Am J Transl Res 2023;15(4):2820-2827
www.ajtr.org /ISSN:1943-8141/AJTR0148781

Original Article

A novel proportional index to differentiate between demographically and clinically matched cases with papillary thyroid carcinoma or non-cancerous nodule: PLR-to-PDW ratio

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Received December 27, 2022; Accepted March 14, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: Objectives: To analyze PLR-to-PDW ratio as a novel diagnostic index in the discrimination of benign thyroid nodules (BTN) and papillary thyroid carcinoma (PTC), and to analyze the discriminatory power of a novel index (platelet-to-lymphocyte ratio divided by platelet distribution width: PLR-to-PDW ratio) in comparison with previously-examined inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), PLR, prognostic nutritional index (PNI), systemic inflammation index (SII), and systemic inflammatory response index (SIRI). Methods: This cross-sectional retrospective research included 459 demographically and clinically-matched participants who underwent thyroid examination with ultrasonography and fine-needle aspiration biopsy. NLR, PLR, SII, SIRI and PLR-to-PDW were calculated manually from complete blood count results. PNI was calculated as albumin (g/dL) + 5 × lymphocyte count. Results: Among the inflammatory indices, NLR, PLR and PLR-to-PDW ratio were significantly higher in patients with PTC compared to those with BTN. Logistic regression showed that NLR (OR: 1.414, P=0.0083), PLR (OR: 1.537, P=0.0065) and PLR-to-PDW (OR: 2.054, P=0.0016) were independently associated with a greater likelihood of PTC. Among the previously-examined indices, PLR had the best discriminatory performance with 73.4% sensitivity and 70.8% specificity for a > 149.6 cut-off (AUC: 0.786, P=0.0011). However, the novel ratio examined in this study, PLR-to-PDW, had better predictive value to distinguish PTC cases from BTN with 78.1% sensitivity and 73.7% specificity at a > 9.11 cut-off (AUC: 0.827, P=0.0001). Conclusions: The presently proposed PLR-to-PDW ratio exhibited the highest diagnostic discriminatory power compared to other inflammatory indices, indicating a relatively better utility to distinguish cases with PTC from those with BTN.

Keywords: Papillary carcinoma, thyroid nodule, inflammation, platelet-to-lymphocyte ratio, platelet distribution width

Introduction

Despite demonstrating a genetic inheritance, thyroid nodules are associated with malnutrition and environmental exposures, which are the two major factors involved in their rising prevalence [1, 2]. Detection is largely incidental since these nodules rarely manifest with overt findings [3, 4]. The recent increase in nodule diagnosis can be explained by increasing awareness and widespread availability of screening methods [5]. In connection with this increase, the incidence of thyroid cancer and the number of deaths due to cancerous thyroid nodules are increasing [6].

To distinguish benign and malignant nodules, it is possible to utilize ultrasonography (USG), thyroid function tests and direct biopsy [7], which are often preferred in the listed order [8]. The majority of cases are benign; however, some malignant nodules may be rarely overlooked [9]. Various factors contribute to the failure of detection, including localization in a posterior locus (which is difficult to reach with biopsy) [10] and limited experience in pathologic evaluations. Although these difficulties often necessitate expensive genetic analyses, they also encourage the search for alternative tests that are cheap and easily accessible.

Inflammatory activation is now recognized as an integral factor in the development of cancer [11]. Hematologic indices, which are increasingly being used for inflammation-related analyses, have also shown successful results in thyroid studies [12, 13]. There is increased inflammation in malignant thyroid nodules and studies have reported elevated neutrophil-to-lymphocyte ratio (NLR) in Hashimoto's thyroiditis [14, 15]. A recent thyroid study reported systemic inflammation index (SII) and platelet-to-lymphocyte ratio (PLR) as variables that were associated with malignant nodules [16]. PLR has emerged as a reliable index compared to other hematologic indices [17]. However, it has not been compared with SII, systemic inflammatory response index (SIRI), and prognostic nutritional index (PNI), which have newly benn described to have diagnostic value, and no studies have assessed all of these parameters or other candidates for the detection of thyroid malignancy.

