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Evaluation of Hemocytometer Parameters as Potential Biomarkers in Benign Multinodular Goiter and Papillary Thyroid Carcinoma

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Abstract

Background: Hemocytometer parameters can be important biomarkers for some types of cancers and diseases. There is a need to evaluate their biomarker potential in thyroid diseases.
Objectives: The current study aimed at contributing to potential biomarker researches to diagnose papillary thyroid carcinoma (PTC) and benign multinodular goiter (BMG), evaluate the role of these markers to determine the PTC characteristics and contribute to clarification of controversial issues.
Methods: The study was designed as a retrospective observational study. The study included 389 patients who underwent total thyroidectomy at private Sani Konukoglu hospital (Sanko University, School of Medicine, Gaziantep, Turkey) due to BMG or PTC diagnosis from November 2011 to May 2017. The study subjects were divided into 3 groups. Groups 1, 2, and 3 were subjects with BMG, PTC, and the control, respectively. The comparisons were made among the groups in terms of hemocytometer parameters. In the group with the thyroid papillary carcinoma diagnosis, the relationship between the hemocytometer parameters and the bilateral tumor presence, single-sided multicentrite, and tumor diameter (size) were investigated.
Results: Red cell distribution width (RDW) levels were 15.50 ± 2.39, 15.68 ± 2.16, and 12.5 ± 1.51 in the BMG, PTC, and control groups, respectively. Mean platelet volumes (MPV) were 7.97 ± 1.19, 8.05 ± 1.20, and 7.23 ± 1.39 in the BMG, PTC, and control groups, respectively. MPV and RDW values were significantly lower in group 3 compared with the groups 1 and 2 ($P < 0.0001$). Plateletcrit (PCT) values were 0.22 ± 0.05, 0.23 ± 0.06, and 0.19 ± 0.05 in the BMG, PTC, and control groups, respectively. PCT was significantly lower in the group 3 compared with the groups 1 and 2 ($P = 0.0001$). In PTC group, no significant relationship was observed between any of the examined hematological parameters in terms of multicentric and bilateral tumor presence.
Conclusions: RDW, MPV, haemoglobin content, and PCT were significantly higher in the BMG and PTC groups. This increase was not specific for either of the 2 groups. No significant difference was found between any of the hemocytometer parameters and the multicentricity and bilaterality of PTC. But, a possible correlation was observed between activated partial thromboplastin time (aPTT), hemoglobin content, and tumor size.

Keywords: Goiter, Papillary Thyroid Carcinoma, Neutrophil, Lymphocyte, Platelet

1. Background

The relationship between the inflammatory and non-inflammatory diseases such as acute appendicitis, varicocele, cancers, coronary artery diseases, idiopathic pulmonary arterial hypertension, and tinnitus and some of the hemocytometer parameters are investigated in recent years (1-3). Among these hemocytometer parameters, neutrophil/lymphocyte ratio (NLR), MPV, platelet/lymphocyte ratio (PLR), platelet indices, and platelet distribution width (PDW) are the most studied ones. NLR especially provides information about many inflammatory conditions as biomarkers. It is also thought that NLR may be associated with pathologic characterization of some tumors and tumor prognosis (2). This relationship is related to the systemic inflammatory process. It is observed that systemic inflammatory is closely associated with all phases of cancer (1). A variety of white blood cell (WBC) and platelet indices such as MPV and PLR are also associated with the clinicopathological characteristics and survival of many cancers (4, 5). It is also stated that there may be a relationship between thyroid diseases and thyroid cancers and some of

the hemocytometer parameters (6). Seretis et al., observed that NLR increased at significant levels in incidental papillary microcarcinomas and thyroid cancers (7). Kim et al., reported the prognostic significance of NLR in advanced papillary thyroid cancer (8).

Thyroid cancer is the most frequent observed endocrine cancer (9). The incidence of thyroid cancer is increasing gradually due to the increase in incidence of papillary thyroid cancer (10). Therefore, new diagnostic and prognostic biomarkers are needed (11). Currently, there is uncertainty in the literature regarding the utility of hemocytometer parameters in thyroid disease; some reporting potential relationships between these parameters and disease, but others not being able to independently replicate these results (7, 12, 13). Therefore, a possible relationship between hemocytometer parameters and thyroid diseases is still debated. Some of the parameters such as MPV, PDW, and PCT are proposed as biomarkers in the diagnosis and treatment of thyroid cancers (10, 14). However, there are also publications indicating that the role of various WBC and platelet indices such as NLR, MPV, and PLR in thyroid cancer are not fully understood (5).

