Can Hemogram Parameters Be Used as a Biomarker for Thyroid Carcinomas?

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AIM: Recently, there have been studies on various parameters that can be used to diagnose and follow up thyroid malignancies. These parameters are mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR), and different results have been reported regarding their diagnostic and prognostic effects. Therefore, there is a need for more comprehensive studies on the use of these parameters in diagnosis and follow-up. In this study, we planned to reveal whether MPV, NLR, PLR, and LMR can be used as biomarkers for thyroid carcinomas and whether they differ according to tumor type and size.

METHODS: A total of 242 patients aged 18–79 years who underwent thyroidectomy between October 2016 and December 2021 were included in this study. The following variables were analyzed retrospectively: age, sex, pathology results of thyroidectomy materials, and parameters such as MPV, NLR, PLR and LMR of the preoperative complete blood count. The patients included in the study were divided into two groups according to malignant and benign thyroidectomy pathologies. Group 1 (n = 160): Benign pathology. Group 2 (n = 82): Malignant pathology.

RESULTS: NLR and PLR were found to be significantly higher in the patients in Group 2 compared to the patients in Group 1 ($p = 0.042$ and $p = 0.003$). For the NLR value, sensitivity was calculated as 67.07%, Specificity as 48.75, and cut-off value as >1.503. Area Under Curve (AUC) value for NLR: 0.580. For the PLR value, sensitivity was calculated as 48.78%, Specificity as 70.62, and cut-off value as >111.429. AUC value for PLR: 0.615. A high level, positive and statistically significant correlation was detected between NLR and PLR in patients with tumor size ≥10 mm within Group 2 ($r = 0.548$, $p < 0.001$).

CONCLUSIONS: We believe that NLR and PLR values may be important predictive biomarkers for thyroid malignancies. As consistent with the literature, NLR and PLR values were statistically significant in our study. An NLR value of >1.503 and a PLR value of >111.429 can be considered a risk factor for thyroid malignancy.

Keywords: thyroid; thyroidectomy; hemogram; platelet; neutrophil; lymphocyte; monocyte

Introduction

Thyroidectomy is frequently performed in diseases such as diffuse toxic goiter (Graves' disease), manifesting with hyperthyroidism, toxic multinodular goiter (Plummer disease) and solitary toxic adenoma, benign thyroid diseases with goiter-related symptoms such as dysphagia, dyspnea, voice change and neck discomfort, and thyroid malignancies [1–3]. Ultrasonography (USG) and fine needle aspiration cytology (FNAC), which is used in the follow-up of thyroid diseases and nodules, have an important role in distinguishing malignant and benign thyroid nodules. Recently, studies on various parameters have been used in diagnosis and follow-up in the literature [4]. These parameters are mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR), and different results have been reported regarding their diagnostic and prognostic effects [4–7]. Therefore, there is a need for more comprehensive studies on the use of these parameters in diagnosis and follow-up. In this study, we planned to reveal whether MPV, NLR, PLR, and LMR can be used as biomarkers for thyroid carcinomas and whether they differ according to tumor type and size.

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Materials and Methods

This study was carried out in Sultan II. Abdulhamid Han Training and Research Hospital, with the approval of the Hamidiye Clinical Research Ethics Committee (approval no/date: 22-15/ 27 May 2022). This study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients. The inclusion criteria for the study were age between 18 and 80, thyroidectomy pathology being benign or differentiated carcinoma, and having a preoperative hemogram result from within the past 1 month. Exclusion criteria from the study were patients under 18 years of age and over 80 years of age, thyroidectomy pathology result being malignant cytology other than differentiated thyroid carcinoma, and the preoperative hemogram examination 1 month before not being available. A total of 242 patients aged 18–79 years who underwent thyroidectomy between October 2016 and December 2021 were included in this study. The following variables were analyzed retrospectively: age, sex, pathology results of thyroidectomy materials, and parameters such as mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR) of the preoperative complete blood count. Patients with malignant cytology were divided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Tumor sizes were recorded. The patients included in the study were divided into two groups according to malignant and benign thyroidectomy pathologies. Group 1 (n = 160): Benign pathology. Group 2 (n = 82): Malignant pathology.

Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, median, maximum) were used to define continuous variables. Categorical variables were defined using frequency (n) and percentages. Conformity of continuous variables to normal distribution was examined using the Shapiro-Wilks test. The comparison of two independent and non-normally distributed variables was reviewed by the Mann-Whitney U test. The relationship between categorical data was examined using the Chi-square test (or Fisher Exact test/Yates continuity correction, if appropriate). The correlation between continuous variables that did not conform to the normal distribution was analyzed using the Spearman Correlation Coefficient. Cut-off values were determined by Receiver Operating Characteristic (ROC) curve analysis. Statistical significance was determined as <0.05. Statistical analyses were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2021).

Power Analysis

The study sample size was calculated as 68 per group, with a Type 1 error of $\alpha = 0.05$ and a power of the study (1-β) of 80% [6].

Table 1. Demographic data and laboratory parameters.

	Female	Male
Sex, n (%)	166 (68.6)	76 (31.4)
	Mean ± SD	Med (min–max)
Age	46.5 ± 14.3	47 (18–79)
NLR	1.8 ± 1.1	1.6 (0.6–10.3)
PLR	103.6 ± 39.2	100.6 (34–280.3)
LMR	7.1 ± 10.0	5.7 (1.6–130)
MPV	9.1 ± 1.4	9.2 (5.5–12.9)

SD, Standard deviation; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume.

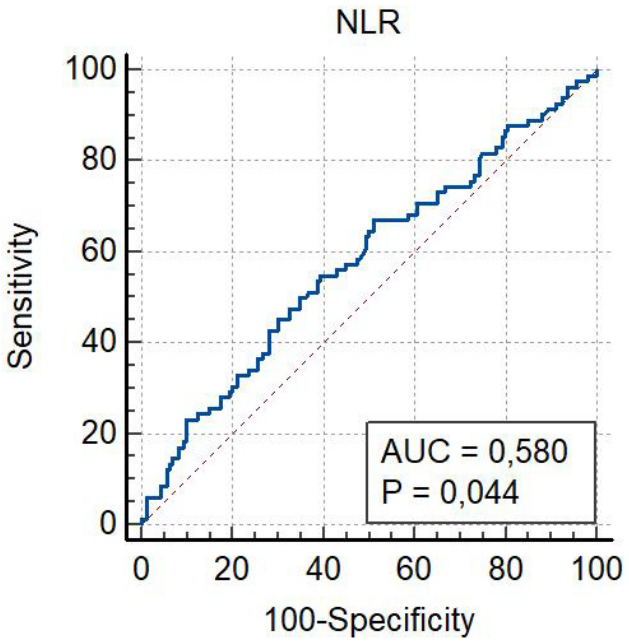

Fig. 1. Evaluation of NLR as a malignancy marker. NLR, neutrophil/lymphocyte ratio; AUC, Area Under Curve.

Results

Of the 242 patients included in the study, 166 (68.6%) were female and 76 (31.4%) were male. The mean age of the patients was 46.5 (±14.3), the mean NLR was 1.8 (±1.1), the mean PLR was 103.6 (±39.2), the mean LMR was 7.1 (±10) and the mean MPV was 9.1 (±1.4). Demographic data and mean laboratory parameters are shown in Table 1. One hundred sixty patients had benign pathology, and 82 had malignant pathology. There was no statistically significant difference in gender and mean age in the patients in Group 1 and Group 2 (respectively, $p = 0.164$, $p = 0.116$). Gender and age distribution between the two groups is shown in Table 2.

No statistically significant difference was detected between the two groups regarding MPV and LMR ($p = 0.582$ and $p = 0.776$, respectively). NLR and PLR were significantly higher in Group 2 compared to Group 1, respectively ($p =$

Table 2. Gender and age distribution.

Sex, n (%)	Female	Male	χ^2	p*
Group 1	105 (65.6)	55 (34.4)	1.934	0.164
Group 2	61 (74.4)	21 (25.6)		
Age	Mean ± SD	Med (min–max)	U/Z	p**
Group 1	47.6 ± 13.8	48 (18–75)	5750/–0.883	0.116
Group 2	44.5 ± 15.1	43 (19–79)		

*Chi-Square (Continuity Correction); **Mann-Whitney U test. SD, Standard deviation.