The current study aimed to analyze PLR-to-PDW as a novel diagnostic index for its possible role in distinguishing papillary carcinoma (PTC) from benign thyroid nodules (BTN), and to investigate its diagnostic power relative to recently reported inflammatory indices, including NLR, PLR, PNI, SII, and SIRI.

Materials and methods

Study design and ethical statement

This retrospective cross-sectional research analyzed 459 participants who had undergone clinical thyroid examination, USG, and fine-needle aspiration biopsy (FNAB) to grade nodules, from October 2021 to August 2022, in the Endocrinology Clinic of Karabük University. We used a previously-reported classification method to assess the nodules on USG imaging [18]. As a result of diagnostic screening, a total of 438 patients with BTN and 21 patients with PTC were diagnosed by histopathology (as a result of single or repeated FNAB). Multiple biopsies were performed in some patients in the BTN group because the initial FNAB was Bethesda classification I or III. In these patients, repeat biopsy was performed after 4-6 weeks (Bethesda I) or 1-3 months (Bethesda III). The local Ethics Committee approved the current study design according to the principles of the Helsinki Declaration (December 2022, #1194). All study participants had provided written informed consent for the use of their data for scientific purposes. The hospital records included demographics, thyroid tests and the pathological results of the participants.

Criteria for inclusion

An initial total of 599 patients were assessed for study inclusion. We excluded 140 of these 599 patients according to inclusion/exclusion criteria. The main exclusion criteria were: use of anticoagulant drugs; history of head or neck radiation, thyroid surgery or diseases; systemic disorders such as chronic inflammatory diseases, coronary arterial disease or autoimmune diseases; pregnancy; other histopathologic thyroid cancers (such as non-papillary thyroid cancer). The remaining 459 adult patients with nodular/multinodular goiter who had complete medical history and blood tests were assessed for inclusion, as shown in the flowchart (**Figure 1**). FNAB had been performed for all 459 patients with a solitary/multi-nodular goiter diagnosis, and 21 patients with a histopathology result showing PTC were referred for surgery. The preoperative FNAB outcome distribution of these patients was as follows according to the Bethesda classification: II (n=1), III-IV (n=20), V (n=5), and VI (n=3). We divided the participants into two groups, benign and malignant: a BTN Group (n=439) and PTC Group (n=21). Pathologic findings were evaluated and classified according to the tumor-node-metastasis (TNM) staging of the American Cancer Committee.

Laboratory assessment

The pathology department evaluated individual types of nodules from post-operative samples or FNAB. A Mindray-BC6400 autoanalyzer was used for complete blood counts. Thyroid hormones, related antibodies, and all biochemical values were analyzed by a Siemens-ADVIA2400 biochemistry-analyzer and a CENTAUR-XPT device with the original kits. NLR and PLR were manually calculated by dividing neutrophil and platelet counts by lymphocyte count. We calculated SII by the following formula: platelet × neutrophil/lymphocyte. SIRI was calculated with the following formula: neutrophil × monocyte/lymphocyte. PNI was calculated by summing albumin value (g/dL) with 5 × lymphocyte count (10^9/L). Hematologic and thyroid param-

