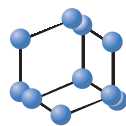


RESEARCH ARTICLE

BENTHAM
SCIENCE

Comparison of Mean Platelet Volume, Platelet Count, Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in the Euthyroid, Overt Hypothyroid and Subclinical Hyperthyroid Phases of Papillary Thyroid Carcinoma

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Abstract: Introduction: Thyroid hormones are essential for the normal development, differentiation, metabolic balance and physiological function of all tissues. Mean platelet volume (MPV) indicates mean platelet size and reflects platelet production rate and stimulation. Increased platelet size has been observed in association with known cardiovascular risk factors. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are known markers of the systemic inflammatory response. This study aimed to investigate the effect of thyroid hormone changes by comparing platelet count, MPV values, NLR and PLR in thyroid papillary carcinoma.

Methods: Forty-nine females and nine males comprising a total of 58 patients were included in the study. Clinical and laboratory parameters of patients were recorded in the following three phases of the disease: euthyroid phase (before thyroid surgery), overt hypothyroid (OH) phase (before radioactive iodine [RAI] treatment) and subclinical hyperthyroid (SCH) phase (six months after RAI treatment).

Results: The mean thyroid-stimulating hormone (TSH) values of the patients in the euthyroid, OH and SCH phases were 1.62 ± 1.17 , 76.4 ± 37.5 and 0.09 ± 0.07 $\mu\text{IU/mL}$, respectively. The mean MPV values of the patients in the euthyroid, OH and SCH phases were 9.45 ± 1.33 , 9.81 ± 1.35 and 9.96 ± 1.21 fL, respectively. MPV was significantly higher in the SCH phase than in the euthyroid phase ($p=0.013$). Platelet count, NLR and PLR were not statistically different between the euthyroid, OH and SCH phases.

Conclusion: The results of this study demonstrated that the levels of MPV increased significantly in the SCH phase in patients with papillary thyroid carcinoma (PTC), and increased MPV values contributed to increased risk of cardiovascular complications. These findings suggest that MPV can be a valuable, practical parameter for monitoring the haemostatic condition in thyroid disorders. No significant difference was observed in platelet count, NLR and PLR in all stages of PTC.

Keywords: Hypothyroidism, hyperthyroidism, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet count.

1. INTRODUCTION

Thyroid hormones are essential for the normal development, differentiation, metabolic balance and physiological function of all tissues. All cells are targets of thyroid hormones. Thyroid hormones regulate human haematopoiesis in the bone marrow [1-3]. Alterations in haematological parameters, such as haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin and

white blood cell count, are associated with thyroid dysfunction [4, 5]. Previous reports have suggested that hyperthyroidism and hypothyroidism are associated with increased risks for leucocytopenia, neutropenia and thrombocytopenia [1, 3, 5-11]. When the euthyroid condition is achieved, it has been reported that all haematological parameters return to normal [2, 12].

Mean platelet volume (MPV) indicates mean platelet size and reflects the platelet production rate and stimulation [13]. Larger platelets are more metabolically and enzymatically active than smaller platelets [14]. Increased platelet size has been observed in association with known cardiovascular risk factors, such as smoking, diabetes mellitus, obesity and hy-

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pertension [15-19]. Panzer *et al.* [11] reported platelet changes, such as lower platelet counts and increased MPV, in hyperthyroidism. Lippi *et al.* [20] demonstrated that a significant, positive and independent association exists between MPV and serum TSH values. The neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are known markers of the systemic inflammatory response. The results of a few studies examining the clinical significance of MPV, NLR and PLR in thyroid diseases are controversial [21, 22].

Papillary thyroid carcinoma is the most common primary thyroid malignancy, and it accounts for 85-90% of all thyroid cancers [23-25]. It is characterised by a triphasic clinical course that includes euthyroidism (preoperative), hypothyroidism (just prior to radioiodine treatment) and subclinical hyperthyroidism (clinical follow-up). This study aimed to investigate the effect of thyroid hormone changes on haematological parameters by comparing platelet count, MPV, NLR and PLR in all three phases of thyroid papillary carcinoma.

