The role of the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio in assessing hypothyroidism Hashimoto's thyroiditis

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ABSTRACT

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune thyroid disorder, influenced by genetic predispositions, environmental factors, and immune dysfunction. High iodine intake has been identified as a potential trigger in susceptible individuals. This study investigates the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as inflammatory markers in patients with hypothyroid HT. Conducted at Thumbay Labs in Ajman, United Arab Emirates, this cross-sectional study involved 150 participants, including 100 diagnosed with hypothyroid HT and 50 healthy controls. Significant differences were found in the mean values of free thyroxine (FT4), thyroid-stimulating hormone (TSH), NLR, PLR, and anti-thyroid peroxidase (ATPO) between the patient and control groups ($p<0.05$). Specifically, mean values were 0.02 for FT4, 0.00 for TSH, 0.000 for NLR, 0.02 for PLR, and 0.01 for ATPO. Gender did not significantly influence these metrics. The results indicate elevated NLR and reduced PLR in hypothyroid HT patients, suggesting their potential utility as cost-effective inflammatory markers in clinical settings. Nevertheless, due to contradictory findings in existing literature, further research is necessary to validate NLR and PLR's roles in managing HT, which may enhance patient care strategies.

Introduction

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most common autoimmune thyroid disorder and a leading cause of hypothyroidism. HT is characterized by the destruction of thyroid cells by cell- and antibody-mediated immune processes. The pathogenesis of HT involves genetic predisposition, environmental triggers, and immune dysregulation. High iodine intake is a notable environmental factor that may precipitate the disease in genetically susceptible individuals.[1]

Inflammation represents an essential part of the pathophysiology of HT. Research indicates that obesity may be a contributing factor in the development and progression of HT. In individuals with obesity, there is often an increased level of systemic inflammation and altered immune function, which could exacerbate autoimmune reactions.[2,3] Recently, several hematological markers have been suggested as useful indica-

tors for measuring systemic inflammation, among which are the ratios of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), associated with a wide spectrum of medical disorders like cardiovascular diseases and autoimmune disorders.[4,5]

NLR and PLR were investigated in thyroid disorders. For example, Bilge *et al.* have shown the examined NLR and PLR in euthyroid HT patients and uncovered considerable changes in both ratios compared with the healthy controls. These findings may indicate that NLR and PLR would be of further value as inflammatory status markers in HT patients.[6,7]

These hematological parameters are not only cost-effective but also easily accessible, which proves to be a very practical tool in clinical assessment. Although preliminary results were encouraging, the literature still includes conflicting results about the usefulness of NLR and PLR in HT; further evaluation is therefore necessary to clarify their role and possible diagnostic significance in condition.[8]

This study aims to evaluate the NLR and PLR in patients with hypothyroid HT and compare these ratios with those in healthy controls.

Materials and Methods

This is a cross-sectional study conducted at the Thumbay Hospital, Ajman, United Arab Emirates. A total of 150 individuals participated in this study, with 100 individuals diagnosed with hypothyroid HT and 50 healthy individuals as the control group. Two samples from patients with hypothyroid HT were obtained: whole blood ethylene diamine tetra acetic acid for the full blood count test, and serum for thyroid function [free thyroxine (FT4), thyroid-stimulating hormone (TSH)] and an anti-thyroid peroxidase (ATPO) test at the biochemistry and hematology department. Samples from patients with major conditions such as those suffering from thyroid disorders, heart attack, infections, traumatic injuries, and kidney failure, and subjects taking medications like contraceptive pills, steroid hormones, anti-inflammatory drugs, lithium, and amiodarone, either singly or in combinations, or availing minerals and vitamin supplements, especially those containing iodine or biotin, were excluded.

The ethical approval was obtained from the Institutional Review Board (IRB) of the Gulf Medical University after the committee reviewed the project. The IRB realized the low risk of this non-interventional research and gave its recommendation for the approval of the project Ref. no. IRB/COHS/STD/98/DEC-2022. This was a retrospective study where informed consent was waived.

The full blood count samples were analyzed using the Beckman Coulter DXH 800 analyzer (Beckman Coulter, Miami, FL, USA), which uses flow cytometry for precise cell counting and differentiation. Thyroid function tests, including ATPO, TSH, FT4, and antithyroglobulin antibodies, were performed using the Cobas e 411/601 analyzer (Roche Diagnostics, Basel, Switzerland). This automated immunoassay system quantifies test results using electrochemiluminescent technology.

