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THYROID DYSFUNCTION IN CRITICALLY ILL PATIENTS AND ITS PROGNOSTIC VALUE IN ICU

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ABSTRACT

Background: Critically ill patients typically present with low or normal plasma thyroxine, low plasma triiodothyronine (T3), increased plasma reverse T3 (rT3) concentrations, in the absence of a rise in thyrotropin (TSH). This constellation is referred to as nonthyroidal illness syndrome (NTI). It is long known that the severity of NTI is associated with risk of poor outcomes of critical illness. **Aim of study**: To evaluate the changes in the thyroid function, T3, T4 and TSH in critically ill patients in the intensive care unit and whether if it can predict the outcome of the critically ill patients. **Patients and Methods:** 40 patients were collected in a prospective cross sectional observational study, We recorded their baseline characteristics, acute physiology and chronic health evaluation (APACHE-II) score and thyroid function test weekly. thyroid dysfunction and ICU mortality were the primary outcomes. **Results**: Higher T3, T4, and TSH levels indicate a good prognosis, as they positively associated with lower mortality, and a higher discharge rate and vice versa. T3 levels decreases significantly in patients in ICU, while the decrease in T4, and TSH was not significant. APACHE II score had a better sensitivity and specificity than thyroid function test, and hence a better indicator of prognosis but the combination of both T3, and APACHE II score analysis had the highest prediction for death (R2= 0.34) than APACHE II score alone (R2=0.28). **Conclusion**: We observed a wide range change in thyroid hormones and thyrotropin, the combination of T3 levels and APACHE-II scores provided for a higher probability for predicting mortality in ICU patients.

KEYWORDS: ICU, APACHE II, Thyroid function, NTI, T3, T4, TSH.

INTRODUCTION

Critical illness is a life-threatening multisystem process that can result in significant morbidity or mortality. In most patients, critical illness is preceded by a period of physiological deterioration; but evidence suggests that the early signs of this are frequently missed. All clinical staff have an important role to play in implementing an effective "Chain of Response" that includes accurate recording and documentation of vital signs, recognition and interpretation of abnormal values, patient assessment and appropriate intervention. Early-warning systems are an important part of this and can help identify patients at risk of deterioration and serious adverse events. Assessment of the critically ill patient should be undertaken by an appropriately trained clinician and follow a structured ABCDE (airway, breathing, circulation, disability and exposure) format. This facilitates correction of life-threatening problems by priority and provides a standardized approach between professionals.

Good outcomes rely on rapid identification, diagnosis and definitive treatment and all doctors should possess the skills to recognize the critically ill patient and instigate appropriate initial management.[1] These patients are best treated in an ICU staffed by experienced personnel.

Some hospitals maintain separate units for special populations (e.g., cardiac, trauma, surgical, neurologic, pediatric, or neonatal patients).

ICUs have a high nurse: patient ratio to provide the necessary high intensity of service, including treatment and monitoring of physiologic parameters.

Supportive care for the ICU patient includes provision of adequate nutrition and treatment and prevention of infection, stress ulcers and gastritis, and pulmonary embolism.[2]

Patients suffering from critical illnesses who require treatment in the intensive care unit (ICU) uniformly present with alterations in circulating thyroid hormone levels that are referred to with several names such as "nonthyroidal illness syndrome", "sick euthyroid syndrome" or "low T3.

Syndrome".[3] The most typical alterations are low plasma concentrations of triiodothyronine (T3), low or normal plasma concentrations of thyroxine (T4), or elevated plasma rT3 in the presence of normal thyrotropin (TSH). Together, these changes differ from those in primary and secondary thyroid disorders, which explains the name "nonthyroidal illness" (NTI). The normal TSH level in the presence of the low plasma T3 and at times also T4 concentrations has been interpreted as indicating a "euthyroid" status, hence the name "sick euthyroid syndrome". The most striking and universal finding, however, is the low plasma T3 concentration, which explains the most neutral name, the "low T3 syndrome". Besides these typical and clinically measurable changes in thyroid hormone parameters, there are alterations in the central regulation of the thyroid axis, as well as alterations in the peripheral components of the thyroid axis. These peripheral changes, which may vary per tissue and per type and severity of illness, comprise altered concentrations of the thyroid hormone binding proteins and their binding affinity, altered thyroid hormone transporters, changes in the expression and activity of the thyroid hormone deiodinases, and alterations in the thyroid hormone receptor (TR) expression.