Table 3. Comparison of laboratory parameters between groups.

	Mean ± SD	Med (min–max)	U/Z	p*
MPV				
Group 1	9.1 ± 1.4	9.2 (6.3–12.6)	6276.5/–0.550	0.582
Group 2	9.2 ± 1.5	9.1 (5.5–12.9)		
NLR				
Group 1	1.7 ± 1.0	1.5 (0.6–8.9)	5513/–2.031	0.042
Group 2	2 ± 1.3	1.8 (0.6–10.3)		
PLR				
Group 1	98.7 ± 37.9	94.2 (34–280)	5046/–2.937	0.003
Group 2	113.3 ± 40.3	108.2 (47.4–249.7)		
LMR				
Group 1	6.4 ± 5	5.7 (1.6–59.1)	6413.5/–0.284	0.776
Group 2	8.4 ± 15.7	5.5 (1.9–130)		

*Mann-Whitney U test. SD, Standard deviation; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume.

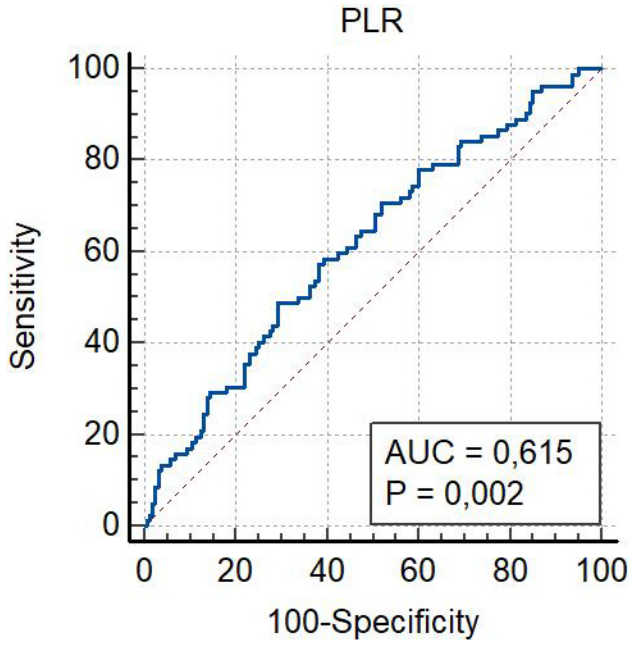

Fig. 2. Evaluation of PLR as a malignancy marker. PLR, platelet/lymphocyte ratio; AUC, Area Under Curve.

0.042 and $p = 0.003$). A comparison of laboratory parameters between the two groups is shown in Table 3. The sensitivity for NLR was 67.07%, Specificity was 48.75, and the cut-off value was >1.503. The sensitivity for PLR was 48.78%, Specificity was 70.62, and the cut-off value was >111.429. Evaluation of NLR and PLR as a marker of malignancy is shown in Figs. 1,2.

When comparing the intragroup laboratory parameters regarding gender, only LMR values were statistically significantly higher in women than in men in Group 1 ($p < 0.001$).

No statistically significant difference was found in the MPV, NLR, PLR, and LMR values of the patients in Group 2 with PTC and FTC (respectively; $p = 0.564$, $p = 0.128$, $p = 0.070$, $p = 0.637$).

The comparison of the laboratory parameters of the patients in Group 2 in terms of PTC and FTC is shown in Table 4.

In Group 2, no significant correlation was found between tumor sizes and laboratory parameters in patients with PTC and FTC. The correlation between tumor sizes and laboratory parameters of the patients in Group 2 is shown in Table 5.

When the MPV, NLR, PLR, and LMR values of the patients in Group 1 and those in Group 2 with a tumor size ≥10 mm were compared, there was no significant difference between MPV and LMR values ($p = 0.744$, $p = 0.240$, respectively), the NLR and PLR value were significantly higher in Group 2 with a tumor size ≥10 mm ($p = 0.025$,

Table 4. Comparison of laboratory parameters of patients in Group 2 in terms of PTC and FTC.

