The neutrophil-to-lymphocyte ratio as a diagnostic marker for malignant thyroid diseases
Malign tiroid hastalıklarında tanisel belirteç olarak nötrofil-lenfosit orani

Introduction

Thyroid diseases are one of the most common endocrine disorders, and the incidences of benign and malignant
thyroid diseases differ according to various factors including the geographical zone and gender [1]. The incidence of thyroid cancer in both genders has been increasing, but it is still very rare in the UK [2]. The American Cancer Society reported 60,220 new thyroid cancer cases in 2013 in the Unites States of America [3] and papillary thyroid carcinoma is the most common subtype among cases [4]. Early detection of thyroid cancer will facilitate timely treatment [3]. The serum thyroglobulin level is used as a prognostic marker during the postoperative follow-up period in patients who undergo treatment for thyroid carcinomas [5]. However, in clinical practice, there is not any early marker that can distinguish between malignant and benign thyroid disorders.

The neutrophil-to-lymphocyte ratio (NLR) is a novel reliable marker for evaluating the level of systemic inflammation [6–8]. Besides, it is also an inexpensive and convenient biomarker. Systemic inflammation plays an important role in many cancers such as thyroid carcinoma, gastric carcinoma, and colorectal carcinoma [9]. The pathophysiology of the inflammatory response to tumors is characterized by increased angiogenesis and disruption of DNA via inhibition of DNA repair [10].

In the present study, we aimed to investigate the predictive value of NLR in patients with malignant thyroid diseases in comparison to those with benign disorders of the thyroid. This is the first study to show the value of NLR as a marker in malignant thyroid diseases including all subgroups.

**Materials and methods**

We performed a retrospective analysis of patients who had undergone thyroidectomy for benign and malignant thyroid diseases at the General Surgery Department of Dumlupınar University, Kütahya, Turkey, between January 2012 and August 2014. Informed consent was obtained from all individual participants included in the study. No patient identity information was disclosed.

A total of 381 patients were evaluated and 128 patients with recurrent thyroid disease, thyroiditis, systemic disorders including diabetes mellitus, rheumatologic disorders, hypertension, ischemic heart diseases, and neurological disorders; as well as, those who had undergone complementary thyroidectomy or head and neck radiotherapy and those under current steroid treatment were excluded. In total, 253 patients were included in the study and were divided into two groups based on pathologic characteristic of the thyroid disease: benign and malignant. The malignant thyroid disease group was not further divided into subgroups according to the type of disease (differentiated vs. undifferentiated). Forty of 253 patients were diagnosed with thyroid cancer including papillary cancer, follicular cancer, medullar cancer and anaplastic cancer. Sixty percent of these patients had papillary cancer. The preoperative complete blood count and biochemical parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, and NLR, were evaluated in both groups.

Statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA). Normality of the distribution of the variables was assessed using Shapiro-Wilk test. The descriptive results were expressed as mean ± SD. Normally distributed data were compared between groups using independent samples t-test, while data with skewed distribution were compared with Kruskal Wallis test. Statistical differences were accepted as significant when p-value was <0.05.

**Results**

The clinical and basic demographic features are shown in Table 1. Of the 253 patients who were finally included in this study, 40 of the patients were in the malignant group, whereas 213 of them were classified as benign thyroid group. Malignant group consisted of 2 (5%) anaplastic thyroid carcinoma, 4 (10%) medullary thyroid carcinoma, 10 (25%) follicular thyroid carcinoma, and 24 (60%) papillary thyroid carcinoma patients. The mean age of the patients in the benign and malignant groups was 52.4 ± 11.7 and 55.8 ± 13.5, respectively. The percentages of female patients in benign and malignant groups were similar (86.1% in benign group and 87.5% in malignant group).

There were no significant differences between the benign and malignant thyroid disease groups with respect to age, gender, and laboratory values such as liver function tests, serum urea levels, creatinine levels, white blood cell count, hemoglobin levels and mean platelet volume (Table 1).

The mean neutrophil count was higher and the mean lymphocyte count was lower in the malignant group than in the benign group. Thus, NLR was significantly higher in the malignant thyroid disease group in comparison with the benign thyroid disease group (p < 0.001) (Figure 1).

**Discussion**

This study investigated the validity of NLR as a predictive marker for malignant diseases of the thyroid. Forty of
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the patients, which are categorized as malignant thyroid disease group, had significantly higher neutrophil counts and lower lymphocyte counts compared to the patients with benign thyroid disease. In cancer patients, a low lymphocyte count has been associated with suppression of immunity [11], whereas a high neutrophil count has been related to paraneoplastic activity of the tumor and production of granulocyte colony-stimulating factor [9]. Therefore, elevated NLR levels are associated with low immunity levels in cancer patients.

Multiple studies indicate that carcinogenesis causes chronic inflammation, which results in an increase in the levels of inflammatory markers such as C-reactive protein and NLR [12, 13]. Moreover, inflammation and carcinogenesis are closely associated with impaired immunity [14]. Thus, in the current study the elevated NLR in malignant patients was thought to be related to the inflammatory response to the cancer.

NLR has been suggested as a marker of inflammatory conditions including cardiac disorders, malignant diseases, neurological disorders, vertigo, systemic diseases such as diabetes mellitus, rheumatologic disorders, hypertension, and renal failure [15–17]. Several studies showed that there is a strong correlation between inflammation and malignancy and have investigated the significance of NLR as a predictive marker in malignant diseases [9, 18, 19]. Dutta et al. [20] investigated the significance of NLR in gastric cancer patients and showed that high NLR values were associated with poor survival. Yao et al. [21] investigated the prognostic value of NLR in breast cancer and found that patients with higher NLR values had significantly lower survival. However, in the present study, we were unable to confirm this data as we did not investigate the association between survival and the NLR values.

