Triiodothyronin (T3) as a Parameter in Sepsis Patients Outcome in The Pediatric Intensive Care Unit (PICU)

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ABSTRACT
Background: Sepsis can result in systemic multi-organ dysfunction and is brought on by an unbalanced host response to infection. TSH, T4 and T3 levels are decreased as a result of the changes in thyroid hormones. This hormonal confluence has been referred to as "Euthyroid Sick Syndrome (ESS)" or "Non-Thyroid Illness Syndrome" since it does not signify intrinsic thyroid dysfunction. **Objective:** To determine whether there is a connection between serum T3 levels and sepsis outcomes, particularly mortality in patients hospitalised to the PICU of Benha University Hospitals.
Patients and methods: This study was prospective cohort study. We studied 100 children aged 1 month-18 years who were diagnosed with sepsis. For each patient, age, gender, mortality and outcome were noted. Study sample included 100 patients were collected from the pediatric intensive care unit at Pediatric Department, Benha University Hospitals over 6 months. All patients had serum free T3 levels measured, and all data were collected at the time of diagnosis. Patients were then followed until discharge or death, and they were separated into two groups based on outcome: the died (70 patients) and survived (30 patients) groups. **Results:** Serum T3 level was low in 93% of septic patients who died, while only 25 % did in the survived group. So, low T3 levels are associated with increased mortality in the paediatric critical care unit. Further investigation found that serum T3 levels of ≤ 1ng/dL had a significant relationship with mortality. **Conclusion:** Our study found that serum T3 level was low in 93% of septic patients who died, while only 25 % did in the survived group. So, low T3 levels had significant relationship with mortality in PICU.
Keywords: Pediatric sepsis**,** Euthyroid sick syndrome, Serum T3 level, PICU.

INTRODUCTION

Sepsis can result in systemic multi-organ dysfunction and is brought on by an unbalanced host response to infection. The kind of bacteria, the amount of time between the onset of the sickness and the start of therapy, the initial illness that existed before the sepsis, and the patient's current immunisation status are some of the variables that affect the cause of death in septic patients. Children's life and health are gravely endangered by sepsis. 64% of the 7.6 million kids who pass away before turning five years old do so from sepsis or septic shock brought on by a serious illness [1]. The surviving sepsis campaign, which debuted in 2018, clearly established the notion of the "hour-1 bundle," emphasising that sepsis should be viewed as an emergency medical event rather than a single sickness. Early response is critical, and identifying risk factors for sepsis on admission can aid in patient triage, individualised therapy, and medical decision making [2]. The control of metabolic homeostasis is greatly influenced by thyroid hormones. By up-regulating B-adrenergic receptors and boosting the inotropic characteristic of the myocardium, they play a crucial role in critical disease. Dopamine's function may be lessened when thyroid hormone levels are low. The cardiovascular system is a primary target for the effects of thyroid hormones, which also control the development and metabolism of different organs [3].

Different endocrine alterations occur during critical illness. TSH, T4 and T3 levels are decreased as a result of the changes in thyroid hormones. This collection of hormonal abnormalities, sometimes known as "Euthyroid Sick Syndrome" or "Non-thyroid Illness Syndrome," does not imply intrinsic thyroid disease. Low amounts of triiodothyronine (T3) and free triiodothyronine (fT3), as well as normal, low, or inappropriate levels of thyroxin (T4), free thyroxin (fT4), and/or TSH, are characteristics of ESS. The severity of clinical and biochemical ESS manifestation varies, and in the more severe instances, decreased fT4 and TSH values occur after the first decline in fT3 levels [4]. This study aimed to determine whether there is a connection between serum T3 levels and sepsis outcomes, particularly mortality in patients hospitalised to the PICU of Benha University hospitals.

PATIENTS AND METHODS

This study was prospective cohort study. We studied 100 children aged 1 month-18 years who were diagnosed with sepsis. For each patient, age, gender, mortality and outcome were noted. Study sample included 100 patients were collected from the pediatric intensive care unit at Pediatric Department, Benha University Hospitals over 6 months.

Inclusion criteria: Patients admitted to PICU one month age until 18 years old age with a diagnosis of sepsis according to American College of Critical Care Medicine (ACCM). **Exclusion criteria:** Patients with hypothyroid and hyperthyroid diagnosed by a pediatric endocrinologist before admission to PICU, patients taking drugs that affect thyroid functions, also patient admitted with surgical conditions. For each patient age, gender, mortality and outcome were noted. Study sample included 100 patients who were collected from the PICU at Pediatric Department, Benha University Hospitals over 6 months.

