



## THYROID HORMONE LEVELS AND ITS RELATION TO OUTCOMES IN ICU PATIENTS

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### ABSTRACT

**Background:** Free thyroid hormone levels were analyzed in critically ill patients, admitted to the ICU who were more than 18 years of age without any underlying thyroid illness. APACHE 2, FT3, FT4, and TSH levels were analyzed and compared using ROC curves. **Aim of the study:** To assess whether free thyroid hormone levels were better predictors of outcomes compared to existing tools. **Study design:** This is a prospective observational study undertaken in the Department of General medicine at Sri Ramachandra institute of higher education and research, Chennai, Tamilnadu has done between 2019 to 2021 with the approval from the ethics committee. A total of 70 critically ill patients were admitted to the ICU, who were more than 18 years of age without any underlying thyroidal illness. Patients with known thyroid disease, pregnancy, and drugs causing alteration of thyroid hormone levels were excluded from the study. Blood samples were collected immediately after admission and APACHE 2 scores were calculated within 24 hours of admission. Parameters were analyzed using various statistical methods. **Results:** A total of 70 patients were included in the study, of which 63 were survivors and 7 patients expired. Most of the study population were males (45) and the mean age of the survivors  $49.71 \pm 10.72$  was and for non-survivors was  $54.29 \pm 15.07$ . Using the Pearson correlation in APACHE 2 and FT3, APACHE 2 and FT4 showed a statistically significant correlation in survivors ( $P 0.02$ ;  $P 0.05$ ), while in non-survivors only APACHE 2 and FT3 showed a significant correlation ( $P 0.008$ ). Using ROC curves, APACHE 2 alone showed significant predictive validity in predicting mortality in critically ill patients in our study ( $AUC 0.985$ ;  $P < 0.001$ ). **Conclusion:** In our study combined APACHE 2 and FT3 showed a significant correlation in both survivors and non-survivors as well. APACHE 2 has better predictive value compared to other parameters and FT3 alone did not have predictive validity. So large sample is required to test the value of free thyroid hormones in predicting outcomes in critically ill patients.

**KEYWORDS :** Critically ill patients, FT3, FT4, TSH, MAPAPACHE 2, Euthyroid sick syndrome.

### INTRODUCTION:

Serum concentrations of thyroid hormones are influenced by the Hypothalamo-Pituitary-Thyroid axis, which is operated through a feedback loop. Thyrotrophin-releasing hormone (TRH) released from the hypothalamus stimulates the pituitary to secrete TSH, which in turn drives the thyroid gland to secrete thyroxine (T4) through thyroid hormone receptor B (TRH B). Thyroxine (T4) released is converted in the peripheral tissues to active Triiodothyronine (T3).<sup>1</sup> Patients without underlying thyroid illness may present with altered thyroid hormone levels in case of trauma, surgery, infection, inflammation, burns, cardiovascular illness, and cancer. This results in low plasma T3, low T4, and low or normal TSH with increased reverse T3 (rT3).<sup>2</sup> This phenomenon is called non-thyroidal illness syndrome (NTIS) or euthyroid sick syndrome or low T3 syndrome.<sup>3</sup> According to some studies, a decrease in T3 or f T3 levels has been associated with mortality in critically ill patients.<sup>4</sup> The APACHE 2 is a tool used for calculating physiological homeostasis as well as for prognosis within 24 hours of admission. Further research is required to find the association between NTIS and the prognosis of patients in the ICU. In turn, low f T3 levels as a prognostic marker in ICU patients' needs further investigation. The purpose of this study is to find the relation between f T3 with the ICU outcomes and its comparison with other existing mortality-predicting scales like APACHE 2.

### MATERIALS AND METHODS:

This is a prospective observational study undertaken in the Department of General medicine at Sri Ramachandra institute of higher education and research, Chennai, Tamilnadu has done between 2019 to 2021 with the approval

from the ethics committee. A total of 70 critically ill patients were admitted to the ICU, who were more than 18 years of age without any underlying thyroidal illness. Patients with known thyroid disease, pregnancy, and drugs causing alteration of thyroid hormone levels were excluded from the study. Blood samples were collected immediately after admission and APACHE 2 scores were calculated within 24 hours of admission. Statistical analysis was done using chi-square, unpaired t-test, univariate and multivariate regression analysis. Pearson correlation was used to establish the significance of different parameters with the outcomes. Receiver operating characteristic (ROC) curves were used to calculate the sensitivity and specificity.

