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Can eosinophil to monocyte ratio be a new marker for recurrence in graves' disease?

Ozden Ozdemir Baser[1], Derya Koseoglu[2], Merve Catak[3]

[1]Yozgat City Hospital, Department of Endocrinology and Metabolism, Yozgat, Türkiye
[2]Hitit University Erol Olcok Education and Research Hospital, Department of Endocrinology and Metabolism, Corum, Türkiye
[3]Gaziosmanpasa University, Department of Endocrinology and Metabolism, Tokat, Türkiye

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Abstract

Prognostic parameters are crucial in the choice of treatment in Graves' disease (GD), thus,these parameters may not be easily achievable in all situations. However hematological parameters is important in inflammation and easy to obtain. In this study we aimed to elucidate whether these parameters could determine the prognosis in patients with Graves Disease. This retrospective analysis consisted of 114 individuals with a diagnosed with GD. The enrolled patients were treated with anti-thyroid drugs for an average of 14 months and the mean follow-up period after treatment discontinuation was 17.4 months. After the follow-up period subjects have been segmented to 2 groups as: Group 1 relapsed (n:61) and Group 2 non-relapsed (n:53). The neutrophil to lymphocyte ratio (NLR) of the relapsing individual was statistically significantly higher compared to other group, while the eosinophil to monocytes ratio (EMR) was lower. In the multiregression analysis, both parameters were found to be independent risk factors in predicting relapse [(OR=3.1, p:0.026 for NLR) (OR=1.5, p<0.001 for EMR)]. In addition, a value of 0.17 EMR had 70% sensitivity and 80% specificity in determining recurrence. EMR was found to be an independent predictor of prognosis with high specificity. The calculation of EMR before initiating treatment could provide beneficial outcomes for the choice of treatment in patients with GD.

Keywords: Graves' disease, neutrophil to lymphocyte ratio, eosinophil to monocytes ratio, prognostic parameters, hematological parameters

Introduction

Graves' disease (GD), is an autoimmune disorder and it is the most common cause of hyperthyroidism and it is characterized by increased thyroid hormone synthesis. Treatment options can be elaborated as: antithyroid drugs (ATDs), radioactive iodine (RAI) and total thyroidectomy [1]. Thyroid surgery is preferred in cases with large goiter, suspected malignancy, and recurrent disease. Recurrence rates are 52% with ATD and 15% with RAI [1]. Increased thyroid volume, presence of orbitopathy, smoking, thyrotropin receptor antibodiy (TRAb) positivity, increased free thyroxin (FT4) and total triiodothyronine (T3) levels are risk factors associated with recurrence. Independent risk factors are young age, high serum TRAb and FT4 levels, larger goiters, PTPN22 C/T polymorphism, and presence of HLA subtypes DQB1*02, DQA1*05, and DRB1*03 [2]. Risk factors indicating relapse are important in the choice of treatment. However, not all of these risk factors can be evaluated in routine examinations. For this reason, it is important to find parameters that will predict recurrence in routine blood tests which may lead to appropriate treatment selection. In recent studies, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have been reported as an important marker in inflammatory diseases and malignancies [3,4]. The hematopoietic system may be affected due to both the type 2 hypersensitivity reaction of GD and the effect of excessively increased thyroid hormones in the serum [5]. Therefore, these changing parameters were used in the diagnosis of GD to distinguish it from other thyrotoxicoses. However, there are not enough studies predicting recurrence with hematological parameters. In a study by Kim et al. on this subject, NLR was found to be an independent risk factor in showing recurrence [6]. Regarding this fact that there are not sufficient studies predicting recurrence with hematological parameters up to date we aimed to elucidate the prognostic effects and recurrence predictivity of these parameters in patients with Graves' disease.