2. MATERIALS AND METHODS

Three hundred fourteen patients with PTC who were followed up at the Gaziosmanpaşa University School of Medicine, Department of Endocrinology and Metabolism and Nuclear Medicine were examined retrospectively. A total of 58 patients (49 females and nine males) who attended the monitoring visits starting in the phase prior to thyroid surgery and continued until the monitoring visit in the sixth month following RAI treatment were included in the study.

Patients with diabetes mellitus, hypertension, chronic inflammatory disease or autoimmune disease, acute or chronic infection, haematologic disease, heart failure, myeloproliferative disorders, hepatic or renal disorders and patients on anticoagulation therapy were excluded from the study.

Clinical and laboratory parameters of all patients were recorded in the following three phases of the disease: euthyroid phase (before thyroid surgery), Overt Hypothyroid (OH) phase (before RAI treatment) and subclinical hyperthyroid (SCH) phase (six months after RAI treatment). The laboratory data of each patient in all three stages of the disease were compared. Patients receiving RAI treatment with the limitation of iodide and withdrawal of thyroid hormone were included. Patients who were prepared for RAI treatment with recombinant TSH were not included in the study. Patients who received 100 mCi RAI treatment were included in the study. On average, RAI treatment was performed 25 days after discontinuation of thyroid hormone. The laboratory data of the patients in the hypothyroid stage were taken the day before RAI treatment.

Complete blood count levels were determined using a Sysmex XN-1000 (Kobe, Japan) analyser. For blood count analyses, samples were obtained after overnight fasting and between 8:30 AM and 9:30 AM. The same standardised blood tubes were used for sampling, and all blood samples were analysed within one hour after venepuncture. The NLR was calculated by dividing the neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count.

2.1. Statistical Analyses

For the statistical analysis, the Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY, USA) program was used. All continuous data are shown as mean \pm standard deviation. In order to compare the mean of the quantitative variables between the groups, independent samples t test was used. Repeated measures ANOVA was used to compare the means of repeated measures by a factor. P values < 0.05 were accepted as statistically significant.

3. RESULTS

Forty-nine females and nine males were included in this study for a total of 58 patients. The mean age of the patients was 52.9 ± 13.28 years. The mean TSH values of the patients in the euthyroid, OH and SCH phases were 1.62 ± 1.17 , 76.4 ± 37.5 and 0.09 ± 0.07 $\mu\text{IU/mL}$, respectively (Table 1). In the euthyroid phase, TSH values were significantly lower in females (1.49 ± 1.04 $\mu\text{IU/mL}$) than in males (2.32 ± 1.64 $\mu\text{IU/mL}$) ($p=0.05$). The mean MPV values of the patients in the euthyroid, OH and SCH phases were 9.45 ± 1.33 , 9.81 ± 1.35 and 9.96 ± 1.21 fL, respectively (Fig. 1). MPV was significantly higher in the SCH phase than in the euthyroid phase ($p=0.013$).

White blood cell (WBC) count, neutrophil count, platelet count, PLR and NLR were not statistically different between the euthyroid, OH and SCH phases ($p>0.05$) (Table 1). WBC and neutrophil counts were significantly higher in males than in females in the SCH phase. In the OH and euthyroid phases, the WBC and neutrophil counts were similar in females and males. The lymphocyte count was significantly higher in the OH phase ($2.48 \pm 0.74/\text{mm}^3$) than in the SCH phase ($2.2 \pm 0.6/\text{mm}^3$) ($p=0.008$). Haemoglobin, haematocrit and MCV values were significantly lower in females than in males ($p<0.001$). In all three phases of PTC, other laboratory parameters (glucose, aspartate aminotransferase and calcium) were within normal limits.

