Original Article

PLATELET-LYMPHOCYTE RATIO AS A NOVEL SURROGATE MARKER TO DIFFERENTIATE THYROTOXIC PATIENTS WITH GRAVES DISEASE FROM SUBACUTE THYROIDITIS: A CROSS-SECTIONAL STUDY FROM SOUTH INDIA

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ABSTRACT

Objective: Graves disease (GD) and the toxic phase of subacute thyroiditis (SAT) have similar clinical and biochemical presentations, and differentiating them requires sophisticated investigations. Since thyroid hormones have been noted to affect all hematologic cell lines, we have used the platelet lymphocyte ratio (PLR)—an index usually utilized in inflammatory or malignant disorders—to compare patients with and without thyrotoxicosis and to analyze its use in distinguishing between patients with GD and SAT prior to therapy.

Methods: This was a cross-sectional study conducted in the Department of Endocrinology, Christian Medical College, Vellore, India. During the study period, 800 patients with features of thyrotoxicosis visited the outpatient clinic. Those who had thyroid radioiodine (^{131}I) uptake (RAIU) study and complete blood count (CBC) at diagnosis were included (N = 500). Based on the RAIU values, these were divided as GD (n = 354) and SAT (n = 146). Baseline characteristics, thyroid function tests, and components of the CBC and PLR were obtained. The data were compared with a group of 250 matched euthyroid controls. Analyses were performed using SPSS version 21.0 software.

Results: PLR showed significant reductions in both GD and SAT patients when compared to euthyroid controls (P = .01), with greater reductions seen in GD than SAT (74.5 ± 19 vs. 84.4 ± 26; *P* = .01). Using receiver operating characteristic analysis of PLR, an optimal PLR cut-off of 70.4 was found to differentiate GD from SAT with a sensitivity of 86% and specificity of 74%.

Conclusion: PLR can be used as a novel surrogate marker to differentiate between patients with GD and SAT prior to therapy, especially in resource-limited settings. **(Endocr Pract. 2020;26:939-944)**

Abbreviations:
AUC = area under the curve; **BMI** = body mass index; **CBC** = complete blood count; **GD** = Graves disease; **MCV** = mean corpuscular volume; **PLR** = platelet-to-lymphocyte ratio; **RAIU** = radioiodine uptake; **ROC** = receiver operating characteristic; **SAT** = subacute thyroiditis; **T3** = triiodothyronine; **T4** = tetraiodothyronine; **TSH** = thyroid-stimulating hormone; **TSHRAb** = thyroid-stimulating hormone receptor antibody; **WBC** = white blood cell

INTRODUCTION

The thyroid gland and its hormones are critical determinants of metabolic activity (1). Two common conditions associated with its dysfunction are Graves disease (GD) and chronic autoimmune thyroiditis. The toxic phase of subacute thyroiditis (SAT) is often difficult to differentiate from GD due to their similar clinical and biochemical presentations, though inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein (CRP) are found to be elevated more often in patients with

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SAT than GD (1). These two conditions can ideally only be differentiated based on an ^{131}I uptake study or serum levels of thyroid-stimulating hormone receptor antibodies (TSHRAbs) (2), both of which are expensive and not universally accessible tests. Studies with color Doppler of the thyroid gland have shown promising results in differentiating GD from destructive thyroiditis, painless thyroiditis, and thyrotoxicosis factitia (3). However, thyroid ultrasonography remains inconclusive in SAT and early phases of Hashimoto thyroiditis, where any degree of vascularization is possible, rendering the differential diagnosis a challenging one (4). Therefore, finding an alternate, cheaper, and readily available surrogate marker to differentiate the two conditions may be useful in resource-limited settings.

The prevalence of hyperthyroidism in India, in a population-based study in Kerala, was found to be 3%, and of those with thyroid dysfunction, around 22% were seen to have hyperthyroidism (5). Thyroid hormones affect the function of virtually every organ system, including metabolism and proliferation of blood cells. The effect induced by thyrotoxicosis on various blood cell lines is most often not clinically manifested. An association between a reduced total leukocyte count, relative and absolute neutropenia in thyrotoxicosis due to GD, when compared with healthy subjects, has been recognized, along with a relative lymphocytosis (6). An increase in erythropoiesis has been proposed as well, with no clear change in the hematocrit (7). At the same time, a reduction in platelets has been associated with thyrotoxicosis (8).