All the statistical analyses were done using the SPSS software (IBM, Armonk, NY, USA) for Windows Version 3.5.1. Comparisons of continuous variables between the two groups were performed with the Mann-Whitney U test, for categorical variables were compared using the chi-square test. The mean and standard deviation (SD) were obtained, and the "t" independent test. Moreover, for the correlation, linear regression is used to identify the significant differences among the sufficiency, insufficiency, and deficiency groups. Parametric correlations were performed by using Pearson's test. The correlations between other variables were calculated using multiple linear regression models. Variables that were statistically significant by univariate analysis and known risk factors were added to a multiple logistic regression model to identify independent predictors of the presence of HT. The mean value of continuous data is expressed as mean ± SD. A p-value <0.05 was considered statistically significant.

Results

A total of 150 individuals participated in this study, including 100 patients with hypothyroid HT and 50 healthy individuals as a control group. This study aimed to evaluate the NLR and PLR in patients with hypothyroid HT. As shown in Table 1, there were significant differences in the mean values of FT4, TSH, NLR, PLR, and ATPO between the patient and control groups, as determined by an independent *t*-test. The p-values for these parameters were 0.02, 0.00, 0.000, 0.02, and 0.01, respectively.

On the other hand, the analysis presented in Table 2 indicates no significant differences in the mean values of age, FT4, TSH, NLR, PLR, and ATPO in patients with hypothyroid HT according to gender (78 females, 78%, and 22 males, 22%). The corresponding p-values for these parameters were 0.20, 0.30, 0.10, 0.40, 0.33, and 0.25, respec-

Table 1. Comparison of the mean and standard deviation of age, free thyroxine, thyroid-stimulating hormone, anti-thyroid peroxidase, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio between the study group and the control group.

Variables	Hypothyroidism n (mean±SD)	Control group n (mean±SD)	p
Age	100 (36.5±11.9)	50 (34.9±14.4)	0.08
FT4	100 (5.26±1.55)	50 (15.5±2.5)	0.02
TSH	100 (65±54)	50 (1.91±1.05)	0.00
ATPO	100 (129±65.8)	50 (9.5±2.8)	0.00
NLR	100 (2.1±0.6)	50 (1.77±1.3)	0.02
PLR	100 (8.6±4.9)	50 (11.2±2.9)	0.01

SD, standard deviation; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ATPO, anti-thyroid peroxidase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. The table shows the mean±SD and probability value (p); the t-test was used for comparison; $p \leq 0.05$ is considered significant.

Table 2. Comparison of the mean age, free thyroxine, thyroid-stimulating hormone, anti-thyroid peroxidase, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in the study group and the control group according to gender.

Variables	Male n (mean±SD)	Female n (mean±SD)	p
Age	22 (37.8±10.2)	78 (36.0±12.5)	0.2
FT4	28 (4.8±1.8)	78 (5.4±1.3)	0.3
TSH	28 (59±34)	78 (67.0±30)	0.1
ATPO	28 (117±36)	78 (134±34)	0.4
NLR	28 (1.8±3.4)	78 (1.7±0.4)	0.33
PLR	28 (8.8±5.1)	78 (7.9±4.4)	0.25

SD, standard deviation; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ATPO, anti-thyroid peroxidase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. The table shows the mean±SD and probability value (p); the t-test was used for comparison; $p \leq 0.05$ is considered significant.

tively. In Figure 1, the scatterplot illustrates a moderate positive correlation between TSH and NLR in patients with hypothyroid HT (R=0.220, p=0.033). In Figure 2, the scatterplot shows the correlation between ATPO and NLR in patients with hypothyroid HT (R=0.20, p=0.846). In Figure 3, the scatterplot shows no significant correlation between TSH and PLR in patients with hypothyroid HT (R=0.02, p=0.982). In Figure 4, the scatterplot shows a negative correlation between ATPO and PLR in patients with hypothyroid HT (R=-0.15, p=0.881). In Figure 5, the scatterplot shows a weak positive correlation between ATPO and TSH in patients with hypothyroid HT (R=0.126, p=0.021).

