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Evaluation of serum thyroid hormone profile and its correlation with the clinical outcome in critically ill children

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***Abstract*---**Critical illness is often accompanied by sick euthyroid syndrome, an endocrine anomaly with characteristically low triiodothyronine (T3), low thyroxine (T4), and altered thyroid-stimulating hormone (TSH) levels in the serum. This warrants exploration of the relationship between thyroid hormone levels and clinical outcome of critical illness. To evaluate the thyroid hormone profile in critically ill children and assess its correlation with disease severity and outcome. Fifty critically ill children, aged 1 month-15 years, admitted to the pediatric intensive care unit with organ dysfunction and requiring pharmacological/mechanical support to maintain vital function, were recruited into this observational study. Risk of Mortality (PRISM) scores were evaluated for all patients as an indicator of disease severity and their thyroid profile investigated for serum T3, T4, and TSH levels. These were correlated with each other and with the disease outcome using statistical software R version 3.6.3. At the end of hospital stay, mean T3, T4, and TSH levels were significantly increased in discharged patients ($p<0.001$) but reduced in expired patients ($p=0.01$) compared to their values at admission. Mean T4 levels at discharge/death showed a significant negative correlation with the mean PRISM score recorded 24 h after admission. Chance of death was more for patients with a PRISM score of >10 at admission and >9 after 24 h, T3 level <61 ng% at admission and after 24 h, T4 level <4.9 ng% at admission and <7.1 ng% after 24 h as well as TSH level >2.4 ng% at admission and <2.7 ng% after 24 h. Low serum levels of T3, T4, and TSH are associated with a poor prognosis and an increased incidence of mortality in critically ill pediatric patients.

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Keywords---critical illness, thyroid hormones, pediatrics, intensive care units, prognosis.

Introduction

Critical illness (CI) is any disease or condition that is potentially life threatening. The resulting stress leads to a catabolic state with increased energy expenditure, hypermetabolism, hyperglycemia, muscle loss, and sick euthyroid syndrome (SES).[1-3]. SES is an endocrine disorder characterized by low triiodothyronine (T3), low/normal thyroxine (T4), and altered thyroid-stimulating hormones (TSH) levels in the serum.[4,5] These hormonal alterations without preexisting pituitary/hypothalamic/thyroid dysfunctions are known as non-thyroid illnesses (NTI).[6] These may be mediated by cytokines or other inflammatory mediators (tumor necrosis factor, interferon-alpha, nuclear factor-kappa B, interleukin-6, etc.), drugs used for CI treatment (amiodarone, propranolol, glucocorticoids, etc.,) as well as circulating free fatty acids. These agents inhibit 5`deiodinase-mediated monodeiodination of T4 into T3, or binding of thyroxine to thyroid-binding globulin.[5,7] SES may also reflect a protective phenomenon to limit protein catabolism and decrease energy requirements.[3]

Various studied have reported that a decline in the levels of T3 and T4 is associated with an increase in disease severity and unfavorable prognosis.[8-10] However, few researchers did not find any significant association between clinical outcome and T4 or TSH levels.[11] This warrants exploration of the relationship between thyroid hormone levels and clinical outcome of CI in children. If this prognostic correlation could be established, children with a poor prognosis could be identified earlier in the course of the disease based on their thyroid hormone levels, allowing closer observation and intervention, including therapeutic use of thyroid hormones. Also, most studies have explored this relationship in adults but not the pediatric population, especially in the Indian scenario.[9,10,12]. Therefore, the objective of this study was to evaluate the thyroid hormone profile in CI children and assess its correlation with disease severity and outcome.

Materials and Methods

Study design and setting

This hospital-based, prospective, observational study was conducted at the Department of Pediatrics at a tertiary care teaching hospital in Karad, Maharashtra, India, from December 2017 to September 2019, after obtaining ethical clearance from the Institutional Review Board.