### RESULTS:

In our study, out of 70 patients, 63 recovered while 7 patients had expired. The mean age of non-survivors  $54.29 \pm 15.07$  was more compared to survivors  $49.71 \pm 10.72$ . The majority of the study population includes males (45) compared to females (25). Both age and Sex did not show a statistically significant difference between survivors and non-survivors ( $p = 0.308$ ;  $p = 0.678$ ). (Table 1)

Of the entire study population, among survivors 33 (52.4%) had acute CVA, and 3 (4.8%) had CVT. CKD, Leptospirosis, Myocardial infarction, and seizure disorder each constitute 3.2% (2). Acute pyelonephritis, ADEM, AIDP, AOCKD, ARDS, Autoimmune encephalitis, Autoimmune hemolytic anemia, Benzodiazepine overdose, carcinoma colon, cardiogenic shock, Dengue with warning signs, hypertensive emergency and urgency, hypocalcemia, hypokalaemic periodic paralysis, hyponatremia, ITP, recurrent CVA and scrub typhus

each constitute 1.6% (1). Among non-survivors 3 (42.9%) had a cardiogenic shock while acute CVA, Myocardial infarction, Non-Hodgkins lymphoma, and recurrent CVA each constitute 14.3% (1). (Table 2)

When FIO2 levels were analyzed in survivors and non-survivors, 71.4% of the non-survivors were intubated and 28.6% were non-intubated, and 100% of the survivors were non-intubated. Median days of ICU stay in survivors and non-survivors were 3 and 6 respectively. Both FIO2 and ICU stay showed a statistically significant difference in both survivors and non-survivors (P = < 0.001; P= 0.010). (Table 1)

In our study mean FT3 levels were low in non-survivors 2.64 ± 0.67 compared to survivors 3.09 ± 1.08. While mean FT4 levels were almost the same in both survivors 1.03 ± 0.31 and non-survivors 1.10 ± 0.26. In contrast to FT3 levels, mean TSH levels were high in non-survivors at 3.62 ± 2.40 than in survivors at 2.47 ± 2.07. There is no statistically significant difference between FT3, FT4, TSH, and outcomes in critically ill patients (P = 0.290; P= 0.596; P= 0.171). (Table 1)

Mean APACHE 2 scores calculated within 24 hours of ICU admission were approximately twice in non-survivors 22.86 ± 6.36 than in survivors 5.65 ± 4.48. There was a statistically significant relationship between APACHE 2 scores and the outcomes in ICU patients (P < 0.001). Mean pre-op and post-op mortality is high in non-survivors (41.14 ± 18.95 and 10.50 ± 14.18) than in survivors (7.57 ± 5.99 and 2.03 ± 2.016). Statistically significant differences were observed in survivors and non-survivors concerning pre-op and post-op mortality (P < 0.001). (Table 1)

When the mean of serum creatinine, sodium, and potassium was calculated, it is almost the same in both groups. There was no statistically significant observed between these parameters and outcomes in critically ill patients (P = 0.652; P= 0.514; P= 0.848 respectively). Mean arterial Pressure (MAP) is higher in non-survivors 109 ± 38.99 compared to recovered 98.95 ± 13.65, but there was no statistically significant relationship between non-survivors and survivors (P = 0.153). (Table 1)

In survivors, APACHE 2/FT3 and APACHE 2/FT4 showed a significant correlation with the outcomes using the Pearson correlation (r = - 0.279, P = 0.02; r = 0.247, P= 0.05). In non-survivors APACHE 2/FT3 alone showed a significant correlation with the outcomes in critically ill patients (r = 0.885, P = 0.008). (Table 3)

A univariate logistic regression analysis was performed in all the parameters that influence the mortality in the study population an Odds ratio was calculated at 95% CI. ICU stay, APACHE 2, and pre-op mortality showed statistically significant differences at 95% CI and the odds ratio was 1.280(P= 0.03), 1.610 (P = 0.012), and 1.262 (P = 0.05) respectively. When multivariate regression analysis was applied to the above parameters, no significant relationship was observed. (Tables 4 and 5)

