The Egyptian Journal of Hospital Medicine (July 2020) Vol. 80 (2), Page 857-864

Thyroid Dysfunction as a Mortality Predictor for ICU Patients

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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. These changes correlate with the outcome and mortality of critically ill patients treated in ICUs.

Objective: Our study was conducted to determine thyroid dysfunction as a risk predictor for ICU patients.

Patients and Methods: This is a prospective observational cross-sectional non-randomized hospital-based study. The study was performed at the Internal Medicine Intensive Care Units and Surgical Intensive Care Unit of Aswan University hospital at the duration between 1-6-2017 to 30-1-2019 for 200 patients.

Results: Regarding TSH, 61.8% sensitivity, 37.1% specificity, 61.3% negative predictive value and 37.6% positive predictive value. Regarding the FT3, 63.2% sensitivity, 50.8% specificity, 69.2% negative predictive value and 44.0% positive predictive value. Regarding the FT4, 15.0 was the cut off value with 61.8% sensitivity, 50.0% specificity, 68.1% negative predictive value, and 43.1% positive predictive value. It showed 54.5% Accuracy & the area under the curve (AUC) was 0.601. From results, FT3 is the most sensitive thyroid function in predicting prognosis and mortality of critically ill patients in ICU. The increase in the APACHE II score could significantly predict the increased risk of mortality while a decrease in FT3 and FT4 could significantly increase the risk of mortality.

Conclusions: FT3 was the strongest predictor of ICU mortality. Further, the combination of FT3 levels and APACHE-II scores provided for a higher probability for predicting mortality in ICU patients.

Keywords: Thyroid dysfunction, MV, ICU, FT3, APACHE-II

INTRODUCTION

During any critical illness, a common phenomenon experienced is the alteration in the levels of thyroid hormones [(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 no survivors [(7)], while others failed to show any such association [(8)]. 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 [(9)].

Some authors have reported a relationship between hypothyroxinemia and mortality in critically ill patients. More so, it has been suggested that primary hypothyroidism affects respiration by causing abnormalities in the respiratory system; however, the mechanism underlying the need for mechanical ventilation (MV) in patients with SES is still unclear [(10)].

Subsequent studies confirmed the association between NTIS and adverse outcomes in patients with sepsis, multiple trauma, acute respiratory distress syndrome respiratory failure, and mechanically ventilated patients, as well as in unselected ICU patients. However, the performance of the thyroid hormones to predict adverse outcomes in general ICU patients is unimpressive until now [(9)].

Conflicting results also existed in terms of other indicators, such as total triiodothyronine (TT3) total thyroxin (TT4) and TSH. Most of these studies were rather small and just evaluated the prognostic value of some but not the complete thyroid hormonal indicators. Until now, which one among the complete thyroid hormonal indicators is best for predicting

Received:12 /5 /2020
Accepted:22 /6 /2020

ICU mortality has not been recommended Limited studies detected the independent predictive ability of thyroid hormones or assessed additive ability of thyroid hormones to the scoring system for predicting ICU mortality [9].

APACHE II score and C-reactive protein (CPR) have been shown as independent predictors of ICU mortality. Whether thyroid hormonal indicators can predict ICU mortality independently of both predictors is unclear. The performance of these variables to predict ICU mortality has not yet been compared [9].

AIM OF THE WORK

Our study was conducted to determine thyroid dysfunction as a risk predictor for ICU patients.

PATIENTS AND METHODS

This is a prospective observational cross-sectional non-randomized hospital-based study. The study was performed at the Internal Medicine Intensive Care Units and Surgical Intensive Care Unit of Aswan University hospital at the duration between 1-6-2017 to 30-1-2019 for 200 patients who are eligible for inclusion/exclusion criteria of the study.

Inclusion criteria: Age: > 18 years old. Gender: males or females. Intensive Care Unit admitted critically ill patient. Cause of admission: any cause except thyroid dysfunction due to previous thyroid disease. Female patient is not pregnant or last delivery was more than 5 months before admission to the ICU. The patient is not receiving any hormonal medications including insulin and thyroid replacing drugs or anti-thyroid medications. Mechanical ventilation: with or without and fulfilling the ethical considerations.

Exclusion criteria: Age < 18 years old. Cause of admission: thyroid dysfunction due to previous thyroid disease. The pregnant patients or last delivery was 5 months before admission to the ICU. The patient receiving thyroid hormone preparations or anti-thyroid medications. The patient receiving hormonal medications including insulin and doesn't fulfill the ethical considerations.

