To Study the Prognostic Efficacy of Thyroid Hormones with S.O.F.A. Score in Predicting Mortality of Critically Ill Patients Admitted in ICU

Sayed Wasim Ahmad[1], Surendra Kumar[2], Imran Ali[3], Manoj Kumar Mali[4], Harish Kumar[5], Naveen Jeengar[6], Navneet Kumar[7], Chandrapal[8], Surendra Kumar Prajapat[9], Sandeep Kumar Dangi[10], Kokila R[11]

[1,7,8,9,10,11]**Resident, Department of Medicine, SPMC, Bikaner**
[2]**Additional Principal and Senior Professor and Unit Head, Department of Medicine, SPMC, Bikaner**
[3]**Senior resident, Department of Medicine, SPMC, Bikaner**
[4]**Associate Professor, Department of Medicine, SPMC, Bikaner**
[5,6]**Assistant Professor, Department of Medicine, SPMC, Bikaner**

Abstract:

Background: Intensive care unit (ICU) scoring systems have been in use for more than three decades to objectify and quantify the physician's clinical decision in critically ill patients.

Aim: A study for prognostic efficacy of thyroid hormone with SOFA score in predicting mortality, serum uric acid and serum albumin in critically ill patients.

Material & Methods: This was a prospective cross sectional study conducted on 400 randomly selected patients during one year period. All patients admitted in intensive care unit had age >16 years and gave informed consent were included in the study.

Results: Mean age in non survivors and survivors patients wee was 55.66±18.03 age 46.21±20.08 years (p<0.001). Mean serum albumin in non survivors and survivors patients were 3.01±0.46, and 3.13±0.56 respectively (p<0.05). Mean serum uric acid in non survivors and survivors were 5.29±0.79mg/dl and 5.34±0.83mg/dl respectively (p>0.05). Mean TSH in SOFA group 0-9, 10-14 and >14 groups were 3.01±0.93, 2.92±0.68 and 2.20 respectively (p>0.05).

Conclusion: We concluded that Free T3 level can be used independently as a predictor of mortality in critically ill patients admitted in intensive care unit. The addition of Free T3 to SOFA can significantly improve the ability of SOFA score to predict mortality in critically ill patients. The addition of Free T3 level to SOFA score can significantly improves is ability to predict mortality in critically ill patients. Low serum albumin level on day of admission to ICU also appears to be a significant marker in predicting outcome of critically ill patients in the form of mortality and morbidity. Thus, serum albumin level measurement can be used as a prognostic marker in critically ill patients in addition to SOFA Score along with clinical judgment.

Keywords: SOFA Score, Thyroid Hormones, Critical Care.

Introduction

Intensive care unit (ICU) scoring systems have been in use for more than three decades to objectify and quantify the physician's clinical decision in critically ill patients5. Probability of mortality may not be accurately indicated by Global performance indicators for critically ill patients admitted to ICU [1].

The changes in hormone axis of critically ill patients are common, however rarely have been given emphasis with regard to its ability to predict mortality. Changes in thyroid function test (TFT) are commonly seen in critically ill patients. These changes are referred to as sick euthyroid syndrome. [2]

Critical illness in sepsis and other systemic disorders exerts a state of stress which results in hyper metabolism, increased energy expenditure, hyperglycaemia, and cachexia. Thus, the metabolic response to sepsis involves every organ and tissue of the body and yet very little is known about the underlying mechanism. In critically ill patients, thyroid hormone dysfunction is noted even when there is no history of previous intrinsic thyroid disease [3-5], often referred as Euthyroid Sick

Syndrome (ESS) or Non-Thyroidal Illness Syndrome (NTIS).[6]

