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Original Article

Evaluation of the Relationship Between Thyroid Function Tests and Markers of Infection Severity in Children Presenting with Acute Infections

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ABSTRACT

Aim: In cases of mild to moderate infections, a phenomenon known as non-thyroidal illness syndrome may occur, characterized by reduced thyroid hormone levels despite an intact thyroid gland. This study aimed to investigate the relationship between thyroid function tests and inflammatory markers in children with acute infections.

Materials and Methods: Children under the age of 18 years who had previously presented to the Pediatric Outpatient Clinics of University of Health Sciences Türkiye, İzmir City Hospital with acute infections and had blood tests performed were included in this study. Data of thyroid functions and infection markers were collected from the records.

Results: A total of 50 patients and 112 individuals in a control group under the age of 18 years were included in this study. No statistically significant differences were observed between the groups in terms of demographic or baseline clinical characteristics. Serum triiodothyronine (T3) and thyroid-stimulating hormone levels were significantly lower in the patient group, while levels of C-reactive protein (CRP), procalcitonin, and erythrocyte sedimentation rate, as well as the CRP/lymphocyte ratio (CLR), neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) were significantly higher in the patient group. The median T3 level was significantly lower in the patient group. A subgroup analysis was performed in order to assess the relationship between T3 levels and complete blood count/infection markers. A negative correlation was observed between T3 levels and CRP, procalcitonin, neutrophil counts, as well as CLR, NLR, MLR, and disease severity.

Conclusion: Thyroid function tests, in conjunction with infection markers, may serve as potential predictive tools for clinical outcomes. There is a correlation between infection/inflammation markers and thyroid function in pediatric patients with acute infections.

Keywords: Inflammation, disease severity, non-thyroidal illness

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Introduction

Non-thyroidal illness (NTI) is a condition characterized by low thyroid hormone (TH) levels, typically without intrinsic thyroid gland dysfunction (1). As the severity of a critical illness worsens, there is initially a decline in triiodothyronine (T3) levels, followed by significant reductions in thyroxine (T4) and thyroid-stimulating hormone (TSH) over time. The reduction in T4 and TSH levels, particularly when T4 falls below 3 µg/dL, is associated with poor prognosis (2). Studies have shown that in cases of mild illness, serum T3 levels decline, and with an increasing severity and duration of the illness, serum T4 levels also decrease. Unlike primary hypothyroidism, these decreases in serum TH concentrations are not accompanied by an increase in serum TSH levels. This alteration in TH levels has been termed low T3 syndrome, euthyroid sick syndrome, or more recently, NTI syndrome (NTIS). The prevalence of NTIS is particularly high (up to approximately 80%) in critically ill patients with T4 levels below 3 µg/dL (2).

The bidirectional interaction between the hypothalamic-pituitary-thyroid axis and the immune system has been a topic of ongoing discussion for many years (3). Animal models have demonstrated that, in addition to TSH, THs such as T4 and T3 play a crucial role in the homeostatic regulation and functional activity of lymphocyte populations. The essential role of thyroid function in lymphopoiesis has been documented in numerous studies. In critically ill patients, particularly those in intensive care units (ICUs), a marked decline in T3 concentrations is commonly observed, followed by low or normal plasma T4 levels, while TSH concentrations may remain normal or become reduced (3-5).

Patients with severe illnesses have been reported to exhibit reduced TSH levels (6,7). Declines in serum T4 and TSH concentrations have been associated with increased mortality in cases of sepsis and septic shock, with the decrease in T4 identified as the most significant predictor of mortality (8-10). Studies have also investigated the potential effects of TSH and THs on various components of the immune system (11). Circulating TH levels have been found to correlate positively with immunological reactivity, such as the preservation of lymphocyte subpopulations, in healthy individuals (12).

A recent study suggested potential associations between TSH, and THs and lymphopenia observed during coronavirus disease-2019 (COVID-19) infections. It was demonstrated that patients with severe lymphopenia had significantly lower levels of TSH, free T3, and free T4, and higher levels of inflammatory markers, findings which are comparable to those seen in bacterial sepsis (13).

