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Correlation of thyroid hormone profile and acute physiology and chronic health evaluation II (APACHE II) score with the survival in sepsis in a tertiary care centre

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ABSTRACT

Background: Thyroid hormone plays a pivotal role in the adaptation of metabolic function to stress and critical illness like sepsis. Thyroid dysfunction is associated with increased mortality in sepsis. The role of thyroid dysfunction as a prognostic marker in sepsis remains unclear. **Aims and Objectives:** To correlate the baseline thyroid function tests with APACHE II score and mortality in adult patients admitted with sepsis in Intensive Care Unit (ICU). **Materials and Methods:** This was a cross sectional, observational study done for a period of one year from September 2019 to September 2020 in a tertiary care referral hospital. Patients admitted with sepsis to ICU were scored on admission using APACHE II score. Blood was sent for thyroid function tests on admission. Patients were divided into survivors and non-survivors based on the outcome. Statistical analysis was done by calculating mean values, Fisher's exact test and Pearson's correlation. **Results:** A total of 52 patients were included. The mean age was 55.65 ± 18.55 years with a male predominance (M: F = 1.4:1). Pneumonia was the commonest cause of sepsis in the study (20 patients,38.5%). Mortality was seen in 20 patients (38.5%) The mean values of thyroid hormones were lower in non-survivors. APACHE II Score was higher among the non-survivors as compared to survivors. (21.7 ± 5.571 vs 19.78 ± 5.939, p value > 0.05). Thyroid hormones (T3, T4, FT3, FT4) had a negative correlation with APACHE II score in non-survivors. TSH had significant positive correlation with APACHE II score in non-survivors (p value = 0.027). **Conclusion:** Thyroid hormone levels did not correlate significantly with APACHE II score and mortality among the non-survivors of sepsis.

Key words: Thyroid hormone; acute physiology; chronic health evaluation score; survival in sepsis; tertiary care centre; Karnataka

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INTRODUCTION

Sepsis is a systemic inflammatory response induced by an infection with deleterious host response to the pathogen which may often progress to severe sepsis and septic shock. Thyroid hormone plays a vital role in the adaptation of metabolic function to stress and critical illness like sepsis. Such changes in thyroid hormones is referred to as nonthyroidal illness syndrome(NTIS) or euthyroid sick syndrome (ESS). NTIS is characterized by low serum levels of total and free triiodothyronine (FT3) and thyroid stimulating hormone (TSH), elevated levels of reverse T3(rT3) and low or normal levels of free thyroxine (FT4).[1] Proposed mechanism includes increased deiodination of T4 to reverse T3 rather than T3 and increased catabolism of T3 to 3,3 diiodothyronine (T2).[2]

The acute physiology and chronic health evaluation II (APACHE II) scoring system is a widely accepted tool to evaluate the outcomes in ICU patients with 77% accuracy.[3]

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The scoring is based on the baseline values of 12 routine physiologic measurements, age, and pre-existing health condition, which measures the disease severity. Simple calculations and the best calibration technique makes the APACHE II scoring a preferred method to accurately predict the mortality.[4]

Critically ill sepsis patients admitted to the intensive care unit (ICU) manifest thyroid dysfunction, which is associated with adverse outcomes. Thyroid dysfunction has been found to be associated with increased mortality among ICU admitted patients.[5-7] Thyroid hormones play an important role in the modulation of our body metabolism and immunity.[8,9] The duration and severity of the disease has an impact on the magnitude of the thyroid dysfunction.[10]

The role of thyroid dysfunction as a prognostic marker in critically ill patients with sepsis remains unclear. Some studies showed that low thyroid hormones were associated with adverse outcomes, whereas other studies failed to prove any correlation between thyroid dysfunction and mortality in critically ill patients.[11,12] Hence, the primary objective of the present study was to correlate the thyroid profile with the survival in sepsis and correlating thyroid dysfunction with APACHE II score in critically ill patients with sepsis was the secondary objective.

MATERIALS AND METHODS

This was a cross sectional, observational study conducted in a tertiary care referral centre in Karnataka from September 2019 to September 2020. Ethical clearance was obtained from the institutional ethics committee prior to the commencement of the study. The present study included adult patients >18 years of age admitted to intensive care unit with the diagnosis of sepsis. In the present study, sepsis was defined as life threatening organ dysfunction caused by a dysregulated host response to infection.[13] Patients with history of any thyroid disease, pregnancy and those on medications altering thyroid functions were excluded.

