Correlation of Thyroid Hormones in the Prognosis of Critically Ill Patients

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ABSTRACT

Objective: Non-thyroidal illness syndrome (NTIS) is associated with outcomes in Intensive Care Unit (ICU) patients. The objectives of the study were to assess the prognostic value of complete thyroid profile in critically ill patients and to determine the effect of thyroid hormone level in predicting mortality when used along with acute physiology and chronic health evaluation (APACHE) II score.

Methods: The observational study was conducted at a tertiary care centre in Kolhapur, India. Critically ill adult patients admitted to intensive care units with APACHE II >10 was included (n=50). Relevant clinical investigations along with thyroid profile evaluation was carried out and APACHE II was calculated. Baseline characteristics of patients were compared. Performance of variables in predicting mortality was analysed. Correlation of APACHE II score with thyroid was also assessed in R software v-3.6.1.

Results: The survival rate at ICU discharge was 54%. Mean T3, FT3, and T4 levels were significantly low in non-survivors (p=0.006758, p=0.0245 and p=0.00070 respectively). Mean APACHE II score was significantly high in non- survivor (p=2.94E-^{06}). APACHE II score was significantly associated with the severity of disease (p=0.0235). APACHE II scores and FT3 were better predictors of mortality compared to other thyroid hormones (AUC =0.8519 ± 0.0535). FT3 showed high correlation with APACHE II score (r=-0.4083; p=0.0032). Inclusion of thyroid hormone levels with APACHE II scores improved the prediction of mortality in critically ill patients by 5.63%.

Conclusion: Among thyroid hormones, FT3 is a better predictor of mortality. Use of thyroid hormone levels in conjunction with APACHE II scores improves the prognostication.

Keywords: APACHE; euthyroid sick syndrome; thyroid (Siriraj Med J 2021; 73: 161-166)

INTRODUCTION

During critical illness, alteration in hormone levels is a commonly noted phenomenon.[1] The severity of the illness and the outcomes of the patients in Intensive care units (ICU) are associated with these alterations.[2,3] Thyroid hormones regulate the body's metabolism and immunity and thereby plays a vital role in maintaining body homeostasis.[4] Alterations in the thyroid hormone levels are characterized by relatively low levels of triiodothyronine (T3), high levels of reverse T3 (rT3) along with normal or low levels of thyroid-stimulating hormone (TSH) and thyroxine (T4); this alteration in thyroid hormone level is known as 'euthyroid sick syndrome or non-thyroidal illness syndrome' (NTIS).[5,6] Previous studies have reported the association between NTIS and outcomes in critically ill patients with various disorders such as multiple trauma, sepsis, respiratory failure, acute respiratory distress syndrome, mechanical ventilation and also in a few unselected critically ill patients.[7-12]

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Although, there are many prognostic models that considers biochemical and clinical parameters, their accuracy is low and hence not reliable.[13] The Acute physiology and chronic health evaluation (APACHE) II score with 77% accuracy is the most common method used to predict outcomes of patients in ICUs.[13] However, APACHE II scores do not consider hormonal responses, especially the levels of thyroid and cortisol hormones, which show association with outcomes in critically ill patients.[14]

Therefore, the study was designed to evaluate the usefulness of thyroid hormone levels in predicting mortality and also to ascertain if the inclusion of thyroid hormone levels at admission to ICU along with APACHE II improves mortality prediction in critically ill patients.

MATERIALS AND METHODS

The observational study was conducted at a tertiary care centre in Kolhapur, India. The study was approved by the Institutional Ethics and Research Committee (DYPU/2013/493). Written informed consent was obtained. The minimum sample size was calculated (n=~ 44) considering 80 % power with 95 % level of significance in R studio (v 1.2.5001) software using appropriate R code (pwr.t.test (effect size = 0.43, power = 0.80, significance level = 0.05, type =»one.sample»)). A total of 50 critically ill patients above the age of 18 years, admitted to the ICU with APACHE II scores > 10 were included in the study. Pregnant women, patients with a history of thyroid disease, patients on medications such as corticosteroids, dopamine, amiodarone, iodine & iodine containing contrast agents which alters the levels of thyroid hormones and those undergoing hormonal therapy for any reason were excluded.

Data regarding demographics and clinical history were recorded at the time of ICU admission. Thorough clinical examination was carried out. Total blood count, renal function, serum electrolytes, serum protein and arterial blood gas analysis were recorded, and APACHE II score was calculated for all the patients. Apart from other relevant examination, thyroid hormone analysis (T3, fT3, T4, fT4 and TSH) was done by Electro-chemiluminescence assay method on Roche Cobas e411. The normal reference ranges of thyroid hormone taken were T3 (1.2-2 nmol/L), fT3 (3.5-6.5pmol/L), T4 (70-150 nmol/L), ft4 (11.5-23 pmol/L) and TSH (0.3-4.5 µIU/L).[15]

Statistical analysis

The data collected was analysed in R software (version 3.6.1). Baseline characteristics of survivor and non-survivor patients at ICU discharge was compared by T test and Wilcoxon-Sign-Rank Test. Univariate logistic regression was used to obtain receiver operating characteristic (ROC) curve, from which AUC was calculated (cut-off value=0.5) to analyse the performance of variables in predicting mortality. Spearman Rank correlation test was used to assess the correlation of APACHE II score with thyroid profile.

