ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2022:29(4):611-618 doi: 10.17343/sdutfd.1179733

EVALUATION OF INFLAMMATION-RELATED HEMOGRAM PARAMETERS AS A USEFUL MARKER IN PAPILLARY THYROID CARCINOMA

PAPİLLER TİROİD KARSİNOMUNDA YARARLI BİR BELİRTEÇ OLARAK İNFLAMASYONLA İLİŞKİLİ HEMOGRAM PARAMETRELERİNİN DEĞERLENDİRİLMESİ

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Cite this article as: Sözen M, Cantürk Z, Selek A, Çetinarslan B, Sevinç B, Gezer E, Köksalan D. Evaluation of Inflammation-Related Hemogram Parameters as a Useful Marker in Papillary Thyroid Carcinoma. Med J SDU 2022; 29(4): 611-618.

Öz

Amaç
İnflamasyona bağlı hemogram parametreleri son zamanlarda kanser hastalarında faydalı bir belirteç olarak tanımlanmaya başlamıştır. Bu çalışmada, papiller tiroid kanserli (PTC), malignite potansiyeli belirsiz iyi diferansiye tiroid tümörü ve foliküler adenomlu (FA) hastalarda hemogram parametrelerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem
Çalışmada 287 hastanın verileri analiz edildi. Çalışma popülasyonu 5 farklı gruba ayrıldı. 1. Grup: kontrol, 2. grup: FA, 3. grup: WDT-UMP, 4. grup: metastatik olmayan PTC, 5. grup: metastatik PTC. Ameliyat öncesi yapılan kan testlerini değerlendirdik.

Bulgular
Ortalama yaş 50 (37-59) idi. Ortalama TSH değeri 1.2 (0.5-2.2) µIU/mL idi. Total tiroidektomi materyalinde saptanan lezyonun ortalama boyutu 1.7 (1.0-3.0) cm idi. Grup 3'te beyaz kan hücreleri (WBC), nötrofiller ve lenfositler grup 4'e göre daha düşüktü (p<0.05). NLR, kontrol grubu ile tüm gruplarda benzer bulundu (p=0.173). Kontrol hastalarında MPV istatistiksel olarak daha yüksek oranda bulundu (p=0.000). MPV 2. grupta, 3. grup ve 4. grupa göre anlamlı derecede yüksekti (sırasıyla p=0.001, p=0. 016;). RDW, kontrol grubunda diğer gruplara göre anlamlı derecede düşüktü (p=0.000). Tümör boyutu ile hemogram parametreleri arasında korelasyon yoktu.

Sonuç
Tiroid nodülü nedeniyle takip edilen hastalarda düşük MPV olası malignite açısından şüphe uyandırmalıdır. Artmış RDW, tiroid nodülü gelişimini öngörmede faydalı olabilir. Bu kolay erişilebilir, uygun maliyetli belirteçler, malign nodülleri benign nodüllerden ayırt etmek için diğer tanı yöntemlerini destekleyebilir.

Anahtar Kelimeler: Foliküler adenom, MPV, Papiller tiroid kanseri, RDW, WDT-UMP

Abstract

Objective
Inflammation-related hemogram parameters have recently started to be defined as a useful marker in cancer patients. In this study, we aimed to comparison

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Müracaat tarihi/Application Date: 24.09.2022 • Kabul tarihi/Accepted Date: 27.10.2022
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of hemogram parameters in papillary thyroid cancer (PTC) patients, well differentiated thyroid tumor of uncertain malignant potential (WDT-UMP) and follicular adenoma (FA).

Material and Method
The 287 patients' data were analyzed in study. Study subjects were divided into 5 different groups. 1st group: control, 2nd group: FA, 3rd group: WDT-UMP, 4th group: non-metastatic PTC, 5th group: metastatic PTC. We evaluated the preoperative blood tests.