An informed consent was obtained from the patients or their legal guardians prior to their enrolment in the study. Detailed medical history and baseline characteristics of the patient were recorded in a predesigned proforma.

On admission, the patients were examined and the severity of sepsis was scored by APACHE II score.[14] Blood was sent for relevant investigations and thyroid function tests (T3,T4, FT3, FT4 and TSH) on admission. Thyroid function tests were performed using chemiluminescence assay using COBAS 6000. The primary outcome of our study was ICU mortality. Based on the outcome, the patients were divided into two groups, namely survivors and non-survivors. The thyroid parameters and APACHE II score were correlated among the two groups.

Statistical analysis

Collected data was summarized by mean±SD, frequencies and percentages. Fisher's exact test and student t test were used appropriately to obtain the significance. A p value was generated for all variables with a value of less than 0.05 considered as significant. Odds ratio(OR) along with confidence interval (CI) were calculated for statistically significant parameters to assess the risk of fatal outcome in patients with sepsis. FT3,FT4,T3,T4 and TSH were correlated with APACHE II score using Karl Pearson's correlation coefficient. All analysis were carried out using SPSS, version 23. Significance level was set at the 5% level.

RESULTS

A total of 52 patients were included in the study. Majority were in the age group of 51-70 years (48%) with a mean age of 55.65 ± 18.55 years (mean ± SD) There was a male preponderance with a M:F ratio of 1.4:1.

Table 1 depicts the diagnosis of the patients on admission. Pneumonia outnumbered other diagnosis in our patients (38.5%). Clinical profile of the patients is shown in Table 2. One interesting finding was that nearly half of the patients were diabetics. Closer inspection of the table reveals that approximately half of the patients presented with shock and similar percentage of patients needed ventilator. The presence of acute kidney injury in our study participants was strikingly high (76.9%).In the current study, mortality was seen in 20 patients (38.5%).

The presence of septic shock (OR67.857,CI 7.682-599.415, p value 0.000) and the need for ventilator (OR 32.143, CI 5.965-173.193, p value 0.000) had a statistically significant association with mortality in the non-survivor group (Table 2).

Table 3 compares the mean value of various physiological and biochemical parameters including thyroid function tests along with APACHE II scoring among the two groups, survivors and non-survivors with statistical significance. As shown in the top half of the Table 3, the mean values of T3, FT3, FT4 and TSH were lower among the non-survivors. However, the difference in thyroid function tests among the two groups was not statistically significant. The APACHE II score was higher among the non-survivors as compared to survivors, though this was not statistically significant. It is interesting to note that the

Table 1: Etiology of sepsis in the study subjects (N=52)

Diagnosis	Total (n=52) n (%)	Non-survivors (n=20) n(%)	Survivors (n=32) n(%)
Acute Gastroenteritis	1(1.9%)	0(0%)	1(3.1%)
Appendicular Abscess	1(1.9%)	0(0%)	1(3.1%)
Cellulitis	2(3.8%)	0(0%)	2(6.3%)
Chronic Liver Disease,Peritonitis	2(3.8%)	1(5%)	1(3.1%)
Empyema	1(1.9%)	0(0%)	1(3.1%)
Leptospirosis	5(9.6%)	2(10%)	3(9.4%)
Meningitis	1(1.9%)	0(0%)	1(3.1%)
Necrotising Fascitis	1(1.9%)	0(0%)	1(3.1%)
Pneumonia	20(38.5%)	9(45%)	11(34.4%)
Secondary Peritonitis With Perforation	1(1.9%)	1(5%)	0(0%)
Urosepsis	17(32.7%)	7(35%)	10 (31.3%)

p value 0.771, Fisher's exact test

Table 2: Clinical profile of the study subjects (N=52)

