Original Article

The diagnostic value of blood cell-derived indexes in subacute thyroiditis patients with thyrotoxicosis: a retrospective study

Peichun He, Haiyan Yang, Qingsun Lai, Yaqi Kuang, Zhenxing Huang, Xinghuan Liang, Hong Huang, Yingfen Qin, Zuojie Luo^

Department of Endocrinology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

Contributions: (I) Conception and design: P He, Y Kuang; (II) Administrative support: Z Luo, Y Qin; (III) Provision of study materials or patients: Z Huang, X Liang, H Huang; (IV) Collection and assembly of data: P He, Q Lai (V) Data analysis and interpretation: P He, H Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zuojie Luo. Department of Endocrinology, the First Affiliated Hospital of Guangxi Medical University, No. 6 of Shuangyong Road, Nanning, China. Email: zluo888@163.com.

Background: Both subacute thyroiditis (SAT) and Graves' disease (GD) can lead to thyrotoxicosis, but the methods to distinguish these two diseases are relatively complex. Therefore, it is necessary to find biomarkers which can quickly and efficiently identify the two kinds of thyrotoxicosis. Blood cell-derived indexes are widely used to evaluate systemic inflammation. We aimed to evaluate the diagnostic value of blood cell-derived indexes in SAT patients with thyrotoxicosis.

Methods: Totally 139 SAT patients with thyrotoxicosis, 146 GD patients, and 100 euthyroid individuals were enrolled in the study. Complete blood cell (CBC) count, thyroid function, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune-inflammatory index (SII), systemic inflammation response index (SIRI), aggregate inflammation systemic index (AISI), and mean platelet volume to platelet ratio (MPR) were evaluated in all subjects. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the capacity of blood cell-derived indexes in differentiating SAT patients with thyrotoxicosis from GD patients. We also evaluated the association between blood cell-derived indexes and other laboratory indicators and clinical outcomes in SAT patients.

Results: NLR, PLR, MLR, SII, SIRI, and AISI were significantly higher in the SAT group. MPR was significantly lower in the SAT group. A formula including NLR, PLR, MLR, SII, SIRI, AISI and MPR was developed. The combination formula with an optimal cutoff of 0.426 showed the better diagnostic value [area under the curve (AUC) =0.921; 95% confidence interval (CI): 0.891–0.950; P<0.001; sensitivity, 87.1%; specificity, 83.6%]. However, thyroid function, erythrocyte sedimentation rate (ESR), thyroid peroxidase antibodies (TPOAb), and blood cell-derived indexes, were not found to be significantly associated with hypothyroidism and recurrence.

Conclusions: We developed a formula combining 7 blood cell-derived indexes. The combination formula could be a novel biomarker to distinguish SAT patients with thyrotoxicosis from GD patients. However, we did not find significant association between the blood cell-derived indexes and clinical outcomes in SAT patients.

Keywords: Subacute thyroiditis (SAT); thyrotoxicosis; Graves' disease (GD); blood cell-derived indexes

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^ ORCID: 0000-0003-2969-8329.

Introduction

Thyrotoxicosis is a syndrome characterized by increased excitability and hypermetabolism of nervous, circulatory, and other systems, affecting about 1.2% of the population in the United States (1). Subacute thyroiditis (SAT) is a self-limited inflammatory thyroid disease, whose pathogenesis is unclear. Human leukocyte antigen (HLA)-B*35 is considered a susceptibility factor and virus infection is considered a trigger factor (2). The disease typically occurs in middle-aged women complaining of fatigue, neck pain, and acute fever (3). In some cases, destruction of thyroid follicles caused by inflammation can lead to transient thyrotoxicosis (4). A Japanese study reported that 62.1% of SAT patients had typical symptoms associated with thyrotoxicosis (5). In another study from Finland, up to 41.7% of SAT patients were initially misdiagnosed by the primary physician (6).

Graves' disease (GD) is the most common causes of thyrotoxicosis. Although SAT and GD can both lead to thyrotoxicosis, their treatment is different. SAT is mainly treated with β-receptor blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids, while GD is mainly treated with antithyroid drugs, surgery, and iodine-131 therapy. Radioactive iodine uptake (RAIU) is reduced in SAT patients, which is helpful to differentiate between GD and SAT. However, RAIU is a complex, expensive, and time-consuming test which is not universally accessible in some primary care centers, and a low-iodine diet is often required before RAIU. RAIU is also contraindicated during pregnancy, breastfeeding, or after recent iodine exposure (1). Thyroid stimulating hormone (TSH) receptor antibodies (TRAb) is useful for diagnosis of GD but is negative in some GD patients (7). Therefore, it is necessary to find a reliable alternative biomarker that can quickly clarify the 2 types of thyrotoxicosis.