All patients were subjected to the following:

For all patients who are fulfilling the inclusion and exclusion criteria of the study, all these data will be recorded: The medical history of the patient. Full examination including conscious level, vital signs, chest, heart, abdominal, neuromuscular examination. Monitor records including pulse, blood pressure, oxygen saturation, and ECG. Laboratory investigations: complete blood count, coagulation profile, renal functions, liver functions, serum electrolytes (sodium, potassium, calcium, magnesium), and arterial blood gases. CRP. All other investigations ordered for the patient including laboratory, radiological, cultures, etc. Length of stay in ICU. Daily update for all clinical, laboratory, and radiological changes. Severity assessment using the APACHE II score. Venous blood samples for thyroid function tests (TSH, FT3, and FT4) will be collected after 24 hours of ICU admission. The normal reference ranges for thyroid hormones are as following [11]**:** TSH (0.4 - 4.5 mIU/L), FT3 (4.0 - 8.0 pmol/L) and FT4 (10.0 - 24.0 pmol/L).

Any deviation from the normal range is considered abnormal: Hypothyroidism: high TSH with low FT3 and low FT4. Hyperthyroidism: low TSH with high FT3and high FT4. And Sick euthyroid syndrome (SES): low or normal TSH with low FT3 and low or normal FT4.

At the end of the study all these data were collected and analyzed to detect:

- Thyroid function and their abnormalities in ICU patients.
- Correlation between thyroid function and mortality.
- The most sensitive thyroid hormone in the detection of the prognosis of the critical illness in ICU.

Primary outcome: Correlation between thyroid abnormalities of ICU patients and mortality.
Secondary outcome: sensitivity of thyroid function as a mortality predictor for ICU patients.

Ethical approval and written informed consent :
Approval of the study was obtained from Aswan University's academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing two means. Chi-square (x^2) test of significance was used to compare proportions between two qualitative parameters. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated by MedCalc version 12.1.4.0 (MedCalc Software bvba, Mariakerke, Belgium). The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following: P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant & P-value >0.05 was considered insignificant.

RESULTS

Correlations between mortality and thyroids function status among ICU patients:

Table (1): Correlations between mortality and thyroids function status among ICU patients.

		Survived	Non-survived	R	P-value
Total patients					
Total (200 patients)		124	76	0.198	0.005*
Normal (117 patients)		82	35		
Abnormal	**Total (83 patients)**	42	41		
	Hyperthyroidism (7)	6	1		
	Hypothyroidism (34)	18	16		
	SES(42)	18	24		
Medical ICU					
Total (135 patients)		85	50	0.066	0.444
Normal (76 patients)		50	26		
Abnormal	**Total (59 patients)**	35	24		
	Hyperthyroidism (6)	5	1		
	Hypothyroidism (24)	15	9		
	SES (29)	15	14		
Surgical ICU					
Total (65 pats)		39	26	0.482	0.0001*
Normal (41 pats)		32	9		
Abnormal	**Total (24 pats)**	7	17		
	Hyperthyroidism (1)	1	0		
	Hypothyroidism (10)	3	7		
	SES (13)	3	10		