Reduced serum total T3 (tri-iodo-thyroxine) is probably the most common finding in moderate to severely ill patients in ICU whereas total T4 (Thyroxine) and free T4 concentrations may be found to be reduced in more severe disease. According to most accepted belief, this is a result from reduced peripheral deiodination of T4 and reduced binding by plasma thyroid hormone binding proteins. There is reduction in plasma thyrotropin levels in acute critical illness. Ileus, insulin resistance, impaired triglyceride levels, reduced inotropy, and reduced protein synthesis and metabolism in muscles are few effects of reduced plasma concentrations of T3 and T4 may cause. [7] These effects are mostly result of increased catabolism in sepsis. TT3 and TT4 concentrations are lower in non-survivors than in survivors, and therefore thyroid hormone dysfunction could affect outcome and increase mortality in critical illness.

ESS is characterised by low level of total triiodothyronine (T3) and free T3 (FT3) and high level of reverse T3 (rT3) along with normal or low level of thyroxine (T4) and thyroid stimulating hormone (TSH) [11]. Thyroid hormones play an important role in the adaptation of metabolic function to stress and critical illness [12].

Thyroid hormone alterations, particularly in critical illness are very common and are correlated with the severity of disease and the outcomes of patient in Intensive Care Unit (ICU) [13-15]. Alteration in levels of thyroid hormones during severe illness may also be attributed to decrease in plasma T4-binding globulin or transthyretin and accumulation of substances that lower the plasma thyroid hormone-binding capacity.[16] Studies have shown that low thyroid hormone may act as independent predictors of mortality in patients admitted to ICU like other parameters such as hyperglycaemia, hyperprolactinaemia, procalcitonin (PCT), brain natriuretic peptide (BNP) etc. suggesting the inclusion of the thyroid profile in the scoring system, which are used to predict the mortality of the ICU patients.[17]

Sequential organ failure assessment or sepsis-related organ failure assessment score (SOFA score) is used to predict the severity of the critically ill patients admitted in ICU. SOFA score was developed to quantify the severity of patient's illness based on the degree of organ dysfunction data on six organ failures, i.e. haematologic-platelets count, hepatic-serum bilirubin, renal-serum creatinine, cardiovascular- mean arterial pressure (MAP), central nervous system (CNS)-Glasgow coma score (GCS), respiratory-PaO2/FIO2. The mortality risk is >25% if SOFA score is >9 and >50% if SOFA score is >13 [18].

SOFA score during the first few days of ICU admission is a good indicator of prognosis. Highest SOFA scores and it's mean values both are useful predictors of outcome. An increase in SOFA score during the first 48 hrs past admission to ICU predicts a mortality rate of at least 50% [28,29], and is independent of initial SOFA score.

Studies show that there is correlation between low level of thyroid hormones and severity of illness along with SOFA [34,35]. Serum uric acid levels and serum albumin levels also affect the outcome of seriously ill patients. Therefore, this prospective cross-sectional study was intended to detect the thyroid hormones (FT3, FT4 and TSH), serum uric acid levels and serum albumin levels as independent predictors of ICU mortality in patients.

Material and Methods

This is a prospective cross sectional study was conducted for 1 year at Department of Medicine, S.P. Medical College & P.B.M. Associated Group of Hospitals, Bikaner. All patients admitted in intensive care unit who gave consent for the study were included in the study. The patients with prior thyroid disease, Age <16 years, pregnant females and pregnancy in last 6 months, patient expired within 24 hours of admission in ICU, patients taking drugs which causing thyroid dysfunction like amiodarone, lithium, estrogens, imatinib, phenobarbitone, carabamazepine, phenytoin and rifampicin etc, known case of hyperuricemia, chronic liver disease, malabsorption syndrome and nephrotic syndrome were excluded.

Demographic data along with routine biochemical parameters and thyroid hormone assessment were recorded for all the patients along with their primary outcome as mortality at the time of admission to ICU however the patients who expired within 24 hrs of admission were excluded from the study. SOFA score was used to determine severity of illness. It was calculated from all patients along with their thyroid hormone profile. Venous blood samples were collected along with arterial blood gas analysis. Thyroid hormones were measured by radioimmunoassay technique.

