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Original Research Article

Study of Thyroid Hormone Profile in Children with Sepsis

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Conflict of interest: Nil

Abstract:

Background: Sepsis remains a major cause of morbidity and mortality among children. A hormonal disorder that often affected in sepsis is thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS). AIM- To evaluate thyroid hormone profile in children with sepsis and its association between thyroid hormone level and sepsis. To find out correlation between thyroid hormone level with clinical profile and outcome in these children.

Method: In this study 70 patients with sepsis is enrolled in a hospital based observational cohort study conducted in S.P.M.C.H.I and attached group of hospital Jaipur during July 2019 to July 2020. After making diagnosis of sepsis first sample was sent for measuring of free T3, free T4 and TSH on day 1 and then second sample for the same was sent on 7th day or on discharge whichever is earlier.

Result: We recorded patient outcome and analyse the relationship with chi –square test. Level of T3 and T4 were decreased on day 1 in paediatric sepsis. Of total 70 subject, 52(74.2%) with low level T3 and 38(54.2%) with low T4. There is a significant relationship between level of T3 and T4 with patient outcome ($p<0.05$).

Conclusion: The Euthyroid sick syndrome in children with sepsis does exist. There was a significant relationship between T3 and T4 level on day 1 with patient outcome.

Keywords: Sepsis, Thyroid Hormone Profile, Euthyroid Sick Syndrome.

Introduction

Sepsis is the most common cause of mortality in infants and children. The incidence of sepsis and septic shock were increasing in the last 30 to 40 years [1]. To define sepsis a child must have a confirmed or suspected infection and signs of that infection. Severe sepsis requires diagnosis of end organ system involvement. Septic shock requires cardiovascular dysfunction that is not resolved by initial fluid resuscitation. These definitions are aimed at identifying sepsis in an early stage to facilitate early intervention, with the goal of stopping further spread of infection and preventing. [2] Bacterial infection in the newborn account for a considerable morbidity and mortality, as the newborn especially the premature are prone to serious infections by organisms and partly because the signs of these infections may be absent or minimal and are hard to detect. Hence the timely diagnosis of sepsis in neonates is important as the illness can be rapidly progressive and in some instances fatal [3]. Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. A hormonal disorder that often affected in sepsis is thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) [4]. Euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) is a condition of decreased thyroid hormone levels without disruption of thyroid hormone function that occurs in severe systemic non-thyroid disease. Changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death [5-9]. A study in the Netherlands showed decreased in T4 that affected mortality, but a study in Belgium showed that T3 was decreased due to changes in metabolism in thyroid hormones [10-12]. A study in Cipto Mangunkusumo Hospital in 2014 reported decreased thyroid hormone levels especially T3 in sepsis, while in Semarang showed the decreased of T3 levels were followed by increased of T4 and TSH which was by the definition of ESS. Both studies showed patients with low thyroid hormone levels associated with poor outcome, as measured by pediatric logistic organ dysfunction (PELOD) or pediatric index of

mortality (PIM) score. There are few studies about thyroid hormone level changes in sepsis, so we a planned this study to evaluate thyroid hormone changes and the clinical outcomes in children with sepsis.

Aims and Objectives

Aim: To evaluate thyroid hormone profile in children with sepsis.

Objectives:

- To assess the association between thyroid hormone level and sepsis.
- To find out correlation between thyroid hormone level with clinical profile and outcome in these children.

Materials and Methods

Study Type: Hospital based observational cohort study.

Study Period: July 2019 to till sample size achieved.

Study Place: The study was conducted at SPMCHI Hospital, SMS Medical College Jaipur during the study period fulfilling the inclusion criteria were enrolled for the present study.

- Sepsis was diagnosed clinically and by lab investigation using the International Pediatric Sepsis Consensus Conference definition. [3]
- Clinically :
- hypothermia or hyperthermia
- Tachypnea
- Tachycardia/Bradycardia (In less than 1yr children)
- Lab Investigations :
- CBC with DLC with PBF
- Leucocytocsis or leucopenia
- Neutrophilia
- Thrombocytopenia
- Band cells
- CRP
- Chest X-ray
- CSF examination if required
- Blood culture sensitivity
- Urine culture sensitivity
- Then after making diagnosis of sepsis first sample was sent for measuring of free T3, free T4 and TSH
- Then second sample for the same was sent on follow up (7^{th} day).
- Lab sample analysis by method : Chemiluminescence immunoassay (CLIA)
- Machine : Snibe Macelumi 800

Sample Size:

- Sample size is calculated at 95% confidence level expecting 71.2% of low T3 levels among children with sepsis as per reference seed article. Yanni GN, D
- At 11% absolute allowable error the require sample size were 70 cases of children suffering from sepsis.

Statistical Analysis: Data was recorded on a Proforma. Analysis of data was done with suitable statistical method. For categorical variables chi-square test was used. For continuous variables independent samples t-test was used. p-value <0.05 was considered as significant.

Inclusion Criteria: Patients from one month to 18 years with a diagnosis of sepsis.

Exclusion Criteria

- Patients with hypothyroid and hyperthyroid diagnosed before admission were excluded.
- Mother having hypothyroid/hyperthyroid or taking medication for thyroid disorder.
- Refusal for consent

