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Comparison of Mean Platelet Volume, Platelet Distribution Width, Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio and Lymphocyte/Monocyte Ratio in Patients with Differentiated Thyroid Cancer According to TSH Levels

Differansiye Tiroid Kanserli Hastalarda TSH Düzeylerine Göre Ortalama Platelet Volümü, Platelet Dağılım Genişliği, Nötrofil/ Lenfosit Oranı, Platelet/Lenfosit Oranı ve Lenfosit/Monosit Oranının Karşılaştırılması

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ABSTRACT

Aim: The standard treatment in differentiated thyroid cancer (DTC) is total thyroidectomy followed by lifelong levothyroxine (LT4) replacement. However, what should be the level of exogenous LT4 and Thyroid stimulating hormone (TSH) is still a matter of debate.

Material and Methods: 162 patients with a prospective diagnosis of non-metastatic DTC and 69 healthy volunteers were included. DTC patients were divided into 3 groups according to their TSH level. If TSH is less than 0.1µIU/mL, between 0.11-0.49 µIU/mL, 0.5-2µIU/mL, the groups were named as suppressed thyrotropin, moderately suppressed thyrotropin and low-normal thyrotropin group, respectively.

Results: No statistical difference was observed between mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR) when the DTC group and the healthy control group were compared. When the patients were divided into 3 groups according to their TSH levels, only PDW levels were found to be higher in the moderately suppressed group compared to the other groups ($p < 0.001$). Besides, a positive correlation was found between TSH levels and LMR ($r=0.154$, $p=0.020$), and fT4 levels were negatively correlated with LMR ($r=-0.146$, $p=0.028$). In the linear regression analysis, it was found that 1 unit increase in duration of LT4 use increases MPV by 0.070 units ($p=0.031$), and 1 unit increase in TSH increases LMR 0.517 units ($p=0.041$). An increase of T3 by 1 unit reduces the NLR by 0.282 units ($p=0.032$).

Conclusion: In DTC patients, excessive LT4 dose for target TSH level may increase the risk of inflammatory and cardiovascular disease as well as low dose. Each patient should be treated individually and when making LT4 dose adjustment their age, comorbid diseases, and disease stage should be taken into account. Long-term studies are needed to determine what the target TSH optimum value should be.

Keywords: Mean platelet volüme, Differantieted thyroid cancer, Platelet distrubition width

ÖZ

Amaç: Diferansiye tiroid kanseri (DTK) standart tedavi total tiroidektomi ve sonrasında ömür boyu levotiroksin (LT4) replasmanı yapılmasıdır. Fakat ekzojen LT4 ile TSH düzeyinin ne olması gerektiği halen tartışma konusudur.

Gereç ve Yöntemler: Prospekif non metastatik DTK tanısı olan 162 hasta ile 69 sağlıklı gönüllü alındı. DTK hastaları TSH seviyesine göre 3 gruba ayrıldı. TSH: 0,1µIU/mLden küçük ise suprese tirotropin TSH:0,11-0,49 µIU/mLarasında ise ılımlı suprese tirotropin TSH :0,5- 2µIU/mL arasında düşük -normal tirotropin grubu olarak adlandırıldı.

Bulgular: DTK ve sağlıklı kontrol grubu arasında ortalama trombosit volmü (OTV), trombosit dağılım genişliği (TDG), nötrofil/ lenfosit oranı (NLO), trombosit/ lenfosit oranı (PLO), lenfosit/monosit oranı açısından istatistiksel fark saptanmadı.HastalarTSH düzeyine göre 3 gruba ayrılınca sadece PDW düzeyleri diğer 3 gruba göre ılımlı suprese grupta yüksek saptandı. (p <0,001).Ayrıca TSH düzeyleri ile LMR arasında pozitif yönlü (r=0,154 p=0,020), sT4 düzeyleri LMR ile negatif yönde düşük korelasyon saptanmıştır. (r=-0,146 p=0,028) Lineer regresyon analizinde LT4 kullanma süresinin 1 birim artması MPW'ı ortalama 0,070 birim (p=0,031), TSH'ın 1 birim artması LMR'yi ortalama 0,517 birim arttırmaktadır (p=0,041). T3'ün 1 birim artması NLR'ı ortalama 0,282 birim azaltmaktadır (p=0,032).