Also, there is no common consensus about the parameters that benefit in the diagnosis and treatment of thyroid cancer and thyroid diseases. Although there was low patient volume in some of the reported studies, only a single hemocytometer parameter was analyzed in the others. In addition, meta-analysis studies about the subject are not enough. The number of studies examining hemocytometer parameter and thyroid cancer relation is very small (15). For this reason, new studies are needed. It is reported that the cost effectivity in the phase of diagnosis, treatment, and follow-up may increase by the appropriate use of hemocytometer parameters (16).

In the current study, hemocytometer parameters considered as potential biomarkers in BMG and PTC were collected and their efficacy in differential diagnosis was evaluated. The relationships between bilateral, multicentric tumor, and tumor size in PTC and hematological parameters were also assessed. The current study is important because of the extensive hemocytometer parameters list, the examination of the role of hemocytometer parameters in the discrimination between BMG and PTC, the assessment of PTC multicentry, bilaterality, and tumor size association in a single study with relatively a large sample size.

2. Objectives

The current study aimed at contributing to potential biomarker to diagnose PTC and BMG, evaluate the role of these markers to determine the PTC characteristics, and contribute to clarification of controversial issues.

3. Methods

3.1. Study Design and Data Collection

The current retrospective observational study was conducted in a single hospital. The study included 389 patients who underwent total thyroidectomy at private Sani Konukoglu hospital (Sanko University, School of Medicine, Gaziantep, Turkey) due to BMG or PTC from November 2011 to May 2017. The study subjects were from the same geographical area. The hospital was a private and non-referral hospital. In addition, 61 patients in the outpatient clinic that did not undergo thyroidectomy and had no thyroid disease were randomly determined as control group patients. Control group was age-matched to the patient population. Control group was inflammation free with no history of malignancy. Patient data were retrospectively obtained through the data recorded in the patients' files and electronic records.

3.2. Sample Collections and Analysis

Samples were obtained from patients admitted to the hospital. All patients were residents of the same geographical area. Preoperative hematologic parameters were obtained from samples stored in the ethylenediaminetetraacetic acid (EDTA) tubes. Measurements of hemocytometer parameters were performed with a calibrated automatic hematology analyzer (Cell-dyn ruby, Abbott, Chicago, USA).

3.3. Measurements and Protocols

All the variables were selected based on the previous literature reports hypothesized to be important as biomarkers. All necessary criteria were followed as required in a clinical measurement setting. The comparisons were made between the groups in the study by recording hemocytometer parameters such as NLR, PLR, RDW, MPV, MPV/platelet count, (MPV/P) ratio, PCT, mean cell volume (MCV), and erythrocyte count. PCT = platelet count $\times$ MPV / 10000 formula was used in PCT calculation (17, 18). The pathologic diagnoses such as tumor size, bilaterality, and multicentricity in single lobe were recorded by examining the pathologic reports of patients who underwent total thyroidectomy and diagnosed with PTC. The study subjects were divided into 3 groups. Group 1 was determined as benign multinodular goitre group, group 2 as thyroid papillary carcinoma group, and group 3 as the control group. The comparisons were made among the groups in terms of hemocytometer parameters. The values of activated partial thromboplastin time (aPTT), thyrotropin-stimulating hormone (TSH), and free T4 were also compared among the groups. In the group with the thyroid papillary carcinoma

diagnosis, the relationship between the hemocytometer parameters and the bilateral tumor presence, single-sided multicentric, and tumor diameter were investigated. The study was conducted in accordance with the declaration of Helsinki. Informed consent was obtained from all patients prior to thyroidectomy. The current study was approved by the research registry com. (RR.UINID 2017/3134).

3.4. Inclusion Criteria

The current study included 389 patients who underwent total thyroidectomy due to BMG or PTC from November 2011 to May 2017. The age range of the patients was 17 - 81 years.

3.5. Exclusion Criteria

In order to reduce the impact of the confounding factors, patients with severe diabetes, chronic inflammatory disease, autoimmune disease, other site cancers, hepatitis, and renal or hematologic disease were not included in the study. Twenty-two patients due to the exclusion criteria and 12 patients due to the missing data were also excluded.

3.6. Statistical Analysis

Based on literature findings, it was calculated that to detect a 15% difference in population means with 80% power and Cronbach's alfa of 0.05, at least 100 individuals were required for each group. In addition, the study aimed at increasing the sample size to compare the tumor characteristics and the effect of hematologic parameters on tumor size in a linear regression model. Firstly, the normality (normal distribution) of the continuous variables was assessed by the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Any non-normal distributed variables were transformed (such as square root, log, etc.) to conform normality before analysis. Normally distributed variables were compared among the 3 diagnostic groups (BMG, PTC, and control) by the one-way ANOVA. The Kruskal-Wallis test was used to compare variables with unequal distributions among the 3 groups. The Tukey multiple comparisons test was used for pairwise differences among the groups. Distribution of categorical factors, such as gender, among the diagnostic groups was compared by chi-square test. The effect of hematological parameters on tumor size was assessed by the regression analysis. Nearly all comparisons were performed with the full data. No variables had more than 2% missing data. P values less than 0.05 were considered statistically significant. All statistical analyses were conducted by SAS/STAT version 9.3 (SAS Institute, Inc., Cary, North Carolina, USA).

