

## **Correlation of thyroid profile with the apache ii score as a prognostic marker in patients with sepsis**

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### **Abstract**

**Background:** Any severe illness can cause abnormalities of thyroid hormone level and TSH in the absence of underlying thyroid disease. This study was conducted to find if any correlation between thyroid profile and sepsis and associate it with the acute physiology and chronic health evaluation II (APACHE II) score.

**Methods:** A hospital based cross sectional observational study was conducted among 100 critically ill sepsis patients admitted to tertiary care centre in central Rajasthan. Continuous data were compared using independent sample t-test. The correlation of free triiodothyroxine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) with APACHE II score was done using Pearson's correlation coefficient. At 95% confidence interval,  $p < 0.05$  was considered as statistically significant. The hormone estimation was done by chemiluminescence assay.

**Results:** Out of 100 patients, 58 patients were men and 42 were women. The mean age of patients was  $57.31 \pm$

19.08 years for male and  $56.9 \pm 19.42$  years for females. DM and COPD were the most frequently (44.00% and 41.00% respectively) found comorbidities followed by HTN and IHD (25.00% and 23.00% respectively). The mean APACHE II score was higher in nonsurvivors as compared to survivors ( $23.46 \pm 7.62$  vs.  $14.13 \pm 5.14$ ;  $p < 0.001$ ). In the study, 48 patients survived, while 52 of them died. Among nonsurvivors, APACHE II was inversely correlated with fT3 and TSH levels.

**Conclusions:** In critically ill patients with sepsis, thyroid profile in combination with the APACHE II score may prove to be a better indicator of critically ill patients' morbidity and mortality as compared to the APACHE II score alone.

**Keywords:** APACHE II, DM, COPD

### **Introduction**

Sepsis is a complex syndrome and is defined as the body's systemic inflammatory response to infection. (1) It results in systemic manifestations, tissue hypoperfusion and hypoxia and eventually death. (2) Sepsis

affects the endocrine system of body causing alterations in the thyroid function test. The abnormal thyroid activity is referred to as euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS), which is often observed in critically ill patients with no history of intrinsic thyroid disease. Patients present with low serum levels of free triiodothyronine (fT3) and thyroidstimulating hormone (TSH), and low or normal levels of free thyroxine (fT4).(3 )Also, high levels of reverse T3 (rT3) are observed in nonthyroidal illness due to the reduced conversion of rT3 to diiodothyronine (T2) due to the inhibition of 5'-monodeiodinase activity.(4)

Critically ill patients of sepsis admitted to the intensive care unit (ICU) exhibit thyroid dysfunction, which is associated with morbidity and mortality. Thyroid hormones modulate the metabolism and immune system in the body (5, 6) and, the magnitude of the thyroid dysfunction depends on the duration and severity of the disease.(7 )Based on the previous research studies, fT3 levels are significantly reduced in nonsurvivors when compared to survivors. Reports were also published in which there no association between fT3 and outcome was observed in ICU patients. Hence, there are several conflicting results regarding the association of thyroid hormones with the morbidity and mortality in ICU sepsis patients.(8-10)

The acute physiology and chronic health evaluation II (APACHE II) scoring system is a widely accepted method to determine the outcomes in ICU patients with an accuracy level of 77%.(11) It is a point score system based on the initial values of 12 routine physiologic measurements, age, and previous health status, which provide a measure of severity of the disease. APACHE II is the preferred method, as it involves simple calculations and the best calibration technique to

accurately predict mortality.(12) It does not include hormonal responses, such as thyroid function in critical illness, although the levels of hormones are highly associated with mortality.(13 )However, the APACHE II scores, when combined with an accurate description of the disease, and thyroid profile in critically patients can provide a better prognostic profile of thepatients.(12)

Role of thyroid hormones in predicting the outcome in sepsis patients is still debatable. In India, correlation of metabolic parameters with the APACHE II score in sepsis patients is non-existent. Hence, this study was designed to find a correlation if any between thyroid profile and sepsis and associate it with APACHE II score

### Methodology

**Study Design and data collection:** The study was conducted at the tertiary care centre in central Rajasthan. It was a 1-year cross-sectional study conducted from September 2018 to august 2019.Total of 100 patients aged 18 years and more admitted to the intensive care unit (ICU) for treatment of sepsis were enrolled in the study. Patients fulfilling sepsis 3 criteria included in the study were defined as “Suspected (or documented) infection and an acute increase in  $\geq 2$  sepsis-related organ failure assessment (SOFA) points”.SOFA score is a 24 pointmeasure of organ dysfunction that uses six organ systems (renal, cardiovascular, pulmonary, hepatic, neurologic, hematologic), where 0-4 points are assigned per organ system.

