Original Article

Correlation Between Pattern of Thyroid Dysfunction (ESS-Like Changes) and Outcome in Mechanically Ventilated Children in ICU Using PRISM III

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Abstract

Background: Non-thyroidal illness syndrome (NTIS), also known as euthyroid sick syndrome (ESS), is characterized by altered thyroid hormone profiles in critically ill patients without intrinsic thyroid disease. Mechanically ventilated children admitted to paediatric intensive care units (PICUs) frequently develop ESS-like hormonal alterations that may correlate with disease severity and clinical outcomes. The objective is to evaluate the correlation between thyroid hormone abnormalities (FT3, FT4, and TSH) and clinical outcomes in mechanically ventilated paediatric patients using PRISM III scoring, and to assess the prognostic significance of ESS-like changes. **Material and Methods:** A hospital-based prospective observational study was conducted in the PICU of MGM Medical College and M.Y. Hospital, Indore, India, over a period of 1 year. 100 mechanically ventilated children were enrolled. Serum FT3, FT4, and TSH levels were measured on Day 1 and Day 3 of mechanical ventilation. PRISM III scores were calculated within the first 24 hours of admission. Clinical outcomes including mortality, duration of mechanical ventilation, and PICU stay were analyzed. Correlations between thyroid hormone levels, PRISM III score, and clinical outcomes were assessed statistically. **Results:** NTIS was observed in 67% of mechanically ventilated children, with Type I NTIS (isolated low FT3) present in 34% and Type II NTIS (combined low FT3 and FT4) in 33% of patients. Overall mortality was 21%. Non-survivors had significantly lower FT4 levels on both Day 1 and Day 3 and lower FT3 levels on Day 3 compared with survivors ($p<0.05$). FT4 Day 1 showed significant negative correlations with PRISM III score ($r= -0.230$, $p=0.021$), duration of mechanical ventilation ($r= -0.233$, $p=0.019$), and PICU stay ($r= -0.240$, $p=0.016$). Type II NTIS was significantly associated with higher mortality (39.4%, $p=0.007$). ROC analysis demonstrated moderate predictive utility of FT4 Day 3 for mortality prediction (AUROC=0.747), while PRISM III showed excellent predictive performance (AUROC=0.914). **Conclusion:** ESS-like thyroid dysfunction is highly prevalent among mechanically ventilated paediatric patients and correlates significantly with illness severity and adverse clinical outcomes. Combined FT3 and FT4 suppression appears to have important prognostic significance and may complement PRISM III scoring for early risk stratification in critically ill children.

Keywords: Non-thyroidal illness syndrome, Mechanical ventilation, PICU, PRISM III, Free triiodothyronine, Thyroid dysfunction, Paediatrics.

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Introduction

Non-thyroidal illness syndrome (NTIS), also termed euthyroid sick syndrome (ESS), represents a spectrum of alterations in thyroid hormone metabolism observed in critically ill patients without intrinsic thyroid disease. These biochemical derangements are particularly common among mechanically ventilated children admitted to paediatric intensive care units (PICUs), where severe systemic illness, inflammation, and metabolic stress profoundly affect endocrine homeostasis.[1,2]

Thyroid hormones play a crucial role in growth, metabolism, thermoregulation, cardiovascular function, and neurodevelopment during childhood. Under physiological conditions, the hypothalamic-pituitary-thyroid (HPT) axis maintains hormonal balance through tightly regulated feedback involving thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3).[3] In critical illness, however, this axis undergoes significant dysregulation. The characteristic endocrine pattern in NTIS includes reduced serum T3 concentrations, elevated reverse T3 (rT3), variable FT4 levels, and absent compensatory elevation of TSH.[4,5]

The pathophysiology of NTIS is multifactorial and involves cytokine-mediated suppression of deiodinase activity, altered thyroid hormone binding, impaired hypothalamic-pituitary signalling, and the effects of medications commonly used in intensive care settings such as dopamine and corticosteroids.[4,6] Interleukin-1, interleukin-6, and tumour necrosis factor-α suppress peripheral conversion of T4 to biologically active T3, thereby contributing to low T3 syndrome.[6]

Mechanically ventilated children represent a particularly vulnerable subgroup with severe physiological derangements and

