scientific reports

Check for updates

OPEN

Changes in thyroid hormone status following induction chemotherapy in patients with pediatric acute lymphoblastic leukemia

Jingzi Zhong, Haini Yang, Dan Zeng & Dan Lan✉

This study evaluates the prevalence and implications of Non-thyroidal Illness Syndrome (NTIS) in children with acute lymphoblastic leukemia (ALL), marking a focus shift towards pediatric patients who have been less studied in this context. Through a prospective analysis of 96 newly diagnosed ALL patients against healthy controls, we assessed thyroid function at diagnosis and after induction chemotherapy. Our findings highlight a significant reduction in T3/FT3 and FT4 levels in the ALL group, with NTIS prevalence jumping from 44.8% pre-chemotherapy to 74.2% post-chemotherapy, illustrating the profound impact of treatment-related factors and inflammation on thyroid health. Unlike previous beliefs, NTIS's occurrence was independent of ALL risk categories and induction therapy outcomes. Factors like elevated C-reactive protein, low serum albumin, and lymphoblast count emerged as NTIS risk indicators. Most thyroid dysfunctions normalized post-chemotherapy without needing hormonal interventions, suggesting a transient NTIS that favors conservative management focused on long-term monitoring. This study not only confirms the high incidence of NTIS in pediatric ALL patients but also challenges existing thyroid health management paradigms in pediatric oncology, calling for nuanced treatment approaches.

Keywords Non-thyroidal illness syndrome (NTIS), Acute lymphoblastic leukemia (ALL), Pediatric endocrinology, Chemotherapy, Thyroid function

Non-thyroidal illness syndrome (NTIS), also known as euthyroid sick syndrome or low T3 syndrome, is characterized by reduced levels of free triiodothyronine (FT3) and/or free thyroxine (FT4), with normal or decreased thyroid-stimulating hormone (TSH), in the absence of primary thyroid gland dysfunction[1]. NTIS frequently occurs in critically ill patients and reflects the severity of underlying health problems[2]. While NTIS has been extensively studied in adults with conditions such as sepsis, burn injuries, and heart failure, its characterization in children, particularly those with acute lymphoblastic leukemia (ALL), remains limited. Most pediatric NTIS studies focus on patients undergoing cardiac surgery for congenital heart defects, with sparse research on NTIS in children with ALL treated solely with chemotherapy.

The prognostic value of NTIS in identifying high-risk patients has been established in adult hematologic malignancies, such as diffuse large B-cell lymphoma and chronic lymphocytic leukemia, where NTIS is an independent predictor of progression-free survival and overall survival[3,4]. However, the association between NTIS and ALL in children, especially during the metabolically stressful induction chemotherapy phase, is underexplored. Induction chemotherapy for ALL induces significant systemic inflammation, altered energy metabolism, and treatment-related toxicities, which may exacerbate NTIS and impact treatment outcomes. Given the limited literature, there is a critical need to investigate the prevalence, risk factors, and prognostic implications of NTIS in pediatric ALL.

Previous studies on thyroid function in children with leukemia have primarily focused on long-term effects[5], with limited analysis of patterns during the induction remission stage. To address this gap, our study aimed to evaluate thyroid function, auxological changes, endocrinopathy/treatment factors, and the natural course of thyroid dysfunction in children with ALL during induction chemotherapy. Specifically, we sought to: (i) determine the prevalence and association of NTIS with ALL risk stratification, (ii) examine the relationship between clinical/metabolic parameters and thyroid hormones, and (iii) assess the role of NTIS as a prognostic tool during induction chemotherapy.

Department of Pediatrics, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. ✉email: landan@stu.gxmu.edu.cn

Methods

Patients and study design

This prospective study included inpatients diagnosed with ALL who were treated according to the South China Children's Leukemia Group-ALL-2016 (SCCLG-ALL-2016) protocol at the first affiliated hospital of Guangxi Medical University, from January 1, 2021 to January 31, 2024. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (NO.2022-KT-15). All methods were performed in accordance with the relevant guidelines and regulations. Blood samples were collected from children after signing an informed consent by their parents or relatives. To reduce selection bias, laboratory measurements of thyroid function were conducted using standardized chemiluminescent immunoassay techniques, and laboratory personnel were blinded to patient risk stratification and clinical outcomes. Additionally, data entry was verified by two independent investigators to minimize errors.

Exclusion criteria eliminated patients with a clear history of intrinsic thyroid disorders, those who had received thyroid function-altering drugs such as amiodarone, corticosteroids, and dopamine at admission, and patients with inherited metabolic or autoimmune diseases. Patients with Down syndrome were excluded due to their inherent risk of thyroid dysfunction, which could confound NTIS diagnosis.

The required sample size was calculated using an expected NTIS prevalence of 30% in pediatric ALL patients, with a power of 80% and a significance level of 5%. The minimum sample size required for cases and controls was determined to be 85 participants in each group. We recruited 104 ALL patients and 88 controls to account for potential dropouts. The control group consisted of 88 children admitted for growth assessment who were otherwise healthy with no known acute or chronic systemic illnesses, making them a suitable comparison group for assessing baseline thyroid function. While controls were not systematically matched to cases, no significant differences were observed in age or sex distribution between the two groups ($P > 0.05$).

Chemotherapy protocol

The chemotherapy protocol's drug classes and composition were consistent across both regimens. This included a diagnosis and assessment of sensitivity after 7 days of pretreatment with prednisone upon enrollment, followed by the initiation of VDLD (vincristine + dexamethasone + L-asparaginase + daunorubicin) induction remission therapy according to risk stratification criteria, and three triple intrathecal injections to prevent central nervous system (CNS) leukemia. Minimal residual disease (MRD) and bone marrow morphology examinations were performed on Day 15 and Day 33 to dynamically adjust the risk level, with dexamethasone tapering off between days 29–38.

Complete remission (CR) was defined as less than 5% lymphoblasts in active hematopoietic BM in the absence of clinical evidence of disease at the end of induction. Relapse was defined as the presence of lymphoblasts (> 25%) in the BM or on histological documentation of blasts in extramedullary sites after achievement of CR. MRD-positive on Day 15 was defined as MRD ≥ 0.1%, while MRD-positive on Day 33 was defined as MRD ≥ 0.01%.

Data collection

Data regarding age, sex, weight, height, body surface area (BSA), body mass index (BMI), somatotype, risk stratification, central nervous system (CNS) status, hospital stay, ICU admission were collected from medical records. Additional clinical data, including the need for mechanical ventilation, antihypertensive use, seizure history, hypoxemia, COVID-19 infection, neurocritical events, and fever with neutropenia, or coagulation dysfunction were collected and analyzed for potential associations with NTIS. Somatotype was categorized using BMI-for-age percentiles based on Chinese growth curves[6,7]: underweight (< 5th percentile), normal weight (5th–85th percentile), overweight (85th–95th percentile), and obese (> 95th percentile). Laboratorial data within 24 h after first ALL admission including white blood cell count (WBC) absolute lymphoblast count (ALC), hemoglobin (Hb), platelet count (PLT), liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), renal function (serum creatinine [SCr]), inflammatory markers (C-reactive protein [CRP]), tumor burden-related indices (lactate dehydrogenase [LDH], uric acid [UA]), albumin, and prealbumin. Treatment-related data included the number of RBC transfusions and grams of albumin administered during induction. Non-chemotherapy drugs (e.g., antihypertensive, antibiotics, antifungals, antivirals) used during induction were documented. Complications such as febrile neutropenia, severe infections (e.g., sepsis), coagulopathy, hepatotoxicity (ALT/AST > 2.5 times upper limit of normal), and neurotoxicity (e.g., seizures, hypoxemia) were recorded. COVID-19 infection status was assessed via PCR testing.