Sonuç: DTK hastalarında hedef TSH düzeyi için verilen LT4 dozunun fazla olması kadar, az olması da inflamatuar, kardiovasküler hastalık riski artırmaktadır. Her hasta bireysel ele alınıp, yaş, ek hastalıkları, hastalık evresi gibi durumları göz önüne alınarak LT4 doz ayarlaması yapılmalıdır. Hedef TSH optimum değerinin ne olması gerektiği için uzun süreli çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Differansiye tiroid kanser, Ortalama platelet volümü, Ortalama platelet dağılımı

INTRODUCTION

Thyroid cancer is responsible for 1% of all malignancies. Differentiated thyroid cancer (DTC) is composed of papillary and follicular thyroid cancer. It generally has a good prognosis. Standard treatment is total thyroidectomy and/or cervical lymph node dissection and/or radioactive iodine ablation (RAI) (1). The next treatment is the lifelong replacement of levothyroxine (LT4) and suppression of TSH (Thyroid Stimulating Hormone). The purpose of TSH suppression is to prevent disease recurrence. Because TSH is a trophic hormone, its high level stimulates the growth of thyroid follicular cells. But it is not right to apply this suppression in the same way in every patient. Patients should be classified as low-medium and high-risk, and the dose of the drug should be titrated to suppress TSH levels according to the risk group. Long-term, excessive suppression of TSH in the non-high-risk patient group, even in the high-risk group in some cases, is not recommended in recent years. Because this condition has a negative effect on many systems, especially the cardiac system and skeletal system (2).

Mean platelet volume (MPV), platelet distribution width (PDW) provide information about the morphology of the peripheral platelet population as well as the platelet function. These two parameters are the indicatives of immature platelets that are newly released from the bone marrow. In other words, increased MPV and PDW indicate large platelets. Large platelets are more metabolically active than old-mature platelets. They produce a higher amount of prothrombotic factors such as thromboxane A2 (3). Therefore, MPV and PDW correlate with metabolic, cardiovascular, inflammatory conditions, and even cancer prognosis (4).

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) are the indicators of the systemic inflammatory response (5). The number of studies investigating these indicators in thyroid diseases is few and the studies are contradictory (6,7). It has been suggested that it can be used as a marker to show the response of the tumor to treatment, the risk of metastasis, and poor prognosis in many solid tumors. Apart from malignancies, it provides information on the severity of inflammation in diabetes, cardiovascular disease and autoimmune diseases (8-10).

Our hypothesis is that MPV, PDW, NLR, PLR, and LMR are high in DTC patients and this level is correlated with the degree of suppression of TSH. No study has been conducted regarding the association of these factors with the degree of TSH suppression in DTC. In this study, we aimed to determine whether there was a difference in MPV, PDW, NLR, PLR, and LMR between the patients with non-metastatic DTC in remission (with TSH levels between <0.01 and 2 μIU/mL under LT4 treatment) and healthy controls, and whether these parameters were related with the degree of TSH suppression or not.

MATERIAL and METHODS

Study Design

This prospective study was approved by the Ethics Committee of Recep Tayyip Erdoğan University Training and Research Hospital with an Approval Number of 2021/07 (Approval Date: 07.01.2021). Written informed consent was obtained from the all participants. All practices in this study were made in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later revisions or comparable ethical standards.

In this cross-sectional study, patients aged 18-70 years who were consequtively applied to, and diagnosed with DTC in the Endocrinology Clinics of Recep Tayyip Erdoğan Uni-

versity Training and Research Hospital between January 2021 and June 2021, and healthy individuals who applied to the clinics for any other reason and who did not have any disease were included in the study. Inclusion criteria of the patients were: 1) History of Total Thyroidectomy and/or RAI 2) Having papillary or follicular cancer pathology 3) At least 6 months of LT4 suppression. In addition, 1) Pregnant patients and patients who were breastfeeding 2) Patients with TSH >2 μIU/mL 3) Patients who were diagnosed with uncontrolled diabetes mellitus (patients who had been taking insulin, did have HbA1c of >7, or had microvascular and macrovascular complications) 4) Patients with a history of co-existent malignancy 5) Patients with autoimmune disease, coronary artery disease, history of cerebrovascular disease, liver and kidney failure 7) Patients who had been taking anti-platelet drugs 8) Patients with hematological diseases 9) Patients with platelet count of <150000/mm^3 or >450000/mm^3, leukocyte count of <3000/mm^3 or >4500/mm^3, hemoglobin level of <13 g/dL and <14 g/dL for female and male, respectively, were not included in the study.

Data Collection

Sociodemographic characteristics of the patients such as age, sex, educational background, smoking status, date of diagnosis, clinical features such as RAI, comorbidities, the LT4 dose and duration of LT4 use were recorded.