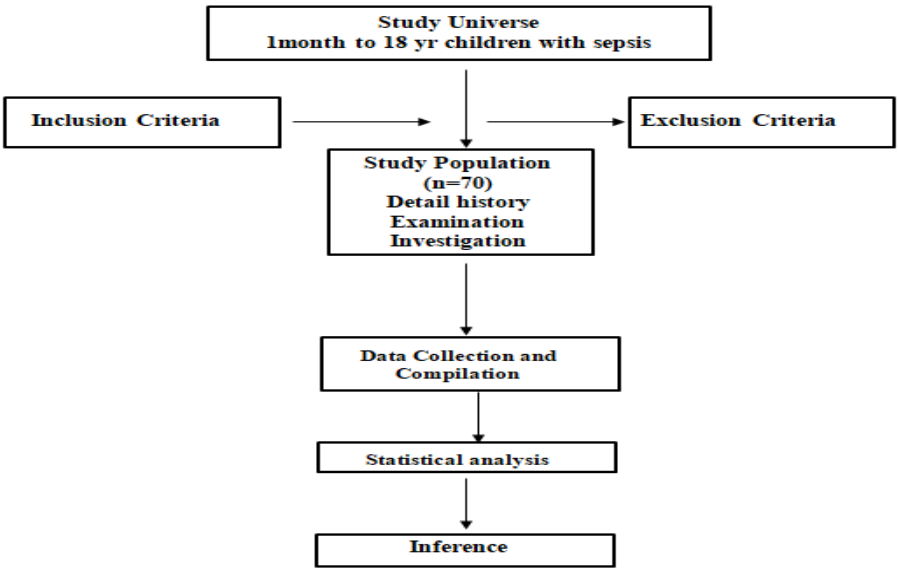


Figure 1: Flow Chart

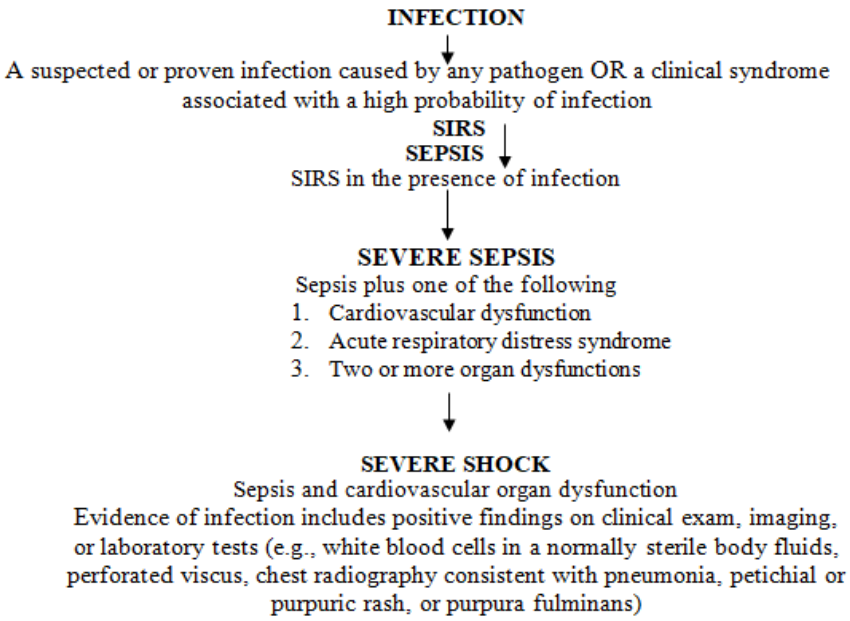
Review of Literature

The dilemma with addressing sepsis in any age group is the heterogeneity inherent in this disease state and patient population. The definition of adult sepsis has undergone continuing revision to keep pace with the high volume of published research; however, it is only recently that attention has been given to the pediatric patient and the many caveats that separate the pediatric patient from the adult. Prior to 2005, there was not a standard definition for pediatric sepsis which resulted in a lack of uniformity among sepsis studies. [13] Defining sepsis in the pediatric patient is made more difficult due to age specific vital signs, and their tremendous physiologic reserve which often masks the seriousness of their condition. In 2005, the Pediatric Sepsis Consensus Congress (PSCC) met to standardize the definition of sepsis, the PSCC divided age into six distinct categories in order to take into account age specific vital signs as well as age specific risk factors for invasive infections which in turn affect antibiotic coverage guidelines [14]

Pediatric severe sepsis is defined [15]

- As two or more systemic inflammatory response syndrome criteria
- Confirmed or suspected invasive infection,
- Cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions.

Determination of altered physiology is specific to age dependent vital signs.



Although the PSCC provided a more uniform set of diagnostic criteria, the SPROUT (Sepsis Prevalence, Outcomes, and Therapies) trial found that only 42% of sepsis patients were identified as such by both the clinician and the consensus criteria. [16] It is therefore important to realize that retrospective reviews based on ICD-9 codes or administrative data bases do not describe the same patient population as trials utilizing consensus criteria.

At present, there is no single biomarker that has proven specific or sensitive enough to diagnose sepsis or prognosticate outcome in selected cohorts. Similar to studies of sepsis in adults, there is active research examining both clinical and research measurements applicable to a pediatric population. Although there are still some obstacles to overcome concerning the diagnosis of sepsis, timely recognition and institution of treatment is imperative. Borkowski J et al (2005) [17] was found significant decrease of fT3 and TSH serum levels (respectively 2.36 +/- 0.79 pg/ml and 0.76 +/- 1.12mU/I) in compare to the control group (respectively 3.28 +/- 0.61 pg/ml and 0.95 +/- 0.46mU/l). Non survivors had significantly lower TSH serum level (0.37 +/- 0.62 mU/I) in comparison to survivors (1.27 +/- 1.45 mU/I) in spite of very similar fT3 serum level (respectively 2.45 +/- 0.87 pg/ml and 2.22 +/- 0.66 pg/ml). It could mean that there were disturbances in the pituitary-thyroid axis function in patients who did not survive.

This study did not show any correlations between thyroid hormones serum levels and APACHE (Acute Physiology and Chronic Health Evaluation) II score, APACHE III score, ALI or ARDS. This study show that low TSH serum level could be a significant prognostic factor of death in patient with septic shock especially with low fT3 serum level. The results also suggest that ESS could be a

consequence of pituitary TSH releasing disturbances. Den Brinker M et al (2005) [18] observed that children had decreased total T3 (TT3)/rT3 ratios without elevated TSH. T4 sulfate levels were decreased in 88%. Nonsurvivors had paradoxically higher TT3/rT3 ratios than shock survivors (0.71 vs. 0.30); this ratio also correlated with shorter duration of disease (r = -0.43). TT4 and T4-binding globulin (TBG) levels declined with increasing disease severity.