2.4. Thyroid function and NTIS definition

The thyroid function was evaluated at the time of ALL diagnosis and the day 33 evaluation in all patients via chemiluminescent immunoassay (AutoBio 12 Co., Ltd., Zhengzhou, China). If the thyroid function was abnormal in the day 33 evaluation, thyroid function would be assessed again after early intensive CAM therapy.

Euthyroidism was defined based on standard reference ranges[8,9]: FT3 3.45–6.50 pmol/L, FT9.65–23.01 pmol/L, TSH 0.27–4.2 μIU/mL. NTIS was defined when (F)T3 and/or (F)T4 were decreased and TSH concentrations were normal or decreased.

Liver function was assessed using ALT (normal: 11–45 U/L) and AST (normal: 14–50 U/L)[10], with hepatotoxicity defined as ALT/AST > 2.5 times the upper limit of normal.

AKI was defined according to the Kidney Disease/Improving Global Outcomes (KDIGO) serum creatinine and/or urine output criteria[11]:

Stage 1: Serum creatinine 1.5–1.9 × baseline or ≥ 0.3 mg/dL (≥ 26.5 μmol/L) increase, or urine output < 0.5 mL/kg/h for 6–12 h.

Stage 2: Serum creatinine 2.0–2.9 × baseline or urine output < 0.5 mL/kg/h for ≥ 12 h.

Stage 3: Serum creatinine 3.0 × baseline or urine output < 0.3 mL/kg/h for ≥ 24 h, or anuria for ≥ 12 h.

Statistical analysis

All data were analyzed by using the Statistical Package for Social Sciences version 20.0 software (SPSS Inc., Chica go, IL) and the data entry was examined twice. All data underwent tests for normality and homogeneity of variances.

Descriptive analysis was conducted, with normally distributed measurements represented by mean ± standard deviation, and non-normally distributed measurements displayed as median and interquartile range (IQR) [P50(P25, P75)]. Incidence rates and other count data were described using frequency and percentage. The independent samples t-test was used to analyze differences between groups for normally distributed continuous data, while the paired samples t-test was used for within-group comparisons before and after treatment. The Mann–Whitney U test was applied to non-normally distributed data. Count data were analyzed using the chi-square or Fisher's exact test. Factors such as gender, age stratification, risk levels, and immunophenotypes were tested using the chi-square test. Univariate and multiple linear regression analyses distinguished factors independently influencing thyroid function, with a log transformation of TSH data for linear regression. Univariate and multivariate logistic regression analyses pinpointed risk factors for NTIS. Data significance was based on a two-tailed test, with thresholds set at $P < 0.1$ for univariate and $P < 0.05$ for other analyses.

Missing data were assessed for key variables, including thyroid function tests, clinical parameters, and treatment outcomes. The extent of missing data was minimal, with less than 5% of patients missing any single variable, primarily due to hospital discharge (n = 8) or death (n = 7) before the Day 33 evaluation. Missing data were handled using complete case analysis, whereby only patients with complete data for a given analysis were included. To assess the potential impact of missing data, the baseline characteristics of patients with missing data were compared with those of patients with complete data. Sensitivity analyses to assess the robustness of findings to missing data were not performed, which is noted as a limitation in the discussion section.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

General characteristics

Our study commenced with 88 healthy children and 104 newly diagnosed ALL patients. After excluding 8 ALL patients due to hospital discharge, 96 participants (79 B-lineage, 17 T-lineage) remained (Table 1). Seven patients died during the study, but 89 completed the Day 33 evaluation and received induction remission treatment (VDLD) (see Fig. 1). No significant differences in age or sex distribution were found between the control group and the ALL group ($P > 0.05$). The ALL patient demographics included 63 boys (65.6%) and 33 girls (34.4%), with a mean age of 6.78 ± 3.86 years. Risk stratification categorized participants as low risk (LR) in 22.9% (22 cases), intermediate risk (IR) in 37.5% (36 cases), and high risk (HR) in 39.6% (38 cases). No cases of COVID-19 infection, renal failure, seizures, significant neurotoxicity or use of antihypertensive were observed. Three of seven deaths (42.9%) had NTIS. Causes of death included sepsis (n = 4, 57.1%), multiple organ dysfunction (n = 2, 28.6%), and leukemia progression (n = 1, 14.3%). Among the 7 deceased patients, all required ICU admission (median ICU stay: 5 days, IQR: 3–7). Missing data were minimal, with less than 5% of patients missing any single variable, primarily due to hospital discharge (n = 8) or death (n = 7) before the Day 33 evaluation. The baseline characteristics (e.g., age, sex, risk stratification) of patients with missing data did not differ significantly from those of patients with complete data ($P > 0.05$ for all comparisons).

Thyroid function comparison and change

Prior to treatment initiation, thyroid function profiles were compared between the ALL cohort and healthy controls. ALL patients had lower T3 ($P < 0.001$), FT4 ($P < 0.001$), and FT3 ($P < 0.001$) compared to controls, with no significant differences in T4 ($P = 0.112$) or TSH ($P = 0.087$) (Table 2).

Among the 96 ALL patients evaluated at baseline, 54 (56.3%) cases presented with abnormal thyroid function, including low FT3, low FT4, high FT4, high TSH and low TSH levels. NTIS characterized by low FT3 and/or low FT4 levels with normal or reduced TSH concentrations, was identified in 37.5% (36/96) of the cohort. Of the 54 cases with abnormal thyroid function, 28 (29.2%) had low serum FT3 levels and/or low FT4 levels indicative of NTIS, with either normal (25 patients, 26%) or reduced (3 patients, 3.2%) serum TSH levels. Eight patients (8.3%) exhibited low FT4 levels with normal FT3 and TSH levels. Eleven patients (11.5%) had high FT4 levels with normal FT3 and TSH levels. Two patients (2%) had reduced serum TSH levels but normal FT3 levels. Eleven patients (11.5%) presented with increased serum TSH levels but normal FT3 and FT4 levels (see Fig. 2). Patients with abnormal TSH and normal peripheral thyroid laboratory values were formally classified as having subclinical hyperthyroidism or subclinical hypothyroidism, although these changes may have a different interpretation in ALL patients, potentially indicating NTIS. Patients with NTIS displayed significantly lower thyroid hormone levels compared to those without NTIS ($P < 0.05$).