***Corresponding Author:** Ozden Ozdemir Baser, Yozgat City Hospital, Department of Endocrinology and Metabolism, Yozgat, Türkiye
E-mail: ozdemir.83@hotmail.com

Materials and Methods

Patients and Treatment

The study included 114 newly diagnosed or previously treated Graves patients who applied to Hitit University Erol Olçok Education and Research Hospital between 01.02.2017-30.06.2021, and Tokat State Hospital between 27.11.2018-01.02.2021. Demographic data (age, gender, smoker, drugs used) and biochemical values of the individuals were retrospectively obtained from patient files. Laboratory parameters of the patients when they were diagnosed with GD were recorded from the hospital database before initiating ATDs.

The diagnosis of GD has been performed viaincreased serum FT3 and FT4 levels, suppressed thyroid stimulating hormone (TSH) concentration, TRAb positivity, increased diffuse involvement in technetium scintigraphy, hypervascular and hypoechoic thyroid gland in thyroid ultrasonography and presence of orbitopathy [2,7]. Orbitopathy was diagnosed according to the diagnostic criteria of the European Group on Graves' Orbitopathy (EUGOGO) [8]. Smoking status and thyroid gland sizes of the patients were recorded. Thyroid ultrasonography was performed with high resolution B mode US images (Hitachi EUB 8500) with a 12-MHz linear array transducer. Thyroid gland volume was calculated via anterior-posterior diameter x transverse diameter x longitudinal diameter x 0.52 [9].

All patients diagnosed with GD were treated with methimazole (MMI) or propylthiouracil (PTU) for a mean period of 14 months. The average dose of MMI was 15-20mg (maximum dose 60mg), and the average dose of PTU was 300-600mg. PTU treatment was initiated in patients who could not tolerate MMI, had allergic skin reaction, and elevated liver function tests [1].

MMI was the first choice of treatment. The longest follow-up period of the patients with treatment discontinuation was 32 months and the shortest monitoring has been conducted for 6 months. The least expected time for recurrence was 6 months. The mean follow-up period of the patients after discontinuation of ATDs was 17.4 months. Remission has been as euthyroid status, and no recurrence during the follow-up period after drug discontinuation. Relapsed subjects were those who reapplied with hyperthyroidism due to Graves' disease during the follow-up period.

Individuals >18 years of age or pregnant women, patients who had any cardiovascular or cerebrovascular disease, renal or liver failure, hematological or solid organ malignancy, immunological diseases, infectious diseases, inflammatory or autoimmune disorders except GD, active infections were excluded from the analysis. Additionally patients on any kind of medication that affects hemogram parameters were also excluded. Other patients excluded from the study are those who underwent thyroid surgery or RAI due to the side effects of ATDs, patients who do not use ATDs regularly, and patients who do not attend regular doctor visits.

Biochemical parameters and Assays

TSH (0.55-4.78mIU/mL), FT4 (0.89-1.76ng/dL), FT3 (2.3-4.2pg/ml), acetylaminotransferase (AST 0-35u/L), alanine aminotransferase (ALT 0-35u/L), gamma glutamyltransferase (GGT 0-38u/L), alkaline phosphatase (ALP 30-120u/L) results during diagnosis and last admission were obtained from patient files. TSH, FT4 and FT3 were processed with the Electro Chemiluminecance Immune Assay (ECLIA) method (by Beckmann Coulter DXI 800). Hematological parameters were measured with standard complete blood count (CBC) device. NLR with neutrophil and lymphocyte, PLR with platelet and lymphocyte, MLR with monocyte and lymphocyte, and eosinophile to monocyte ratio (EMR) with eosinophile and monocyte were calculated. The hematological parameters obtained are the values before the initiation of ATDs. The TRAb, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies present at the first admission as well as the TRAb levels at the end of the treatment were recorded. The TRAb elisa method was performed (Medizym T.R.A. human, Medipan GmbH, Germany). While the TRAb reference range was 0-14IU/L, anti-TG and anti-TPO were taken as positive and negative.