Discussion

HT (chronic lymphocytic thyroiditis) is the most common disease that causes hypothyroidism and an enlarged thyroid gland in children and adolescents, and at the same time, is the primary acquired cause of hypothyroidism and goiter in regions that are non-endemic for iodine deficiency.[9,10] Its etiology implies certain environmental factors such as excess iodine intake, various viral infections, and medications. Based on investigations of HT pathophysiology, the disease develops due to increased T-cell activation, and there are relationships between certain groups of tissues, such as HLA, DR3, DR4, and DR5. Furthermore, the appearance of the disease is thought to be connected to multiple genetic factors that regulate immunologic reactions, and this notion has been supported by numerous studies.[6] NLR is a measure of inflammation and is often used to assess the severity of a disease. Neutrophil and lymphocyte counts undergo certain temporary changes under inflammatory conditions. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. As a systemic inflammation index, NLR was determined to be a useful index for the differential diagnosis of diseases and the prediction of their prognoses.[11] NLR is also an available marker that can communicate important information about the inflammatory activity of the patient. Certain epidemiological studies have determined that chronic inflammation measured by NLR is correlated with other conventional risk factors such as obesity and hypertension. Recent studies have shown that an abnormal NLR level is related to autoimmune diseases.[12] In our

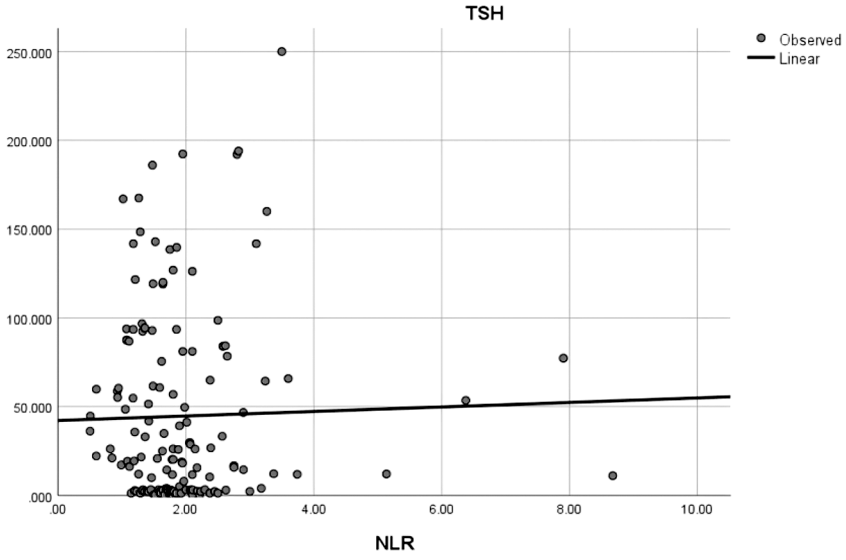

Figure 1. Scatterplot shows the positive correlation between the thyroid-stimulating hormone (TSH) and neutrophil-to-lymphocyte ratio (NLR) in hypothyroid Hashimoto's thyroiditis patients (R=0.220 and p=0.033).

study, patients diagnosed with HT showed higher NLR levels and lower PLR levels compared to the healthy control group, with statistical significance, contrary to previous literature studies. HT is merely an inflammatory process that is initiated by the stimulation of T lymphocytes by the autoimmune system, with an elevation particularly seen in NLR values. This agrees with several studies discussed in the literature review; in patients with hypothyroid HT, the NLR is typically ele-

