Original Article

Platelet to Lymphocyte and Neutrophil to Lymphocyte Ratios are useful in differentiation of thyroid conditions with normal and increased uptake

Hamdi Afsin[1], Gülali Aktas[2]

Abstract

Background: Thyroid uptake scintigraphy is a useful diagnostic tool in differentiation of thyroid conditions, especially in differentiation of hyperthyroidism from other causes of thyrotoxicosis. Hemogram parameters were introduced as novel inflammatory markers.

Objective: To study the association between hemogram indices and thyroid uptake in patients with thyroid diseases in Abant Izzet Baysal University Hospital internal medicine clinic.

Methods*:* Medical data of the patients with thyroid conditions were obtained from institutional databases between January 2019 and January 2020 in Abant Izzet Baysal University Hospital, Bolu, Turkey. According to the uptake the study population was grouped into three groups, decreased uptake, normal uptake and increased uptake groups. Laboratory parameters, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were compared between study groups.

Results: Median NLR of normal, increased and decreased uptake groups were 1.5 (1-2.9) %, 2.1 (1.1-26) %, and 2.2 (1.1-10) %, respectively ($p<0.001$). Median PLR of normal, increased and decreased uptake groups were 99 (42-201) %, 144 (69-264) %, and 121 (67-270) %, respectively ($p<0.001$). NLR was significantly and positively correlated with CRP ($r=0.59$, $p<0.001$), and with ESR ($r=0.30$, $p<0.001$). Similarly PLR was also significantly and positively correlated with CRP ($r=0.54$, $p<0.001$), and with ESR ($r=0.28$, $p<0.001$).

Conclusions: We suggest that NLR and PLR could serve as additional diagnostic tools in the differentiation of thyroid conditions with increased uptake from that with normal uptake. [*Ethiop. J. Health Dev.* 2020; 35(3):000-000]

Keywords: thyroid uptake, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, thyroid diseases, inflammatory markers

Introduction

Thyroid scintigraphy plays an important role in differential diagnosis of thyroid conditions, such as Graves' disease and thyroiditis, by providing crucial information about the radiopharmaceutical uptake of the thyroid gland. For this purpose, technetium-99m (99mTc) pertechnetate is the most preferred radionuclide agent since it has an inexpensive nature and lower burden of radiation (1). Differentiation of hyperthyroidism from the other causes of thyrotoxicosis is the most important role of the measurement of thyroid uptake (2). While subacute thyroiditis is associated with very low or absent uptake in a diffuse pattern, scintigraphic characteristics of toxic nodular goiter and Graves' disease is associated with uptake in thyroid scintigraphy (3). Despite uptake having specific features for certain diseases, sometimes it could not be as helpful as desired in clinical practice. For instance, though Graves' disease is associated with increased uptake, sometimes it may appear as normal intake in thyroid scintigraphy (2). Inflammatory markers, such as elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are useful in accordance with thyroid uptake scintigraphy in differentiation of thyroiditis and hyperthyroidism. For instance, elevated CRP levels have been reported in patients with subacute thyroiditis, which is characterized with low or absent thyroid uptake (4).

Hemogram derived indices are suggested as novel inflammatory markers recently. These indices include platelet distribution width (PDW), plateletcrit (PCT), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR). Studies in literature confirmed association between PDW and cancer (5), coronary heart disease (6, 7), diabetes mellitus (8), and sepsis (9). The inflammatory role of PCT has been shown in hepatitis (10), in gestational diabetes mellitus (11), and in tuberculosis (12). Associations between NLR and type 2 diabetes mellitus (13, 14), thyroid conditions (15), and vitamin D deficiency (16) are well established in the studies in literature. Similarly, literature data suggest close relationship between PLR and type 2 diabetes mellitus (17), rheumatic disease (18), pulmonary thromboembolism (19), and malignant conditions (20).

This study aimed to compare hemogram indices of the patients who had undergone thyroid uptake scintigraphy with those who had normal uptake to those in patients with increased and decreased uptake in Abant Izzet Baysal University Hospital internal medicine clinic.