RESULTS

The mean age of the participants was 53.68±14.70 years. The gender distribution was balanced with 62% male patients (n=31) and 38% female patients (n=19).

Rate of NTIS was 80% (n=40). Low Free T3 was observed in 52% cases (n=26). Whereas, low T3, T4, Free T4 and TSH were present in 40% (n=20), 44% (n=22), 38% (n=19) and 10% (n=5) of the cases, respectively. Of the 50 patients, 27 (54%) survived and were discharged from ICU.

Baseline characteristics of all the patients and the mean difference among the survivor and non-survivor patients is given in Table 1.

APACHE II score was significantly associated with the severity of disease and had the highest probability for predicting the mortality (p=0.0235; AUC=0.8519±0.0535) followed by FT3 (AUC=0.7536±0.0688) (Table 2). TSH was more likely to increase the chances of mortality (OR-0.75403; p=0.0235).

Significant negative correlation was observed between APACHE II score and T3 (r= -0.307; p=0.0302), FT3 (r= -0.4083; p=0.0032) and TSH (r=-0.2887; p=0.0419).

Significant positive correlation was observed between APACHE II score (r= 0.6106). Inclusion of thyroid hormone levels with APACHEE II scores, improves the prediction of mortality in critically ill patients by 5.63%. (Table 3, Fig 1)

DISCUSSION

Chronic critical illness is known to be linked with dysfunction of thyroid, adrenal gland and neuroendocrine axes resulting in decreased levels of various factors including thyroid hormones, insulin-like growth factor 1, sexual hormones, dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), prolactin and cortisol.[12] Therefore, this study was conducted to determine the use of thyroid hormones level along with APACHE II score for prediction of mortality in 50 critically ill patients. Majority of patients were above 40 years with a mean age of 53.68±14.70 years. Male predominance was noticed in the study (62%). Incidence of NTIS was 80%. Low levels of Free T3 in 52% of cases, T3 in 40% cases, T4 , Free T4 and TSH in 44%, 38% and 10% respectively were noticed

TABLE 1. Baseline characteristics.

Variables	All (n=50)	Survivor (n=27)	Non-survivor (n=23)	*p* - values
Mean age (years)	53.68 ± 14.70	52.04±15.22	55.61±14.16	0.3947
Male (%)	62	55	45	0.6115
Female (%)	38	53	47	1
Mean T3 [86-187 ng/dl]	89.98 ± 26.08	99.48±23.74	78.83 ± 24.67	0.006758*
Mean T4 [4.5-10.9 mcg/dl]	5.11 ± 2.13	5.72±2.15	4.39 ±1.91	0.0245*
Mean FT3 [3.10-6.80 pmol/L]	2.93 ± 1.06	3.38±1.01	2.41±0.87	0.00070*
Mean FT4 [11.4-22.1 pmol/L]	12.82 ± 3.93	13.44±3.25	12.10±4.57	0.2476
Mean TSH 0.35-5.5 mIU/L	0.86 ± 0.42	0.92±0.33	0.79±0.50	0.2936
Mean APACHE II score	24.38 ± 7.07	20.33±4.76	29.13±6.41	$2.94E^{-06*}$

*statistically significant; T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine; TSH- Thyroid stimulating hormone; APACHE- Acute Physiology And Chronic Health Evaluation

TABLE 2. Performance of variables in prediction of mortality using AUC.

Variable	AUC ROC	Sensitivity (%)	Specificity (%)
T3 [86-187 ng/dl]	0.7246 ± 0.0754	81.48	65.22
T4 [4.5-10.9 mcg/dl]	0.6844 ± 0.0790	74.07	65.22
FT3[3.10-6.80 pmol/L]	0.7536 ± 0.0688	74.07	65.22
FT4[11.4-22.1 pmol/L]	0.6457 ± 0.0856	85.19	52.17
TSH 0.35-5.5 mIU/L	0.6095 ± 0.0853	77.78	43.48
APACHE II score	0.8519 ± 0.0535	81.48	73.91

T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine;
TSH- Thyroid stimulating hormone; APACHE- Acute Physiology And Chronic Health Evaluation

TABLE 3. Inclusion of thyroid hormone level with APACHE II score in prediction of mortality.

