]. In our study, PLR values were similar between the two groups.

Limited patient count, especially with regard to some analyses, must be noted as a limitation of this study. Furthermore, the lack of a healthy control group and the retrospective single-centered study design are also limitations. In addition, it should be kept in mind that NLR and PLR values are far from being definitively specific to inflammation and many factors can alter their levels. Even though we excluded patients with conditions that could alter these parameters, it is evident that many undetectable characteristics could have influenced these indices.

Conclusion

We based this study on the hypothesis that PLR and NLR values could be valuable for the non-invasive prediction of malignancy likelihood in patients with thyroid nodules, which was a particularly attractive hypothesis considering the cost-effectivity, safety and availability of hemogram measurement throughout the world. However, in our study, we found that NLR and PLR could not differentiate between PTC and NG. Considering the possibility of sizeable variations in hemogram indices due to numerous factors and the fact that the literature is largely conflicted regarding the role of NLR and PLR, future studies should seek ways to normalize patient characteristics, perform comparisons with regard to lesion/nodule size, and aim to conduct longitudinal assessment of these parameters in various disease states.

Competing interests

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Eskisehir Osmangazi University (Decision no: 18, Decision date: 24.11.2020).

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