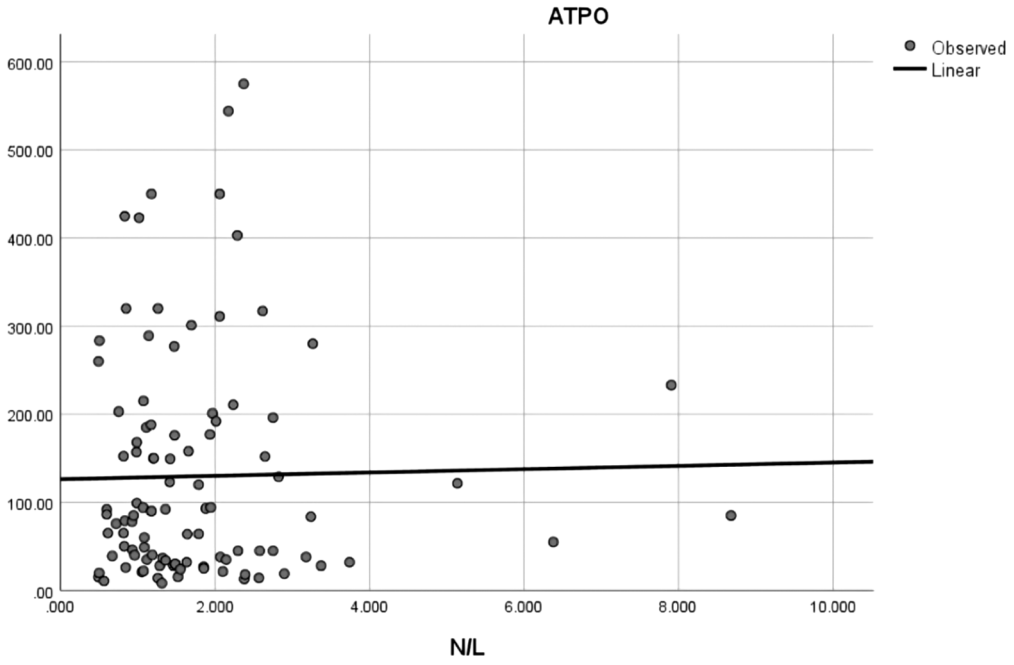

Figure 2. Scatterplot shows the correlation between the anti-thyroid peroxidase (ATPO) and neutrophil-to-lymphocyte ratio (N/L) in hypothyroid Hashimoto's thyroiditis patients (R=0.20 and p=0.846).

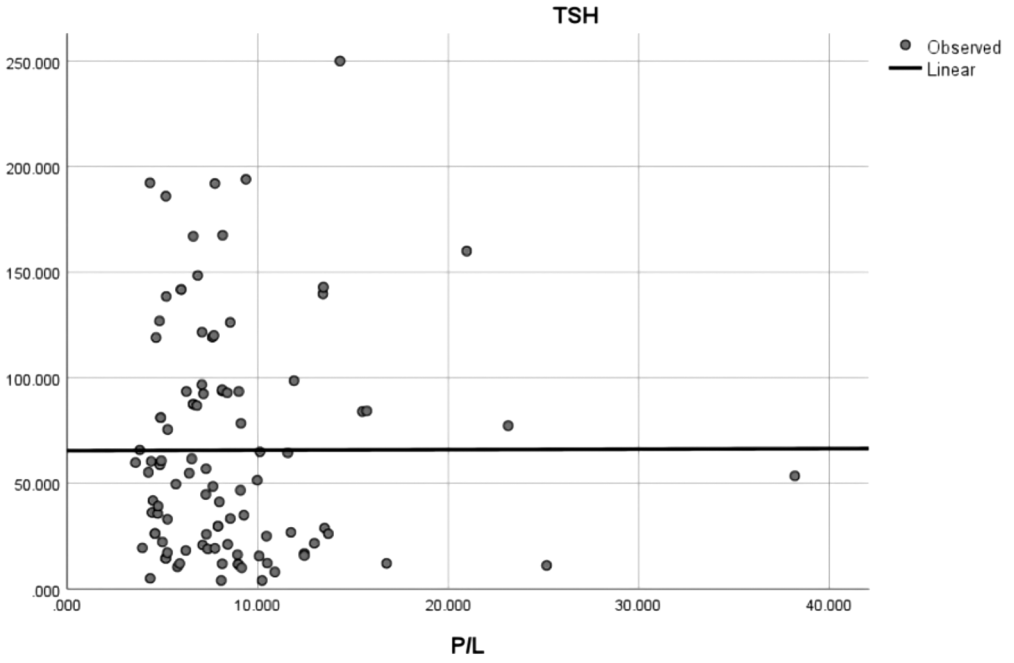

Figure 3. Scatterplot shows the correlation between the thyroid-stimulating hormone (TSH) and platelet-to-lymphocyte ratio (P/L) in hypothyroid Hashimoto's thyroiditis patients (R=0.02 and p=0.982).

