



STUDY ON THYROID HORMONE PROFILE IN CRITICALLY ILL PATIENTS IN A TERTIARY CARE HOSPITAL IN KOLKATA

M.K. Gupta¹, K. Sarkar^{*2}, D. Gonjhu³, S.N. Haldar⁴, P.K. Kundu⁵ and N. Pramanik⁶

¹MD Tropical Medicine Post Graduate Trainee, School of Tropical Medicine, Kolkata.

^{2,3,4}M. B. B. S., MD, Assistant Professor, Tropical Medicine, School of Tropical Medicine, Kolkata.

⁵M. B. B. S., MD, Head of Dept of Endocrine, Nutrition and Metabolism, School of Tropical Medicine, Kolkata.

⁶M. B. B. S., DTM&H, MD, Associate Professor, Department of Tropical Medicine, School of Tropical Medicine, Kolkata.

***Corresponding Author: Dr. K. Sarkar**

M. B. B. S., MD, Assistant Professor, Tropical Medicine, School of Tropical Medicine, Kolkata.

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ABSTRACT

Objective: Critical illness is a life threatening condition and the greatest challenge for a physician. Our objective was to study the thyroid hormone profile in critically ill patients and to determine the relationship between thyroid hormone level and mortality /morbidity in critically ill patients. **Materials and Methods:** In our single centre, prospective, observational study, 114 consecutive patients admitted to CCU irrespective of diagnosis were included. Patients with previous thyroid disorders and drugs affecting thyroid function, pregnant woman and age <18 year were excluded from this study. All participants underwent complete physical examination and total triiodothyronine (TT3), total thyroxine (TT4), thyroid stimulating hormone (TSH), free thyroxine (FT4). The patients were divided into two groups: Group 1 - survivors (discharged from the hospital) and Group 2 - nonsurvivors (patients succumbed to their illness inside the hospital). The data were analyzed by appropriate statistical methods and a *P*-value of <0.05 was considered significant. **Results:** 31.5% of the patients died and were in the non survivor group, and 68.5% patients were in the survivor group. The mean age group of the patients was 51.38±13.25 years. Low T3 and T4 were shown to increase the risk of dying from critical illness by 3.77 & 9.61 times more respectively. Morbidity data analysis showed that low values of all the thyroid hormones were significantly associated with longer duration of hospital stay (*p*<0.001). **Conclusion:** Our study showed that low T3 and low T4 levels during critical illness, increases the risk of mortality. Low T3 is the strongest predictor among the thyroid hormones along with APACHE II scores for mortality.

KEYWORDS: Critically ill, medical CCU, thyroid hormone profile.

INTRODUCTION

Critical illness impairs the homeostasis including instability of the endocrine system. Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease.^[1] Euthyroid sick syndrome (ESS) is commonest endocrine change seen in critically ill patients. It is described as abnormality in circulating thyroid hormone without pre-existing hypo-thalamic – pituitary or thyroid gland dysfunction in the setting of a non thyroidal illness (NTI). It reverts back to normal after recovery from NTI.^[2] Disturbance in the hypothalamus-Pituitary-thyroid axis are frequently observed in ICU pt. It is unclear that this phenomenon is protective and appropriate adaptation to a stressful event or a maladaptive response to illness that needs correction.^[3] ESS is characterised by low triiodothyronine (T₃), low or normal thyroxine (T₄) and normal thyroid stimulating hormone (TSH) and these

depends on the different stages on a continuum and severity of illness.^[2] Mortality and Morbidity of the critically ill patients depends on the severity and duration of the underlying NTI.^[4] In cases of protracted critical illness, thyroid hormone abnormalities may also be explained by a decreased TRH release by the hypothalamus, which results in a decrease in the pulsatile frequency of TSH secretion.^[5-9, 14] In this phase, thyroid function tests usually reveal low circulating levels of T₃ and T₄ and low or normal levels of TSH. Additionally, the pulsatile secretion of TSH significantly decreases because of reduced hypothalamic stimulation.^[9] Finally, during a patient's recovery from critical illness, a modest increase in serum TSH concentrations may occur.^[5,6] Full restoration of the patient's normal physiological biochemical state may not occur until several months after hospital discharge.^[12-15] In the critically ill patient, several medications and clinical conditions may induce or maintain NTIS by various mechanisms.