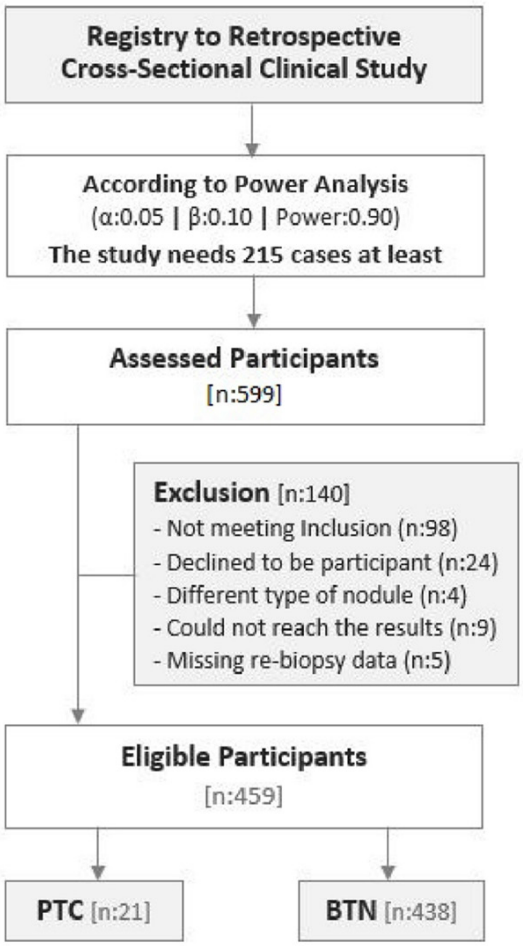

Figure 1. Flowchart for the selection and enrollment of study participants. Benign thyroid nodules (BTN) and papillary thyroid carcinoma (PTC).

eters were analyzed within one hour after blood withdrawal on the second day of hospitalization following 8-hour fasting.

Statistical analysis

We retrospectively collected data, including demographics, thyroid function, and clinical findings and performed statistical analyses with the IBM SPSS v26.0 software for the Windows operating system. The GraphPad Prism v9.4.1 software was used to draw scatter plots and column bar graphs. Data included thyroid function tests, antibodies and hormones. The manually calculated SII, SIRI, PNI, NLR and PLR values were entered into the database. Chi-square tests were used to analyze categorical data which were summarized with count (*n*) and percentage, while continuous data were expressed as mean ± standard deviation. We used the Mann-Whitney *U* test to compare variables with non-normal distribution, whereas the independent samples *t*-test was used for normally distributed variables. We performed a multivariable logistic regression analysis to evaluate potential diagnostic indices. In the receiver operating characteristics (ROC) analysis, PNI, NLR, PLR, SII, SIRI and PLR-to-PDW ratio were evaluated in a single graph depicting area under curve (AUC) data, and specificity and sensitivity values were reported. Results with the detection of a *p* value of < 0.05 (two-sided) were considered significant.

Results

Patient characteristics

Patients' demographic data and the frequencies of smoking and comorbidities were similar in the PTC and BTN groups. The groups did not differ in terms of thyroid function classification (euthyroid, hyperthyroid or hypothyroid), the number of nodules (solitary or multinodular) or the mean diameter of nodules (P > 0.05) (**Table 1**).

Group comparison

There was no difference between the groups in the analysis of FT_3, FT_4, TSH, thyroglobulin, anti-TG and anti-TPO (P > 0.05). Calcitonin was higher in the PTC group compared to the BTN group (9.5 ± 4.5 vs. 2.5 ± 2.1 pg/mL; P=0.008). There was no difference in the comparison of the PTC and BTN groups with respect to PNI (P=0.661), SII (P=0.102), or SIRI (P=0.244), while NLR (P=0.043) and PLR (P=0.002) were significantly higher in the PTC group compared to the BTN group. PLR-to-PDW, the proportional index we propose, also demonstrated a significant difference between patients with PTC compared to those with BTN (12.7 ± 3.9 vs. 7.87 + 2.5; P=0.0001) (**Table 2**).