The platelet to lymphocyte ratio (PLR), like the neutrophil to lymphocyte ratio, is a commonly used marker of subclinical inflammation. Due to their simplicity, they have been used in many medical conditions (9) and are obtained from the complete blood count (CBC). The PLR has also been noted to provide good prognostication information and is being used as a mortality indicator in various cardiovascular diseases, infections, inflammatory conditions, and certain malignancies (10-16), but its application in thyroid disorders is still being studied. In view of the hematologic changes that have been reported in patients with thyrotoxicosis and the need for a surrogate marker to differentiate GD, an autoimmune condition, from SAT, which is inflammatory in nature, we considered exploring the utility of the PLR in patients with benign thyrotoxic disease.

The aim of our study was to compare the PLR between patients with thyrotoxicosis (GD and SAT) and euthyroid controls. In addition, to further analyze its use in distinguishing GD from SAT, we also aimed at deriving a cut-off for the PLR that could suitably differentiate between patients with GD and SAT.

METHODS

We conducted a cross-sectional study in the Department of Endocrinology, Christian Medical College, Vellore, between December 2016 and December 2018, based on a retrospective review of the medical records of all patients attending the thyroid clinic outpatient department (OPD) during that period. The hospital records of the patients were obtained through the centralized hospital information processing services. The demographic, clinical, biochemical, treatment, and radionuclear imaging data of all the patients were analyzed. The study was approved by the institutional review board (no. 20719).

The clinical assessment of the patients included duration of symptoms of thyrotoxicosis, presence of a goiter and ophthalmopathy with clinical activity score, dermopathy, and other thyrotoxicosis-related systemic manifestations. Laboratory parameters including thyroid-stimulating hormone (TSH) (normal, 0.5 to 4.5 IU/L), total tetraiodothyronine (T4) (normal, 4 to 12 μg/dL), free tetraiodothyronine (FT4) (normal, 0.8 to 2 ng/dL), total triiodothyronine (T3) (normal, 90 to 190 ng/dL), thyroid peroxidase antibodies (TPOAbs) (normal, <50 IU/mL), and TSHRAbs were obtained from the clinical workstation, which had password-protected unique access for the authors. Thyroidal hormonal profile and TPOAb evaluation was done using a chemiluminescent immunoassay in which the interassay and intra-assay coefficients of variation (CVs) were less than 4%. TSHRAbs were measured using a third-generation solid-phase competitive chemiluminescent immunoassay (CobasR6000; Roche Analyzer). The interassay CV was 3.2% at 17.1 IU/L and 4.8% at 5.3 IU/L. The lower limit of detection was 0.3 IU/L, and the upper limit of detection was 40 IU/L. Details of ^{131}I-uptake percentages were obtained at 2 (normal, 8 to 17%), 6 (normal, 13 to 25%), and 24 (normal, 23 to 40%) hours in subjects who underwent thyroidal radioiodine uptake (RAIU) study using ^{131}I isotope tracer. Amongst subjects with clinical evidence of thyrotoxicosis with biochemical findings of subnormal TSH with a normal or elevated T4, FT4, and/or T3 at first presentation, those with an elevated RAIU (>17% at 2 hours, >25% at 6 hours, and >40% at 24 hours) were designated as GD, while those with suppressed uptake were designated as SAT. All patients aged >18 years who were diagnosed to have GD or SAT were included in the study. Of the 6,002 patients who visited the endocrinology-thyroid clinic OPD during the study period, 5,202 were hypothyroid. Amongst the remaining subjects with clinical and biochemical features of thyrotoxicosis (n = 800), only those who had documented ^{131}I thyroid uptake study and CBC (including platelets) prior to initiation of therapy, along with no features of any other serious concurrent illnesses, active infections, or malignancy, were included (n = 500) and divided into two groups based on the RAIU values: GD (n = 354) and SAT (n = 146). The data were compared with a group of 250 age-, gender-, and body mass index (BMI)-matched healthy controls.