Participants

Fifty CI children aged 1 month - 15 years, admitted to the pediatric intensive care unit (PICU) of this hospital with malfunction of one/more organs/systems and requiring support to maintain vital functions with any pharmacological or mechanical aids such as dopamine >5 mcg/kg/min, any dose of adrenaline, and/or mechanical ventilation, serum creatinine >1 mg/dL, platelet count <1,00,000/mm^3, and urine output <1 mL/kg/h were recruited into the study

after obtaining written informed consent from their parents/guardians. Patients with family/maternal history of any thyroid illness, goiter, orbitopathy, intake of any thyroid medications, and those who expired within 24 h of admission were excluded from the study.

Measurements and Variables

Consecutive type of non-probability sampling was followed. A detailed history was recorded and thorough clinical examination as well as relevant investigations done for the included patients.

- PRISM III scoring – The Pediatric Risk of Mortality (PRISM) III score[13] was used to predict the severity of disease and clinical outcome. It was calculated on admission and at 24 h after admission. For this, 8 mL of venous blood sample was collected and divided into 3 mL of plain sample, 3 mL of sodium citrate sample, and 2 mL of EDTA sample. Along with this, 1 mL of arterial blood sample was also collected, and appropriate laboratory investigations were conducted.
- Thyroid hormone profiling - Plain sample (5 mL) was collected twice from each patient, first at the time of admission and again at discharge or at the time of resuscitation, depending on the outcome of the patient. Serum T3, T4, and TSH levels were evaluated for all the patients and correlated with their respective PRISM scores and clinical outcomes.

Study size

Sample size was calculated by assuming thyroid hormone levels and PRISM scores are negatively correlated with Correlation coefficient equal to -0.486 (from below reference). At 95% confidence level and 90% power, the sample size required was found to be 39.497≈ 40. As sample size increases, accuracy of result increases. So, 50 samples are considered in this study.

Statistical analysis

The data was collected, compiled, and analyzed using the R version 3.6.3 statistical software and Microsoft Excel. Categorical variables were represented by frequency tables. Wilcoxon tank or test t-test was used to compare clinical parameters at different time points. Chi-square test was used to check the association between attributes. $P \leq 0.05$ indicated statistical significance.

Results

Participants and descriptive data

The study comprised 50 CI children, of whom 29 (58%) were males and 21 (42%) were females, with a mean age of 5.74±4.61 years. Most of them were in the age range of 1-5 years (38%), 6-10 years (26%), 11-15 years (22%), and <1 year (14%). Majority of the children (58%) had a single organ system affected by the critical illness, while 42% had multiple organ systems involved; 48% of these patients were on mechanical ventilation. For majority of the patients, hospitalization lasted

<15 days (68%); 20% of the patients needed a longer stay of 15-30 days; and 12% >30 days. The mean of number of days of admission was 14.38 days. 84% patients were discharged after treatment but 16% expired. At the time of admission, a PRISM score of <25 was seen in 92% patients, 25-40 in 6%, and >40 in 2% of the patients. After 24 h, 96% of the patients had a PRISM score of <25 and the remaining had between 25 and 40.

Table-1 presents the comparison of clinical, hematological, and thyroid parameters at different time points. Two-sample paired t-test analysis revealed a significant increase in the mean values of SBP, pH, and total CO_2 as well as a significant fall in the mean HR at 24 h after admission compared to the values at the time of admission ($P<0.05$). The Wilcoxon test for paired samples demonstrated that the mean values of temperature, acidosis, PT, creatinine, and BUN showed a significant decline whereas those of PaO_2, GCS, and glucose showed a significant increase at 24 h after admission compared to the values at the time of admission ($P<0.05$). No significant difference was observed in the mean levels of potassium, TLC, platelet count, and $PaCO_2$ recorded at the time of admission and after 24 h of admission ($P>0.05$). A significant increase in mean serum T3, T4, and TSH levels was noted at the time of discharge/death compared to the levels at the time of admission, using two-sample paired t-test analysis ($P<0.001$).

Outcome data

Table-2 presents the association of thyroid profile with disease outcome. Applying Mann-Whitney test, it is observed that towards the end of hospital stay, the mean T3 level for patients who got discharged was significantly greater than those who expired ($P<0.001$). At the time of both beginning ($P=0.01002$) and end of hospital stay ($P<0.001$), the T4 level of patients who got discharged was significantly higher than that of those who expired. At the time of admission, the TSH level of patients who got discharged was significantly less than that of those who expired ($P=0.03913$). Among the patients who got discharged, the mean T3, T4, and TSH levels significantly improved at the time of discharge ($P<0.05$) but decreased in the patients who expired ($P<0.05$).