All children underwent the following:

A thorough history taking process that included their personal history (age and sex), a history of any current illnesses, and a prior history of any significant medical events. All patients underwent thorough physical and general examinations as well as

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monitoring of vital signs such as heart rate, non-invasive blood pressure readings, skin and core temperatures, and transcutaneous oxygen saturation. Then, a neurological, abdominal, cardiac, and chest examination were performed. According to WHO guidelines, anthropometric measures such as weight, height, and BM were computed.

The Paediatric Logistic Organ Dysfunction (PELOD)-2 is a revised scoring method for measuring organ dysfunction in critically sick patients in order to predict mortality in septic patients based on laboratory data from the medical record was generated and then classified as score ≥ 5 or < 5. Investigations done included free T3 level, which was done on first day of sepsis diagnosis, serum T3 levels were measured in all patients through blood samples (1 cm) were collected by venipuncture and analyzed by ELISA, and categorized as low (≤ 1 ng/dL) or normal (> 1 ng/dL). Baseline investigations were done, including CBC, CRP, ABG, kidney functions tests, liver functions tests and electrolytes' measurement. Blood, sputum, CSF, urine and stool cultures were done also. All data were taken at the time of diagnosis and patients were followed until the discharge or death, then they were into two groups according to outcome: died (70 patients) and survived (30 patients) groups.

Ethical approval: Benha Medical Ethics Committee of the Benha Faculty of Medicine gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis: The data were coded, handled, and analysed using version 24 for Windows®. To evaluate if the data had a normal distribution, Shapiro Walk test was used. Frequencies and relative percentages were used to depict qualitative data. The Chi square test (X^2) was used to compare the differences between two or more sets of qualitative variables. The mean ± SD of quantitative data was used. The Mann-Whitney test is a non-parametric test that was used to compare two non-parametric quantitative variables. To compare two independent groups of regularly distributed variables (parametric data), the independent samples t-test was employed. Significant was defined as $P \leq 0.05$.

RESULTS

Serum T3 level was low in 93% of septic patients who died, while only 25 % were in the survived group. So, low T3 levels were associated with increased mortality in the paediatric critical care unit. Further investigation found that serum T3 levels of ≤ 1 ng/dL had a significant relationship with mortality. The Paediatric Logistic Organ failure (PELOD)-2 scoring system has been modified to measure organ failure in critically unwell patients in order to predict mortality in septic children. Further investigation found that septic patients with a PELOD-2 score of ≥ 5 were at a considerably increased risk of death than those with a score of < 5 (Table 1).

Table (1): Demographic data, laboratory data and characteristics of the studied patients

		Total No. = 100 pts
Age (years)	Median (IQR) Range	2 (0.33 - 4) 0.08 – 16
Sex	Female Male	34 (34.0%) 66 (66.0%)
Weight	Normal Underweight	54 (54.0%) 46 (46.0%)
TLC	Normal Leucopenia Leucocytosis	38 (38.0%) 32 (32.0%) 30 (30.0%)
Anemia	No Yes	34 (34.0%) 66 (66.0%)
Platelets (mcL)	Normal Thrombocytosis Thrombocytopenia	62 (62.0%) 22 (22.0%) 16 (16.0%)
CRP (mg/L)	Negative Positive	24 (24.0%) 76 (76.0%)
FT3 (ng/dL)	Normal Low	54 (54.0%) 46 (46.0%)
FT3 numeric Values(pg/ml)	Median (IQR) Range	2.05 (0.8 - 2.8) 0.4 – 4.1
Culture	Negative Positive	48 (48.0%) 52 (52.0%)
Type of culture	Blood Sputum Urine Pus CSF	36 (69.2%) 10 (19.2%) 2 (3.8%) 2 (3.8%) 2 (3.8%)
Pelod 2 score	< 5 ≥ 5	74 (74.0%) 26 (26.0%)
Outcome	Survived Died	70 (70.0%) 30 (30.0%)