Methods

Patients: After institutional board approval was received, (Abant Izzet Baysal University Hospital Board approval no: 2020/33443051-929) a retrospective analysis was conducted on the patients with thyroid conditions from database of the institution and the patients' files. The study population consisted of patients with thyroid disorders that undergone

[1]Department of Nuclear Medicine, Abant Izzet Baysal University Hospital, Bolu, Turkey
[2]Department of Internal Medicine, Abant Izzet Baysal University Hospital, Bolu, Turkey. * Corresponding author e-mail address: hamdiafsin@hotmail.com

thyroid uptake scintigraphy. According to the uptake the study population was grouped into three groups, decreased uptake, normal uptake and increased uptake groups. Patients with inflammatory conditions, cancer or active infections were excluded. The sample was calculated as 23 in both groups by power analysis in order to have a 95% power and a change of 20%. In order to protect the study from possible losses during follow-up, a sample of at least 25 patients (10% more of the calculated) for both groups were planned to be included to the study.

Laboratory Data: General characteristics and laboratory data of the participants; age, sex, uptake, CRP, serum creatinine, ESR, free triiodothyronine (FT3), free thyroxin (FT4), and thyroid stimulating hormone (TSH) were recorded. Hemogram parameters; white blood cell count (WBC), hemoglobin (Hb), hematocrit (Htc), platelet count (PLT), PDW and PCT were also obtained. NLR and PLR were calculated with the division of neutrophil count by lymphocyte count and PLT by lymphocyte count, respectively.

Statistical Analyses: The SPSS software (SPSS 15.0 for Windows, IBM Co, Chicago, Il, USA) was used in statistical analyses. Kolmogorov Smirnov test was conducted to determine whether the variables were distributed normally or not in study groups. Comparison of the variables with normal distribution was held with One Way ANOVA test and these variables were expressed as mean ± standard deviation (SD). Comparison of the variables without normal distribution was held with Kruskal Wallis test and these variables were expressed as median (min.-max.). Post Hoc analyses were conducted with Tukey test. Chi-square test was used in the comparison of categorical variables. Pearson's correlation analysis was held to find out correlation between study variables. Statistical significance was set at the p value lower than 0.05 levels.

Results

The numbers of subjects in normal, increased and decreased uptake groups were 60, 97 and 25, respectively. Age (p=0.07), sex (p=0.14), Hb (p=0.23), Htc (p=0.20), PLT (p=0.27), PCT (p=0.29), PDW (p=0.18), creatinine (p=0.1), FT4 (p=0.15) and TSH (p=0.81) of the study groups were not statistically different. WBC (p=0.003), thyroid uptake (p<0.001), CRP (p<0.001), ESR (p=0.001), and FT3 (p<0.001) were significantly different between study groups. General data of study population is summarized in table 1.

Table 1. **General characteristics of the study population (Abant Izzet Baysal University Hospital between January 2019 and January 2020)**

		Normal uptake group	**Increased Uptake group**	**Decreased uptake group**	**P**
Sex	Male (n,%)	22 (37)	30 (30)	12 (52)	0.14
	Female (n,%)	38 (63)	69 (70)	11 (48)	
		Mean ± SD			
Age (years)		61 ± 14	55 ± 17	56 ± 17	0.07
Hb (g/dL)		13.5 ± 1.4	13.8 ± 1.5	13.8 ± 1.6	0.23
Htc (%)		42 ± 4	43 ± 4	43 ± 5	0.20
WBC (k/mm^3)		7.5 ± 1.9	6.5 ± 1.6	7 ± 1.8	**0.003**
		Median (Min.Max.)			
Uptake (%)		0.9 (0.4-1.7)	3.3 (1.8-60)	0.1 (0.1-0.3)	**<0.001**
CRP (mg/L)		1.8 (0.1-41)	6 (0.1-76)	6 (0.1-34)	**<0.001**
ESR (mm/hour)		13 (2-53)	21 (3-104)	28 (2-64)	**0.001**
PLT (k/mm^3)		254 (145-493)	257 (115-418)	235 (113-351)	0.27
PDW (%)		17.3 (15.9-19.5)	17.6 (15.6-20.6)	17.4 (16.1-20.8)	0.18
PCT (%)		0.21 (0.1-0.48)	0.20 (0.11-0.34)	0. 19 (0.1-0.30)	0.29
FT3 (pg/mL)		3.4 (1-6.4)	4 (1-19.9)	3 (1.8-5.1)	**<0.001**
FT4 (ng/dL)		1.1 (0.8-1.6)	1 (0.5-3.1)	1.1 (0.7-2.7)	0.15
TSH (uIU/mL)		0.18 (0.01-6.8)	0.12 (0.01-6.2)	0.24 (0.01-11.3)	0.81
Creatinine (mg/dL)		0.8 (0.6-1.5)	0.8 (0.5-1.6)	0.8 (0.6-1.4)	0.1
NLR (%)		1.5 (1-2.9)	2.1 (1.1-26)	2.2 (1.1-10)	**<0.001**
PLR (%)		99 (42-201)	144 (69-264)	121 (67-270)	**<0.001**