A complete blood cell (CBC) count provides information on the number and morphology of various cells, and it is cheap and readily available. Some blood cell-derived indexes, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune-inflammatory index (SII), systemic inflammation response index (SIRI), aggregate inflammation systemic index (AISI), and mean platelet volume to platelet ratio (MPR), have been proposed as biomarkers for inflammatory diseases, respiratory diseases, carcinoma, and rheumatic diseases (8-14). Recent research demonstrated that NLR, PLR, and MLR are increased in SAT patients (15). NLR and PLR have been used as new indicators to distinguish thyrotoxicosis caused by SAT and GD (16). However, the sensitivity and specificity of these indicators need to be further improved.

In this retrospective study, blood cell-derived indexes were compared among SAT patients with thyrotoxicosis, GD patients, and euthyroid individuals. Receiver operating characteristic (ROC) curve analysis was used to determine their capacity for differentiating SAT from GD. A recent study found that elevated levels of C-reactive protein (CRP) is a risk factor for hypothyroidism in SAT patients (17). Blood cell derived indexes, also as inflammatory markers of SAT, may be associated with the occurrence of hypothyroidism. Although previous study indicated that NLR PLR, and MPV are not associated with recurrence (18), no data are available about the performance of SII, SIRI, AISI, and MPR in SAT patients. Thus, we explored the relationships between these indexes and outcomes in SAT patients, aiming to evaluate the effect of blood cell derived indexes on recurrence and hypothyroidism in this study. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-719/rc).

Methods

Subjects

A retrospective analysis was made of 139 SAT patients with thyrotoxicosis who had diagnosed and treated in the Endocrinology and Metabolism outpatient clinic, First Affiliated Hospital of Guangxi Medical University between July 2016 and July 2021. SAT was confirmed by the typical systemic symptoms, Physical examination, increased erythrocyte sedimentation rate (ESR), elevated serum thyroid hormone and decreased RAIU (19). A total of 146 GD patients and 100 euthyroid individuals were also enrolled in this study. GD was confirmed by hyperthyroidism, positive TRAb, diffuse lesions detected by B-ultrasound, and/or high RAIU. The exclusion criteria for all subjects were as follows: (I) age <18 years old; (II) pregnancy; (III) patients with diabetes, inflammatory disorder, heart disease, renal failure, liver disease, hematological disease, cancer, or rheumatic diseases; (IV) people who had been taking drugs that may have affected the blood system during the preceding 3 months, such as immunosuppressants, anticoagulants, and antiplatelet drugs, etc.; (V) subjects who had undergone thyroid surgery or

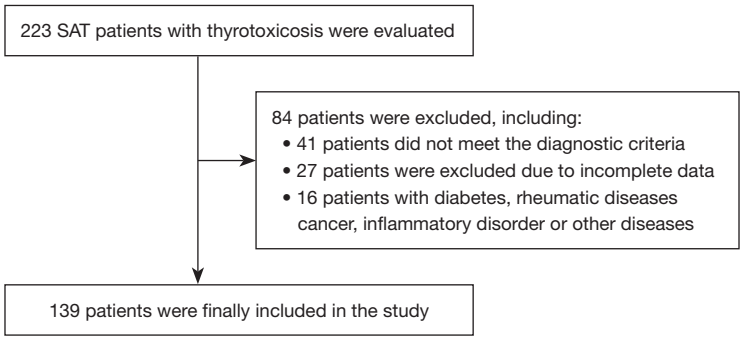

Figure 1 Flow chart of patient selection. SAT, subacute thyroiditis.

iodine-131 therapy. Flow chart of SAT patient selection is shown in *Figure 1*. Recurrence was defined as the presence of symptoms such as fever, thyroid pain, and elevated inflammatory factors (20). Hypothyroidism is defined as the FT4 level is lower than the normal reference value range, and TSH level is higher than the normal reference value range.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Guangxi Medical University [No. 2022(KY-E-021)]. Individual consent for this retrospective analysis was waived.