Statistical analysis was done using SPSS version 17.0 statistical analysis software. The values were represented as number (%) and mean ±standard deviation (SD). The results are presented in frequencies, percentages for categorical variables, and mean±SD for continuous variables. The Chi-square test was used to assess the association between categorical variables. The binary logistic regression was used to find the strength of associations. Stepwise multivariate logistic

regression analysis was used to determine the independent predictors of ICU mortality.

Results: In present study, out of total 400 cases, mortality was observed in 139 (34.8%) cases while all other patients were Survivors from the hospital. Mean age of non-survivor group was 55.66±18.03 years while mean age in Survivors patients was 46.21±20.08 years which was statistically highly significant (p<0.001) [Image 1]. Fifty-six (40.3%) of non survivors were females while 83 (59.7%) males while in control group 105 (40.2%) patients were females and 156 (59.8%) were males.

There is clear-cut male predominance over female with male to female ratio was 1.48:1 and the difference was found statistically insignificant (p>0.05).
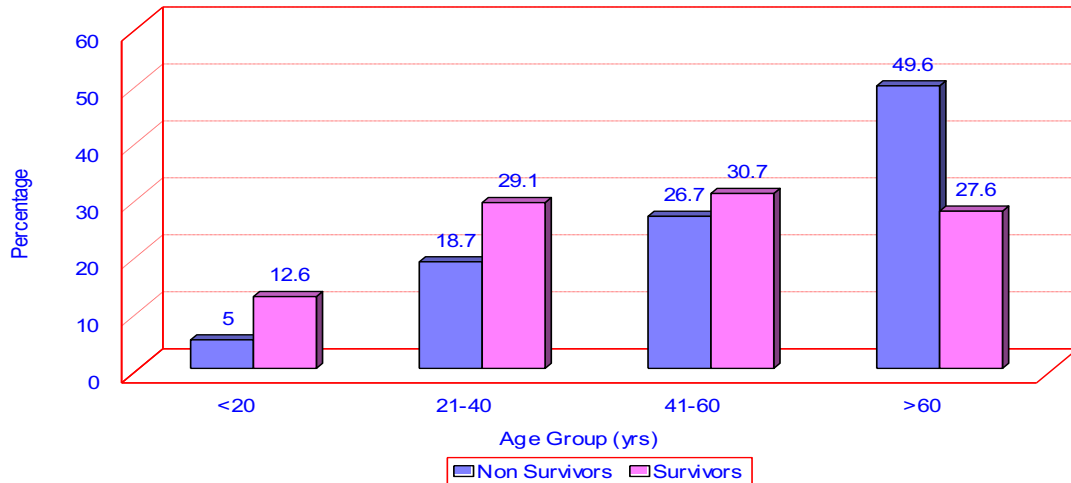

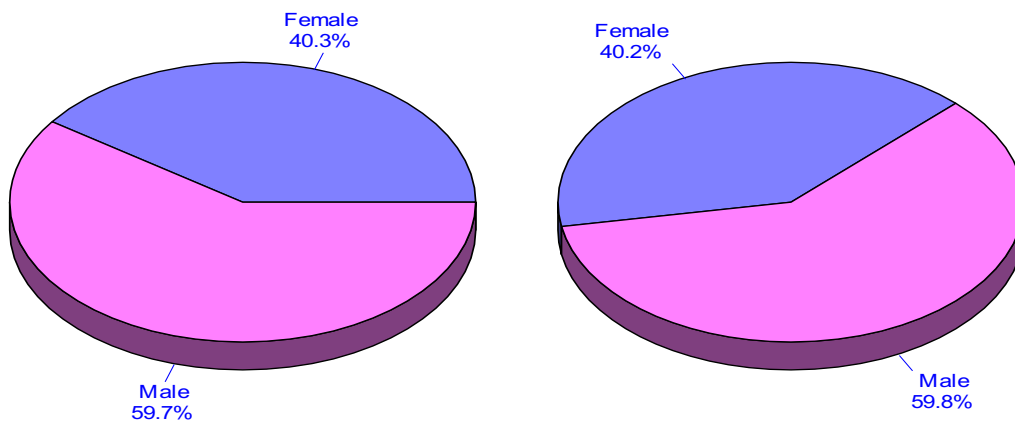**Image 1: Distribution of cases according to age group in relation to outcome**