Table (2) shows that 34% of patients were females, while 66% were males. 46% of patients admitted to PICU were underweight. 66% were anemic, 22% were thrombocytopenic and CRP of 76% of the patients was positive. FT3 was low in 46% of the patients. Culture results were positive in 52% of patients of studied group. The most common positive culture was blood culture (69%) followed by sputum culture (19%), urine culture (4%), pus culture (4%) and CSF culture (4%). It also showed that PELOD2 score was more than or equal 5 in 26% of patients admitted to PICU. Outcome of patients admitted to PICU was that 30 % of patients died and 70% of patients survived. Also, there was highly statistically significant difference found between the two groups regarding TLC, anemia, CRP and FT3. There was increased incidence of leucopenia in died group compared to survived group, increased incidence of anemia in died group compared to survived group, increased incidence of positive CRP in died group compared to survived group and increased incidence of low FT3 in died group compared to survived group. While there was no statistically significant difference found between the two groups regarding age, sex, weight and platelets number.

Table (2) Relation between outcome of the studied patients and their demographic data, laboratory parameters and level of FT3

		Survived No. = 70	Died No. = 30	Test value	P-value	Sig.
Age (years)	Median (IQR) Range	1.5 (0.33 - 5) 0.08 - 16	3 (0.42 - 4) 0.25 - 7	1.116•	0.264	NS
Sex	Female Male	28 (40.0%) 42 (60.0%)	6 (20.0%) 24 (80.0%)	3.743*	0.053	NS
Weight	Normal Underweight	42 (60.0%) 28 (40.0%)	12 (40.0%) 18 (60.0%)	3.382*	0.066	NS
TLC	Normal Leucopenia Leucocytosis	34 (48.6%) 14 (20.0%) 22 (31.4%)	4 (13.3%) 18 (60.0%) 8 (26.7%)	17.521*	0.000	HS
Anemia	No Yes	30 (42.9%) 40 (57.1%)	4 (13.3%) 26 (86.7%)	8.157*	0.004	HS
Platelets (mcL)	Normal Thrombocytosis Thrombocytopenia	44 (62.9%) 16 (22.9%) 10 (14.3%)	18 (60.0%) 6 (20.0%) 6 (20.0%)	0.534*	0.766	NS
CRP (mg/L)	Negative Positive	22 (31.4%) 48 (68.6%)	2 (6.7%) 28 (93.3%)	7.059*	0.008	HS
FT3 (ng/dL)	Normal Low	52 (74.3%) 18 (25.7%)	2(6.7%) 28 (93.3%)	38.655*	0.000	HS
FT3 numeric values (pg/ml)	Median (IQR) Range	2.4 (1.6 - 3.4) 0.8 - 4.1	0.6 (0.5 - 0.8) 0.4 - 2.7	6.958•	0.000	HS

*: Chi-square test; •: Mann-Whitney test

Table (3) showed that there was highly statistically significant difference between the two groups regarding antibiotics used number and PELOD2 score, increased incidence of antibiotics number used in died group compared to survived group, increased incidence of PELOD2 score ≥ 5 in died group compared to survived group and increased incidence of PELOD2 score < 5 in survived group compared to died group. And there was statistically significant difference found between the two groups. Regarding use of inotropes, there was increased use of inotropes in died group compared to survived group. Besides, there was no statistically significant difference between the two groups in terms of the outcomes of the culture tests and the types of organisms present.

Table (3): Relation between outcome of the studied patients and culture results, use of iontropes, antibiotics used number and PELOD2 score

		Survived No. = 70	Died No. = 30	Test value*	P-value	Sig.
Culture	Negative Positive	36 (51.4%) 34 (48.6%)	12 (40.0%) 18 (60.0%)	1.099	0.295	NS
Type of culture	Blood Sputum Urine Pus CSF	24 (70.6%) 6 (17.6%) 0 (0.0%) 2 (5.9%) 2 (5.9%)	12 (66.7%) 4 (22.2%) 2 (11.1%) 0 (0.0%) 0 (0.0%)	0.085 0.159 3.929 1.101 1.101	0.770 0.690 0.047 0.294 0.294	NS NS S NS NS
Type of organism	Staphyloccocus aureus Gram negative bacilli Staphylococcus epidermidis Acinetobacter MDR Klibsiella MDR MRSA	10 (29.4%) 6 (17.6%) 6 (17.6%) 4 (11.8%) 4 (11.8%) 4 (11.8%)	2 (11.1%) 6 (33.3%) 2 (11.1%) 4 (22.2%) 0 (0.0%) 4 (22.2%)	2.220 1.631 0.386 0.989 2.294 0.989	0.136 0.201 0.534 0.319 0.129 0.319	NS NS NS NS NS NS
Use of ionotropes	No Yes	64 (91.4%) 6 (8.6%)	22 (73.3%) 8 (26.7%)	5.711	0.017	S
Antibiotics used number	One Two Three Four	14 (20.0%) 46 (65.7%) 8 (11.4%) 2 (2.9%)	0 (0.0%) 20 (66.7%) 10 (33.3%) 0 (0.0%)	12.458	0.006	HS
Pelod 2 score	< 5 ≥ 5	62 (88.6%) 8 (11.4%)	12 (40.0%) 18 (60.0%)	25.750	0.000	HS