Statistics analysis

The statistical analysis has been conducted via SPSS 20 (IBM Corp, Armonk, NY, USA) software. Data has been elabrated as mean ±standard deviation and percentiles. The distribution of normality data has been determined with the help of Kolmogorov-Smirnov test. Numerical evaluation (three-group comparisons) has been analyzed by non-parametric Kruskal–Wallis test. In terms of comparison analysis non-parametric Mann–Whitney U test has been utilized for two-group comparisons of non-normally distributed numerical data. The parametric Student's T-test was preferred for normally distributed numerical data. Independent parameters to determine recurrence in GD were analyzed by univariate and multivariate logistic regression analysis. ROC curve analysis has been performed in order to assess with laboratory parameters as diagnostic tests and to calculate cut-off values in 95% confidence intervals (CI). P value <0.05 has been considered statistically significant.

Results

Between the specified periods, 197 GD cases were accepted into our study. Of these cases, 114 (57.9%) met the inclusion criteria (Figure 1). These patients were divided into group-1 as non-recurring patients (n:53) and group-2 as relapsed patients (n:61) after an average of 14 months of ATDs treatment. The mean time to recurrence was 10 months. Demographic data and laboratory data of both groups were compared in Table-1.

When the hematological parameters of both groups were evaluated, lymphocyte and eosinophil count were found to be statistically significantly decreased in relapsed than other group ($p<0.05$). While NLR, MLR were high in patients with relapse, EMR was lower in this group. There was no statistically significant difference between the groups in other parameters (Table-2).

The multivariate logistic regression analysis in patients with relapse revealed that EMR and NLR were independent risk factors for relapse relapse [(OR =3.1, p:0.026 for NLR) (OR =1.5, $p<0.001$ for EMR)] (Table-3).

When ROC analysis was performed on independent risk factors, it was seen a value of 0.17 EMR had 70% sensitivity and 80% specificity in determining recurrence (AUC=0.736, $p<0.001$). (Table-4 and Figure-2).

Table 1. Clinical features of Graves' patients.

	Grup-1 Nonrelapse n=53	Grup-2 Relapse n=61	P
Age (years)	44±11	46±16	0.535
Sex, Male	20 (37.7%)	26 (42.6%)	0.596
Smoker	2 (3.8%)	17 (28.3%)	0.002
TRAb	36.98±17.98	60.78±56.21	0.420
Anti TPO (Positive)	27 (50.9%)	32 (52.5%)	0.872
TSH (mIU/L)	0.052±0.096	0.024±0.44	0.047
FreeT3 (pg/ml)	8.31±4.83	16.14±5.60	<0.001
FreeT4 (ng/dL)	2.70±1.86	4.51±1.22	<0.001
ALT	25.28±12.83	27.26±16.66	0.829
AST	22.00±8.76	25.37±8.98	0.023
FT3FT4R	3.23±0.92	3.59±0.75	0.026
Right thyroid volume, mL (mm^3)	11132.74±6476.17	19153.64±16900.66	0.007
Left thyroid volume, mL (mm^3)	9720.29±5129.81	18548.05±12666.20	<0.001

TRAb: thyrotropin receptor antibody, Anti-TPO: thyroid peroxidase antibody, TSH: thyroid-stimulating hormone, Free T3: Free triiodothyronine, FreeT4: Free thyroxin ALT: alanine aminotransferase, AST: acetylaminotransferase, FT3FT4R: freeT3-to-freeT4 ratio. **P-value, calculated by chi-square (for categorical variables; age), Student t test (for parametric variables), and Mann Withney U test (for nonparametric variables). P<0.05 is significant.