Study methods

All hematologic analyses were performed using Coulter LH780 Hematology Analyzer (Beckman Coulter Inc., Brea, CA, USA). Free thyroxine (FT4), and TSH were measured by electrochemiluminescence using the UniCel DxI 800 immunoassay system (Beckman Coulter Inc.). TRAb, and thyroid peroxidase antibodies (TPOAb) were detected by radioimmunoassay. ESR was measured by fully automated ESR analyzer Monitor-100 (Vital Diagnostics, Italy). Reference ranges were defined as: FT4, 7.86–14.41 pmol/L, TSH, 0.34–5.65 mIU/L. TRAb, 0–1.5 IU/L, TPOAb, 0–34 IU/mL. ESR, 0–20 mm/h. 2 h and 24 h I-131 RAIU, 10–30% at 2 hours, 25–60% at 24 hours. NLR, PLR, MLR, SII, SIRI, AISI, and MPR were calculated using the following formulas: NLR = neutrophils/lymphocytes, PLR = platelets/lymphocytes, MLR = monocytes/lymphocytes, SII = (neutrophils × platelets)/lymphocytes, SIRI = (neutrophils × monocytes)/lymphocytes, AISI = (neutrophils × platelets × monocytes)/lymphocytes, and MPR = mean platelet volume (MPV)/platelets.

Statistical analysis

Statistical analyses were performed by SPSS 22.0 (IBM, Armonk, NY, USA). Chi-square test was used for categorical variables. The measurement data were normally distributed, expressed by the mean ± standard deviation ($\bar{x}\pm s$), and independent samples t test and one-way analysis of variance (ANOVA) was used for comparisons. Nonnormally distributed measurement data were expressed as median (M), 25–75th percentile (P25–P75), and Mann-Whitney U test and Kruskal-Wallis H test were used for comparisons. Spearman correlation was used for correlation analysis between variables, and ROC curve analysis was used to evaluate diagnostic sensitivity and specificity of blood-cell derived indexes. The optimal cutoff value was determined as the value corresponding to the maximum Youden index (sensitivity + specificity − 1). P value <0.05 was considered statistically significant.

Results

Table 1 shows the demographic and laboratory data of all subjects, including 139 SAT patients, 146 GD patients, and 100 euthyroid subjects. There was no significant difference in age or gender between the SAT group and the other 2 groups. When compared with the control group, white blood cells (WBCs), neutrophils, platelets, monocytes, FT4, NLR, PLR, MLR, SII, SIRI, and AISI were significantly higher and lymphocytes, MPV, TSH, and MPR were significantly lower in the SAT group. (*Table 1*). When compared with the GD group, WBCs, neutrophils, platelets, TSH, NLR, PLR, MLR, SII, SIRI, and AISI were significantly higher and lymphocytes, MPV, FT4, and MPR were significantly lower in the SAT group. However, there

Table 1 Demographic and laboratory data of SAT group, GD group, and control group

	SAT group (n=139)	GD group (n=146)	Control group (n=100)
Gender (F/M)	109/30	109/37	78/22
Age (years)	41.97±9.11	38 (33, 49)	40.5 (33, 52.25)
WBC (10^9/L)	8.47±2.38[ab]	6.51±1.49	6.47±1.56
Neutrophils (10^9/L)	5.81±2.06[ab]	3.53±1.19	3.7±1.29
Platelets (10^9/L)	334.86±75.3[ab]	263.47±59.39	258.51±58.1
Lymphocytes (10^9/L)	1.89±0.65[ab]	2.18±0.67	2.15±0.61
Monocytes (10^9/L)	0.62 (0.46, 0.77)[b]	0.61 (0.51, 0.75)[b]	0.44 (0.37, 0.56)
MPV (fl)	8.73±1.21[ab]	9.39±1.40	9.24±1.27
FT4 (pmol/L)	23.65 (18.77, 30.55)[ab]	34.74 (24.62, 48.44)[b]	11.18 (10.23, 12.30)
TSH (mIU/L)	0.01 (0.01, 0.02)[ab]	0.01 (0.01, 0.01)[b]	1.52 (1.09, 2.37)
NLR	3.02 (2.13, 4.15)[ab]	1.63 (1.15,2.12)	1.62 (1.29,2.17)
PLR	183.04 (136.9, 245.88)[ab]	124.61 (97.21, 154.16)	116.5 (97.45, 151.14)
MLR	0.33 (0.25, 0.47)[ab]	0.29 (0.24, 0.36)[b]	0.21 (0.17, 0.26)
SII	1,036.25 (702.23, 1,369.73)[ab]	394.68 (305.45, 579.67)	420.89 (304.79, 581.36)
SIRI	1.98 (1.23, 2.73)[ab]	0.96 (0.7, 1.42)[b]	0.74 (0.55, 1.05)
AISI	663.75 (406.9, 964.38)[ab]	253.21 (177.83, 385.78)[b]	177.31 (131.75, 281.31)
MPR	0.026 (0.022, 0.032)[ab]	0.036 (0.03, 0.044)	0.035 (0.03, 0.044)