Following induction chemotherapy, 69/89 (77.5%) cases exhibited abnormal thyroid function. The prevalence of NTIS increased to 74.2% (66/89), with significant decreases in T3, T4, FT4, and TSH levels observed, while FT3 levels did not change markedly (Table 3, Fig. 3). Among the 69 cases with abnormal thyroid function, 50 (56.2%) had low serum FT3 levels and/or low FT4 levels indicating NTIS, either with normal (37 patients, 41.6%) or reduced (13 patients, 14.6%) serum TSH levels. Thirteen patients (14.6%) had low FT4 levels with normal FT3, either with normal (13 patients, 14.6%) or reduced (3 patients, 3.3%) serum TSH levels. Two patients (2%) had high FT4 levels with normal FT3 and TSH levels. Three patients (3.4%) had reduced serum TSH levels but normal FT3 levels. One patient (1.1%) presented with non-manifested hypothyroidism (Fig. 2). Of the 66 NTIS cases identified post-induction treatment, 28 had pre-existing NTIS, while 38 were newly diagnosed.

Feature	Value
Initial diagnosis age, years,mean (range)	6.78 (1.5–15)
Sex, N (%)	
Male	63 (65.6)
Female	33 (34.4)
BMI, SDS, mean (SDS)	− 0.73 (− 5.98 to 2.09)
WBC 10^9 /L, mean (range)	59.82 (0.78–480.10)
Haemoglobin g/L, mean (range)	83.05 (31.40–136.00)
PLT 10^9/L, mean (range)	100.60 (5.00–961.00)
ALC 10^9/L, mean (range)	33.51 (0.38–243.40)
CRP mg/L,mean (range)	24.63 (0.50–145.04)
ALB g/L, mean (range)	39.64 (28.60–48.30)
Prealbumin mg/L,mean (range)	145.74 (59.70–335.50)
LDH U/Lmean (range)	929.38 (152.00–4347.00)
Uric acid umol/L, mean (range)	425.03 (105.00–2678.00)
Somatotype N (%)	
Normal weight	81 (84.38)
Underweight	10 (10.42)
Overweight	5 (5.21)
Immunophenotype N (%)	
B-lineage	79 (82.30)
T-lineage	17 (17.70)
Risk stratification N (%)	
Low risk	22 (22.90)
Intermediate risk	36 (37.50)
High risk	38 (39.60)
Outcome number N (%)	
Complete remission	82 (85.40)
Relapse	7 (7.30)
Deceased	7 (7.30)
Hospital stay, day, mean (range)	31 (22.25–33)

Table 1. Clinical and laboratory characteristics of 96 patients at ALL onset. SDS, standard deviation score; BMI, body mass index; ALB, serum albumin; LDH, lactate dehydrogenase; ALC,absolute lymphoblast count.

NTIS rates and induction treatment outcome

Before treatment, the incidence of NTIS in the LR, IR, and HR groups was 9.4%, 11.5%, and 16.7%, respectively. The incidence of NTIS before and after treatment did not significantly differ among the risk groups ($p = 0.551$), indicating that risk stratification did not affect the incidence rate of NTIS in ALL patients. Based on the induction treatment outcomes, patients were divided into three groups: complete remission (CR), no response (NR), and deceased. The NTIS rates were 31.3%, 3%, and 3%, respectively, with no significant differences observed ($P = 0.829$).

Correlation of NITS with clinic, metabolic and inflammatory markers

At ALL onset, participants with NTIS had higher CRP levels ($p < 0.001$), lower hemoglobin ($p = 0.010$), albumin ($p = 0.026$), and prealbumin ($p = 0.005$) levels compared to non-NTIS participants (see Table 4). After the complete of the induce VDLD therapy, participants with NTIS continued to show lower hemoglobin ($p = 0.043$), longer median hospital stay ($P = 0.004$) (see Table 5). No significant differences in clinical factors like age, sex, BSA, risk stratification, leukocyte count, immunophenotype, risk stratification, absolute lymphoblast count, WBC count, LDH, UA, ALT, AST between NTIS and non-NTIS groups (all $P > 0.05$). Among the 89 case complete the VDLD therapy, RBC transfusions, albumin administration, ICU admission rates, complications included mechanical ventilation, febrile neutropenia, and coagulation dysfunction did not differ significantly.

Factors associated with thyroid function indicators and NTIS

Univariate logistic regression analysis revealed that FT3 levels negatively correlated with CRP and positively correlated with hemoglobin and albumin. Multivariate analysis confirmed the positive correlation between FT3 and hemoglobin. FT4 levels positively correlated with underweight somatotype. TSH levels did not correlate with any clinical or laboratory factors. For NTIS, univariate logistic regression identified higher CRP and lower hemoglobin, albumin, and prealbumin as risk factors. Multivariate analysis confirmed higher CRP (OR = 1.021, 95% CI 1.002, 1.041, $P = 0.0034$) and lower hemoglobin (OR = 0.962, 95% CI 0.931–0.994, $P = 0.021$) as independent risk factors for NTIS (see Tables 6 and 7).

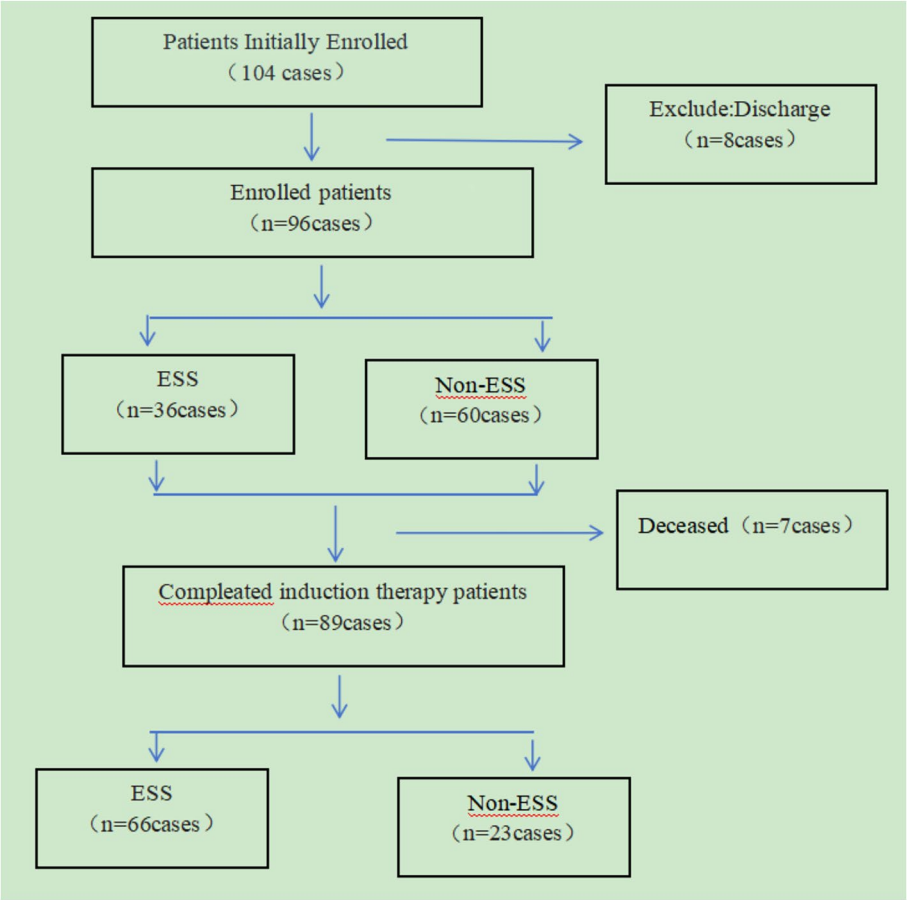

Fig. 1. A flow chart detailing the selection of patients in this study.