Table 2. Hematological parameters in the diagnosis of Graves' disease

	Grup-1 Nonrelapse n=53	Grup-2 Relapse n=61	P
Leukocyte (10^3/µL)	6976.98±1502.72	6968.69±2249.86	0.402
Neutrophil (10^3/µL)	3921.32±1189.36	4161.15±1742.32	0.656
Lymphocyte (10^3/µL)	2283.77±567.89	2009.67±543.82	0.006
Monocyte (10^3/µL)	578.49±162.79	651.64±262.71	0.251
Eosinophil (10^3/µL)	168.62±145.43	78.69±43.07	<0.001
Platelet (10^3/µL)	265.32±60.74	263.79±72.01	0.725
MPV	10.02±0.94	9.85±0.99	0.150
NLR	1.81±0.72	2.15±0.94	0.027
PLR	0.12±0.04	0.14±0.05	0.051
MLR	0.27±0.12	0.34±0.15	0.004
EMR	0.31±0.28	0.13±0.07	<0.001

MPV: mean platelet volume, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, EMR: eosinophil-to-monocyte ratio, **P-value, calculated by chi-square (for categorical variables; age), Student t test (for parametric variables), and Mann Withney U test (for nonparametric variables). P<0.05 is significant.

Table 3. Multivariate and univariate logistic regression analysis of parameters contributing to relapse in patients with relapse.

	Multivariate			Univariate		
	B	**P**	**OR**	**B**	**P**	**OR**
Lymphocyte (10^3/µL)	-0.001	0.380	1.0	-0.001	0.013	1.0
Eosinophil (10^3/µL)	0.000	0.977	1.0	-0.013	0.000	1.0
NLR	1.134	0.026	3.1	0.530	0.042	1.7
MLR	3.189	0.479	0.0	4.029	0.013	1.6
EMR	-0.402	<0.001	1.5	-0.322	<0.001	1.4
TSH (mIU/L)	8.757	0.071	6.4	-5.575	0.061	0.0
FT4 (ng/dL)	7.682	0.393	0.0	9.171	<0.001	0.0
FT3 (pg/ml)	0.128	0.642	1.1	0.863	<0.001	2.4

NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, EMR: Eosinophil-to-monocyte ratio, TSH: Thyroid-stimulating hormone, Free T3: Free triiodothyronine, FreeT4: Free thyroxin

Table 4. ROC curve characteristics of prognostic factors.

	Auc	Se	P	95% Ci	Cutoff Value	Sensitivite %	Spesifite %
EMR	0.736	0.051	<0.001	0.64-0.84	0.17	70%	80%
NLR	0.621	0.053	0.027	0.517-0.724	1.80	62%	58%

ROC, Receiver operating characteristic, AUC: area under curve, SE: standart eror, Cl: confidence interval, EMR: eosinophil-to-monocyte ratio, NLR: neutrophil-to-lymphocyte ratio