Univariate and multivariate analysis

Calcitonin, PLR, NLR and PLR-to-PDW were found to have value in discriminating between PTC and BTN. We conducted logistic regression to exclude variables that were not directly associated with the discrimination, which revealed that NLR (OR: 1.414, 95% CI: 1.138-1.758;

Table 1. Demographic and clinical characteristics of patients

Variable	PTC group *n: 21*	BTN group *n: 438*	*P* value
Sex, *m/f*	5/16	87/351	0.659
Age, *years*	48 ± 14	55 ± 13	0.148
BMI, *kg/m²*	29.5 ± 7.1	29.7 ± 5.7	0.537
Hypertension, *y/n*	4/17	158/280	0.122
Diabetes, *y/n*	9/12	167/271	0.178
Smoking, *y/n*	17/4	368/70	0.117
Thyroid, *Eu/Hypo/Hyper*	16/2/3	253/7/178	0.089
Solitary/Multinodular	20/1	92/346	0.307
Diameter of nodule, *mm*	15.4 ± 4.8	16.1 ± 5.4	0.278

BMI: Body Mass Index, Eu: euthyroid, Hypo: hypothyroid, Hyper: hyperthyroid. Benign thyroid nodules (BTN) and papillary thyroid carcinoma (PTC).

Table 2. Summary and comparison of laboratory values in patients with papillary thyroid cancer and benign thyroid nodules

Variable	PTC group *n: 21*	BTN group *n: 438*	*P* value
FT_3, *pg/ml*	3.39 ± 0.46	3.52 ± 3.03	0.816
FT_4, *ng/dl*	1.29 ± 0.25	1.28 ± 0.36	0.858
TSH, *uIU/ml*	2.63 ± 1.37	2.59 ± 5.2	0.764
Thyroglobulin, *IU/mL*	106.3 ± 98	113.5 ± 101	0.914
Anti-TG, *IU/mL*	41.5 ± 54	30.4 ± 40.3	0.535
Anti-TPO, *IU/mL*	201.8 ± 198	214.1 ± 162.4	0.343
Calcitonin, *pg/mL*	9.5 ± 4.5	2.6 ± 2.2	0.008
Leukocyte count	7.89 ± 3.32	7.22 ± 2.08	0.079
Neutrophil count	5.64 ± 3.1	4.96 ± 11.9	0.441
Lymphocyte count	1.67 ± 0.52	2.16 ± 0.67	0.012
Platelet count	296 ± 65.4	258 ± 68.8	0.125
Hemoglobin, *g/dL*	13.2 ± 2.1	12.8 ± 1.9	0.107
PLR	203 ± 92.2	126 ± 42.5	0.002
NLR	3.78 ± 2.85	2.52 ± 2.1	0.042
PNI	55.3 ± 4.5	55.7 ± 4.9	0.661
SII	513 ± 298	739 ± 480	0.102
SIRI	0.91 ± 0.58	1.22 ± 0.91	0.244
PLR-to-PDW ratio	12.7 ± 3.9	7.87 ± 2.5	0.0001

FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, Anti-TG: anti-thyroglobulin antibody, Anti-TPO: anti-thyroid peroxidase antibodies, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-platelet ratio, PNI: prognostic nutrition index, SII: systemic immune-inflammation index, SIRI: systemic inflammatory response index, PDW: platelet distribution width. Benign thyroid nodules (BTN) and papillary thyroid carcinoma (PTC).

P=0.0083), PLR (OR: 1.537, 95% CI: 0.896-1.015; P=0.0065) and PLR-to-PDW (OR: 2.054, 95% CI: 0.954-0.985; P=0.0016) were independently associated with a greater likelihood of PTC presence.

ROC curves of the inflammation-based indices

ROC analysis showed that PNI, SII, and SIRI did not have diagnostic value to distinguish between PTC and BTN [AUC: 0.498, P=0.97; AUC: 0.391, P=0.09; and AUC: 0.424, P=0.24; respectively]. NLR showed a predictive potential for PTC with 62% sensitivity and 75.1% specificity at a > 2.57 cut-off (AUC: 0.699, P=0.002). PLR showed better predictive capability, with 73.4% sensitivity and 70.8% specificity at a > 149.6 cut-off (AUC: 0.786, P=0.0011). PLR-to-PDW had the best predictive value, with 78.1% sensitivity and 73.7% specificity at a > 9.11 cut-off (AUC: 0.827, 95% CI: 0.714-0.915; P=0.0001) (**Figure 2**).