MATERIALS AND METHODS

Study population- It was a single centre, prospective, observational study done on 114 consecutive patients admitted to CCU irrespective of diagnosis at the Carmichael Hospital for Tropical Disease, School of Tropical Medicine, Kolkata. Patients with previous thyroid disorders and drugs affecting thyroid function, pregnant woman and age <18 year were excluded from this study. Thorough history was taken and systemic examination was done.

Biochemical measurements- Venous Blood was taken after 24 hrs up to 48 hrs— sample 1 and at discharge — sample 2 for thyroid profile. The patients who die during the study will have only one sample taken –Sample 1 Patient shall be assessed according to clinical and biochemical parameters APACHE II scores shall be taken at baseline on admission to CCU. The blood for sodium, potassium, Hb and pH shall be assessed at admission by AGB machine (Opti CCA). Random blood glucose shall be seen by CBG by Accu –Chek machine at admission.

Thyroid hormones were tested by employing standard Immunoassay based kits.

The normal values in our laboratory were T3- 0.52-1.85 ng/ml, T4- 4.4-11.6 µg/dl, FT4- 0.82-2.04 ng/dl, and TSH – 0.39-6.16µIU/ml.

Statistical analysis: In Analysis the Demographic data were summarised along with comparison of the surviving Vs the non survivor group and mortality relation was deduced. In the surviving group the sample 1 of thyroid hormones were compared with the sample 2 of thyroid hormones. The morbidity data were seen in the survivor group in relation to the sample 1 of the thyroid hormones. Analysis was also done for prediction of ICU mortality with comparing the APACHE II score with the thyroid hormones.

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and chi-square test was performed to find the associations. Corrected chi square test was used where any one of the cell frequencies was less than 5. T-test was used to compare the means. Odds ratio (OR) with 95% Confidence Interval (CI) was calculated to measure the different risk

factor. Significance level was set at 0.05 and confidence intervals were at 95 percent level. $p < 0.05$ was taken to be statistically significant.

RESULTS

114 patients were included in the study with application of the inclusion and exclusion criteria. 31.5 % of the patients died and were in the non survivor group, and 68.5% patients were in the survivor group. The mean age group of the patients was 51.38 ± 13.25 yrs and was higher in the Non survivor group (55.11 ± 14.72 vs 49.13 ± 3.33), but it was not statistically significant. There was male preponderance in both the survivor and non survivor group, but male and female were equally distributed in the two groups. The mean duration hospital stay (mean $\pm$ s.d.) of the patients was 14.37 ± 5.95 days with range 2 - 28 days and the median was 14.5 days. Test of proportion showed that the proportion of the patients with duration of stay between 2-3 weeks (77.2%) were significantly higher ($Z = 9.36$; $p < 0.0001$).

Among the admitted patients the primary disorder was Neurological (28.1%) followed by Respiratory (22.8%) and Septicemia. The non survivor group showed similar causation whereas in the survivor group the primary disorder was Respiratory. The Neurological causes were CVA followed by Encephalopathy and Meningitis, and the Respiratory causes were AECOPD followed by Pneumonia and ARDS.

Among the total patients 38.6% of the patients were Intubated with a mean duration of 3.88 ± 1.61 days, with range 2 - 8 days and the median was 3.5 days. Only 1(2.3%) was intubated for more than 7 days and the rate of intubation in the non survivor group was higher than that of the survivor group (47.2% vs 34.6%) but was not significant statistically.

Among the patients 57% developed AKI and AKI was significantly higher in the non survivor (69.4% vs 51%) group.

51.8% of the patients required pressor support with a mean duration of 3.84 ± 1.73 days with range 1 - 11 days and the median was 4.0 days. Only 3.4% were on pressor support for more than 7 days. It was statistically significantly ($p < 0.0001$) higher in the non survivor group (83.3% vs 37.2%).

The co morbidities seen in the study population were Diabetes, Hypertension, Chronic Liver Disease and IHD in that order. The co morbidities of the two groups were not associated significantly.

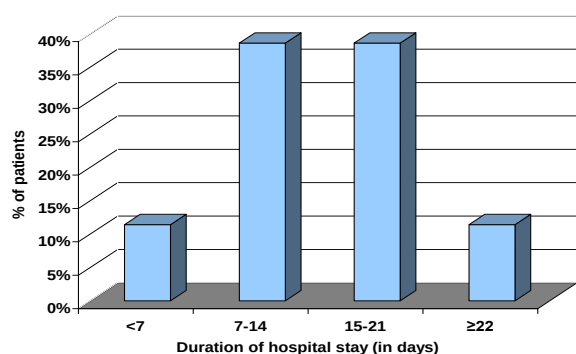


Figure 1: Bar diagram showing the Duration of hospital stay of the patients (in Days)

