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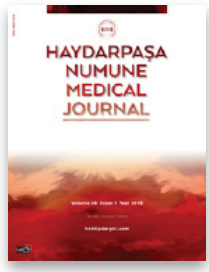

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ORIGINAL ARTICLE

Use of Hemogram Parameters in the Differentiation of Benign Thyroid Nodules and Thyroid Papillary Carcinoma Cases

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Abstract

Introduction: We aimed to compare red cell distribution width (RDW), mean platelet volume (MPV), and some other laboratory parameters in patients with papillary thyroid carcinoma (PTC) or benign thyroid nodule (BTN).

Methods: A total of 365 cases (186 with PTC and 179 with BTN) who underwent lobectomy or bilateral total thyroidectomy were included in the study. The patients were divided into two groups, PTC and BTN, according to histopathological diagnosis.

Results: 76.4% of the patients were female and the mean age was 54.94±13.76 years. The median RDW value was 13.3% (12.7–13.9) in the PTC group and 13.2% (12.7–14.2%) in the BTN group. Mean MPV value was 10.28±1.20 fL in the PTC group and 10.26±1.07 fL in the BTN group. The groups were similar in terms of MPV and RDW values (p=0.477 and p=0.883, respectively). Thyroid gland size and detected nodule sizes were significantly greater in the BTN group compared to the PTC group (p<0.001 for all).

Discussion and Conclusion: Complete blood count results, including RDW and MPV, were found to have no clinical value in distinguishing between PTC and BTN.

Keywords: Benign thyroid nodule, hemogram, mean platelet volume, papillary thyroid cancer, red cell distribution width

According to the 2020 data of the global cancer monitoring center, which examines 36 cancer types in 185 countries, the most common endocrine tumor was identified as thyroid cancer, with 586,202 (3%) cases and 43,646 (0.44%) deaths worldwide[1]. When thyroid cancer types are classified according to histopathological features, papillary thyroid cancer (PTC) is the most common and least invasive type[2,3].

Physical examination, imaging methods, histopathological data, and other markers can be used for diagnostic purposes in thyroid cancer[4]. Due to the importance of inflammation in the development and prognosis of cancer, various studies have been conducted to identify inflammatory markers that can be used in the diagnosis and follow-up of various malignancies, including PTC.[4]. One of these markers is red cell distribution width (RDW) which reflects the variability in the size of circulating erythrocytes. Studies have shown that RDW is a marker of chronic inflammation in cancer patients[5,6]. It has also been shown that RDW is an effective

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independent prognostic factor on malignancy-specific survival in patients with laryngeal squamous cell carcinoma and nasopharyngeal carcinoma[5,6]. Another such marker is mean platelet volume (MPV) which shows platelet activity and is associated with inflammation. It has been shown that elevated MPV value is associated with many cancers and various studies emphasize that MPV can be used as an indicator of systemic inflammation[7-11]. Some studies have reported that MPV values of patients with malignant thyroid nodules are higher compared to controls and patients with benign disease[12,13].

Numerous studies are carried out to explore whether cost-effective and readily-available markers can be used to assess various characteristics of patients with cancer. RDW and MPV are two markers that meet these specifications, particularly due to their relationship with inflammation. Thus, in this study, we aimed to compare RDW and MPV values in patients with papillary thyroid carcinoma (PTC) and benign thyroid nodules (BTNs), and also, to assess possible relationships with various clinical characteristics.

Materials and Methods

The research was carried out at Eskisehir Osmangazi University, Department of General Surgery. Data were collected retrospectively from hospital records. The files of patients who underwent lobectomy or bilateral total thyroidectomy between February 01, 2018, and February 01, 2021, were evaluated. Approval for the study was obtained from Non-Interventional Clinical Trials Ethics Committee of Eskisehir Osmangazi University (Decision no: 08, Decision date: June 15, 2021).

Patients

Patients who underwent lobectomy or bilateral total thyroidectomy were divided into two groups, the PTC group (n=186) and the BTN group (n=179) according to histopathological diagnosis.

Patients with active infection, diabetes mellitus, chronic inflammatory disease, other known malignancy, cirrhosis, autoimmune disease, and myeloproliferative disease were excluded, in addition to those who had used corticosteroids in the last 6 months and patients with incomplete data.