Discussion

Differentiated thyroid cancers make up the majority of cancer cases in thyroid tissue, and PTCs are responsible for most of these cases throughout the world. However, since their frequencies varies between countries and even between different geographic regions within countries, it is challenging to conduct prognostic studies of thyroid cancer. In the present analysis, the increased value of the PLR-to-PDW index, which we compared to NLR, PLR, PNI, SII, and SIRI, appeared to have the best efficacy in distinguishing PTC from BTN, thereby providing supportive data for diagnosis.

Inflammatory activity in tissues or systems may influence systems involved in active immunity, such as natural killer cells, by suppressing their anti-tumor activity [19, 20]. Although the direct relationships have not been clearly defined, it is now accepted that lymphocyte, neutrophil, platelet counts or their proportional indices, which are established markers of inflammation, are effective in the diagnostic distinction of various cancers [21, 22]. Despite the diffi-

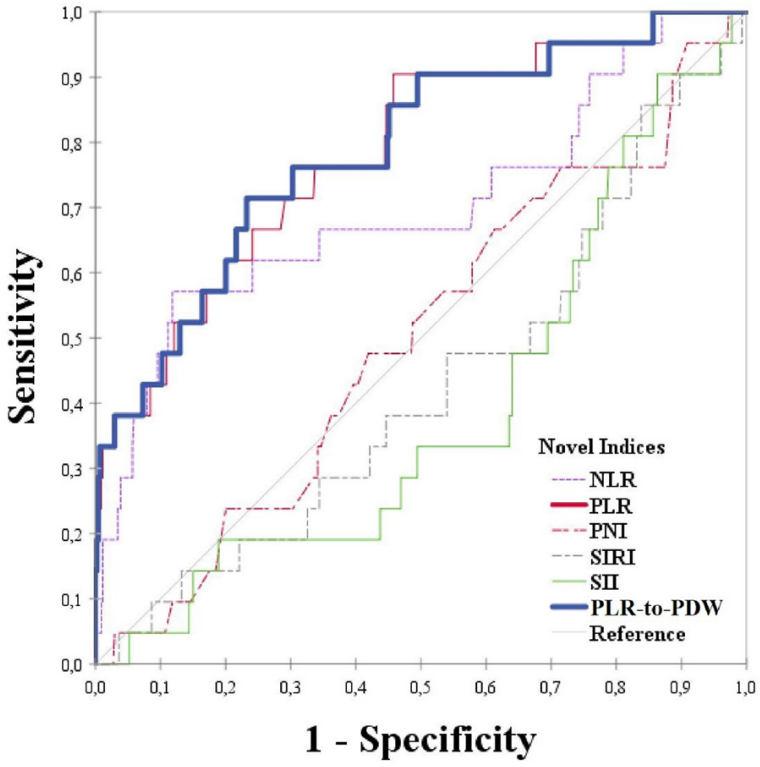

Figure 2. ROC analysis results for the discrimination of PTC from BTN with all variables. Benign thyroid nodules (BTN) and papillary thyroid carcinoma (PTC).

culty of conducting a large-scale study due to the small incidence of thyroid cancer at our center, we believe the results demonstrate that these indices can be utilized as supportive evidence for the distinction of malignant nodules when assessing patients with thyroid nodules.