During the course of any critical illness, a common phenomenon experienced is the alteration in the levels of thyroid hormones, sex hormones, and corticosteroids.[4] These changes correlate with the outcome and mortality of critically ill patients treated in Intensive Care Units (ICUs).[5]

In the 20th century, various studies observed that thyroid dysfunction is associated with increased morbidity and mortality in ICU-admitted patients.[6] Such alterations in thyroid hormone levels during critical illness is described as "euthyroid sick syndrome" or "nonthyroidal illness syndrome".[7] It is characterized by low levels of free and total triiodothyronine (T3) and high levels of reverse T3 (rT3) with variable values of thyroxine (T4) and thyroid-stimulating hormone (TSH) in the low to normal range.

Various studies were conducted to demonstrate an association of thyroid dysfunction in critically ill patients with mortality and morbidity of such patients. Whether thyroid hormones can independently predict mortality in ICU patients remains a matter of debate.

Aim of study

- Evaluation of thyroid dysfunction in critically ill patients in ICU.
- Whether these changes can predict the outcome of critically ill patients in ICU.

PATIENTS AND METHODS

After we had obtained approval from the Iraqi scientific council of anesthesia and intensive care unit and a written informed consent from all patients or their family members if they were unable or incompetent, we conducted a prospective cross sectional observational study involving a total of 40 adult patients admitted to the ICU. Thyroid dysfunction and ICU mortality were the primary outcome.

APACHE II was calculated and baseline TFT was done for all admitted patients, all patients then followed up weekly for TFT until whether they discharged or died.

The data of this study were collected from January 2020 to September 2020, 5 units of ICU in Baghdad participated in this study which are: Baghdad Teaching hospital ICU, Ghazi al-Hariri hospital for specialized surgeries ICU, Specialized Burn Hospital ICU, Nursing Home Hospital ICU and Al-Yarmouk Teaching hospital ICU.

We exclude patients with these criteria

- Refusal (Patient or responsible relatives)
- Patients with previous history of thyroid diseases or any disorder in the hypothalamic pituitary adrenal axis and hypothalamic pituitary gonadal axis.
- Pregnancy.
- Diabetes mellitus.
- Liver disease and chronic kidney disease.
- Patients on hormone replacement therapy within the previous six months.
- Patients on medications affecting thyroid function.

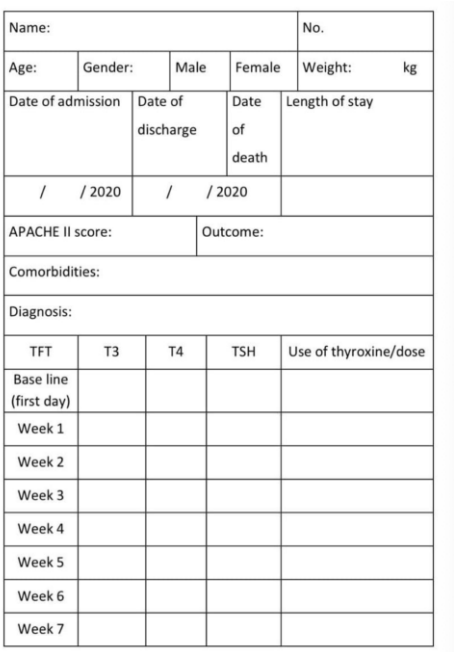
All the patients had a detailed clinical examination and were managed appropriate to their primary condition.

Fasting venous blood samples were taken on the first day of admission to ICU from all patients and hormone analyses were done. Samples were tested for total T3, total T4, and TSH.

The normal reference range for thyroid hormones in our laboratory are:

- T3 → 1.26 - 2.75 nmol/l.
- T4 → 57.9 - 161 nmol/l.
- TSH→ 0.3500 - 4.9400 mmol/ml.

Any deviation of the hormone results from the normal ranges is considered to be abnormal.



Name:				No.
Age:	Gender:	Male	Female	Weight: kg
Date of admission	Date of discharge	Date of death	Length of stay	
/ / 2020	/ / 2020			
APACHE II score:	Outcome:			
Comorbidities:				
Diagnosis:				

TFT	T3	T4	TSH	Use of thyroxine/dose
Base line (first day)				
Week 1				
Week 2				
Week 3				
Week 4				
Week 5				
Week 6				
Week 7				

Figure 1: Patient's data collection form.

The data was carried out using the SPSS (Statistical Packages for Social Sciences) version 24. Data was presented in simple measures of mean, standard deviation for the numerical data, along with frequency, and percentages for the categorical data.

The significance of association was tested using the independent samples t- test, paired samples t- test, and Pearson Chi-square test, with Fischer exact test being used for the cells with small expected counts less than (5). Statistical significance was considered with P-value equal or less than0.05.

RESULTS

Total sample of the study was 40 patients; they had mean age of (45.5) years, with mean weight of 73.17 (kg), and the mean length of stay was 17.93 (days).