*: Chi-square test.

Table (4) and figure (1) showed the diagnostic accuracy of low FT3 level in predicting patients' outcome. FT3 has sensitivity of 93.3% and specificity of 74.3% as predictor of mortality.

Table (4): Cut off point of FT3 level to predict outcome of the studied patients

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
FT3 ≤ 1	0.94	80.00	97.14	92.3	91.9
	AUC	**Sensitivity**	**Specificity**	**+PV**	**-PV**
Low FT3	0.800	93.30%	74.30%	60.78	96.3

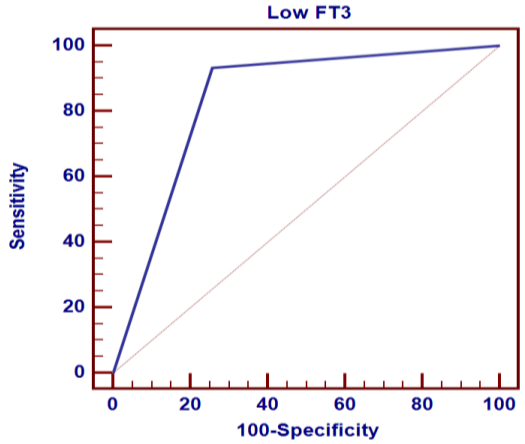

Figure (1): Receiver operating characteristic curve for the diagnostic accuracy of low FT3 level

Table (5) showed that there was highly statistically significant difference found between the two groups regarding PELOD2 score, staphylococcus aureus as culture growth and patient outcome.

There were increased incidence of PELOD2 score ≥ 5 in group with low FT3 compared to group with normal FT3, increased incidence of PELOD2 score < 5 in group with normal FT3 compared to group with low FT3, increased incidence of died patients in group with low FT3 compared to group with normal FT3 and increased incidence of staphylococcus aureus as culture growth in group with normal FT3 compared to group with low FT3.

Also, there was statistically significant difference found between the two groups regarding use of inotropes. There was increased incidence of use of inotropes in group with low FT3 compared to group with normal FT3.

While, there was no statistically significant difference found between the two groups regarding culture results and antibiotics used number.

Table (5): Relation between FT3 level of the studied patients and their culture results, use of inotropes, antibiotics used number, PELOD2 score and patient outcome

10		Normal FT3 No. 54	Low FT3 No. 46	Test value*	P-value	Sig.
Culture	Negative	28 (51.9%)	20 (43.5%)	0.698	0.404	NS
	Positive	26 (48.1%)	26 (56.5%)			
Type of culture	Blood	16 (61.5%)	20 (76.9%)	1.444	0.229	NS
	Sputum	6 (23.1%)	4 (15.4%)	0.495	0.481	NS
	Urine	0 (0.0%)	2 (7.7%)	2.080	0.149	NS
	Pus	2 (7.7%)	0 (0.0%)	2.080	0.149	NS
	CSF	2 (7.7%)	0 (0.0%)	2.080	0.149	NS
Type of organism	Staphylococcus aureus	10 (38.5%)	2 (7.7%)	6.933	0.008	HS
	Gram negative bacilli	6 (23.1%)	6 (23.1%)	0.000	1.000	NS
	Staphylococcus epidermidis	2 (7.7%)	6 (23.1%)	2.364	0.124	NS
	Acinetobacter MDR	2 (7.7%)	6 (23.1%)	2.364	0.124	NS
	Klebsiella MDR	2 (7.7%)	2 (7.7%)	0.000	1.000	NS
	MRSA	4 (15.4%)	4 (15.4%)	0.000	1.000	NS
Use of inotropes	No	50 (92.6%)	36 (78.3%)	4.238	0.040	S
	Yes	4 (7.4%)	10 (21.7%)			
Antibiotics used number	One	10 (18.5%)	4 (8.7%)	4.241	0.237	NS
	Two	34 (63.0%)	32 (69.6%)			
	Three	8 (14.8%)	10 (21.7%)			
	Four	2 (3.7%)	0 (0.0%)			
PELOD 2 score	< 5	50 (92.6%)	24 (52.2%)	21.092	0.000	HS
	≥ 5	4 (7.4%)	22 (47.8%)			
Outcome	Survived	52 (96.3%)	18 (39.1%)	38.655	0.000	HS
	Died	2 (3.7%)	28 (60.9%)			