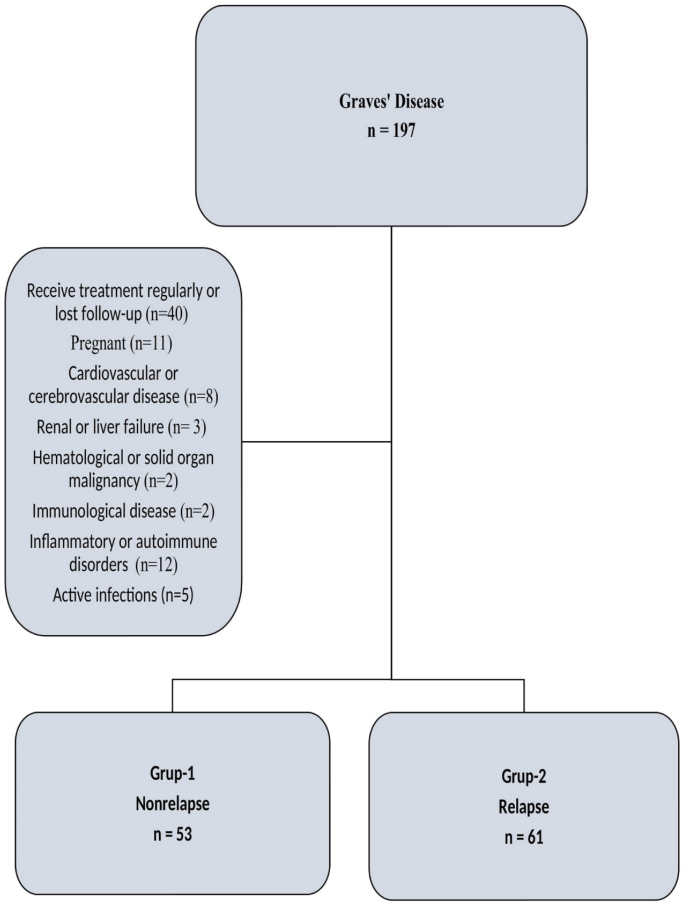

Figure-1. Details of the sample size distribution (Flowchart)

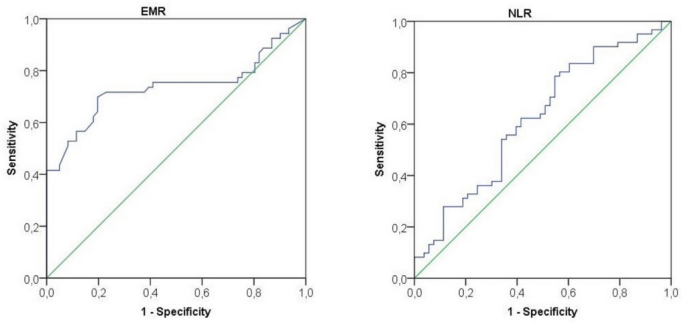

Figure-2. ROC curve analysis for EMR and NLR

Discussion

In this study, hemogram parameters of patients with recurrent GD and non-recurring GD has been compared. While NLR and MLR were statistically increased in relapsed Graves' study group compared to non-relapsed patients, lymphocyte count, eosinophil count, and EMR were statistically significantly lower in the relapsed study population compared to other group. It has also been shown that EMR and NLR are independent risk factor in increasing the risk of recurrence. When evaluated by ROC analysis, 0.17 value of EMR was found to predict recurrence with 70% sensitivity and 80% specificity.

As it is known GD is a type 2 hypersensitivity reaction and autoantibodies that attack against cell surface receptors are held responsible [10]. These patients have all types of T lymphocytes in their thyroid glands and GD is thought to be a mixture of autoimmune responses of T helper-1 (Th1), Th2 Thelper-2 (Th2) and B lymphocytes [11]. As a result of cytokines released from Th lymphocytes, other leukocytes such as neutrophils, eosinophils and monocytes migrate to the site of inflammation [12,13]. Eventually changes occur in hemogram parameters due to both the effects of thyroid hormones on the hematopoietic system and inflammation. Therefore, hemogram parameters have been studied in many thyroid diseases.

In a study investigating the role of hemogram parameters in the diagnosis of GD, it was observed that NLR was low and improved with treatment, unlike other autoimmune events[14]. This has been attributed to the effects of thyroid hormones on the hematopoietic system. Taşkaldıran et al. published that NLR, PLR, MLR were statistically significantly different from other causes of thyrotoxicosis and the control group in subacute thyroiditis (SAT). They also found that MLR was significantly higher in GD than the toxic adenoma and control group [15]. In the study of Çetin et al., NLR and PLR were found to be statistically significantly higher in SAT patients. However, no significant relationship was found between other thyrotoxicosis including GD [16]. In most of the studies, these ratios have been used in the differential diagnosis of thyrotoxicosis, and there is not enough study about the place of GD in the prognosis. For this purpose, recently Kim et al. divided Graves' patients into two groups as low and high NLR in their study and concluded that high NLR is associated with relapse [17]. In this study, it was stated that hematological changes actually depend on the immune mechanism and neutrophils were responsible for the initiation and maintenance of inflammation. Similarly, statistically significantly higher rates were found in the group with NLR and MLR recurrence in our study. ($p<0.05$). As far as we know no research other than these two studies investigating the relationship between recurrence and hematological parameters in GD and identifying elevated NLR has been published yet.

