RELATIONSHIP BETWEEN THYROID FUNCTION AND INTENSIVE CARE UNIT MORTALITY IN CRITICALLY ILL PATIENTS AT ZAGAZIG UNIVERSITY HOSPITAL

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ABSTRACT

Introduction: Thyroid hormones play a key role in the maintenance of body growthby modulating metabolism and the immune system. In the 20th century,researchers found that thyroid dysfunction is associated with theincreased mortality of patients admitted to the intensive care units (ICU).This study was conducted to evaluate the prognostic value of the thyroid functions; free triiodothyronine(FT3), total triiodothyronine (TT3), free thyroxin (FT4), total thyroxine (TT4) and thyroid-stimulating hormone (TSH) in unselected ICU patients.

Methods: A total of 183 unselected critically ill patients without known thyroid diseases were screened for eligibility and followed up during their ICU stay. Patient's baseline characteristics, the Acute Physiology and Chronic Health Evaluation II (APACHE II), thyroid hormones and C-reactive protein (CRP) levels were determined. The primary outcome was ICU mortality. The patients were divided into two groups; group (1) survivors and group (2) non-survivors. Potential predictors were analysed for possible association with outcomes. We also evaluated the ability of thyroid hormones together with APACHE II score to predict ICU.

Results: Among thyroid hormone functions, FT3had the greatest power to predict ICU mortality, as suggested by the largest area under the curve (AUC) of 0.838. The AUC for FT3 was nearly the same for APACHE II score (0.822) but greater than that for CRP (0.722). Multiple regression analysis revealed that FT3 and TSH levels, APACHE II score and CRP level could independently predict primary outcome. The addition of FT3 and TSH levels to APACHE II score gave an NRI of 55.80%. The level of FT3 showed a significant negative correlation with APACHE II score (r = - 0.382, p = 0.000) and with CRP (r = - 0.244, p = 0.001).The level of TSH showed a significant negative correlation with APACHE II score (r = - 0.194, p = 0.008).

Conclusion: Among thyroid functions, the serum levels of both FT3 and TSH are the most powerful and independent predictors of ICU mortality. Moreover, the addition of FT3 and TSH to APACHE II score could significantly improve the ability to predict ICU outcome.

Key words: Thyroid Function, ICU, APACHE, Mortality

INTRODUCTION

During critical illness, changes in circulating hormone levels are acommon phenomenon .These alterations are correlated with the severityof morbidity and the outcomes of patients in ICU. Thyroid hormones play a key role in the maintenance of body growthby modulating metabolism and the immune system. In the 20th century,researchers found that thyroid dysfunction is associated with theincreased mortality of patients admitted to the ICU [(1)] .

These alterations in thyroid hormone levels are referred to as"euthyroid sick syndrome" (ESS) [(2)] or"nonthyroidal illness syndrome" (NTIS) [(3)], which ischaracterized by low serum levels of FT3 and TT3and high levels of reverse T3 (rT3) accompanied by normal or low levelsof T4 and TSH.Many studies have confirmed the association between NTIS andadverse outcomes in patients with sepsis [(4)],multiple trauma [(5)], acute respiratory distress syndrome[(6)], respiratory failure [(7)], mechanicalventilation [(8)]and even in unselected ICU patients[(9)].

Although there are several validated prognostic models that use a variety of clinical and biochemical parameters, all models still far fromthe desired levels of accuracy [(10)].The score on the APACHE II is the most widely used method to predict outcomes in ICUpatients, with an accuracy that is reported to be 77% [(10)]. However, this score does not consider hormonal responses toillness, particularly serum levels of cortisol and thyroid hormones, whichhave been shown to be highly associated with mortality in critically illpatients [(11)].

SUBJECTS AND METHODS

This prospective study has been carried out on patients admitted to the ICU of Internal Medicine Department,Faculty of Medicine, Zagazig University, during the period from November 2012 to April 2014.

*** Subjects**:

A total number of 183 patients were included and were classified into two main groups:

Group I:

Included 135 survived patients (75 males and 60 females), with age ranged from 18 to 85 years with a mean value and SD of 57.16 ±15.36 years.This group was divided into 6 subgroups according to the diagnosis; 50neurological, 36 gastrointestinal, 13 renal, 21 cardiac, 10 pulmonary and 5poisoning patients.

2) Group II:

Included 48 non-survived patients (28 males and 20 females), with age rangedfrom 37 to 81 years with a mean value and SD of 60.71 ±10.58 years.This group was divided into 6 subgroups according to the diagnosis; 10neurological, 20

gastrointestinal, 2 renal, 8 cardiac, 6 pulmonary and 2sepsis patients.