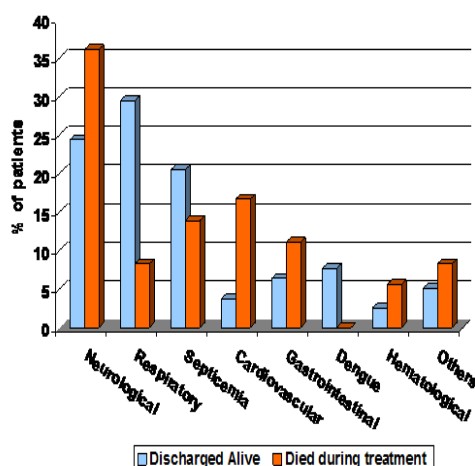


Figure 2. Bar Diagram showing the distribution of primary disorder of the patients of the two groups

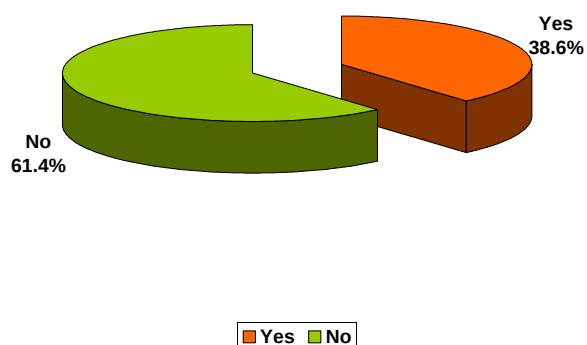


Fig 3: Pie diagram showing the Distribution of patients who underwent intubation

The mean APACHE II Score (mean $\pm$ s.d.) of the patients was 12.76 ± 3.12 with range 7 – 20 and the median was 12.0. Most of the patients were having APACHE II Score between 10-14 (57.9%) followed by 15-19 (23.7%) which was significantly higher ($Z=4.92$; $p<0.0001$). No patients had score less than 5. APACHE II was higher in the non survivor group than the survivor group (16.30 ± 2.17 vs 11.12 ± 1.90) Corrected Chi-square (χ^2) test showed that there was significant association between APACHE II Score at admission to ICU and patients of the two groups ($p<0.0001$).

Rate of death was significantly higher for the patients having more APACHE II Score at Admission to ICU. t-test showed that mean APACHE II Score at Admission to ICU of the patients who died during treatment was significantly higher than that of the patients who were discharged alive ($t_{112}=12.92$; $p<0.0001$).

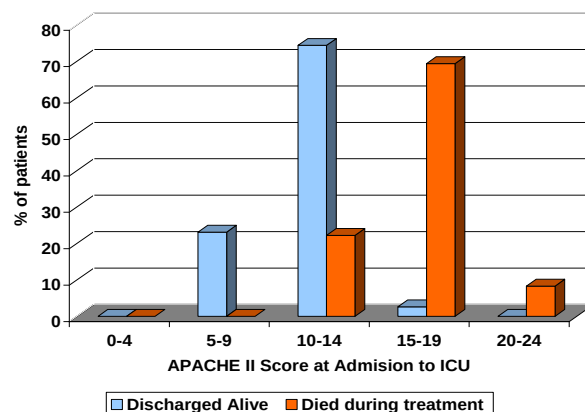


Fig 4: Bar diagram showing the Distribution of APACHE II Score at admission to ICU of the patients of the two groups

The first sample of thyroid hormones were seen and in that Chi-square (χ^2) test showed that there was significant association between level of T3 and T4 and patients of the two groups ($p<0.0001$) but there was no significant association between levels of FT4 and TSH and patients of two groups. Low T3 and T4 were shown to increase the risk of dying from critical illness by 3.77 & 9.61 times more respectively, compared to the patients having normal limit of T3 and T4, and the values were statistically significant ($p<0.001$). Low FT4 and TSH were associated with increased risk of dying from critical illness by 1.66 & 1.47 times more respectively, compared to the patients having normal limit of FT4 and TSH, but the values were not statistically significant.