Results
The average age was 50 (37-59). The mean TSH value was 1.2 (0.5-2.2) µIU/mL. The mean size of the lesion detected in the total thyroidectomy material was 1.7 (1.0-3.0) cm. White blood cells (WBC), neutrophils and lymphocytes were lower in 3rd group than 4th group ($p<0.05$). NLR was found to be similar in all groups with the control group ($p=0.173$). MPV was found to be statistically higher in the control patients ($p=0.000$). MPV was significantly higher in 2nd group compared to 3rd group and 4th group ($p=0.001$, $p=0.016$; respectively). RDW was significantly lower in the control group compared to all other groups ($p=0.000$). There was no correlation between tumor size and hemogram parameters.

Conclusion
In patients followed up for thyroid nodules, low MPV should raise a suspicion in terms of possible malignancy. Increased RDW may be useful in predicting thyroid nodule development. These easily accessible, cost-effective markers may support other diagnostic methods to distinguish malignant from benign nodules.

Keywords: Follicular adenoma, MPV, Papillary thyroid cancer, RDW, WDT-UMP

Introduction

The immune system is the main determinant of the tumor microenvironment, and recent studies investigating cancer patients show that the inflammatory profile of the tumor microenvironment can determine disease prognosis (1). Inflammatory molecules such as macrophage, tumor necrosis factor, leukocyte, interleukin-1, interleukin-6, CCL2 and CXCL8 in tumor microenvironment can affect tumor progression by increasing resistance to apoptosis, promoting tumor cell proliferation, angiogenesis and remodeling, and inhibiting the establishment of antitumor immunity (2). It has been suggested that changes in the ratio of white blood cells, monocytes, neutrophils, and lymphocytes that reflect changes in peripheral blood-based immune response may be associated with systemic inflammatory responses (3). Many studies have demonstrated the relationship between the immune system and cancer prognosis by using hematological parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) (4–6).

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma worldwide. Its incidence has been increasing in recent years all of the world. Ten-year cancer-specific survival is >90% (7). Many studies and meta-analyzes have found a higher incidence of thyroid cancer in thyroiditis presenting with chronic inflammation (8, 9). Numerous studies have investigated the relationship of PTC with hematological inflammatory markers. Although NLR is recommended as a good biomarker in thyroid cancer patients in many large-scale studies, the use of NLR as a prognostic marker is still controversial due to the inconsistency of long-term results (10). Mean platelet volume (MPV) has been recommended as an auxiliary diagnostic tool in differentiating between malignant and benign thyroid nodules in studies conducted on patients with thyroid cancer (11). Preoperative low LMR dramatically predicted a high risk for recurrence in patients (5). PLR was significantly higher in patients with both thyroiditis and papillary cancer compared to the control group (4).

In this study; inflammation-related hemogram parameters such as MPV, red cell distribution width (RDW), NLR, RDW-platelet ratio (RPR), MPV-lymphocyte ratio (MLR) and MPV-platelet ratio (MPR) which are considered as potential biomarkers in tumorigenesis, were collected and their efficacy in differential diagnosis in follicular adenoma (FA), well differentiated thyroid tumor of uncertain malignant potential (WDT-UMP) and PTC were evaluated. Although there are many studies investigating the relationship between PTC and FA with hemogram parameters, as far as we know, this is the first study involving WDT-UMP.

Materıal and Method

The study was conducted in accordance with the Declaration of Helsinki. In this observational

retrospective study, 240 patients who underwent total thyroidectomy at Kocaeli University Medical Faculty Hospital due to multinodular goiter, benign nodules causing a tracheal compression and thyroid cancer between January 2011-January 2021 were included. In addition, 47 random patients without thyroidectomy, autoimmune thyroid disease and thyroid nodules were determined as the control group (Figure 1). In the control group, autoimmune thyroid disease and thyroid nodule were excluded by evaluation with thyroid antibodies and ultrasonography. The results of patients with total thyroidectomy between the ages of 18-85 were included in the study. Patients with malignancy, hematological benign and malignant diseases, inflammatory diseases, systemic autoimmune disease, diabetes mellitus, liver and kidney failure, anemia, steroid or immunosuppressive drug use were excluded to reduce the effect of confounding factors. The data of the patients were obtained retrospectively from the patient archive files and the hospital data processing system. Study subjects were divided into 5 groups. Group 1: control group, group 2: FA group, group 3: WDT-UMP group, group 4: non-metastatic PTC group, group 5: metastatic PTC group. Comparisons of the hemogram parameters associated with inflammation such as MPV, NLR, RPR, MPR, MLR were made between the groups. The NLR was calculated by dividing the neutrophil count by the absolute lymphocyte count. The RPR was calculated by dividing the RDW count by the platelet count. The MPR was calculated by dividing the MPV count by the platelet count. The MLR was calculated by dividing the MPV count by the lymphocyte count. The postoperative pathological diagnoses of the patients were obtained from the result tracking system of pathology department with the approval of the chief physician.