In our study, although the eosinophil concentration of the individuals in Group-2 was statistically significantly lower than group-1 ($p<0.05$), the monocyte levels were similar in both groups. EMR was statistically significantly lower in patients with relapse and was found to be an independent parameter indicating relapse. Hidaka et al. found that relapses in GD were related to increased peripheral eosinophil level and TRAb after episodes of allergic rhinitis. As a result, they suggested that GD is a Th2 dominant disease. In addition, Hidaka et al. stated that increased serum Ig E, higher TRAb levels in patients with elevated IgE levels, and peripheral eosinophilia was observed in GD patients [18]. This may be attributed to the synthesis of IgE by interleukin 4 released from Th2 cells and the stimulation of eosinophil development by IL-5 released from Th2 cells [19,20]. They also reported that intrathyroidal lymphocytes were more than peripheral lymphocytes in this study. Hu et al. conducted another study evaluating serum eosinophil, monocyte, and monocyte-to-eosinophil ratio (MER). In this study, eosinophil level was found to be higher in GD than in SAT. In that study, individuals with GD and SAT were grouped into 2 as moderate and severe. MER was elevated in the severe GD group compared to moderate GD study population, but the statistical significance has not been revealed [21]. Additionally monocyte and eosinophil concentrations of patients with moderate and severe course were not identified in their study leading to the fact that it is not clear whether the MER was high in severe GD due to high monocyte or low eosinophil levels. In our analysis we

have observed a statistically significant decrease in EMR in the group which developed relapse. The reason for this was the low eosinophil count in the relapsed group and we concluded this fact as the difference between our research and other studies. Migration of eosinophils to the thyroid gland may increase with the effect of cytokines secreted by increased intrathyroidal lymphocytes. As a result intrathyroidal eosinophil infiltration, growth and proliferation can be observed in thyrocytes due to the secretion of cytokines such as transforming growth factors (TGF)-alpha and –beta that remodel tissue, and mediators such as platelet-activating factor (PAF). This situitation may be the cause of relapse. In order to evaluate the increase in intrathyroidal eosinophil concentration, examination of thyroid tissue samples of patients with and without relapse might elaborate more comprehensive outcomes. ROC analysis was performed to determine the cut-off in patients with relapse. Since EMR was found to be statistically low and it was an independent risk factor for relapse, a value of 0.17 was found to determine recurrence with 70% sensitivity and 80% specificity. The major outcome of this researchwas that EMR is an independent risk factor and has a cut-off value for recurrence. It should be emphasized that EMR is easy to obtain and fairly beneficial to determine the prognosis of the disease and the choice of treatment.

No significance has been observed between the groups in TRAb levels, which is one of the prognostic factors in Graves' disease. However, smoking, thyroid gland size and FT3/FT4 ratio, which are among the other prognostic factors, were statistically significantly higher in the relapsed group [1,17].

The main limitation of this study could be attributed to its retrospective nature. The follow-up period after discontinuation of ATDs could have been a little longer however, there are not enough studies comparing recurrence and hematological parameters in GD, and the results of our research are important in this aspect.

Conclusion

In conclusion, our study shows that EMR is a suitable diagnostic tool in demonstrating relapse in GD. Calculation of EMR may be useful for deciding treatment strategies at the time of diagnosis. NLR and MLR were found to be higher in patients with recurrence. Since these parameters are easy to obtain, cost-effective and routinely analyzed in daily practice clinicians should consider their importance. However, these results need to be supported by further controlled studies with larger sample size.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
The study protocol was approved by the local ethics committee of Hitit University, Faculty of Medicine, Corum, Turkey (ethic number: 478).

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