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high mortality risk. Several studies have demonstrated significant associations between reduced FT3 and FT4 levels and adverse clinical outcomes including mortality, prolonged mechanical ventilation, and extended PICU stay.[7-10] However, heterogeneity exists regarding the prognostic significance of thyroid dysfunction, particularly concerning its relationship with validated severity scoring systems such as the Paediatric Risk of Mortality (PRISM III) score.[11]

The PRISM III score is a widely validated severity scoring system used in paediatric critical care to estimate mortality risk based on physiological and laboratory variables.[12] Integration of endocrine biomarkers such as FT3 and FT4 with PRISM III scoring may improve prognostic stratification and facilitate early identification of high-risk patients requiring intensive monitoring and aggressive management.

The present study was therefore undertaken to evaluate the correlation between ESS-like thyroid hormone alterations and clinical outcomes in mechanically ventilated children admitted to a tertiary care PICU using PRISM III scoring as an indicator of illness severity.

Materials and Methods

Study Design and Setting: This hospital-based prospective observational study was conducted in the PICU of the Department of Paediatrics, Mahatma Gandhi Memorial Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India.

Study Duration: The study was conducted over a period of one year after approval from the Institutional Ethics Committee.

Study Population: The study included mechanically ventilated paediatric patients admitted to the PICU during the study period.

Sampling and Sample Size: The study population comprised all eligible mechanically ventilated children admitted to the Paediatric Intensive Care Unit (PICU) of Mahatma Gandhi Memorial Medical College and M.Y. Hospital, Indore, during the study period. Consecutive sampling was employed, and all patients fulfilling the inclusion criteria were enrolled prospectively in order to minimize selection bias and improve representativeness of the critically ill ventilated paediatric population encountered in routine clinical practice.

A total of 100 children were included over the one-year study period. The sample size was determined based on feasibility, PICU admission rates, and the number of eligible mechanically ventilated patients available during the study duration.

Inclusion Criteria

Children admitted to the Paediatric Intensive Care Unit (PICU) requiring invasive mechanical ventilation during the study period were considered eligible for inclusion in the study. Paediatric patients across the admitted age spectrum whose parents or legal guardians provided written informed consent were enrolled consecutively.

Exclusion Criteria

Patients with known thyroid disorders, prior thyroid hormone supplementation, congenital endocrine abnormalities, or conditions likely to independently alter thyroid function were excluded from the study. Children with incomplete clinical or laboratory data, including unavailable thyroid hormone measurements, were also excluded to ensure accuracy and completeness of analysis.

Study procedure and Data Collection: Detailed demographic data including age, sex, primary diagnosis, and relevant clinical history were recorded at admission using a predesigned structured case record proforma. Clinical parameters, ventilatory support details, lab investigations, and severity of illness assessment using the PRISM III score were documented within the first 24 hours of PICU admission.

Venous blood samples for thyroid function assessment, including serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), were collected on Day 1 and Day 3 of mechanical ventilation under aseptic precautions and analyzed using standard laboratory methods. Patients were subsequently monitored throughout their PICU stay for clinical outcomes including duration of mechanical ventilation, length of PICU stay, and survival outcome. All clinical and laboratory data were systematically recorded and verified to ensure completeness and accuracy prior to statistical analysis.

PRISM III Scoring and Outcome Measures: Severity of illness was assessed using the Paediatric Risk of Mortality III (PRISM III) scoring system. PRISM III scores were calculated for all enrolled patients within the first 24 hours of PICU admission using standard validated criteria based on physiological and laboratory variables. The score was used as an objective indicator of disease severity and mortality risk for correlation with thyroid hormone abnormalities.

The primary outcome measures included correlation of thyroid hormone parameters (FT3, FT4, and TSH) with PRISM III score and all-cause PICU mortality. Secondary outcome measures included duration of mechanical ventilation, length of PICU stay, and the prognostic significance of different patterns of non-thyroidal illness syndrome (NTIS). Clinical outcomes were assessed throughout the PICU stay until discharge or death.