Main results and analysis

The correlation of the PRISM score with the number of systems involved, disease outcome, duration of hospital stay, and thyroid parameters is summarized in Table-3 and Table-4. The mean PRISM score at admission was significantly greater than that seen after 24 h, irrespective of the number of systems involved. A similar trend was observed for patients who were discharged eventually, as per the Wilcoxon test for paired samples. However, this difference was found to be insignificant, in the two-sample paired t-test, for patients who expired. The Chi-square test revealed that the PRISM score groups on admission showed no significant relation with the duration of hospital stay. It also indicated that there was a significant association between the disease outcome and the PRISM score groups recorded at admission as well as after 24 h.

Table-5 details the cutoff values for the continuous variables (predictors) predicting the outcome (discharged/expired). It can be inferred that the risk of death was more for the patients with a PRISM score >10 at the time of admission and >9 after 24 h, T3 level <61 ng% at admission and after 24 h, T4 level <4.9 ng% at admission and <7.1 ng% after 24 h as well as TSH level >2.4 ng% at admission and <2.7 ng% after 24 h. There was a strong correlation between the predictor variables T3 on admission and at the time of discharge/death, T4 on admission and at the time of discharge/death, TSH on admission and at the time of discharge/death, and the PRISM score on admission and after 24 h with the outcome of the CI patients.

Table-6 depicts the prediction of outcome variable using various analyses. From univariate logistic regression analysis, it can be observed that with one unit increase in T3 at the time of discharge/death, odds of discharging from the hospital increases by a factor of 0.88. With one unit increase in T4 at the time of discharge/death, odds of discharging from the hospital increases by a factor of 0.37. Using univariate cox proportional hazard model analysis, it can is concluded that T3 and T4 recorded at time of discharge/death have significant effect on outcome variable. With one unit increase in T3 at the time of discharge/death, odds of discharging from the hospital increases by a factor of 0.93. With one unit increase in T4 at the time of discharge/death, odds of discharging from the hospital increases by a factor of 0.4.

Discussion

Key Results

This prospective observational study was conducted to evaluate the thyroid hormone profile in critically ill children and to correlate it with disease severity and clinical outcome. SES was used to describe the thyroid hormonal changes in such patients in the setting of NTI. Low serum levels of T3, T4, and TSH were found to be associated with an increased incidence of mortality, and hence, could be employed as predictors of poor prognosis, facilitating timely management in these patients. All patients had low serum levels of these hormones at admission in the presence of CI. However, those patients who were discharged had a significantly higher T3 and T4 levels at admission than those who expired. Similarly, by the end of hospital stay, these thyroid hormone levels showed significant improvements in the discharged patients, but significant deterioration in those who expired.

Interpretation and generalisability

Akin to the present study, the T3 and T4 values were found to be significantly lower among expired patients compared to discharged patients in the studies conducted by Sayarifard et al and Suvarna et al.[16,17] However, certain researchers found this relationship to be significant with T3 only ($p<0.05$) but not T4 and TSH ($p>0.05$).[12,18] Similar to the present study, Patki et al and Suvarna et al observed that serum T3, T4, and TSH levels improved in those who survived and not in those who expired.[12,17]

Suresh et al also found that the severity of illness had a significantly inverse relationship with serum T3, but not T4 or TSH.[19] It was also suggested that the T3 levels reflected the patients' clinical status, and T4 levels could predict death.[12] A similar study involving PICU patients concluded that low T3 is a reliable predictor of mortality, and the risk is increased by 30 times when it is associated with low T4.[17] A significant association between the levels of T3 and T4 with the disease outcome (P=0.0001, OR 24.706; P=0.014; OR 3.086, respectively) was also observed by Yanni et al and others.[16,20] In concordance with the present study, many authors concluded that the thyroid biomarkers, specifically serum T3 and T4, might be efficient for evaluating the prognosis of the postoperative CI patients.[17,21,22]