***Inclusion criteria:**

Unselected critically ill patients admitted to medical ICU with their age more than 18 years.

***Exclusion criteria:**

1. Age less than 18 years old.
2. Patients who refused to enter the study.
3. History of any thyroid disease.
4. Patients with a history of pregnancy within the previous 6 months.
5. Patients under any hormonal therapy except insulin use or taking oralamiodarone.
6. Patients with palpable thyroid nodule.
7. Patients who died or were discharged from ICU within 4 hours afteradmission.
8. Patients with a history of ICU admission within the previous 6 months.

*** Methods:**

All subjects of the study were subjected to the following:

A) Thorough history and full clinical examination

B) Routine investigations:

They were all done according to the methods applied in the laboratories of Zagazig university hospitals and included:

1- Complete blood picture (by automated blood counter).

2- Liver function tests: serum albumin, measured by kinetic method

3- Renal function tests: serum creatinine.

4- Arterial blood gases.

5- Serum electrolytes: sodium and potassium.

C- Special Investigation :

Specimen collection and preparation

Measurement of TT3, TT4, FT3, FT4 and TSH using Enzyme Linked Immuno-Sorbent Assay (ELISA).Five milliliters of peripheral blood were withdrawn from each patient in plain tube.Samples were collected by venipuncture, and the samples were centrifuged.The serum was removed and stored at 2 - 8°C until testing could be performed. If not tested within 8 hours of collection, the sampleswere storedat - 70°C and tested within 1 month.

***Follow up:**

The patients' outcomes were observed after their ICU stay days formortality.

***STATISTICAL ANALYSIS**

Data were coded and entered using the statistical package SPSS version21. Data were summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparison of quantitative variables was done using unpaired Student's t-test or the Mann Whitney U test. For comparing categorical data, Chi square ($\chi 2$) test wasperformed. Exact test was used instead when the expected frequency is lessthan 5.

Correlations between variables were done using Pearson correlation coefficient. Receiver operating characteristic (ROC) curves were used to examine the performance of variables in predicting ICU mortality. The AUC was calculated from the ROC curve.

Univariate logistic regression analyses were performed to examine the association between mortality and each of the predictors separately. Odds ratio (OR) with 95% confidence intervals was calculated. We also conducted forward stepwise multivariate logistic regression analysis to determine the independent predictors of ICU mortality. Criteria of $P < 0.05$ for entry and $P \geq 0.10$ for removal were imposed in this procedure. Cox & Snell R2 and Nagelkerke R2 correlation coefficients were calculated to assess the goodness of fit of the models. P value <0.05 was taken as statistically significant

RESULTS

Table (1): Demographic data of the studied groups:

		Mortality			P value
		Survivor (n=135)	non-survivor (n=48)		
Age	Mean	57.16	60.71	T= -1.481	0.140
	Standard Deviation	15.36	10.58		
	Median	57.00	60.00		
	Minimum	18.00	37.00		
	Maximum	85.00	81.00		
Gender	Female Number (%)	60 (44.4%)	20 (41.7%)	X^2= 0.111	0.739
	Male Number (%)	75 (55.6%)	28 (58.3%)		

Table (1) describes demographic data of the studied groups and shows that there were non statistical significant differences between died and survived groups as regard age or gender (P =0.14).

Table (2): Association between diagnosis and mortality:

		Group I (survivor) (n=135)		Group II (non-survivor) (n=48)		X^2	P value	X^2	P value
		Count	%	Count	%				
DIAGNOSIS	Neurologic	50	37.0%	10	20.8%	26.3	<0.001	15.2	0.024
	GIT	36	26.7%	20	41.7%	4.5	0.02		
	Renal	13	9.6%	2	4.2%	8.06	0.009		
	Cardiac	21	15.6%	8	16.7%	5.8	0.01		
	Pulmonary	10	7.4%	6	12.5%	1.1	0.2		
	Poisoning	5	3.7%	0	0%				
	Sepsis	0	0.0%	2	4.2%				

Table (2) shows association between diagnosis and mortality in studied groups, there was significant statistical association between diagnosis and mortality in general and at the level of individual subgroups except for pulmonary subgroup.

There were 5 cases of poisoning, all of them survived and there were 2 cases of sepsis, both of them died.