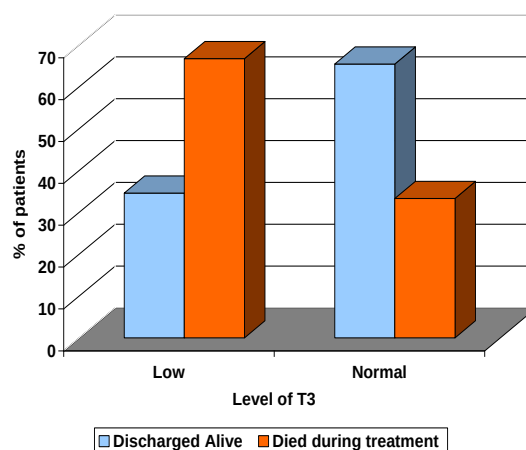


Fig 5: Bar diagram showing the Distribution of level of T3 (first sample) of the patients between the two groups

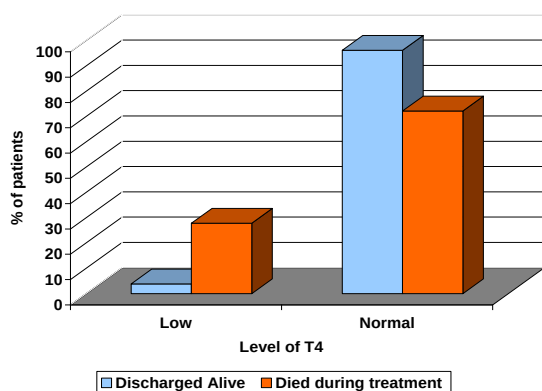


Fig 6: Bar diagram showing the Distribution of level of T4 (first sample) of the patients between the two groups

In the survivor group, between the two samples of the thyroid hormones T3 and FT4 were significantly higher in the second sample compared with the 1st sample. The

values of T4 and TSH was also increased in the second sample but were not significant statistically.

Morbidity data analysis showed that low values of all the thyroid hormones were significantly associated with longer duration of hospital stay ($p < 0.001$). Low T4 was associated with more patients being put on intubation, and low T3 was associated with more development of AKI in the survivor group. None of the thyroid hormones were significantly associated with need for more pressor support.

With regards to prediction of ICU mortality it was seen that the best variable was APACHE II scores (>15), followed by low T3 and T4 values which had good sensitivity, specificity, PPV and NPV.

Regression analysis data showed that low T3 among all the thyroid hormones had the best correlation with APACHE II scores for prediction of ICU mortality.

Table 1: Distribution of the values of thyroid hormone (first sample) and its relation with the hospital stay of the Survivor group (n=78)

Parameter (lower than normal value)	Duration (7-14 days)	Duration(>15 days)	P value
T3 (<0.52)	22.2 %	77.8%	*
T4 (<4.4)	0%	100%	*
FT4(<0.82)	15.4%	84.6%	*
TSH(<0.39)	33.3%	66.6%	*

*Statistically Significant

The average duration of hospital stay in the survivor group was 15.87 ± 3.847 days.

Table 2: Distribution of the level of thyroid hormones (lower than its normal value) and its relation with need for intubation, development of AKI and need for Pressor support

Intervention	T3 (<0.52)	T4 (<4.4)	FT4(<0.82)	TSH(<0.39)
Intubation	29%	66.7%	15.4%	33.3%
AKI	69%	33%	49.2%	0%
Pressor support	29%	0%	30.8%	33%

Table 3: Performance of the variables in predicting ICU mortality

Parameters	Sensitivity (%)	Specificity (%)	PPV	NPV
APACHE II (>15)	77	97	93	90
T3 (<0.52)	66	65	78	80
T4 (<4.4)	27	96	77	74
FT4(<0.82)	25	83	40	70.6
TSH(<0.39)	15	96	40	68

Table 4: Logistic Regression table for Prediction of ICU mortality

Parameters	Odds ratio	95% Confidence interval	P value
APACHE II (>15)	4.118	(2.229-7.610)	0.00 *
T3 (<0.52)	30.3	(4.7-200)	0.00 *
T4 (<4.4)	1.1	(0.91-1.33)	0.295
FT4(<0.82)	1.32	(0.5-3.74)	0.603
TSH(<0.39)	1.43	(1.07-1.88)	0.013

*Significant.

DISCUSSION

The primary aim of this study was to study the thyroid hormone profile in critically ill patients and to determine

the relationship between thyroid hormone level and mortality/morbidity in critically ill patients. In our present study total T3 (1st sample) when compared

between the two groups showed that 66.7% of the non survivor group had low T3, whereas only 34.6% of the surviving group had low T3. The risk of dying from critical illness was 3.77 times more among the patients having the level of T3 below the normal limit as compared to the patients having normal limit of T3 and the risk was significant [OR-3.77 (1.63, 8.71); $p < 0.0001$]. t-test showed that mean level of T3 of the patients who died during treatment was significantly lower than that of the patients who were discharged alive ($t_{112} = 3.96$; $p < 0.0001$).

