



# Thyroid Function Tests in Critically Ill Children; Any Correlation with Disease Severity or Outcome?

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## Abstract

**Background:** Sick euthyroid syndrome (SES) is the most common endocrine disorder in critically ill patients. It has been shown that the decrease in T4 levels correlates with disease severity and prognosis. Whether SES is a compensatory response to the disease course or needs to be treated is not known yet.

**Objectives:** To our knowledge, there are only a few studies on critically ill infants and children investigating the correlation between thyroid function and disease severity as well as its outcome. Therefore, this study aimed to investigate thyroid hormone levels in critically ill patients.

**Methods:** In this study, thyroid function tests including thyroid stimulating hormone (TSH), total T3 (TT3), free T3 (FT3), total T4 (TT4), free T4 (FT4), and reverse T3 (rT3) were measured in 35 critically ill children admitted to intensive care unit (ICU) on days 1 and 3 of admission. Disease severity was evaluated using pediatric logistic organ dysfunction score (PELOD). Then the patients were divided into groups of survivors and non-survivors and the results were compared between these two groups accordingly.

**Results:** Thirty-five patients, including 19 (54.3%) female and 16 (45.7%) male, with the mean age of 2 years (SD:  $\pm 3.8$  years, range: 4 months -15 years) had entered the study based on the inclusion criteria. 25 (71.6%) patients were transferred from PICU to other wards and 10 (28.4%) patients died. Age and sex were not statistically different in survivors and non-survivors ( $P > 0.05$ ). It was revealed that there was a significant reduction in mean TT3 levels in non-survivors compared to survivors on the first day of admission ( $P = 0.007$ ). On the third day of admission, however, a significant reduction in TT4 levels were seen in non-survivors ( $P = 0.03$ ).

**Conclusions:** Thyroid function assessment, especially TT3 on the first day and TT4 on the third day of admission, along with PELOD score, might be helpful in predicting disease outcome and patient's survival.

**Keywords:** Thyroid Function Tests, Critically Ill Patients, PELOD Score

## 1. Background

Sick euthyroid syndrome (SES), is the most common endocrine disorder in critically ill patients (1). This syndrome is defined as low levels of three-iodothyronine (T3), low or normal levels of thyroxine (T4) and normal levels of thyroid stimulating hormones (TSH) in the serum (2). In critically ill patients, the most common disorder in thyroid hormones is low T3 levels (3). Additionally, T4 level also decreases with disease severity (4-6) and it has been shown that low T4 level is associated with prognosis (7-10). Whether SES promotes recovery and is adaptive or it is a direct result or cause of the illness and organ failure and therefore maladaptive is unclear (2). On the other hand,

there is not enough information on the effectiveness of thyroid hormones replacement in critically ill patients (11).

So far, most studies on thyroid function and its association with prognosis or illness severity have been carried out on adults, especially surgical patients (12,13), and there are only a few studies on critically ill children. Therefore, this study was performed to evaluate thyroid function in critically ill children to assess the correlation between thyroid hormone levels and disease outcome.

## 2. Methods

This is a single center, cross sectional study conducted in the pediatric intensive care unit (PICU) at Children's

Medical Center affiliated to Tehran University of Medical Sciences. Children admitted to the PICU within a 4 months (March 2016 to June 2017) period were enrolled in this study.