Median NLR of normal, increased and decreased uptake groups were 1.5 (1-2.9) %, 2.1 (1.1-26) %, and 2.2 (1.1-10) %, respectively. NLR was significantly different between study groups (p<0.001). In post hoc analysis, NLR of decreased uptake group was not different from the NLR of normal uptake (p=0.008), and NLR of the increased uptake (p=0.98) groups. However, NLR of the normal uptake group was significantly lower than that of the increased uptake group (p=0.002).

Median PLR of normal, increased and decreased uptake groups were 99 (42-201) %, 144 (69-264) %, and 121 (67-270) %, respectively. PLR was significantly different between study groups (p<0.001). In post hoc analysis, PLR of decreased uptake group was not different from the PLR of normal uptake (p=0.28), and PLR of the increased uptake (p=0.25) groups. However, PLR of the normal uptake group was significantly lower than that of the increased uptake group (p<0.001).

In correlation analyses, NLR was significantly and positively correlated with CRP (r=0.59, p<0.001), and with ESR (r=0.30, p<0.001). On the other hand, PLR was significantly and positively correlated with CRP Figure 1 shows the NLR's correlation with CRP and ESR. Figure 2 shows the PLR's correlation with CRP and ESR.

Figure 1. **NLR's correlation with CRP and ESR in study population in Abant Izzet Baysal University between January 2019 and January 2020.**

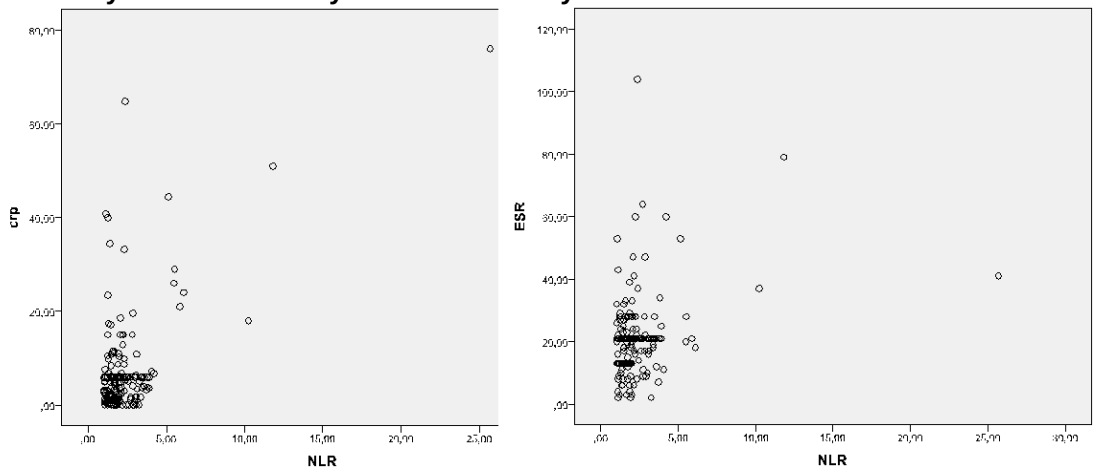
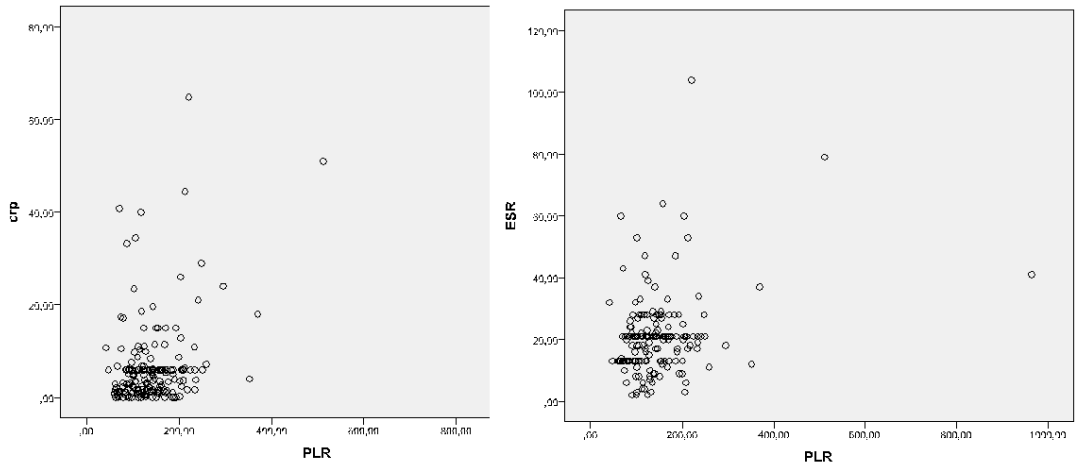


