

## Prognostic Value Of Thyroid Profile In Critical Care Patients

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### Abstract:

**Background:** Patients suffering from various critical illness admitted to the Intensive Care Unit (ICU) exhibit alterations in their thyroid hormone levels, collectively termed as "EUTHYROID SICK SYNDROME" or "NON THYROIDAL ILLNESS SYNDROME (NTIS)". It is characterized by low serum levels of free and total triiodothyronine (T3) and high levels of reverse T3 (rT3) accompanied by normal or low levels of thyroxine (T4) and thyroid-stimulating hormone (TSH). NTIS is caused because of alterations in the regulation of H-P-T AXIS and thyroid hormone transport and peripheral metabolism which are thought to be influenced by various inflammatory mediators released in critical care patients secondary to the underlying non-thyroidal illness. Our study was undertaken to determine the correlation between these altered thyroid hormone levels and outcomes in critical care patients

**Materials and Methods:** It is a cross-section study done in a tertiary care hospital. A total of 100 patients of age above 18yrs, of both sexes, were admitted to intensive care units with the following diseases, namely Septicemia, AKI, Respiratory failure, CCF, MI, DKA, STROKE with no previous history of thyroid disorder were included in the study. Relevant hematological and radiological examinations were done. Venous samples were obtained at the time of admission and tested for TotalT3, TotalT4 and TSH values. Need for ventilation and mortality were taken as primary outcomes, and we analyzed the ability of thyroid profile to predict the primary outcomes in the participants.

**Results:** Out of a total of 100 Patients included in the study, 60 patients (60%) had low T3 level, 26 patients (26%) had low T4, and TSH was low in 15 patients (15%). Our study showed low T3 (54%) is the commonest abnormality in ICU admitted patients. Out of 100 patients included in the study, the need for ventilation was seen in 54 (54%) patients, and 26 (26%) patients succumbed to death. There is a significant relation present between T3 and mortality (p value-0.003) and need for ventilation (p value 0.001), between T4 and outcome, namely mortality (p-value 0.01) and need for ventilation (p-value 0.01). A significant correlation was also noted between TSH and outcome (p-value 0.001).

**Conclusion:** we observed low T3 was the commonest finding in critical care patients and the thyroid profile was the strongest predictor of ICU mortality and need for ventilation with a significant p value (<0.05)

**Key Word:** Intensive care unit, critical illness, Total T3, Total T4, TSH

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### I. Introduction

Patients who are suffering from critical illness admitted to the Intensive Care Unit (ICU) exhibit alterations in their thyroid hormone levels, collectively termed as "EUTHYROID SICK SYNDROME" <sup>2</sup> or "NON THYROIDAL ILLNESS SYNDROME (NTIS)" <sup>3</sup>. It is characterized by low serum levels of free and total tri-iodothyronine (T3) and high levels of reverse T3 (rT3) accompanied by normal or low levels of thyroxine (T4) and thyroid-stimulating hormone (TSH). Altered thyroid profile in critically ill patients is postulated to be because of following reasons

1. Alterations in the activity of various de-iodinase enzymes primarily D1 and D3 which are primarily involved in the peripheral metabolism of thyroid hormones, resulting in low T3 and elevated ReverseT3 levels.
2. Reduction in TRH synthesis at PVN of hypothalamus resulting in decreased nocturnal TSH surge and 24hrs mean TSH levels
3. TSH secreted is of less biological activity.

These changes are thought to be influenced by various inflammatory mediators namely IL1, IL6, TNF $\alpha$  released in critical care patients secondary to underlying non thyroidal illness. In acute phase of illness fall in serum concentration of T3, where as rise in rT3 is observed after few hours of onset of illness. Patients with mild to moderate NTIS have normal serum T4, TSH levels, where as low levels are seen in severely ill patients. Various studies have shown that NTIS is of prognostic value in patients in critical care patients and can be used to predict outcome in patients admitted in ICU. <sup>4,5,6,19</sup>

## **II. Material And Methods**

This was a prospective observational study carried out on patients who were being admitted to ICU at Narayana Medical College and Hospital, Chinthareddy Palem, Nellore, Andhra Pradesh. A total of 100 adult subjects, both male and females aged  $\geq 18$ , years who fulfilled the inclusion and exclusion criteria were included in this study

**Study Design:** It was a prospective observational study.

**Study Location:** This was carried out at tertiary care teaching hospital under the guidance of the Department of General Medicine, at Narayana Medical College and Hospital, Chinthareddy Palem, Nellore, Andhra Pradesh.