However, the extent to which changes in TSH and TH concentrations are linked to components of the immune system in patients with mild, moderate, or severe infections remains unclear. Based on the existing literature, it is hypothesized that abnormal thyroid function may be associated with changes in the infection markers observed in these patients. To date, the relationship between thyroid function and inflammatory markers in both infectious and non-infectious conditions in children has not been thoroughly examined.

In this study, we aimed to evaluate whether infection markers in children presenting with acute infections could serve as predictors of clinical outcomes and to assess their relationship with thyroid function tests.

Materials and Methods

This study was approved by the Non-interventional Ethics Committee of University of Health Sciences Türkiye, University of Health Sciences Türkiye, İzmir City Hospital, in accordance with the Helsinki Declaration (decision no.: 2025/18, date: 13.02.2025).

Children under the age of 18 years who had previously presented to the pediatric outpatient clinics of Izmir City Hospital with acute infections and had blood tests performed were included in this study. All patients had their weight, height, and body mass index recorded and evaluated according to age and sex norms. Any findings suggestive of acute infection or thyroid disease identified during physical examination were documented.

In the study group, the following laboratory parameters were recorded from the patient files: inflammatory markers including C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR); complete blood count parameters including hemoglobin, white blood cell count, neutrophils, lymphocytes, platelets, eosinophils, monocytes, and mean platelet volume; biochemical parameters including glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, and albumin; and thyroid function tests including free T3, free T4, and TSH. If available, anti-thyroglobulin and anti-thyroid peroxidase antibody levels were also recorded in order to exclude chronic thyroiditis.

Infections such as acute sinusitis, otitis media, and pneumonia were grouped as severe infections compared to acute upper respiratory tract infections and gastroenteritis as they require higher doses and longer duration of antibiotics.

A control group consisting of children of similar age who had no diagnosis of acute infection and who had undergone

haematological and biochemical testing for other reasons was also evaluated. In this group, the relationship between thyroid function tests and laboratory parameters was analysed and compared to the study group. Additionally, this study aimed to assess whether these laboratory parameters could be used to predict infection severity, to determine in which clinical scenarios thyroid function tests might provide diagnostic utility, and to evaluate when they might lead to diagnostic uncertainty, especially in distinguishing thyroid disease from transient changes due to infection.

Following power analysis, it was determined that a minimum of 50 patients and 112 controls would be required. Those patients with chronic diseases such as chronic kidney disease, type 1 diabetes mellitus, or celiac disease; those with signs of chronic inflammation or diagnosed with chronic inflammatory conditions; patients using medications known to affect thyroid function tests or infection markers (e.g., antidepressants, anticonvulsants, anxiolytics); and those with incomplete data were excluded from this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0. The distribution of the data was assessed using the Kolmogorov-Shapiro test. Descriptive statistics are expressed as numbers, percentages, means, and standard deviations for normally distributed variables, and as medians with interquartile ranges (25^{th}-75^{th} percentiles) for non-normally distributed variables. The Student's t-test was used to compare normally distributed variables between groups, while the Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were analysed using the chi-square test. Pearson or Spearman correlation analysis was performed in order to evaluate associations between parameters, depending on the data distribution. One-Way analysis of variance (ANOVA) was used to compare the mean values of continuous variables between the groups. Additionally, Tukey's post-hoc test was used for pairwise comparisons between the groups if the initial value of ANOVA test was statistically significant. The sample size was calculated based on a power analysis with 80% power ($1-\beta=0.80$) and a significance level of 5% ($\alpha=0.05$), which are commonly accepted thresholds in behavioural sciences.

Results

A total of 162 children under the age of 18 years, who had previously presented to the pediatric outpatient clinics and had blood tests performed for various reasons, were included in this study. Fifty patients with a documented diagnosis of acute infection (mean age: 5.77±3.91 years; 54% female, n=27) were designated as the study group. Thirty-two patients had presented as acute upper respiratory tract infections, 4 patients as acute otitis media, 7 patients as acute gastroenteritis, 2 patients as acute sinusitis and 5 patients as acute pneumonia. A control group of 112 children from a similar age range (mean age: 6.65±4.73 years; 54.5% female) who had no diagnosis of acute infection at the time of evaluation was also included. Demographic data, anthropometric measurements (adjusted for age and sex), and laboratory findings for all of the participants are presented in Table I.