Figure 2. **PLR's correlation with CRP and ESR. In study population in Abant Izzet Baysal University between January 2019 and January 2020.**



Discussion

The most important outcomes of the present study are; (a) NLR of the subjects with increased uptake in thyroid uptake scintigraphy is significantly higher than the NLR of the subjects with normal uptake, (b) PLR of the subjects with increased uptake in thyroid uptake scintigraphy is significantly higher than the PLR of the subjects with normal uptake, and (c) both NLR and PLR are positively and strongly correlated with two important inflammatory predictors, CRP and ESR.

Careful clinical examination, appropriate imaging, proper treatment and if necessary, close clinical follow-up are all important steps in management of the thyroid diseases (2). Significant information about the thyroid disorders could be obtained by radionuclide imaging. Focal and multifocal uptake, diffusely increased uptake and diffusely decreased uptake are patterns in imaging during thyroid scintigraphy (2). For instance, while some thyroid conditions are often associated with decreased uptake pattern, others (i.e. Graves' disease) could show diffusely and homogenously increased uptake. Differentiation of hyperthyroidism from the other causes of thyrotoxicosis is the most important role of the measurement of thyroid uptake (2). While subacute thyroiditis is associated with very low or absent uptake in a diffuse pattern, scintigraphy characteristics of toxic nodular goiter and Graves' disease is associated with increased uptake in thyroid scintigraphy (3). Moreover, uptake could be high in subjects with iodine deficiency, too. Nevertheless, importance of thyroid uptake scintigraphy is mostly dependent on its discriminatory role in hyperthyroidism as compared to the other causes of thyrotoxicosis.

Toxic nodular goiter and Graves' disease, which are characterized with increased uptake, both produce inflammatory burden, therefore, NLR, a novel inflammatory predictor, is found to be higher in these subjects compared to the patients with normal uptake.

Inflammatory burden is also increased in patients with thyroiditis, which is usually associated with decreased uptake. Indeed, studies in literature reported increased NLR, mean platelet volume (MPV) and red cell distribution width (RDW) in subjects with Hashimoto's thyroiditis (21-23). Similar to NLR, both MPV and RDW are also considered as hemogram derived inflammatory indices. Present study proved significantly different NLR between normal and increased uptake groups, however, NLR of the decreased uptake group was similar to that in the subjects with normal uptake. This may be due to smaller population of decreased uptake group, which were only 25.

The NLR has been found to be associated with various thyroid conditions in other studies in literature. Increased levels of NLR in patients with thyroid ophtalmopathy compared to control subjects were reported in 2017 (24). Both NLR and PLR were increased in patients with Hashimoto's thyroiditis compared to healthy subjects in Bilge et al's study (25). Moreover, NLR was proposed to be useful in differentiating malignant and benign thyroid conditions (15, 26). Elevated NLR in patients with increased thyroid uptake compared to the subjects with normal uptake, which is a major finding in the present study, is in accordance with literature data. We also determined the correlation of NLR with CRP and ESR.