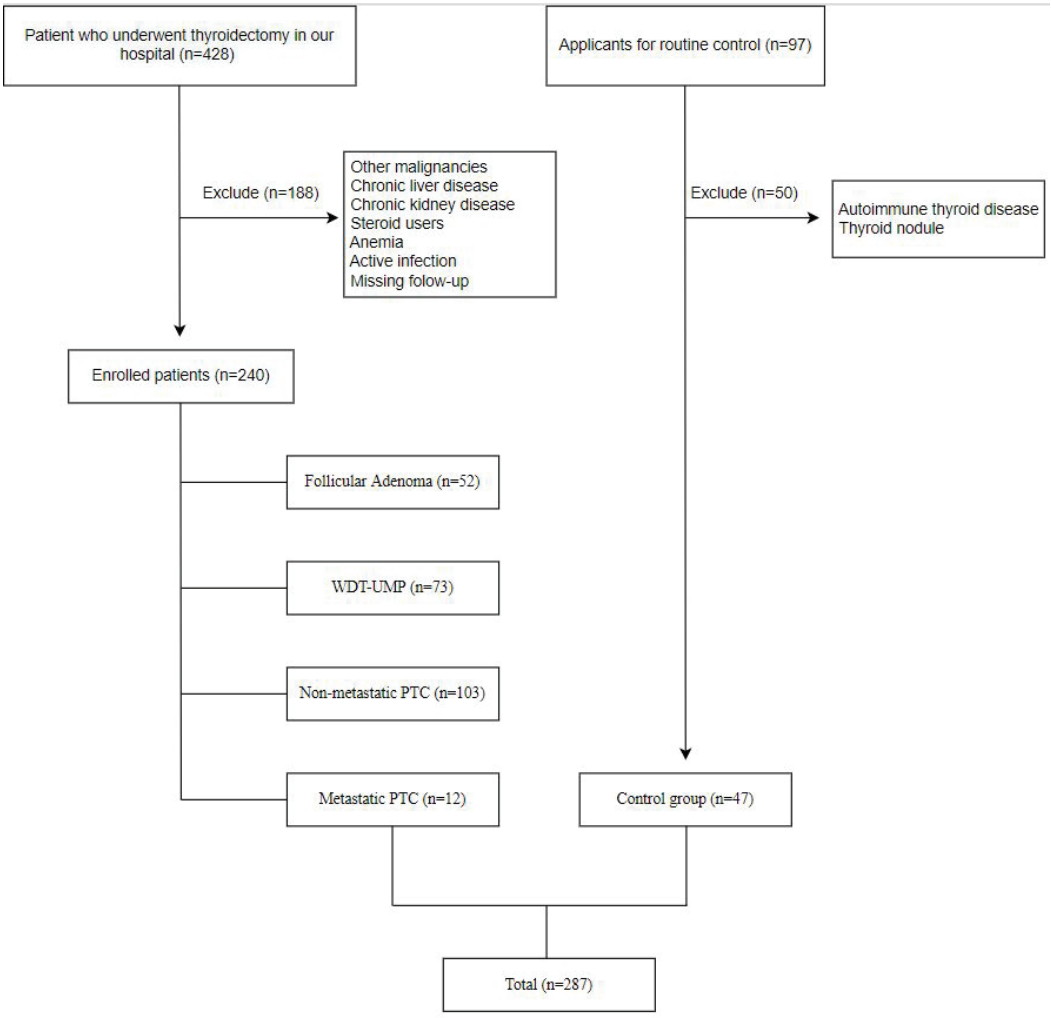

Figure 1
Flowchart on study population.