Variables	AUC ROC	Percentage change in AUC (%)
APACHE II	0.8519	-
APACHE II + FREE T3	0.8712	1.93
APACHE II + FREE T4	0.8792	2.73
APACHE II + T3	0.88	2.81
APACHE II + T4	0.8824	3.05
APACHE II + T3 + T4 + free T3 + free T4 + TSH	0.9082	5.63

T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine;
TSH- Thyroid stimulating hormone; APACHE- Acute Physiology and Chronic Health Evaluation

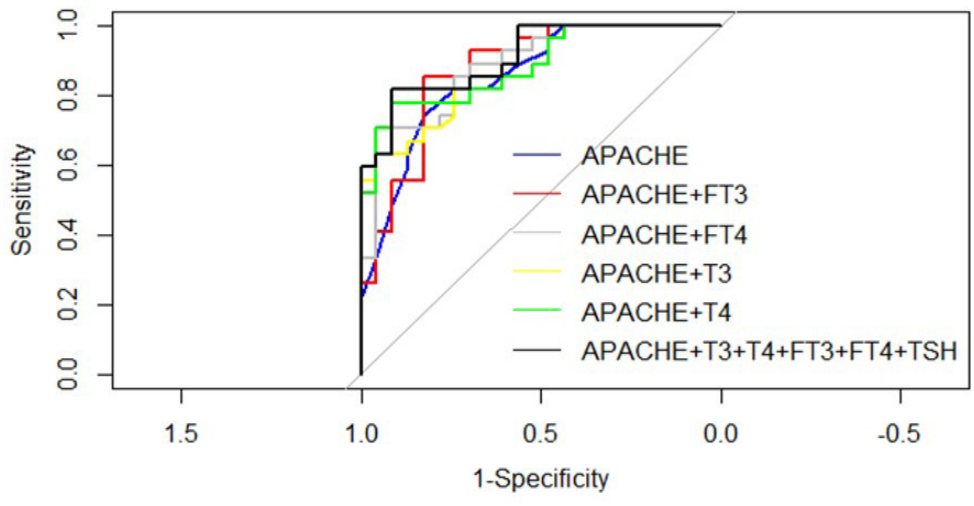

Fig 1. ROC curve showing the improvement in prediction of mortality with inclusion of thyroid level hormone.

and was probably due to the relationship between stress, illness and thyroid hormones.[15] Chronic stress leads to various illnesses ranging from mild to severe forms and also slows down the function of the thyroid gland.[15,16] Due to this, hormone production slows down resulting in fall in hormone level.[16] However, fall in the thyroid hormone level will have an effect on the functioning of the thyroid hormone including myocardial contractility, neural growth and differentiation, bone formation, regulation and resorption, metabolism, development and functioning of white and brown adipose tissue and cholesterol.[17] TSH level remains normal or slightly reduced and this is noticed in the study by low TSH in only 10% of the patients.[18] Of the cases, 56% of them survived at ICU discharge. Although, the high mean age of non-survivors depicted that there might be some correlation between age and outcome of the patients, there was no significant difference in age among both the groups (p=0.3947). This concurs with the study conducted by Gutch M et al. who also reported that there was no significant difference in age between the groups.[1] There was no significant difference in gender distribution among both the groups in this study (Male-p=0.6115; Female p=1).

Among non-survivors, the levels of T3, T4 and FT3 were significantly low (p<0.05). No significant difference was observed in FT4 levels between survivors and non-

survivors. Zargar AH et al., Hari Kumar K. V. S et al., Wang F et al. and Topla Y et al. have reported significant difference in levels of T3 and FT3 between survivor and non-survivors but not in T4 levels.[19-22] This can be attributed to the nature of illness. Interestingly, Faber J et al., has reported normal levels of FT3 and FT4 but has emphasized that reduction in T4 levels is proportional to severity of illness as well as length of illness.[23] This could be due to ultrafiltration technique which fails to exclude the thyroid hormone–binding proteins from the filtrate and gives spuriously high free hormone values.[24] No significant difference has been found in TSH level among both the groups (p=0.2936).[19-22] However, the varied assay methods may have contributed to the differences in the levels of thyroid hormone among the various studies.

APACHE II score is frequently used to predict mortality in patients with various kinds of illnesses.[25] Among the non-survivors, the APACHE II scores was significantly high indicating the severity of illness (p=2.94E-06). Khoshfetrat M et al. also reported significantly high APACHE II score among non- survivors.[26] APACHE II scores and FT3 had high probabilities in the prediction of mortality.[15] Comparatively, FT3 is highly correlated with APACHE II score (r= -0.4083; p=0.0032).[20] Hence is better suited for the prediction of mortality. Interestingly, Ray DC et al., Chinga-Alayo E et al. and Plikat et al. reported that T4, T3, FT4 and TSH are good predictors of mortality.[27-29] This difference in the findings can be attributed to the small sample size of these studies, no comparison with FT3 and population based differences.

The addition of all thyroid hormone levels to APACHE II score increases the rate of prediction by 5.63%. Plikat K et al. have also reported that considering baseline thyroid hormone levels can improve the predictive capacity of APACHE II.[29]

Usually, the dysfunction of thyroid in critically ill patients depends on the onset time of the illness. However, the study is limited as the onset time of the critical illness was not recorded. Also, the thyroid profile was assessed only during the admission to ICU. Moreover, hypothalamic pituitary axis parameters were also not considered in this study. However, considering the onset time, the more frequent assessment of the thyroid hormone profile and assessment of hypothalamic pituitary axis parameters would help in better prediction of mortality among the critically ill patients.

CONCLUSION

Among the thyroid hormones, FT3 is a better predictor of mortality. Combining thyroid hormone levels with APACHE II score improves the mortality prediction of critically ill patients and can be included as a part of the protocol in managing critically ill cases requiring intensive care.

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