Image 2: Distribution of cases according to gender in relation to outcome

Non-Survivors Survivors

Table 1: Various parameters recorded for non-survivor and survivor group

Characteristic	Survivors (n=261)		Non-survivors (n=139)		P value
Mean (SD) age (years)	46.21	20.08	55.66	18.03	0.001*
Gender (M: F)	2.13:1		3.23:1		0.460
Mean (SD) SOFA scores	9.45	1.01	12.71	2.80	<0.001**
Systolic BP	127.44	25.71	114.83	29.07	<0.001**
Diastolic BP	79.01	16.07	71.14	18.36	<0.001**
MAP	95.15	18.29	85.70	20.27	<0.001**
Mean (SD) fT3 (pg/mL)	1.18	0.11	0.95	0.23	<0.001**
Mean (SD) fT4 (ng/dL)	1.01	0.22	0.97	0.15	0.054
Mean (SD) TSH (mIU/mL)	2.98	0.87	2.85	0.36	0.097
TLC	11042.40	6112.87	18801.4	8775.90	<0.001**
Platelets	1.99	1.19	1.69	1.05	0.016*
Serum Albumin	3.13	0.56	3.01	0.46	0.040*
SGOT	82.73	162.95	88.72	140.68	0.714

SGPT	70.90	112.20	77.23	85.45	0.562
Total Bilirubin	1.27	1.22	1.45	1.34	0.158
Direct Bilirubin	0.56	0.78	0.65	0.80	0.232
Indirect Bilirubin	0.71	0.48	0.81	0.58	0.079
Alkaline Phosphatase	123.98	110.71	138.18	85.06	0.188
Blood Urea	56.97	44.35	67.30	53.01	0.042*
Serum Creatinine	1.61	1.75	2.01	1.97	0.045*
GCS	10.84	1.01	8.50	1.21	<0.001**

In our study, the survivors had a higher systolic blood pressure (SBP), diastolic blood pressure, mean arterial blood pressure, higher Glasgow coma scale score and lower total leukocyte counts as compared to the non-survivor group and show highly significant correlation with SOFA score and mortality of patients.

Mean platelet count, serum albumin in liver function tests and blood urea, serum creatinine in renal function tests show significant association within survivor and non-survivor groups.

According to thyroid function, Free T_3 had highly significant difference (p<0.001) while Free T_4 and TSH had an insignificant correlation when these parameters were compared between died and Survivors patients (p>0.05). There was a significant correlation between T3 and fT3 and mortality of patients. longer duration of illness, higher T3 and fT3 levels and lower SOFA score. Whereas, all other parameters like SGOT, SGPT, Total bilirubin, Direct bilirubin, Indirect bilirubin and alkaline phosphatise had an insignificant correlation (p>0.05 in all) when they compared between died and Survivors patients. According to ABG, only FiO_2 AND PCO_2 had a significant correlation when these parameters were compared between died and Survivors patients (p<0.05) while all other parameters like pH, FiO_2, PaO_2, PaO_2/FiO_2 and HCO_3^- had an insignificant correlation when they compared between died and Survivors patients (p>0.05 in all).

Table 2: Regression analysis between Parameters of Thyroid function and other paraments recorded in the study.

