

# Could Red Cell Distribution Width be a Marker of Thyroid Cancer?

Gulali Aktas<sup>1</sup>, Mustafa Sit<sup>2</sup>, Ibrahim Karagoz<sup>3</sup>, Edip Erkus<sup>1</sup>, Bahri Ozer<sup>2</sup>, Mehmet Zahid Kocak<sup>1</sup>, Semih Yaman<sup>2</sup>, Fatih Keyif<sup>2</sup>, Rabia Altinordu<sup>1</sup>, Hayri Erkol<sup>2</sup> and Haluk Savli<sup>1</sup>

## ABSTRACT

**Objective:** To study red cell distribution width (RDW) values, a novel inflammatory marker in routine hemogram, of patients with benign or malignant thyroid nodules and to compare with healthy population.

**Study Design:** Descriptive study.

**Place and Duration of Study:** Abant Izzet Baysal University Hospital, Bolu, Turkey, from November 2015 and February 2017.

**Methodology:** The hemogram values of patients undergone thyroid surgery for thyroid nodule between November 2015 and February 2017 were retrospectively analyzed, and compared to those in healthy subjects. Subjects with infectious or inflammatory diseases were excluded. Patients' characteristics and laboratory data were obtained from institutional computerized database. Preoperative hemogram values of thyroid nodule patients were recorded. One-way ANOVA and Kruskal-Wallis tests were performed to compare variables with significance at  $p < 0.05$ .

**Results:** Median RDW of malignant nodule group was 15.8 (12.9-19.5) and was significantly higher than both of those in benign nodule (15) and control groups (14), ( $p < 0.001$ ).

**Conclusion:** Elevated RDW in patients with thyroid nodules in preoperative period should alert the physician for possible malignancy and this cost-effective marker also can help support other modalities (ultrasound scan, and fine needle aspiration biopsy) to distinguish malignant from benign nodules.

**Key Words:** Thyroid nodule. Cancer. Inflammation. Red cell distribution width.

## INTRODUCTION

An important clinical issue in routine medical practice is classifying thyroid nodules as either malignant or benign. Population in iodine deficient regions may suffer from nodules in thyroid gland and the prevalence of these nodules may reach as high as 5%, especially in women.<sup>1</sup> The rate of thyroid nodules detected by ultrasound scan is even higher (19-68%).<sup>2</sup> Diagnostic challenge to investigate malignancy begins as soon as the detection of thyroid nodules, because a significant portion of these nodules are malignant.

Inflammatory markers have attracted great attention in clinical cancer research since inflammation has crucial role in cancer development.<sup>3</sup> For the sake of cost effectiveness, simple inflammatory markers have been developed by researchers. One of these markers is red cell distribution width (RDW), which refers the size variation of erythrocytes in a routine hemogram test. It is usually increased in iron deficiency anemia but novel studies suggest that RDW is also associated with conditions characterized with prominent or low inflammatory burden.<sup>4,5</sup> Because inflammation plays

crucial role in development of cancer, inflammatory status of the patients with thyroid nodules may help distinguish benign and malignant nodules.

It was hypothesized that RDW could be useful in differential diagnosis of thyroid nodules being whether benign or malignant. Therefore, the aim of the study was to analyze RDW of patients with thyroid nodules who underwent thyroid surgery; and to compare it with that in healthy population without thyroid nodules.

## METHODOLOGY

The subjects who underwent surgery for thyroid nodule at Abant Izzet Baysal University Hospital between November 2015 and February 2017 were included to the study. Institutional Directory Board approved the study. The patients were grouped into two, as either malignant nodule group or benign nodule group, according to the pathological examination of the surgical specimen of thyroid gland. Healthy volunteers without thyroid nodule were selected as control group from subjects visiting Outpatient Internal Medicine Clinics of the institution for a routine check-up.