Several studies have introduced the importance of NLR values in differentiating between malignant and benign conditions [22, 23]. Kum et al. [22] investigated NLR values for differentiating laryngeal squamous cell carcinoma from benign and precancerous laryngeal lesions and reported that the NLR values in patients with laryngeal squamous cell carcinoma and precancerous laryngeal lesions were significantly higher than those in patients with benign laryngeal lesions. Further, Yildirim et al. [23] investigated the role of NLR in the early diagnosis of malignant ovarian masses. They found that NLR is a novel marker for distinguishing between benign and

Table 1: Laboratory findings and demographic features of the study participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Benign group (n=213)</th>
<th>Malignant group (n=40)</th>
<th>p-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.4±11.7</td>
<td>55.8±13.5</td>
<td>0.105</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>86.1</td>
<td>87.5</td>
<td>0.734</td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>25.6±7.8</td>
<td>25.7±5.8</td>
<td>0.924</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8±0.2</td>
<td>0.8±0.1</td>
<td>0.275</td>
</tr>
<tr>
<td>AST</td>
<td>23.0±6.9</td>
<td>23.8±6.8</td>
<td>0.471</td>
</tr>
<tr>
<td>ALT</td>
<td>28.9±7.1</td>
<td>30.1±5.7</td>
<td>0.315</td>
</tr>
<tr>
<td>WBC (10³/mm³)</td>
<td>6.5±2.1</td>
<td>7.1±2.5</td>
<td>0.081</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>13.4±1.4</td>
<td>13.5±0.9</td>
<td>0.770</td>
</tr>
<tr>
<td>Platelet count (10³/mm)</td>
<td>262.6±66.1</td>
<td>252.7±67.5</td>
<td>0.384</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.7±1.0</td>
<td>8.8±1.3</td>
<td>0.746</td>
</tr>
<tr>
<td>Neutrophil count (10⁹/L)</td>
<td>4.1±1.4</td>
<td>5.6±2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte count (10⁹/L)</td>
<td>2.3±0.8</td>
<td>1.9±0.6</td>
<td>0.003</td>
</tr>
<tr>
<td>NLR</td>
<td>2.1±1.2</td>
<td>3.1±1.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio. *p-Values <0.05 indicate significance.

Figure 1: Graphical view of the neutrophil-lymphocyte ratio in patients with benign and malignant thyroid disorders.
malignant ovarian masses. In the present study, we also investigated the value of NLR as a marker for distinguishing between benign and malignant thyroid diseases and found that thyroid carcinomas had higher NLR values than benign thyroid disorders.

The relationship between NLR and thyroid cancer were also reported earlier. Seretis et al. [9] found that higher NLR values were associated with a higher risk of papillary thyroid microcarcinoma and showed that NLR values were markedly increased in patients with incidental papillary thyroid microcarcinoma. The patient population consisted of 26 patients with benign goiter, 31 patients with incidental papillary thyroid microcarcinoma, and 26 patients with thyroid carcinoma. In the present study, we investigated a larger series of patients with malignant thyroid disease, as well as, a larger series of patients with benign thyroid disease. Yet, we did not divide the thyroid cancers into subgroups such as papillary, follicular, medullary and anaplastic cancers.

In another study on papillary thyroid carcinoma, Kim et al. [24] investigated the prognostic significance of NLR in patients with advanced papillary thyroid carcinoma and found that NLR was correlated with poor prognosis. They also reported that higher NLR values may be a negative prognostic marker for disease-free survival in patients with stage 3 and 4. However, no significant difference was found in NLR values between the patients with benign and malignant thyroid diseases [24]. This may have resulted from the study design which covered only thyroid papillary carcinoma cases in the malignant thyroid disease group. Our study, which includes almost all types of malignant thyroid diseases, indicated higher NLR values in patients with malignant thyroid diseases compared with benign cases.

The association between NLR and tumor size in patients with differentiated thyroid cancer was previously investigated by Liu et al. [25] who reported a correlation between the elevated NLR values and tumor diameter in patients with differentiated thyroid cancer. They also suggested an association between the high NLR values and high risk of recurrence according to the American Thyroid Association guidelines. Smaller sample size is the most obvious limitation of the present study since it seems necessary to statistically confirm the correlation between NLR and tumor diameter in a larger series of patients.

There have been some studies showing the relationship between NLR and benign thyroid disorders including multinodular goiter, Hashimoto’s thyroiditis and nodular goiter. Olt [26] reported that there is no significant association between NLR values and non-inflammatory disease of the thyroid (multinodular goitre), whereas Aksu et al. [27] suggested that NLR is a valuable parameter for monitoring Hashimoto’s thyroiditis as well as other autoimmune and chronic inflammatory diseases. Also, NLR values were found higher in lymphocytic thyroiditis [28]. Considering these previous studies, we preferred to compare the benign and malignant conditions rather than including the patients with multinodular goitre or thyroiditis.

To conclude, NLR was found to be significantly higher in malignant thyroid disease group than benign thyroid disease group in the present study. This is the first study showing the value of NLR as a marker for malignant thyroid diseases, including both the differentiated and undifferentiated types. However, further studies with larger series including both differentiated and undifferentiated thyroid cancers are needed to support these findings.

Conflict of interest statement: The authors have no conflict of interest.

References