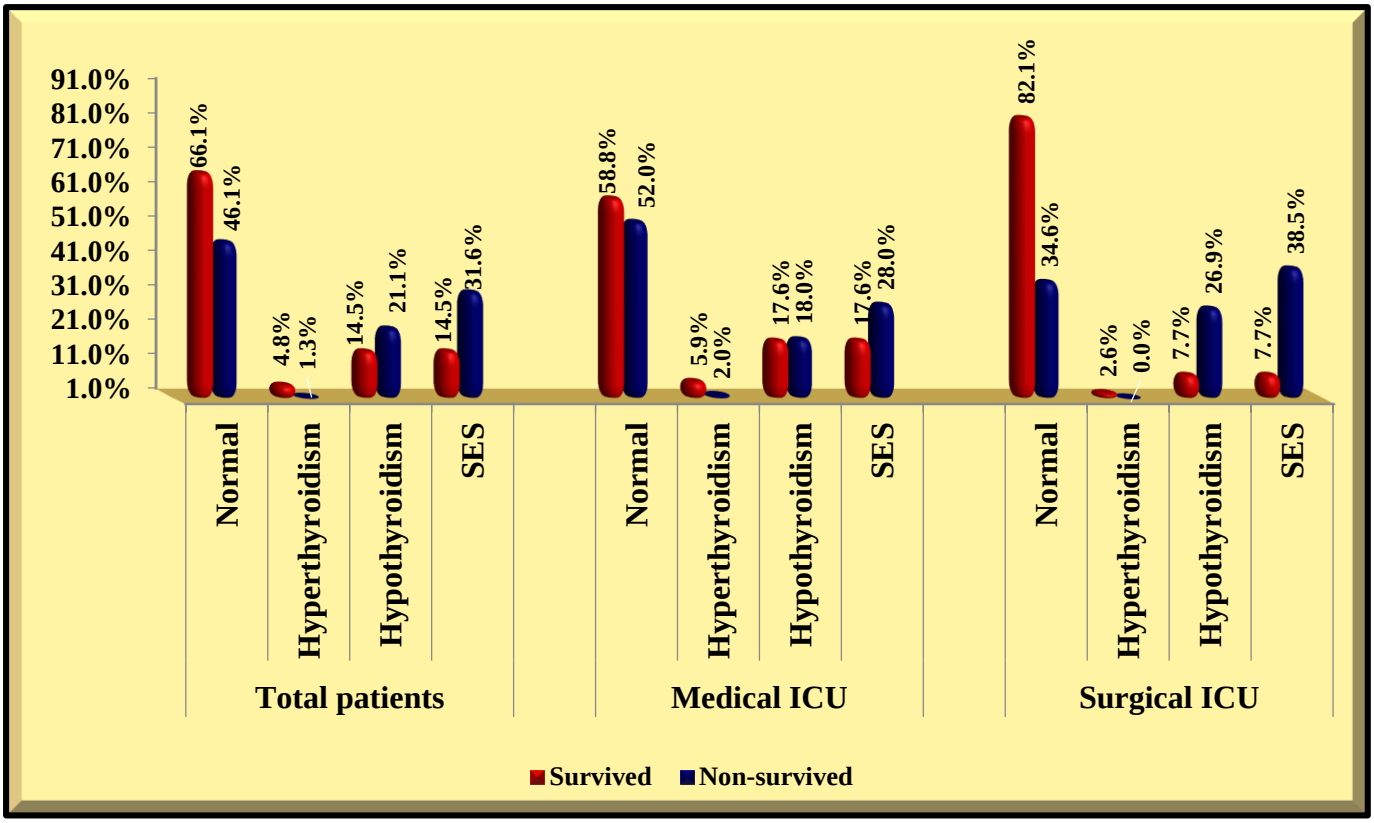

Figure (1): Survival of the study patients according to thyroid function status.

- 66.1% of the survived patients had normal thyroid status while 53.9% of the non-survived patients had abnormal thyroid status with a highly significant positive correlation between survival & thyroid function status surgical ICU patients (P=0.000). That led also to a highly significant positive correlation between survival & thyroid function status in all ICU patients (P=0.005).
- Mortality frequency among abnormal thyroid function patients was 49.4% while among normal thyroid function patients were 29.9%, which means that abnormal thyroid function in a critically ill patient who has no previous history of thyroid disease indicates poor prognosis of this patient.
- Mortality among different types of thyroid abnormalities in total patients of the study: 57.1% of total SES patients.47% of total hypothyroid patients. 14.35% of total hyperthyroid patients.

Which shows that SES patients have the highest mortality frequency compared with other thyroid abnormalities, which means SES has the worst prognosis for the critically ill patient in the ICU.

Diagnostic validity of thyroid function tests in predicting mortality:

Regarding TSH, 1.43 was the cut off value with 61.8% sensitivity, 37.1% specificity, 61.3% negative predictive value, and 37.6% positive predictive value. It showed 46.5% Accuracy & the area under the curve (AUC) was 0.507.

Regarding the FT3, 5.04 was the cut off value with 63.2% sensitivity, 50.8% specificity, 69.2% negative predictive value, and 44.0% positive predictive value. It showed 55.5% Accuracy & the area under the curve (AUC) was 0.610.

Regarding the FT4, 15.0 was the cut off value with 61.8% sensitivity, 50.0% specificity, 68.1% negative predictive value, and 43.1% positive predictive value. It showed 54.5% Accuracy & the area under the curve (AUC) was 0.601.