Gender distribution was 62.5% male patients, with 37.5% female patients.

Table 1: Descriptive statistics of the study sample.

	Minimum	Maximum	Mean (SD)
Age (years)	22	93	45.5 (16.89)
Weight (kg)	50	110	73.17 (16.69)
ICU stay (days)	6	65	17.93 (13.86)
Gender	Male No. (%)		25 (62.5%)
	Female No. (%)		15 (37.5%)

Table 2: Descriptive statistics of the whole study sample, percent of discharged and died patients.

Outcome	No.	Percent (%)
Discharged	26	65%
Died	14	35%
Total	40	100%

Table 3: Comparison in mean age (yrs.) among the study participants, according to the outcome.

	Outcome	No.	Mean age (years)	Std. Deviation	p-Value
Age (years)	Discharged	26	46.35	16.73	0.678
	Died	14	43.93	17.69	

The previous table shows no significant difference in the age distribution according to the outcome.

Table 4: Comparison between the two groups in average length of stay.

	Outcome	Mean	Std. Deviation	p-Value
ICU stay (days)	Discharged	18.27	12.18	0.834
	Died	17.29	17.04	

Patients who discharged stayed non-significantly for a longer period than those who died.

Table 5: Associated co-morbidities and smoking of the participants.

Co-morbidities	No.	Percent (%)
None	18	45
Hypertension	10	25
COPD	5	12.5
Hypertension +COPD	1	2.5

Malignancy	1	2.5
Multiple Sclerosis	1	2.5
Smoking	4	10
Total	40	100

Table shows the co-morbidities of the participants that includes 25% of patients were hypertensive, 12.5% had COPD, while only one patient had both HT, and COPD, and another one patient had malignancy, and single patient had multiple Sclerosis, another 10% of the sample were smokers.

Table 6: Distribution of the sample by cause of admission (diagnosis).

Cause of admission	No.	Percent(%)
Post operative	2	5
Chest infection	5	12.5
TBI	1	2.5
Soft tissue injury	2	5
CVA	1	2.5
RTA	8	20
GBS	3	7.5
Sepsis	14	35
COVID-19	4	10
Total	40	100

Table 6 illustrates the cause of admission of patients, that 5% of patients were post operatively admitted to the ICU, 12.5% of patients had chest infection, 2.5% TBI, 5% were with soft tissue injury, single patient had CVA, 20% admitted due to RTA, 7.5% GBS, 35% Sepsis, and 10% COVID-19.

The next table demonstrates that T3 levels were higher in patients who discharged from the ICU than those who died as a whole; but the difference was not significant on the following occasions: Base line T3, third week T3, fifth week T3, and sixth week T3.

T3 levels were significantly higher in the first, second, and fourth weeks; in patients who discharged than those who died.

T4 levels were higher in patients who discharged from the ICU than those who died as a whole (except for the 7th week); but the difference was not significant at the Base line T4, second week T4, fifth week T4, and sixth week T4 levels.

T4 levels were significantly higher in the first, third, and fourth weeks; in patients who discharged than those who died.

TSH levels were higher in patients who discharged from the ICU than those who died as a whole (except for the 5th week); but the difference was not significant at the Base line TSH, third week TSH, fourth week TSH, fifth week TSH, and sixth week TSH levels.

TSH levels were significantly higher in the first, and second weeks; in patients who discharged than those who died.

Higher T3, T4,and TSH levels indicate a good prognosis, as they positively associated with lower mortality, and a higher discharge rate.

Table 7: Comparison of T3 test among the patients according to the outcome.

T3 (nmol/L)	Outcome	Mean (SD)	p-Value
Baseline	Discharged	1.34(0.37)	0.646
	died	1.28(0.33)	
1st week	Discharged	1.25(0.36)	0.009
	died	0.94(0.3)	
2nd week	Discharged	1.24(0.37)	0.023
	died	0.82(0.29)	
3rd week	Discharged	1.21(0.3)	0.07
	died	0.81(0.32)	
4th week	Discharged	1.35(014)	0.027
	died	0.79(0.33)	
5th week	Discharged	1.28(0.03)	0.116
	died	1.05(0)	
6th week	Discharged	1.2(0.21)	0.366
	died	0.81(0)	

7th week	Discharged	0.87(0)	*
	died	0.62(0)	
8th week	Discharged	0.91(0)	*
	died	0	

*: p-value could not be computed for seventh, and eighth weeks; due to the fact that only two patients stayed for 7 weeks, and only single patient stayed for the eighth week.

Table 8: Comparison of T4 test among the patients according to the outcome.