The subjects were thus divided into three groups: untreated GD (Group 1), SAT (Group 2), and euthyroid

healthy controls (Group 3). Along with the baseline characteristics and thyroid function tests, components of the CBC such as hemoglobin, total leukocyte count, platelet count, and lymphocyte count were also compared. The PLR was calculated from the CBC and compared between the three groups.

Statistical Analysis

Analyses were performed using SPSS version 21.0 software (SPSS Inc, Chicago, IL). Between-group comparisons for quantitative variables were performed using Student's *t* test and Mann-Whitney *U* test according to a normal or a nonparametric distribution of data. One-way analysis of variance and the Kruskal-Wallis test were used to compare more than two groups. Chi-square test was used to compare categorical variables, using Fisher's correction when appropriate. A *P* value ≤.05 was considered significant. Receiver operating characteristic (ROC) curves were constructed to derive cut-off values of the PLR for diagnosing GD. An area under the curve (AUC) ≥0.5 was considered significant.

RESULTS

The baseline characteristics of Group 1, Group 2, and Group 3 are outlined in Table 1. The mean age, BMI, and gender distribution were similar in all three groups, with no significant differences. As expected, the TSH was significantly lower in Group 1 and Group 2 compared to the controls, while total and FT4 were significantly higher. However, these were not significantly different between the GD and SAT subjects (*P* = .11), though numerically greater biochemical derangement was seen in the GD group. The hematocrit was lower in patients with thyrotoxicosis (GD and SAT), and the mean corpuscular volume (MCV) was higher when compared to controls, but with no statistically significant difference. On comparison with euthyroid controls, the total leukocyte count and platelet count were numerically reduced in patients with GD, while the SAT group showed numerically greater leukocyte count but reduced platelet count. In both the groups (GD and SAT) lymphocytes were elevated, though individually they failed to show statistically significant differences (all *P*>.05). However, on analyzing the PLR, it was found that there was a significant reduction in the PLR in both the GD and SAT groups when compared to the controls (*P*<.05), thus suggesting the PLR to be significantly reduced in thyrotoxicosis compared to euthyroid controls.

Comparing the GD and SAT groups, the baseline age, gender distribution, and BMI were well matched. FT4 and total T4 were higher in patients with GD, and TSH was lower, with no significant difference between the two groups. The hematocrit was reduced in GD more than SAT, whereas the MCV was increased, though not significantly altered. Also, the lymphocytosis and reduction in platelet count were more predominant in GD when compared with

Table 1
Baseline Characteristics in the Three Groups, With Comparisons

Parameter	Group 1 GD (n = 354) (Mean ± SD)	Group 2 SAT (n = 146) (Mean ± SD)	Group 3 Euthyroid (n = 250) (Mean ± SD)	*P* value (group 1 vs. 3)	*P* value (group 2 vs. 3)	*P* value (group 1 vs. 2)
Age ± SD (in years)	47.6 ± 11.6	45.2 ± 13.8	44.3 ± 12.5	.38	.44	.42
Female (%)	209 (59)	91 (62)	150 (60)	.32	.58	.26
BMI (in kg/m^2)	22.3 ± 6.6	24.1 ± 8.3	23.7 ± 7.5	.19	.31	.16
Total T4 (μg/dL)	**22.8** ± 10.5	**20.2** ± 7.7	**8.5** ± 2.6	**.001**	**.001**	.33
Free T4 (ng/dL)	**3.7** ± 1.4	**2.9** ± 1.0	**1.3** ± 0.5	**.01**	**.01**	.14
TSH (IU/L)	**0.001** ± 0.02	**0.01** ± 0.06	**1.6 ± 0.5**	**.01**	**.02**	.11
Hemoglobin (g/dL)	13.1	13.6	13.5	.15	.26	.35
Hematocrit (%)	40.8	41.2	41.4	.24	.12	.19
MCV (fL)	88.8 ± 19.5	86.5 ± 16.7	89.3 ± 14.4	.33	.17	.23
Total WBC count (cells/mL)	7,350 ± 1,855	7,700 ± 2,515	7,580 ± 2,100	.51	.28	.52
Platelets (×10^3 cells/mL)	219 ± 74	238 ± 88	262 ± 84	.14	.22	.12
Neutrophils (cells/mL)	5,033 ± 2,022	5,156 ± 2,213	4,844 ± 1,984	.45	.13	.48
Lymphocytes (cells/mL)	3,414 ± 1,285	3,219 ± 1,416	2,896 ± 988	.27	.41	.17
PLR	**74.5** ± 19	**84.4** ± 26	**118.8 ± 35**	**.01**	**.01**	**.01**