In this study, a critically ill child is referred to as a child who has functional impairment in one or more organs or body systems, and requires supportive care to maintain the function (14). Thirty five patients with the mean age of 2 years (range, 4 months - 15 years) were evaluated. Patients who did not have a prior history of thyroid disease were considered eligible for recruitment. Age, sex, the reason for ICU admission, length of stay in the hospital and in the intensive care unit, and number of days the patient was on mechanical ventilation were also recorded. The severity of the patient's condition was assessed using pediatric logistic organ dysfunction (PELOD) scores (15). Mortality and survival were also recorded. In order to evaluate disease severity on the first and the third days of admission using PELOD score, the most undesirable clinical and laboratory findings during the early 24 hours (referred to as PELOD-24) as well as over the 48 to 72 hours of ICU admission (referred to as PELOD-72) were considered. Blood samples for the evaluation of thyroid hormone profile including TSH, total T3 (TT3), total T4 (TT4), free T3 (FT3), free T4 (FT4), and reverse T3 (rT3), were also obtained accordingly. Serum thyroid hormones were measured by the enhanced chemiluminescence (ECL) method in the laboratory of the Children's Medical Center using the Chemiluminescence System Kit (Nichols Institute Diagnostics, San Juan Capistrano, USA). Serum RT3 was assayed by using enzyme-linked immunosorbent assay (ELISA) (DBC Kit, Ontario, Canada). Results were summarized collectively and compared according to survival status in two groups of survivors and non-survivors. The local ethics committee approved this study and written informed consent was obtained from the patients' parents.

### 2.1. Statistical Analysis

In this study, SPSS software version 21 was used for data analysis. To compare the levels or the mean of two independent samples of quantitative data, *t*-test with independent samples was used. Non-parametric Mann-Whitney U test was used in cases where the distribution of data was not normal. Chi-square test ( $\chi^2$ ) was used to determine the correlation between two qualitative variables in two or more independent groups.

## 3. Results

Thirty-five patients were enrolled in the study (16 boys, 19 girls; mean age, 2 years; SD:  $\pm 3.8$  year; range, 4 month -15

**Table 1.** Reasons for PICU Admission of Patients

	Number	Percent (%)
Respiratory distress	20	57.1
Loss of consciousness	11	31.4
Diabetic ketoacidosis	2	5.7
Multiple trauma	1	2.9
Post operation	1	2.9

years). Reasons for ICU admission are listed in Table 1. Seventeen patients discharged and two patients died in less than 72 hours of their admission to PICU. Therefore, 16 patients were evaluated on the third day of PICU admission. Overall, 25 (71.6%) patients were transferred from PICU to other wards and 10 (28.4%) patients died. Age and sex were not statistically different in survivors and non-survivors ( $P > 0.05$ ).

In addition, duration of mechanical ventilation was significantly longer in non-survivors ( $13.10 \pm 16.98$  days) compared to survivors ( $3.32 \pm 6.46$  days  $P = 0.001$ ). Mean hospital stay in survivors and non-survivors was 16.00 days (SD:  $\pm 11.48$ ), and 26.20 days (SD:  $\pm 27.07$ ), respectively. In addition, PICU stay was significantly longer in non-survivors ( $P = 0.02$ ) (Table 2).

Although mean TT3, TT4, FT3, and FT4 levels on the first day of admission were lower in non-survivors, only TT3 and FT3 mean levels were within abnormal ranges. However, it was revealed that there was a statistically significant reduction only in mean TT3 levels in non-survivors compared to survivors on the first day of admission ( $P = 0.007$ ). No significant changes were seen in mean rT3 and TSH levels in both groups on the first and the third days of admission.

Comparing mean levels of FT3, FT4, TT3, and TT4 on the third day of admission between survivors and non-survivors, there was a significant decrease in mean TT4 levels in non-survivors ( $P = 0.03$ ).

Regarding illness severity assessment, mean calculated PELOD scores on the first day of admission were 10.08 (SD:  $\pm 8.39$ ) and 25.50 (SD:  $\pm 14.44$ ) in survivors and non-survivors respectively. Hence, PELOD score on the first day of admission (PELOD-24) was significantly higher in non-survivors. PELOD score on the third day of admission (PELOD-72) showed rather the same results (Tables 3 and 4). Higher PELOD-24 correlated with lower TT3 levels on the first and the third day of admission. On the other hand, higher PELOD-72 correlated with lower TT3, TT4, FT4 levels on the first day and lower TT3, FT3 levels on the third day.