4. Results

The mean age of the control group was significantly lower than those of the PTC and BMG groups ($P < 0.0001$). The gender distribution difference was also statistically significant between the groups ($P < 0.0001$). RDW and MPV values were significantly lower in the control group in comparison with those of the other groups ($P < 0.0001$). The plateletcrit values were significantly lower in the control group compared with other groups ($P = 0.0001$). Hemoglobin content, hematocrit, and erythrocyte counts were significantly higher in the control group compared with the other groups ($P < 0.0001$). No significant difference was found between the groups in terms of NLR, PLR, platelet count, MPV/P ratio, and MCV ($P > 0.05$) (Table 1) (Figure 1). Similar trends were observed when male and female patients were analyzed separately, however the observed trends were not as significant due to reduction in sample size. In the PTC group, no significant relationship was observed between any of the hematological parameters examined in terms of multicentric and bilateral tumor presence ($P > 0.05$) (Table 2) (Figures 2, 3). A possible correlation was observed between aPTT and hemoglobin content and the tumor size in a multivariate regression analysis ($P = 0.005$) ($P = 0.001$) (Table 3) (Figure 4).

4. Discussion

Thyroid diseases are frequently encountered in clinical practice. In particular, BMG and PTC are on the top among the thyroid diseases. There is a worldwide increase in the incidence of differential thyroid carcinomas (19). PTC is the most frequent observed thyroid cancer (20).

Several studies showed that hemocytometer parameters can increase or decrease in some cancer types and diseases. Especially, increased NLR, PLR, and MPV were associated with some types of cancer (21, 22). Increased NLR and MPV are also associated with inflammatory diseases (23). These parameters were thought to be useful laboratory markers in the diagnosis of these diseases (24-26).

Hemocytometer parameters can also change in some thyroid gland diseases such as the Hashimoto thyroiditis, benign nodular goitre, PTC, and thyroid medullary carcinoma. Carlioglu A et al., reported a close relationship between high MPV values and the Hashimoto thyroiditis (27). Baldane S et al., showed a correlation between increased MPV and PTC (10). Dincel O et al., reported a possible relationship between platelet indices and PTC (14). Jiang K et al., defined PLR as a predictive and prognostic factor in patients with medullary thyroid carcinoma (28).

NLR measured in preoperative period reflects the status of the systemic inflammatory response and the condi-

Table 1. Relationship Between Diagnosis and Hematological Parameters[a]

Variables	BMG Group 1 (N = 280)	PTC Group 2 (N = 109)	Control Group 3 (N = 61)	P Value
Age	48.9 ± 12.7[A]	46.7 ± 12.9[A]	39.5 ± 17.8[B]	< 0.0001
Gender, %				< 0.0001
Male	56	13	31	
Female	64	27	9	
Neutrophil	4.70 ± 1.93[A]	4.85 ± 1.47	5.42 ± 2.33[B]	0.03
Lymphocyte	2.43 ± 0.73	2.52 ± 0.69	2.68 ± 1.12	0.07
NLR	2.12 ± 1.34	2.06 ± 0.92	2.36 ± 1.69	0.35
PLR	125.32 ± 49.62	119.79 ± 41.94	109.81 ± 50.72	0.07
RDW	15.50 ± 2.39[A]	15.68 ± 2.16[A]	12.5 ± 1.51[B]	< 0.0001
MPV	7.97 ± 1.19[A]	8.05 ± 1.20[A]	7.23 ± 1.39[B]	< 0.0001
Platelet count	278.75 ± 63.17	284.91 ± 64.78	264.77 ± 61.05	0.14
MPV/P	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.64
PCT	0.22 ± 0.05[A]	0.23 ± 0.06[A]	0.19 ± 0.05[B]	0.0001
Hemoglobin content	13.50 ± 1.59[A]	13.24 ± 1.56[A]	14.51 ± 1.89[B]	< 0.0001
Hematocrit	40.32 ± 4.27[A]	39.70 ± 4.22[A]	44.02 ± 4.95[B]	< 0.0001
MCV	84.93 ± 7.22	83.68 ± 6.99	85.82 ± 6.36	0.13
Erythrocyte count	4.74 ± 0.47[A]	4.75 ± 0.47[A]	5.13 ± 0.54[B]	< 0.0001
WBC	7.91 ± 2.19[A]	8.21 ± 1.73	8.92 ± 2.59[B]	0.004
aPTT	30.20 ± 2.93	30.67 ± 2.53	31.10 ± 4.82	0.12
TSH	2.32 ± 8.74	2.48 ± 8.51	1.53 ± 0.93	0.85
FT_4	1.13 ± 0.79	1.02 ± 0.28	1.02 ± 0.12	0.33