Table (3): Relation between (APACHE II score, CRP, albumin and thyroid functions) and mortality in whole patients:

	Group I Survivor (n=135)		Group II Non-survivor (n=48)		T value	P value
	Mean	SD	Mean	SD		
APACHE II	13.04	6.06	20.71	6.56	-7.367	<0.001
CRP	35.60	24.27	57.25	32.38	-4.841	<0.001
Albumin	3.33	0.86	2.86	.90	3.25	0.001
TT3	.88	0.26	.88	0.26	0.104	0.917
TT4	9.87	2.39	8.45	2.84	3.36	0.003
FT3	2.00	0.42	1.39	0.51	8.03	<0.001
FT4	1.27	0.36	1.19	0.30	1.479	0.141
TSH	1.26	1.25	.88	0.28	2.115	0.001

Table (3) shows relation between APACHE II score, CRP, albumin and thyroid functions and mortality in whole cases of studied groups, there were significant statistical differences between died and survived groups as regarding APACHE II score , CRP , Albumin , FT3 , TSH and TT4 ($P < 0.05$), while there were non-significant statistical differences as regarding TT3 and FT4.

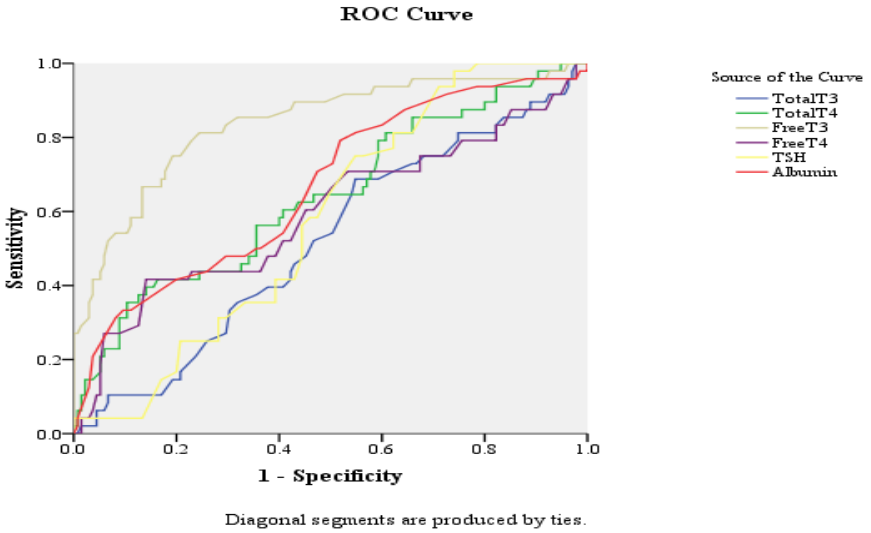
Table (4): Correlations between thyroid functions and other variables

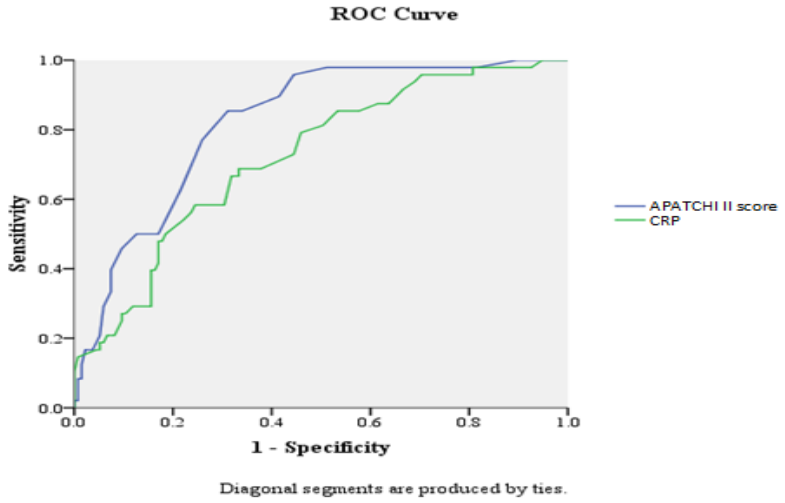
		TT3	TT4	FT3	FT4	TSH
APACHE II score	r	-0.018	-0.393**	-0.382**	-0.218**	-0.194**
	P value	0.811	0.000	0.000	0.003	0.008
	N	183	183	183	183	183
CRP	r	-0.070	-0.113	-0.244**	-0.099	-0.131
	P value	0.349	0.129	0.001	0.181	0.077
	N	183	183	183	183	183
Albumin	r	-0.134	0.646**	0.269**	0.139	0.171*
	P value	0.071	0.000	0.000	0.060	0.021
	N	183	183	183	183	183

*. Correlation is significant if ≤ 0.05.
**. Correlation is significant if ≤ 0.01.