T4 (nmol/L)	Outcome	Mean (SD)	p-Value
Baseline	Discharged	87.15(22.45)	0.150
	died	77.(12.6)	
1st week	Discharged	87.22(22.51)	0.021
	died	71(91(10.21)	
2nd week	Discharged	85.97(25.46)	0.148
	died	69.02(16.42)	
3rd week	Discharged	83.63(5.97)	0.001
	died	58.27(10.63)	
4th week	Discharged	84.31(5.65)	0.005
	died	65.17(4.53	
5th week	Discharged	79.06(10.38)	0.613
	died	70.22(0)	
6th week	Discharged	75.55(18.59)	0.804
	died	68.3(0)	
7th week	Discharged	54.6(0)	*
	died	64.21(0)	
8th week	Discharged	-	*
	died	-	

*: p-value could not be computed for seventh, and eighth weeks; due to the fact that only two patients stayed for 7 weeks, and only single patient stayed for the eighth week.

Table 9: Comparison of TSH test among the patients according to the outcome.

TSH (nmol/L)	Outcome	Mean (SD)	p-Value
Baseline	Discharged	1.7(0.87)	0.207
	died	1.4(0.75)	
1st week	Discharged	1.86(0.79)	0.002
	died	1.06(0.59)	
2nd week	Discharged	1.84(0.59)	0.02
	died	1.12(0.6)	
3rd week	Discharged	1.88(0.74)	0.153
	died	1.18(0.64)	
4th week	Discharged	1.73(0.59)	0.208
	died	0.99(0.75)	
5th week	Discharged	1.51(0.43)	0.764
	died	1.72(0)	
6th week	Discharged	1.65(0.96)	0.8
	died	1.27(0)	
7th week	Discharged	1.14(0)	*
	died	0.93(0)	
8th week	Discharged	1.09(0)	*
	died	0	

*: p-value could not be computed for seventh, and eighth weeks; due to the fact that only two patients stayed for 7 weeks, and only single patient stayed for the eighth week.

APACHE II score was significantly higher in patients who died than those who survived as table 10 shows:

Table 10: Comparison in APACHE II score between discharged and died patients.

Variables	Outcome	No.	Mean(SD)	p-Value
APACHE II score	Discharged	26	21.2(4.32)	0.005
	Died	14	29.14(8.49)	

AUC = (0.800 ±0.089), and the sensitivity and specificity of (APACHE II score) as indicator of prognosis.

APACHE II score had Sensitivity = 85%, and specificity = 44%, along with PPV (Positive Predictive Value) = 60%, and NPV (Negative Predictive Value) = 74%.

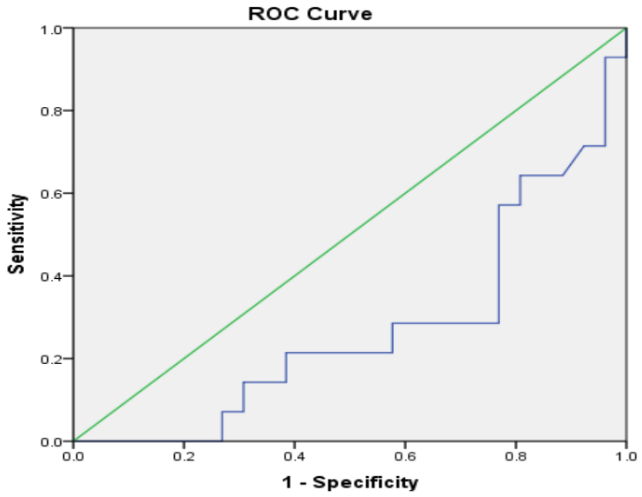


Figure 2: Receiver Operating Characteristics (ROC) Curve.

Figure 2 shows: AUC = (0.27± 0.083) and the sensitivity and specificity of (T3) as indicator of prognosis. Sensitivity = 60%, and specificity = 20% of T3, PPV (Positive Predictive Value) = 42%, and NPV (Negative Predictive Value) = 33%.

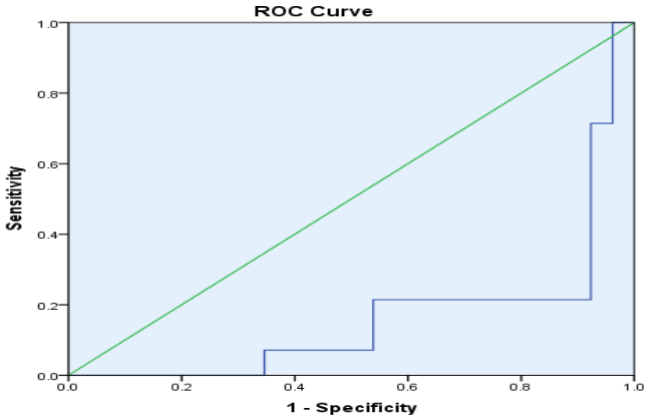


Figure 3: Receiver Operating Characteristics (ROC) Curve.