Variable	Normal control group (n = 88)	ALL group (n = 96)	*P* value
Age (years) mean (SDS)	6.3 (4.9, 10.0)	5.6 (3.6, 10.1)	0.185
Gender, Male (%)	51 (58.0)	63 (65.6)	0.284
T3 (nmol/L)	2.34 ± 0.31	1.51 ± 0.48	**< 0.001**
T4 (nmol/L)	110.12 ± 20.70	116.42 ± 29.90	0.096
FT3 (nmol/L)	5.49 ± 0.64	3.63 ± 0.90	**< 0.001**
FT4 (pmol/L)	15.68 ± 2.77	12.74 ± 3.46	**< 0.001**
TSH (mIU/L)	2.08 (1.51, 2.74)	2.43 (1.30, 4.33)	0.123

Table 2. A comparison between the thyroid function of the normal and ALL groups. fT3, free triiodothyronine, fT4, free thyroxine, TSH, thyroid stimulating hormone. Significant values are in [bold].

Thyroid function follow up

66 cases exhibited abnormal thyroid function in day33 evaluated. 21 cases' thyroid Function were monitored in the flowing therapy. Most (20/21) of their thyroid function recover without replacement therapy. One of them still had low T3, T4 and TSH levels at the end of the treatment regimen, and there was a suspected diagnosis of hypothyroidism. The patient was then given replacement therapy by administration of levothyroxine. He was followed up during the whole chemotherapy period. Finally, his thyroid hormone levels recovered before the evaluation of maintained treatment, and then levothyroxine was withdrawn (see Fig. 4).

Discussion

NTIS in pediatric leukemia: an under-explored territory

NTIS in children is less studied compared to adults, with prior research primarily focusing on pediatric patients undergoing cardiac surgery for congenital heart defects. There is a lack of comprehensive characterization of NTIS in children with ALL, particularly during induction chemotherapy. Our study provides novel insights into the prevalence, progression, and risk factors of NTIS in pediatric ALL patients. We found a high prevalence of

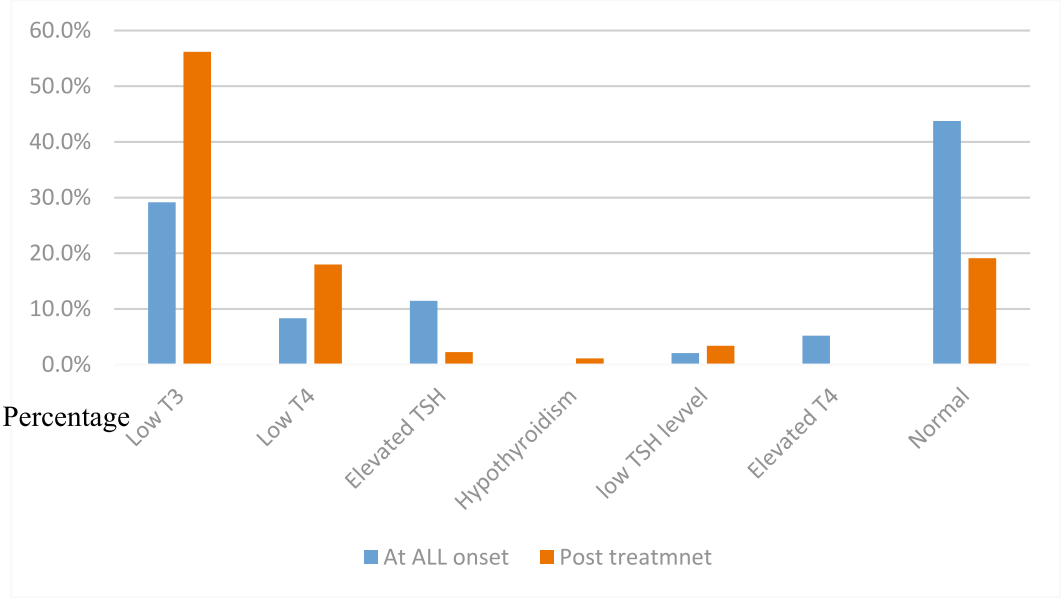

Fig. 2. The variations of thyroid function observed be before and after treatment. Pre-treatment, NTIS was identified in 37.5% of the cohort. The prevalence of NTIS increased to 79.8% post-treatment.

	At ALL onset	Post treatment	*P* value
T3, nmol/L	1.52 ± 0.48	1.21 ± 0.60	< **0.001**
T4, nmol/L	117.31 ± 30.12	58.22 ± 20.90	< **0.001**
FT3, nmol/L	3.66 ± 0.88	3.59 ± 1.22	0.663
FT4, pmol/L	12.78 ± 3.39	10.52 ± 2.68	< **0.001**
TSH, mIU/L	2.54 (1.30, 4.44)	1.10 (0.51, 2.12)	< **0.001**

Table 3. Thyroid hormone concentrations before and after treatment. fT3, free triiodothyronine, fT4, free thyroxine, TSH, thyroid stimulating hormone. Significant values are in [bold].

thyroid function abnormalities, with NTIS identified in 37.5% of patients at baseline, increasing to 74.2% post-induction chemotherapy. These findings align with prior reports of NTIS in pediatric ALL populations, 66.67% case were diagnosed with NTIS during induction chemotherapy[12], but lower than the prevalence of chronic lymphocytic leukemia(14.34%)[3] and diffuse large B cell lymphoma(12.77%)[4] in adults.

Few studies have assessed thyroid function in ALL patients before chemotherapy[1]. A study conducted in 1988[13] involved 41 children with ALL found that the FT3 level was significantly decreased before the start of therapy. However, it is important to note that this study is quite dated (1988), our study provides updated data, showing significant reductions in T3, FT4, and FT3, reflecting changes in treatment protocols and diagnostic precision over time. Low T3 syndrome was the most common form, though other patterns, such as low T4 or combined low T3/T4, were also observed.

Transient nature of NTIS and implications for thyroid replacement therapy

The marked increase in NTIS prevalence post-induction is a key finding, not previously reported in ALL populations. Induction chemotherapy, including vincristine, dexamethasone, L-asparaginase (L-Asp), and daunorubicin, likely exacerbates NTIS through multiple mechanisms. First, chemotherapy can be considered a severe stress on the body that induces a strong inflammatory response, as evidenced by higher CRP levels in NTIS patients ($P < 0.001$), which negatively correlated with FT3 levels. Second, chemotherapy agents like methotrexate and L-Asp impair thyroid function by inhibiting iodine uptake and coupling. Glucocorticoids, used in our protocol, further suppress FT4 and TSH levels, consistent with prior studies[14]. A 1992 A Ferster et al[15]'s study attributed thyroid dysfunction during ALL induction to L-Asp, but our use of Peg- asparaginase (Peg-Asp), a modified form, warrants further investigation into dosage-related effects on thyroid hormones.