	PTC	FTC	U/Z	*p**
MPV			376/–0.577	0.564
Mean ± SD	9.3 ± 1.3; 70	9 ± 2.1; 12		
Med (min–max)	9.2 (6.7–12.2)	9 (5.5–12.9)		
NLR			304/–1.522	0.128
Mean ± SD	2.1 ± 1.3; 70	1.6 ± 0.6; 12		
Med (min–max)	1.8 (0.6–10.3)	1.6 (0.9–2.9)		
PLR			282/–1.810	0.070
Mean ± SD	116.6 ± 41.6; 70	93.8 ± 25.2; 12		
Med (min–max)	111.6 (47.4–249.7)	85.9 (58.5–132.7)		
LMR			384/–0.472	0.637
Mean ± SD	8.9 ± 17; 70	5.6 ± 1.7; 12		
Med (min–max)	5.6 (1.9–130)	5.2 (3–9)		

*Mann-Whitney U test. SD, Standard deviation; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

Table 5. Correlation between tumor sizes and laboratory parameters of patients in Group 2.

r, *p*	MPV	NLR	PLR	LMR
PTC Tumor size	–0.064, 0.567	0.161, 0.182	0.192, 0.111	–0.158, 0.192
FTC Tumor size	0.098, 0.762	–0.018, 0.957	0.081, 0.803	–0.126, 0.696

Spearman Rho correlation coefficient. NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

p = 0.006, respectively). The differences between MPV, NLR, PLR, and LMR between Group 1 and Group 2 with tumor size ≥10 mm are shown in Table 6.

When the correlation between MPV, NLR, PLR, and LMR was examined in patients in Group 2 with tumor size ≥10 mm, high level, positive, and statistically significant correlation was found between NLR and PLR, high level, negative, and statistically significant correlation was found between NLR and LMR, and a weak level negative and statistically significant correlation was found between PLR and LMR. Correlation between MPV, NLR, PLR and LMR was examined in patients in Group 2 with tumor size ≥10 mm is shown in Table 7.

Discussion

In this study, it was found that NLR and PLR values increased statistically significantly in the malignant group. In the malignant group, NLR and PLR values were statistically significantly higher in tumors 10 mm and above than in the benign group. In Group 2, a high level of positive correlation was found between NLR and PLR in tumors 10 mm and above. This study has several limitations: being retrospective, limited number of patients, lack of data on comorbidity and drug use, wide age range, and lack of data on preoperative antithyroid drug use.

Although FNAC is considered to be the most important diagnostic method in malignant thyroid nodules, it is known that its false positive and false negative rates are around 10% [8]. For this reason, it has been reported that combining parameters such as MPV may contribute to cost-effectiveness and diagnostic accuracy in malignant cytology [9]. Although no significant difference was found in MPV in our study, PLR values, another hemogram parameter, were significantly higher in malignant cytology. Combined with FNAC, it may contribute to the accuracy of diagnosis in malignant cytology. Different results are reported in studies indicating that hemogram parameters can be used in the diagnosis and prognosis of malignant thyroid pathologies [4–7]. Therefore, there is a need for more comprehensive studies from different centers. In this study, we revealed the effect of preoperative hemogram parameters in detecting malignant thyroid pathology in 242 patients and whether there is a significant relationship between malignant tumor diameter and these parameters. MPV, one of the hemogram parameters, is an early indicator of platelet activation [10]. It has been studied frequently recently and has increased in various malignancies [4]. In a study with 146 patients by Bayhan *et al*. [4], it was reported that MPV values were significantly higher in patients with malignant thyroid pathology than benign ones and could be an important predictive biomarker for thyroid malignancies. However, the Specificity, sensitivity, and cut-off values for MPV were not specified in this study. A similar study conducted by Sit *et al*. [9] with 199 patients reported that MPV values were significantly higher in patients with malignant thyroid pathology than benign ones. This study revealed speci-

Table 6. The differences between MPV, NLR, PLR, and LMR between Group 1 and Group 2 with tumor size ≥10 mm.