Statistical Analysis: Data were entered in Microsoft excel and analyzed using SPSS 25.0 trial version. Continuous data were expressed in terms of mean and standard deviation. Categorical data were expressed in terms of frequencies and percentages. Comparisons between survivors and non-survivors were performed using independent t-tests or Mann-Whitney U tests as appropriate. Correlation analysis between thyroid hormones and PRISM III scores was performed using Pearson or Spearman correlation coefficients. Categorical variables were analyzed using chi-square testing. A p-value <0.05 was considered statistically significant.

Results

A total of 100 mechanically ventilated paediatric patients admitted to the PICU were enrolled in the study. The mean age of the study population was 86.10 ± 50.68 months with nearly equal gender distribution. Majority (67.0%) of them residing in rural areas. The mean weight and height of the study population were 25.31 ± 13.84 and 117.71 ± 26.86 respectively. 40.0% of the study participants were in normal BMI category and the mean

BMI of the study participants was 16.91 ± 4.19. Overall mortality was 21.0%, while 79.0% of patients survived to discharge.

Table 1: Baseline Characteristics of Study Participants

Variable	categories	Frequency (%)
Age	Mean ± SD	86.10 ± 50.68
Gender	Male	50 (50.0%)
	Female	50 (50.0%)
Residence	Rural	67 (67.0%)
	Urban	33 (33.0%)
Weight (Mean ± SD)	25.31 ± 13.84	
Height (Mean ± SD)	117.71 ± 26.86	
BMI Categories	Underweight	24 (24.0%)
	Normal	40 (40.0%)
	Overweight	22 (22.0%)
	Obese	14 (14.0%)
BMI (Mean ± SD)	16.91 ± 4.19	
Outcome	Survived	79 (79.0%)
	Died	21 (21.0%)

Table 2: PRISM III Score and Predicted Mortality Risk Among Study Participants

Parameter	Overall Mean ± SD	Survivors (n=79) Mean ± SD	Non-survivors (n=21) Mean ± SD	p-value
PRISM III Score	14.85 ± 9.16	11.42 ± 4.60	27.76 ± 10.54	< 0.001
Predicted PRISM III Mortality Risk (%)	20.59 ± 26.74	10.26 ± 8.78	59.48 ± 35.06	< 0.001

[Table 2] summarizes the severity of illness among mechanically ventilated paediatric patients using the Paediatric Risk of Mortality (PRISM III) scoring system. The table compares overall PRISM III scores and predicted mortality risk between survivors and non-survivors. Non-survivors demonstrated significantly higher PRISM III scores (27.76 ± 10.54) and predicted mortality percentages (59.48 ± 35.06) compared with survivors, indicating greater physiological derangement and illness severity at admission. The findings support the strong prognostic utility of PRISM III scoring in critically ill ventilated children. (p-value < 0.001)

Table 3: Prevalence and Classification of NTIS

NTIS Category	Frequency (%)
NTIS Absent (Normal Thyroid Function)	33 (33.0)
NTIS Present (Total)	67 (67.0)
Type I NTIS - Low FT3 only	34 (34.0)
Type II NTIS - Low FT3 + FT4	33 (33.0)

Non-thyroidal illness syndrome was identified in 67.0% of mechanically ventilated children. Type I NTIS (isolated low FT3) was observed in 34.0%, while Type II NTIS (combined low FT3 and low FT4) was present in 33.0% of patients.

Table 4: Thyroid Hormone Profile on Day 1 and Day 3 of Mechanical Ventilation

Parameter	Day 1 (Mean ± SD)	Day 3 (Mean ± SD)
FT3 (pmol/L)	4.30 ± 2.66	4.33 ± 2.63
FT4 (pmol/L)	15.10 ± 5.61	16.78 ± 3.60
TSH (pmol/L)	2.62 ± 1.51	1.99 ± 1.08

The baseline thyroid hormone profile (on Day 1) demonstrated early features of NTIS. Mean FT3 on admission was 4.30 ± 2.66 pmol/L, while mean FT4 and TSH levels were 15.10 ± 5.61 pmol/L and 2.62 ± 1.51 mIU/L respectively.

By Day 3 of mechanical ventilation, FT3 levels remained largely unchanged (4.33 ± 2.63), FT4 levels increased modestly (16.78 ± 3.60), while TSH levels demonstrated significant suppression (1.99 ± 1.08), suggesting ongoing hypothalamic-pituitary-thyroid axis dysfunction.