Regarding the APACHE II score, 28.0 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000.

Regarding CRP, 42.55 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000.

Regarding Albumin, 2.035 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000.

Table (2): Diagnostic Validity of thyroid function tests.

Diagnostic Validity		APACHE II	CRP	Albumin	TSH	FT3	FT4
AUC		1.000	1.000	1.000	0.507	0.610	0.601
P-value		0.000	0.000	0.000	0.860	0.009	0.016
95%CI	**Lower bound**	1.000	1.000	1.000	0.418	0.529	0.521
	Upper bound	1.000	1.000	1.000	0.597	0.960	0.682
Cutoff-value		28.000	42.55	2.035	1.43	5.04	15.0
Sensitivity		100%	100%	100%	61.8%	63.2%	61.8%
Specificity		100%	100%	100%	37.1%	50.8%	50%
PPV		100%	100%	100%	37.6%	44.0%	43.1%
NPV		100%	100%	100%	61.3%	69.2%	68.1%
Accuracy		100%	100%	100%	46.5	55.5%	54.5%

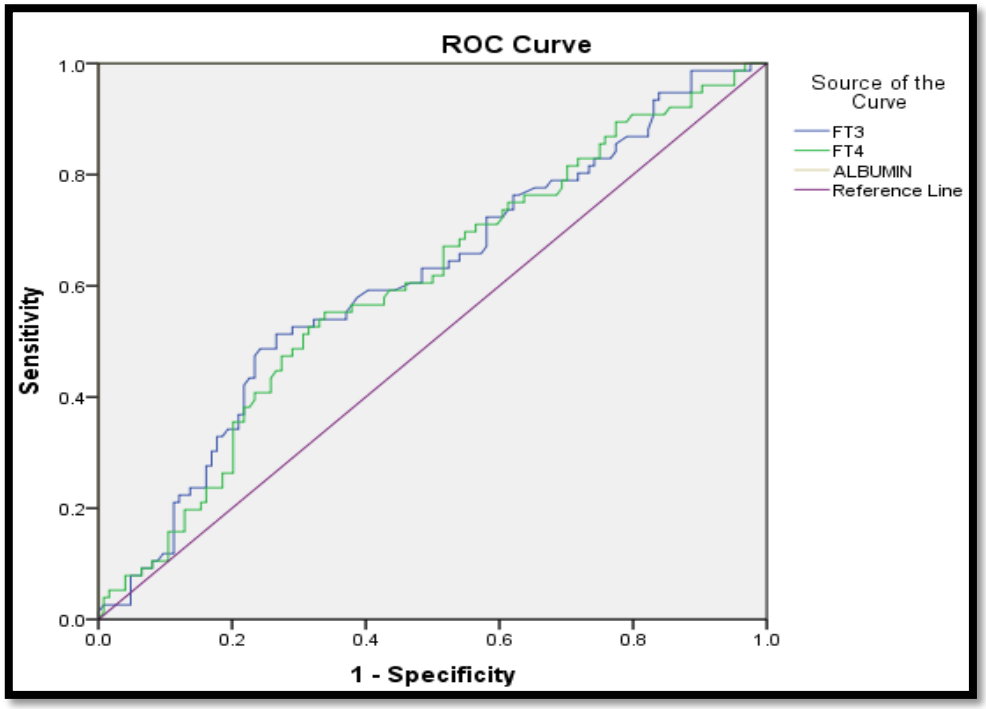

Figure (2): ROC curve for FT3, FT4, and Albumin for predicting mortality.