Data

The data collected in the study were as follows: demographic characteristics (age, gender), clinical and operational characteristics (operation type, thyroid gland size, nodule size), disease characteristics (type of malignancy, presence of thyroiditis, lymph node metastasis), pre-operative complete blood count results, including white blood cell (WBC), neutrophil, lymphocyte, platelet counts, hemoglobin and hematocrit values, RDW, MPV, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

Statistical Analysis

All analyses were performed on SPSS v21 (IBM, Armonk, NY, USA). Histogram and Q–Q plots were used to determine whether variables were normally distributed. Data are given as mean±standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann–Whitney U-test. Categorical variables were compared with Pearson Chi-square or Fisher's exact tests. Prediction performance of the variables was evaluated using receiver operating characteristic (ROC) curve analysis. Two-tailed $p<0.05$ was considered as statistically significant.

Results

A total of 365 cases (186 with PTC and 179 with BTN) were included in the study. 76.4% of the patients were female and mean age was 54.94±13.76 years. The median RDW value was 13.3% (12.7–13.9) in the PTC group and 13.2% (12.7–14.2) in the BTN group. Mean MPV value was 10.28±1.20 fL in the PTC group and 10.26±1.07 fL in the BTN group. There was no significant difference between the groups in terms of RDW and MPV values ($p=0.477$ and $p=0.883$, respectively). In addition, there were no significant differences between the PTC and BTN groups in terms of WBC, neutrophil, lymphocyte, platelet counts and NLR, PLR, hemoglobin, and hematocrit values ($p>0.05$). Thyroid gland size and nodule sizes were significantly greater in the BTN group compared to the PTC group (all, $p<0.001$). Summary of patient characteristics with regard to groups is shown in Table 1.

According to the results of the ROC analysis performed to distinguish PTC from BTN, it was determined that RDW, MPV, NLR, and PLR values were not able to significantly distinguish BTN from PTC at any cutoff point ($p>0.05$ for all). Although all values were non-significant, the most ideal cutoff points according to the Youden Index are shown in Table 2.

Table 1. Summary of patient characteristics with regard to groups

	Pathology		Total (n=365)	p
	Malign (n=186)	Benign (n=179)		
Age (year)	54.04±13.96	55.88±13.53	54.94±13.76	0.204
<45	49 (26.34%)	43 (24.02%)	92 (25.21%)	0.610
≥45	137 (73.66%)	136 (75.98%)	273 (74.79%)	
Sex				
Female	144 (77.42%)	135 (75.42%)	279 (76.44%)	0.653
Male	42 (22.58%)	44 (24.58%)	86 (23.56%)	
Operation				
BTT	175 (94.09%)	170 (94.97%)	345 (94.52%)	0.521
BTT+CND	3 (1.61%)	5 (2.79%)	8 (2.19%)	
BTT+UMRND	7 (3.76%)	4 (2.23%)	11 (3.01%)	
BTT+BMRND	1 (0.54%)	0 (0.00%)	1 (0.27%)	
Thyroid gland size (cm)				
Vertical	5.5 (4.5–7)	7 (5.5–9)	6 (5–8)	<0.001
Transverse	5 (4.2–6)	6 (4.5–7.5)	5.5 (4.5–7)	<0.001
Greatest nodule size (cm)	2 (1.1–3)	2.5 (1.5–3.5)	2.3 (1.3–3.4)	<0.001
Sum of nodule sizes (cm)	3.25 (1.8–5.5)	4.4 (2.8–6.6)	3.8 (2.2–6)	<0.001
Type of malignancy				
Classic variant of PTC	54 (29.03%)	-	54 (14.79%)	-
Follicular variant of PTC	132 (70.97%)	-	132 (36.16%)	
Thyroiditis	54 (29.03%)	39 (21.79%)	93 (25.48%)	0.112
Lymphocytic	42 (22.58%)	27 (15.08%)	69 (18.9%)	0.136
Hashimoto	12 (6.45%)	10 (5.59%)	22 (6.03%)	
Subacute granulomatous	0 (0.00%)	2 (1.12%)	2 (0.55%)	
Lymph node metastasis	11 (5.91%)	-	11 (3.01%)	-
WBC (×1000)	7.05 (5.91–8.52)	7.23 (6.00–8.60)	7.18 (5.96–8.57)	0.659
Neutrophil (×1000)	4.14 (3.30–5.07)	4.34 (3.28–5.40)	4.19 (3.30–5.20)	0.639
Lymphocyte (×1000)	2.09 (1.62–2.56)	2.03 (1.69–2.58)	2.06 (1.64–2.56)	0.720
Platelet (×1000)	264 (229–309)	250 (219–299)	259 (222–305)	0.130
NLR	1.94 (1.58–2.60)	2.03 (1.54–2.72)	2.00 (1.57–2.67)	0.555
PLR	126.56 (104.80–154.17)	126.42 (100.77–153.82)	126.43 (101.89–153.82)	0.871
Hemoglobin (g/dL)	13.73±1.42	13.73±1.57	13.73±1.49	0.983
Hematocrit (%)	41.59±3.79	41.44±4.55	41.52±4.17	0.747
RDW (%)	13.3 (12.7–13.9)	13.2 (12.7–14.2)	13.3 (12.7–14.1)	0.477
MPV (fL)	10.28±1.20	10.26±1.07	10.27±1.14	0.883