Data were expressed as 25–75th percentile (P25–P75) and mean ± standard deviation. [a], P<0.05 *vs.* GD group; [b], P<0.05 *vs.* control group. SAT, subacute thyroiditis; GD, Graves' disease; WBC, white blood cell; MPV, mean platelet volume; FT4, free thyroxine; TSH, thyroid stimulating hormone; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation systemic index; MPR, mean platelet volume to platelet ratio.

was no significant difference in monocytes between SAT group and GD group. ESR correlated positively with NLR (r: 0.340, P<0.001), PLR (r: 0.380, P<0.001), MLR (r: 0.289, P=0.001), SII (r: 0.451, P<0.001), SIRI (r: 0.303, P<0.001), and AISI (r: 0.401, P<0.001), and it correlated negatively with MPR (r: –0.243, P=0.004).

ROC curve analysis was used to evaluate the diagnostic accuracy, sensitivity, and specificity of the blood cell-derived indexes in differentiating SAT patients from GD patients (*Figure 2* and *Table 2*). Among 7 blood cell-derived indexes, SII with an optimal cutoff of 607.93 showed the best diagnostic value [area under the curve (AUC) =0.896; 95% confidence interval (CI): 0.861–0.931; P<0.001; sensitivity, 82.7%; specificity, 78.8%]. A formula combining NLR, PLR, MLR, SII, SIRI, AISI and MPR was as follows: exp (0.32988–0.37411×NLR+0.01351×PLR–15.59617×MLR +0.00049×SII+2.88741×SIRI+0.00219×AISI–69.10163×MPR)/[1+exp (0.32988–0.37411×NLR+0.01351×PLR–15.59 617×MLR+0.00049×SII+2.88741×SIRI+0.00219×AISI–69 .10163×MPR)]. The combination formula with an optimal cutoff of 0.426 showed the better diagnostic value (AUC = 0.921; 95% CI: 0.891–0.950; P<0.001; sensitivity, 87.1%; specificity, 83.6%).

In this study, 15 SAT patients lost to follow-up. Hypothyroidism occurred in 23 of 124 SAT patients (18 females and 5 males). The mean age was 42.61±8.92 years.

When compared with the SAT patients without hypothyroidism or recurrence, there was no significant difference in Gender, Age, WBCs, FT4, TPOAb positivity, ESR, NLR, PLR, MLR, SII, SIRI, AISI, or MPR in patients with hypothyroidism (P>0.05) (*Table 3*). In addition, 20 of 124 SAT patients developed recurrence (17 females and 3 males). The mean age was 42.15±9.23 years. When

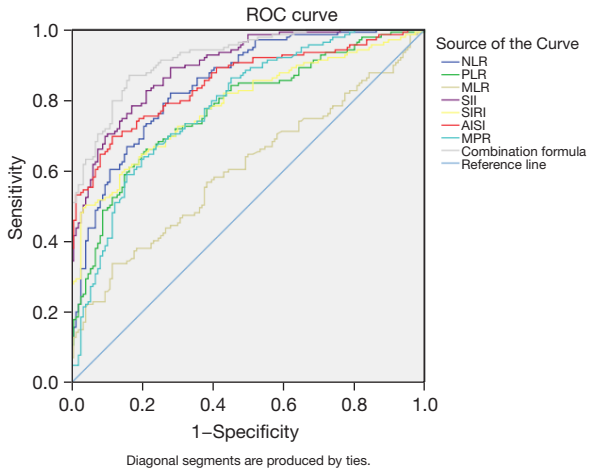

Figure 2 ROC curve evaluating blood cell-derived indexes for differentiating SAT from GD. ROC, receiver operating characteristic; SAT, subacute thyroiditis; GD, Graves' disease; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation systemic index; MPR, mean platelet volume to platelet ratio.

compared with the patients without hypothyroidism or recurrence, there was no significant difference in Gender, Age, WBCs, thyroid function, thyroid antibodies, blood cell-derived indexes, or ESR in patients with recurrence ($P>0.05$).