Table (4) shows that the level of FT3 showed significant negative correlation with APACHE II score (r = - 0.382, p = 0.000), CRP (r = - 0.244, p = 0.001) and significant positive correlation with albumin (r = 0.269, p = 0.000). The level of TSH showed significant negative correlation with APACHE II score (r = - 0.194, p = 0.008) and significant positive correlation with albumin (r =0.171, p = 0.021). The level of TT4 showed significant negative correlation with APACHE II score (r = - 0.393, p = 0.000) and significant positive correlation with albumin (r = - 0.646, p = 0.000). The level of FT4 showed significant negative correlation with APACHE II score (r = - 0.218, p = 0.003). The level of TT3 showed non-significant correlation with APACHE II score, CRP or albumin.

Graph (1&2) &Table (5): ROC curve showing performance of thyroid functions,APACHE II score, CRP and albumin to predict ICU mortality in whole patients.





Test Result Variable(s)	Area under curve	P value	95% CI		Cutoff value	Sensitivity (%)	Specificity (%)
			Lower Bound	Upper Bound			
TT3	0.519	0.695	0.425	0.613			
TT4	0.640	0.004	0.547	0.734	<9.08	56.2	64.4
FT3	0.838	<0.001	0.768	0.909	<1.845	81.2	75.6
FT4	0.596	0.048	0.495	0.698	<1.215	60.4	54.8
TSH	0.579	0.106	0.495	0.662			
Albumin	0.667	0.001	0.577	0.756	<3.35	70.8	52.6
APACHE II score	0.822	<0.001	0.759	0.884	>15.5	85.4	68.9
CRP	0.722	<0.001	0.641	0.803	>37	68.8	66.7

Graph (1)&Table (5) shows that by ROC curve analysis, the best cutoff values for predicting mortality were FT3 of 1.845 with sensitivity 81.2% and specificity 75.6% (P < 0.001) , albumin of 3.35 with sensitivity 70.8% and specificity 52.% (P=0.001) FT4 of 1.215 with sensitivity 60.4% and specificity 54.8% (P=0.048) and TT4 of 9.08 with sensitivity 56.2% and specificity 64.4% (P = 0.04) . Patients with values below these cutoff values were at higher risk of mortality.

Graph (2) &Table (5) shows that by ROC curve analysis, the best cutoff values for predicting mortality were APACHE II score of 15.5 with sensitivity 85.4 % and specificity 68.9% (P < 0.001) and CRP of 37 with sensitivity 68.8% and specificity 66.7% (P < 0.001) . Patients with values above these cutoff values were at higher risk of mortality.

Table (6): Univariate logistic regression to detect odds ratios of variables (APACHE II score, CRP, albumin and thyroid functions) for predicting ICU mortality.

	B	P value	OR	95.0% CI	
				Lower	Upper
APACHE II score	**0.180**	**<0.001**	**1.197**	**1.122**	**1.277**
CRP	**0.026**	**<0.001**	**1.026**	**1.014**	**1.039**
Albumin	**-0.632**	**0.002**	**0.532**	**0.357**	**0.793**
TT3	**-0.069**	**0.917**	**0.933**	**0.255**	**3.410**
TT4	**-0.212**	**0.001**	**0.809**	**0.710**	**.921**
FT3	**-2.873**	**<0.001**	**0.057**	**0.023**	**0.142**
FT4	**-0.882**	**0.143**	**0.414**	**0.127**	**1.348**
TSH	**-1.010**	**0.019**	**0.364**	**0.157**	**0.847**

Table (6)shows that by univariate logistic regression , the increased APACHE II score and CRP could significantly predict the increased risk of mortality (odds ratio >1) while decrease albumin , TT4, FT3 and TSH could also significantly predict the increased risk of mortality (odds ratio <1), (all P <0.05). TT3 and FT4 showed a non-significant prediction for mortality.

Table (7): Multivariate logistic regression to detect independent predictors of ICU mortality.