In our cohort, most of the thyroid hormone recovered after the induce CAM chemotherapy period. This aligns with literature highlighting NTIS's transiency during acute illness phases and questions the necessity for NTIS treatment. Although Hui Yu et al.[12] suggested levothyroxine benefits for clinical hypothyroidism (low FT4/FT3 with symptoms), they found no survival benefit in subclinical cases. However, their definition of hypothyroidism (low FT4/FT3) overlaps with NTIS, complicating interpretation. In our study, most of the patients recover without replacement therapy aligns with previous reports that illustrate the transient nature of NTIS during

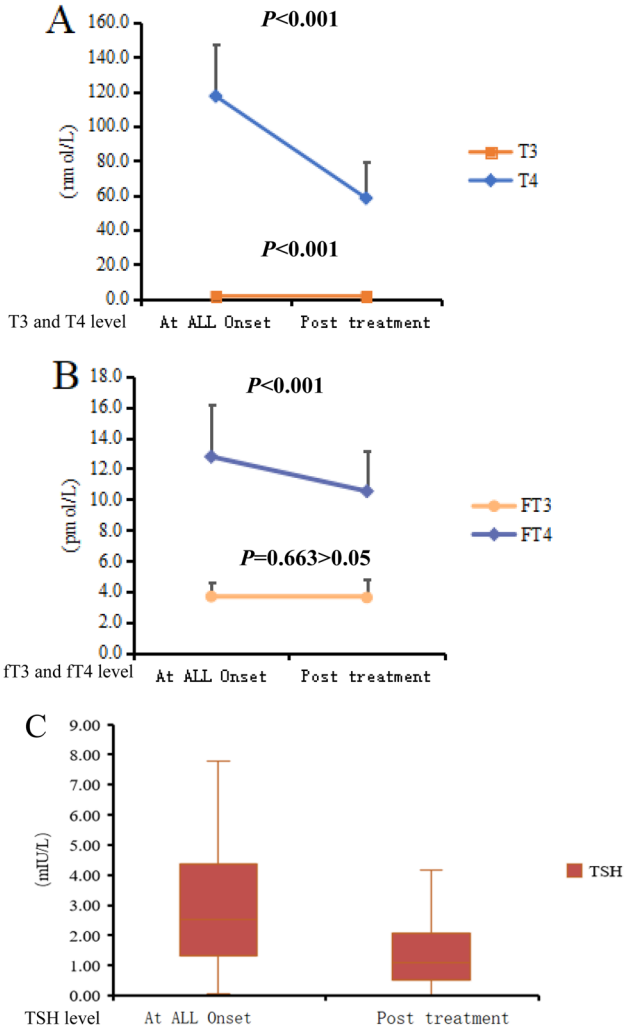

Fig. 3. The changes in thyroid hormone levels before and after treatment. Post treatment, the thyroid function significantly decreases in T3, T4, FT4, and TSH levels, while FT3 levels did not change markedly. (**A**) Change of T3 and T4; (**B**) Change of FT3 and FT4. (**C**) Change of TSH level.

phases of acute illness. Replacement therapy is not recommended for low T3 syndrome, such alterations might be a physiologic adaptation to counteract excessive catabolism and support the immune response during the acute phase. In our experience, thyroid function generally returns to normal as the acute illness resolves. But we should pay attention to the thyroid complications in long-term survivors. V. G. Bebeshko[5] found that incidence of thyroid disease in children who had been treated for ALL and being subsequently in remission which lasted from 6 to 25 years was 22.8%. In addition, the incidence of hypothyroidism and autoimmune thyroiditis in these patients was 14.1 and 7.6%, respectively. The high prevalence of NTIS in patients with ALL and the extent of HPT axis changes in these patients can make it difficult to distinguish NTIS from untreated primary hypothyroidism. Long term follow-up of thyroid function in children with ALL is crucial, and more prospective clinical study learning when and how to admin levothyroxine should be conducted.

NTIS: adaptive significance and clinical impacts

While the clinical implications of NTIS are unclear, some evidence links NTIS with worse outcomes like increasing mortality[16]. In contrast, the present results did not detect an association between different risk, the induction stage clinical endpoints and NTIS. Methodological differences and limited samples may account for discrepancies between studies. Larger and longer prospective investigations are still needed to definitively characterize NTIS as an independent prognostic factor. On the other hand, our data underscore the lack of significant difference in the rate of NTIS across different risk classifications of ALL, which adds a new dimension to the existing literature that typically correlates greater severity of underlying illness with higher NTIS rates. The findings might suggest that ALL and its treatment alone are sufficient to induce NTIS, regardless of the risk category. This conjecture warrants further investigation to elucidate the mechanisms that link NTIS with leukemia, independent of disease severity.

Clinic feature	Non-NTIS (n = 60)	NTIS (n = 36)	*P*
Initial diagnosis age (years) mean (range)	5.29 (3.6, 8.3)	6.5 (3.6, 12.3)	0.194
Sex number (%)			0.781
Male	40 (41.7)	23 (24.0)	
Female	17 (20.8)	13 (13.5)	
Body surface area, m^2	0.87 ± 0.22	0.76 ± 0.2	0.584
Immunophenotype N (%)			0.369
B-lineage	51 (53.1)	28 (29.2)	
T-lineage	9(9.4)	8 (8.3)	
Somatotype N (%)			0.328
Normal weight	50 (52.1)	31 (32.3)	
Underweight	8 (8.3)	2 (2.1)	
Over weight	2 (2.1)	3 (3.1)	
Risk stratification N (%)			0.551
Low risk	13 (13.5)	9 (9.4)	
Intermediate risk	25 (26.0)	11 (11.5)	
High risk	22 (22.9)	16 (16.7)	
Outcome N (%)			0.829
Complete remission	52 (54.2)	30 (31.3)	
Relapse	4 (4.2)	3 (3.1)	
Deceased	4 (4.2)	3 (3.1)	
BMI-SDS	− 0.92 ± 1.40	− 0.43 ± 1.15	0.080
ICU admission rates (%)	11.7 (12.3)	13.9 (14.8)	0.759
WBC, $\times 10^9$/L	12.45 (6.16, 60.79)	7.79 (2.46, 73.86)	0.184
Haemoglobin, g/L	87.17 ± 20.66	76.17 ± 18.08	**0.010**
PLT, $\times 10^9$/L	73.00 (35.28, 119.55)	46.95 (29.95, 127.85)	0.160
ALC, $\times 10^9$/L	9.90 (3.71, 34.19)	5.68 (1.92, 27.79)	0.057
CRP, mg/L	3.60 (0.86, 15.22)	18.02 (7.19, 68.67)	**0.001**
ALB, g/L	40.37 ± 3.89	38.43 ± 4.09	**0.026**
Prealbumin, mg/L	151.1 (121.1, 177.0)	123.6 (96.8, 152.9)	**0.022**
LDH, U/L	555.0 (351.0, 1090.5)	479.5 (325.5, 1292.8)	0.666
Uric acid, umol/L	316.0 (248.0, 431.5)	297.0 (202.8, 459.0)	0.403
AST, U/L	34 (26, 56.25)	32 (24.25, 47.5)	0.486
ALT, U/L	15 (10.25, 25.75)	13.5 (11, 23.75)	0.808
CREA, umol/L	30 (25, 39.75)	32 (28, 41.5)	0.182

Table 4. Clinical and laboratory characteristics of 96 patients and of the patients with and without NTIS at ALL onset. ALC, absolute lymphoblast count; ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase, CREA, creatinine. Significant values are in [bold].