In the distinction of PTC from benign nodules, PLR and NLR have been demonstrated to have practical value. Jung and colleagues analyzed survival in PTC and reported worse results in the presence of higher NLR [23]. Conversely, another analysis of similar patients showed no significant relationship [24]. Other relationships have also been reported, including results showing that NLR was associated with multifocal tumors and metastasis [22] and others describing that PLR positively correlated with tumor size [25]. According to the study by Shrestra and colleagues, increasing values of NLR or PLR were associated with malignant behavior in cancers, and the authors concluded that measuring these indices would be helpful in detecting malignancy [12]. In a study with limited patient count, Cheong and colleagues found that the size and stage of PTCs were associated with NLR and PLR [26]. Although the number of participants was somewhat low in the present study (with respect to PTC cases), we achieved similar results; however, our results showed that PLR was more efficient than NLR to discriminate PTC from noncancerous nodules.

SIRI and SII, novel inflammation-based indices calculated with neutrophil, lymphocyte, lymphocyte and monocyte counts, reflect the inflammatory response and have prognostic value in many diseases, including cancers [27]. They have the potential to reflect the inflammatory state in various diseases, with better accuracy relative to NLR and PLR [28-30]. In a rare study examining genetic factors and inflammation, SIRI was found to be associated with the presence of the BRAF mutation in PTC [31]. Zhang and colleagues retrospectively analyzed PTC cases who had undergone curative surgery and reported that their SII model effectively predicted lymph node metastasis in patients with PTC [32]. According to the study by Kars and colleagues, SII was higher in patients with thyroid carcinoma compared to controls. In addition, it was found to be associated with multifocality, but not histologic type, invasion, or extrathyroidal spread [33]. An extensive research described preoperative PNI as a diagnostic factor for PTC, as demonstrated by its link with stage and recurrence [33]. In our analysis, NLR and PLR both showed predictive value to distinguish PTC from BTN; whereas, PNI, SII and SIRI did not show any diagnostic value.

Among the previously-studied indices, PLR was the most effective in PTC discrimination in the present study, illustrated by better results compared to NLR, PLR, SII, or SIRI. However, combining PDW with PLR further raised the sensitivity and specificity values for the discrimination of PTC from noncancerous nodules. PDW has

been shown to have a role in assessing cancer patients in previous studies. In our analysis, PLR-to-PDW ratio was found to be significantly higher in patients with PTC compared to those with BTN. In multivariable analysis, higher PLR-to-PDW was found to be associated with an approximately 2-fold increase in the likelihood of having PTC rather than BTN. Furthermore, this ratio showed the best predictive value for PTC among all of the indices examined in this research, as illustrated by its 78.1% sensitivity and 73.7% specificity values with cut-off value of > 9.11.

The most salient aspect of the present study is that, to our knowledge, it is the first one investigating inflammation-based hematological indices, including PLR, NLR, SII, SIRI, and PNI in patients with PTC, as well as describing PLR-to-PDW ratio as a novel index that had better discriminatory value. Although the size distribution of thyroid nodules was not considered in previous studies, we included tumor size due to its potential effect on systemic inflammation; however, the groups were similar with respect to size. The study's main limitations are its retrospective design with limited PTC cases and the routine variability of hemogram parameters due to acute physiological changes. The number of participants with BTN was much higher compared to PTC, which is a factor that could have caused selection bias. Although cytopathology results were used to define the benign group in this study, it should be kept in mind that 1-3% of patients with benign cytopathology are found to have malignancy following histopathological analysis. Nonetheless, this low error likelihood can be further minimized to negligible levels when USG is performed by highly-experienced physicians. Overcoming the limitations and making generalizable presentations will be possible only in studies with a larger population and a prospective design.

In our study, which was conducted in patients with similar demographic and clinical data, indices such as SII, SIRI, and PNI were not found to have capability to distinguish between PTC and BTN. On the contrary, both PLR and NLR were significantly capable of PTC discrimination. The presently proposed PLR-to-PDW ratio exhibited the highest diagnostic discriminatory power, indicating that it is a novel supportive index that can be used to differentiate PTC from BTN. In centers where there is no specialized cytopathologist, this marker can assist clinicians in the decision for surgery or follow-up in patients with non-diagnostic or indeterminate thyroid nodules as result of FNAB.

Disclosure of conflict of interest

None.

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