A ROC analysis of FT3, FT4 and TSH done showed cut-off values of 2.79,1.12 and 2.07 with AUC of 0.304(sensitivity: 28.6%, specificity 66.7%),0.671 (sensitivity: 57.1%, specificity: 23.8%) and 0.671(sensitivity: 57.1%, specificity: 44.4%) respectively. (Table 6 and fig.1)

A ROC analysis of APACHE 2 and MAP showed a cut-off value of 14 (AUC: 0.985; sensitivity: 85.7%, specificity: 7.9%) and 105 (AUC: 0.533; sensitivity: 42.9%, specificity: 31.7%). (Table 6,fig.1 and 2)

**Table 1: Comparison of mean overall parameter between outcome (N=70)**

Overall parameters	Outcome		P value
	Recovered (N=63)	Death (N=7)	
Age	49.71 ± 10.72	54.29 ± 15.07	0.308
Gender			
Male	41 (65.1%)	4 (57.1%)	0.678
Female	22 (34.9%)	3 (42.9%)	
FIO2			
Intubated	0 (0%)	5 (71.4%)	<0.001
Non intubated	63 (100%)	2 (28.6%)	
Days of stay	3 (2, 4)	6 (3, 8)	0.010
FT3	3.09 ± 1.08	2.64 ± 0.67	0.290
FT4	1.03 ± 0.31	1.10 ± 0.26	0.596
TSH	2.47 ± 2.07	3.62 ± 2.40	0.171
MAP	98.95 ± 13.65	109 ± 38.99	0.153
APACHE 2	5.65 ± 4.48	22.86 ± 6.36	<0.001
S.Creatinine	1.32 ± 1.58	1.60 ± 1.17	0.652
S. Sodium	135.81 ± 5.03	134.43 ± 7.46	0.514
S. Potassium	3.99 ± 0.57	3.94 ± 0.48	0.848
Mortality pre op (%)	7.57 ± 5.99	41.14 ± 18.95	<0.001
Mortality post op (%)	2.03 ± 2.016	10.50 ± 14.18	<0.001

**Table 2: Comparison of diagnosis with outcome (N=70)**

Diagnosis	Outcome		Total
	Recovered	Death	
Acute CVA	33 (52.4%)	1 (14.3%)	34 (48.6%)
Acute pyelonephritis	1 (1.6%)	0 (0.0%)	1 (1.4%)
ADEM	1 (1.6%)	0 (0.0%)	1 (1.4%)
AIDP	1 (1.6%)	0 (0.0%)	1 (1.4%)
AOCKD	1 (1.6%)	0 (0.0%)	1 (1.4%)
ARDS	1 (1.6%)	0 (0.0%)	1 (1.4%)
Autoimmune encephalitis	1 (1.6%)	0 (0.0%)	1 (1.4%)
Autoimmune haemolytic anaemia	1 (1.6%)	0 (0.0%)	1 (1.4%)
Benzodiazepine overdose	1 (1.6%)	0 (0.0%)	1 (1.4%)
Carcinoma colon	1 (1.6%)	0 (0.0%)	1 (1.4%)
Cardiogenic shock	1 (1.6%)	3 (42.9%)	4 (5.7%)
CKD	2 (3.2%)	0 (0.0%)	2 (2.9%)
CVT	3 (4.8%)	0 (0.0%)	3 (4.3%)
Dengue with warning signs	1 (1.6%)	0 (0.0%)	1 (1.4%)
Hypertensive emergency	1 (1.6%)	0 (0.0%)	1 (1.4%)
Hypertensive urgency	1 (1.6%)	0 (0.0%)	1 (1.4%)
Hypocalcemia	1 (1.6%)	0 (0.0%)	1 (1.4%)
Hypokalaemic periodic paralysis	1 (1.6%)	0 (0.0%)	1 (1.4%)
Hyponatremia	1 (1.6%)	0 (0.0%)	1 (1.4%)
ITP	1 (1.6%)	0 (0.0%)	1 (1.4%)
Leptospirosis	2 (3.2%)	0 (0.0%)	2 (2.9%)
MI	2 (3.2%)	1 (14.3%)	3 (4.3%)
Non hodgkins lymphoma	0 (0.0%)	1 (14.3%)	1 (1.4%)
Recurrent cva	1 (1.6%)	1 (14.3%)	2 (2.9%)
Scrub typhus	1 (1.6%)	0 (0.0%)	1 (1.4%)
Seizure disorder	2 (3.2%)	0 (0.0%)	2 (2.9%)
Total	63 (100%)	7 (100%)	70 (100%)