Inflammatory mediators, nutrition, and thyroid dysfunction

The underlying mechanisms of NTIS are multifaceted and incompletely understood. A leading hypothesis is that inflammatory mediators like cytokines and inflammatory signal transduction inhibit thyroid hormone production and conversion. The current study found thyroid dysfunction was associated with increased inflammation biomarkers including CRP. Inflammatory reaction played an important role in thyroid dysfunction of ALL. In previous study[17], significantly higher CRP was found in Coronavirus disease with NTIS. Furthermore, On Day 33, participants with NTIS show longer median hospital stay. This aligns with studies in critically ill adults, where NTIS is associated with prolonged hospitalization and increased resource utilization[18]. The longer stay in NTIS patients may reflect greater illness severity. Interesting, the hemoglobin levels was correlated with NTIS. Participants with NTIS had lower hemoglobin levels when diagnosis. Gao, R. et al.'s study in chronic lymphocytic leukemia patients found that serum T3 was positively correlated with anemia (Hb)[3]; Hideaki Tsuji et al.'s study[19] rheumatoid arthritis patients with low fT3 were with lower hemoglobin. A decrease in hemoglobin levels indicates anemia, which can lead to reduced oxygen delivery to tissues and organs. This can impair the body's ability to maintain normal metabolic processes, potentially contributing to the development of NTIS[20].

Furthermore, we identified associations between thyroid function and factors related to metabolism, such as albumin and prealbumin levels. These findings lend weight to previous reports suggesting malnutrition and systemic illness, which often result in hypoalbuminemia, can substantially contribute to the development of NTIS[21]. It is also known that NTIS is associated with nutritional intake. Pierluigi Marzuillo[22] reported that participants with NTIS had lower BMI in T1DM population. Keşkek's study[23] found a potent association between NTIS and obesity patients without any comorbid disease. In our study, NTIS was not related to BMI

Clinic feature	Non-NTIS (n = 23)	NTIS (n = 66)	*P*
Initial diagnosis age (years) mean (range)	5.0 (3.3,7.7)	5.6 (3.6,10.4)	0.509
Sex, N (%)			0.126
Male	18 (20.2)	40 (44.9)	
Female	5 (5.6)	26 (29.2)	
Risk stratification N (%)			0.068
Low risk	3 (3.4)	19 (21.3)	
Intermediate risk	13 (14.6)	20 (22.5)	
High risk	7 (7.9)	27 (30.3)	
Immunophenotype N (%)			0.799
B-lineage	19 (21.3)	56 (62.9)	
T-lineage	4 (4.5)	10 (11.2)	
CNS leukemia, N (%)			0.601
CNS < 2,	21 (23.6)	63 (70.8)	
CNS ≥ 2,	2 (2.2)	3 (3.4)	
D33 Bone marrow morphology, N (%)			0.128
Complete remission	19 (21.3)	63 (70.8)	
Relapse	4 (4.5)	3 (3.4)	
D33 MRD, N (%)			0.954
< 0.01%	21 (23.6)	60 (67.4)	
≥ 0.01%	2 (2.2)	6 (6.7)	
BMI-SDS	− 0.81 ± 1.78	− 0.71 ± 1.12	0.763
Somatotype, N (%)			0.200
Normalweight	18 (20.2)	57 (64.0)	
Underweight	2 (2.2)	7 (7.9)	
Overweight	3 (3.4)	2 (2.2)	
Hospital stay, day, mean (range)	33 (31–36)	30.5 (20–33)	0.004
ICU admission rates (%)	4.3 (4.9)	6.1 (7.0)	0.760
Mechanical ventilation, N (%)	6 (10)	4 (11.1)	0.859
Febrile neutropenia, N (%)	33 (55)	19 (36.5)	0.067
Coagulation dysfunction, N (%)	12 (21.7)	13 (36.1)	0.114
RBC transfusion, N (%)	3.09 ± 2.275	2.91 ± 1.982	0.722
Albumin substitution, N (%)	0.43 ± 1.441	1.14 ± 2.601	0.115
WBC, × 109/L	12.49 (8.19, 60.52)	8.85 (3.01, 26.25)	0.080
Haemoglobin,g/L	89.75 ± 18.32	79.78 ± 20.54	0.043
PLT, × 109/L	52.00 (28.90, 122.30)	71.95 (34.15, 123.48)	0.439
ALC, × 109/L	11.75 (3.99, 35.16)	6.78 (2.29, 19.07)	0.082
CRP, mg/L	8.78 (0.81, 24.32)	8.78 (1.40, 39.23)	0.792
ALB, g/L	39.65 ± 4.56	39.76 ± 3.95	0.910
Prealbumin, mg/L	142.60 ± 51.66	147.12 ± 48.33	0.705
LDH, U/L	636.0 (501.0,851.0)	490.0 (312.5, 1173.8)	0.177
Uric acid, umol/L	287.0 (215.0,315.0)	320.5 (247.8, 407.0)	0.105
AST, U/L	26 (20,31)	24 (17, 30.5)	0.786
ALT, U/L	41 (29,58)	37.5 (27, 58)	0.940
CREA, umol/L	17 (13,18)	17 (14, 23.25)	0.535

Table 5. Clinical and laboratory characteristics of the 89 patients in this study based on those with and without NTIS on day 33. CNS, central nervous system; MRD: Minimal residual disease.

and obesity somatotype at diagnosis. Future research could focus on longitudinal studies to assess changes in BMI and nutritional status over time in relation to NTIS development and resolution in this patient population.

Limitations and future directions

This study has several limitations. First, controls were not systematically matched to cases, which may introduce confounding despite the lack of significant age or sex differences. Second, patients with missing thyroid function data were excluded from certain analyses, potentially introducing selection bias. Although the extent of missing data was minimal, and the baseline characteristics of patients with missing data did not differ significantly from those with complete data, the exclusion of these patients may have affected the generalizability of our findings.