	Group 1	Tumor size ≥10 mm	U/Z	*p*
MPV			4741/–0.327	0.744
Mean ± SD, n	9.1 ± 1.4, 160	9.2 ± 1.4, 61		
Med (min–max)	9.2 (6.3–12.6)	9.1 (6.8–12.9)		
NLR			3926/–2.245	0.025
Mean ± SD, n	1.7 ± 1.0, 160	2.1 ± 1.4, 61		
Med (min–max)	1.5 (0.6–8.9)	1.9 (0.6–10.3)		
PLR			3715/–2.742	0.006
Mean ± SD, n	98.7 ± 37.9, 160	115.6 ± 43.2, 61		
Med (min–max)	94.2 (34–280)	107.2 (47.4–249.7)		
LMR			4380.5/–1.176	0.240
Mean ± SD, n	6.4 ± 5, 160	8.5 ± 17.6, 61		
Med (min–max)	5.7 (1.6–59.1)	5.2 (1.9–130)		

SD, Standard deviation; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume.

Table 7. Correlation between MPV, NLR, PLR, and LMR was examined in patients in Group 2 with tumor size ≥10 mm.

r, *p*	MPV	NLR	PLR	LMR
MPV	1	0.119, 0.362	–0.085, 0.514	–0.063, 0.632
NLR	0.119, 0.362	1	0.548, <0.001	–0.647, <0.001
PLR	–0.085, 0.514	0.548, <0.001	1	–0.363, 0.004
LMR	–0.063, 0.632	–0.647, <0.001	–0.363, 0.004	1

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; MPV, mean platelet volume.

ficity, sensitivity, and cut-off values for MPV as 66%, 81% and 8.25, respectively. A study by Baldane *et al*. [11] reported that MPV is significantly higher in thyroid carcinomas than benign thyroid pathologies. Specificity, sensitivity, and cut-off values for MPV were revealed to be 80%, 60%, and 7.81, respectively. In another study, Yu *et al*. [12] revealed that MPV values were significantly lower in the thyroid malignant carcinoma group in contrast to these studies conducted by Bayhan *et al*. [4], Sit *et al*. [9] and Baldane *et al*. [11]. However, in that study specificity, sensitivity, and cut-off value for MPV have not been reported. In our study, unlike these studies, no significant difference was found in MPV values. In consistency with our study, Dincel *et al*. [13], Yaylaci *et al*. [14], and Yildiz *et al*. [6] reported that MPV values in patients with PTC did not show a significant difference compared to patients with benign thyroid pathologies. Nevertheless, Yildiz *et al*. [6] reported that MPV values were significantly higher in patients with thyroid malignancy of 1 cm or more compared to the benign group. However, no significant difference was found between those with ≥1 cm malignant tumors and Group 1 regarding MPV values in our study.

In this study by Yildiz *et al*. [6], PLR values are higher in patients with malignant thyroid pathology. Zhang *et al*. [15] revealed that PLR values were higher in patients with PTC than in benign thyroid patients. On the other hand, Ozmen *et al*. [16] reported that PLR and NLR values were higher in thyroid carcinomas. In line with the results of these studies, our PLR and NLR values were significantly higher in the malignant group. Therefore, simultaneous increases in NLR and PLR may have stronger diagnostic value in predicting malignancy. Our study found that the NLR value was significantly lower in Group 1 than in patients with malignant tumor diameter ≥10 mm. Specificity, sensitivity, and cut-off values for PLR were revealed to be 64%, 59%, and 117.14, respectively by Yildiz *et al*. [6] and 65–70%, 65–75%, >134.25 respectively by Zhang *et al*. [15]. In our study specificity, sensitivity and cut-off values for PLR were 48.78%, 70.62% and 111.429, respectively. Kim *et al*. [17] reported that NLR and PLR values may be associated with higher lateral lymph node metastasis in 1194 PTC patients, but no comparison was made with benign cytology. A study conducted by Machairas *et al*. [18] with 228 patients revealed that hemogram parameters do not contribute to the differentiation of PTC. However, this study has reported that it may contribute to excluding T3 tumors and extrathyroidal involvement. In the study conducted by Senoymak *et al*. [19], it was reported that NLR values were significantly higher in malignant thyroid nodules, and the cut-off value was 2.06. Sensitivity of 82.4% and a specificity of 83.4% were reported for NLR. In our study, it was found that NLR values were higher in malignant thyroid nodules, which was consistent with the results of this study. However, according to this study, cut-off values, specificity and sensitivity for NLR were found to be lower. There are not enough studies on NLR values