4. DISCUSSION

Thyroid hormones play an important physiological role in humans. The association between thyroid disorders and abnormalities in haematological parameters is well known. MPV has been an important focus of research in thyroid disease. Studies investigating the relationship between thyroid functions and MPV levels demonstrated conflicting results [26]. Lippi *et al.* [20] demonstrated a significant positive correlation between MPV and serum TSH values, whereas Ren *et al.* [27] could not confirm the relationship. Studies reported elevated MPV levels in subclinical hypothyroidism and described this case as having an increased risk of cardiovascular complications. MPV values were decreased after subclinical hypothyroid patients became euthyroid [12, 15, 28-30]. Kim *et al.* [31] found that the mean MPV increased in a statistically significant manner by increasing tertiles of the TSH concentration, and the highest was in SCH. In 15 patients with hyperthyroidism, Panzer *et al.* [11] compared platelet counts and MPV before and three weeks after initiation of antithyroid drug therapy when the patients were euthyroid. After three weeks of antithyroid drug therapy,

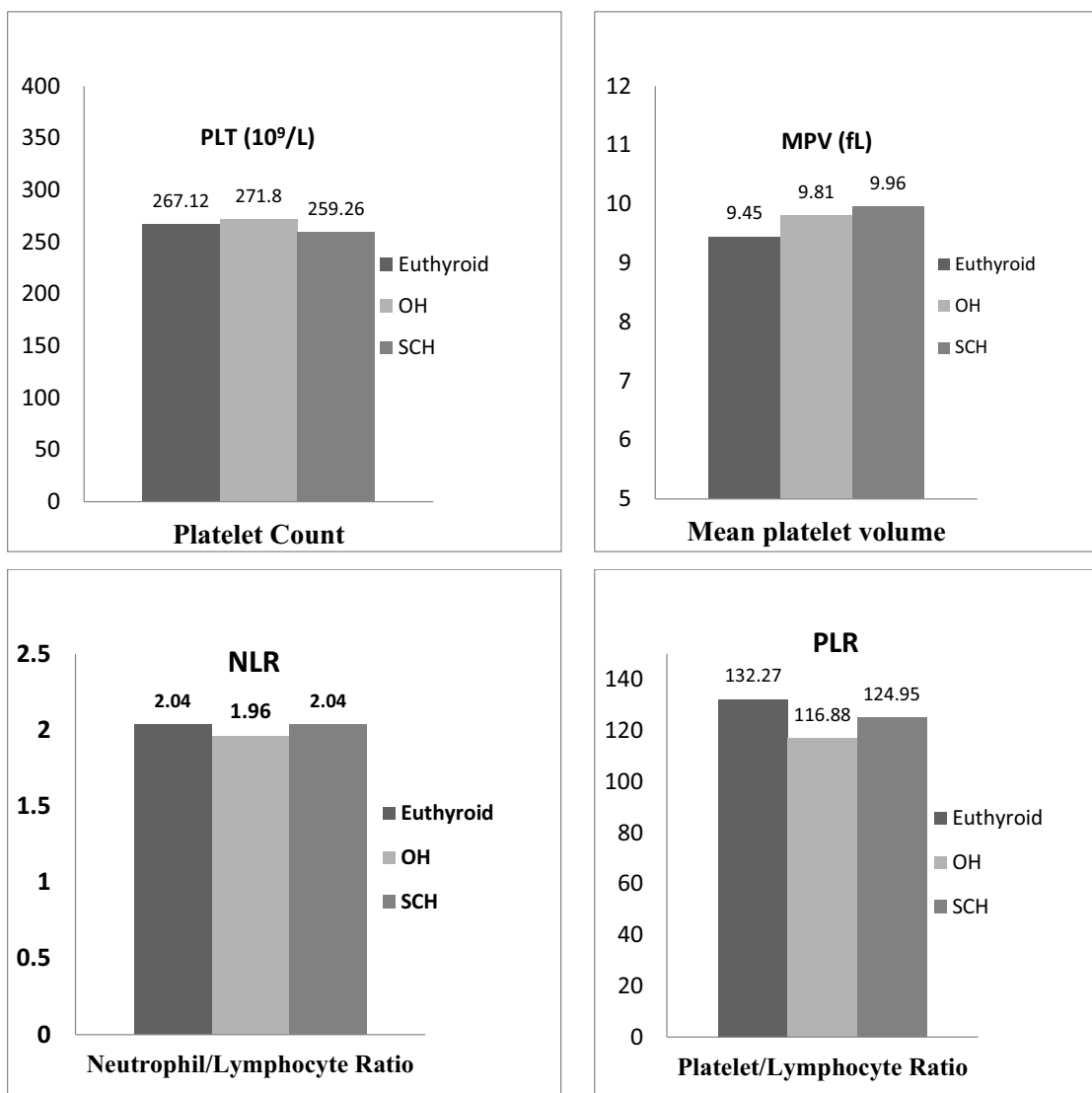


Fig. (1). Graphical view of platelet count, MPV values, NLR, and PLR in all phases of patients with papillary thyroid carcinoma. Mean platelet volume was significantly higher in the SCH phase than in the euthyroid phase ($p=0.013$). Platelet count, NLR, and PLR were not statistically different between euthyroid, OH and SCH phase.