TBG levels correlated inversely with elastase levels (r = -0.46). Only TSH levels were significantly lower in 24 dopamine-treated children compared with non-dopamine-treated children (0.65 vs. 0.84), whereas other thyroid hormones did not significantly differ. Both higher TT3/rT3 ratios and lower TT4 levels were predictive for mortality, but this disappeared when IL-6 was entered into the regression model. All children with meningococcal sepsis showed signs of euthyroid sick syndrome. Alterations in peripheral thyroid hormone metabolism related inversely to the duration of disease and seemed to be enacted by profound induction of type 3 deiodinase rather than by down-regulation of type 1. Lower TT4 levels were related to increased turnover of TBG by elastase. Dopamine was found to suppress only TSH secretion, not other thyroid hormone levels, on PICU admission. Both the TT3/rT3 ratio and TT4 levels were predictive for mortality, but were not superior to IL-6.

Wang F et al (2012) [19] observed that the thyroid hormone indicators, FT3 had the greatest power to predict ICU mortality, as suggested by the largest area under the curve (AUC) of 0.762 ± 0.028. The AUC for FT3 level was less than that for APACHE II score (0.829 ± 0.022) but greater than that for NT-proBNP level (0.724 ± 0.030) or CRP level (0.689 ± 0.030). Multiple regression analysis revealed that FT3 level (standardized β = -0.600, P = 0.001), APACHE II score (standardized β = 0.912, P < 0.001), NT-proBNP level (standardized β = 0.459, P = 0.017) and CRP level (standardized β = 0.367, P = 0.030) could independently predict primary outcome. The addition of FT3 level to APACHE II score gave an NRI of 54.29% (P < 0.001) and an IDI of 36.54% (P < 0.001). The level of FT3 was significantly correlated with NT-proBNP levels (r = -0.344, P < 0.001) and CRP levels (r = -0.408, P < 0.001). In unselected ICU patients, FT3 was the most powerful and only independent predictor of ICU mortality among the complete indicators. The addition of FT3 level to the APACHE II score could significantly improve the ability to predict ICU mortality

Shikha s et al (2014) [20] conducted a study on Forty neonates with sepsis were included in the study as cases. Neonates with gestational age less than 37 weeks, body weight less than 2,500 grams or with congenital abnormalities were excluded from the study. Septic neonates were further divided into sepsis survivors (n = 19), shock-survivors (n = 9) and non-survivors. Forty full term neonates without sepsis served as controls. Thyroid hormones and CRP were estimated by chemiluminescent immunometric assay and The FT3 and FT4 hormones levels were significantly decreased (P < 0.001) in neonates with sepsis as compared to controls. No significant difference was observed in TSH levels. Non survivors had lower FT3 and FT4 levels (P < 0.05) compared to sepsis-survivor group. There was also a significant negative correlation between CRP and FT3 level in non-survivor group (r = -0.60; P = 0.02) and septic shock survivor group (r = -0.78; P = 0.006).Low levels of FT3 and elevation in CRP correlate closely with decreased survival in septic neonates

Agung G et al (2014) [21] evaluate the thyroid hormone profile in children with sepsis as well as to assess for a correlation between the thyroid levels and PELOD scores, Procalcitonin levels, and patient outcomes. Methods this cross-sectional study included children aged 1-18 years admitted to the pediatric intensive care unit (PICU) with a primary diagnosis of sepsis. PELOD scores and thyroid hormonal levels were assessed once during the first 24 hours after PICU admission. Thirty subjects were included in the study. The median values of T3, free T4, and TSH were 45 (range 17-133) ng/dL, 0.81 (range 0.3-1.57) ng/dL, and 1.36 (range 0.05-7.78) μIU/L, respectively. The T3, free T4, and TSH levels were decreased in 97%, 50% and 40% of the subjects. There were no significant differences between low and normal to high TSH with regards to the PELOD score (P=0.218), PCT level (P=0.694), or patient outcomes (P=0.55). The risk of death increased by 15 times among the subjects with PELOD score >20 compared to those with PELOD score.

Bhat K et al (2014) [22] conducted a study on 340 inpatients of SMI Hospital admitted during the period January 2014 to December 2014 to study thyroid hormone profile in critically ill patients. The patients with history of thyroid disorders or any family history of thyroid disorders were excluded from the study. Serum free triiodothyronine (fT3), free tetraiodothyronine (fT4) and TSH (Thyroid Stimulating Hormone) levels were assessed in critically ill patients admitted in wards and Intensive Care Units (ICUs). 59% of the critically ill patients admitted in wards and ICUs showed abnormality in one or more than one parameters of the thyroid profile. Low fT3 level was the most common abnormality found in these patients.

High TSH and low fT4 levels were the other common abnormalities. Assessment of thyroid function should be carried out in the critically ill

patients, only if the clinical suspicion is very high. Otherwise the results may be misleading. The clinicians should consider that abnormal thyroid function test results in critically ill patients are more likely to be due to the alteration in the metabolism of thyroid hormones secondary to the disease process, rather than the thyroid disorder itself.

Halil Ibrahim Tasci et al (2017) [23] conducted a study involved four groups, each containing seven female Wistar albino rats: Group 1: Sham, Group 2: Control (Sepsis), Group 3: Hyperthyroidism-Sepsis, and Group 4: Hypothyroidism-Sepsis. Group 1 only received laparotomy. Group 2 only had sepsis.

Sepsis was induced in Group 3 and Group 4 following formation of hyperthyroidism and hypothyroidism, respectively. After 24 hours, relaparotomy and thoracotomy were performed, and tissue and blood samples were drawn. Dysfunctions seen in the liver, lungs, and kidneys during sepsis and other findings of sepsis were milder in the hyperthyroidism group in comparison to both the control and hypothyroidism groups.

The results of Simon's grade, histopathological organ damage, and laboratory parameters revealed that the progression of sepsis was milder in the hyperthyroid group than in the hypothyroid and euthyroid groups. The progression in the hypothyroid group was the most severe.

Therefore, the results of the study raise the question of whether immediate treatment in cases of hypothyroidism and slow return of thyroid function to normal levels in cases of hyperthyroidism are adequate treatment approaches in patients who may develop sepsis or septic shock." To determine the answer to this question, more detailed studies are required with a higher number of subjects.