**Table 2.** Demographic Data, Hospital and ICU Stay and Duration of Mechanical Ventilation in Survivor and Non-Survivor Groups

Variables	Survivors (n = 25)	Non-Survivors (n = 10)	P Value
Age (months) <sup>a</sup>	37.72 ± 42.14	66.20 ± 66.94	0.35
Gender (f/m)	16/9	3/7	0.07
Hospital stay (days) <sup>a</sup>	16.00 ± 11.48	26.20 ± 27.07	0.27
ICU stay (days) <sup>a</sup>	7.12 ± 7.92	15.20 ± 16.65	0.02
Mechanical ventilation (days) <sup>a</sup>	3.32 ± 6.46	13.10 ± 16.98	0.001

<sup>a</sup>Values are expressed as mean ± SD.**Table 3.** PELOD Parameters and Thyroid Function Tests in Survivors and Non-Survivors on the First Day of Admission

Variables	Survivors (n = 25) <sup>a</sup>	Non-Survivors (n = 10) <sup>a</sup>	P Value
PELOD-24	10.08 ± 8.39	25.50 ± 14.44	0.008
TT3-24 (ng/dL)	100.46 ± 27.60	76.70 ± 18.85	0.007
TT4-24 (microg/dL)	6.40 ± 1.57	5.1 ± 2.32	0.132
FT3-24 (picomol/L)	3.36 ± 0.88	3.07 ± 1.36	0.46
FT4-24 (ng/dL)	1.10 ± 0.29	0.90 ± 0.29	0.078
TSH-24 (mIU/mL)	3.16 ± 6.10	5.73 ± 6.97	0.67
rT3-24 (ng/mL)	0.33 ± 0.24	0.43 ± 0.24	0.276

<sup>a</sup>Values are expressed as mean ± SD.**Table 4.** PELOD Parameters and Thyroid Function Tests in Survivors and Non-Survivors on the Third Day of Admission

Variables	Survivors (n = 8) <sup>a</sup>	Non-Survivors (n = 8) <sup>a</sup>	P Value
PELOD-72	4.88 ± 5.38	29.25 ± 14.73	0.002
TT3-72 (ng/dL)	120.79 ± 100.71	67.87 ± 41.40	0.177
TT4-72 (microg/dL)	7.56 ± 3.34	3.94 ± 2.86	0.030
FT3-72 (pmol/L)	3.89 ± 1.46	2.96 ± 1.53	0.222
FT4-72 (ng/dL)	1.29 ± 0.66	0.78 ± 0.45	0.085
TSH-72 (mIU/mL)	1.45 ± 1.81	2.09 ± 3.95	0.685
rT3-72 (ng/mL)	0.57 ± 0.23	0.67 ± 0.30	0.484

<sup>a</sup>Values are expressed as mean ± SD.

#### 4. Discussion

According to previous studies, sick euthyroid syndrome (SES) is the most common endocrine disorder in critically ill patients (1). In our study, 77.14% of the critically ill children on the first day and 100% of the patients on the third day of admission showed some evidence of sick euthyroid syndrome.

As shown by Galusova et al., evaluation of thyroid hormones serially on days 1, 2, 3, and 7 is more valuable than a one-time measurement (16). Accordingly, in our study, evaluation of thyroid function tests (TFT) on the third day of admission seemed to be more valuable than TFT on the first day in predicting disease outcome. That is because TFT on the third day showed more variation compared to the

TFT on the first day and was associated with illness severity based on PELOD-72. So that patients with higher PELOD-72 scores had greater thyroid dysfunction (notably TT3 and FT3 level on the third day), while this correlation was less observed between TFT on the first day of admission and the illness severity on the same day based on PELOD-24 (only at the TT3 level on the first day).

In previous studies the decrease in TT3 levels was the most common form of the sick euthyroid syndrome (3), in our study also, most patients had low TT3 levels on the first day of admission.

Since there was a significant reduction in mean TT3 levels on the first day of admission and mean TT4 levels on the third day of admission in survivors compared to

non-survivors, it can be concluded that in assessing thyroid function on the first day of admission, TT3 levels and the third day of admission, TT4 levels would be better predictors of outcome or survival rate. In a study by Van den Berghe et al. also, it has been shown that TT4 levels may decrease during the prolonged phase of an illness compared to the acute phase (17).