Table 5: Thyroid Hormone Trend (Day 1 vs Day 3) Stratified by Outcome

Parameter	Survivors Day 1 Mean ± SD	Survivors Day 3 Mean ± SD	Non-survivors Day 1 Mean ± SD	Non-survivors Day 3 Mean ± SD	p-value Day 1	p-value Day 3
FT3 (pmol/L)	4.52 ± 2.75	4.65 ± 2.64	3.49 ± 2.18	3.13 ± 2.26	0.153	0.005
FT4 (pmol/L)	16.05 ± 5.24	17.31 ± 3.58	11.52 ± 5.66	14.78 ± 2.97	0.002	0.001
TSH (mIU/L)	2.75 ± 1.59	2.08 ± 1.15	2.13 ± 1.09	1.66 ± 0.68	0.126	0.058

When stratified by outcome, non-survivors had significantly lower FT4 levels both on admission and on Day 3 (p-value 0.002 & 0.001). FT3 levels on Day 3 were also significantly lower among non-survivors (p-value 0.005), whereas TSH differences did not reach statistical significance.

Table 6: Mortality According to NTIS Classification

NTIS Category	Mortality (%)	p-value
Normal Thyroid Function	12.1%	0.007
Type I NTIS (Low FT3)	11.8%	
Type II NTIS (Low FT3 + FT4)	39.4%	

Type II NTIS demonstrated significantly higher mortality (39.4%) compared with Type I NTIS and patients with normal thyroid function. (p-value 0.007)

Table 7: Clinical Outcome, Mechanical Ventilation Duration and PICU Stay

Parameter	Survivors (n=79)	Non-survivors (n=21)	p-value
Duration of Mechanical Ventilation (days)	6.91 ± 3.06	15.00 ± 5.34	< 0.001
PICU Stay (days)	12.22 ± 4.91	21.76 ± 6.29	< 0.001

[Table 7] compares important clinical outcome parameters between survivors and non-survivors, including duration of mechanical ventilation and length of PICU stay. Non-survivors required significantly prolonged ventilatory support (15.00 ± 5.34) and had longer PICU stays (21.76 ± 6.29) compared with survivors. These findings indicate that increased disease severity and poorer clinical outcomes are associated with prolonged intensive care requirements in mechanically ventilated paediatric patients. (p-value < 0.001)

Table 8: Correlation Between Thyroid Hormones, PRISM III Score and Clinical Course

Hormonal Parameter	PRISM III Score r (p value)	Duration of Mechanical Ventilation r (p-value)	PICU Stay r (p-value)
FT3 Day 1	-0.154 (0.126)	-0.181 (0.071)	-0.176 (0.079)
FT4 Day 1	-0.230 (0.021)	-0.233 (0.019)	-0.240 (0.016)
TSH Day 1	-0.284 (0.004)	-0.121 (0.231)	-0.116 (0.249)
FT3 Day 3	-0.189 (0.060)	-0.196 (0.051)	-0.201 (0.045)
FT4 Day 3	-0.216 (0.031)	-0.208 (0.038)	-0.214 (0.033)
TSH Day 3	-0.208 (0.038)	-0.142 (0.159)	-0.136 (0.177)

[Table 8] demonstrates the correlation between serial thyroid hormone levels and markers of disease severity and clinical outcome in mechanically ventilated paediatric patients. FT4 levels on both Day 1 and Day 3 showed significant negative correlations with PRISM III score (p-value 0.021 & 0.031), duration of mechanical ventilation (p-value 0.019 & 0.038), and PICU stay (p-value 0.016 & 0.033), indicating that lower FT4 levels were associated with greater illness severity and prolonged intensive care requirement. TSH levels also demonstrated modest inverse correlation with PRISM III score. Although FT3 levels showed negative trends with severity indices and clinical course, statistical significance was not consistently achieved. Overall, worsening thyroid dysfunction correlated with increasing severity of critical illness and adverse clinical outcomes.

Table 9: ROC Analysis for Prediction of Mortality

Parameter	AUROC
FT4 Day 3	0.747
PRISM III at Admission	0.914
PRISM III at Day 3	0.938

ROC analysis demonstrated moderate predictive performance for FT4 Day 3, whereas PRISM III score showed excellent discriminatory ability for mortality prediction.