Abbreviations: aPTT, Activated Partial Thromboplastin Time; BMG, Benign Multinodular Goiter; FT_4, Free T_4; MCV, Mean Cell Volume; MPV, Mean Platelet Volume; MPV/P, MPV/Platelet Count Ratio; NLR, Neutrophil/Lymphocyte Ratio; PCT, Plateletcrit; PLR, Platelet/Lymphocyte Ratios; PTC, Papillary Thyroid Carcinoma; RDW, Red Blood Cell Distribution Width; TSH: Thyrotropin-Stimulating Hormone; WBC, Mhite Blood Cell.

[a] Continuous variables are expressed as mean ± SD. ANOVA result P values comparing the 3 groups are presented. Mean values in 1 row followed by the same superscript letter are not significantly different, values with superscripts of different capital letters in the rows of the each analysis are significantly different (P < 0.05) based on the Tukey test.

tion of immune system (6). The efficiency of systemic inflammatory response on the progression and metastasis of tumors is reported. It is also known that inflammation plays a role in every phase of cancer such as proliferation, angiogenesis, and invasion (1). The inflammatory response causes the release of cytokines and chemokines from cancer cells (29).

Since NLR is a biomarker that gives information about the inflammatory condition, it is thought that cancers containing an inflammatory process can be evaluated preoperatively with NLR. In recent years, it is emphasized that NLR and PLR are important markers in various types of cancer (30). NLR and PLR are also associated with thyroid cancers in many studies. Ozmen S et al., found that NLR and PLR values were higher in differentiated thyroid cancer groups than the control group (15). Kocer et al., found significantly higher NLR level in patient group with papillary thyroid carcinoma than the benign goitre group (12). Gong W et al., showed a correlation between increased NLR level and PTC phase (6). On the other hand, Yaylaci et al., observed no significant relationship between NLR and PTC (13). Kim SM et al., also reported a lack of significant relationship between preoperative NLR levels and clinicopathological characteristics of PTC in patients with PTC (31). Similar to these reports, no significant relationship was observed between the patient groups in terms of NLR levels in the current study. These results collectively suggest that the benefit of NLR in the clinicopathological and prognostic evaluation of PTC is controversial. Therefore, the relationship between NLR and PTC is still uncertain.

MPV is a marker that can be easily assessed in the routine hemocytometer associated with changes in platelets (32). Correlation between MPV and some types of cancer was previously reported (33, 34). Dincel O et al., found no

Table 2. Relationship Between Bilateral, Multicentric Tumor, Tumor Size, and Hematological Parameters[a]