	Number (%)	Non-Survivors (N=20)	Survivors (N=32)	p value
Shock	26 (50%)	19 (95%)	7 (21.9%)	0.000*
Diabetes	29 (55.8%)	10 (50%)	19 (59.4%)	0.508
Chronic Kidney Disease	10 (19.2%)	4 (20%)	6 (18.8%)	0.911
Ventilator Requirement	25 (48.1%)	18 (90%)	7 (21.9%)	0.000*
Acute Kidney Injury	40 (76.9%)	18 (90%)	22 (68.8%)	0.077
Severe Organ Insufficiency Or Immunocompromised	27(51.9%)	12 (60%)	15 (46.9%)	0.332
Post Operative Status	2 (3.8%)	0 (0%)	2 (6.3%)	0.254
Age (Years)				
30 and below	7 (13.5%)	4 (20%)	3 (9.4%)	0.141
31 - 50	10 (19.2%)	4 (20%)	6 (18.8%)	
51 - 70	25 (48.1%)	6 (30%)	19 (59.4%)	
Above 70	10 (19.2%)	6 (30%)	4 (12.5%)	

*Highly significant, Fisher's exact test

presence of tachycardia, low mean arterial pressure (MAP) and a low Glasgow Coma Scale among the non-survivors as compared to the survivors was statistically significant.

In the present study, we correlated the thyroid function tests with the APACHE II score in both the groups which is depicted in Table 4. Among the non-survivors, FT3 and FT4 negatively correlated with APACHE II score. But this was not statistically significant. Surprisingly, there was statistically significant positive correlation between TSH and APACHE II score (p value=0.027) among the non-survivors. Among the survivors, FT3 and TSH had a positive correlation and FT4 had a negative correlation with APACHE II score. However, this was not statistically significant.(Table 4)

DISCUSSION

The age and gender distribution of the present study was similar to study done by Kothiwale et al and Kumar et al.[11,15] The results of the previous studies done on the correlation of T3, T4, FT3 and FT4 and prognosis in critically ill patients have been inconsistent. A study done by Ray et al failed to establish an association between FT3 and mortality, a finding similar to the current study.[16] A study done by Kothiwale et al found FT3 to be lower among the non-survivors and the finding was statistically not significant, similar to the present study.[11] Other studies found an association of the T3, TSH and FT4 with the adverse outcome in ICU patients.[17,18] Many studies opine that a low FT3 level in critically ill, ICU-admitted patients could be taken as the powerful indicator of mortality. [9,19,20] A large population study done on 480 critically ill patients showed that the addition of FT3 to APACHE II score improved the accuracy in predicting the fatal outcome.[9] In the present study, thyroid hormones had a negative correlation with APACHE II score while TSH correlated positively with APACHE II score among the non-survivors. Similar results were found in other studies.[9,11]

The mechanisms underlying low T3 levels in critically ill patients is still unclear. During critical illness such as sepsis, cytokines like interleukins and tumour necrosis factor alpha inhibit the enzyme, 5'-deiodinase, which is needed for conversion of T4 to T3.[11,21-23] This results in low levels of T3 in these patients. In a study done by Wang et al, FT3 was found to be significantly lower among the non-survivors in critically ill ICU patients. He concluded that FT3 was the single, most powerful independent predictor of ICU mortality.[9] A meta-analysis done by Jae Kim et al on 1578 adult patients with sepsis

Table 3: Physiological and biochemical parameters among the survivors (N=32) and non-survivors (N=20) and its statistical significance

