Prognostic Value of Thyroid Profile in Critical Care Condition

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Abstract

Background: Patients suffering from critical illness admitted to the Intensive Care Unit (ICU) exhibit alterations in their thyroid hormone levels, collectively termed as euthyroid sick syndrome or nonthyroidal illness syndrome. Our study was conducted to determine the correlation between these changes in thyroid hormone levels and the prognosis of ICU-admitted patients. **Methods:** A total of 270 ICU-admitted patients without previous history of thyroid disorder were included in the study. We recorded their baseline characteristics, acute physiology and chronic health evaluation (APACHE-II) score, thyroid hormone levels, lactate, and other parameters on admission. ICU mortality was the primary outcome. We analyzed the ability of each parameter to predict mortality in the participants. Further, we also evaluated whether the combination of thyroid hormone levels with APACHE-II score could improve the mortality prediction. **Results:** The mean age of the study population was 38.99 ± 18.32 years. A total of 81 patients (30%) expired during their ICU treatment. Both fT3 and fT4 levels were lower in nonsurvivors compared to survivors. 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). Univariate logistic regression analysis showed that fT3 ($\beta = 140.560$) had the highest predictive potential for ICU mortality compared with APACHE-II score ($\beta = 0.776$), fT4 ($\beta = 17.62$) and other parameters. Multivariate logistic regression analysis revealed that the combination of fT3 and APACHE-II ($R^2 = 0.652$) was superior in predicting mortality than APACHE-II alone ($R^2 = 0.286$). **Conclusion:** We observed that fT3 was the strongest predictor of ICU mortality compared to all other parameters included in our study. Further, the combination of fT3 levels and APACHE-II scores provided for a higher probability for predicting mortality in ICU patients.

Keywords: Intensive care, sick euthyroid syndrome, thyroid profile

INTRODUCTION

During the course of any critical illness, a common phenomenon experienced is the alteration in the levels of thyroid hormones, sex hormones, and corticosteroids.[1] These changes correlate with the outcome and mortality of critically ill patients treated in Intensive Care Units (ICUs).[2,3] In the 20th century, various studies observed that thyroid dysfunction is associated with increased morbidity and mortality in ICU-admitted patients.[4] Such alterations in thyroid hormone levels during critical illness is described as "euthyroid sick syndrome" or "nonthyroidal illness syndrome."[5,6] 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. Initial studies showed inconsistent results with some showing decreased free T3 (fT3) levels in nonsurvivors,[7,8] while others failed to show any such association.[9] Whether thyroid hormones can independently predict mortality in ICU patients remains a matter of debate. A large prospective trial involving 480 critically ill patients admitted to ICU showed fT3 levels to be an independent and powerful predictor of mortality.[10] A few Indian studies have also tried to demonstrate the association of low T3 levels with poor clinical outcome in critically ill patients.[11,12]

Owing to lack of data in India regarding endocrine dysfunction in critically ill patients, we conducted this prospective, observational study to evaluate the thyroid hormone levels

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in critically ill patients and to determine whether they can be used as a predictor of outcome in these patients.

METHODS

Having obtained approval from the Ethical Committee of the institution, we conducted a prospective, observational study involving a total of 270 adult patients admitted to the medical ICU of a tertiary care hospital in North India. ICU admission was based on the clinical conditions of the patient not related to the main objective of our study. Excluded from this study were patients with known history of thyroid disease, patients taking drugs altering thyroid functions, pregnant patients or those who were pregnant in the past 6 months, or patients taking amiodarone or any hormonal therapy except insulin. They were treated according to their primary medical illnesses. We obtained an informed and written consent from the patients or their legal guardians. The patients were classified as survivors and nonsurvivors based on the outcome of treatment.

On admission to ICU, fasting blood samples were obtained from all eligible patients and were subject to thyroid hormone analysis (TSH, T3, T4, fT3, and fT4) besides other relevant investigations. Thyroid hormones were assayed using solid-phase chemiluminescence immunoassay. The normal reference ranges are TSH (0.3–4.5 µIU/L), T3 (1.2–2 nmol/L), T4 (70–150 nmol/L), fT3 (3.5–6.5 pmol/L), and ft4 (11.5–23 pmol/L). TSH was not repeated for a second time during ICU stay or at the time of discharge.

Baseline demographic and clinical characteristics of the eligible patients were recorded on admission and the acute physiology and chronic health evaluation (APACHE-II) score was calculated. Summary data are presented in the form of mean value ± standard deviation for continuous variables and expressed and percentage for categorical variables. Baseline characteristics between the two groups were compared using unpaired Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. We used receiver operating characteristic (ROC) curves to assess the performance of variables in predicting mortality; area under the curve (AUC) was calculated from the ROC curve. Cutoff value was determined using Youden's index. We further performed univariate logistic regression analysis to assess the association between ICU mortality and each of the mortality predictors. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using software SPSS version 17 (233, South Wacker Drive, 11th floor, Chicagon I).