Variables	Bilateral			Multicentric			Tumor Size[b]	
	Yes (N = 32)	No (N = 74)	P Value[c]	Yes (N = 42)	No (N = 64)	P Value[c]	(N = 106)	P Value[c]
Age	46.91 ± 12.56	46.84 ± 13.01	0.99	46.83 ± 12.07	46.91 ± 13.38	0.97	-1.01 ± 0.79	0.20
Gender, %			0.64			0.09		0.54
Male	13	9		17	6		2.06 ± 2.16	
Female	87	91		83	94		1.75 ± 1.51	
Neutrophil	4.84 ± 1.27	4.85 ± 1.57	0.97	5.04 ± 1.59	4.73 ± 1.40	0.29	0.006 ± 0.09	0.95
Lymphocyte	2.34 ± 0.62	2.59 ± 0.70	0.08	2.49 ± 0.66	2.54 ± 0.71	0.71	0.007 ± 0.04	0.88
NLR	2.23 ± 1.08	2.00 ± 0.85	0.24	2.16 ± 0.99	2.01 ± 0.88	0.43	0.001 ± 0.06	0.99
PLR	122.01 ± 37.67	119.37 ± 44.13	0.77	118.01 ± 38.18	121.58 ± 44.76	0.67	0.76 ± 2.52	0.76
RDW	16.01 ± 2.25	15.49 ± 2.12	0.26	15.97 ± 2.09	15.44 ± 2.20	0.22	0.02 ± 0.13	0.87
MPV	8.23 ± 1.41	7.99 ± 1.10	0.35	8.19 ± 1.27	7.98 ± 1.16	0.40	0.06 ± 0.07	0.41
Platelet count	269.53 ± 53.40	291.81 ± 69.02	0.11	278.40 ± 57.64	289.47 ± 69.91	0.40	2.13 ± 4.03	0.60
MPV/P	0.03 ± 0.01	0.03 ± 0.01	0.15	0.03 ± 0.01	0.03 ± 0.01	0.46	-.0001 ± 0.001	0.78
PCT	0.22 ± 0.05	0.23 ± 0.05	0.31	0.23 ± 0.05	0.23 ± 0.06	0.79	0.004 ± 0.003	0.29
Hemoglobin content	12.97 ± 1.80	13.37 ± 1.44	0.22	13.15 ± 1.79	13.32 ± 1.40	0.58	0.08 ± 0.09	0.41
Hematocrit	38.93 ± 4.87	40.05 ± 3.94	0.22	39.35 ± 4.78	39.95 ± 3.89	0.48	-0.04 ± 0.26	0.89
MCV	82.69 ± 7.78	84.16 ± 6.73	0.33	82.66 ± 7.44	84.40 ± 6.77	0.21	-0.47 ± 0.44	0.29
Erythrocyte count	4.70 ± 0.45	4.76 ± 0.48	0.55	4.76 ± 0.45	4.74 ± 0.48	0.83	0.02 ± 0.03	0.49
WBC	7.97 ± 1.51	8.30 ± 1.80	0.36	8.33 ± 1.95	8.11 ± 1.56	0.51	-0.02 ± 0.11	0.87
APTT	30.59 ± 2.08	30.64 ± 2.71	0.92	30.68 ± 2.25	30.60 ± 2.71	0.88	0.32 ± 0.17	0.06
TSH	3.25 ± 10.42	2.17 ± 7.76	0.56	2.91 ± 9.21	2.24 ± 8.30	0.71	-0.50 ± 0.54	0.36
FT_4	0.99 ± 0.35	1.03 ± 0.25	0.50	0.98 ± 0.33	1.04 ± 0.25	0.33	0.03 ± 0.02	0.11

Abbreviations: aPTT, Activated Partial Thromboplastin Time; FT_4, Free T_4; MCV, Mean Cell Volume; MPV, Mean Platelet Volume; MPV/P, MPV/Platelet Count Ratio; NLR, Neutrophil/Lymphocyte Ratio; PCT, Plateletcrit; PLR, Platelet/Lymphocyte Ratios; RDW, Red Blood Cell Distribution Width; TSH, Thyrotropin-Stimulating Hormone; WBC, White Blood Cell.

[a] Continuous variables are expressed as mean ± standard deviation.

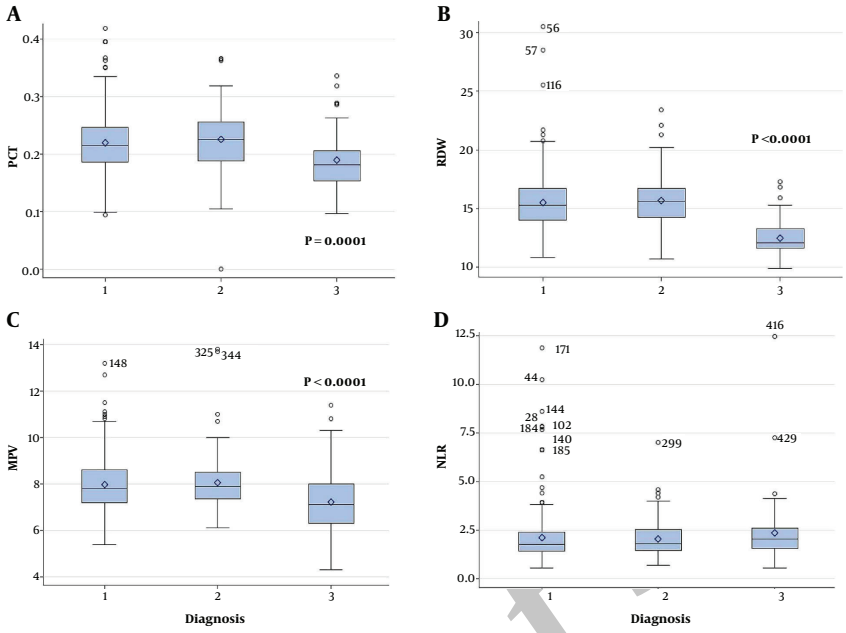
[b] Regression coefficients ± standard error.