there was a significant increase in platelet count and a decrease in MPV compared with pretreatment levels [11]. In the present study, changes in thyroid hormone levels did not cause any change in thrombocyte levels. Supporting the previous study, the results of the present study revealed that MPV was significantly higher in the SCH phase than in the euthyroid phase ($p=0.013$). In addition, MPV values in hypothyroid patients were higher than euthyroid patients but not to a statistically significant degree. High MPV values in patients with both OH and SCH suggest that MPV elevation contributed to increased cardiovascular risk in thyroid patients.

Accurate measurement of MPV is important for clinical and research purposes. However, there are several crucial factors that can influence the results. Dastjerdi *et al.* [32] revealed in their study that MPV can be measured accurately by both methods of anticoagulation (EDTA and citrate) if

analysis is performed within one hour of sampling. In the present study, the same standardised blood tubes were used for sampling, and all blood samples were analysed within one hour after venepuncture.

Recent studies showed that several biomarkers, especially NLR and PLR, are associated with the inflammatory response [33, 34]. However, only a few studies have evaluated the significance of the NLR in thyroid disease [35-37]. The NLR has been widely used to determine the severity of inflammation in cardiovascular disease, malignancies, diabetes mellitus, hypertension and autoinflammatory diseases [38-40]. Keskin *et al.* [38] showed that the increased NLR values in euthyroid chronic autoimmune thyroiditis are statistically different compared with healthy control group values. These studies suggest that the NLR could be an important tool for measuring systemic inflammation in hypothyroid patients since it is cost effective, readily available and

Table 1. Changes in laboratory parameters in euthyroid, overt hypothyroid, and subclinical hyperthyroid phase of papillary thyroid carcinoma (N=58).

	Euthyroid	OH	SCH	p	Comparison of groups		
					Euthy.-OH	Euthy.-SCH	OH-SCH
Metabolic and Hormonal Parameters							
TSH, μ IU/mL	1.62 \pm 1.17	76.4 \pm 37.5	0.09 \pm 0.07	<0.001	<0.001	<0.001	<0.001
Free T4, ng/dL	1.34 \pm 0.26	0.35 \pm 0.27	1.54 \pm 0.15	<0.001	<0.001	<0.001	<0.001
ALT, U/L	16.85 \pm 7.48	22.24 \pm 12.17	18.41 \pm 7.53	0.943	NS	NS	NS
AST, U/L	18.46 \pm 7.58	25.08 \pm 10.67	17.96 \pm 6.04	0.016	0.999	0.906	0.011
Glucose, mg/dl	101.43 \pm 22.42	101.6 \pm 28.92	100.91 \pm 15.61	0.966	NS	NS	NS
Calcium, mg/dl	9.26 \pm 0.57	9.23 \pm 0.68	9.21 \pm 0.55	0.585	NS	NS	NS
Hematologic Parameters							
Leucocytes, /mm ³	7.41 \pm 1.72	7.55 \pm 1.51	7.27 \pm 1.82	0.418	NS	NS	NS
Neutrophil, /mm ³	4.39 \pm 1.38	4.39 \pm 1.12	4.38 \pm 1.43	0.995	NS	NS	NS
Lymphocytes, /mm ³	2.25 \pm 0.68	2.48\pm0.74	2.2\pm0.6	0.002	0.033	0.999	0.008
Hemoglobin, gr/dl	13.01 \pm 1.37	13.1 \pm 1.73	13.08 \pm 1.51	0.768	NS	NS	NS
HCT, %	38.87 \pm 3.94	39.38 \pm 4.39	39.02 \pm 4.24	0.332	NS	NS	NS
MCV, fl	84.78\pm5.44	84.96\pm5.21	82.98\pm5.07	0.001	0.999	0.004	0.002
Platelet, 10 ⁹ /L	267.12 \pm 52.93	271.8 \pm 61.7	259.26 \pm 56.23	0.221	NS	NS	NS
MPV, fL	9.45\pm1.33	9.81 \pm 1.35	9.96\pm1.21	0.006	0.112	0.013	0.818
NLR	2.04 \pm 0.78	1.96 \pm 0.92	2.04 \pm 0.79	0.718	NS	NS	NS
PLR	132.27 \pm 61.2	116.88 \pm 44.9	124.95 \pm 35.92	0.081	NS	NS	NS