RESULTS

A total of 270 patients (138 male and 132 female) admitted to the medical ICU were found eligible for enrollment in our study. The baseline characteristics of both survivors and nonsurvivors have been listed in Table 1. The mean

Table 1: Demographic profile

Characteristics	All	Survivors	Nonsurvivors	*P*
n	90	63	27	
Males (%)	51.1	66.7	14.8	<0.001
Age (years)	38.99±18.32	36.94±17.96	43.78±18.60	0.105
SBP	104.56±20.45	110.86±16.60	89.85±21.28	<0.001
DBP	63.29±13.61	67.24±11.81	54.07±13.23	<0.001
GCS	10.87±4.44	11.67±4.04	9.00±4.81	0.008
APACHE score	17.88±8.62	14.83±5.95	25.00±9.75	<0.001
Duration of illness (days)	8.43±7.48	8.19±7.87	9.00±6.60	0.641
Hypertension (%)	14.4	11.1	22.2	0.169
Thyroid functions				
T3	1.03±0.45	0.95±0.38	1.23±0.56	0.007
T4	73.69±34.63	72.89±34.18	75.54±36.24	0.742
TSH	3.31±11.85	3.69±13.99	2.41±3.58	0.640
FT3	3.38±0.34	3.57±0.19	2.94±0.15	<0.001
FT4	14.95±1.30	15.60±0.42	13.44±1.40	<0.001
Hemoglobin (mg/dl)	10.94±2.78	11.09±2.80	10.59±2.76	0.437
HCT	42.59±10.56	42.73±9.81	42.24±12.34	0.840
Serum urea (mg/dl)	74.82±52.61	59.17±35.84	111.32±66.61	<0.001
Serum creatinine (mg/dl)	1.78±1.05	1.51±0.80	2.41±1.29	<0.001
Serum lactate	3.14±2.81	2.80±2.28	3.93±3.69	0.080
Serum protein (gm/dl)	6.13±0.98	6.21±0.97	5.94±0.99	0.234
Serum albumin (gm/dl)	3.20±0.81	3.38±0.83	2.79±0.61	0.001
pH <6.80 (%)	7.8	4.8	14.8	0.103
HCCO3 <3 mmol/L (%)	32.2	33.3	29.6	0.730

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GCS: Glasgow coma scale, TSH: Thyroid-stimulating hormone, HCT: Hematocrit, APACHE: Acute Physiology and Chronic Health Evaluation, T3: Triiodothyronine, T4: Thyroxine, FT3: Free T3, FT4: Free T4, HCCO3: Bicarbonate

age of the study population was 38.99 ± 18.32 years. A total of 81 patients (30%) succumbed to their illness during ICU admission. The mean APACHE-II score was 17.88 ± 8.62. It was significantly lower among nonsurvivors compared with survivors (25.00 ± 9.75 vs. 14.83 ± 5.95, *P* < 0.001). The levels of both fT3 and fT4 were lower in nonsurvivors as compared to survivors (*P* < 0.001). Nonsurvivors were older (43.78 ± 18.60 years) compared to survivors (36.94 ± 17.96 years). We recorded higher levels of blood urea, creatinine, and lactate, and lower levels of hemoglobin and albumin among patients who did not survive.

We constructed ROC curves for assessment of each predictor of ICU mortality and the AUC was calculated for each [Table 2]. We observed that among the thyroid hormone indicators, fT3 had the highest power for predicting ICU mortality as it had the highest value for AUC (0.990 ± 0.007). The AUC for fT3 was greater than that for APACHE-II score (0.824 ± 0.051). Furthermore, it exceeded the AUC values for serum lactate, urea, creatinine, and albumin, as seen in Figures 1 and 2, respectively.

We also performed a univariate logistic regression analysis to realize the association between ICU mortality and each predictor by calculating the standard coefficient (β) and OR for each variable [Table 3]. Among the thyroid hormone indicators, fT3 was seen to have the greatest absolute value of standardized β (140.560). The absolute value of fT3 was greater than that of fT4 (17.62) as well as that of APACHE score indicating that fT3 has a greater power for predicting mortality in ICU patients than fT4 or APACHE score.