Patients with DTC were defined as Group A, and healthy controls as Group B. The patients in Group A were divided into 3 groups according to their TSH levels and in accordance with the recommendations of the ATA guideline. (11) If TSH is less than 0.1 μIU/mL, it will be classified as suppressed thyrotropin group (Group A1). If TSH is between 0.11-0.49 μIU/mL, it will be classified as a moderately suppressed thyrotropin group (Group A2). If TSH is between 0.5 and 2 μIU/mL it will be classified as low-normal thyrotropin group (Group A3). Normal reference ranges for TSH in our hospital laboratory are between 0.35 and 4.94 μIU/mL.

Complete blood count was determined using the Sysmex XN-1000 (Kobe, Japan) analyzer. The samples were taken after 8 hours of fasting and between 8:30 and 9:30 in the morning. The same standard blood tubes were used for sampling and analyzed within 1 hour at the latest. NLR was calculated by dividing the neutrophil count by the absolute lymphocyte count, PLR was calculated by dividing the platelet count by the lymphocyte count, and LMR was calculated by dividing the lymphocyte count by the monocyte count. MPV and PDW are provided automatically.

Statistical Analysis

The data obtained from the research were analyzed in a computer environment with the SPSS (Statistical Package for Social Sciences) 18.0 packaged software. In descriptive analyses, frequency data were presented as numbers (n) and percent (%), and numerical data were shown using mean±standard deviation, median (minimum-maximum). Chi-square (X^2) test and Fisher's exact Chi-square test were used when comparing categorical data. The Kolmogorov-Smirnov and Shapiro Wilk tests were used to test the suitability of the numerical data for the normal distribution. The Independent Samples T-test was used for the analysis of normally distributed numerical data in two independent groups, and the Mann Whitney U test was used for the analysis of data that were not normally distributed in two independent groups. The Kruskal Wallis test was used to compare the numerical data that was abnormally distributed in more than two independent groups. Mann Whitney U test was used in the post hoc analysis of the comparisons whose Kruskal Wallis test was found to be significant and Dunn Bonferoni correction was made. The correlation between normally distributed numerical variables, and the relationship between two non-normally distributed numerical variables were analyzed with Pearson correlation analysis and Spearman Correlation analysis, respectively. Multivariate linear regression analysis was used to determine the effects of independent variables on hematological parameters. The results were evaluated at the 95% confidence interval and the significance level was p<0.05.

RESULTS

A total of 231 people, 162 patients with DTC and 69 healthy controls, were included in the study. Age, sex, height, weight, waist circumference, BMI, alcohol and cigarette consumption were similar in Group A and B (p>0.05). There was no statistical difference in MPV, PDW, NLR, PLR and LMR between Group A and B (p>0.05). Among the hemogram parameters, white blood cell (WBC), neutrophil and monocyte counts were higher in Group A compared to B (p=0.006, p=0,009, p=0.024, respectively). Although calcium and phosphorus values were similar in both groups (p>0.05), PTH levels were lower in group A (p=0.022) (Table 1).

There was no statistical difference in MPV, NLR, PLR and LMR values among Group A1, A2, A3, and B. Only PDW levels were higher in group A2 comparing to Group A1, A3, and B (p<0.001). In addition, the duration of LT4 use was higher in Group A3 comparing to Group A1 (p= 0.001) (Table 2).

A low positive correlation was found between TSH levels and LMR (r= 0.154, p= 0.020). There was a positive correlation between fT4 levels and PDW or NLR, and a low negative correlation between fT4 and LMR (r=0.184, p=0.005; r=0.150, p=0.024; r=-0.146, p=0.028; respectively) (Table 3).

An increase of 1 unit in duration of LT4 use increases MPV by an average of 0,070 units (p=0,031). An increase of T3 by 1 unit reduces the NLR by an average of 0.282 units (p=0.032). An increase in TSH by 1 unit increases the LMR by an average of 0.517 units (p=0.041) (Table 4).

Table 1: Sociodemographic, Clinical, Hormonal and Biochemical Characteristics of Patients with Differentiated Thyroid Cancer and the Healthy Controls.