Discussion

SAT is the most common thyroid pain disease and developed most often in female patients aged 40 to 50 years (5). In this study, 45.3% of SAT patients were in the 40–50 age range, and 78.4% of SAT patients were female. In the acute phase of SAT, the destruction of thyroid follicular cells leads to the release of thyroid hormone. About half of SAT patients develop thyrotoxicosis, which lasts for about 3 to 6 weeks. After this period, some patients may have transient hypothyroidism, which can last for several weeks to six months. SAT patients generally return to normal thyroid function within 6 to 12 months (21,22). However, some patients develop recurrence or persistent hypothyroidism (3,4).

Neutrophils, lymphocytes, monocytes, and platelets are considered to be involved in modulating inflammation (23). When compared with euthyroid individuals, neutrophils, platelets, and monocytes were significantly increased and lymphocytes were significantly decreased in SAT patients. Neutrophils, as part of the immune system, play an important role in defense against bacterial or fungal infection. At the onset of SAT, cytologic findings show an inflammatory response composed of neutrophils (24), and neutrophils may be involved in thyroid follicular destruction in SAT patients. During inflammation, interleukin 6 is released from macrophages, promoting the production of thrombopoietin in the liver and resulting in an increase in platelet production (25). The mechanism of lymphocytopenia in SAT patients is unclear, but Calapkulu *et al.* (18) suggested it may be related to the elevated cortisol caused by the stress response in SAT patients. Since glucocorticoids can redistribute circulating cells to bone marrow or other body parts, the lymphocytes in the peripheral blood are reduced (26). In addition, virus infection of T cells may also be a potential factor leading to lymphopenia (27).

NLR, PLR, MLR, SII, SIRI, AISI, and MPR are blood-cell indexes derived from CBC, and the proportions of these may better express the inflammatory state of a disease than the counting of a single cell (23). Our research showed that all blood cell-derived indexes changed significantly. In ROC curve analysis, all blood cell-derived indexes were able to significantly differentiate SAT patients with thyrotoxicosis from GD patients. Among these indexes, SII was the index which performed best. SII, as a novel index, integrates neutrophils, lymphocytes, and platelets and has been reported as a prognostic indicator in some diseases, including COVID-19 (27), coronary artery disease (28), and cancers (11). To our knowledge, this is the first study to evaluate the value of SII in the diagnosis of SAT patients. Besides, we developed a novel formula combining NLR, PLR, MLR, SII, SIRI, AISI and MPR. Compared with other blood cell derived indexes, the combination formula showed the better diagnostic value. Our study indicated that the combination formula could help primary physicians to identify the etiology of thyrotoxicosis and reduce misdiagnosis of SAT patients before conducting more difficult examination.

It has been reported that the rate of hypothyroidism is 15.7–34% (17,29,30). In this study, 18.5% of SAT patients developed hypothyroidism, which was compatible with prior research findings. In a study of 103 SAT patients, 10.7% developed persistent overt hypothyroidism, of which 72.7% had thyroid antibodies positivity (31). Another study also found positive TPOAb was the risk factor associated with persistent hypothyroidism (32).

Table 2 ROC curves and diagnostic accuracy of blood cell-derived indexes

	AUC	95% CI	P value	Cutoff	Sensitivity (%)	Specificity (%)
NLR	0.846	0.802–0.89	<0.001	>2.043	82.0	71.9
PLR	0.775	0.721–0.829	<0.001	>157.916	66.2	78.8
MLR	0.604	0.538–0.67	0.002	>0.429	33.8	88.4
SII	0.896	0.861–0.931	<0.001	>607.930	82.7	78.8
SIRI	0.787	0.734–0.84	<0.001	>1.968	50.4	95.9
AISI	0.851	0.806–0.896	<0.001	>469.504	69.8	88.4
MPR	0.783	0.731–0.836	<0.001	<0.029	79.5	64.0
Combination formula	0.921	0.891–0.950	<0.001	>0.426	87.1	83.6

ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation systemic index; MPR, mean platelet volume to platelet ratio.