Further, we conducted a multivariate logistic regression analysis to determine the independent predictors of ICU mortality [Table 4]. We observed that using combined values of fT3 and APACHE II, there was higher probability of predicting mortality (Cox and Snell R^2 = 0.652, Nagelkerke R^2 = 0.924) than with APACHE II alone (Cox and Snell R^2 = 0.286, Nagelkerke R^2 = 0.405).

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.[5,6] In the acute phase, it is characterized by low levels of T3, increased levels of rT3, and variable levels of T4 and TSH, hence known as the "low T3 syndrome." However, with the progression of severity of illness, one may find low levels of T4 in addition to the changes mentioned above. This is known as the "low T4 syndrome" and carries a dismal prognosis.[13] During the recovery phase, 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, and FT4 levels varied from either normal to low-normal; however, a low T3 or fT3 value was consistently found in all the patients. The T4 and T3
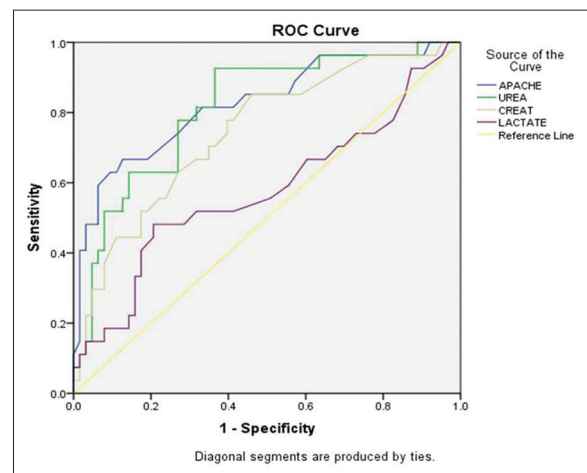

Figure 1: Receiver operating characteristic showing relationship between acute physiology and chronic health evaluation, urea, creatinine, and serum lactate

Table 2: Performance of variables in predicting mortality

	AUC ROC	*P*	Cutoff value	Sensitivity (%)	Specificity (%)
T3 (nmol/l)	0.364±0.065	0.042			
T4 (nmol/l)	0.496±0.067	0.947			
TSH	0.500±0.074	0.996			
HCT	0.497±0.070	0.961			
Serum urea (mg/dl)	0.812±0.049	<0.001	≥55.50	92.6	61.9
Serum creatinine (mg/dl)	0.745±0.057	<0.001	≥1.580	70.4	65.1
Serum lactate	0.577±0.071	0.251			
APACHE score	0.824±0.051	<0.001	≥18.50	74.1	73.0
Hemoglobin	0.560±0.065	0.371			
FT3	0.990±0.007	<0.001	≤3.19	100	95.2
FT4	0.917±0.049	<0.001	≤15.150	92.6	95.2
Serum protein	0.565±0.067	0.333			
Serum albumin	0.714±0.056	0.001	≤3.050	70.4	60.3
GCS	0.657±0.065	0.019	≤11.00	63.0	60.3

AUC: Area under the curve, ROC: Receiver operating characteristic, TSH: Thyroid-stimulating hormone, HCT: Hematocrit, GCS: Glasgow coma scale, APACHE: Acute Physiology and Chronic Health Evaluation, T3: Triiodothyronine, T4: Thyroxine, FT3: Free T3, FT4: Free T4

levels can be affected by alterations in the thyroxine-binding globulin (TBG) levels, which in turn can be affected by liver disease, pregnancy, and drugs such as oral contraceptives, corticosteroids, and furosemide. Since fT3 and fT4 levels are not affected by the changes in TBG levels, they may be better suited to predict ICU mortality outcomes.

In our study, of 270 ICU-admitted patients, we found that fT3 levels were the strongest indicator of ICU mortality among all thyroid function markers (T3, T4, TSH, fT3, and fT4) by calculating the AUC from the ROC curve, standardized β, and OR. FT3 fared better than fT4, APACHE-II scores, lactate, urea, creatinine, albumin, and other markers for predicting ICU mortality. Furthermore, the combination of APACHE-II scores and fT3 values strengthened the ability to predict the mortality outcomes.

Previous studies conducted to demonstrate any association between thyroid hormone levels and prognosis in critically ill patients yielded inconsistent results. Either they could not establish an association between fT3 and adverse outcomes,[9] or they found association between T4,[9,14] T3,[8,15] TSH,[15] and FT4.[16] Such results may be ascribed to small sample sizes and different population included in the different studies. However, a large-scale study[10] involving 480 adult patients admitted to the ICU demonstrated that fT3 was the most powerful predictor of ICU mortality among other indicators and that addition of fT3 to APACHE-II score improved the ability to predict mortality. This result was similar to that observed in our study of 90 critically ill ICU-admitted patients.