M.S. El Shimi et al (2018) [24] conducted a case control study was carried out over 12 months on 50 critically ill fullterm newborns admitted to the Neonatal Intensive Care Unit (NICU) in Ain-Shams University Hospitals. Fifty healthy fullterm newborns served as controls. All cases underwent detailed history taking including maternal medical conditions, maternal infections, maternal drug intake, maternal hypo- and hyperthyroidism. Presence of PROM, meconium staining, Apgar scoring at one minute and at 5minutes, neonatal resuscitation and congenital malformations. Neonates were diagnosed using sepsis score. CBC, blood culture and CRP were done for all neonates on 3rd day and on 10th day of antibiotic therapy. Serum total T3 (TT3), T4 (TT4), and TSH were determined and compared with age matched reference values.

From the 50 sick neonates; 32 (64%) were survivors and 18 (36%) were non- survivors. 52% had PROM, 46% needed ventilation, 64% were discharged. A mortality rate of 36% was recorded. On day 3; there was low T3 with mean of 58.77 + 17.07 ng/dl, low T4 (mean¼ 2.10 + 2.57ug/dl) and high TSH levels (6.73 + 2.08uU/ml). However, on day 10; serum T3 returned to be within normal range, with mean of 114.38 + 26.5ng/dl), serum T4 returned to normal range (11.72 + 2.54ug/dl) and TSH was lowered to half its value to reach normal levels (mean¼ 3.17 + 2.57 uU/ml). T4 was significantly correlated in patients to the septic clinical parameters, the diastolic BP, the WBC count, hemoglobin level, Neutrophil count and the CRP levels (p values < 0.05). TSH was significantly correlated to the septic clinical parameters, the HR, hemoglobin levels, and monocyte count (P values < 0.05). Hypothyroxinemia has considerable prevalence in neonatal intensive care setting and is related with critical illness as neonatal sepsis.

Pikala Tarakeswara Rao et al (2019) [25] conducted a prospective study in a level III neonatal intensive care unit. Neonates who were admitted with diagnosis of sepsis beyond day 3 of life were recruited as cases. Normal gestation matched neonates beyond day 3 were enrolled as control. Total 51 cases and 48 controls were enrolled in the study. Thyroid Function Tests (TFTs) were obtained at enrollment. Cases were divided into 'survivors' (86.3%) and 'non-survivors' (13.7%).

Analysis was done using statistical software packages SPSS and Microsoft Excel. Comparison of mean levels of thyroid hormones between cases and controls was done by t-test or Mann-Whitney U test. Serum T3, T4, Free T3 and Free T4 levels were significantly lower among cases as compared to gestational age matched control. {For both groups respectively T3: median (IQR) 69 (55,112) vs. 118 (81.5,142), p=0.002; for T4: 8.3 (5.9,11.7) vs. 12.7 (11.3,16.9); Free T3: 2.1 (1.7,2.6) vs. 3.1 (2.4,3.4) p=0.002; Free T4: 1.18 (0.9,1.48) vs. 1.72 (1.46,2.05). TSH was not significantly different among the groups.

The non-survivors among cases had significantly lesser T3,T4 and Free T4 levels as compared to survivors. {For both groups respectively T3:median (IQR) 38 (34,48) vs. 89 (61.2,112); for T4: 6.2 (5.9,7.5) vs. 9 (6.4,12), Rest of the TFTs were similar in both the groups. Neonatal sepsis causes significant decrease of thyroid hormones. Non survivor group of Septic neonates had significant low levels of T3 and T4 at admission. Low T3 and T4 levels at admission may serve as prognostic indicator in neonatal sepsis.

Yanni G N et al (2019) [26] conducted a observational cohort study in 80 children with sepsis from October 2015 to January 2016 in Haji Adam Malik General Hospital. T3 and T4 level were measured on day 1 and after > 72 hours of sepsis diagnosed. They recorded length of stay in PICU, patient outcome and analysed the relationship with the chisquare test. Level of T3 and T4 were decreased on day 1 in pediatric sepsis. Of 80 subjects, 57 (71.2%) with low-level T3 and 41 (51.2%) with low T4 were found. The relationship between T3 and T4 level on day 1 with the length of stay were not found (P = 0.500; P = 0.987).

There were a significant relationship between level of T3 and T4 with outcome (P = 0.0001; OR 24.706; P = 0.014; OR 3.086). Subject with normal T3 and T4 level had 24 and 3 times life chances compare to lower level. The Euthyroid Sick Syndrome in children with sepsis does exist. There was a significant relationship between T3 and T4 level on day 1 with patient outcome.

Observation and Results

Table 1: Distribution of subjects according to age group

Age group (in months)	No.	%
1-60	55	78.57
61-120	7	10
121-180	7	10
>180	1	1.4
Total	70	100

Table1 shows that maximum children in the study were aged 1 – 60 months (78.5%) followed by 61-120 months (10%). and least only1 (1.4%) child was aged >180 months. Pie chart 1. Shows that in our study female were more 38 (54.3%) than male 325.7%). The female: male ratio in the study was 1.19: 1.