Parameters	Group A DTC (n=162)	Group B Control (n=69)	p-value
Age (years), mean±SD	51.29 ± 10.34	50.00 ± 9.31	0.373*
Sex, n(%) (Female/Male)	131/31 (80.90/19.10)	62/7 (89.90/10.10)	0.092**
Height (cm), median(min.-max.)	159.50 (143.00-186.00)	158.00 (143.00-189.00)	0.181***
Weight (kg), median(min.-max.)	81.00 (51.00-107.00)	77.00 (53.00-105.00)	0.057***
Waist Circumference (cm), mean±SD	103.53 ± 12.20	100.23 ± 13.90	0.072*
BMI (kg/m^2), median(min.-max.)	32.26 (20.57-42.32)	30.81 (18.69-42.60)	0.185***
Alcohol Consumption, n(%)			
Present	4 (2.50)	0 (0.00)	0.320****
Absent	158 (97.50)	69 (100.00)	
Cigarette Consumption, n(%)			
Still Smoking	25 (15.40)	3 (4.30)	
Quit Smoking	28 (17.30)	14 (20.30)	0.061**
Never Smoked	109 (67.30)	52 (75.40)	
Hypoparathyroidism, n(%)			
Present	9 (5.60)	0 (0.00)	0.061****
Absent	153 (94.40)	69 (100.00)	
DM, n(%)			
Present	16 (9.90)	0 (0.00)	**0.004****
Absent	146 (90.10)	69 (100.00)	
HT, n(%)			
Present	51 (31.50)	15 (21.70)	
Absent	111 (68.50)	54 (78.30)	0.134**
Calcium (mg/dL), median(min.-max.)	9.60 (8.00-10.70)	9.70 (8.50-10.50)	0.273***
Phosphorus (mg/dL), median(min.-max.)	3.70 (2.13-5.71)	3.56 (2.26-4.86)	0.089***
Free T3 (pq/ mL), mean±SD.	2.86 ± 0.47	2.71 ± 0.35	**0.010***
Free T4(ng/dL), median(min.-max.)	1.14 (0.47-1.71)	0.97 (0.72-1.90)	**<0.001*****
TSH (μIU/mL), median(min.-max.)	0.36 (0.01-2.00)	1.53 (0.27-2.89)	**<0.001*****
PTH(pq/ mL), median(min.-max.)	55.35 (2.94-156.30)	65.70 (24.50-132.90)	**0.022*****
Anti -Tg (IU/mL), median(min.-max.)	3.00 (2.85-14.76)	-	-
Tg(ng/mL), median(min.-max.)	0.14 (0.10-1.31)	-	-
Duration of LT4 use (years), median(min.-max.)	6.00 (1.00-12.00)	-	-
LT4 dose (mcg/day), median(min.-max.)	125.00 (75.00-250.00)	-	-
RAI Treatment, n(%)			
Present	107 (66.00)	-	-
Absent	55 (34.00)	-	
Hemoglobin (g/dL), median(min.-max.)	13.50 (12.00-16.90)	13.40 (12.00-16.30)	0.117***
Platelet count, median(min.-max.)	262,000(142,000-445,000)	272,000 (138,000-450,000)	0.520***
WBC (/mm^3) ,median(min.-max.)	6898.58 ± 1497.34	6299.84 ± 1374.27	**0.006***
Lymphocyte (/mm^3), median(min.-max.)	2373.95 ± 632.91	2301.69 ± 677.04	0.447*
Neutrophil (/mm^3), median(min.-max.)	3735.00 (1830.00-7090.00)	3440.00 (1670.00-6430.00)	**0.009*****
Monocyte (/mm^3), median(min.-max.)	430.00 (200.00-840.00)	370.00 (250.00-690.00)	**0.024*****
MPV (fL), median(min.-max.)	10.00 (8.30-19.40)	10.20 (8.30-12.40)	0.682***
PDW, median(min.-max.)	16.10 (15.40-16.80)	16.00 (15.50-17.10)	0.418***
NLR, median(min.-max.)	1.61 (0.66-6.58)	1.52 (0.54-3.73)	0.183***
PLR, median(min.-max.)	115.86 (51.46-279.87)	119.80 (62.84-270.21)	0.277***
LMR, median(min.-max.)	5.50 (2.30-11.54)	5.66 (3.02-11.81)	0.341***

:** Independent Sample's T-Test, *:** Pearson Chi-square Test, *****:** Mann Whitney U Test, ******:** Fisher's Chi-square Test

BMI: Body mass index, **sT3:** free triiodothyronine, **sT4:** free thyroxine, **TSH:** Thyroid Stimulating Hormone, **PTH:** Parathoyroid hormone, **LT4:** levothyroxine, **RAI:** Radioactive iodine, **Tg:** Thyroglobulin, **Anti-Tg:** Anti-Thyroglobulin, **HT:** Hypertension, **DM:** Diabetes Mellitus, **WBC:** White Blood Cell, **MPV:** Mean Platelet Volume, **PDW:** Platelet Distribution Width, **NLR:** Neutrophil/Lymphocyte Ratio, **PLR:** Platelet/Lymphocyte Ratio, **LMR:** Lymphocyte/Monocyte Ratio.