vated. This is due to the increased inflammation associated with the autoimmune disorder, which leads to an increase in neutrophils and platelets and a decrease in lymphocytes. Elevated NLR values can be used to help diagnose HT and to monitor the effectiveness of treatment.[13] NLR and PLR are two important markers of inflammation that may be elevated in patients with hypothyroid HT. Recent studies have shown that patients with HT exhibit higher NLR and PLR when compared to healthy individuals, suggesting a state of systemic inflammation. These findings have been corroborated in both adults and adolescents with HT. The increased levels of NLR and PLR could potentially be used to monitor disease activity and thus guide treatment decisions. Therefore, it is important to evaluate NLR and PLR in patients with hypothyroid HT, as they are also available markers that can communicate important information about the inflammatory activity of the patient. Certain epidemiological studies have determined that chronic inflammation measured by NLR is correlated with other conventional risk factors such as obesity and hypertension. Recent studies have shown that an abnormal NLR level is related to autoimmune diseases.[14] PLR is calculated by dividing the absolute platelet count by the absolute lymphocyte count and is recommended as a potential marker to determine inflammation. Similarly, to NLR, PLR is also used as an index for the differential diagnosis of certain diseases, such as cancer and inflammatory diseases, and for the prediction of their prognoses.[15] Arpaci *et al*. found that NLR and PLR were significantly different in a group of HT patients

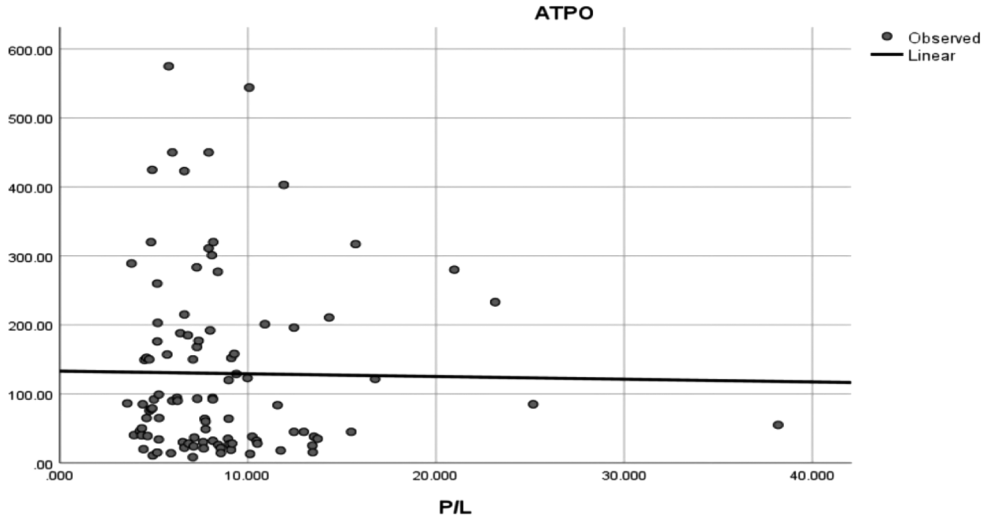

Figure 4. Scatterplot shows negative correlation between the anti-thyroid peroxidase (ATPO) and platelet-to-lymphocyte ratio (P/L) in hypothyroid Hashimoto's thyroiditis patients (R=-0.15 and p=0.881).