Abbreviations: BMI = body mass index; GD = Graves disease; MCV = mean corpuscular volume; PLR = platelet-to-lymphocyte ratio; SAT = subacute thyroiditis; T4 = tetraiodothyronine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

SAT. Though the differences in the individual blood parameters were not statistically significant, the PLR between the two groups showed significantly lower values for GD when compared to SAT ($P = .01$), probably bearing out the greater degree of lymphocytosis and thrombocytopenia in those with GD (Table 1). Data on TPOAbs was available in 189 (53%) patients with GD and found to be elevated in 139 (74%) of them. On the contrary, TPOAbs were documented in 115 (79%) patients with SAT, of which 26 (23%) patients had elevated levels. However, there were no significant differences in the mean levels of TPOAbs between the GD and SAT groups (456.25 ± 112.8 U/mL vs. 444.18 ± 133.6 U/mL; $P = .22$). Data on TSHRAb levels were available in 92 (26%) subjects with GD and 22 (15%) subjects with SAT, with mean TSHRAb levels in the GD group being significantly elevated compared with the SAT group (11.2 ± 2.8 U/L vs. 1.1 ± 0. 2 U/L; $P = .01$). Further, GD patients with elevated TSHRAb levels showed significantly increased uptake on ^{131}I RAIU scan. Considering the subset of study patients with documented TPOAb levels, PLR was not significantly different between the GD (n = 189) and SAT (n = 115) groups ($P = .15$). In contrast, amongst those with documented TSHRAb levels, the PLR was found to be significantly lower in GD (n = 92) compared to SAT (n = 22) patients ($P = .01$).

We subsequently used a ROC curve analysis to derive an optimal cut-off for the PLR to differentiate GD from SAT. Results showed that the PLR had an AUC of 0.74, with a 95% confidence interval of 0.63 to 0.88 (standard error, 0.03; $P = .01$) (Fig. 1). With an optimal cut-off of 70.4, the PLR was found to have a sensitivity of 86% and specificity of 74% in differentiating GD from SAT, with a positive predictive value (PPV) of 91.5% and a negative predictive value of 82.7%. The likelihood ratio of having GD with a PLR <70.4 was 2.26, with a Youden's index of 0.60.

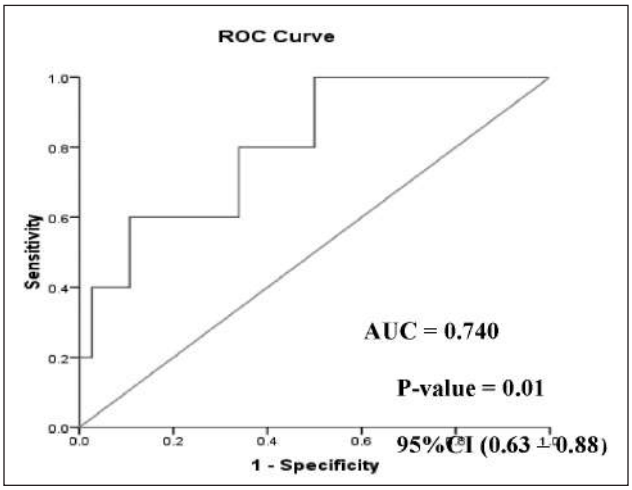

Fig. 1. Receiver operating characteristic (ROC) curve showing the area under the curve (AUC) for the platelet-to-lymphocyte ratio in patients with thyrotoxicosis (Graves disease and subacute thyroiditis). *CI* = confidence interval.