Overall, free T3 and TSH levels were significantly lower in the patient group when compared to the control group, while CRP, procalcitonin, and ESR values, as well as the CRP/lymphocyte ratio (CLR), neutrophil/lymphocyte ratio (NLR), and monocyte/neutrophil to lymphocyte ratio, were significantly higher in the patient group when compared to the controls. Except for body weight, no statistically significant differences were observed in any other patient characteristics between the groups.

Based on the clinical findings (persistent high fever, prolonged illness, need for antimicrobial therapy) and laboratory parameters (leukocytosis, elevated CRP, and procalcitonin), the patients were categorized into "severe disease" and "mild disease" groups. Comparisons of thyroid function tests and infection markers were made between the control group and the patients with mild and severe disease. The laboratory characteristics of these subgroups are presented in Table II. Levels of free T3, TSH, ESR, and CLR differed significantly between the severe and mild disease groups. CRP levels and monocyte/neutrophil to lymphocyte ratios showed significant differences both between the overall control and patient groups and also according to disease severity. Procalcitonin levels and NLRs did not significantly differ between the control group and the mild disease subgroup but were significantly elevated in the severe disease group when compared to both the mild disease and control groups.

A subgroup analysis was conducted in order to examine the relationship between significantly decreased T3 levels and hemogram as well as other infection markers within the study group. The median T3 level in the study group was 3.96±0.75, which was significantly lower when compared to the control group. Table III presents the correlation between T3 levels and infection parameters. A negative correlation was found between T3 levels and CRP, procalcitonin, neutrophil count, CLR, NLR, monocyte/lymphocyte ratio (MLR), and disease severity.

Table I. Baseline characteristics of the cohort

Parameter	All participants (n=162)	Control group (n=112)	Study group (n=50)	p value
Age (years)	6.38±4.50	6.65±4.73	5.77±3.91	0.25
Female, n (%)	88 (54.3)	61 (54.5)	27 (54)	0.956
Free T3 (pg/mL)	4.31±0.70	4.47±0.61	3.96±0.75	<0.001
Free T4 (ng/dL)	1.33±0.16	1.33±0.15	1.34±0.19	0.743
TSH (µIU/mL)	2.67±1.51	3.06±1.52	1.80±1.06	<0.001
Weight SDS*	0.37±0.80	0.23±0.83	0.51±0.76	0.077
Height SDS*	0.78±1.03	0.63±1.04	0.92±1.01	0.167
BMI SDS*	-0.14±0.70	-0.17±0.71	-0.11±0.71	0.685
CRP (mg/L)	8.97±18.25	1.10±1.23	16.52±22.91	<0.001
Lymphocytes (/mm^3)	3,758±1,952	3,466±1,460	3,976±2,241	0.181
Procalcitonin (ng/mL)	0.10±0.18	0.05±0.02	0.15±0.24	0.003
ESR (mm/h)	8.29±7.78	5.24±3.92	11.30±9.36	<0.001
CRP/lymphocyte ratio	0.00365±0.00805	0.00037±0.00048	0.00687±0.01035	<0.001
Neutrophil/lymphocyte ratio	1.62±1.70	1.10±0.55	2.18±2.17	0.001
Monocyte/lymphocyte ratio	0.25±0.17	0.18±0.09	0.31±0.21	<0.001

*Standard deviation scores adjusted for age and sex
T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone, SDS: Standard deviation score, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table II. Baseline laboratory findings of the groups

Parameters	General control (n=112)	Mild illness (n=39)	Severe illness (n=11)	p value
T3 (pg/mL)	4.47±0.61	3.99±0.80[a]	3.86±0.60[b]	<0.001[a], 0.012[b]
T4 (ng/dL)	1.33±0.15	1.34±0.19	1.35±0.19	>0.05
TSH (µIU/mL)	3.06±1.52	1.76±0.86[a]	1.96±1.63[b]	<0.001[a], 0.039[b]
CRP (mg/L)	1.10±1.23	12.26±19.88[a]	31.64±27.35[b,c]	0.003[a], <0.001[b], 0.001[c]
Lymphocyte (/mm^3)	3,466±1,460	3,893±2,164	4,273±2,586	>0.05
Procalcitonin(ng/mL)	0.05±0.02	0.12±0.16[a]	0.28±0.36[b,c]	>0.05[a], <0.001[b], 0.013[c]
Sedimentation rate (mm/h)	5.24±3.92	10.59±7.41[a]	14.22±15.31[b]	0.002[a], 0.002[b]
CRP/lymphocyte ratio	0.00037±0.00048	0.00599±0.01062[a]	0.00999±0.00909[b]	0.002[a], <0.001[b]
Neutrophil/lymphocyte ratio	1.10±0.55	1.88±1.84[a]	3.24±2.95[b,c]	>0.05[a], <0.001[b], 0.03[c]
Monocyte/lymphocyte ratio	0.18±0.09	0.28±0.17[a]	0.40±0.31[b,c]	0.004[a], 0.037[b], <0.001[c]