In the present study, illness severity on the first day correlated with lower TT3 levels as well as lower FT3 and TT3 on the third day of admission. In contrast, in a study by Maldonado et al., only TT4 levels associated with illness severity and could be considered as a prognostic factor (18). However, there are controversial results in the literature regarding parameters related to thyroid function and prognosis (19-21).

Meyer et al. showed that FT3 and TT3 levels were not associated with prognosis in the acute phase of a disease (22), while in the study of Ture et al., there was a significant difference between FT3 levels in survivors and non-survivors (23). Additionally, as shown in a study by F Wang et al., FT3 was the most powerful and the only independent predictor of ICU mortality amongst the other thyroid function indicators (24). However, most studies have been conducted on adult patients that are physiologically different from children. A systematic review of the literature on children and adolescents with a history of septic shock showed that there is a correlation between thyroid function impairment in critically ill patients and the disease outcome (25).

In our study, mean TSH levels on the first and the third day of admission, in spite of changes in other components of the thyroid function tests, were within the normal range, and therefore confirmed the euthyroid state in hospitalized patients. It has been shown that TSH may increase in the acute phase of the disease and return to normal levels during the course of an illness. However, in case of decreased thyroid hormones, normal levels of TSH are considered abnormal (26). In a study by Peeters et al., rT3 was reported as a predictor of patients' survival (27), while in our study, mean rT3 levels were within normal ranges and there was no significant difference between rT3 levels in survivors and non-survivors.

Considering the correlation between PELOD-72 and the level of TT3, TT4, and FT4 on the first day of admission, it can be concluded that lower levels of TT3, TT4, and FT4 on the first day of admission could be a warning for the worse course of the illness on the third day of admission.

In this study, also, we did not find any significant difference in free thyroid hormone levels including FT3 and FT4 on the first and the third days of admission between survivors and non-survivors. This may be justified by the mechanism of the sick euthyroid syndrome, as described

previously. On the other hand, the effectiveness of thyroid hormone replacement in critically ill patients with sick euthyroid syndrome still remains controversial (26). It has been shown that thyroid hormone replacement had no benefit and did not change the outcome in critically ill patients (28-30). In contrast, in a study by Bettendorf et al., it was revealed that treatment of children with triiodothyronine after cardiopulmonary bypass operations reduced the need for postoperative intensive care (31). Based on the results of our study, insignificant differences in levels of free thyroid hormones on the first and third days of admission in survivors and non-survivors suggest that replacement of thyroid hormones in these patients may not have an effect on the disease outcome. In other words, although free thyroid hormones may be reduced in the course of a critical illness, it seems that low levels of FT3 and FT4 are still sufficient to maintain cell function.

Regarding the limitations of our study, it should be noticed that this study was conducted only on the patients who were not treated with the drugs affecting Hypothalamus-pituitary-thyroid axis (32). Since many patients admitted to intensive care units receive dopamine due to various reasons, including hemodynamic instability, results of this study cannot be generalized to all patients admitted to PICUs.

#### 4.1. Conclusion

Based on the results of our study, low TT3 is the most common form of SES in critically ill children. Thyroid function assessment, especially TT3 on the first day and TT4 on the third day of admission along with PELOD score, might be helpful in predicting disease outcome and patient's survival.

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#### Footnotes

**Authors' Contribution:** Study conception and design: Fatemeh Sayarifard and Bahareh Yaghmaie; acquisition of data: Bahareh Yaghmaie, Masood Mohammadpour, Meisam Sharifzadeh, Marjan Kouhnavard and Mohammad Taghi Haghi Ashtiani. Analysis and interpretation of data: Azadeh Sayarifard; drafting of manuscript: Marjan Kouhnavard; critical revision: Fatemeh Sayarifard, Azadeh Sayarifard, Farzaneh Abbasi.

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