Model		-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square		
1		156.920	0.254	0.372		
2		138.657	0.325	0.476		
3		122.617	0.382	0.558		
4		117.665	0.398	0.583		
Model		B	P value	OR	95.0% CI	
					Lower	Upper
1	FT3	-2.873	<0.001	0.057	0.023	0.142
2	APACHE II	0.142	<0.001	1.153	1.071	1.241
	FT3	-2.255	<0.001	0.105	0.041	0.269
3	APACHE II	0.184	<0.001	1.202	1.104	1.308
	FT3	-2.371	<0.001	0.093	0.034	0.254
	TSH	-1.326	0.034	0.265	0.078	0.903
4 final	APACHE II	0.172	<0.001	1.187	1.089	1.295
	CRP	0.019	0.030	1.019	1.002	1.037
	FT3	-2.329	<0.001	0.097	0.036	0.267
	TSH	-1.377	0.033	0.252	0.071	0.897

Table (7) shows that by forward stepwise multivariate logistic regression analysis , the independent predictors of ICU mortality in the final model were APACHE II score (P < 0.001) , FT3 (P < 0.001) , CRP (P = 0.03) and TSH (P=0.033).The tables also show that increasedAPACHE II score and CRP could significantly predict the increased risk of mortality (odds ratio= 1.187 and 1.019, respectively) while decreasedFT3 and TSH could also significantly predict the increased risk of mortality (odds ratio= 0.097 and 0.252, respectively).

DISCUSSION

Several endocrine disorders may be encountered in intensive care patients, either due to severe stress posed by the underlying disorder or as a result of drugs used. The most commonly encountered condition is ESS, common contributors being the underlying disorder, drugs administered and nutritional status[(1)].

The APACHE II score is the most commonly used predictor of mortality in intensive care patients. This score involves 12 routine physiological measurements, age and previous health status. It ranges from 0 to 71 points and correlates with the severity of illness [(1)].However, this score does not consider hormonalresponses to illness, particularly serum levels of cortisol and thyroid hormones, which have been shown to be highly associated with mortality in critically ill patients[(10)].

The accurate prediction of mortality among ICU patients has several potential benefits. First, accurate predictions can aid in evaluating the performance of a particular ICU. Second, they allow a more unbiased comparison of the performance of several ICUs because the predictions

canbe used to adjust for case mix. Finally, accurate predictions provide a means of "risk adjustment" that is necessaryto control for confounding variables in studiesevaluating interventions in the ICU [(10)].

In our study, we found that APACHE II scores were significantly higher in non-survivors than in survived patients (20.71± 6.65 vs 13.04±6.06; P <0.001). This is in parallel with other studies like **Chinga-Alayo et al., [(10)]and Tas et al., [(12)]**as they have reported that higher APACHE II scores were associated with higher mortality rates. We found that the levels of CRP were significantly higher in non-survivors than in survivors (57.25 ± 32.38 vs 35.6 ± 24.27; p-value <0.001). These results match the findings reported by **Wang et al., [(13)]**, who found that the levels of CRP were

significantly higher in non-survivors than in survivors and that CRP was independent predictor for mortality.

While many studies have reported association between the thyroid hormone levels and the prediction of mortality in intensive care patients like **Gou et al., (14)** and **Taset al., [12],** other studies like **Anand et al.,[15]** and **Mayer et al., [16]** have reported that measurement of thyroid hormone levels did not have any value in predicting mortality**.**

In this study, levels of FT3, TSH and TT4 were significantly lower in non-survivors than in survivors (1.39± 0.51 vs 2.00± 0.42, 0.88±0.28vs 1.26± 1.25 and 8.45± 2.84 vs 9.87± 2.39 respectively; all $P < 0.05$). The levels of FT3 were negatively correlated ($P < 0.05$) with both APACHE II score and with CRP .while levels of TSH and TT4 were negatively correlated($P < 0.05$) only with APACHE II score.

The reduction of serum thyroid hormone levels is generally agreed to be a result of concomitant impairment of both central regulation caused by decrease in the levels of TRH and the decreased pulsatile frequency of TSH secretion and by peripheral hormone metabolism caused by changes in peripheral deiodination by means of induction of type 3 deiodinase. Increased levels of cytokines,glucocorticoids, as well as catecholamines, are implicated in the dysregulation of thyroid hormones that occurs in critical illness. Moreover,elevated levels of free fatty acids and bilirubin, found in different pathological conditions, have been proposed as adjunctive factors contributing to the onset of the ESS, by indirectly promoting the reduction of hormone binding protein synthesis and the inhibition of FT3 binding to its receptor [17]**.**

Low T3 level in our study, match the results reported by **Chinga-Alayo et al., [10]** who proposed several mechanisms that may explain how acute critical illness causes lower levels of T3, a defect in the enzyme 5¯deiodinase that converts thyroxin to T3, a reduction in the number of thyroid receptors mediated by interleukin 1b and the presence of a thyroid protein binding inhibitor.