Patients with known cases of thyroid disorder, adrenal insufficiency, pregnant womenPatient taking Medicines like Lithium, Iodine, Amidarone, Propranolol, Adrenaline, Phenytoin and patients not fulfilling the criteria predefined for sepsis were exempted from the study. Before the commencement of study, ethical

clearance was obtained from the Institutional Ethical Committee. After explaining the purpose of the study, a written informed consent was obtained from all the participants before data collection. The data were recorded in a predesigned and pretested Performa.

**Statistics and data analysis**

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The unpaired t test was used for quantitative data comparison of all clinical indicators. Level of significance was set at  $P \leq 0.05$ . correlation was calculated by Multivariate Pearson correlation test.

**Results**

The mean age of the studied patients was  $57.14 \pm 19.08$  years. Maximum patients (53.00%) were more than 60 years of age. Among the studied patients 58.00% were male and 42.00% were female.

Minimum, Maximum, Mean and Std. Deviation of Vital Parameters as well as laboratory values including thyroid hormones are shown in table no 1

Table 1: Distribution according to Vital Parameters& laboratory values

Vitals	Minimum	Maximum	Mean	Std. Deviation
HR	58	146	99.21	18.322
SBP	60	190	107.96	26.756
Mean BP	37	138	82.33	20.182
RR	9	42	22.03	6.240
Temp.	34.1	39.1	37.095	1.1127
GCS	4	15	11.14	3.624
Hematocrit	14.60	49.90	37.5600	7.84347
WBC Count	3300	88000	20525.60	12282.594
Platelets	20400	542000	253417.40	131836.138
S. Creatinine	.40	14.50	2.4580	2.39385

Regarding vital parameters, it was found that the mean value of heart rate was  $99.21 \pm 18.32$  per minute, mean value of SBP was  $107.96 \pm 26.76$  mm Hg, mean BP was  $82.33 \pm 20.18$  mm Hg, mean value of respiration rate was  $22.03 \pm 6.24$  per minute, mean temp. was  $37.09 \pm 1.11$  °c and mean GCS was  $11.14 \pm 3.624$ .

Among the laboratory parameters, mean value of haematocrit was  $37.56 \pm 7.84$ , mean value of WBC was  $20525.60 \pm 12282.59$ , mean value of platelets was  $253417.40 \pm 131836.14$ , mean value of serum creatinine was  $2.46 \pm 2.39$ , mean value of bilirubin was  $1.26 \pm 1.49$ , mean value of  $Na^+$  was  $140.96 \pm 8.84$  and mean value of  $K^+$  was  $4.43 \pm 1.07$ .

Regarding thyroid level, the mean FT3 level was  $2.15 \pm 0.99$ , mean FT4 was  $1.15 \pm 1.25$  and mean TSH was  $2.35 \pm 1.65$ .

The mean FT3 and TSH level was significantly lower in non-survivor ( $1.56 \pm 0.79$  and  $1.79 \pm 1.26$  respectively) as compared to the survivor ( $2.78 \pm 0.77$  and  $2.96 \pm 1.82$  respectively) as shown in table no 2

In the Pearson correlation calculation, it was found that APACHE2 score were very significantly, negatively correlated with FT3 and TSH.

Bilirubin	.30	9.60	1.2596	1.48821
Na+	125.0	165.6	140.957	8.8434
K+	2.00	8.30	4.4280	1.07356
FT3	.47	3.90	2.1466	.99406
FT4	.61	9.54	1.1486	1.25445
TSH	.56	5.60	2.3544	1.65312
APACHE2	6	35	18.98	8.026

Table 2: Correlation between Outcome and thyroid status

	Nonsurvivor		Survivor		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
FT3	1.5577	.79685	2.7846	.77008	0.001 (S)
FT4	1.2710	1.70599	1.0160	.34944	0.31
TSH	1.7947	1.26368	2.9608	1.81697	0.001 (S)

Table 3: Correlation between APACHEII score and thyroids levels

		APACHE2
FT3	Pearson Correlation	-0.365**
	Sig. (2-tailed)	0.0001 (S)
FT4	Pearson Correlation	-0.122
	Sig. (2-tailed)	0.227
TSH	Pearson Correlation	-0.353**
	Sig. (2-tailed)	0.0001 (S)

**Discussion**

The present study was conducted on 100 critically ill patients admitted to tertiary care centre in central Rajasthan. This study is an attempt to identify thyroid profile as a prognostic marker in sepsis and to find if any correlation between thyroid profile and associate it with APACHEII scores in sepsis in critically ill patients to predict outcome. These patients with sepsis were above 18 years of age. Sepsis is a systemic infection that overwhelms the body's immune system, triggering an exaggerated inflammatory response. The infectious process may progress to septic shock, multiple organ failure syndrome, and ultimately to death. Identification

of appropriate indicators of sepsis in the patient is critical to facilitate prompt intervention.