Figure 3 is showing AUC=(0.14 ± 0.065), and the sensitivity and specificity of (T4) as indicator of prognosis, as T4. Sensitivity=57% and specificity=10% , PPV (Positive Predictive Value) = 63%, NPV (Negative Predictive Value) = 18%.

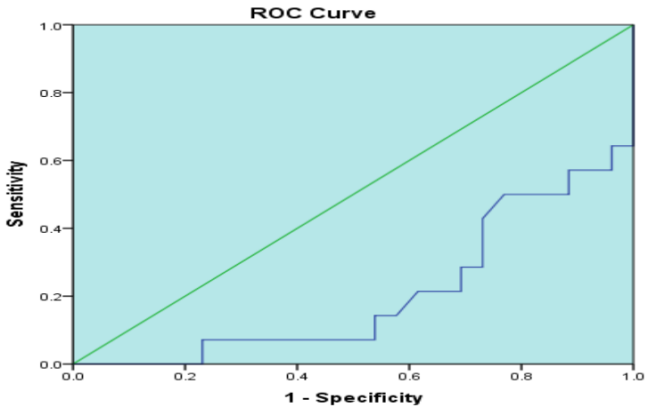


Figure 4: Receiver Operating Characteristics (ROC) Curve.

Figure 4 is showing AUC = (0.20 ± 0.074), and the sensitivity and specificity of (TSH) as indicator of prognosis, as TSH Sensitivity = 56% and specificity = 8%, PPV (Positive Predictive Value) = 37%, NPV (Negative Predictive Value) = 15%.

This indicates that APACHE II score had a better sensitivity and specificity, and hence a better indicator of prognosis.

Univariate logistic regression analysis showed that T3 had β=0.407, but APACHE II score had β=0.539, so APACHE II score had a higher predictive potential for death.

Multivariate logistic regression analysis showed that a combination of both T3, and APACHE II score analysis had the highest prediction for death (R^2= 0.34) than APACHE II score alone (R^2=0.28).

The following table shows that T3 levels decreases significantly in ICU patients, while the decrease in T4, and TSH was not significant.

Table 11: Comparison among T3, T4, and TSH on admission and outcome (discharge or death) of all patients.

Test (n mol/L)	Mean (SD)	Std. Error Mean	p-Value
Baseline T3 (on admission)	1.32 (0.35)	0.05	0.0001
Outcome T3 (discharge or death)	1.14 (0.37)	0.05	
Baseline T4 (on admission)	83.81 (19.93)	3.152	0.07
Outcome T4 (discharge or death)	81.86 (20.35)	3.219	
Baseline TSH (on admission)	1.63 (0.84)	0.1336	0.487
Outcome TSH (discharge or death)	1.58 (0.82)	0.129	

Table 12: Frequency and percentages of discharged and died patients, according to changes in T3 levels. (total N = 40).

Variables	Outcome	
	Discharged No. (%)	Died No. (%)
T3 level lower than normal	18 (69.2%)	11 (78.6%)
T3 level within ranges	8 (30.8%)	3 (21%)
Total	26 (65%)	14 (35%)

Previous table shows 69.2% of discharged patients had T3 levels lower than the normal range, compared to 78.6% of died patients.

Table 13: Comparison among the study group needing for the treatment with thyroxine, according to the outcome.

Variables		Outcome		Total	p-Value
		Discharge	died		
Use of thyroxine	Yes	1	2	3	0.539
	no	25	12	37	
Total		26	14	40	

The difference was statistically not significant in comparing the patients who discharged, and those who died regarding the treatment with thyroxine.

DISCUSSION

The "euthyroid sick syndrome" or "nonthyroidal illness syndrome" refers to the phenomenon of change in the thyroid hormone levels during the course of critical illness.[20] In the acute phase, it is characterized by low levels of T3 and variable levels of T4 and TSH, hence known as the "low T3 syndrome". However, with the progression of severity of illness, we also found decrease the levels of T4 and TSH in addition to the T3 hormone and carries a bad prognosis. During the recovery phase of the discharged patients, the first change observed is an elevation of TSH values followed by rise in T4 levels to its normal range.

While assessing the ICU patients in different stages of critical illness, we observed that their T4, TSH, levels varied from either normal to low-normal; however, a low T3 value was consistently found in the majority of patients.