**Study Duration:** The study was conducted between June 2019 to November 2019, over a duration of 6 months.

**Sample size:** 100 patients.

**Subjects & selection method:** A sample of 100 patients who were admitted and treated as in-patients in medical ICU are taken in our study.

### **Inclusion criteria :**

Patients of age above 18yrs, both males and females, admitted to the intensive care unit (ICU) with the following common critical illness, namely

1. Septicemia,
2. Acute renal failure (AKI),
3. Acute respiratory failure,
4. Myocardial Infarction (MI),
5. Congestive Cardiac Failure (CCF),
6. Diabetic Ketoacidosis (DKA), and
7. Cerebro Vascular Accidents (CVA)

### **Exclusion criteria:**

1. History of any thyroid diseases, such as hyperthyroidism, hypothyroidism and thyroid tumors
2. History of Radioactive Iodine therapy or Radiation therapy to Head and neck in the past
2. Thyroid nodule found by physical examination when admitted to the ICU
3. Pregnancy
4. History of any hormonal therapy except insulin within the previous six months
5. Patients receiving a massive blood transfusion or having steroid or dopamine therapy and
6. Intake of drugs known to interfere with thyroid hormone metabolism, e.g., Amiodarone, rifampicin, ketoconazole, antiepileptics.

### **Procedure methodology :**

Patients fulfilling the above criteria are taken into the study. After initial resuscitation and stabilization, relevant history regarding the presenting condition and past medical, surgical and treatment history were collected. A detailed physical examination was performed on all the patients. Relevant hematological and radiological investigations were done in all the patients for diagnosis and confirmation of primary condition for which they were admitted to ICU and Fasting Venous samples were collected from all the patients who fulfilled the study criteria upon admission to ICU and sent for thyroid hormone assay namely total T3, total T4 and TSH. The hormone estimation was done by chemiluminescence assay. The normal reference range for thyroid hormones in our laboratory are TSH (0.3-6.02  $\mu$ U/ml), T3 (0.5-2ng/mL), T4 (4.4-12  $\mu$ g/dL). Any deviation of the hormone results from the normal ranges is considered abnormal (low or elevated). Furthermore, the thyroid hormone levels obtained were correlated with the respective patients' outcomes during their stay in ICU to evaluate the prognostic value of Thyroid profile in patients with a critical illness.

The outcomes that were taken into study

1. Need for ventilator
2. Mortality

### **Statistical analysis :**

Summary data are presented in the form of mean value and standard deviation (SD) for continuous variables and percentages for categorical variables. P values were reported for all statistical tests using Microsoft Excel data analysis, and a value of  $<0.05$  was considered to be significant.

### III. Results

Table no 1 Shows that Out of 100 critically ill patients included in the study, 22 patients had Sepsis, 18 had acute renal failure, 20 patients had acute respiratory failure, 8 patients had Diabetic ketoacidosis, 12 patients had Myocardial Infarct, 6 patients had congestive Cardiac failure, and 14 patients had a stroke(CVA).

**Table no 1:**Distribution of study population based on the underlying critical illness.

CRITICAL ILLNESS	NO.OF CASES
Sepsis	22
Acute kidney injury	20
Acute Respiratory failure	18
Myocardial Infarction	12
Congestive Cardiac Failure	6
Diabetic ketoacidosis	8
Stroke (CVA)	14
Total	100

**Table no 2** As per the total T3, total T4 and TSH analysis done on the study population, 60 patients (60%) had low T3 level, 38(38%) patients had normal T3and 2 patients (2%) had low T3. Twenty-six patients (26%) had low T4, 74 patients (74%) had normal T4 levels, and TSH was low in 15 patients (15%), 84 patients (85%) had normal TSH and two patients (2%) slightly high.All the patients with low T4 and TSH had low T3 whereas all patients with Low T3 were not accompanied by low T4 and TSH. 2 patients with low T3 had high TSH and normal T4 levels