Demographic features and laboratory data were obtained from computerized database of the Hospital. Preoperative haemogram values of thyroid nodule patients, white blood cell count (WBC), haemoglobin (Hb), haematocrit (Htc), mean corpuscular volume (MCV), platelet count (PLT), and RDW were recorded. Thyroid stimulating hormone (TSH), tri-iodo-thyronine (T3), and tetra-iodo-thyronine (T4) levels were also obtained to determine thyroid hormone status. Active

*Department of Internal Medicine<sup>1</sup> / General Surgery<sup>2</sup> / Anesthesiology<sup>3</sup>, Abant Izzet Baysal University Hospital, Bolu, Turkey.*

*Correspondence: Dr. Gulali Aktas, Associate Professor, Department of Internal Medicine, Abant Izzet Baysal University Hospital, Bolu, Turkey.*

*E-mail: draliaktas@yahoo.com*

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infection, diabetes mellitus, thyroiditis, any other type of malignancy, inflammatory diseases, were set as exclusion criteria. Patients on corticosteroid or aspirin treatment were also excluded.

Automatic analyzer of LH 780 model of Beckman Coulter Device (Beckman Coulter Inc.; Bre CA) was used for performing haemogram tests. Hemogram and other biochemical and pathological assays were conducted in laboratories of the University Hospital. Statistical analysis conducted by SPSS software (SPSS15.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean  $\pm$  SD or median (minimum-maximum). One-way ANOVA test (for homogeneously distributed variables) or Kruskal-Wallis test (for non-homogeneously distributed variables) used to compare variables between study groups. A p-value lower than 0.05 was set for statistically significance.

## RESULTS

Two hundred and forty-three patients were included to the study. Of these, 98 had malignant thyroid nodule, 84 had benign thyroid nodule and 61 were controls.

Demographic characteristics of the study groups were not statistically different. Mean age (minimum to maximum) of malignant nodule, benign nodule and control groups were 44 (22-72), 43.5 (26-60) and 43 (31-61) years, respectively ( $p=0.67$ ). Most of the study population (80.2%, 195 of 243) were women. Seventy-eight of the 98 (79.6%) in malignant nodule, 64 of the 84 (76.2%) in benign nodule, and 53 of the 61 (86.9%) in control group were women. The number of women and men in study groups was not statistically different ( $p=0.27$ ).

Most of the hemogram parameters, WBC ( $p=0.52$ ), Hb ( $p=0.67$ ), Htc ( $p=0.66$ ), MCV ( $p=0.10$ ) and PLT ( $p=0.24$ ) levels were not statistically different between study groups.

Median RDW of malignant nodule group [15.8 (12.9-19.5)] was higher than both those in benign nodule [15 (13-16.4)] and control groups [14 (12-16.2)]. The

**Table I:** General characteristics and laboratory data of the study groups.

	Groups			p
	Malignant nodule	Benign nodule	Control	
Gender				
Men (n, %)	20 (20.4%)	20 (23.8%)	8 (13.1%)	0.27
Women (n, %)	78 (79.6%)	64 (76.2%)	53 (86.9%)	
	Mean $\pm$ SD			
WBC (k/mm <sup>3</sup> )	6.7 $\pm$ 1.4	7.3 $\pm$ 1.9	7.2 $\pm$ 1.5	0.52
Hb (g/dl)	13.6 $\pm$ 1	13.6 $\pm$ 1.1	13.7 $\pm$ 1.2	0.67
Htc (%)	40 $\pm$ 3	41 $\pm$ 3	41 $\pm$ 4	0.66
MCV (fL)	87 $\pm$ 4	87 $\pm$ 4	86 $\pm$ 4	0.10
PLT (k/mm <sup>3</sup> )	250 $\pm$ 60	262 $\pm$ 61	263 $\pm$ 50	0.24
	Median (min-max)			
Age (years)	44 (22-72)	43.5 (26-60)	43 (31-61)	0.67
RDW (%)	15.8 (12.9-19.5)	15 (13-16.4)	14 (12-16.2)	<0.001
TSH (uIU/ml)	1.2 (0.1-4.2)	0.94 (0.1-4.3)	1.5 (0.3-4.3)	0.001

difference between groups was statistically significant ( $p<0.001$ ). Median RDW of benign nodule group was not significantly increased as compared to the RDW in control group.