Discussion

The present study evaluated thyroid hormone alterations in mechanically ventilated paediatric intensive care patients and examined their association with disease severity, PRISM III score, duration of mechanical ventilation, PICU stay, and mortality. This study observed a high prevalence of non-thyroidal illness syndrome (NTIS), with 67% of critically ill ventilated children exhibiting ESS-like thyroid dysfunction. The predominant abnormality was low FT3 syndrome, while combined low FT3 and FT4 abnormalities were associated with the poorest outcomes. Significant inverse correlations were found between thyroid hormone levels and PRISM III scores, indicating that worsening thyroid dysfunction paralleled increasing severity of critical illness.

In this study, NTIS was identified in 67% of mechanically ventilated children, with Type I NTIS (isolated low FT3) seen in 34% and Type II NTIS (low FT3 with low FT4) in 33% of patients. Alike findings were reported by Abu El-Ella et al. (2019) in Egypt, who observed NTIS in 62.9% of critically ill children and demonstrated significantly higher mortality among patients with combined FT3 and FT4 suppression.[13] Similarly,

Sayarifard et al. (2018) in Iran found a high prevalence of low T3 syndrome among critically ill paediatric ICU patients and found thyroid dysfunction to correlate with disease severity.[14]

The predominance of low FT3 syndrome in present study aligns with the classical pattern of NTIS described in critical illness. Decreased peripheral conversion of T4 to T3 due to inhibition of type 1 deiodinase activity by inflammatory cytokines such as IL-1, IL-6, and TNF-α has been considered the principal mechanism responsible for reduced T3 concentrations.[4] Fliers E et al. (2015) from the Netherlands emphasized that inflammatory mediators, altered hypothalamic-pituitary signalling, and reduced deiodinase activity collectively contribute to thyroid hormone suppression during critical illness.[2]

Present study showed significantly lower FT4 levels among non-survivors both on Day 1 and Day 3 of mechanical ventilation. FT4 Day 1 and Day 3 demonstrated significant negative correlations with PRISM III score, duration of mechanical ventilation, and PICU stay. Similar observations were made by Jacobs A et al. (2007), who reported that reduced FT4 levels were independently associated with increased mortality in critically ill children.[7] In another paediatric ICU study by Lodha R et al. (2007) found that low FT4 concentrations were significantly associated with septic shock severity and adverse outcomes.[8]

The current study also found that FT3 levels on Day 3 were significantly lower among non-survivors compared with survivors, suggesting progressive endocrine deterioration during ongoing critical illness. Abdelaziz TA et al. (2025) in Egypt similarly reported that persistent reduction in FT3 levels among mechanically ventilated children was associated with extubation failure and mortality.[9] Bello et al. (2009) in Italy also demonstrated that low T3 syndrome was associated with increased mortality and prolonged ICU stay in critically ill patients.[10]

An important finding in the present study was the significant association between Type II NTIS and mortality. Mortality among children with combined low FT3 and FT4 was substantially higher than in patients with isolated low FT3 or normal thyroid function. This observation supports the concept that progression from isolated T3 suppression to combined T3/T4 suppression reflects increasing severity of systemic illness. Van den Berghe (2014) in Belgium described progressive suppression of the hypothalamic-pituitary-thyroid axis as a marker of prolonged and severe critical illness.[1] Similarly, Warner and Beckett (2010) in the United Kingdom explained that more severe forms of NTIS involving both FT3 and FT4 suppression are associated with poorer prognosis and advanced metabolic dysregulation.[4]

The relationship between thyroid dysfunction and severity of illness was further supported by significant inverse correlations between FT4 and PRISM III score in the present study. PRISM III is a validated paediatric mortality prediction tool widely used in PICUs. Pollack et al. (1996) in the United States originally demonstrated the strong predictive performance of PRISM III for mortality risk assessment in critically ill children.[12] Present study findings suggest that thyroid hormone alterations, particularly FT4 suppression, may complement PRISM III in prognostic stratification.