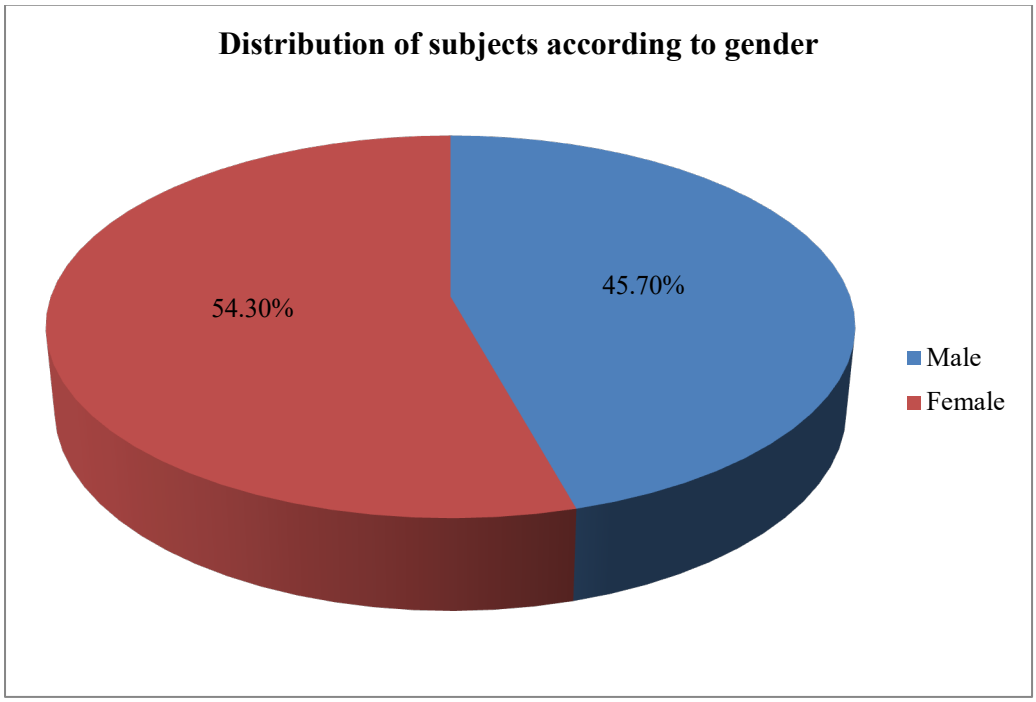


Figure 2: Distribution of subjects according to gender

Table 2: Distribution of subjects according to Thyroid hormone levels on day 1

Thyroid Hormones	Status		
	Low (%)	**Normal (%)**	**High (%)**
Serum F T3	40 (57.2)	30 (42.8)	0 (0.0)
Serum F T4	12 (17.2)	58 (82.8)	0 (0.0)
TSH	2 (2.9)	66 (94.2)	2 (2.9)

Table 2, depicts that Serum FT3 level was low in 40 (57.2%) subjects and was normal in 30 (42.8%) subjects. Serum FT4 level was low in 12 (17.2%) subjects and was normal in most (82.8%) subjects. TSH was normal in most (94.2%) of subjects and equally low and high (2.9%). Same depicted in bar chart.

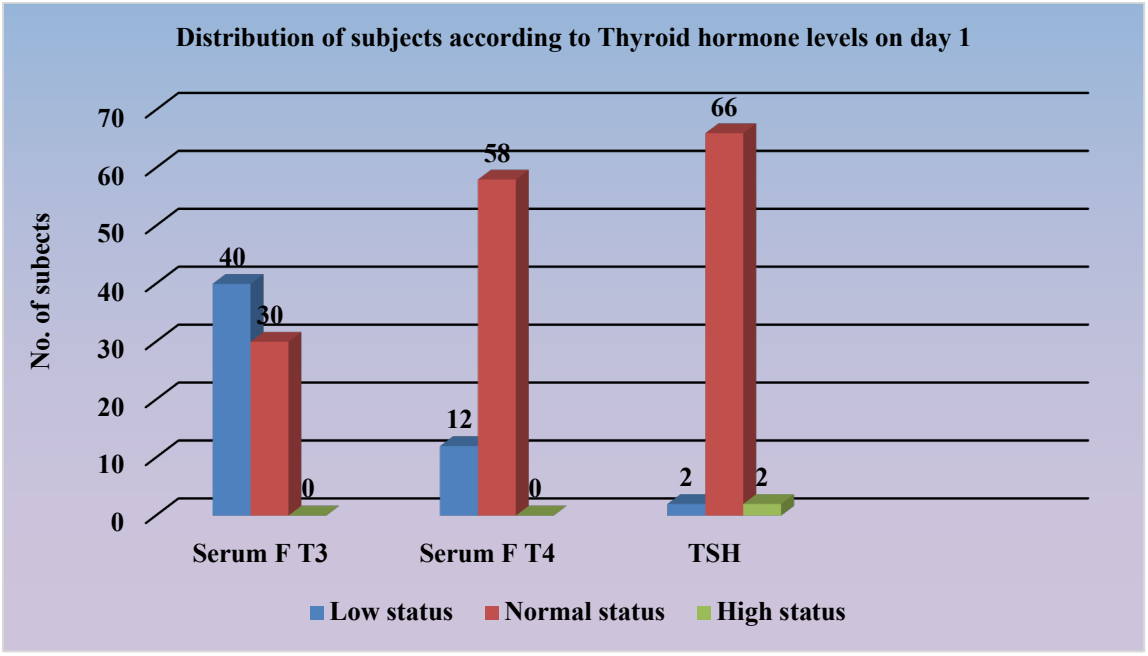


Figure 3: Distribution of subjects according to Thyroid hormone levels on day 1

Table 3: Distribution of subjects according to Thyroid hormone levels on follow up

Thyroid Hormones	Status		
	Low	Normal	High
Serum F T3	31(44.3)	39(55.7)	0(0.0)
Serum F T4	5(7.2)	65(92.8)	0(0.0)
TSH	1(1.4)	68(97.2)	1(1.4)

Table4 depicting thyroid hormone values on follow up , Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%). Serum FT4 level was low in 5 (7.2%) of the subjects and was normal in most (92.8%) of the subjects. TSH was normal in most (97.2%) of subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject. Same depicted in bar chart.