	Free T3		Free T4		TSH	
Parameters	r value	p value	r value	p value	r value	p value
GCS	0.490	<0.001**	0.473	<0.001**	0.383	<0.001**
SOFA	0.438	<0.001**	0.368	<0.001**	0.368	<0.001**
Free T_4	0.84	0.094	0.084	0.094	0.159	0.001*
TSH	0.159	0.001**	0.137	0.006*	0.137	0.006*
Age	0.131	0.009*	0.136	0.007*	0.089	0.074
Hb	0.008	0.878	0.129	0.010*	0.128	0.010*
TLC	0.038	0.448	0.047	0.348	0.125	0.013*
Platelet	0.090	0.074	0.007	0.895	0.020	0.684
Serum Albumin	0.011	0.829	0.017	0.735	0.300	0.549
Total Bilirubin	0.096	0.057	0.024	0.632	0.074	0.140
Blood Urea	0.014	0.035*	0.038	0.451	0.129	0.011*
Serum Creatinine	0.103	0.042*	0.103	0.042*	0.018	0.717
pH	0.083	0.099	0.059	0.236	0.163	0.001*
FiO_2	0.062	0.219	0.061	0.220	0.165	0.001*
PaO_2	0.051	0.314	0.080	0.110	0.005	0.924
FiO_2/PaO_2	0.062	0.217	0.097	0.053	0.184	<0.001**
PCO_2	0.019	0.715	0.078	0.122	0.045	0.373
HCO_3^-	0.045	0.376	0.030	0.554	0.106	0.034

Above table shows regression analysis of different parameters in relation to Free T_3. GCS, SOFA, Free T_4, TSH had a highly significant correlation (p<0.001 in all), significant correlation was observed in Age and blood urea (p<0.01) while all other parameters like Hb, TLC, Platelet Count, Serum Albumin, Total Bilirubin, Serum Creatinine, pH, FiO_2, PaO_2, FIO_2/PaO_2, PCO_2 and HCO_3^- had an insignificant correlation (p>0.05 in all). Regression analysis of different parameters in relation to Free T_4 show that GCS, SOFA, Free T_3, TSH had a highly significant correlation (p<0.001 in all), significant correlation was observed in Age and haemoglobin (p<0.01) while all other parameters like Hb, TLC, Platelet Count, Serum Albumin, Total Bilirubin, Blood Urea, Serum Creatinine, pH, FiO_2, PaO_2, FIO_2/PaO_2, PCO_2 and HCO_3^- had an insignificant correlation (p>0.05 in all).Regression analysis of different parameters in relation to TSH show that, GCS, SOFA, Free-T3,

free-T4 had a highly significant correlation (p<0.001 in all), significant correlation was observed in Hb, TLC, Blood Urea, Serum Creatinine, pH, FiO_2, FIO_2/PaO_2, and HCO_3^- (p<0.05 in all).

While insignificant correlation was observed in platelet count, serum albumin, total bilirubin, PaO_2 and PCO_2 (p>0.05) in all.

Table 3: Regression analysis of different parameters in relation to SOFA Score

Parameters	r value	p value
GCS	0.495	<0.001**
Free FT$_3$	0.280	<0.001**
Free FT$_4$	0.076	0.127
TSH	0.116	0.020*
Age	0.198	<0.001**
Hb	0.037	0.458
TLC	0.055	0.269
Platelet	0.149	0.003
Serum Albumin	0.007	0.896
Total Bilirubin	0.007	0.885
Blood Urea	0.103	0.043*
Serum Creatinine	0.046	0.365
pH	0.029	0.568
FiO_2	0.015	0.772
PaO_2	0.007	0.889
FiO_2/PaO_2	0.028	0.574
PCO_2	0.038	0.449
HCO_3^-	0.017	0.734

Above table shows regression analysis of different parameters in relation to SOFA Score. GCS, Free-T3, free-T4, TSH, Age had a highly significant correlation (p<0.001 in all), while all insignificant correlation was observed in Hb, TLC, platelet count, serum albumin, total bilirubin, Blood Urea, Serum Creatinine, pH, FiO_2, PaO_2, FIO_2/PaO_2, PCO_2 and HCO_3^- (p>0.05) in all.