Repeated measures ANOVA was used. OH;overt hypothyroidism, SCH;subclinical hyperthyroidism, NS;Not significant.

easily calculated [38, 41]. However, little is known regarding the relationship between the NLR and thyroid disorders. The results of the present study showed that the NLR and PLR were not statistically significant in all three phases of the disease.

Demir *et al.* [42] found significant increases in the NLR and PLR and a significant decrease in MPV after RAI treatment. Monzen *et al.* [43] evaluated the effect of RAI treatment on the haematopoietic system, and they found that the WBC count, the number of neutrophils and lymphocytes, the platelet count and haemoglobin were all significantly decreased by day 30 versus the first day after RAI treatment [42]. In this study, the haematological parameters were evaluated six months after RAI treatment. This study showed that the NLR and PLR did not change after RAI treatment in differentiated thyroid cancer (DTC) patients. The present study did not support previous studies. In other studies, these parameters were evaluated one month after RAI treatment, but these parameters were evaluated after six months in the present study. This can be explained by the reduction of the effectiveness of RAI treatment in the sixth month.

Several studies examined the relationship between PTC and MPV levels. Bayhan *et al.* [44] suggested that an overall increase in MPV values in malignant thyroid diseases was

significantly higher than in patients with benign thyroid disorders. Dincel *et al.* [45] found no significant difference between PTC, multinodular goitre and control groups in terms of MPV values. Yaylaci *et al.* [46] also did not find any significant relationship between benign nodular goitre and PTC groups in terms of MPV values.

Additionally, some studies demonstrated a correlation between the NLR and several types of cancer, especially PTC [38, 47-50]. Several studies reported that NLR levels were significantly higher in elderly patients with PTC [36, 51, 52]. Kocer *et al.* [49] found that the NLR was higher in patients with PTC than in other groups. On the other hand, Yaylaci *et al.* [46] observed no significant relationship between the NLR and PTC. The PLR has been analysed as a prognostic biomarker. Higher PLR has been associated with poor overall survival in various solid tumours [53]. Kim *et al.* [35] reported that higher preoperative PLR had a significantly increased incidence of lateral lymph node metastasis in patients with PTC. As a result, the relationship between these parameters (MPV values, NLR and PLR) and PTC is still uncertain. In the present study, the effect of thyroid hormone changes on haematological parameters in patients with PTC was investigated. Therefore, no comment can be made on the effect of PTC on these parameters.

The present study has two main limitations. The first is the limited number of patients, and the second is the short follow-up period.

CONCLUSION

In conclusion, the results of this study demonstrated that the levels of MPV increased significantly in the SCH phase in patients with PTC, and increased MPV values contributed to an increased risk of cardiovascular complications. These findings suggest that MPV can be a valuable and practical parameter for monitoring haemostatic conditions in thyroid disorders. In this study, no significant difference was observed in platelet count, the NLR and the PLR in all stages of PTC. These findings should be confirmed in future studies with larger numbers of patients.

LIST OF ABBREVIATIONS

AST	=	Aspartate aminotransferase
ft4	=	Free Thyroxine
MPV	=	Mean Platelet Volume
NLR	=	Neutrophil/Lymphocyte Ratio
OH	=	Overt Hypothyroidism
PLR	=	Platelet/Lymphocyte Ratio
SCH	=	Subclinical Hyperthyroidism
TSH	=	Thyroid Stimulating Hormone

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Clinical Research Ethics Committee of Gaziosmanpaşa University's School of Medicine, Turkey (17-KAEK-172).

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

A written informed consent was obtained from patients involved in the study.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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