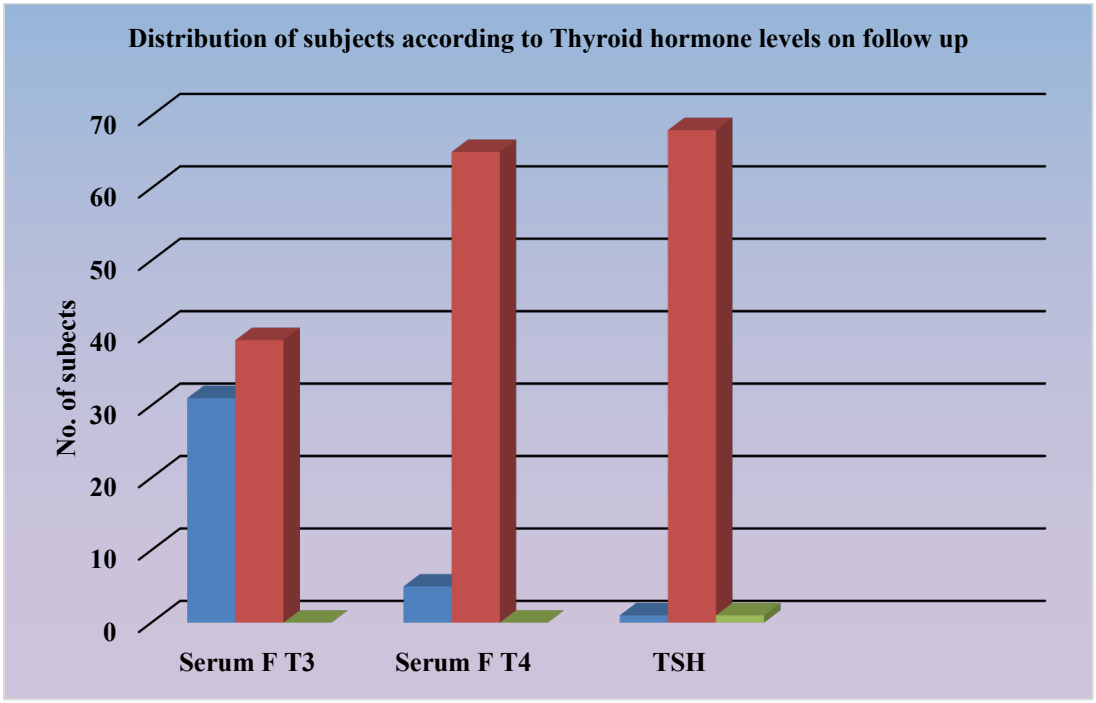


Figure 4: Distribution of subjects according to Thyroid hormone levels on follow up

Pie chart 2, shows, that 10 children with sepsis died giving a mortality rate of 14.3%.

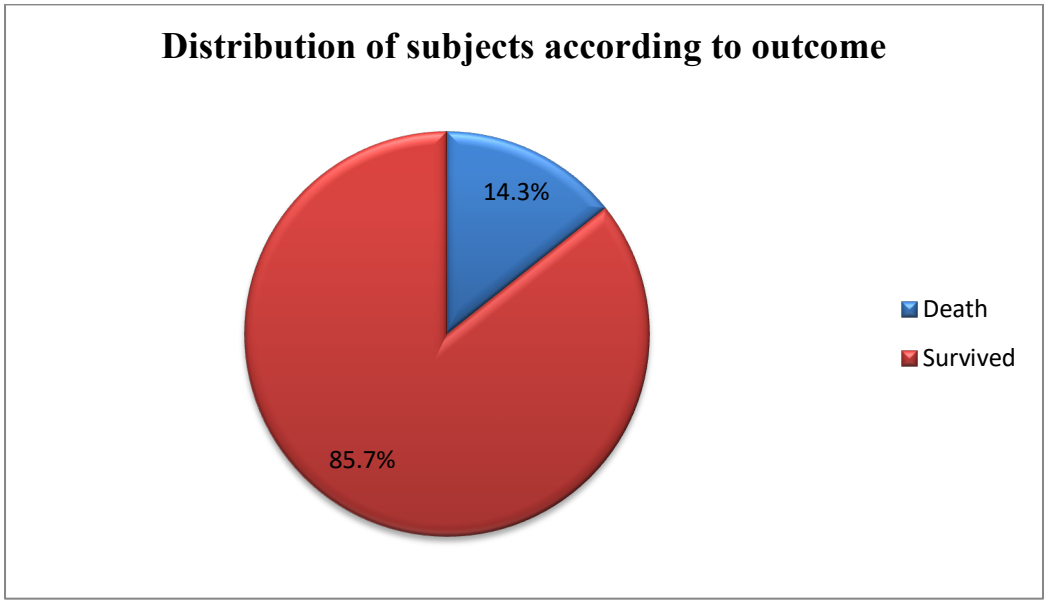


Figure 5: Distribution of subjects according to outcome

Table 4: Association of outcome with Thyroid hormone levels on day 1

Thyroid Hormones	Levels	Outcome		Total	P Value
		Death (%)	Survived (%)		
Serum F T3	**Low**	9 (22.5)	31 (77.5)	40 (100)	**0.023 (S)**
	Normal	1 (3.4)	29 (96.6)	30 (100)	
Serum F T4	**Low**	5 (41.6)	7 (58.4)	12 (100)	**0.002 (S)**
	Normal	5 (8.7)	53 (91.3)	58 (100)	
TSH	**Low**	0 (0.0)	2 (100)	2 (100)	**0.702 (NS)**
	Normal	10 (15.2)	56 (84.8)	66 (100)	
	High	0 (0.0)	2 (100)	2 (100)	

Table 4, shows that mortality was more in children with low serum T3 (22.5%) on Day 1 as compared to those with normal T3 (3.4%) and this difference was found to be statistically significant (p=0.023). Mortality was also more in children with low serum T4 level (41.6%) as compared to those with normal T4 level (8.7%), this difference was found to be statistically significant (p=0.002). However serum TSH level was not statistically significant found to be associated with mortality (p>0.05). Same depicted in bar chart.