Low T4 in the survivor group was 3.8% and in comparison the non survivor group had 27.8% low T4. The risk of dying from critical illness was 9.61 times more among the patients having the level of T4 below the normal limit as compared to the patients having normal limit of T4 and the risk was significant [OR-9.61 (2.45, 37.65); $p < 0.0001$].

The level of low FT4 (1st sample) in our study was 25% in the nonsurvivor group compared to 16.7% in the survivor group. The risk of dying from critical illness was 1.66 times more among the patients having the level of FT4 below the normal limit as compared to the patients having normal limit of FT4 but the risk was not significant [OR-1.66 (0.63, 4.35); $p = 0.29$].

In our study TSH (1st sample) showed low values in 2.6% in the survivor group and 5.6% in the non survivor group. The risk of dying from critical illness was 1.47 times more among the patients having the abnormal level of TSH as compared to the patients having normal limit of TSH but the risk was not significant [OR-1.47 (0.23, 9.20); $p = 0.57$].

In a review by *Foteini E et al*⁵ of thyroid function in critical illness showed majority of critically ill patients had low T3, T4 which can be low in NTI due to decrease in binding to carrier protein such as TBG, TBPA and albumin but FT4 remains normal except in severe and protracted illness and TSH generally tend to be normal in NTI but only in some cases of prolonged illness it can be low due to central hypothyroidism, which are comparable with our study.

Another study by *Feilong et al*² showed low T3 in about 4.79% whereas low FT3 in about 54.38% and T3 and FT3 both were lower in non survivor than in survivor ($p < 0.01$), low FT4 of about 10% but there was significant difference in FT4 levels within the survivor group and non survivor group and TSH was lower in non survivors compared to survivor ($p < 0.01$), but this low TSH did not predict mortality statistically. These findings are also consistent with our study.

In a study by *Sahana PK et al*^[11] sick euthyroid syndrome was seen in 80 % of the patients and low T3 was a predictor of mortality. In a study by *Alayo EC et al*⁴ on thyroid hormone level improve the prediction of

mortality among the patients admitted to ICU which showed that T3 has the best logistic regression model for ICU mortality ahead of APACHE II scores.

Survana JC⁷ et al in their study on thyroid hormone profile in critically ill children showed that when both T3 and T4 are low the mortality risk is increased 30 times.

*Sahana et al*¹¹ showed that low FT4 was associated with increased mortality and low TSH was not associated with increased mortality.

There was a risk of increased mortality from low FT4 of about 1.66 times but was not statistically significant in our study, a bit different from the previous studies.

On analysis of the survivor group for the two samples of thyroid hormone in our study we found that all the parameters related to thyroid profile of second sample increased than that of first sample. However, t-test showed that mean level of T3 and FT4 of the patients who discharged alive were significantly increased in second sample than that of first sample ($p < 0.0001$), whereas that of T4 and TSH was not statistically significant.

CONCLUSION

- Low T3 and low T4 levels during critical illness, increases the risk of mortality.
- Low T3 is the strongest predictor among the thyroid hormones along with APACHE II scores for mortality.
- The survivors with low T3 levels show a higher incidence of development of AKI.
- The survivors with low T4 levels show a higher incidence of Intubation.
- Low values of thyroid hormones are associated with a longer duration of hospital stay.
- Second samples obtained at discharge showed thyroid hormones within the normal range. Therefore it can be concluded that, thyroid hormones are very important not only in health but also during the periods of critical illness, where they play an important role and can be used as a prognostic marker for mortality and morbidity.

LIMITATIONS

This study has several limitations.

First, the inclusion of some patients with undetected thyroid diseases before ICU admission may not be ruled out in the present study, even though we tested patients by palpation of the thyroid carefully to exclude those with thyroid nodules.

Second, although we excluded patients undergoing any replacement therapy except insulin use, as well as those taking oral amiodarone, it is clear that many other drugs may have interfered with thyroid function; it is difficult to adjust for these potential confounders. We could not measure the RT3 and FT3 in our present study and so

could not get the levels of these hormones in cases of critical illness.

Although the present study was aimed to study the thyroid hormone level in critical illness, it would have been more apt if other endocrine hormones like Growth hormone, Serum cortisol etc could also be measured and a complete endocrine response to critical illness be evaluated.

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