[c] P values represent comparisons between the 2 groups for bilateral and multicentric analyses. Regression analysis P values were used to express tumor size.

significant difference between PTC, multinodular goitre, and control groups in terms of MPV values (14). Yaylaci et al., also did not find any significant relationship between benign nodular goitre and PTC groups in terms of MPV values (13). On the other hand, Bayhan Z et al., observed significantly higher MPV values in the thyroid malignancy group than in the benign thyroid disease group. Bayhan Z et al., reported that MPV may be a biomarker in thyroid carcinomas (22), while Baldane S et al., found significantly higher MPV levels in the group with papillary thyroid carcinoma (10). The MPV value was significantly higher in both the BMG and the PTC groups than the control group in the current study. However, no significant difference was observed between the benign and malignant groups. The current study findings indicated that MPV can increase in both PTC and BMG groups. However, MPV cannot be a specific marker in distinguishing PTC or BMG.

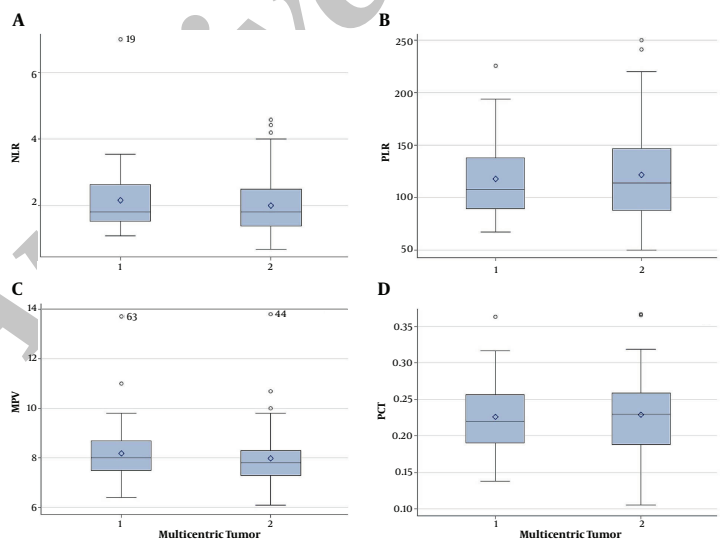
PCT is the platelet mass index measured using platelet and MPV values (35). PCT can be used to determine the need for platelet transfusion (17). It is emphasized that platelet indices (platelet count, PCT, MPV) can be used as inflammatory markers in patients with cancer in recent years. Dincel O et al., found that PCT was significantly higher in patients with PTC than the BMG and control group (14). It is also reported that platelet indices may be useful to diagnose and follow-up cardiovascular, cerebrovascular, thromboembolic, and inflammatory diseases (36). In the current study, PCT values were significantly higher in both BMG and PTC groups than the control group. However, no significant difference was observed between the benign and malignant groups. The correlation between PCT and thyroid diseases is not proven yet.

Figure 1. Distribution of Selected Hematological Parameters Among the Diagnostic Groups



1, group 1; 2, group 2; 3, group 3. A, plateletcrit and groups; B, red blood cell distribution width; group C, mean platelet volume and group D, neutrophil/lymphocyte ratio and groups.

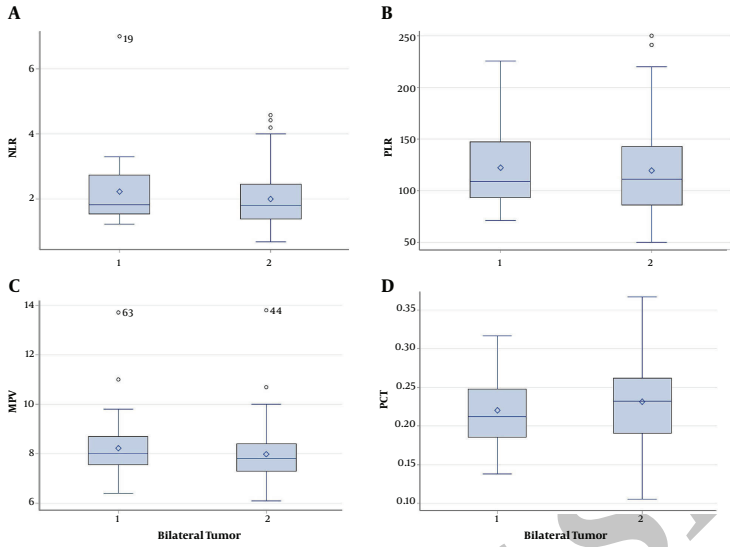
Figure 2. Relationship Between Multicentric Tumor and Selected Hematological Parameters



1, multicentric tumor; 2, no multisentric tumor; A, neutrophil/lymphocyte ratio and multicentric tumor; B, platelet/lymphocyte ratio and multicentric tumor; C, mean platelet volume and multicentric tumor; D, plateletcrit and multicentric tumor.