BTT: Bilateral total thyroidectomy; CND: Central neck dissection; UMRND: Unilateral modified radical neck dissection; BMRND: Bilateral modified radical neck dissection; MPV: Mean platelet volume; NLR: Neutrophil/ lymphocyte ratio; PLR: Platelet/lymphocyte ratio; RDW: Red cell distribution width; WBC: White blood cell. Data are given as mean±standard deviation or median (1st quartile–3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables.

Table 2. Performance of various parameters in distinguishing malignancy PTC from benign thyroid nodules

	RDW	MPV	NLR	PLR
Cutoff	>13.05	>10.15	>1.4833	>103.8545
Sensitivity	64.52%	56.45%	80.11%	75.81%
Specificity	40.22%	50.28%	24.02%	30.73%
Accuracy	52.60%	53.42%	52.60%	53.70%
PPV	52.86%	54.12%	52.28%	53.21%
NPV	52.17%	52.63%	53.75%	55.00%
AUC (95% CI)	0.478 (0.419–0.538)	0.500 (0.441–0.560)	0.482 (0.423–0.541)	0.505 (0.445–0.564)
p	0.477	0.987	0.555	0.871

AUC: Area under ROC curve, CI: Confidence intervals, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, NPV: Negative predictive value, PLR: Platelet-to-lymphocyte ratio, PPV: Positive predictive value, RDW: Red cell distribution width, PTC: Papillary thyroid carcinoma.

Discussion

Since the 1980s, there has been a relatively stable increase in the incidence of PTC in most countries with relevant data[14]. Many studies have shown that complete blood count parameters may be valuable for diagnostic or prognostic purposes in various cancer types. In particular, increased RDW and MPV values have been associated with the characteristics of various cancer types[5-13]. In the light of the latest technological developments in the field of medicine, the frequency of detection of thyroid nodules is increasing due to the widespread use of high-resolution USG[15]. Although most of the detected nodules are benign, long-term follow-up may be required and it may be critical to determine whether the detected thyroid nodules are benign or malignant. However, in this study, which examined the utility of some parameters obtained from complete blood count for the differentiation of PTC and BTN, no significant results were found for any of the parameters.

Studies have shown that inflammation is a risk factor for cancer and that chronic inflammation can lead to cancer in various organs[16-19]. On the other hand, the relationship of the RDW parameter with many inflammatory disorders such as Hashimoto's thyroiditis, inflammatory bowel disease, lupus, rheumatoid arthritis, pneumonia, acute pancreatitis, and septic shock has been demonstrated[20-27]. Various studies have suggested that RDW can predict the presence of malignancy. In these studies, it has been reported that RDW values increase in breast cancer, lung cancer, prostate cancer, and colorectal cancers[28-33]. When the publications on RDW and thyroid cancer are reviewed, although there are studies advocating that RDW is associated with malignant thyroid nodules,[34-37] there are very few studies focusing on PTC in particular[37].