*: Chi-square test

DISCUSSION

Sepsis is characterised by an unbalanced host response to infection and can result in multi-organ system malfunction. The cause of mortality in septic patients is determined by a number of factors, including the kind of bacteria, the length of time between the beginning of sickness and the onset of therapy, the underlying disease that preceded the sepsis, and the patient's current immunisation status. Sepsis is a major threat to children's lives and health. 64% of the 7.6 million children who die before the age of five die from sepsis or septic shock induced by a serious illness [1].

Thyroid hormones play a key function in metabolic homeostasis control. They play an important function in critical disease by boosting the inotropic property of myocardium and upregulating B-adrenergic receptors. Thyroid hormone deficiency may be linked to a reduction in dopamine impact. Thyroid hormones also influence the development and metabolism of different organs, with the cardiovascular system being a primary focus [3].

Our study showed that, the median serum T3 level in septic patients who died was 0.6 ng/dL. Statistical analysis indicated that 90% of these participants had blood T3 levels of ≤ 1 ng/dL, whereas just 20% of the survivors did. Further investigation found that serum T3 ≤ 1 ng/dL had a significant relationship with mortality (P <0.001). Our findings agree with those of a European systematic review that looked at seven paediatric researches and two adult studies. They discovered that a fall in total T3 level below 1 ng/dL increased the risk of mortality in 8 investigations, but not in one [5].

According to the maximum AUC of (0.8) in our investigation, FT3 levels were an independent predictor of death. These results agree with those of the study conducted on adults by **Hosny *et al.*** [6].

In order to quantify organ dysfunction in critically sick patients and predict mortality in septic patients, the PELOD-2 scoring system has been modified. According to our study's statistical analysis, sepsis patients with PELOD-2 scores > 5 died substantially more often than they survived (60% vs. 11.4%, respectively; (P<0.001). Further investigation showed that septic patients with PELOD-2 scores ≥ 5 had a statistically substantially greater risk of death than those with scores < 5 (P<0.001) [7].

Our study showed that concerning infection (68%), pneumonia, and sepsis were the most frequent causes of ICU admission, which is in line with earlier research by **Tazebew *et al.*** [8]. In this trial, the death rate was 30%. The mortality rate that was previously reported ranged from 2.1 to 41% [9]. The greatest mortality rates are found in poor nations due to a lack of resources. Although within the recommended range, our patients' mortality was nevertheless somewhat high. This is because there aren't enough resources, which leads to a higher death rate, comparable to other nations with scarce resources. Additionally, one of the tertiary hospitals where critically sick children are being referred has our PICU system.

Our study showed that anemia was a common problem, affecting 66% of patients admitted to PICU these results are in accordance to results done by **Bateman *et al.*** [10]**.** Our study also showed increased incidence of anemia in died group compared to survived group this is similar to results done by **Corwin *et al.*** [11]**.**

Based on the WHO growth curves, the total prevalence of malnutrition during PICU admission was 46%. This conclusion is identical to that of a Brazilian research, which found that 45.5% of PICU patients were malnourished [12].

Even though it was less than studies conducted in Iran and India, where more than half of the patients, 55.1% and 57.2% respectively, were found to be malnourished at admission. Our research's prevalence of malnutrition after admission to the PICU is greater than that of a study conducted in the Netherlands, a developed nation, which found a 24% prevalence [13]. The occurrence of malnutrition was not linked to the death rate in our investigation, as was the case in an Indian study that found no statistically significant link between mortality and malnutrition [14].

CONCLUSION

Our study found that serum T3 level was low in 93% of septic patients who died, while only 25 % did in the survived group, so low T3 levels had significant relationship with mortality in pediatric intensive care unit.

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