Table 2: Comparison of Hormonal and Biochemical Data of Patients with Differentiated Thyroid Cancer According to Their TSH Levels With the Control Group.

Parameters	Group A1 Supresse (TSH<0,1 μIU/mL) (n=48)	Group A2 Moderately Suppressed (TSH 0.11-0.49 μIU/mL) (n=43)	Group A3 Low-Normal (TSH 0.5-2 μIU/mL) (n=71)	Group B Healthy Controls (n=69)	p-value	Post-hoc analysis
	mean±SD. Median (min-max.)					
TSH (μIU/mL)	0.03±0.02 0.02 (0.01-0.10)	0.26±0.11 0.26 (0.11-0.48)	1.08±0.47 1.01 (0.50-2.00)	1.51±0.74 1.53 (0.27-2.89)	**<0.001***	A1-A2, A1-A3, A1-B, A2-A3, A2-B, A3-B
Free T4 (ng/dL)	1.24±0.20 1.20 (0.85-1.67)	1.19±0.17 1.17 (0.95-1.71)	1.10±0.15 1.10 (0.47-1.53)	0.97±0.16 0.97 (0.72-1.90)	**<0.001***	A1-A3, A1-B, A2-A3, A2-B, A3-B
Free T3 (pq/ mL)	3.12±0.50 3.15 (1.04-4.00)	2.81±0.41 2.80 (1.33-3.68)	2.72±0.40 2.65 (1.70-3.57)	2.71±0.35 2.71 (1.87-3.57)	**<0.001***	A1-A2, A1-A3, A1-B
LT4 use time (years)	4.47±2.90 4.50 (1.00-12.00)	5.06±2.77 5.00 (1.00-10.00)	6.39±2.77 7.00 (1.00-11.00)	-	**0.001***	A1-A3
LT4 dose (mcg/day)	137.60±29.39 135.00 (100.00-225.00)	136.27±33.45 125.00 (100.00-250.00)	127.88±30.05 125.00 (75.00-200.00)	-	0.163*	
Hemoglobin (g/dL)	13.58±1.10 13.30 (12.00-16.70)	13.99±1.18 14.00 (12.10-16.90)	13.56±0.93 13.40 (12.00-16.20)	13.45±1.07 13.40 (12.00-16.30)	0.070*	
Platelet (/mm^3)	272,687± 546,365 262,500 (184,000-419,000)	263,069 ±628,779 262,000 (142,000-445,000)	271,211±612,453 261,000 (170,000-440,000)	274,246±626,435 272,000 (138,000-450,000)	0.830*	
WBC (/mm^3)	6938±1557 6530 (4460 -1031)	6858.37±1318 6840 (4030-10340)	6896±1575 6610 (4430 -1220)	6299±137 6190 (9400-3830)	0.084*	
Lymphocyte (/mm^3)	2378 ±658 2255 (1050-3750)	2402±572 2450.00 (1400.00-3420.00)	2353±657 2210 (1060-4580)	2301± 677 2280 (940-3830)	0.754*	
Neutrophil (/mm^3)	3860±1122 3730 (2090-6910)	3758±1100 3590 (2110-6330)	3907±1214 3780 (1830-7090)	3381±931 3440 (1670-6430)	0.061*	
Monocyte (/mm^3)	457±137 465 (220-840)	445±103 430 (240-680)	422±113 430 (200-830)	400±97 370 (250-690)	0.054*	
MPV (fL)	10.01±0.90 9.90 (8.40-12.00)	10.40±0.88 10.30 (9.10-13.20)	10.08±1.42 9.90 (8.30-19.40)	10.14±1.04 10.20 (8.30-12.40)	0.125	
PDW	15.98±0.27 16.00 (15.50-16.80)	16.23±0.27 16.20 (15.80-16.80)	16.02±0.27 16.10 (15.40-16.80)	16.05±0.33 16.00 (15.50-17.10)	**<0.001***	A1-A2, A2-A3, A2-B
NLR	1.74±0.89 1.59 (0.78-6.58)	1.66±0.65 1.46 (0.86-3.31)	1.76±0.68 1.64 (0.66-4.84)	1.57±0.57 1.52 (0.54-3.73)	0.376*	
PLR	122.47±38.22 120.46 (57.58-250.48)	116.88±46.13 108.78 (51.46-279.87)	122.33±39.61 117.32 (52.26-265.12)	127.30±41.70 119.80 (62.84-270.21)	0.335*	
LMR	5.44 ±1.50 5.36 (3.15-8.77)	5.65 ±1.86 5.27 (3.15-11.54)	5.84 ±1.82 5.56 (2.30-10.90)	5.93±1.85 5.66 (3.02-11.81)	0.489*	