Data are presented as mean ± standard deviation, *p<0.05
[a]indicates a significant difference between mild illness and control groups
[b]indicates a significant difference between mild illness and severe illness groups
[c]indicates a significant difference between severe illness and control groups
T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone, CRP: C-reactive protein

Table III. Pearson correlation of clinical parameters with T3 levels

Parameters	Crude r	p value
CRP	-0.210	0.039
Procalcitonin	-0.239	0.018
Sedimentation rate	-0.193	0.063
Neutrophil	-0.243	0.016
Platelet	0.156	0.123
Lymphocyte	0.132	0.193
AST	0.108	0.287
ALT	0.084	0.408
Albumin	0.009	0.928
CRP/lymphocyte ratio	-0.242	0.017
Neutrophil/lymphocyte ratio	-0.288	0.004
Monocyte/lymphocyte ratio	-0.267	0.008
Disease severity	-0.326	<0.001

T3: Triiodothyronine, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Discussion

In our study, T3 and TSH levels were found to be significantly lower in the patient group compared to the control group, while CRP, procalcitonin, sedimentation rate, and the ratios of CLR, NLR, and MLR were significantly higher.

NTIS refers to alterations in thyroid function tests observed during starvation, malnutrition, acute and chronic illnesses, or surgical procedures, despite the absence of primary thyroid disease. Various thyroid dysfunction patterns may be observed depending on the severity and progression of the underlying illness. In less severe illnesses, low T3 levels with normal or elevated T4 levels and normal or low TSH levels are expected. In our study, the patient group exhibited significantly decreased T3 levels. In acute illnesses, particularly in critically ill patients, a rapid decline in T3 levels may occur, known as "low T3 syndrome" (5). Previous studies have reported the presence of low T3 syndrome in approximately 60-70% of critically ill patients admitted to ICUs (14-16). When our patient group was stratified into "severe" and "mild" illness categories, T3 and TSH levels were significantly lower in the severe illness subgroup.

There is evidence suggesting the development of central hypothyroidism during severe NTIs. In such cases, the diurnal rhythm of TSH is disrupted, although the TSH response to TRH remains intact. Additionally, decreased messenger ribonucleic acid expression involved in TRH synthesis within the hypothalamic paraventricular neurons has been demonstrated. These findings collectively indicate TRH deficiency in severe NTIS. Consistent with this, TSH levels in our patient group were significantly lower when compared to the controls. During the recovery phase, TSH levels typically rise and may exceed normal limits before a normalization of TSH is observed (17).

When the patient group was categorized into "severe illness" and "mild illness," T3, TSH, sedimentation rates, and CLR were found to be significantly different between severe and mild illness, while CRP levels and MLRs differed both between the overall control and patient groups and according to disease severity. Procalcitonin levels and NLRs did not show significant changes when compared to the controls in the mild illness group; however, in the severe illness, these markers were significantly elevated in comparison to both the mild illness and control groups.

In a study examining low T3 syndrome during COVID-19 infection, patients within the lowest tertile of T3 levels demonstrated higher CRP levels and lower average lymphocyte counts (18). Another study assessing the relationship between acute illness severity and NTIS found a positive correlation between disease severity and reverse T3 (rT3) levels, with higher rT3 values associated with severe disease (19). The same study also reported a negative correlation between disease severity and total T3 and T4 levels, while no statistically significant relationship was found with free T3 and T4 levels (19).