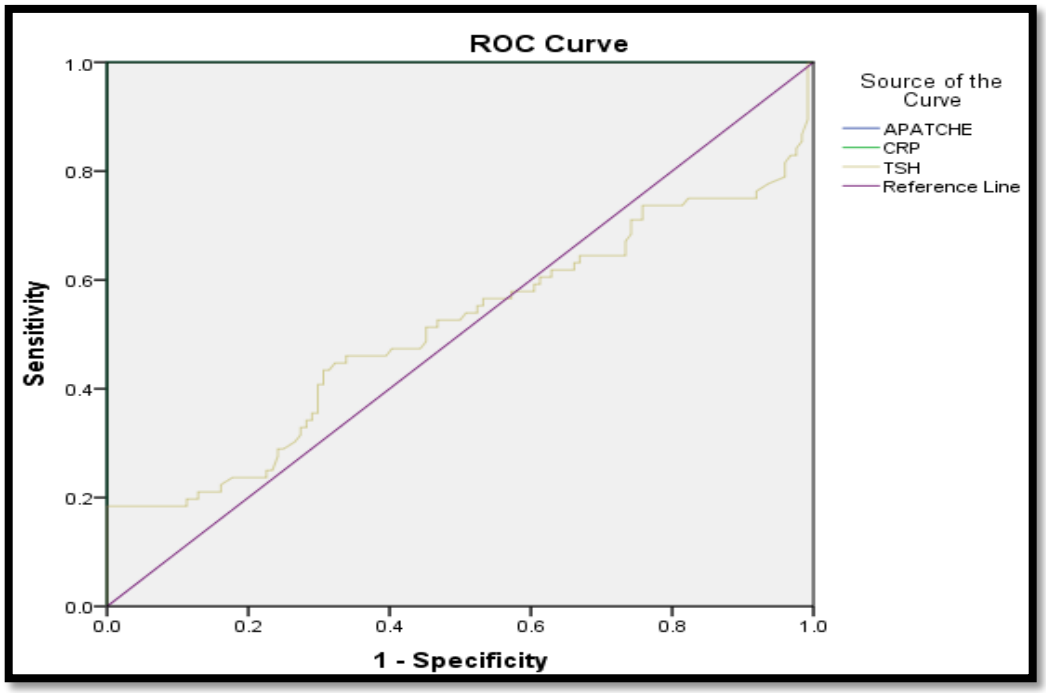

Figure (3): ROC curve for TSH, APACHE II score, and CRP for predicting mortality.

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

Mean ± SD	Survived (n=124)	Non-survived (n=79)	T	P-value
APACHE II	10.4±4.0	54.3±9.9	-43.923	< 0.001
CRP	14.1±3.6	73.5±4.7	-100.839	< 0.001
Albumin	3.3±0.4	1.6±0.3	33.429	< 0.001
FT3	4.9±2.4	3.9±2.2	2.911	0.004
FT4	14.3±7.1	11.7±6.5	2.602	0.010
TSH	2.8±2.7	7.7±13.2	-3.982	< 0.001

Regarding the relation between the 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 the APACHE II score, CRP, Albumin, and TSH (P < 0.001), FT3, FT4 (P< 0.05).

Table (4): Correlation between thyroid functions, and other variables.

		FT3	FT4	TSH
APACHE II	**R**	-0.176*	-0.161*	0.247**
	P-value	0.012	0.022	0.0001
CRP	**R**	-.199**	-0.177*	0.271**
	P-value	0.005	0.012	0.0001
Albumin	**R**	0.197**	0.170*	-0.231**
	P-value	0.005	0.016	0.001

R: Pearson correlation. **Correlation is significant at the 0.01. *Correlation is significant at the 0.05.

The level of FT3 showed significant negative correlation with APACHE II score (r = - 0.176, p = 0.012), CRP (r = - 0.199, p = 0.005) and significant positive correlation with albumin (r = 0.197, p = 0.005). The level of FT4 showed significant negative correlation with APACHE II score (r = - 0.161, p = 0.022), CRP (r = 0.177, p = 0.012) and significant positive correlation with albumin (r = - 0.170, p = 0.016). The level of TSH showed significant positive correlation with APACHE II score (r = 0.247, p = 0.000), CRP (r = 0.271, p = 0.000) and significant negative correlation with albumin (r =0.231, p = 0.001).

Table (5): Univariate logistic regression to detect an odds ratio of variables (APACHE II score, CRP, albumin &thyroid functions) for predicting ICU mortality.

	B	P-value	OR	95.0% CI	
				Lower	Upper
APACHE II	0.154	0.001*	1.166	0.095	0.224
CRP	0.622	0.001*	1.863	0.539	0.675
Albumin	-2.521	0.001*	0.080	-3.797	-1.438
FT3	-0.244	0.139	0.783	-0.567	0.116
FT4	0.045	0.400	1.046	-0.069	0.175
TSH	-0.16	0.626	0.984	-0.082	0.063

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 could also significantly predict the increased risk of mortality (odds ratio <1), (all P <0.05).