On correlation analysis, the PLR was found to have a good correlation with platelet counts ($P = .01$; $r = 0.77$) and lymphocytes ($P = .01$; $r = 0.72$) in both the GD and SAT groups, but not with the MCV, hemoglobin, total white blood cell (WBC) count, or neutrophil count. Suppressed TSH and elevated FT4 levels in those with GD ($P = .03$, $r = 0.48$; $P = .02$, $r = 0.56$, respectively) and SAT ($P = .04$, $r = .38$; $P = 0.04$, $r = .43$, respectively) showed significant correlations with the PLR, although slightly stronger correlations were observed in patients with GD. Further elevated TSHRAb levels in the GD group showed significant correlation with the PLR ($P = .01$; $r = 0.73$), though TPOAbs did not correlate significantly with the PLR in either the GD or SAT groups. Moreover, the PLR did not show any correlation with the baseline characteristics, including age, gender, and BMI, in either group, thus suggesting that PLR values were not influenced by the baseline demographic characteristics of the study population.

DISCUSSION

In Western literature, the prevalence of thyrotoxicosis is 1.2% of the general population, including both overt and subclinical cases, with peak age being between 20 and 50 years. GD is the most commonly seen cause of thyrotoxicosis (17). In certain regions of India (hilly northern areas), it has been seen that almost one-third of the population (18) has thyroid dysfunction, which is most commonly hypothyroidism, analyzed to be due to iodine deficiency. However, in a hospital-based study in Southern India, the highest prevalence of thyroid dysfunction was seen to be 22%, mostly affecting the age group between 30 and 49 years, of which 38% have hyperthyroidism (19). The latter is also known to be more prevalent in women (19). In our study, the mean age for GD was slightly higher, but as reported, both GD and SAT were more common in women. Thyroid hormone effects on the proliferation of blood cells has been studied over the years, but most of the hematologic changes that are reported cannot be adequately explained due to the paucity of larger studies and incomplete understanding of the action of thyroid hormones (7). Some recent studies also show abnormalities in hematologic parameters in patients with thyroid diseases, and it has been postulated that thyroid hormones regulate human hematopoiesis in the bone marrow, resulting in a hyperplasia of all myeloid cell lines in hyperthyroidism and their hypoplasia in hypothyroidism, as reported by Axelrod and Berman (20).

Definitive changes have been noticed in erythrocytes in cases of thyrotoxicosis, but the changes in WBCs and platelets remain controversial. It has been shown that thyroid hormones augment erythropoiesis in vitro (21) along with causing erythroid hyperplasia (22), though the mechanism is not clear. They are also known to increase the peripheral red cell mass (7,20), and there have been case reports of thyrotoxic erythrocytosis (23), but there

are also contrasting studies which show anemia in some patients with longstanding hyperthyroidism, which has been hypothesized to be due to reduced iron uptake (24). Reduced red cell survival, probably due to ineffective erythropoiesis along with a reduction in MCV, possibly within the normal range, may often be seen as part of the hematologic changes in longstanding hyperthyroidism (25). Due to co-existing changes in the plasma volume, the hematocrit in a hyperthyroid patient may be above or below normal. In our study, a reduction in the hematocrit along with a slightly reduced MCV was noted in patients with GD, though not statistically significant. An association between a reduced total leukocyte count along with a relative and absolute neutropenia in GD when compared with healthy subjects has been recognized for at least 80 years, but there has been a considerable amount of speculation with regard to variations in white cell counts in thyrotoxicosis (8). Lymphocytosis has also been documented with elevated thyroid hormones. In some studies, the lymphocytosis was attributed to an increase in the B-lymphocyte subpopulation, which has been noticed in both GD and SAT, and is believed to be due to a primary immunologic change rather than an effect secondary to the thyrotoxicosis. Another hypothesis considered is that the extensive B cell infiltration into the thyroid gland in both these disorders enters the blood stream during active disease (toxicosis) and causes a rise in the B cell population in the peripheral blood (26). It has also been shown that T3 is a prerequisite for normal B cell production in the bone marrow through its regulation of pro–B cell proliferation (27). This picture of an absolute and relative neutropenia and an absolute and relative lymphocytosis seen in GD came to be known as 'Kochers blood picture' (8). In our study, reduced total WBC and neutrophil counts were noted in the GD patients compared with the euthyroid controls, while they were numerically greater in the SAT patients, possibly owing to the inflammatory nature of SAT. Lymphocytosis was seen in both GD and SAT with respect to euthyroid controls, though it was numerically greater in GD than that in SAT, despite the latter being usually preceded by a viral infection. Mechanisms for lymphocytosis, as discussed above, need to be studied in greater detail in larger prospective studies to explain this interesting finding amongst these two groups of thyrotoxic patients.