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		p value	
					Lower bound	Upper bound		
T3	Non-survivors	20	.52390	.183402	.43807	.60973	.252	NS
	Survivors	32	.61241	.308737	.50109	.72372		
	Total	52	.57837	.268999	.50348	.65326		
T4	Non-survivors	20	5.63950	2.198618	4.61052	6.66848	.874	NS*
	Survivors	32	5.54738	1.901822	4.86170	6.23305		
	Total	52	5.58281	2.000361	5.02590	6.13971		
TSH	Non-survivors	20	1.45515	1.124199	.92901	1.98129	.574	NS
	Survivors	32	1.66366	1.386849	1.16364	2.16367		
	Total	52	1.58346	1.284688	1.22580	1.94112		
FT4	Non-survivors	20	.97760	.368481	.80515	1.15005	.089	NS
	Survivors	32	1.17431	.415413	1.02454	1.32408		
	Total	52	1.09865	.405976	.98563	1.21168		
FT3	Non-survivors	20	2.40095	1.543130	1.67874	3.12316	.527	NS
	Survivors	32	2.89669	3.250274	1.72484	4.06854		
	Total	52	2.70602	2.714381	1.95033	3.46171		
APACHE score	Non-survivors	20	21.75	5.571	19.14	24.36	.240	NS
	Survivors	32	19.78	5.939	17.64	21.92		
	Total	52	20.54	5.826	18.92	22.16		
Mean arterial pressure	Non-survivors	20	57.80	21.496	47.74	67.86	.025	sig**
	Survivors	32	72.84	23.591	64.34	81.35		
	Total	52	67.06	23.770	60.44	73.68		
Heart rate	Non-survivors	20	114.90	20.973	105.08	124.72	.042	sig
	Survivors	32	104.22	15.835	98.51	109.93		
	Total	52	108.33	18.543	103.16	113.49		
Respiratory rate	Non-survivors	20	26.30	5.913	23.53	29.07	.812	NS
	Survivors	32	25.84	7.158	23.26	28.42		
	Total	52	26.02	6.649	24.17	27.87		
Bicarbonate	Non-survivors	20	13.460	3.7227	11.718	15.202	.205	NS
	Survivors	32	15.859	7.8022	13.046	18.672		
	Total	52	14.937	6.5996	13.099	16.774		
pH	Non-survivors	20	7.3670	.13421	7.3042	7.4298	.533	NS
	Survivors	32	7.3419	.14381	7.2900	7.3937		
	Total	52	7.3515	.13940	7.3127	7.3903		
Total count	Non-survivors	20	15775.00	5500.419	13200.72	18349.28	.053	NS
	Survivors	32	19575.00	7394.156	16909.12	22240.88		
	Total	52	18113.46	6927.412	16184.86	20042.07		
Sodium	Non-survivors	20	131.00	8.253	127.14	134.86	.906	NS
	Survivors	32	130.72	8.344	127.71	133.73		
	Total	52	130.83	8.229	128.54	133.12		
Potassium	Non-survivors	20	3.9050	.86662	3.4994	4.3106	.018	sig
	Survivors	32	4.5394	.93502	4.2023	4.8765		
	Total	52	4.2954	.95306	4.0301	4.5607		
Creatinine	Non-survivors	20	3.2895	1.82066	2.4374	4.1416	.742	NS
	Survivors	32	3.0781	2.46324	2.1900	3.9662		
	Total	52	3.1594	2.22122	2.5410	3.7778		
Haematocrit	Non-survivors	20	35.300	6.2344	32.382	38.218	.160	NS
	Survivors	32	32.350	7.8050	29.536	35.164		
	Total	52	33.485	7.3218	31.446	35.523		
Glasgow coma scale	Non-survivors	20	11.75	3.193	10.26	13.24	.010	sig
	Survivors	32	13.53	1.626	12.94	14.12		
	Total	52	12.85	2.484	12.15	13.54		

t test , *Not significant. **Significant

showed that T3, T4, FT3 and FT4 were significantly lower among the non-survivors whereas TSH did not have statistically significant difference between the survivors and the non-survivors.[24] LowT3 levels might possibly reflect a collective measure of pathological processes during critical illness, such as circulatory dysfunction and pro inflammatory status.[19]

The study was limited by a small sample size. Critically ill patients are administered many drugs, which are integral part of their management, which can interfere with the thyroid hormone levels. Hence, the blood samples were collected on admission in the present study. Further large population studies are needed to explore the role of thyroid dysfunction in sepsis.

Table 4: Correlation of thyroid profile with APACHE II score among the two groups (N=52)

Out come		Correlation	p	
Non-survivors	APACHE score & T3	-.346	.135	NS*
	APACHE score & T4	-.045	.852	NS
	APACHE score & TSH	.495	.027	Sig**
	APACHE score & FT4	-.244	.300	NS
	APACHE score & FT3	-.109	.648	NS
Survivors	APACHE score & T3	-.160	.382	NS
	APACHE score & T4	-.178	.331	NS
	APACHE score & TSH	.224	.217	NS
	APACHE score & FT4	-.187	.307	NS
	APACHE score & FT3	.227	.212	NS

Karl Pearson's coefficient. *Not significant, **Significant

CONCLUSION

In this study, we found that the thyroid hormone levels did not have significant correlation with APACHE II score and mortality among the non-survivors of sepsis. TSH had a significant positive correlation with APACHE II score in non-survivors. Future large-scale studies should aim to clearly establish the causal relationship between thyroid hypofunction and adverse outcome in critically ill patients.

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