***:** Kruskal Wallis Test

f**T3:**free triiodothyronine **fT4:**free thyroxine **TSH:**Thyroid Stimulating Hormone **LT4:**levothyroxine **WBC:**White Blood Cell **MPV:**Mean Platelet Volume **PDW:**Platelet Distribution Width **NLR:** Neutrophil/Lymphocyte Rate **PLR:**Platelet/Lymphocyte ratio **LMR:**Lymphocyte/Monocyte ratio

Table 3: Correlation of MPW, PDW, NLR, PLR, LMR with Hormonal and Biochemical Data.

	MPV		PDW		NLR		PLR		LMR	
	r value	p value	r value	p value	r value	p value	r value	p value	r value	p value
TSH (μIU/mL)	-0.039	0.557*	-0.082	0.220*	-0.059	0.376*	0.026	0.702*	**0.154**	**0.020***
Free T4(ng/dL)	0.103	0.123*	**0.184**	**0.005***	**0.150**	**0.024***	-0.016	0.816*	**-0.146**	**0.028***
Free T3 (pq/ mL)	0.025	0.709*	0.010	0.882*	-0.081	0.223*	-0.095	0.154*	-0.046	0.493**
Duration of LT4 use (years)	0.089	0.260*	0.064	0.416*	0.035	0.656*	-0.021	0.789*	0.069	0.385*
LT4 dose (mcg/day)	0.046	0.564*	0.097	0.221*	-0.012	0.877*	-0.080	0.313*	-0.071	0.367*
Hemoglobin (g/dL)	0.098	0.140*	**0.305**	**<0.001***	0.116	0.081*	-0.121	0.069*	-0.126	0.058*
WBC (/mm³)	-0.009	0.889*	-0.050	0.454*	**0.229**	**<0.001***	**-0.251**	**<0.001***	-0.001	0.984*
Lymphocyte (/mm³)	-0.044	0.510*	-0.103	0.123*	**-0.573**	**<0.001***	**-0.695**	**<0.001***	**0.549**	**<0.001****
Neutrophil (/mm³)	0.021	0.752*	-0.043	0.520*	**0.647**	**<0.001***	0.091	0.174*	**-0.274**	**<0.001***
Monocyte (/mm³)	0.063	0.344*	0.029	0.665*	**0.141**	**0.034***	**-0.215**	**0.001***	**-0.509**	**<0.001***
MPV (fL)	-	-	**0.481**	**<0.001***	0.082	0.219*	**-0.213**	**0.001***	-0.101	0.129*
PDW	**0.481**	**<0.001***	-	-	0.066	0.321*	**-0.227**	**0.001***	-0.116	0.081*
NLR	0.082	0.219*	0.066	0.321*	-	-	**0.587**	**<0.001***	**-0.656**	**<0.001***
PLR	**-0.213**	**0.001***	**-0.227**	**0.001***	**0.587**	**<0.001***	-	-	**-0.449**	**<0.001***
LMR	-0.101	0.129*	-0.116	0.081*	**-0.656**	**<0.001***	**-0.449**	**<0.001***	-	-

*: Spearman Correlation Test **: Pearson Correlation Test

sT3: free triiodothyronine, **sT4:** free thyroxine, **TSH:** Thyroid Stimulating Hormone, **LT4:** Levothyroxine, **WBC:** White Blood Cell, **MPV:** Mean Platelet Volume, **PDW:** Platelet Distribution Width, **NLR:** Neutrophil/Lymphocyte Ratio, **PLR:** Platelet/Lymphocyte Ratio, **LMR:** Lymphocyte/Monocyte Ratio