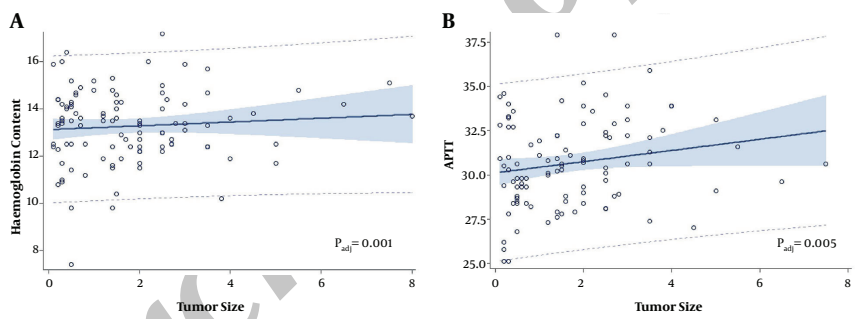
PLR is a marker that reflects the degree of systemic inflammation. PLR can be useful to predict the prognosis of some tumors (37, 38). Kim SM et al., investigated the relationship between PLR and clinicopathologic features of PTC, reported a correlation between high PLR value and lateral lymph node metastasis in female patients (31). Jiang K

Figure 3. Relationship between bilateral tumors and selected hematological parameters



1, Bilateral tumor; 2, No bilateral tumor; A, neutrophil/lymphocyte ratio and bilateral tumor; B, platelet/lymphocyte ratio and bilateral tumor; C, mean platelet volume and bilateral tumor; D, plateletcrit and bilateral tumor.

Figure 4. Plots of (A) Hemoglobin Content (B) aPTT vs. Tumor Size



Shaded area shows 95% confidence intervals. Dotted lines show 95% prediction limits. Multivariate regression model adjusted P values are presented on the figures. Overall multivariate regression model $R^2 = 0.35$, P = 0.03.

et al., reported a significant correlation between preoperative PLR value, lymph node metastasis, and recurrence in medullary thyroid carcinoma (39). However, Machairas N et al., reported that PLR was not useful to distinguish patients with benign goitre and thyroid cancer (5). In the current study, no significant difference was observed between the study groups in terms of PLR. The LR values had no benefit to distinguish BMG and PTC.

RDW is used to differentially diagnose iron deficiency anemia, thalassemia, and hemoglobinopathies. However, it was reported that it can be used as a diagnostic tool in acute appendicitis, colonic cancer, cardiac diseases, and celiac disease (40-42). Aktas G et al., found that RDW values were significantly higher in patients with the Hashimoto thyroiditis. Aktas G et al., suggested that patients with high RDW, but without iron deficiency anemia, should be evaluated in terms of the Hashimoto thyroiditis (43). Yu HM et al., showed a correlation between RDW and subclinical hypothyroidism in a large population study (44). Yaylaci S et al., did not find any significant relationship between the groups consisting of patients with benign nodular goitre and PTC in terms of RDW values (13). RDW values in PTC and BMG groups were significantly higher than that of the control group in the current study. However, no significant difference was found between PTC and BMG groups. The current study observations supported by the literature in-

Table 3. Multivariate Regression Model Examining the Effect of Hematological Parameters on Tumor Size[a]

Variable	Estimate[b]	SE	P Value[c]
Age	0.02	0.01	0.10
Neutrophil	-0.40	0.58	0.49
Lymphocyte	-0.63	0.93	0.50
NLR	0.40	0.40	0.32
PLR	-0.01	0.01	0.38
RDW	0.14	0.07	0.07
MPV	-0.09	1.15	0.94
Platelet count	0.00	0.02	0.89
MPV/P	-7.54	84.59	0.93
PCT	15.80	32.61	0.63
Hemoglobin content	0.86	0.25	0.001
Hematocrit	-0.08	0.25	0.76
MCV	-0.10	0.12	0.38
Erythrocyte count	-1.55	1.95	0.43
WBC	0.10	0.54	0.86
aPTT	0.18	0.06	0.005
TSH	0.00	0.02	0.91
FT_4	-0.36	0.62	0.57

Abbreviations: aPTT, Activated Partial Thromboplastin Time; FT_4, Free T_4; MCV, Mean Cell Volume; MPV, Mean Platelet Volume; MPV/P Count, MPV/Platelet Count Ratio; NRL, Neutrophil/Lymphocyte Ratio; PCT, Plateletcrit; PLR, Platelet/Lymphocyte Ratios; RDW, Red Blood Cell Distribution Width; SE, Standard Error; TSH, Thyrotropin-Stimulating Hormone; WBC, White Blood Cell.
[a] Total sample size = 109.
[b] Regression coefficients.
[c] Multivariate regression model adjusted P values. Adjusted model includes all variables in the model.

dicated that RDW was not effective in the diagnosis and differential diagnosis of PTC. However, RDW can be used to diagnose subclinical hypothyroidism and the Hashimoto thyroiditis.