The present study showed a significant negative correlation of T4 levels measured at discharge/death with the mean PRISM score recorded 24 h after admission. A similar relationship was observed for T3 levels, but not T4 and TSH levels, by Suvarna et al.[17] The PRISM score is known to be directly related to disease severity and risk of mortality.[23,24] Bora et al observed that mortality increased with an increase in the PRISM III score, approaching almost 100% with a PRISM III score of 25 or more.[23] Patel et al deduced that PRISM III can help in selecting sick children for PICU admission and optimum utilization of the limited PICU resources.[24]

Lodha et al noted that low T3 level was the earliest finding, followed by low T4 levels and low TSH levels, indicating a continuum of changes in the disease spectrum.[25] Anand et al noted that both serum T3 and T4 levels, increased with recovery.[8] They also suggested that the above-mentioned changes in the thyroid indices probably occurred as a temporary adaptive mechanism to limit catabolism in states of stress. The cofactors for both the enzymes deiodinase (needed for T4 to T3 conversion) and glutathione peroxidase (defensive strategy of the body to combat oxidative stress) are postulated to be glutathione and selenium. Stress or CI reduces the activity of deiodinase, thereby sparing the cofactors for glutathione peroxidase activity (to combat stress). Low T3 level reduces catabolism, thus decreasing the generation of mitochondrial free radicals and allowing energy to be utilized for the defense processes.[8]

Limitations

This study has its limitations in being a single-center study with a limited sample size. Multicentric, prospective studies with larger sample size are encouraged to validate the results.

Conclusion

Low serum levels of T3, T4, and TSH are associated with a poor prognosis and an increased incidence of mortality in critically ill pediatric patients.

Research quality and ethics statement

The ethical principles framed in the Declaration of Helsinki applied to clinical research under the governance of Institute ethics committee.

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Table 1
Comparison of clinical, hematological, and thyroid parameters at different time points

Parameters	On admission	After 24 hours	At discharge/death	p-value
	Mean ± SD (Min, Max)	Mean ± SD (Min, Max)	Mean ± SD (Min, Max)	
Systolic blood pressure (mmHg)	99.67 ± 23.08 (52, 140)	104.3 ± 15.62 (60, 150)	-	0.03241*
Heart rate (/minute)	125.2 ± 30.88 (64, 192)	115.2 ± 23.91 (70, 162)	-	0.001053*
Temperature (^{0}C)	100.47 ± 1.47 (98, 105)	99.59 ± 1.37 (94.6, 102.4)	-	<0.001^{W*}
Acidosis	1.20 ± 1.85 (0, 6)	0.6 ± 1.16 (0,6)	-	0.004621^{W*}
pH	7.25 ± 0.18 (6.7, 7.46)	7.32 ± 0.12 (6.97, 7.46)	-	<0.001*
Total CO_2	18.8 ± 6.25 (4.4, 33)	21.23 ± 6.2 (8.2, 35.7)	-	<0.001*

PaO_2	100.11 ± 40.87 (34.9, 220)	118.84 ± 32.76 (78, 221)	-	<0.001[W*]
$PaCO_2$	38.37 ± 24.73 (11, 130)	35.6 ± 15.11 (16, 112)	-	0.6154[W*]
Glasgow Coma Scale score	11.84 ± 3.34 (4, 15)	12.38 ± 2.93 (4, 15)	-	0.008213[W*]
Prothrombin time	23.75 ± 25.42 (13, 180)	19.65 ± 9.27 (13, 56)	-	< 0.001[W*]
Creatinine (/mm^3)	1.1 ± 0.49 (0.6, 3.2)	0.95 ± 0.25 (0.6, 1.9)	-	< 0.001[W*]
Blood urea nitrogen	42.86 ± 36.47 (14, 191)	33.86 ± 21.62 (12, 142)	-	< 0.001[W*]
Potassium (mEq/L)	4.02 ± 0.84 (1.5, 6)	3.97 ± 0.76 (2, 5.6)	-	0.4507
Glucose (mg%)	112.38 ± 60.11 (36, 400)	118.16 ± 39.69 (68, 256)	-	0.02126[W*]
Total leukocyte count (/mm^3)	13816 ± 8283.78 (1200, 32000)	13261 ± 7885.64 (2200, 30100)	-	0.2198
Platelets (/mm^3)	217360 ± 152694.41 (15000, 600000)	218500 ± 58633.35 (30000, 600000)	-	0.8599
T3 (ng%)	76.74 ± 33.30 (20, 155)	-	94.52 ± 42.31 (20, 198)	<0.001*
T4 (ng%)	7.24 ± 2.54 (2.4, 10.7)	-	8.58 ±3.08 (1.9, 13)	<0.001*
TSH (ng%)	2.81 ± 1.54 (0.8, 8.9)	-	3.67 ±1.55 (0.8, 6.9)	<0.001*