Another commonly noticed alteration in the hematologic picture in thyrotoxic patients is a reduction in platelet count, which is most often not clinically manifested, but there have been case reports of thrombocytopenic purpura in association with thyrotoxicosis, where the platelet counts recovered when the thyroid function normalized (28-31). The exact mechanism to explain this phenomenon is not known; however, these patients have been seen to show increased levels of bound IgG (29). Another theory attempting to explain the same attributes the reduction in platelets in thyrotoxicosis to an increased sequestration potency of the reticulo-endothelial phagocyte system and a shortened platelet survival stimulated by thyroid hormone (9). This well-recognized thyrotoxicosis-induced reduction in platelet count was seen in our study as well, with a reduced platelet count in both those with GD and SAT, though the reduction was greater in the group with GD. The changes seen in the blood cell counts have a physiologic basis due to the differences in disease pathogenesis, but in our study, these changes did not prove to be statistically significant in individually differentiating between the two conditions.

The PLR is used as a marker of subclinical inflammation and for prognostication in various benign and malignant conditions, but it is not often used for benign thyroid disease. In a recent study involving 145 subjects with Hashimoto thyroiditis, the PLR was found to be significantly higher when compared to age-matched healthy controls, though there were no significant differences when the neutrophil, lymphocyte, and platelet counts were considered individually (32). However, GD or SAT were not included in that study, and it was limited only to patients in which the findings were not validated against definitive diagnostic tools like RAIU uptake or TSHRAb positivity. In our study, we found the PLR to be significantly different in thyrotoxic patients when compared with healthy controls, with greater reductions in the PLR seen in the group with GD. Further, our data from ROC curve analyses suggested a PLR cut-off of 70.4 to have a fairly good sensitivity of 86% and moderate specificity of 74%, thus making it a reliable screening tool for differentiating GD from SAT.

This is the first study examining the utility of the PLR in a relatively large cohort of patients with thyrotoxicosis and provides evidence that the PLR is significantly reduced in patients who are thyrotoxic when compared with healthy individuals. We also identified an appropriate cut-off for the PLR that can be used as a reliable, cost-effective, and easily accessible surrogate marker for identifying GD, thus precluding the use of RAIU and TSHRAb analyses. In low- and middle-income countries (LMICs), thyroid uptake studies including 99-Technetium and radioiodine-based scans are currently used for definitive diagnosis of thyrotoxic conditions like GD and SAT, though cost is a limiting factor in most cases. Estimation of TSHRAb levels, though strongly emphasized by the American Thyroid Association (33), is restricted in its usage due to limited availability of standardized assays, inherent functional properties of TSHRAbs, assay methodology used, paucity of data from different ethnic groups, and discrepancies in the TSHRAb cut-off levels defined in different studies (34). Thus, initial evaluation of thyrotoxic patients is still largely guided by subjective clinical findings and inconsistent biochemical markers. The PLR is a marker that can be obtained by a clinician with the help of a CBC, thus providing a novel and accessible method to differentiate GD from SAT. In

LMICs, where thyroid uptake studies and TSHRAb tests are prohibitive due to cost and accessibility, we envisage the use of the PLR as an inexpensive and sensitive screening tool to differentiate patients with GD and SAT, which will subsequently help in identifying patients that need further sophisticated investigations. The changes in the PLR in patients with GD and SAT documented in our study are confirmed by the physiologic changes seen due to the effect of elevated thyroid hormones on blood cell proliferation, although the exact physiologic mechanisms causing the same remain unclear.

CONCLUSION

The strength of our study lies in the fact that we included only those patients with thyrotoxicosis who had documented ^{131}I uptake studies done at presentation in the nuclear medicine department of the same hospital, thus using the gold-standard diagnostic technique as the comparator. However, the retrospective study design and relatively lower specificity are limitations that necessitate future prospective studies. Moreover, relationship of the PLR with thyroid autoantibodies and its possible role in deciding treatment modalities for GD are areas which need further elucidation in prospective multicenter studies.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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