Table 3 Demographic and laboratory data of SAT patients with different outcomes

	Patients without hypothyroidism or recurrence (n=84)	Patients with hypothyroidism (n=23)	Patients with recurrence (n=20)
Gender (F/M)	67/17	18/5	17/3
Age (years)	41.07±9.13	42.61±8.92	42.15±9.23
WBC (10^9/L)	8.21±1.97	8.57±2.85	8.73±1.93
FT4 (pmol/L)	22.96 (18.80, 30.02)	28.58±9.91	22.74±8.02
ESR (mm/h)	64.00 (34.25, 84.50)	66.22±27.54	58.65±22.73
TPOAb positivity (%)	13.7%	19.0%	11.8%
NLR	2.93 (2.17, 4.12)	3.43 (2.23, 4.33)	3.09(2.17, 3.66)
PLR	182.42 (139.06, 242.53)	192.70 (165.70, 285.00)	162.73(115.30, 240.17)
MLR	0.33 (0.25, 0.47)	0.32 (0.27, 0.46)	0.33 (0.22, 0.54)
SII	1,024.43 (715.30, 1,357.65)	1,243.67 (741.96, 1,761.31)	881.08 (611.67, 1,294.83)
SIRI	2.00 (1.23, 2.64)	1.82 (0.91, 3.60)	1.91(1.21, 3.41)
AISI	659.27 (422.58, 945.71)	656.56 (366.30, 1,361.52)	711.41 (344.89, 962.26)
MPR	0.025 (0.022, 0.031)	0.026 (0.022, 0.031)	0.027 (0.022, 0.033)

Data were expressed as 25–75th percentile (P25–P75) or mean ± standard deviation unless otherwise noted. SAT, subacute thyroiditis; WBC, white blood cell; FT4, free thyroxine; ESR, erythrocyte sedimentation rate; TPOAb, thyroid peroxidase antibodies; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation systemic index; MPR, mean platelet volume to platelet ratio.

Our study did not show a significant correlation between elevated TPOAb and hypothyroidism. However, due to the small sample size, the finding need to be further confirmed in multicenter, prospectively designed studies. Tang *et al.* reported that CRP levels of more than 97.80 mg/L was a risk factor for hypothyroidism (17). Another study found that acute ESR was significantly associated with persistent subclinical hypothyroidism (33). On the other hand, other studies have found no effect of CRP and ESR levels on hypothyroidism (34-36). Our study showed that blood cell-derived indexes and ESR had no significant association with hypothyroidism. In a retrospective study of 56 SAT

patients, patients who developed hypothyroidism had a longer duration of disease (36). Long-term inflammation could lead to the continuous destruction of thyroid follicles, the depletion of thyroid hormone and the occurrence of hypothyroidism. Thus, to understand the relationship between hypothyroidism and inflammation, it is necessary to continuously monitor blood cell-derived indexes and other inflammatory indicators in future researches.

Studies have reported that the incidence of SAT recurrence is 9–22% (20,32,36). In this study, 16.1% of SAT patients developed recurrence. We did not find a significant difference in blood inflammatory indexes between recurrent patients and nonrecurrent patients. Recent studies have demonstrated that the recurrence of SAT patients may be related to HLA haplotype and glucocorticoid treatment (3,22), and that the severity of inflammation may not predict recurrence (20,35).

This study had some limitations. Firstly, this is a retrospective study, some patients may have missed a short period of hypothyroidism, which may make the incidence rate of hypothyroidism underestimated. Secondly, CRP was not been evaluated due to the lack of some data. Finally, the smoking status of the participants has not been assessed in this study.

Conclusions

We developed a formula combining 7 blood cell-derived indexes. The combination formula could be a novel biomarker to distinguish SAT patients with thyrotoxicosis from GD patients. We also found that blood cell-derived indexes had no significant association with clinical outcomes in SAT patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-719/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-719/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-719/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Guangxi Medical University [No. 2022(KY-E-021)]. Individual consent for this retrospective analysis was waived.

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