**Table 3: Pearson Correlation between FT3, FT4, TSH, MAP and APACHE 2 among recovered and death (N=70)**

Parameter	Pearson Correlation (r)	P value
Recovered		
APACHE 2 & FT3	-0.279	0.027
APACHE 2 & FT4	0.247	0.05
APACHE 2 & TSH	-0.030	0.814
APACHE 2 & MAP	0.157	0.219
Death		
APACHE 2 & FT3	0.885	0.008
APACHE 2 & FT4	-0.536	0.215

APACHE 2 & TSH	-0.513	0.239
APACHE 2 & MAP	-0.213	0.647

**Table 4: Factors associated with mortality in study population univariate logistic regression analysis**

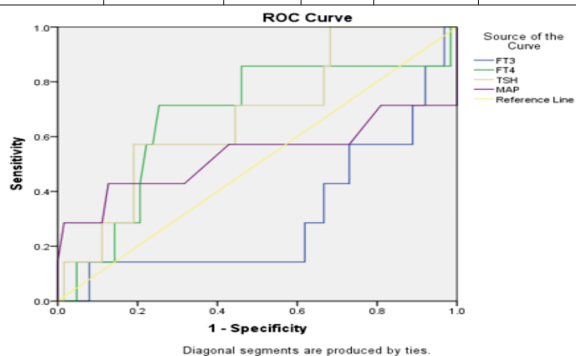
Factors	Odds Ratio	95% CI	P value
Age	1.043	0.96 - 1.13	0.311
Gender (baseline=Female)			
Male	0.715	0.15 - 3.49	0.679
ICU Stay	1.280	1.02 - 1.61	0.033
FT3	0.357	0.09 - 1.48	0.157
FT4	1.843	0.19 - 17.22	0.592
TSH	1.235	0.91 - 1.69	0.183
MAP	1.027	0.99 - 1.07	0.170
APACHE2	1.610	1.110 - 2.34	0.012
Serum creatinine	1.102	0.72 - 1.68	0.651
Serum sodium	0.961	0.85 - 1.08	0.515
Serum potassium	0.868	0.21 - 3.59	0.845
Mortality pre op (%)	1.262	1.07 - 1.48	0.005
Mortality post op (%)	1.261	0.99 - 1.61	0.061

**Table 5: Multivariate logistic regression analysis ICU stay, APACHE 2 and Mortality pre op (%) associated with mortality in study population**

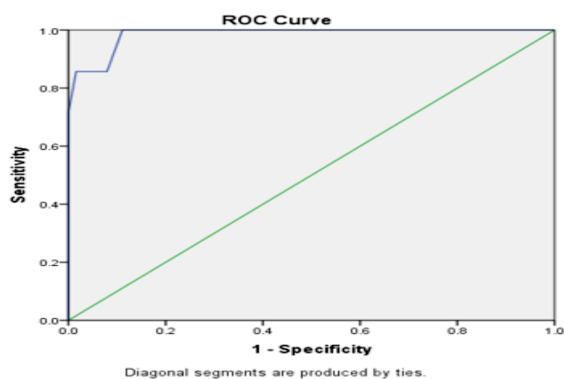
	Exp(B)	95% CI	P value
ICU stay	1.137	0.86 - 1.50	0.366
APACHE 2	1.086	0.45 - 2.63	0.855
Mortality pre op (%)	1.203	0.79 - 1.85	0.397

**Table 6: Predictive validity of FT3, FT4, TSH, MAP APACHE 2 in predicting mortality status**

	Area Under the Curve	P value	Cut off Value	Sensitivity	Specificity
FT3	0.304	0.090	2.79	28.6%	66.7%
FT4	0.671	0.139	1.12	57.1%	23.8%
TSH	0.671	0.139	2.07	57.1%	44.4%
MAP	0.533	0.777	105	42.9%	31.7%
APACHE 2	0.985	<0.001	14	85.7%	7.9%