In the current study, hemoglobin content as well as hematocrit and erythrocyte count values were significantly higher in the control group compared with the other groups. Similar to the current study, Yaylaci S et al., also identified a significant relationship between patients with benign nodular goitre and PTC in terms of hematocrit and hemoglobin content (13). Findings showed that these parameters were inadequate in the differential diagnosis of PTC and BMG.

It was reported that the hemocytometer parameters in preoperative period may be associated with cancer phase, lymph node involvement, and prognostic factors (45, 46). Kim SM et al., investigating the clinicopathological characteristics of patients with papillary thyroid carcinoma, did not find any significant relationship between NLR and tumor size, and multifocality. However, they reported a significant relationship between tumor size and PLR (31). On the other hand, Gong W et al., reported that the tumor size and multifocality correlated with the NLR values. It was reported that multifocality and tumor size increased significantly in the group with NLR value > 2 (6). Machairas et al., found no significant association among PTC multifocality, tumor size, and hemocytometer parameters (5). In the current study, no significant relationship was observed between any hemocytometer parameters based on the bilaterality of the PTC and the multifocality of the single lobe.

It is known that hemostatic defects develop in patients with cancer. It was reported that the metastatic lesions, in particular, cause abnormalities in some of the hemostatic parameters (47, 48). Lee S et al., investigating the clinical significance of coagulation factors in operable colorectal cancer, found a correlation between the plasma fibrinogen level and depth of tumor invasion and the tumor size. They also reported that prolonged prothrombin time level was associated with overall survival (49). In agreement with these studies, a correlation was also observed between aPTT and haemoglobin content, and the tumor size.

Hemocytometer parameters associated with thyroid diseases are evaluated for different purposes in many studies. It was reported that some of these parameters were associated with PTC, the Hashimoto thyroiditis, and benign goiters, whereas in some others no relationship was observed with thyroid diseases. In the current study, significant RDW, MPV, PCT, and hemoglobin content differences were observed between the control and case groups. But, none of these changes were specific to PTC or BMG. Increased values in comparison with the control group were observed both in the PTC and BMG groups. Machairas et al., reported that hemocytometer parameters did not allow for the differentiation of multinodular hyperplasia and PTC (5). Similar to the results of the study by Machairas et al., none of the hemocytometer parameters were useful to distinguish benign or malignant disease in the current study.

According to the current study results and the literature reports, no hemocytometer parameters in the current study had the power to be clinical biomarkers to evaluate thyroid diseases. The results obtained in the literature are in a wide spectrum. For this reason, the relationship between hemocytometer parameters and thyroid diseases should be revealed ultrastructurally. In addition, similar mete-analysis studies with large series are useful.

5.1. Limitations

The current study had some limitations. It was a retrospective study and consisted of a small number of patients with PTC. A larger study population would provide a higher statistical power. The study was planned as a single-center study in a relatively small geographic area; hence, data on patient characteristics and hematological parameters would be more homogeneous and less prone to errors. However, a drawback of this study design was that it may

not reflect the general population. Another shortcoming of the current study was that it could not evaluate other parameters such as height, weight, body mass index (BMI), and systolic and diastolic pressures, because it was a retrospective study. Prospective studies with large scales are needed to evaluate the changes of hemocytometer parameters in patient with BMG and PTC.

In conclusions, RDW, MPV, hemoglobin content, and PCT were significantly higher in benign multinodular goitre, and papillary thyroid carcinoma groups. However, this increase was not specific for either of the 2 groups. No significant difference was observed between any of the hemocytometer parameters and the multicentricity and bilaterality of papillary thyroid carcinoma in the study. But, a possible correlation was observed between aPTT, hemoglobin content, and tumor size. The hemocytometer parameters evaluated in the current study cannot be considered as ideal biomarkers to evaluate thyroid diseases.

Footnotes

Authors' Contribution: Erdal Uysal, study investigation, analysis, interpretation of the results, writing the primary draft of manuscript; Seyit Mehmet Ceylan, data collection, interpretation of results, and review and critique of the manuscript; Ahmet Orhan Gurer, proposing the idea, and revising the primary draft of manuscript; Hasan Bakir and Efe Sezgin: study design and data analysis; Efe Sezgin, data analysis; Basar Aksoy and Mehmet Bastemir, study investigation. All the authors read and approved the final manuscript.

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