In the Indian scenario, very few studies have been performed to determine any relationship between thyroid hormone levels and prognosis of ICU-admitted patients. A study of 100 ICU-admitted patients showed that low T3 was an important marker of prognosis in critically ill patients compared to HbA1C, prolactin, T4, and TSH levels.[11] Yet, another study of 100 ICU-admitted patients showed a similar relationship between low T3 levels and severity of critically ill patients.[12]

The mechanisms behind the association of low T3 levels with poor prognosis of critically ill patients are yet to be properly defined. The low thyroid hormone levels during critical illness may be viewed both as an adaptive response or a maladaptive response.[17] Inhibition of the 5'-deiodinase enzyme is a possible mechanism underlying euthyroid sick syndrome resulting in decreased peripheral conversion of T4 to T3. With respect to critical illness, cytokines (tumor necrosis factor, interferon-alpha, and interleukin) are the most important

Table 3: Univariate odds ratio of variables for predicting mortality

Predictor	β	OR	95% CI		P
			Lower	Upper	
GCS	−4.191	0.015	0.000	-	0.995
APACHE	0.776	2.172	0.000	-	0.999
FT3	−140.560	0.000	0.000	-	0.992
FT4	−17.620	0.000	0.000	-	0.995
T3	28.879	3.485	0.000	-	0.997
Serum urea	−0.069	0.933	0.000	-	0.999
Serum creatinine	−1.372	0.254	0.000	-	1.000
Serum albumin	11.985	160354.779	0.000	-	0.999

GCS: Glasgow coma scale, APACHE: Acute Physiology and Chronic Health Evaluation, T3: Triiodothyronine, FT3: Free T3, FT4: Free T4, CI: Confidence interval, OR: Odds ratio, T4: Thyroxine
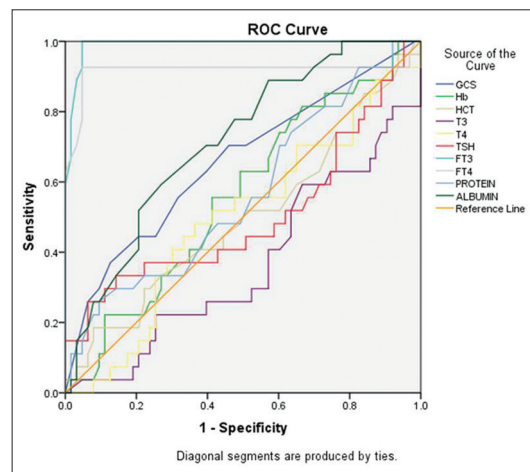

Figure 2: Receiver operating characteristic showing relationship between biochemical parameters and thyroid profile

Table 4: Multivariate logistic regression analysis for independent predictors of Intensive Care Unit mortality (summary)

Predictor	β	OR	P	−2 log likelihood	Cox and Snell R^2	Nagelkerke R^2
Model 1						
APACHE II	0.195	1.216	0.000	79.659	0.286	0.405
Model 2						
fT3	−15.509	0.000	0.004	15.075	0.652	0.924
APACHE II	0.151	1.163	0.192			
Model 3						
fT3	−133.952	0.000	0.992	0.000	0.705	1.000
APACHE II	2.239	9.382	0.996			
fT4	−40.479	0.000	0.990			
T3	88.642	3.138	0.992			

APACHE: Acute Physiology and Chronic Health Evaluation, T3: Triiodothyronine, fT3: Free T3, fT4: Free T4, OR: Odds ratio, T4: Thyroxine

mediator of this enzyme inhibition. Low T3 levels might reflect a collective measure of pathological processes occurring during critical illness, such as cardiovascular dysfunction and inflammatory status. Further studies are required to establish the role of T3 as a prognostic marker in critically ill patients.

Limitations

Our study has a few limitations. First, the presence of undiagnosed thyroid disease before ICU admission cannot be ruled out; we only clinically examined for the presence of thyroid nodule. Second, although we excluded patients on hormone replacement therapy (except those taking insulin) or those taking amiodarone, the interference of other drugs with thyroid function (e.g., furosemide, benzodiazepines, barbiturates, and dopamine) could not be completely eliminated because most of these drugs form an integral part of management of the critically ill patient. However, the fT3 levels are not much affected by the alterations in TBG levels due to the above causes.

CONCLUSION

In our study of ICU-admitted patients, we observed that fT3 was the strongest predictor of ICU mortality compared to all other parameters included in our study. Further, the combination of fT3 levels and APACHE-II scores provided for a higher probability for predicting mortality in ICU patients.

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Conflicts of interest

There are no conflicts of interest.

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