**Table no2:**Distribution study population with various critical illness based on their thyroid profile T3, T4, and TSH

VARIABLE	SEPSIS	AKI	ARF	MI	CCF	DKA	CVA	TOTAL
Low T3	14(63.63%)	12(60%)	11(61.1%)	6(50.%)	4(66.6%)	5(62.5%)	8(57.14%)	60(60%)
Low T4	8(36.36%)	4(21.05%)	4(22.22%)	3(41.6%)	1(16.6%)	2(25%)	4(28.5%)	26(26%)
Low TSH	4(18.18%)	2(10.5%)	3(16.6%)	2(16.6%)	1(16.6%)	1(12.5%)	2(14.28%)	15(15%)
Both LowT3 and Low T4	8(36.36%)	4(21.05%)	4(22.22%)	3(41.6%)	1(16.6%)	2(25%)	4(28.5%)	26(26%)
Low T3,T4 and TSH	4(18.18%)	2(10.5%)	3(16.6%)	2(16.6%)	1(16.6%)	1(12.5%)	2(14.28%)	15(15%)

**Table no3:**Out of 100 critically ill patients, 26 patients (26%) succumbed to death during their course of stay in the ICU. Among these 26 patients,8 patients with Sepsis, 4 patients with acute Kidney Injury, 6 patients with acute respiratory failure, 1 patient with DKA, 2 patients with CCF, 2 patients with MI and 3 patients with stroke had died.Out of 100 patients included in the study, a total 54(54%) patients were intubated eventually on admission and during their course of stay in hospital. Out of these 54 patients, 14(14%) patients has Sepsis, 9(9%) patients were diagnosed with AKI, 12 (12%) with Acute Respiratory Failure, 5(5%) patients with Myocardial Infarction, 4(4%) patients with Congestive Cardiac Failure, 4(4%) patients with DKA and a total of 6(6%) patients with CVA.

**Table 3:** Distribution of study population based on outcomes

OUTCOME	SEPSIS	AKI	ARF	MI	CCF	DKA	CVA	TOTAL
Need for ventilation	14(63.3%)	9(45%)	12(66.6)	5(41.6%)	4(66.6%)	4(50%)	6(42.8%)	54(54%)
Mortality	8(36.3%)	4(20%)	6(33.3%)	2(16.6)	2(33.3%)	1(12.5%)	3(21.4%)	26(26%)

**Table 4:** Relation between T3 and Need for Ventilation

Variable	Need for ventilation	N	Minimum	Maximum	Mean	SD	p- value
	NO	46	0.16	1.75	0.67	0.43	
T3	YES	54	0.10	1.75	0.49	0.47	0.001
	TOTAL	100	0.10	1.75	0.56	0.46	

**Table 5:** Relationship between T3 and mortality

Variable	Mortality	N	Minimum	Maximum	Mean	SD	p- value
	NO	74	0.10	1.75	0.63	0.43	
T3	YES	26	0.10	1.70	0.40	0.47	0.004
	TOTAL	100	0.10	1.75	0.56	0.46	

**Table 6:** Relationship between T4 and Mortality

Variable	Mortality	N	Minimum	Maximum	Mean	SD	p- value
	NO	74	1.41	11.99	5.72	2.15	
T4	YES	26	1.41	11.74	5.75	2.89	0.01
	TOTAL	100	1.41	11.99	5.68	2.36	

**Table no 7:** Relationship between TSH and mortality

Variable	Mortality	N	Minimum	Maximum	Mean	SD	p- value
	NO	74	0.10	8.90	2.91	2.18	
TSH	YES	26	0.10	8.30	3.75	2.44	0.001
	TOTAL	100	0.10	8.90	3.14	2.28	

**Table no 8:** Relationship between no. of patients with low thyroid profile and need for ventilation

Variable	NO. of patients	Need for ventilation	p-Value
Low T3	60	54	0.001
Low T4	26	54	0.01
Low TSH	15	54	0.001
Low T3 and T4	26	54	0.01

**Table no 9:** Relationship between no. of patients with low thyroid profile and mortality

Variable	NO. of patients	Mortality	p-Value
Low T3	60	25	0.003
Low T4	26	25	0.015
Low TSH	15	25	0.001
Low T3 and T4	26	25	0.01