In a retrospective study conducted on patients with indeterminate thyroid nodules, a strong correlation was found between RDW and malignancy risk, and it was reported that RDW was capable in distinguishing thyroid malignancy with a 14.1% cutoff (sensitivity: 53%, specificity: 75%)[35]. In a study examining RDW and MPV in differentiated thyroid cancer (in which PTC is a subgroup), it was reported that patients with differentiated thyroid cancer had higher MPV and RDW values than controls[38]. In two different studies examining RDW values in patients with thyroid nodules, RDW was found to be significantly higher in those with malignant nodules compared to those with benign nodules and controls[34,36]. In a study specific to PTC, Sevinç et al. [37] reported that the RDW value showed 88% sensitivity and 70% specificity in distinguishing PTC with an optimal cutoff value of 12.95% (AUC=0.718, p<0.001). In our study, it was determined that RDW could not predict PTC at any cutoff point and that values were similar in the BTN and PTC groups.

Tumor cells produce proinflammatory cytokines such as chemokines, IL-1, IL-6, and other growth factors that stimulate platelet production. As a result, it has been revealed that platelet activation is an important trigger of angiogenesis and increases metastatic and proteolytic activities; thus, making it an important factor in the development and prognosis of various cancers[12,13,39-41]. MPV is an indicator of platelet function and activation because larger platelets exhibit greater metabolic and enzymatic activity than smaller platelets. In addition, it has long been known that MPV is a marker of inflammation[42]. Considering the effects of platelets on the development and prognosis of cancers, studies have been conducted on various cancer types to determine whether the MPV value (reflecting platelet activity) can be used as a diagnostic or prognostic marker[7,8,40,43,44]. These studies have reported higher MPV values than controls in patients with ovarian cancer,[7] endometrial cancer,[43] gastric cancer,[8] and colorectal cancer[44,45]. Previous studies examining the relationship between MPV and PTC reported conflicting results[12,13,38,46,47].

In studies comparing PTC, benign goiter, and healthy controls, MPV levels were reported to be significantly higher in patients with PTC[12,13,38]. Contrary to these studies, it has been reported that there is no relationship between malignancy of the thyroid gland and MPV value[46]. In a recent study evaluating MPV value between patients with and without thyroid nodules, no significant difference was found between the two groups; in addition, it was emphasized that the MPV value was also unassociated with nodule size[48]. Although we found significant differences between the PTC and BTN groups in terms of gland and nodule sizes, these differences did not translate to changes in inflammatory markers. Similarly, in a study examining hemogram parameters in patients with PTC or benign nodular hyperplasia, no diagnostic relationship was found between MPV and PTC[49]. Furthermore, there are studies in the literature showing that patients with malignant thyroid nodules have lower MPV compared to healthy controls,[50] indicating a disparity from the majority of the literature. In our study, it was determined that MPV value did not have any diagnostic significance in distinguishing between PTC and BTN. Although there are publications in the literature reporting results similar

to our study, there are also studies that describe the opposite. Although underlying differences between patient groups and clinical characteristics of patients may have weighed in on these variations in the literature, it appears that much larger and more detailed studies are needed to determine whether these inflammatory markers actually have diagnostic or prognostic roles.

The retrospective and single-center design of this study are important limitations. Despite the exclusion of patients based on factors that could alter complete blood count results, it is evident that various other parameters may affect the analyses; thus, the lack of data concerning these possible features is another limitation. Although our study purpose was to assess possible distinction between PTC and BTN with these parameters, the absence of a healthy control group must be noted as a possible limitation. The fact that RDW and MPV were not found to be significant in the differentiation of PTC and BTN in our study may be due to the small number of patients. Since the number of PTC cases was low in our study, our data may provide limited representation of PTC cases, especially if and when stratification is needed for stage and/or subtype.

Conclusion

The current study shows that complete blood count parameters, including RDW and MPV, had no clinical value in distinguishing between PTC and BTN. To assess the possible role of such parameters, future studies should aim to conduct multicenter research and categorize patients based on various clinical parameters (stage, comorbidities, etc.) that could possibly influence evaluated parameters.

Ethics Committee Approval: Approval for the study was obtained from Non-Interventional Clinical Trials Ethics Committee of Eskisehir Osmangazi University (Decision no: 08, Decision date: June 15, 2021).

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