Clinical factors	FT3				FT4				TSH			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	P	β (95% CI)	*P*
Somatotype, N (%)												
Normal weight	1				1				1			
Underweight	0.347 (−0.247, 0.940)	0.249			2.527 (0.275, 4.779)	**0.028**			0.165 (−0.113, 0.443)	0.242		
Overweight	−0.605 (−1.417, 0.208)	0.143			0.471 (−2.704, 3.646)	0.769			0.006 (−0.379, 0.391)	0.977		
BMI-SDS	−0.133 (−0.269, 0.003)	0.055			−0.326 (−0.857, 0.205)	0.226			−0.022 (−0.086, 0.043)	0.508		
WBC, $\times 10^9$/L	−0.001 (−0.003, 0.000)	0.13			−0.001 (−0.008, 0.006)	0.837			0.000 (−0.001, 0.000)	0.26		
Haemoglobin,g/L	0.013 (0.004, 0.021)	**0.004**	0.012 (0.004, 0.021)	**0.006**	0.009 (−0.026, 0.044)	0.615			0.002 (−0.002, 0.006)	0.328		
ALC, $\times 10^9$/L	−0.001 (−0.005, 0.002)	0.417			0.003 (−0.010, 0.015)	0.691			7.546E−6 (−0.002, 0.002)	0.992		
CRP, mg/L	−0.005 (−0.010, 0.000)	**0.035**	−0.003 (−0.009, 0.002)	0.181	0.005 (−0.015, 0.025)	0.63			−0.002 (−0.004, 0.000)	0.083		
ALB, g/L	0.052 (0.008–0.096)	**0.022**	0.011 (−0.038, 0.060)	0.659	0.055 (−0.120, 0.229)	0.535			−0.001 (−0.022, 0.021)	0.962		
Prealbumin, mg/L	0.004 (0.000, 0.007)	0.05			−0.003 (−0.017, 0.012)	0.701			0.001 (−0.001, 0.003)	0.164		
LDH, U/L	0.000 (0.000, 0.000)	0.128			0.001 (0.000, 0.001)	0.146			−2.972E−5 (0.000, 0.000)	0.517		
Uric acid., umol/L	0.000 (−0.001, 0.000)	0.294			0.000 (−0.001, 0.002)	0.777			−6.268E−5 (0.000, 0.000)	0.532		
AST, U/L	−0.001 (−0.006, 0.004)	0.652			−0.005 (−0.024, 0.014)	0.594			−0.003 (−0.014, 0.008)	0.583		
ALT, U/L	−0.001 (0.003, −0.036)	0.779			−0.002 (−0.022, 0.019)	0.877			−0.004 (−0.016, 0.008)	0.503		
CREA, umol/L	−0.010 (−0.020, 0.000)	0.061			−0.006 (−0.048, 0.036)	0.778			−0.005 (−0.029, 0.020)	0.711		
Hospital stay, day, mean (range)	0.017 (2.723, 4.400)	0.14			−0.029 (−0.121, 0.064)	0.540			0.012 (−0.042, 0.066)	0.661		

Table 6. Univariate and multivariate analysis of factors correlating with FT3, FT4, and TSH. The lgx logarithm transformation Perform was Performed in TSHa analysis. Significant values are in [bold].

Third, sensitivity analyses were not performed to assess the robustness of our findings to key methodological choices. This limits our ability to evaluate the impact of these factors on our results and may reduce the generalizability of our findings. Fourth, while NTIS was identified as transient in most cases, long-term thyroid function was not systematically evaluated. Future studies should include larger cohorts, sensitivity analyses, and long-term follow-up to address these limitations.

Conclusion

NTIS is prevalent in children with newly diagnosed ALL and increases following induction chemotherapy, independent of ALL risk classification. Inflammatory markers, particularly CRP, and lymphoblast count are significant predictors of NTIS. These findings suggest that NTIS in pediatric ALL may be driven by treatment-related inflammation rather than nutritional status. This work underscores the importance of considering NTIS in the differential diagnosis of thyroid dysfunction in ALL, shaping future therapeutic strategies for managing thyroid health in pediatric leukemia patients.

Clinical factors	Univariate		Multivariate	
	β (95% CI)	*P*	β (95% CI)	*P*
Initial diagnosis age (years) mean (range)	1.081 (0.972, 1.202)	0.078		
Sex N (%)				
Male	1			
Female	0.885 (0.372, 2.104)	0.782		
Immunophenotype N (%)				
B-lineage	1			
T-lineage	0.618 (0.214, 1.779)	0.372		
BMI-SDS	1.371 (0.956, 1.966)	0.086		
Somatotype N (%)				
Normal weight	1			
Underweight	0.403 (0.080, 2.023)	0.270		
Overweight	2.419 (0.383, 15.301)	0.348		
Risk stratification N (%)				
Low risk	1			
Intermediate risk	0.636 (0.210, 1.923)	0.422		
High risk	1.051 (0.362, 3.051)	0.928		
Outcome N (%)				
Complete remission	1			
Relapse	1.300 (0.272, 6.205)	0.742		
Deceased	1.300 (0.272, 6.205)	0.742		
WBC, $\times 10^9$/L	1.000 (0.996, 1.004)	0.820		
Haemoglobin, g/L	0.970 (0.947, 0.994)	**0.013**	0.962 (0.931, 0.994)	**0.021**
PLT, $\times 10^9$/L	0.997 (0.993, 1.002)	0.245		
ALC, $\times 10^9$/L	0.998 (0.991, 1.006)	0.672		
CRP, mg/L	1.019 (1.006, 1.032)	**0.005**	1.021 (1.002, 1.041)	**0.034**
ALB, g/L	0.883 (0.791, 0.985)	**0.026**		
Prealbumin, mg/L	0.990 (0.980, 1.000)	**0.046**		
LDH, U/L	1.000 (1.000, 1.000)	0.976		
Uric acid, umol/L	1.000 (0.999, 1.001)	0.727		
AST, U/L	1.000 (0.988, 1.012)	0.969		
ALT, U/L	1.005 (0.992, 1.017)	0.456		
CREA, umol/L	1.015 (0.990, 1.040)	0.241		
Hospital stay, day, mean (range)	0.997 (0.948, 1.049)	0.913		

Table 7. Analysis of factors potentially associated with NTIS. Significant values are in [bold].

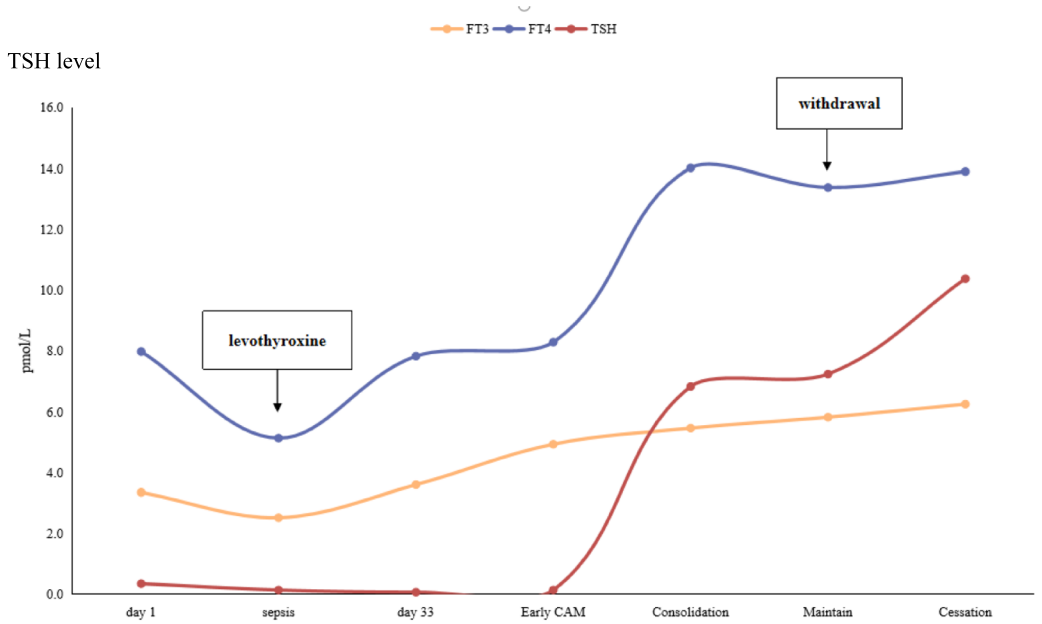

Fig. 4. Thyroid function of one case in this study who was treated with levothyroxine.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Received: 17 June 2024; Accepted: 24 June 2025
Published online: 08 July 2025