Table 4: Relation between free-T3, free-T4, TSH and SOFA score

	SOFA Score						Total		F Value
	0-9		10-14		>14				P-Value
	No.	%	No.	%	No.	%	No.	%	
Free T$_3$									
<1.4	135	95.1	242	94.5	2	100.0	379	94.8	9.386
1.4-4.2	6	4.2	13	5.1	0	-	19	4.8	<0.001
>4.2	1	0.7	1	0.4	0	-	2	0.5	
Free T4									
<0.8	25	17.6	20	7.8	0	-	45	11.3	0.349
0.8-2.2	117	82.4	235	91.8	2	100.0	354	88.5	0.705
>2.2	0	-	1	0.4	0	-	1	0.3	
TSH									
<0.35	0	-	0	-	0	-	0	-	1.636
0.35-4.94	140	98.6	250	97.7	2	100.0	392	98.0	0.196
>4.94	2	1.4	6	2.3	0	-	8	2.0	

Mean Free T$_3$ in SOFA group 0-9, 10-14 and >14 groups were 1.22±0.39, 1.07±0.31 and 0.90±0.00 respectively. On applying ANOVA test, the difference was found statistically highly significant (p<0.001).

Mean Free T$_4$ in SOFA group 0-9, 10-14 and >14 groups were 1.01±0.24, 0.99±0.20 and 0.90±0.00 respectively. On applying ANOVA test, the difference was found statistically insignificant (p>0.05). Mean Free TSH in SOFA group 0-9, 10-14 and >14 groups were 3.01±0.93, 2.92±0.68 and 2.20±0.00 respectively. On applying ANOVA test,

the difference was found statistically insignificant (p>0.05).

Discussion

ICU studies have demonstrated the association between variation in hormone levels and mortality of critically ill patients. Changes in thyroid function test (TFT) are commonly seen in critically ill patients. These changes are referred to as sick euthyroid syndrome. [2]It is commonly associated with low levels of total triiodothyronine and low free triodothyronine with changes in levels of thyroxine and free thyroxine in prolonged critical

illnesses. These changes have been attributed to decreased peripheral deiodination of thyroid hormones along with altered binding to thyroid hormone-binding proteins. Sick euthyroid syndrome has been associated with poor outcomes in patients.

In our study we found that mean age in non-survivor group was significantly higher than the survivor group (with p<0.001). There is clear-cut male predominance over female with male to female ratio was 1.48:1 but the difference was found statistically insignificant (p>0.05). Similar results related to age and sex were published by Hosney et al.[19]

Higher mean TLC and lower mean platelet count was found in non survivors as compared to survivor group which showed statistically significant correlation with mean SOFA score (p<0.001). Similar result was found in studies done by Hosney et al63 and Juan Carlos Lopez-Delgado et al.[20]

In present study, according to LFT, mean serum albumin was found significant (p<0.05) while all other parameters like SGOT, SGPT, total bilirubin, direct bilirubin, indirect bilirubin and alkaline phosphatase had an insignificant correlation (p>0.05 in all). Similar findings were reported by Gosavi et al.[21]

According to RFT, mean blood urea and mean serum creatinine both show significant association with prognosis and SOFA score. Similar study done by Gutch et al [22] reported that both parameters had the significant correlation when they compared between died and survivors patients (p<0.05).

In present study, according to thyroid function, mean Free T3 was significantly lower in non-survivors as compared to survivors and had highly significant difference (p<0.001) while mean Free T4 and TSH had a insignificant correlation when these parameters were compared between died and survivors patients (p>0.05).

Similar study done by Mishra et al [23] who reported that low T3 and fT3 were associated with poor outcomes. Our study also shows that the non survivors had lower mean MAP and low GCS (6-9).