Abbreviations: *Significant at 5% level of significance; CO_2 = Carbon dioxide; L = liter; Max = Maximum value; mEq = milliequivalent; Min = Minimum value; mm = millimeter; ng = nanogram; PaO_2 = Arterial partial pressure of oxygen; $PaCO_2$ = Arterial partial pressure of carbon dioxide; SD = Standard deviation; TSH = Thyroid stimulating hormone; T4 = Thyroxine; T3 = Triiodothyronine; W = Wilcoxon test

Table 2
Association of thyroid profile with disease outcome

Thyroid parameter	Outcome	No. of patients	Mean ± SD [in ng%] (95% CI) {Min, Max}	*P* value ##	*P* value of paired *t*-test #	
					Discharged	Expired
T3 (on admission)	Discharged	42	80.33 ±33.53 (69.88, 90.78) {20,155}	0.08028	<0.001[W]*	0.01415[W]*
	Expired	8	57.88 ± 26.32 (35.87,79.88) {31,96}			
T3 (at the time of discharge /death)	Discharged	42	107.79 ±31.42 (97.99, 117.58) {34,198}	<0.001[W]*		
	Expired	8	24.88 ± 12.21 (14.67, 35.08) {20,55}			
T4 (on admission)	Discharged	42	7.64 ± 2.39 (6.89, 8.38) {2.4,10.7}	0.01002*	<0.001[W]*	0.01427[W]*
	Expired	8	5.16 ±2.45 (3.11, 7.21) {2.9,9.1}			
T4 (at the time of discharge /death)	Discharged	42	9.56 ±2.12 (8.90,10.22) {4.4,13}	<0.001[W]*		
	Expired	8	3.41 ±1.89 (1.83,4.99) {1.9,6.7}			
TSH (on admission)	Discharged	42	2.62 ±1.19 (2.24,2.99) {0.8,4.8}	0.03913*	<0.001[W]*	0.01028[W]*
	Expired	8	3.84 ±2.63 (1.64, 6.04) {1.6,8.9}			
TSH (at the time of	Discharged	42	3.85 ±1.39 (3.42,4.29) {0.8,6.9}	0.0554		

discharge /death)	Expired	8	2.71 ±2.04 (1.01, 4.41) {0.8,6.7}			

Abbreviations: *Significant at 5% level of significance ## = P value for comparison between the thyroid parameters in patients at given time point for the outcome (discharged/expired); # = P value for the comparison between the thyroid parameters on admission and at the time of discharge/death of the patients; CI = Confidence interval; ng = Nanogram; SD = Standard deviation; TSH = Thyroid stimulating hormone; T4 = Thyroxine; T3 = Triiodothyronine; W = Wilcoxon test

Table 3
Association of PRISM score with number of systems involved and disease outcome

Parameter	Sub-category	On admission Mean ± SD (Min, Max) [Median]	After 24 hours Mean ± SD (Min, Max)	p-value
Systems involved	Single	9.17 ± 5.57 (3, 30) [8]	6.62 ± 5.12 (3, 30) [6]	0.0012W*
	Multiple	13.9 ± 10.899 (3, 41) [9]	9.67 ± 7.75 (3, 37) [7]	0.0046W*
Disease outcome	Discharged	9.48 ± 6.37 (3, 39) [8]	5.95 ± 2.36 (3, 13) [6]	<0.001W*
	Expired	20 ± 12.6 (8, 41) [15]	18.52 ± 10.86 (4, 37) 16.5]	0.3618