Table 4: Differences between MPV, NLR, and NLR and Independent Parameters in Patients with Differentiated Thyroid Cancer.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
MPV	Duration of LT4 use (years)	0.070	0.032	0.176	2.174	**0.031**	0.00	0.133
	TSH	-0.288	0.166	-0.143	-1.734	0.085	-0.617	0.040
	T3	0.013	0.203	0.005	0.062	0.950	-0.389	0.414
NLR	Duration of LT4 use (years)	-0.013	0.021	-0.051	-0.627	0.531	-0.054	0.028
	TSH	-0.076	0.107	-0.058	-0.707	0.481	-0.287	0.136
	T3	-0.282	0.131	-0.179	-2.159	**0.032**	-0.540	-0.024
LMR	Duration of LT4 use (years)	0.019	0.048	0.032	0.391	0.696	-0.077	0.115
	TSH	0.517	0.251	0.170	2.061	**0.041**	0.022	1.012
	T3	0.081	0.306	0.022	0.265	0.792	-0.524	0.686

*: Linear Regression Analysis

sT3: free triiodothyronine, **TSH:** Thyroid Stimulating Hormone, **LT4:** levothyroxine, **MPV:** Mean Platelet Volume, **NLR:** Neutrophil/Lymphocyte Ratio, **LMR:** Lymphocyte/Monocyte Ratio

DISCUSSION

This is the first case-controlled study to compare the MPV, PDW, NLR, PLR and LMR levels between non-metastatic DTC patients in remission and healthy controls. MPV, NLR, PLR, LMR were similar in Group A and B, or Group A1, A2, A3 and B. WBC, neutrophil and monocyte counts were higher in the Group A than in B. PDW levels were higher in group A2 comparing group A1, A3, or B. The duration of LT4 use was higher in group A3 compared to A1. LMR was positively correlated with TSH but negatively with fT4. fT4 was positively correlated with PDW or NLR. Duration of LT4 use was a predictor for MPV, TSH for LMR. fT3 was a negative predictor for NLR. In the literature, the results of studies on

hematological parameters in patients with DTC have been contradictory. Recently, the relationship between cancer and chronic inflammation has been the focus of attention for studies (12). MPV, PDW, NLR, PLR and LMR, which are regarded as indicators of inflammation and obtained simply by blood count, are widely used to predict the prognosis of some types of solid cancer (nasopharynx, gastric...) (13, 14). There are studies that found that these markers can predict tumor-node-metastasis (TNM) staging, response to treatment, recurrence and poor prognosis in DTC (15-19). There are also studies that did not detect this relationship (20, 21) or could not comment (22). In some studies, it has been suggested that the positive correlation with inflammatory hematological parameters might be applied to the elderly population (>55 years) (16,17). In our study, we think that there was no difference in MPV, PDW, NLR, PLR and LMR levels in terms of showing inflammation, since all patients were non-metastatic, in remission, and the age distribution of our patients was partially younger (< 55 years). The age factor, which is also used in the TNM staging of DTC, is also very important in determining the prognosis. We think that different results can be found in studies conducted with older patients with undiagnosed and untreated or active thyroid cancer.

Thyroid hormones are very important in ensuring growth, development, energy balance and physiology. The coagulation-fibrinolytic system is very sensitive to thyroid function tests, and the effect of these tests on hematological parameters has been the focus of studies (23). In a study comparing the MPV levels of patients between hyperthyroid period and then euthyroid status maintained with treatment, a 16% decrease was found in MPV values.(24) Similarly, in another study, decreased platelet count was found in addition to increased MPV in hyperthyroidism (25). These are studies conducted in patients with hyperthyroidism. As is known in hypothyroidism, the atherosclerotic process is accelerated. Moreover, subclinical hypothyroidism (normal fT3 and fT4, and high TSH) has been reported to be an independent risk factor for cardiovascular events. (26) MPV values were found to be higher in patients with subclinical hypothyroidism than in euthyroid patients (27). The physiology of this situation has been explained as an increase in hypercoagulability by increasing prothrombic factors and decreasing anti-thrombotic factors. In other words, an increase was detected in inflammatory hematological parameters (especially in MPV) in both hyperthyroidism and hypothyroidism. In this case, the question of whether the increase and decrease of TSH (high-normal / low-normal) when TSH is within the normal reference ranges affect these parameters comes to mind. Because in recent studies, it has been suggested that high-normal TSH values also accelerate the atherosclerotic process, even when they are within the normal reference ranges. There are two important studies related to this. The first of these was in Italy (TSH: 0.4-2.5 IU/mL in the normal reference range) euthyroid patients were divided into 4 groups according to their TSH levels, and their MPV values were compared, and the highest MPV values were observed in patients with TSH values in the highest range (28). In the other study, euthyroid cases in Korea were grouped retrospectively according to TSH level, and similarly, they found an increase in MPV values as TSH increased (29). In this study, when we divided the patients into 3 groups according to their TSH levels, no difference was found between MPV, NLR, PLR and LMR levels between groups and compared to healthy controls. However, the weak positive correlation between TSH levels and LMR in correlation analysis, and findings of liner regression (TSH as positive predictor for LMR, fT3 as negative predictor for NLR) suggests that even if TSH is within the normal range, the inflammation, and hence the risk of cardiovascular disease, will increase as the TSH approaches the upper limit. We found that there was no difference in MPV, NLR, PLR and LMR level according to TSH subgroups. Only PDW was higher in the moderately suppressed TSH group compared to the other groups. Considering the previous inflammatory hematological parameters, PDW is the least studied and the least known. In 2 studies analyzing PDW values in DTC, it was shown as lower in patients with DTC compared to the controls (20,21) PDW shows the irregularity of the size of the platelets. In other words, it is indicative of larger immature, enzymatically more active platelets which may be a precursor of atherosclerosis by predisposing to aggregation and adhesion. In this context, our findings suggest the hypothesis. The possible clinical significance of finding of the lower PDW in suppressed TSH group than moderately suppressed TSH group should be evaluated in further studies.