#### IV. Discussion

Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease. These alterations together constitute non-thyroidal illness syndrome, also known as the low T3 syndrome or euthyroid sick syndrome. This syndrome is characterized by low serum levels of triiodothyronine (T3) and high levels of reverse T3, with normal or low levels of thyroxine (T4) and normal or low levels of thyroid-stimulating hormone (TSH). In our study, we have taken Total T3 and Total T4 values instead of free T3 and free T4 values as total protein content is known to undergo alterations in critically ill patients resulting in false positive or false negative values when free T3 and T4 are used for evaluation.

AS per the analysis of our results, out of 22 patients who presented with Sepsis, 14 patients (63.3%) had low serum T3 level, 6 (27.3%) patients had low T4 level, and TSH is low in 4 (18.18%) patients. Compared to the other critically ill patients, sepsis patients constituted the highest percentage of patients with low TSH and T4. Van der poll et al. found that inflammatory cytokines, such as IL1b, IL6, and TNF-alpha, can suppress the thyroid function at different levels via direct or indirect pathways,<sup>8,9</sup> and production of pro-inflammatory cytokines is more pronounced in Sepsis than that in other types of critical illness.<sup>10,11</sup> which goes in favor of our findings.

Out of 20 patients who had acute Kidney Injury, 12 (60%) patients had low serum T3 level, 4 (21.05%) patients had low serum T4 level, and 2 (10.5%) had low serum TSH. Fernandez-Reyes MJ et al. documented a relationship between serum triiodothyronine (T3) and several markers of inflammation, nutrition and endothelial activation in patients with renal failure (AKI/CKD)<sup>12,13</sup> supporting our findings.

In this study, out of 100 patients, 8 patients had diabetic ketoacidosis. Among these 8 patients, 5 (62.5%) patients had low serum T3 level, 2 (25%) patients had low T4 level, and TSH was low in 1 (12.5%) patients. Hu YY, Li GM et al., found that Serum T3 levels are inversely related with levels of glycated Hb in patients with DKA.<sup>14</sup>, supporting our findings.

In this study, out of 6 patients with congestive cardiac failure, 4 (66.6%) patients had low serum T3 level, 1 (16.5%) patients had low T4 level, and 1 (16.6%) had low TSH in correlation with the findings by Daneil M et al.,<sup>16,17</sup>

Out of 18 patients who presented with acute renal failure, 11 (61.6%) 7 had low serum T3 level, 4 (22.2%) Patients low serum T4 level and 3 (16.6%) had low serum TSH in correlation with findings by Karadag F et al.,<sup>15</sup>

In a study conducted by Pande A et al.,<sup>18</sup> patients of acute hemorrhagic stroke, high mortality rates were observed in patients with a low T3 and T4. Consequently, low T3 and low T4 predict a poor outcome in patients of hemorrhagic stroke. These findings correlated well with findings in patients with CVA in our study.

In our study of 100 patients, a total of 60 (60%) had low T3 levels, 26 (26%) patients had low T4 levels, and a total of 15 (15%) patients had low TSH values. Out of the 100 patients who were admitted to ICU with various critical illness, 54 (54%) patients were intubated and put on ventilatory support during their course

of stay and treatment in ICU, and 26 patients (26%) succumbed to death eventually during their stay in the hospital. All the patients who needed ventilatory support had low T3 levels with a significant correlation between low T3 and outcomes of the patients, namely need for ventilation and mortality with a p-value of 0.004 and 0.001, respectively. A significant relation was also found between T4 and the need for ventilation (p-value - 0.01) and mortality (p-value - 0.01). A significant relation between TSH and outcome of the patient, namely mortality and need for ventilation with p-value 0.001.

## V. Conclusion

There is a significant relation present between T3 and outcomes with mortality (p-value 0.004) and need for ventilation (p-value 0.001), between T4 and outcome, namely mortality (p-value 0.01) and need for ventilation (p-value 0.01). So, it can be concluded that low T3 was the commonest finding in critical care patients, and the thyroid profile (total T3, total T4 and TSH) was the strongest predictor of ICU mortality and need for ventilation with a significant p-value (<0.05).

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