Statistical Analysis

All statistical analyzes were performed using IBM SPSS version 20.0 (SPSS, Chicago, IL, USA). Normality assumption was evaluated using Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables were given as mean±standard deviation, median (25-75th percentile) and categorical variables as numbers (percentage). Numerical variables between groups were compared using independent samples t-test/ Mann-Whitney U test and Kruskal-Wallis tests.Dunn test was used for the pairwise multiple comparisons. Spearman and Pearson correlation analysis was used for numerical variables. The relationship between categorical variables was evaluated using the Chi-square test. All statistical analyzes were performed with 5% significance. Bilateral p value <0.05 was considered statistically significant.

Results

In this study, we retrospectively evaluated the medical data of 287 patients. While 77.0% (n=221) of the patients included in the study were female, 23.0% (n=66) were male. 66% (n=31) of the control group were female and 34% (n=16) were male. In the other groups, 79.2% (n=190) were female and 20.8% (n=50) were male. The average age of patients was 50 (37-59). The mean age of the control group was 35.23±12.40, and 51.28±13.67 in the other groups.16.4% (n=47) of the study population consisted of patients without thyroid nodules in ultrasonographic examination. Individuals in the control and patient groups were euthyroid and mean TSH value was 1.2 (0.5-2.2) µIU/mL. The mean size of the lesion detected in the total thyroidectomy material was 1.7 (1.0-3.0) cm. The demographic data and hemogram parameters of all groups are given in table 1.

In terms of WBC counts, there was a difference between group 3 with group 4 and group 5 (p=0.042, p=0.014; respectively). Similarly, neutrophil and lymphocyte counts were lower in group 3 group 4 and group 5 (p<0.005). RDW was significantly lower in the control group compared to all other groups (p<0.001). MPV was found to be significantly higher in the control group compared to all other groups (p<0.001). MPV was significantly higher in FA group compared to WDT-UMP and PTC group (p=0.001 and p=0.016; respectively). When hemogram parameters were compared according to gender, RDW and platelet count were found to be higher in women (p<0.001). MPR was found to be higher in man compared to women (p=0.003). Other parameters are similar for both sexes (Table 2).

Correlation analysis results between tumor size and hemogram parameters between groups are given in Table 3.

Table 1 Comparison of demographic data, hemogram parameters and tumor size among the five groups

Parameters	Group 1 (Control)	Group 2 (Follicular Adenoma)	Group 3 (WDT-UMP)	Group 4 (Non-metastatic PTC)	Group 5 (Metastatic PTC)	p
Number	16.4% (47)	18.1% (52)	25.4% (73)	35.9% (103)	4.2% (12)	
Gender (F/M)	31/16	42/10	56/17	83/20	9/3	0.355*
Age (Year)	32(24-44)	52(38.5-63)	54(48-63.5)	49(38-57)	72(57-83)	<0.001
WBC (x10^3/µL)	6.7(5.7-7.5)	6.9(5.4-8.2)	6.4(5.9-7.7)	7.0(5.5-8.8)	8.4(6.1-9.1)	0.018
Hemoglobin (g/dL)	13.8(12.2-15.0)	13.0(12.0-13.8)	13.4(12.2-14.3)	13.0(12.0-14.2)	12.2(11.4-14.2)	0.190
Neutrophil (x10^3/µL)	3.7(3.1-4.5)	4.2(3.1-5.1)	3.6(0.6-4.4)	4.1(3.3-5.8)	4.9(3.9-5.4)	0.002
Lymphocyte (x10^3/µL)	2(1.7-2.5)	2.1(1.8-2.5)	1.9(1.0-2.3)	2.1(1.7-2.6)	2.3(1.4-2.9)	0.031
RDW (%)	13.0(12.0-13.2)	14.0(13.0-14.6)	14.5(13.1-15.7)	13.6(13.0-14.0)	14.1(13.2-15.7)	<0.001
Platelet (x10^3/µL)	272(214-314)	244(210-284)	246(217-303)	254(214-306)	252(236-356)	0.844
MPV (fL)	9.9(9.2-10.8)	8.7(8.0-9.3)	8.0(7.0-8.7)	8.5(8.0-9.0)	7.5(7.0-8.4)	<0.001
NLR	1.7(1.3-2.2)	2.0(1.4-2.4)	1.7(1.3-2.4)	2.0(1.5-2.8)	1.7(1.3-2.9)	0.173
RPR	0.047(0.041-0.058)	0.056(0.047-0.066)	0.059(0.051-0.067)	0.055(0.045-0.064)	0.058(0.045-0.066)	0.029
MPR	0.037(0.031-0.044)	0.035(0.030-0.043)	0.031(0.025-0.038)	0.033(0.026-0.042)	0.028(0.020-0.039)	0.026
MLR	0.004(0.003-0.006)	0.004(0.003-0.004)	0.004(0.003-0.008)	0.0039(0.0031-0.0053)	0.0031(0.0028-0.0051)	0.023
TSH (µIU/mL)	1.3(0.6-2.0)	1.2(0.5-2.0)	1.3(0.5-2.1)	1.2(0.6-2.3)	1.4(0.3-4.0)	0.989
Tumor size (cm)	-	2.4(1.3-3.2)	1.7(1.0-3.0)	1.5(0.9-2.3)	4.5(3.4-5.0)	<0.001