Medical literature is full of data about the role of PLR in inflammatory conditions. Moreover, a recent study found increased PLR in subjects with thyroiditis compared to healthy individuals (25). Ozmen et al reported that PLR was superior to CRP in predicting differentiated thyroid malignancy (27). In another study, high PLR is believed to be an indicator of lymph node metastasis in subjects with papillary thyroid cancer (28). In contrast, a more recent study suggested that PLR was not associated with the stages of papillary thyroid cancer (29). The results of this study are compatible with studies that suggest higher PLR in patients with increased thyroid uptake compared to the subjects with normal uptake. In contrast Taskaldiran et al has found increased PLR in subjects with subacute thyroiditis, which is characterized with decreased uptake, compared to the PLR in Graves ' disease, which is characterized with increased uptake (30). This study found similarities between increased and decreased uptake groups which could be a result of a small population in the decreased uptake group. This study also determined the correlation of PLR with CRP and ESR.

The PDW and PCT values of the groups in this study were not statistically different. However, PDW has been found to provide significant information about the diagnosis of certain conditions in literature (5). Moreover, PCT has been proposed as a useful diagnostic tool in inflammatory conditions (10). In contrast to other inflammatory markers, neither PDW nor PCT had such high correlation with the differentiation of thyroid uptake groups in present study.

Retrospective nature of the study is a limitation of our work due to the risk of selection bias. Relatively small study population is another limitation. However, to the best of our knowledge, this is the first study in medical literature that found elevated PLR and NLR in thyroid conditions with increased uptake.

Conclusions

We suggest that NLR and PLR could serve as additional diagnostic tools in differentiation of thyroid conditions with increased uptake from that with normal uptake. Therefore, primary care physicians should be alerted with elevated NLR and PLR in subjects with thyroid conditions and refer these subjects for further testing with uptake scintigraphy. The role of elevated PLR in the population with decreased uptake should be more elaborated in future studies.

COI statement and funding statement

The authors have no conflict of interest. This work has not received any funds or grants from any organizations.

Author's Contributions

HA and GA designed the study. HA performed the literature search. GA performed the statistical analyses. GA and HA wrote the manuscript and performed the critical review of the first draft. All authors approved the final version of the manuscript.

References

1. Hoff Wvt, Pover GG, Eiser NM. Technetium-99 m in the diagnosis of thyrotoxicosis. Br Med J. 1972;4(5834):203-6.
2. Macauley M, Shawgi M, Ali T, Curry A, Howe K, Howell E, et al. Assessment of normal reference values for thyroid uptake of technetium-99m pertechnetate in a single centre UK population. Nucl Med Commun. 2018;39(9):834-8.
3. Sahlmann CO, Siefker U, Lehmann K, Harms E, Conrad M, Meller J. Quantitative thyroid scintigraphy for the differentiation of Graves' disease and hyperthyroid autoimmune thyroiditis. Nuklearmedizin. 2004;43(4):124-8.
4. Richard J, Lazarte S, Calame A, Lingvay I. Sweet's syndrome and subacute thyroiditis: an unrecognized association? Thyroid. 2010;20(12):1425-6.
5. Ulutas KT, Sarici IS, Arpaci A. Comparison of Platelet Distribution Width and CA19-9 in Resectable Pancreas Cancer. Med Arch. 2018;72(3):210-3.
6. Sincer I, Mansiroglu AK, Aktas G, Gunes Y, Kocak MZ. Association between Hemogram Parameters and Coronary Collateral Development in Subjects with Non-ST-Elevation Myocardial Infarction. Rev Assoc Med Bras (1992). 2020;66(2):160-5.
7. Sincer I, Mansiroglu AK, Erdal E, Cosgun M, Aktas G, Gunes Y. Could platelet distribution width predict coronary collateral development in stable coronary artery disease? North Clin Istanb. 2020;7(2):112-7.