**Figure 1: Predictive validity of FT3, FT4, TSH and MAP in predicting mortality status**



**Figure 2: predictive validity of APACHE 2 in predicting mortality status**

**DISCUSSION:**

In our study critically ill patients admitted to ICU without underlying thyroid illness were included and in those FT3 and APACHE 2 scores were predominantly correlated with the outcomes. A total of 70 patients were included in the study, of those 63 recovered and discharged while 7 patients expired. Age and sex did not show a statistically significant relationship with the outcomes, thus indicate age and sex do not have a significant role in the survival of critically ill patients. A study done by Kanishka sharma et al.<sup>5</sup> also showed similar results between age and outcomes like our study. 48.6% of the ICU admissions were due to acute CVA and cardiogenic shock constitute 5.7%. A study done by Álvaro Quispe E et al.<sup>6</sup> showed 15.1% of the ICU admission were secondary to haematologic causes followed by 13.1% of cardiac causes.

In this study, when FIO2 levels were analyzed in both survivors and non-survivors there was a statistically significant difference between both groups ( P < 0.001). A study done by Jianying guo et al.<sup>4</sup> also showed a statistically significant relation between oxygenation index and outcomes in critically ill patients. Median days of ICU stay in non-survivors is more than survivors and statistically significant difference between the groups ( P 0.01). A study done by Mevlut Ture et al.<sup>7</sup> also showed similar results concerning ICU stay in both groups and it is statistically significant as well. In particular, oxygenation status and ICU stay could influence the outcomes in critically ill patients.

In our study mean FT3 levels were lower in non-survivors while FT4 and TSH levels were lower in non-survivors. There was no statistically significant relationship between FT3, FT4, TSH, and outcomes. In a study done by Álvaro Quispe E et al.<sup>6</sup> low levels of FT3 were noticed in non-survivors compared to survivors and a statistically non-significant relationship between FT3 and the outcomes ( P = 0.403). This in turn showed similar results to our study about TSH and FT4. A study done by Kanishka sharma et al.<sup>5</sup> showed low mean FT3 levels but demonstrated a significant relationship between survivors and non-survivors. Different studies showed different results concerning low FT3 levels and worse outcomes, so further studies with a large sample size are required to test the correlation.

In this study mean APACHE 2 levels were higher in non-survivors compared to survivors and had a statistically significant relationship between the two groups ( P = 0.01). With the Pearson correlation, APACHE 2/FT3 showed a statistically significant negative correlation (r = -0.279, P = 0.02), while APACHE 2/FT4 showed a significant positive correlation (r = 0.247, P = 0.05) in recovered patients. In non-survivors APACHE 2/FT3 showed a statistically significant positive correlation ( r = 0.885, P= 0.005) with the outcome. In a study done by Adnan Tas et al.,<sup>8</sup> spearman correlation showed a statistically significant correlation between APACHE 2/FT3 and outcomes like in our study ( r= 0.364, P < 0.001). This suggests that combined APACHE 2 and FT3 levels were a better predictor of outcomes in critically ill patients than FT3 alone. APACHE 2 uses both clinical as well as laboratory parameters in predicting mortality.

Univariate regression analysis was performed and ICU stay, APACHE 2, and pre-op mortality emerged as independent factors in predicting mortality, but multivariate regression analysis of those three factors did not show any significant relation in predicting mortality. A study done by Álvaro Quispe E et al.<sup>6</sup> showed APACHE 2, albumin, and IL-10 as independent mortality predictors after multivariate regression analysis in contrast to our study.

A receiver operating characteristic (ROC) analysis done showed cut-off values for FT3 and APACHE 2 in predicting

mortality was 2.79 (sensitivity: 28.6%, specificity: 66.7%; AUC: 0.304) and 14 (sensitivity: 85.7%, specificity: 7.9%; AUC: 0.985) respectively. A study done by Adnan Tas et al.<sup>8</sup> also showed cut-off values of 13.5 with sensitivity and specificity of 88.1% and 71.4% respectively for APACHE 2.