In our study, NLR did not significantly differ between the controls and the mild illness patients but was significantly higher in the severe illness group when compared to both the mild illness and control groups. NLR, defined as the ratio of absolute neutrophil count to absolute lymphocyte count, is an accessible, cost-effective, and easily calculated marker considered a valuable measure of systemic inflammation (20-23). It has been linked to various inflammatory and cardiovascular diseases, with elevated levels observed in conditions such as obesity, hypertension, diabetes mellitus, metabolic syndrome, and several cancers (20-26). Recent studies have also explored the prognostic role of NLR in COVID-19, showing promising results for its use as a biomarker (27-30). NLR has demonstrated strong correlations with adverse outcomes and potential utility as a risk stratification tool (27,31,32). A meta-analysis reported that NLR consistently had the highest predictive value across multiple parameters of severe COVID-19, including disease

severity, ICU admission, progression to acute respiratory distress syndrome, the need for mechanical ventilation, the length and cost of hospital stay, time to negative PCR, and mortality (20).

Recent studies have also highlighted the association of elevated CLR with adverse outcomes in certain clinical contexts. For example, a meta-analysis by Lagunas-Rangel (33) indicated that increased CLR reflects poor prognosis in COVID-19 patients. Furthermore, elevated CLR has been suggested as a prognostic indicator of poor outcomes in patients with malignancies (34-36). Specifically, Mungan et al. (35) found that CLR was more effective than CRP alone in predicting poor prognosis following colorectal surgery. Studies evaluating the role of CLR in predicting disease severity have shown significantly higher ratios in patients with severe illness, although CLR was less predictive compared to NLR (20). Consistent with these findings, our study also observed significantly elevated CLR levels in the severe illness group when compared to the mild illness group.

The MLR has also been found to be associated with morbidity in various infections, inflammatory conditions, certain cancers, and psychiatric disorders such as depression and schizophrenia, and has been reported as a useful prognostic indicator in some studies (37-41). In our study, MLR was significantly higher in the mild illness group compared to the controls and was significantly elevated in the severe illness group when compared to both the mild illness and control groups.

T3 levels, which were significantly decreased in our patient group, showed negative correlations with CRP, procalcitonin, neutrophil counts, CLR, NLR, MLR, and disease severity. A single-centre retrospective study including adult COVID-19 patients classified into moderate, severe, and critical groups demonstrated that dynamic changes in CLR were inversely correlated with disease severity (42). In a retrospective study involving 306 patients with ulcerative colitis, NLR was suggested as a non-invasive marker of disease activity (43). Another study investigating the prognostic role of NLR and MLR during acute exacerbations of chronic obstructive pulmonary disease (COPD) showed that these ratios were elevated in COPD patients when compared to healthy controls, further increased during exacerbations, positively correlated with CRP, and were associated with increased mortality (33). However, data on the correlation of these markers with thyroid function tests remain limited.

It is widely accepted that NTI is a physiological adaptive response during severe disease, which reduces basal metabolic rate in order to minimize caloric and protein expenditure. Whether to treat these alterations remains a matter of debate. The literature includes studies evaluating thyroid function tests during infectious and inflammatory states, demonstrating that thyroid functions can be affected during infections. Several adult studies have assessed correlations between infection markers and hematologic parameters, reporting associations with disease severity. In this study, we demonstrated, for the first time in children, a significant correlation between thyroid function and markers of infection/inflammation, which also varied according to disease severity.

Study Limitations

Our study had some limitations. Its relatively small sample size in the severe illness group and its retrospective design limited the ability to confirm diagnoses with viral swabs or cultures as direct evidence of infection. Nevertheless, this study's novelty lies in it being the first to investigate the relationship between inflammatory markers and thyroid function in pediatric infectious and non-infectious diseases, with significant results obtained.

Conclusion

In conclusion, this is the first study to examine the relationship between markers of inflammation and thyroid function in children with infectious and non-infectious conditions. Thyroid function correlates with infection/inflammation markers in pediatric patients presenting with acute infections, and these correlations can be used to predict disease prognosis according to severity.

Ethics

Ethics Committee Approval: This study was approved by the Non-interventional Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital, in accordance with the Helsinki Declaration (decision no.: 2025/18, date: 13.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., E.E., B.N.D., Concept: G.A., Design: G.A., B.N.D., Data Collection or Processing: S.O., B.A., Analysis or Interpretation: G.A., E.E., Literature Search: G.A., E.E., Writing: G.A., E.E.

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