in the literature. Nevertheless, considering the data suggesting that NLR values may be associated with advanced thyroid carcinomas and the significantly high detection of NLR values in patients with tumors of ≥1cm and above compared to the benign group in our study, it is understood that there is a need for new studies on NLR values. In our study, Specificity, sensitivity, and cut-off values for NLR were 48.75%, 67.07%, and 1.503, respectively. The different results obtained regarding hemogram parameters in the literature show that the discussion on the subject is up-to-date, and these findings reveal the need for more comprehensive studies.

Various studies evaluating MPV value as a predictive biomarker for thyroid carcinomas showed that MPV value was high in some studies and low in others. Therefore, with these results, it is very difficult to establish a cut-off value that can be used in clinical practice and shows the positive predictivity of MPV values. The reported cut-off value of 7.81 fl for MPV by Baldane *et al*. [11] is even higher than the mean MPV values of the benign thyroid patients in our study. Therefore, considering the results obtained in our study, we believe that MPV values cannot be used as a predictive biomarker for thyroid malignancies. Considering the results obtained from our research and studies in the literature, we believe that PLR and NLR values can be important biomarkers that can be used to predict thyroid malignancies. In addition, considering the results of the limited number of studies in the literature and the significantly higher NLR values in tumors ≥1 cm compared to the benign group in our study, NLR values can be used as a biomarker, especially in advanced thyroid carcinomas. Considering the positive correlation between NLR and PLR, there is a strong belief that the simultaneous increase in NLR and PLR values, especially in tumors larger than 1 cm, can be used as a biomarker for thyroid carcinomas. However, it should not be forgotten that preoperative hemogram parameters may vary in conditions such as systemic inflammatory conditions, malignancy, chronic diseases, and subacute inflammatory diseases, which may lead to diagnostic difficulties in distinguishing malignant thyroid nodules from benign ones [20].

Conclusion

Studies show that complete blood count parameters may be predictive biomarkers for thyroid carcinomas. However, different results have been reported in these studies. In particular, the results reported for MPV values make it difficult to obtain a cut-off value that can be used in clinical practice. We believe that MPV cannot be used as a predictive biomarker for thyroid malignancies, considering the lack of a significant difference in MPV values in our study and the different results in the literature. However, we believe that PLR and NLR values may be important predictive biomarkers for thyroid malignancies. Consistent with the literature, our study's PLR and NLR values were statistically significant. Furthermore, considering the significantly higher NLR and PLR values of tumors 1 cm and above compared to the benign group in our study, NLR and PLR values can be used as a biomarker, especially in advanced thyroid carcinomas. Considering the heterogeneity of the patient groups in our study and the literature, we believe prospective randomized controlled studies are needed in more homogeneous patient groups.

Availability of Data and Materials

All patients data included in this study can be obtained by contacting the corresponding author if needed.

Author Contributions

AD: Study design, data analysis, critical revision and literature review. UK: Study design, article writing, data analysis, critical revision and literature review. MSG: Study design, data analysis, critical revision and literature review. AFM: Study design, data analysis, critical revision and literature review. LDE: Study design, data analysis, critical revision and literature review. MGD: Study design, data analysis, critical revision, literature review and English editing; SKa: data analysis and critical revision. SKe: data analysis, critical revision and English editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was carried out in Sultan II. Abdulhamid Han Training and Research Hospital, with the approval of the Hamidiye Clinical Research Ethics Committee (approval no/date: 22-15/ 27 May 2022). This study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients.

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Conflict of Interest

The authors declare no conflict of interest.

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