In our study, 40 critical ill patients admitted to the ICU in which gender distribution was 25 (62.5%) on the male

side, with 15 (37.5%) for the females. They had a mean age of (45.5) years, with mean weight of 73.17(kg), and the mean length of stay was 17.93 (days).

There was no significant difference in the age distribution according to the outcome with the mean age of the discharged patients (46.35) years and the mean age of the dyed patients (43.93) years.

Patients who discharged stayed non-significantly for a longer period than those who died. The mean length of stay of the discharged patients was 18.27 days while the mean for the dyed patients was 17.29 days.

The co-morbidities of the participants include 25% of patients were hypertensive (HTN), 12.5% had COPD, while only one patient had both HTN, and COPD, in addition to another one patient had malignancy, and single patient had multiple sclerosis, another 10% of the sample were smokers.

5% of patients were post operatively admitted to the ICU, 12.5% of patients had chest infection, 2.5% TBI, 5% were with soft tissue injury, single patient had CVA, 20% admitted due to RTA, 7.5% GBS, 35% Sepsis, and 10% COVID.

We noticed a wide range change in thyroid function test in which Higher T3, T4, and TSH levels indicate a good prognosis, as they positively associated with lower mortality, and a higher discharge rate and vice versa.

We compared the sensitivity and specificity of the three hormones T3, T4 and TSH with APACHE II score, we found that APACHE II score had Sensitivity = 85%, and specificity = 44%, along with PPV (Positive Predictive Value) = 60%, and NPV (Negative Predictive Value) = 74% .

While for T3 Sensitivity = 60%, and specificity = 20%, PPV (Positive Predictive Value) = 42%, and NPV (Negative Predictive Value) = 33%.

For T4 the Sensitivity = 57% and specificity = 10%, PPV (Positive Predictive Value) = 63%, NPV (Negative Predictive Value) = 18%.

And for TSH Sensitivity = 56% and specificity = 8%, PPV (Positive Predictive Value) = 37%, NPV (Negative Predictive Value) = 15%.

This indicates that APACHE II score had a better sensitivity and specificity, and hence a better indicator of prognosis.

We found that T3 levels decreases significantly in critical ill patients in ICU, while the decrease in T4, and TSH was not significant, in which 69.2%of discharged patients had T3 levels lower than the normal range, compared to 78.6% of died patients.

Univariate logistic regression analysis showed that T3 had β=0.407, but APACHE II score had β=0.539, so APACHE II score had a higher predictive potential for death.

Multivariate logistic regression analysis showed that a combination of both T3, and APACHE II score analysis had the highest prediction for death (R^2= 0.34) than APACHE II score alone (R^2=0.28).

Also, we found that 3 patients out of 40 indicated for thyroxine treatment when the T4 level was below the normal range. They received 1 to 1.5mcg/kg/day (one patient treated with 50 mcg/day, the other two with 100mcg/day), only one patient (female patient treated with 100mcg daily) discharged while the other two were died so The difference was statistically not significant in comparing the patients who discharged, and those who died regarding the thyroxin treatment with a P value of 0.539.

Maldonado LS, Murata GH, Hershman JM, et al. studied the ability of thyroid function tests to predict hospital survival in 116 critically ill patients and compared the results with independent predictions of survival made by ICU physicians. In patients critically ill with nonthyroidal disease, low T3, low FT3I, low T4, low FT4I, high TSH, and high T3U levels each showed significant correlation with nonsurvivable (all p less than 0.02). Of these, however, only low T3 (p-Value less than 0.001) and high TSH (p value = 0.016) showed significant independent prediction of non-survival, and only low T3 (p value = 0.011) added any significant independent prediction of non-survival beyond that made clinically by them.[8]

Maldonado LS, Murata GH, Hershman JM, et al study agrees with our study in that T3 is a good predictor of outcome.

Loh KC and Eng PC. Study in Singapore they evaluated the prevalence and prognostic relevance of alterations in thyroid function indices in 100 critically ill patients prospectively on admission to their medical ICU.

Eighty-four (84%) of the patients had altered thyroid function indices suggestive of sick euthyroid syndrome (SES). The overall mortality rate for patients with and without evidence of SES were 40% and 6% respectively ($P < 0.01$). Serum total (T3) and total thyroxine (T4) concentrations were reduced in 67% and 24% of the patients respectively.

The low T3 state and the low T3 and T4 state accounted for 55% and 29% of the SES cases respectively. No correlation was noted between the serum T4 concentration and survival outcome while a normal serum T3 value served as a good predictor for survival (97%).[9]

Loh KC, Eng PC. Study agrees with our study in which T3 is a good predictor of survival.