8. Atak BM, Duman TT, Aktas G, Kocak MZ, Savli H. Platelet distribution width is associated with type 2 diabetes mellitus and diabetic nephropathy and neuropathy. National J Health Sci. 2018;3(3):95-8.
9. Ahmad MS, Waheed A. Platelet counts, MPV and PDW in culture proven and probable neonatal sepsis and association of platelet counts with mortality rate. J Coll Physicians Surg Pak. 2014;24(5):340-4.
10. Coskun ME, Alidris A, Temel MT, Akbayram S, Hizli S. Plateletcrit: A possible biomarker of inflammation in hepatitis A infection. Niger J Clin Pract. 2019;22(5):727-30.
11. Sahbaz A, Cicekler H, Aynioglu O, Isik H, Ozmen U. Comparison of the predictive value of plateletcrit with various other blood parameters in gestational diabetes development. J Obstet Gynaecol. 2016;36(5):589-93.
12. Tozkoparan E, Deniz O, Ucar E, Bilgic H, Ekiz K. Changes in platelet count and indices in pulmonary tuberculosis. Clin Chem Lab Med. 2007;45(8):1009-13.
13. Bilgin S, Aktas G, Zahid Kocak M, Atak BM, Kurtkulagi O, Duman TT, et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. Aging Male. 2020;23(5):923-7
14. Duman TT, Aktas G, Atak BM, Kocak MZ, Erkus E, Savli H. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. Afr Health Sci. 2019;19(1):1602-6.
15. Sit M, Aktas G, Erkol H, Yaman S, Keyif F, Savli H. Neutrophil to Lymphocyte Ratio is Useful in Differentiation of Malign and Benign Thyroid Nodules. P R Health Sci J. 2019;38(1):60-3.
16. Erkus E, Aktas G, Atak BM, Kocak MZ, Duman TT, Savli H. Haemogram Parameters in Vitamin D Deficiency. J Coll Physicians Surg Pak. 2018;28(10):779-82.
17. Atak B, Aktas G, Duman TT, Erkus E, Kocak MZ, Savli H. Diabetes control could through platelet-to-lymphocyte ratio in hemograms. Rev Assoc Med Bras (1992). 2019;65(1):38-42.
18. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. Ann Lab Med. 2019;39(4):345-57.
19. Wang Q, Ma J, Jiang Z, Ming L. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute pulmonary embolism: a systematic review and meta-analysis. Int Angiol. 2018;37(1):4-11.
20. Li B, Zhou P, Liu Y, Wei H, Yang X, Chen T, et al. Platelet-to-lymphocyte ratio in advanced Cancer: Review and meta-analysis. Clin Chim Acta. 2018;483:48-56.
21. Aktas G, Sit M, Dikbas O, Erkol H, Altinordu R, Erkus E, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. Rev Assoc Med Bras (1992). 2017;63(12):1065-8.
22. Sit M, Kargi E, Gulaliaktas, Dikbas O, Alcelik A, Savli H. Mean platelet volume should be a useful indicator in diagnosis of Hashimoto's thyroiditis. Acta Medica Mediterranea. 2014;30(6):1263-6.
23. Aktas G, Sit M, Dikbas O, Tekce BK, Savli H, Tekce H, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? Exp Clin Endocrinol Diabetes. 2014;122(10):572-4.
24. Celik T. Neutrophil-to-lymphocyte ratio in thyroid ophthalmopathy. Bratisl Lek Listy. 2017;118(8):495-8.
25. Bilge M, Yesilova A, Adas M, Helvaci A. Neutrophil- and Platelet- to Lymphocyte Ratio in Patients with Euthyroid Hashimoto's Thyroiditis. Exp Clin Endocrinol Diabetes. 2019;127(8):545-9.
26. Kocer D, Karakukcu C, Karaman H, Gokay F, Bayram F. May the neutrophil/lymphocyte ratio be a predictor in the differentiation of different thyroid disorders? Asian Pac J Cancer Prev. 2015;16(9):3875-9.
27. Ozmen S, Timur O, Calik I, Altinkaynak K, Simsek E, Gozcu H, et al. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) may be superior to C-reactive protein (CRP) for predicting the occurrence of differentiated thyroid cancer. Endocr Regul. 2017;51(3):131-6.
28. Kim SM, Kim EH, Kim BH, Kim JH, Park SB, Nam YJ, et al. Association of the Preoperative Neutrophil-to-ymphocyte Count Ratio and Platelet-to-Lymphocyte Count Ratio with Clinicopathological Characteristics in Patients with Papillary Thyroid Cancer. Endocrinol Metab (Seoul). 2015;30(4):494-501.
29. Kutluturk F, Gul SS, Sahin S, Tasliyurt T. 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. Endocr Metab Immune Disord Drug Targets. 2019;19(6):859-65.
30. Taşkaldiran I, Omma T, Önder Ç E, Firat SN, Koç G, Kiliç MK, et al. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-tolymphocyte ratio in different etiological causes of thyrotoxicosis. Turk J Med Sci. 2019;49(6):1687-92.