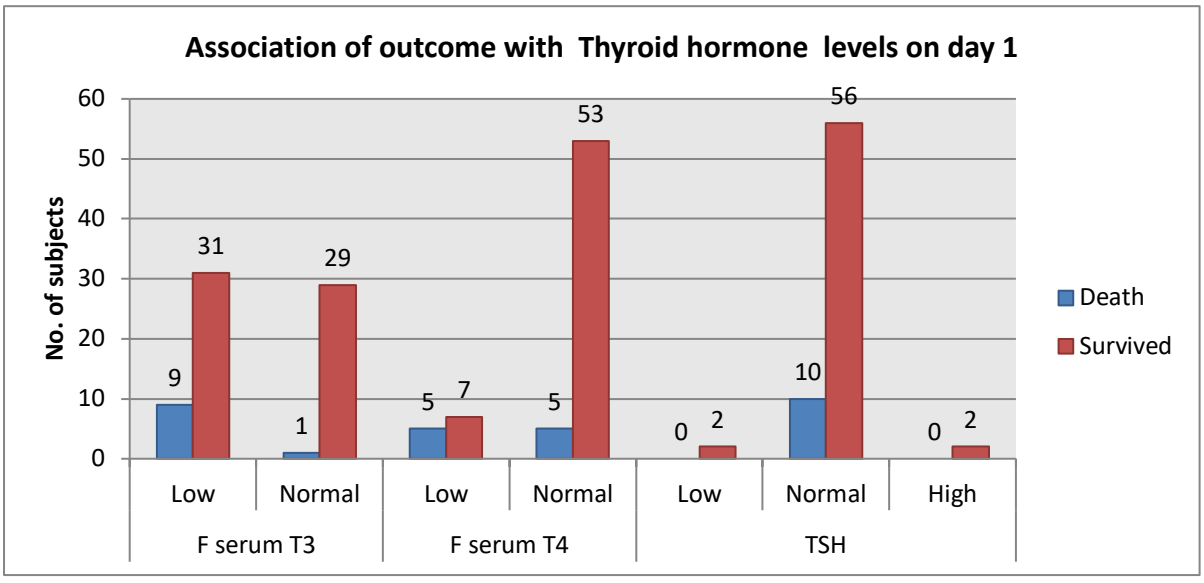


Figure 6: Association of outcome with Thyroid hormone levels on day 1

Table 5: Association of outcome with Thyroid hormone levels on follow up

Thyroid Hormones	Levels	Outcome		Total	P Value
		Death (%)	Survived (%)		
Serum F T3	**Low**	9 (29.0)	22 (71.0)	31 (100)	**0.001(S)**
	Normal	1 (2.5)	38 (97.5)	39 (100)	
Serum F T4	**Low**	1 (20.0)	4 (80.0)	5 (100)	**0.704(NS)**
	Normal	9 (13.9)	56 (86.1)	65 (100)	
TSH	**Low**	0 (0.0)	1 (100)	1 (100)	**0.842(NS)**
	Normal	10 (14.7)	58 (85.3)	68 (100)	
	High	0 (0.0)	1 (100)	1 (100)	

Table 5, shows that mortality was more in children with low serum F T3 (29%) on follow up as compared to those with normal T3 (2.5%) and this difference was found to be statistically significant (p=0.001). Serum free T4 and TSH level was not found to be statistically significant associated with mortality (p>0.05). Same depicted in bar chart.

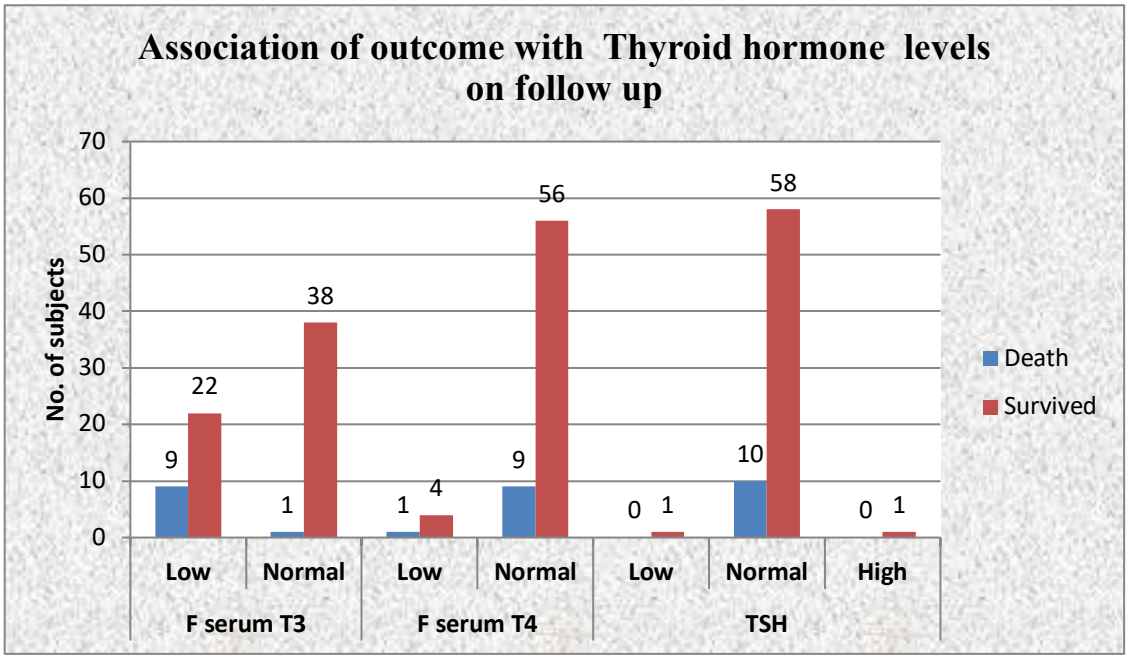


Figure 7: Association of outcome with Thyroid hormone levels on follow up

Discussion

Sepsis is the most common cause of mortality in infants and children. Sepsis and septic shock incidences were found to be increasing in the last 30 to 40 years. Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. In sepsis thyroid hormones disorder observed to occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) , further changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death. The critical disease is characterized by complex and multiple changes in the thyroid pathway.

Along with worsening of a critical illness, the decrease occurs in not only free triiodothyronine (T3) levels but also free thyroxine (T4) and thyroid stimulating hormone (TSH). Decreased levels of FT4 and TSH showed an indication of worsening of disease and poor prognosis.

There are few studies about thyroid hormone level changes in sepsis hence this study conducted to evaluate thyroid hormones changes and the outcome in children with sepsis.