Rothwell PM, Lawler PG. in their study in UK. They found There were significant differences for each endocrine parameter between survivors and non-survivors (all p values were less than 0.01). A multiple logistic regression analysis showed that only thyroxine, thyrotropin, and cortisol concentrations were independent predictors of outcome. Correct prediction of death was more frequent with the Endocrine Index than with APACHE II scores. Overall predictive power of the Endocrine Index, as measured by the area under the ROC, was 0.94 vs. 0.85 for APACHE II scores. Combining APACHE II scores and the endocrine parameters in a single index did not improve prediction (area under ROC = 0.94) so they concluded that an endocrine prognostic index based on ICU admission measurements of thyroxine, thyrotropin, and cortisol concentrations is a superior predictor of patient outcome than the APACHE II score.[10]

Rothwell PM, Lawler PG. study does not agree with our study in that only thyroxine, thyrotropin and cortisol were independent predictors of outcome and that they were superior to APACHE II score.

Ray DC, Macduff A, Drummond GB, et al. in their study in Edinburgh found that TT3 and TT4 concentrations were significantly less in non-survivors than in survivors on admission and on day 1 but not on day 2.

TSH, fT3 and fT4 concentrations did not differ significantly between survivors and non-survivors at any time. Only TT4 and cortisol were independent predictors of outcome. Prediction of outcome from the admission sample values was not better than using APACHE II scoring.

They concluded that Thyroid hormone and cortisol concentrations differ between survivors and non-survivors on admission to intensive care, but the values overlap.[11]

Ray DC, Macduff A, Drummond GB, et al study does not agree with our study in which they found that only T4 from thyroid function test was independent predictor of outcome but on the other side their study found that the prediction of outcome from the admission sample values was not better than using APACHE II scoring.

Tognini S, Marchini F, Dardano A, et al. in their study in Italy: The mortality rate was significantly higher (P = 0.0002) among patients with low T3 syndrome, which emerged as the sole predictive factor of death and it was very common in the hospitalized older population emerging as the most sensitive independent predictor of short-term survival.[12]

Tognini S, Marchini F, Dardano A, et al. study agrees with our study as that low T3 is good predictive factor of non-survival.

Chinga-Alayo E, Villena J, Evans AT, et al. in their study in Chicago, USA. they found that the best logistic regression model for ICU mortality included the APACHE score and TSH and T3 levels. This model had an area under the ROC curve of 0.88, significantly higher than the APACHE score alone with 0.75. The model with hormone levels and APACHE score was also significantly better calibrated than the model with only the APACHE score so they concluded that the addition of thyroid hormones to the APACHE score improves the prediction of mortality for ICU patients.[13]

Chinga-Alayo E, Villena J, Evans AT et al. study agrees partly with our study in that the addition of T3 and TSH to the APACHE score improves the prediction of mortality for ICU patients because in our study we found that only T3 changes were significant in prediction of mortality for critical ICU patients.

Kumar KV, Kapoor U, et al. in their study in India, they found that non-survivors had low T3 when compared with survivors (P = 0.0044).

There was no significant difference observed between survivors and non-survivors with respect to T4, TSH, HbA1c, and prolactin. They concluded that low T3 is an important marker of mortality in critically ill patients. Admission HbA1c, prolactin, T4, and TSH did not vary between survivors and nonsurvivors.[14]

Kumar KV, Kapoor U, et al study agrees with our study in that T3 predicts mortality in critically ill patients.

Suresh M, Jain AK, Nandy P. et al in their study in Sikkim, India, they found that The majority of critically ill patients had a low total (T3) (49%), and there was a significant inverse correlation (P = 0.0235) between severity of illness and low serum total T3 levels whereas there was no relationship between total T4 or TSH levels and severity of illness.[15]

Suresh M, Jain AK, Nandy P et al study agrees with our study in that low T3 has a significant relationship to the severity of critically ill patients.

Manish Gutch, Sukriti Kumar, et al in their study in India they found that Among the thyroid hormones, fT3 had the highest predictive value for ICU mortality, as seen by the largest area under the curve (AUC) value (0.990 ± 0.007) which was even greater than AUC of APACHE-II score (0.824 ± 0.051) and fT4 (0.917 ± 0.049).[16]

Manish Gutch, Sukriti Kumar, et al study goes with our study that T3 is not superior to APACHE II SCORE in predicting mortality but they found that FT3 was superior to APACHE II score in predicting mortality.