WBC: White Blood Cell, MPV: Mean Platelet Volume, RDW: Red Cell Distribution Width, RPR: RDW-Platelet Ratio, MPR: MPV-Platelet Ratio, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio, TSH: Thyroid Stimulating Hormone
* Chi-square test. Other results include the Kruskal-Wallis test.

Table 2 Comparison of demographic data, hemogram parameters and tumor size for both genders

Parameters	Female	Male	p
Number	77.0% (221)	23.0% (66)	
Age (Year)	48.9±15.0	47.6±13.6	0.525*
WBC (x10^3/µL)	6.7 (5.3-8.3)	7.0 (5.8-8.4)	0.418
Hemoglobin (g/dL)	12.9 (11.7-13.7)	15.0 (14.0-15.3)	<0.001
Neutrophil (x10^3/µL)	4.0 (3.1-5.1)	3.8 (3.0-5.0)	0.520
Lymphocyte (x10^3/µL)	2.1 (1.6-2.5)	2.2 (1.6-2.6)	0.461
RDW (%)	14.0 (13.0-15.0)	13.0 (12.7-14.0)	<0.001
Platelet (x10^3/µL)	260 (220-318)	224 (206-274)	<0.001
MPV (fL)	8.5 (8.0-9.3)	9.0 (7.8-9.4)	0.312
NLR	1.9 (1.4-2.5)	1.8 (1.3-2.2)	0.294
RPR	0.05 (0.04-0.06)	0.05 (0.04-0.06)	0.113
MPR	0.033 (0.025-0.040)	0.038 (0.030-0.044)	0.003
MLR	0.004 (0.003-0.005)	0.004 (0.003-0.005)	0.594
TSH (µIU/mL)	1.3 (0.6-2.3)	1.0 (0.4-1.7)	0.094
Tumor size (cm)	1.7 (1.0-2.8)	2.0 (1.0-4.0)	0.132

WBC: White Blood Cell, MPV: Mean Platelet Volume, RDW: Red Cell Distribution Width, RPR: RDW-Platelet Ratio, MPR: MPV-Platelet Ratio, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio, TSH: Thyroid Stimulating Hormone
*Independent samples t test. Other results include the Mann-Whitney U test.