In present study, Mean SOFA score in died patients was 12.71±2.80 and in survivors patients mean SOFA was 9.45±1.01 and the difference was found statistically highly significant (p<0.001). Mean GCS in died and survivor patients were 8.50±1.21 and 10.84±1.01 respectively and this difference was also found statistically highly significant (p<0.001).

Similar study done by Mishra et al [23] also reported that mean SOFA scores of non survivors was 12.18±3.4 and in survivors patients mean SOFA was 9.67±2.36 and the difference was found

statistically highly significant (p<0.001). Mean GCS in died and survivor patients were 4.57±2.77 and 5.85±2.69 respectively and this difference was also found statistically highly significant (p<0.001).

Regression analysis of different parameters in relation to Free T3. GCS, SOFA, Free T4, TSH had a highly significant correlation (p<0.001 in all), significant correlation was observed in Age and blood urea (p<0.01) while all other parameters like Hb, TLC, Platelet Count, Serum Albumin, Total Bilirubin, Serum Creatinine, pH, FiO2, PaO2, FIO2/PaO2, PCO2 and HCO3- had an insignificant correlation (p>0.05 in all).

Regression analysis of different parameters in relation to Free T4. GCS, SOFA, Free T3, TSH had a highly significant correlation (p<0.001 in all), significant correlation was observed in Age and haemoglobin (p<0.01) while all other parameters like Hb, TLC, Platelet Count, Serum Albumin, Total Bilirubin, Blood Urea, Serum Creatinine, pH, FiO2, PaO2, FIO2/PaO2, PCO2 and HCO3- had an insignificant correlation (p>0.05 in all).

Regression analysis of different parameters in relation to TSH. GCS, SOFA, Free-T3, free-T4 had a highly significant correlation (p<0.001 in all), significant correlation was observed in Hb, TLC, Blood Urea, Serum Creatinine, pH, FiO2, FIO2/PaO2, and HCO3- (p<0.05 in all) while insignificant correlation was observed in platelet count, serum albumin, total bilirubin, PaO2 and PCO2 (p>0.05 in all).

Regression analysis of different parameters in relation to SOFA Score. GCS, Free-T3, free-T4, TSH, Age had a highly significant correlation (p<0.001 in all), while all insignificant correlation was observed in Hb, TLC, platelet count, serum albumin, total bilirubin, Blood Urea, Serum Creatinine, pH, FiO2, PaO2, FIO2/PaO2, PCO2 and HCO3- (p>0.05) in all.

Mean Free T3 in SOFA score group 0-9, 10-14 and >14 groups were 1.22±0.39pg/ml, 1.07±0.31pg/ml and 0.90±0.00pg/ml respectively. On applying ANOVA test, the difference was found statistically highly significant (p<0.001). Similar study done by Mishra et al [23] also reported that it was observed that with increasing SOFA score, the proportion of those with low T3 levels significantly increased.

Mean Free T4 in SOFA score group 0-9, 10-14 and >14 groups were 1.01±0.24ng/ml, 0.99±0.20ng/ml and 0.90±0.00ng/ml respectively. On applying ANOVA test, the difference was found statistically insignificant (p>0.05).

Mean TSH in SOFA score group 0-9, 10-14 and >14 groups were 3.01±0.93 uIU/ml, 2.92±0.6893 uIU/ml and 2.20±0.0093 uIU/ml respectively. On applying ANOVA test, the difference was found statistically insignificant (p>0.05). Study done by

Mishra et al [23] also reported that TSH and ft4 not show a significant association with survival status.

Limited studies are available in the Indian background to compare the thyroid functions with prognosis of ICU patients. There have been few studies to compare TFT with multivariable APACHE II (12 variables), there have been limited number of studies involving SOFA score and thyroid function. We feel that our study will provide significant contribution in this area, however further studies are required for more detailed understanding of prognostic capabilities of TFT in critically ill patients alone and with SOFA score within the Indian perspective.

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