Various explanations exist for altered thyroid hormone levels in case of acute stress or chronic illness. Possible reasons for low thyroid hormone levels in case of stress are defective 5-deiodinase activity, defects in thyroid hormone binding proteins and transporter, abnormal secretion of TRH and TSH, and alteration of nuclear thyroid hormone receptor activity. Cytokines like IL-1, IL-6, and TNF-alfa also play a role in some forms of NTIS, but the exact reason for this variability of hormone levels in the disease is still not known.<sup>9</sup>

### CONCLUSION:

In the present study, APACHE 2 and FT3 combined showed promising results in predicting mortality. According to our study, low FT3 levels alone did not show any significant results. As different studies showed different results with thyroid profiles in predicting mortality in ICU patients, further studies with large sample sizes are required. The drawback associated with using thyroid hormones in predicting outcomes is that those who were on thyroid medications have to be excluded, but APACHE 2 can be applied universally irrespective of the thyroid status.

### Limitations Of The Study:

rT3 levels were not calculated because of non-availability of the test in the hospital and logistic reasons as well.

### Abbreviations:

ICU – Intensive Care Unit  
 APACHE – Acute Physiology and Chronic Health Evaluation  
 CVA – Cerebro-Vascular accident  
 AOCKD- Acute Onset Chronic Kidney Disease  
 CVT - Cerebral Venous Thrombosis  
 ADEM- Acute Disseminated Encephalomyelitis  
 AIDP – Acute inflammatory Demyelinating Polyradiculopathy  
 ARDS – Acute Respiratory Distress Syndrome  
 MI - Myocardial Infarction  
 FI02 - Fraction of inspired oxygen

### REFERENCES:

1. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *The Lancet Diabetes & Endocrinology*. 2015;3(10):816–25.
2. S. Lee and A. P. Farwell, "Euthyroid sick syndrome," *Comprehensive Physiology*, vol. 6, no. 2, pp. 1071–1080, 2016.
3. G. Van den Berghe, "Non-thyroidal illness in the ICU: a syndrome with different faces," *Thyroid : official journal of the American Thyroid Association*, vol. 24, no. 10, pp. 1456–1465, 2014.
4. Guo J, Hong Y, Wang Z, Li Y. Prognostic value of thyroid hormone FT3 in general patients admitted to the Intensive Care Unit. *BioMed Research International*. 2020;2020:1–9.
5. Sharma K, Sharma A, Sharma P, Gupta S., Thyroid dysfunction and mortality in critically ill patients in a tertiary care hospital in Jaipur, Rajasthan India. *Int. J. Med. Sci. Educ* 2020; 7(1): 68-71
6. Quispe EA, Li XM, Yi H. Comparison and relationship of thyroid hormones, IL-6, IL-10 and albumin as mortality predictors in case-mix critically ill patients. *Cytokine*. 2016 May;81:94-100. doi: 10.1016/j.cyto.2016.03.004. Epub 2016 Mar 11. PMID: 26974766.
7. Türe M, Memiş D, Kurt I, Pamukçu Z. Predictive value of thyroid hormones on the first day in adult respiratory distress syndrome patients admitted to ICU: comparison with SOFA and APACHE II scores. *Ann Saudi Med*. 2005 Nov-Dec;25(6):466-72. doi: 10.5144/0256-4947.2005.466. PMID: 16438455; PMCID: PMC6089744.
8. Tas A, Tetiker T, Beyazit Y, Celik H, Yesil Y. Thyroid hormone levels as a predictor of mortality in intensive care patients: A comparative prospective study. *Wien Klin Wochenschr*. 2012 Mar;124(5-6):154-9. doi: 10.1007/s00508-012-0125-1. Epub 2012 Feb 15. Erratum in: *Wien Klin Wochenschr*. 2013 Apr;125(7-8):227. PMID: 22388792.
9. Fliers E, Kalsbeek A, Boelen A. Beyond the fixed setpoint of the hypothalamus-pituitary-thyroid axis. *Eur J Endocrinol*. 2014 Nov;171(5):R197-208. doi: 10.1530/EJE-14-0285. Epub 2014 Jul 8. PMID: 25005935.