Table 3 Correlation table of tumor size with hemogram parameters between groups

Parameters	Group 2 (Follicular Adenoma)		Group 3 (WDT-UMP)		Group 4 (Non-metastatic PTC)		Group 5 (Metastatic PTC)	
	r	p	r	p	r	p	r	p
Age (Year)	-,217*	,122	-,087	,462	-,098	,325	,575	,050
WBC (x10^3/µL)	,054*	,705	,025	,831	,019	,847	,081	,802
Neutrophil (x10^3/µL)	,030*	,833	,052	,661	-,027	,783	,230	,473
Lymphocyte (x10^3/µL)	,104*	,462	-,085	,476	-,158	,112	-,312	,324
Hemoglobin (g/dL)	,028*	,843	-,081	,497	-,048	,633	-,595*	,041
Platelet (x10^3/µL)	-,065*	,646	,102	,390	-,117	,239	-,358	,254
MPV (fL)	,072*	,612	,099	,406	,071	,477	-,183	,569
RPR	,003*	,981	-,044	,715	,081	,416	,470	,123
MPR	,053*	,710	-,006	,962	,101	,309	,177	,583
NLR	-,012	,931	,148	,213	,060	,544	,219	,494
RDW (%)	-,142	,315	,017	,886	-,075	,449	-,034	,916
MLR	-,155	,272	,115	,331	,148	,135	,092	,776
TSH (µIU/mL)	-,136	,348	-,088	,457	,209*	,034	,261	,413

WBC: White Blood Cell, MPV: Mean Platelet Volume, RDW: Red Cell Distribution Width, RPR: RDW-Platelet Ratio, MPR: MPV-Platelet Ratio, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio, TSH: Thyroid Stimulating Hormone
*Pearson correlation analysis. Other results include the Sperarman correlation analysis

Discussion

Papillary thyroid cancers' (PTC) incidence is constantly increasing all over the world. However, parameters that can be used as tumor markers in screening are not satisfactory. There is strong evidence that inflammatory cells such as macrophages, neutrophils, lymphocytes interact with the microenvironment and play a role in tumorigenesis (3). In this study, we found a strong association of hemogram-associated systemic inflammatory markers such as MPV and RDW with thyroid cancer.

Common belief is that differentiated thyroid cancers are associated with a low-grade systemic inflammatory response (1). The relationship between NLR and thyroid cancer has been investigated in many previous studies. Although the NLR is inexpensive, practical and easy to access, its use in PTC patients remains controversial. Paliogiannis et al. demonstrated that an increased NLR in thyroid cancer patients compared to benign goiter (12). In a study of differentiated thyroid cancer patients, the NLR was found to be similar to patients with benign thyroid nodules. However, a relation was seen between tumor size and NLR in thyroid cancer patients (13). In a meta-analysis of 6 large cohorts, statistically similar results for NLR were found between differentiated thyroid cancer (DTC) patients and patients with benign nodules (14). In a meta-analysis of nine studies of 3081 patients, NLR was not generally associated with disease-free survival (DFS). However, in the same study, higher NLR was significantly associated with larger tumor size and metastasis status (10). In terms of NLR in our study; FA, WDT-UMP, non-metastatic PTC and metastatic PTC groups were found to be similar compared to controls. Also, there was no correlation between NLR and tumor size. However, WBC, neutrophils and lymphocytes were found to be lower in WDT-UMP compared to non-metastatic PTC and metastatic PTC, although they were similar between NLR groups in post-hoc analysis. A interpretation of our results is that the NLR as an indicator of subclinical chronic inflammation is not a useful parameter in preoperative differentiation of thyroid cancer from WDT-UMP and follicular adenoma.

Stimulated platelets play an important role in the tumorigenesis of cancer. Mean platelet volume (MPV) is an indirect indicator of activated platelets and has been associated with many malignant diseases such as lung, colon and stomach cancer, cardiovascular diseases, and rheumatic diseases (15). In many previous studies, conflicting results were obtained between thyroid cancer and MPV. In a study conducted on patients with malignant thyroid nodules, MPV was found to be statistically higher than those with benign nodules (11). Similar results were obtained in the study conducted by Ozmen et al. on DTC patients (16). In a study of patients with PTC, MPV was found to be similar to multinodular goiter and healthy volunteers (17). On the contrary to these studies, there are several studies in which MPV value was detected to be low in PTC. In patients with thyroid cancer, lower MPV values were found compared to the control group, and MPV was found to be associated with tumor stage and lymph node metastasis (18). Similarly, in a study conducted by Li et al., a significant reduction in MPV was found in patients with thyroid cancer compared to those with benign thyroid lesions (19). In our study, MPV was found to be higher in the control group than those with both benign and malignant thyroid lesions. In subgroup analysis, MPV was found higher in FA group compared to WDT-UMP and PTC group.