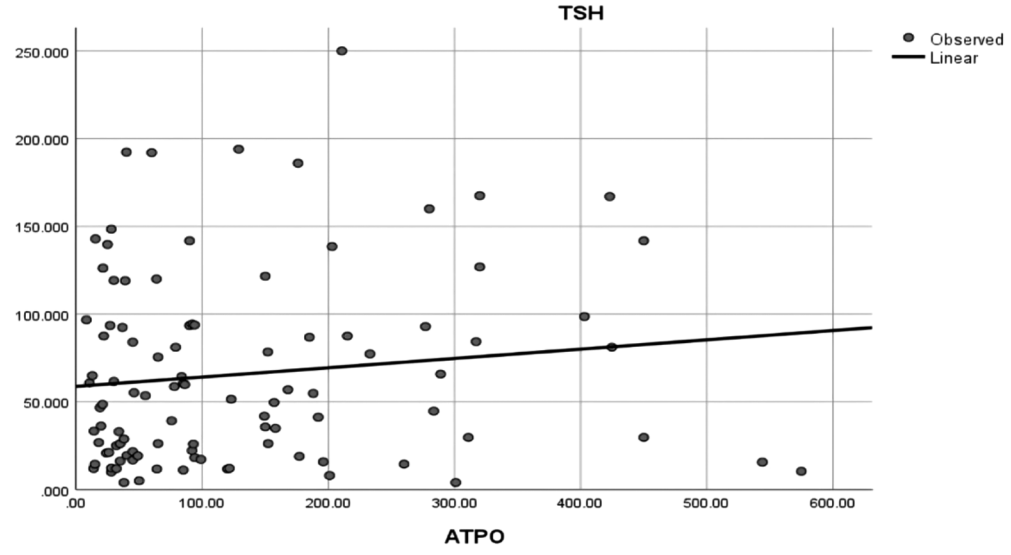

Figure 5. Scatterplot shows the positive correlation between the anti-thyroid peroxidase (ATPO) and thyroid-stimulating hormone (TSH) in hypothyroid Hashimoto's thyroiditis patients (R=0.126 and p=0.021).

compared to healthy individuals ($p<0.05$) in a study that involved 38 HT patients and 38 healthy controls.[16,17] A study conducted by Bilge *et al*. inspected 145 HT patients and 60 healthy age-matched females. The patient group demonstrated a lower lymphocyte count, whereas platelet count, NLR, and PLR were higher compared to the control group ($p<0.001$ for all comparisons).[18] The study concludes that patients diagnosed with HT demonstrated a higher NLR and a lower PLR value compared to the healthy control group with statistical significance, conforming with previous literature studies. HT is merely an inflammatory process that is initiated by the stimulation of T lymphocytes by the autoimmune system, and while we think that the increase in NLR could be related to the similar mechanisms involved in this process, we believe the low PLR levels that do not conform with data in literature could be connected to the limitations of our study. By determining statistically significantly higher NLR and lower PLR values in HT patients compared to the controls, our study can prove that NLR and PLR are useful indices in the detection of autoimmune diseases and inflammation. In addition, there was no negative or positive correlation between NLR and PLR and ATPO in our study. In addition to the increased PLR values, an increase in C-reactive protein (CRP) values was also observed, revealing a strong positive correlation between the PLR and CRP in the HT patients. In the present study, there was a significant weak positive correlation between TSH and ATPO in patients with HT (Figure 5) ($R=0.126$ and $p=0.021$) and a significant positive correlation between the levels of NLR and ATPO in HT patients (Figure 1) ($R=0.220$ and $p=0.033$). In this study, there is an insignificant negative correlation between the levels of PLR and ATPO in HT patients ($R=-0.15$ and $p=0.881$; $R=-0.15$ and $p=0.881$), and this outcome is in disagreement with the study done by Onalan and Dönder. In addition to the present findings, we determined that PLR and NLR were correlated with anti-TPO, TSH, and FT4, although without statistical significance. It has been discovered that there is a significant positive correlation between TSH, NLR with ATPO, and there is a significant negative correlation between PLR with ATPO.[19]

This study has several limitations that may impact the findings. First, the relatively small sample size of 150 participants could limit the generalizability of the results to broader populations. Additionally, a cross-sectional design restricts the ability to draw causal conclusions or assess changes over time. The strict exclusion criteria may introduce selection bias, as individuals with comorbidities were not included, potentially limiting the applicability of the findings. Furthermore, unaccounted confounding factors may influence NLR and PLR.

Conclusions

This study demonstrates that NLR is significantly elevated, and PLR is notably reduced in patients with hypothyroid HT compared to healthy controls. These findings indicate that NLR and PLR can serve as valuable inflammatory markers in assessing the severity of this autoimmune condition. Continued exploration of these markers could contribute to improved management strategies and a better understanding of the underlying mechanisms involved in HT. While our findings indicate a significant association between NLR, PLR, and hypothyroid HT, the relatively small sample size limits the extent to which these results can be generalized. Larger-scale studies are essential to confirm the utility of NLR and PLR as clinical markers in varying demographics.

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