Among admitted patients, 58.00% were male and 42.00% were female. The mean age of the studied patients was 57.14±19.08 years. Maximum patients (53.00%) were more than 60 years of age. It shows majority of the patients were from older age group and sepsis was more prevalent in patients of older age. Angus et al. (2001)<sup>(14)</sup> reported that the chances of developing sepsis differed for men and women by age, the likelihood of dying from sepsis was the same for men and women after adjusting for age, underlying co morbidity, and site of infection. The gender and age distribution pattern observed in this study was

consistent with the study conducted by Kumar et al. (2013) (15) in which 52% of the patients were men and 48% were women and the mean age was  $58.7 \pm 16.9$  years.

In our study following were the observation of vital parameters, mean heart rate was  $99.21 \pm 18.32$  per minute, mean SBP was  $107.96 \pm 26.76$  mm Hg, mean BP was  $82.33 \pm 20.18$  mm Hg, mean respiration rate was  $22.03 \pm 6.24$  per minute, mean temp. was  $37.09 \pm 1.11$  °C and mean GCS was  $11.14 \pm 3.624$ .

The mean APACHEII score in our study was significantly higher in non-survivor ( $23.46 \pm 7.61$ ) as compared to survivor ( $14.13 \pm 5.15$ ). The mean APACHE2 score was  $18.98 \pm 8.03$ . Similar findings were reported by Kothiwale et al. (2018) (16) in which most of the patients had APACHE II scores between 15 and 19 with a mean APACHE II score of  $21.26 \pm 10.07$ .

We observed following thyroid parameters, the mean FT3 level was  $2.15 \pm 0.99$ , mean FT4 was  $1.15 \pm 1.25$  and mean TSH was  $2.35 \pm 1.65$ . APACHE2 was very significantly, negatively correlated with FT3 and TSH. The mean FT3 and TSH level were significantly lower in non-survivor ( $1.56 \pm 0.79$  and  $1.79 \pm 1.26$  respectively) in comparison to the survivor ( $2.78 \pm 0.77$  and  $2.96 \pm 1.82$  respectively). Similar findings have been reported in previous study of Patients present with low serum levels of free triiodothyronine (fT3) and thyroid stimulating hormone (TSH), and low or normal levels of free thyroxine (fT4) (3). Also, high levels of reverse T3 (rT3) are observed in nonthyroidal illness due to the reduced conversion of rT3 to diiodothyronine (T2) due to the inhibition of 5'-monodeiodinase activity (4). Das et al. (2002),<sup>(17)</sup> Yildizdas et al. (2004),<sup>(18)</sup> Lodha et al. (2007)<sup>(19)</sup> also reported lower values of T3, T4, fT3 and fT4 in patients with septic shock. Mean fT4 level was significantly higher than

upper reference limit in non-survivor, but statistically not significant

Abnormal "thyroid function test" results have often been noticed in patients suffering from various infections, because the thyroid hormone plays an important role in the adaptation of metabolic function to stress and critical illness. Such alterations in thyroid hormone levels are referred to as "nonthyroidal illness syndrome (NTIS)", 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 can be attributed to increased deiodination of thyroxine (T4) to reverse T3 (rT3), rather than T3 and increased catabolism of T3 to 3, 3-diiiodothyronine (T2). With increasing severity of illness, low total and free T4 and sometimes low TSH can be observed.<sup>(20)</sup>

The reason behind the decreased fT3 levels in majority of the critically ill patients with nonthyroidal illness is the inhibition of 5'-monodeiodinase which leads to decreased conversion of T4 to T3. Several factors are involved in the inhibition of 5'-monodeiodinase including cytokines, circulating deiodinase inhibitors (free fatty acids), and glucocorticoid therapy. The hormonal changes in patients with sepsis are believed to be mediated through cytokines, because cytokines are the major factors that orchestrate the host response to bacterial infection. Interleukin-1 is the major cytokine which stimulates the hypothalamo-pituitary adrenal axis leading to increase in glucocorticoid level.<sup>(21)</sup> These cytokines also act on hypothalamo-pituitary thyroid axis and inhibit the TSH secretion, biosynthesis and release of thyroid hormone and thyroid growth.<sup>(22)</sup> When compared to other studies the present study included patients without previous history of thyroid

dysfunction, which did not interfere with the study outcomes and proves to be the strength of the study. The critically ill patients are administered with several drugs that can interfere with thyroid functioning which can be a limitation of the study. Because, in critically ill patients it is difficult to adjust this factor, the blood samples were collected on the day of admission. And also fT3 and fT4 are not affected by various drugs, so fT3 and fT4 can be used as indicators for morbidity and mortality in ICU patients

### **Conclusion**

In our study we concluded that APACHE2 score was very significantly, negatively correlated with FT3 and TSH. In critically ill patients with sepsis thyroid profile in combination of APACHEII score may prove to be a better predictor of patients mortality & morbidity than APACHEII score alone, so we recommend inclusion of both APACHEII and thyroid profile assessment in critically ill patients to predict outcome more accurately than APACHEII score alone.

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