Demographic characteristics and laboratory data of the study population is summarized in Table I.

A threshold of RDW higher than 14 has sensitivity and specificity of 78% and 63%, respectively in detecting thyroid nodules in ROC analysis. On the other hand, sensitivity and specificity of RDW higher than 14 was 76% and 38%, respectively, for detecting thyroid cancer.

## DISCUSSION

The main finding in present study is that the patients with malignant thyroid nodules have significantly greater RDW values. Because control subjects and benign thyroid nodule patients have similar RDW, it is suggested that neoplastic process caused increased RDW in patients with malignant nodules.

The close relationship between increased RDW and inflammation is a well-known entity. Studies in literature disclosed elevated RDW in rheumatoid arthritis, Hashimoto's thyroiditis, lupus, pneumonia, septic shock, and acute pancreatitis.<sup>6-13</sup>

Cancer and inflammation is closely linked to each other. Recent investigations about different cancer types established the association between inflammation and cancer.<sup>14-16</sup> It is not surprising that increased RDW was associated with malignant thyroid nodules in this study because of the relation between cancer and inflammation and utmost important role of RDW in inflammatory conditions.

To the best of the authors' knowledge, this is the first report in literature pointing the association between malignant nodules in thyroid gland and increased RDW. However, lung cancer, prostate cancer, and breast tumors have also been suggested to be related with elevation in RDW, apart from the malignant thyroid masses and colorectal cancer.<sup>17-20</sup>

Most of these studies also reported significant difference between study and control group in terms of Hb or Htc levels. That makes it less likely that the increased RDW is due to cancer itself and possible iron deficiency could contribute to that elevation in RDW. However, Hb and Htc levels were similar in both groups in this study population, which makes these results more reliable in the suggestion of cancer as the cause of increased RDW.

Inflammatory markers released in the blood flow from the inflammatory cells in tumor microenvironment may interact with the erythropoiesis in bone marrow and stimulate production of red blood cells of variable sizes. This may be the underlying mechanism of increased RDW in patients with thyroid malignant nodules. Another explanation of the increased RDW in malignant nodules

could be that secretory nodules of thyroid gland are less likely to be malignant.<sup>21</sup> Therefore, lower T4 levels are expected in malignant nodules compared to benign nodules. Literature data shows that T4 levels were inversely correlated with RDW values even in euthyroid patients.<sup>22</sup> Serum T4 levels were significantly lower in malignant thyroid nodule group compared to benign nodule and control groups in present study. On the other hand, study population was not grouped according to the type of the nodule (cold or warm, solitary or multiple).

Patients with benign nodule and healthy controls had similar levels of RDW in this study. It can be speculated that nodule development itself does not stimulate enough inflammatory burden to cause an elevation in RDW. Seretis *et al.* reported similar results in patients with breast cancer, as RDW of subjects with breast tumor was significantly higher than the RDW of the patients with fibroadenomas.<sup>20</sup> The increase in RDW might be stimulated by malignancy.

Although RDW increases in patients with benign thyroid nodules and much more increase in malignant nodules compared to control subjects, sensitivity and specificity of RDW was better in detecting thyroid nodules whether benign or malignant.

Naturally, the present study has two major limitations which make these results difficult to interpret. First, there is a relatively small number of the study population, and the second the retrospective design that may induce selection bias.

## CONCLUSION

Elevated RDW in patients with thyroid nodules in preoperative period should alert the physician for possible malignancy. This cost-effective marker can also help support other modalities (ultrasound scan, fine needle aspiration biopsy, etc.) to distinguish malignant from benign nodules.

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