References

1. Fliers, E. & Boelen, A. An update on non-thyroidal illness syndrome. *J. Endocrinol. Invest.* **44**, 1597–1607. https://doi.org/10.1007/s40618-020-01482-4 (2021).
2. Abdelgawad, T. A., Magdy, S. M., Mahmoud, R. A. A., Taha, S. I. & Ali, S. A. E. Frequency of non-thyroidal illness syndrome in pediatric patients with sepsis and septic shock. *Egypt. Pediatr. Assoc. Gaz.* **70**, 32 (2022).
3. Gao, R. et al. Low T3 syndrome as a predictor of poor prognosis in chronic lymphocytic leukemia. *Int. J. Cancer* **143**, 466–477. https://doi.org/10.1002/ijc.31327 (2018).
4. Gao, R. et al. Low T3 syndrome is a strong prognostic predictor in diffuse large B cell lymphoma. *Br. J. Haematol.* **177**, 95–105. https://doi.org/10.1111/bjh.14528 (2017).
5. Bebeshko, V. G. et al. Thyroid disease in the late observation period upon chemo and radiotherapy in children/survivors of acute lymphoblastic leukemia. *Probl. Radiac. Med. Radiobiol.* **26**, 309–318. https://doi.org/10.33145/2304-8336-2021-26-309-318 (2021).
6. Zong, X. N. & Li, H. Construction of a new growth references for China based on urban Chinese children: comparison with the WHO growth standards. *PLoS ONE* **8**, e59569. https://doi.org/10.1371/journal.pone.0059569 (2013).
7. Li, H., Zong, X. N., Ji, C. Y. & Mi, J. Body mass index cut-offs for overweight and obesity in Chinese children and adolescents aged 2–18 years. *Zhonghua Liu Xing Bing Xue Za Zhi* **31**, 616–620 (2010).
8. Loh, T. P., Sethi, S. K. & Metz, M. P. Paediatric reference interval and biological variation trends of thyrotropin (TSH) and free thyroxine (T4) in an Asian population. *J. Clin. Pathol.* **68**, 642–647. https://doi.org/10.1136/jclinpath-2015-202916 (2015).
9. Verburg, F. A. et al. Reference ranges for analytes of thyroid function in children. *Horm. Metab. Res.* **43**, 422–426. https://doi.org/10.1055/s-0031-1275326 (2011).
10. Chang, Y., Li, H., Ren, H., Xu, H. & Hu, P. Misclassification of chronic hepatitis B natural history phase: Insight from new ALT, AST, AKP, and GGT reference intervals in Chinese children. *Clin. Chim. Acta; Int. J. Clin. Chem.* **489**, 61–67. https://doi.org/10.1016/j.cca.2018.11.034 (2019).
11. Kellum, J. A. & Lameire, N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit. Care* **17**, 204. https://doi.org/10.1186/cc11454 (2013).
12. Yu, H. et al. Hypothyroidism in induction chemotherapy of children with acute lymphoblastic leukaemia: A single-centre study. *Int. J. Cancer* **153**, 669–680. https://doi.org/10.1002/ijc.34535 (2023).
13. Perrone, L. et al. Endocrine function in childhood acute lymphoblastic leukemia before and during therapy. *J. Pediatr. Hematol. Oncol.* **10**, 123–125 (1988).
14. Rupprecht, R., Rupprecht, C., Rupprecht, M., Noder, M. & Mahlstedt, J. Triiodothyronine, thyroxine, and TSH response to dexamethasone in depressed patients and normal controls. *Biol. Psychiat.* **25**, 22–32. https://doi.org/10.1016/0006-3223(89)90143-1 (1989).
15. Ferster, A., Glinoër, D., Van Vliet, G. & Otten, J. Thyroid function during L-asparaginase therapy in children with acute lymphoblastic leukemia: Difference between induction and late intensification. *Am. J. Pediatr. Hematol. Oncol.* **14**, 192–196. https://doi.org/10.1097/00043426-199208000-00002 (1992).
16. El-Ella, S. S. A., El-Mekkawy, M. S. & El-Dihemey, M. A. Prevalence and prognostic value of non-thyroidal illness syndrome among critically ill children. *An. Pediatr. (Engl. Ed)* **90**, 237–243. https://doi.org/10.1016/j.anpedi.2018.01.021 (2019).
17. Zou, R. et al. Euthyroid sick syndrome in patients with COVID-19. *Front. Endocrinol. (Lausanne)* **11**, 566439. https://doi.org/10.3389/fendo.2020.566439 (2020).

18. Geslot, A., Chanson, P. & Caron, P. Covid-19, the thyroid and the pituitary—the real state of play. *Ann. Endocrinol. (Paris)* **83**, 103–108. https://doi.org/10.1016/j.ando.2021.12.004 (2022).
19. Tsuji, H. et al. Persistent anemia and hypoalbuminemia in rheumatoid arthritis patients with low serum triiodothyronine level. *Mod. Rheumatol.* **30**, 640–647. https://doi.org/10.1080/14397595.2019.1649109 (2020).
20. Carreras, L. et al. Non-thyroidal illness syndrome and its relationship with mortality risk in critically ill children. *Front. Pediatr.* **11**, 1142332. https://doi.org/10.3389/fped.2023.1142332 (2023).
21. Besci, T. et al. Biochemical indicators of Euthyroid sick syndrome in critically ill children. *J Pediatr Endocrinol Metab* **35**, 1285–1292. https://doi.org/10.1515/jpem-2022-0232 (2022).
22. Marzuillo, P. et al. Euthyroid sick syndrome and its association with complications of type 1 diabetes mellitus onset. *Pediatr. Res.* **94**, 632–642. https://doi.org/10.1038/s41390-023-02494-5 (2023).
23. Keşkek, Ş et al. Obesity without comorbidity may also lead to non-thyroidal illness syndrome. *Adv. Clin. Exp. Med.* **27**, 1515–1520. https://doi.org/10.17219/acem/70226 (2018).

Acknowledgements
We wish to thank our patients for their support and collaboration. We wish to thank Dr. Dev Sooranna, from Imperial College London for editing the manuscript.

Author contributions
DZ and H Yang collected the specimens， the relevant clinical information and summarized all the information and analyzed the results and together with DL and J Zhong drafted the manuscript. All the authors read and approved the final manuscript.

Funding
We thank the Guangxi Self-funded Research Projects (grant no. Z-A20220552), and the Key Laboratory of Children's Disease Research in Guangxi's Colleges and Universities, Education Department of Guangxi Zhuang Autonomous Region for funding this project.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
We confirm that we have read the Journal's position on issues involved in the ethics of publication and affirm that this report is consistent with those guidelines. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (NO. 2022KY-E-15). Written informed consent was obtained from the participants in the study.

Consent for publication
Consent for publication was obtained from all participants included in the study.

Additional information
Correspondence and requests for materials should be addressed to D.L.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025