The significant negative correlation between FT4 levels and duration of mechanical ventilation observed in this study indicates that more severe thyroid dysfunction may be associated with prolonged respiratory failure. Thyroid hormones play an essential role in respiratory muscle function, cellular metabolism, and oxygen utilization. Chopra (1996) from the United States proposed that low thyroid hormone states during critical illness may contribute to impaired metabolic adaptation and delayed recovery.[15] Peeters (2007) in Belgium also suggested that persistent NTIS may represent maladaptive endocrine failure rather than a purely protective response in prolonged critical illness.[16]

Interestingly, TSH levels in the present study remained relatively within the normal range despite significant reductions in peripheral thyroid hormones. Similar findings have been consistently reported in NTIS literature. De Groot (1999) from the United States described the absence of compensatory TSH elevation as evidence of central hypothalamic-pituitary suppression during severe systemic illness.[5] This phenomenon differentiates NTIS from primary hypothyroidism and supports the concept of adaptive endocrine downregulation during acute stress.

The ROC analysis in this study demonstrated moderate predictive utility of FT4 Day 3 for mortality prediction, whereas PRISM III showed excellent discriminatory ability. Similar findings were reported by Qiu et al. (2019) in China, whose meta-analysis confirmed the robust predictive performance of PRISM scoring systems in paediatric critical care.[17] However, our findings indicate that incorporation of thyroid hormone assessment may provide additional prognostic information beyond conventional severity scoring systems.

The prevalence and prognostic significance of NTIS observed in the present study are also consistent with Indian literature. Suvarna and Fande (2009) in India reported significant reductions in FT3 and FT4 among critically ill children and demonstrated associations with disease severity and mortality.[18] More recently, Rustagi and Anudhakar (2022) in India found inverse correlations between thyroid hormone levels and PRISM scores in critically ill paediatric patients.[11] Sahu UP et al. (2022) in India similarly found that lower thyroid hormone levels were associated with poorer outcomes in PICU patients.[19]

The pathophysiology of NTIS remains incompletely understood. Initially, reduction in thyroid hormone levels may represent an adaptive metabolic response aimed at conserving energy during acute stress. However, persistent or progressive suppression, especially involving both FT3 and FT4, may reflect exhaustion of compensatory endocrine mechanisms and failure of metabolic adaptation. Fliers et al. (2015) emphasized that prolonged NTIS likely represents complex neuroendocrine dysregulation involving cytokine excess, altered deiodinase activity, reduced thyroid hormone transport, and hypothalamic suppression.[2]

Overall, the present study demonstrates that ESS-like thyroid dysfunction is common among mechanically ventilated paediatric patients and correlates significantly with disease severity and adverse outcomes. Progressive suppression of FT3 and FT4, particularly Type II NTIS, appears associated with increased mortality risk. These findings support the potential

utility of thyroid hormone assessment as an adjunctive prognostic marker in critically ill ventilated children.

Strengths and Limitations: The strengths of the present study include evaluation of serial thyroid hormone measurements, use of PRISM III scoring for severity assessment, and focused analysis of mechanically ventilated paediatric patients. Serial hormonal assessment enabled identification of dynamic endocrine changes during the course of critical illness. Additionally, the study contributes valuable data from a resource-limited tertiary care PICU setting where literature on NTIS remains limited.

However, certain limitations must be acknowledged. The study was conducted at a single center with a relatively modest sample size. Reverse T3 levels, which are considered important in NTIS characterization, were not assessed. The observational design limits causal inference regarding thyroid dysfunction and mortality. Furthermore, long-term endocrine follow-up after PICU discharge was not performed.

Conclusion

The present study demonstrates that non-thyroidal illness syndrome (NTIS) is highly prevalent among mechanically ventilated paediatric intensive care patients, with 67% of children exhibiting ESS-like thyroid dysfunction. Type II NTIS, characterized by combined low FT3 and FT4 levels, was significantly associated with higher mortality, prolonged mechanical ventilation, longer PICU stay, and greater disease severity as assessed by PRISM III score. Significant inverse correlations between FT4 levels and PRISM III score, ventilation duration, and PICU stay suggest that worsening thyroid dysfunction parallels increasing severity of critical illness. The findings indicate that thyroid hormone assessment, particularly FT4 and NTIS pattern classification, may serve as a useful adjunctive prognostic tool in critically ill ventilated children. Integration of thyroid hormone profiling with established severity scoring systems such as PRISM III may improve early risk stratification and outcome prediction in PICU settings.

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Conflicts of interest

There are no conflicts of interest.

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