Although the mechanism is not clearly understood, dysregulation in bone marrow cells may contribute to altered MPV. In addition, the decrease in MPV may be associated with the increase in consumption of large platelets in inflammatory events (19). In a study conducted on patients with pancreatic cancer, 5-year overall survival (OS) rates and 5-year cancer-specific survival (CSS) rates were found to be higher in patients with low MPV compared to those with high. In this study, MPV was defined as an independent prognostic indicator for both OS and CSS (20). MPV and CSS, locoregional control (LC), recurrence-free survival (RFS) have been found to be closely related in patients with oropharyngeal cancer. In addition, MPV was identified as an independent prognostic factor in multivariate analysis (21). Low MPV was found to correlate with decreased metastasis in patients with gastric cancer, and it was observed that these patients had a better response to chemotherapy (22). Similar results were obtained in studies conducted in bladder and breast cancer (23, 24). Reduction in platelet size and low MPV in cancer patients may potentially reflect degranulated "exhausted" platelets secreting cytokines that stimulate tumor growth. The result obtained from the literature and our study is that lower MPV values may be a marker in the early diagnosis of thyroid cancer.

RDW is a simple and inexpensive parameter that reflects changes in erythrocyte volume and is used in the differential diagnosis of anemias. Recent studies show that RDW is increased in atherosclerotic heart disease, inflammatory bowel disease, rheumatoid arthritis and many malignancies characterized by inflammation (25,26). A meta-analysis conducted by

Hu et al. on various types of cancers revealed that higher RDW values were associated with worse oncologic outcomes and RDW has been proposed as a prognostic marker (27). There are few studies investigating the usability of RDW in thyroid cancer. In a study conducted by Aktas et al., RDW was found to be significantly higher in malignant thyroid nodules compared to benign nodules and control groups (28). Recent studies showed that RDW was significantly higher in DTC and PTC patients than in the control group (16,29). In another study, when the postoperative results of patients who underwent thyroidectomy due to atypia/follicular lesion of undetermined significance were divided as benign and malignant, preoperative RDW was found to be higher in the malignant group than in the benign group (30). In our study, higher RDW was found in all groups compared to the control group. The conclusion to be drawn from our study is that RDW is not a useful tool to predict thyroid cancer. However, these results suggest that RDW can be used as a tool to predict thyroid nodule development. There are several limitations in this study. Our study is a retrospective nature and it had a relatively small sample size. In addition, the effect of hemogram parameters on the survey could not be evaluated.

Conclusion

In this study we found that thyroid cancer patients had lower MPV and higher RDW compared to controls. Our findings suggest that MPV can be used as a possible biomarker in the diagnosis of PTC patients. Low MPV should alert the physician to possible malignancy in patients being followed up for thyroid nodules. In addition, although high RDW does not distinguish between malignant and benign, it may be useful in demonstrating the presence of a thyroid nodule. Moreover, these simple and low-cost parameters can help to support other costly methods such as ultrasonography and fine-needle aspiration biopsy to differentiate malignant lesions.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was conducted in accordance with the Declaration of Helsinki. This study was approved by Kocaeli University Non-Interventional Clinical Research Ethics Committee with project number GOKAEK-2021/2.05 2021/7.

Consent to Participate and Publish
Not applicable

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors Contributions
MS: Conceptualization; Investigation; Validation; Visualization; Writing-original draft.

ZC: Formal analysis; Investigation; Project administration; Supervision; Writing-review & editing.

AS: Investigation; Validation; Writing-original draft.

BÇ: Formal analysis; Investigation; Visualization; Writing-original draft.

BS: Resources; Supervision; Writing-review & editing.

EG: Project administration; Investigation; Project administration;

DK: Conceptualization; Visualization; Investigation

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