Regarding thyrotropin, **Gangemi et al., [17]**was in agreement with our study that showed that levels of TSH were significantly lower in non survivors than in survivors. This can be attributed to the feedback setting at the pitutary level with decrease the TSH response to TRH [17]**.** Also high concentrations of cytokines such as TNF-α and IL-1 which are present during critical illness may appear to be responsible for that. Cytokines appear to mediate the interaction between the immune and neuroendocrine systems. They have been shown to suppress TSH secretion via direct and indirect pathways [4]**.**

On the contrary, **Joosten et al., [18]** have found that levels of TSH were higher in non-survivors than in survivors. This can be attributed to hormonal changes in critical illness that may result in a mild physiological hypothyroidism, thereby limiting muscle breakdown and oxygen consumption. Increased TSH concentration would be consistent with this transient hypothyroidism. However, clinical signs are likely to be masked by high concentration of catecholamines and steroids that increase in critical illness [11]**).**

ROC curves were constructed to examine the performance of APACHE II score, CRP and different thyroid function as predictors of ICU mortality then AUC for each indicator was calculated. The AUC, optimal cutoff value, sensitivity and specificity of each indicator were determined. APACHE II score had an AUC of 0.82 which is less than the original published reports (area under the ROC curve 0.82 vs. 0.85 in original reports). The reason why APACHE IIscore performed less well may be that our outcome was ICU mortality instead of hospital mortality which was used in the original studies of APACHE II. Also,the eligibility criteria for our studyproduced a patient population much different from that in the original APACHE II studies [10]**.**

Among the thyroid functions, FT3 had the greatest power for predicting ICU mortality as suggested by the largest AUC of about 0.83. The AUC of FT3 was nearly the same as APACHE II score (0.82) but greater than that of CRP (0.72).

We performedunivariatelogistic regression analysis to examine the association between the ICU mortality and each indicator. The increased APACHE II score and CRP could significantly predict the increased risk of mortality (odds ratio >1) while decrease FT3, TSH and TT4 could significantly predict the increased risk of mortality (odds ratio <1); all ($P <0.05$).The same results were also reported by **Wang et al., [13]**who found that the increased APACHE II score and CRP could significantly predict the increased risk of mortality while decrease any of the thyroid hormones including TT3,TT4,FT3,FT4 or TSH could significantly predict the increased risk of mortality.

A forward stepwise multivariatelogisticregression analysis was conducted to determine the independent predictors of ICU mortality and showed that increase levels of APACHE II score and CRP could independently predict the

increased risk of mortality (odds ratio= 1.187 and 1.019 respectively) while decrease levels of FT3 and TSH could independently predict the increased risk of mortality (odds ratio= 0.097 and 0.252 respectively). The independent predictors of ICU mortality in the final model were APACHE II score (P <0.001), FT3 (P < 0.001), CRP (P = 0.03) and TSH (P=0.033).

In our study, the predictive ability of FT3 was independent of APACHE II score or CRP level. This was in agreement with**Bello et al., [8], Tas et al., [12] and Wang et al., [13].** Low FT3 levels have been hypothesized to promote the feeding-resistant catabolic state of prolonged critical illness [17]. In contrast,some studies showed that there was no association between FT3 levels and adverse outcomes of ICU patients [19].

Matching with our study, **Chinga-Alayo et al.,[10]** also reported that decrease TSH level could significantly predict the increase risk of mortality in ICU patients.Suppression of TSH secretion by high concentration of either cortisol or cytokines which are associated with a poor outcome in severe illness might explain the prognostic value of low TSH concentration. In contrast, some studies observed no association between TSH and mortality [19, 20].

Although, in our study, levels of TT4 were lower in non-survivors than in survivors, they showed a non-significant prediction of outcome and mortality of ICU patients. This is in line with that reportedby**Kumar et al., [20]**.

Also, regarding TT3 and FT4 levels, in our study, they showed a non-significant prediction of mortality in ICU patients. The same results were also reported by **Mayer et al., [16]**.

CONCLUSION

Among thyroid functions, the serum levels of both FT3 and TSH are the most powerful and independent predictors of ICU mortality. Moreover, the addition of FT3 and TSH to APACHE II score could significantly improve the ability to predict ICU outcome.

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