On the contrary of our hypothesis, TSH and LMR were positively correlated; fT3 and NLR were negatively correlated with fT4 and LMR. Our findings suggest that both ends of the TSH spectrum may increase the risk of inflammatory status. In a retrospective study analyzing 58 cases with DTC, those were grouped as euthyroid, overt hypothyroid (before RAI), and subclinical hyperthyroid periods (22). They found that MPV was higher in subclinical hyperthyroid group comparing to others. The previous studies suggest that the damage caused by unnecessarily long TSH suppression to the sleep and nervous systems, especially to the cardiac and skeletal systems have been the subject of discussion in recent years. Long-term, excessive suppression of TSH is no longer recommended in the non-high-risk patient group, even in the high-risk group in some cases. Individual treatment decisions should be made by considering the target TSH value, age, disease stage and additional comorbidities of each patient. As a result, it is still unclear what the optimal level of TSH should be to ensure the patient's quality of life,

to maintain well-being and minimize cardiovascular risk and other side effects in patients receiving LT4 therapy, especially in DTC patients.

Similar to our study, there are studies on thyroid cancer and hematological parameters. However, while these studies mostly examine the relationship between cancer stage, recurrence risk, prognosis and hematological parameters, there are few studies on thyroid functions (16). Based on the previous reports, we may propose that thyroid hormone disorders cause an increase in cardiovascular risk with increasing MPV, LNR and LMR, in hypothyroidism and hyperthyroidism, and even in subclinical hypo- or hyperthyroidism. These findings support that inflammatory hematological parameters can be used as a valuable and practical method in thyroid diseases. In addition, these parameters are achievable, inexpensive, repeatable and are obtained by a simple blood count.

Strength and Limitations

Given the reporting a single center experience, we included a valuable number of patients with DTC. To our knowledge, our study is the first to analyze inflammatory hematological parameters in DTC according to TSH levels. The limitation of this study is that it is cross-sectional. More precise results can be obtained with the results of long-term follow-up of the patients and multicenter studies.

In conclusion, although it seems that MPV, PDW, NLR, PLR and LMR can be used to predict the prognosis of the disease in DTC patients, it is difficult to obtain a certain conclusion with the current information. However, it is certain that these inflammatory hematological parameters are easily accessible, cost-effective and reproducible. To understand the role of these parameters in the DTC, more long-term, prospective and multicentered studies are needed.

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Author Contributions

Concept: **Seher Çetinkaya Altuntaş,** Design: **Seher Çetinkaya Altuntaş,** Data collection: **Seher Çetinkaya Altuntaş,** Analysis: **Seher Çetinkaya Altuntaş ,Ömercan Topaloğlu,** Interpretation: **Seher Çetinkaya Altuntaş, Ömercan Topaloğlu,** Writing: **Seher Çetinkaya Altuntaş ,Ömercan Topaloğlu.**

Conflicts of Interest

The authors declare that they have no competing interest.

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Ethical Approval

This prospective study was approved by the Ethics Committee of Recep Tayyip Erdoğan University Training and Research Hospital with an Approval Number of 2021/07 (Approval Date: 07.01.2021).

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