Abbreviations: *Significant at 5% level of significance; Max = Maximum; Min = Minimum; PRISM = Pediatric risk of mortality; SD = Standard deviation; W = Wilcoxon test

Table 4
Frequency distribution of the patients based on PRISM score group and its association with duration of hospital stay and disease outcome

	PRISM score group			*P* value
	<25	25-40	>40	
PRSIM score				
At admission	46	3	1	-

After 24 hours	48	2	0	-
Hospital stay (days)				
<15	31	2	1	0.6022[MC]
15-30	10	0	0	
>30	5	1	0	
Disease outcome (with respect to PRISM score at admission)				
Discharged	41[#]	1[#]	0[#]	0.008[MC] (0.4875) (Cramer's V)
Expired	5[#]	2[#]	1[#]	
Disease outcome (with respect to PRISM score at 24 hours)				
Discharged	42^	0^	0^	0.0245[MC] (0.4677) (Cramer's V)
Expired	6^	2^	0^	

Abbreviations: *Significant at 5% level of significance; [#]No. of subjects with given PRISM score recorded at admission; ^No. of subjects with given PRISM score recorded after 24 hours; MC =Monte Carlo simulation in Chi-square test; PRISM = Pediatric risk of mortality; wrt = with respect to

Table 5
Cutoff values for predictors of death

Variable	AU-ROC (CI)	Cut-off	Sensitivity (CI)	Specificity (CI)
PRISM score at admission	0.805 (0.646-0.965)	(>) 10	71.43% (55.42%-84.28%)	75% (34.91%-96.81%)
PRISM score after 24 hours	0.896 (0.713-1.00)	(>) 9	90.48% (77.37%-97.34%)	87.5% (47.35%-99.69%)
T3 admission	0.698 (0.524-0.871)	(<) 61	80.95% (65.88%-91.34%)	62.5% (24.28%-96.59%)
T3 after 24 hours	0.997 (0.989-1.00)	(<) 61	97.62% (87.43%-99.93%)	100% (89.74%-100%)
T4 admission	0.765 (0.578-0.952)	(<) 4.9	85.71% (71.46%-94.57%)	75% (34.91%-96.85%)
T4 after 24 hours	0.975 (0.935-1.00)	(<) 7.1	88.09% (74.39%-96.02%)	100% (63.06%-100%)
TSH admission	0.621 (0.393-0.848)	(>) 2.4	54.76% (38.67%-70.15%)	50% (15.70%-84.29%)

TSH after 24 hours	0.738 (0.465-1.00)	(<) 2.7	73.81% (57.96%-86.14%)	75% (34.91%-96.81%)

Abbreviations: AU-ROC = Area under the receiver operating characteristics; CI = Confidence interval; PRISM = Pediatric risk of mortality; TSH = Thyroid stimulating hormone; T4 = Thyroxine; T3 = Triiodothyronine

Table 6
Prediction of Outcome variable

Analysis Used	Variable	Coefficient	p-value	Odds Ratio (CI)	Hazard Ratio (CI)
Univariate Logistic Regression	Intercept	5.57	0.019*	0.88 (0.76 - 0.94)	-
	T3 at time of discharge/death	-0.1275	0.0089*		
	Intercept	4.7091	0.0105*	0.37 (0.15 - 0.597)	
	T4 at time of discharge/death	- 1.0064	0.0024*		
	Intercept	0.2196	0.8257	0.56 (0.28 – 0.98)	
	TSH at time of discharge/death	-0.5782	0.0675		
Univariate Cox Proportional Hazard model	T3 at time of discharge/death	-0.0736	0.0058*	-	0.93 (0.88, 0.98)
	T4 at time of discharge/death	- 0.9130	0.0015*	-	0.40 (0.23, 0.71)
	TSH at time of discharge/death	-0.5346	0.0704	-	0.59 (0.33, 1.05)

Abbreviations: CI = Confidence interval; TSH = Thyroid stimulating hormone; T4 = Thyroxine; T3 = Triiodothyronine