T. V. D. Sasi Sekhar, Ramya Appalaneni, et al in their study in India, they found that the Patients (59%) had low T3 level, (41%) of patients had normal T3, (31%) of patients had low T4, (69%) of patients had normal T4 level and TSH was low (11%) of patients, while (76%) of patients had normal TSH and (14%) of patients slightly high. their study showed that low T3 (59%) is the commonest abnormality in ICU admitted patients. There is a significant relation present between T3 and mortality (p value = 0.0001) and need for ventilation (p value 0.004). they suggested that low T3 is an important marker of mortality in ICU admitted patients.[17]

So, their study goes with our study in that there is a significant relation between low T3 and mortality in ICU admitted patients.

Regarding thyroxine therapy there are two famous studies, the first one for Brent GA, Hershman JM, their study — Thyroxine therapy in patients with severe nonthyroidal illnesses and lower serum thyroxine concentration‖: Patients admitted to a medical ICU who had a total serum T4 concentration less than 5 mcg/dl were randomly assigned to a control (12 patients) or a T4 treatment group (11 patients). Levothyroxine in a dose of 1.5 micrograms/kg was given iv each day for 2 weeks. In the treatment group, serum T4 and free T4 concentrations significantly increased by day 3 and were normal on day 5. Serum TSH levels decreased significantly in the T4 treatment group, as did the TSH response to TRH. A significant rise in serum T3 occurred in the control group on day 7, but was delayed until day 10 in the treatment group.

Mortality was equivalent in the 2 groups (75% control vs. 73% treatment). They concluded that T4 therapy was not beneficial in this population of ICU patients, and by inhibiting TSH secretion, it may suppress an important mechanism for normalization of thyroid function during recovery.[18]

Brent GA, Hershman JM study agrees with our study regarding thyroxine treatment in critical ill patient as in our study despite only three patients were given thyroxin treatment because of low T4 but the difference was statistically not significant in comparing the patients who discharged, and those who died with a P- value of 0.539 as only one patient was discharged while the other two were died.

The second study for Acker et al. they studied the treatment with thyroxine in acute renal failure in Pennsylvania, USA. Fifty-nine patients were randomized to receive either thyroxine or placebo. The groups were well matched in terms of basal and entry creatinine, age, sex, APACHE II scores, and percentage oliguric. Baseline thyroid functions, including T3, T4, rT3, and TSH levels, were equal between the two groups and typical of patients with euthyroid sick syndrome. Thyroxine resulted in a progressive and sustained suppression of TSH levels in the treated group, but had no effect on any measure of ARF severity. Mortality was higher in the thyroxine group than the control group (43 vs. 13%) and correlated with suppression of TSH. They concluded that thyroxine has no effect on the course of clinical ARF and could have a negative effect on outcome through prolonged suppression of TSH. Critically ill euthyroid sick patients should not be replaced with thyroid hormone.[19]

ACKER ET AL study goes with our study in that thyroxine has no effect on the course of treatment but further they found that it could have a negative effect on the outcome.

Leslie J DeGroot in her article about the NTIS in South Dartmouth, said that If therapy is to be given, it cannot be thyroxine alone, since this would fail to promptly elevate T3 levels. treatment should include oral, or if this is impractical, intravenous T3.[20]

DeGROOT article goes with our study that in the chronic phase of NTIS, with T4 under 4 µg/dL (51.4880 nmol/l), that this is a target group in whom thyroid hormone administration should be considered but it cannot be thyroxine alone, the treatment should include oral or intravenous T3 and she suggested giving TRH, GHRH and testosterone for future studies.

The Limitations of our study were limited number of cases, the presence of undiagnosed thyroid disease before ICU admission cannot be ruled out; the interference of other drugs with thyroid function (e.g. Furosemide, benzodiazepines, barbiturates, steroids and dopamine) could not be completely eliminated because most of these drugs form an integral part of management of the critically ill patient and lastly the crisis of COVID19 pandemic.

CONCLUSIONS

- There is a wide range change in Thyroid hormones and TSH in critical ill patients in ICU.
- Among T3, T4 And TSH, T3 hormone has the strongest prediction for ICU mortality.
- APACHE II score is still superior to T3 in prediction of ICU mortality but the combination of T3 levels and APACHE-II scores provide a higher probability for predicting mortality in ICU patients.
- Despite that only three patients treated with thyroxine and the small sample size of the study group, it was not clear that the treatment with thyroxine of the chronic critically ill patients in ICU with nonthyroidal illness syndrome is beneficial.

Recommendations

- The study needs to be done on a larger sample size.
- Future studies include in addition to T3, T4 and TSH; FT3 and FT4 levels in critical ill patients in ICU and whether that FT3 and FT4 can give a better

prediction for mortality or even if they are superior to APACHE II score.

- We recommend considering the combinations of T3 and APACHE-II score for a higher probability in predicting mortality in ICU patients.

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