Majority of the children in the study were aged 1 – 60 months (72.8%) followed by 60-120 months (14.3%). About 54.3% of the children were female and 45.7% of the children were males. The male: female ratio in the study was 1: 1.19. On day one serum FT3 level was low in 40 (57.2%) subjects and was normal in 30 (42.8%) subjects. Serum FT4 level was low in 12 (17.2%) subjects and was normal in most 58 (82.8%) subjects. TSH was normal in most 66 (94.2%) subjects, low in 2(2.9%) subjects and high in 2(2.9%) subjects. At follow up investigation, Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%) subjects.

Serum FT4 level was low in 5 (7.2%) subjects and was normal in most 65(92.8%) subjects. TSH was normal in most 68(97.2%) subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject.

1. Sikha s et al (2014) found that The FT3 and FT4 hormones levels were significantly decreased (P < 0.001) in neonates with sepsis as compared to controls without sepsis. No significant difference was observed in TSH levels between the groups.
2. Bhat K et al (2014) found that 59% of the critically ill patients admitted in wards and ICUs showed abnormality in one or more than one parameters of the thyroid profile. Low FT3 level was the most common abnormality found in these patients. High TSH and low FT4 levels were the other common abnormalities.
3. M.S. El Shimi et al (2018) found that on day 3; there was low T3 with mean of 58.77 ± 17.07 ng/dl, low T4 (mean 2.10 ± 2.57ug/dl) and high TSH levels (6.73 ± 2.08uU/ml). However, on day 10; serum T3 returned to be within normal range, with mean of 114.38 ± 26.5ng/dl), serum T4 returned to normal range (11.72 ± 2.54 ug/dl) and TSH was lowered to half its value to reach normal levels (mean 3.17 ±2.57 uU/ml).
4. Yanni G N et al (2019) observed that Level of T3 and T4 were decreased on day 1 in pediatric sepsis. Of 80 subjects, 57 (71.2%) with low level T3 and 41 (51.2%) with low T4 were found. The relationship between T3 and T4 level on day 1 with the length of stay were not found (P = 0.500; P = 0.987). There were a significant relationship between level of T3 and T4 with outcome (P = 0.0001; OR 24.706; P = 0.014; OR 3.086).

Looking at association of age groups with thyroid hormone levels on day 1 all children age >180 months had low FT3, followed by children aged 120-180 months (87.5%) and 60-120 months (60%) and minimum in children aged 1-60 months (51%). This difference in FT3 level in different age groups was however not found to be statistically significant.

All children age >180 months had low FT4, followed by children aged 1-60 months (19.6%) and 61-120 months (10%) and minimum in children aged 121-180 month (0%), This difference in FT4 level in different age groups was not found to be statistically significant. only 2 (3.9%) of children age 1-60 months had high TSH. Only 1 (2%) child in 1-60 months age and only 1 (12.5%) in 120-180 months had low TSH level. This difference in TSH level in different age groups was also not found to be statistically significant.

Den Brinker M et al (2005) observed that children had decreased total T3 (TT3)/rT3 ratios without elevated TSH.

On follow up investigations, 1 (100%) of children age >180 months had low FT3, followed by children aged 121-180 months (75%) and 61-120 months (50%) and minimum in children aged 1-60 months (37.3%). This difference in FT3 level in different age groups was however not found to be statistically significant. 1 (100%) of children age >180 months had low FT4, followed by children aged 1-60 months (7.8%) and none of the children in age group of 61-120 months and 121-180 month (0%). But that difference in FT4 level in different age groups was found to be statistically significant. Only 1 (2%) of children age 1-60 months had high TSH. Only 1 (2%) child in 1-60 months age had low TSH level. This difference in TSH level in different age groups was however not found to be statistically significant.

Around 10 children found to have been died with sepsis depicting a mortality rate of 14.3%.Mortality was more in children with Day 1 low serum FT3 (22.5%) as compared to those with normal FT3 (3.4%) and this difference was found to be statistically significant (p=0.023). Mortality was also more common in children with low serum FT4 level (41.6%) as compared to those with normal FT4 level (8.7%), this difference was also found to be statistically significant (p=0.002).

Serum TSH level was not found to be associated with mortality. On follow up mortality was more found to be among children with low serum FT3 (29%) as compared to those with normal FT3 (2.5%) and this difference was found to be statistically significant (p=0.001). Mortality was also more common in children with low serum FT4 level (20%) as compared to those with normal FT4 level (13.9%), this difference was however not found to be statistically significant (p>0.05). Serum TSH level on follow up also was not found to be associated with mortality.

Borkowski J et al (2005) also found significant decrease of FT3 and TSH serum levels (respectively 2.36 ± 0.79 pg/ml and 0.76 ± 1.12mU/I), but non survivors had significantly lower TSH serum level (0.37 ± 0.62 mU/I) in comparison to survivors (1.27 ± 1.45 mU/I) in spite of very similar FT3 serum level (respectively 2.45 ± 0.87 pg/ml and 2.22 ± 0.66 pg/ml). They concluded that low TSH serum level could be a significant prognostic factor of death in patient with septic shock especially with low ±T3 serum level. Wang F et al (2012) observed that the thyroid hormone indicators, FT3 had the greatest power to predict ICU mortality. Sikha s et al (2014) also found that non survivors had lower FT3 and FT4 levels (P < 0.05) compared to sepsis-survivor

group. Halil Ibrahim Tasci et al (2017) in a study among female Wistar albino rats found that progression of sepsis was milder in the hyperthyroid group than in the hypothyroid and euthyroid groups. The progression in the hypothyroid group was the most severe. Pikala Tarakeswara Rao et al (2019) found that the non-survivors among cases had significantly lesser T3, T4 and Free T4 levels as compared to survivors.

Conclusion

Present study concludes that abnormalities of thyroid hormones are common in children with sepsis. Low level of FT3 was the most common abnormality seen in more than half of the cases of children with sepsis. Mortality was found to be significantly associated more with low levels of serum FT3 & FT4 on day one , on follow up mortality was significantly associated with low level of serum FT3 irrespective of the age of the child. These findings call for evaluation of thyroid hormones in all patients with sepsis at admission for determining prognosis of neonatal sepsis cases.

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