DISCUSSION

This is a prospective observational cross-sectional non-randomized hospital-based study. The study was performed at the Internal Medicine Intensive Care Units and Surgical Intensive Care Unit of Aswan University hospital at the duration between 1-6-2017 to 30-1-2019 for 200 patients who are eligible for inclusion/exclusion criteria of the study. Our study was conducted to determine thyroid dysfunction as a risk predictor for ICU patients.

The accurate prediction of mortality among ICU patients has several potential benefits. First, accurate predictions can aid in evaluating the performance of a ICU. Second, they allow a more unbiased comparison of the performance of several ICUs because the predictions can be used to adjust for case-mix. Finally, accurate predictions provide a means of "risk adjustment" that is necessary to control for confounding variables in studies evaluating interventions in the ICU [(12)].

The APACHE II score is the most 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. However, this score does not consider hormonal responses to illness, particularly serum levels of cortisol and thyroid hormones, which are highly associated with mortality in critically ill patients [(12)].

In this study, we had 117 patients with normal thyroid function, among them 82 survivors and 35 non-survivors while we had 83 patients with abnormal thyroid function, among them 42 survivors and 41 non-survivors. In other words, we observed:

66.1% of the survived patients had normal thyroid status while 53.9% of the non-survived

patients had abnormal thyroid status with a highly significant positive correlation between survival & thyroid function status surgical ICU patients. That led also to a highly significant positive correlation between survival & thyroid function status in all ICU patients. Mortality frequency among abnormal thyroid function patients was 49.4% while among normal thyroid function patients were 29.9%, which means that abnormal thyroid function in a critically ill patient who has no previous history of thyroid disease indicates poor prognosis of this patient. Mortality among different types of thyroid abnormalities in total patients of the study: 57.1% of total SES patients. 47% of total hypothyroid patients. 14.35% of total hyperthyroid patients.

Which shows that SES patients have the highest mortality frequency compared with other thyroid abnormalities, which means SES has the worst prognosis for the critically ill patient in the ICU.

These results of our study are matching with many studies that have reported an association between the thyroid hormone levels and the prediction of mortality in intensive care patients like **Tas *et al.* [12].**

Our study resulted in levels of FT3, TSH and FT4 were significantly lower in non-survivors than in survivors. The levels of FT3 were most sensitive in the prediction of the prognosis of critical illness when compared to its level between survivors and non-survivor patients of the study with P-value < 0.05 followed by FT4 level.

Regarding TSH, 1.43 was the cut off value with 61.8% sensitivity, 37.1% specificity, 61.3% negative predictive value, and 37.6% positive predictive value. It showed 46.5% Accuracy & the area under the curve (AUC) was 0.507. Regarding the FT3, 5.04 was the cut off value with 63.2% sensitivity, 50.8% specificity, 69.2% negative predictive value, and 44.0% positive predictive value. It showed 55.5% accuracy & the area under the curve (AUC) was 0.610. Regarding the FT4, 15.0 was the cut off value with 61.8% sensitivity, 50.0% specificity, 68.1% negative predictive value, and 43.1% positive predictive value. It showed 54.5% accuracy & the area under the curve (AUC) was 0.601. From results, FT3 is the most sensitive thyroid function in predicting prognosis and mortality of critically ill patients in ICU.

Regarding the APACHE II score, 28.0 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000. Regarding CRP, 42.55 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000. Regarding Albumin, 2.035 was the cut off value with 100% sensitivity, 100% specificity, 100% negative predictive value, and 100% positive predictive value. It showed 100% Accuracy & the area under the curve (AUC) was 1.000.

Low FT3 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 FT3, a defect in the enzyme 5 deiodinase that converts thyroxin to FT3, 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.* [13]**, disagreed 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 pituitary level with decrease TSH response to TRH **[13].** 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 **[14].**

On the contrary, **Joosten *et al.* [15],** 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 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 a high concentration of catecholamines and steroids that increase in critical illness **[16].**

The reduction of serum thyroid hormone levels is generally agreed to be a result of concomitant impairment of both central regulations caused by a 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 through 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[13].

In this study, we performed a univariate logistic regression between different variate of mortality predictors for this type of patient as APACHE score, CRP and albumin to compare them

with thyroid function as a main mortality predictor in the study. We found that the increased APACHE II score and CRP could significantly predict the increased risk of mortality while decrease FT3 and FT4 could significantly predict the increased risk of mortality. The same results were also reported by **Wang *et al.* [9],** 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.

In our study, the predictive ability of FT3 was independent of the APACHE II score nor CRP level. This agreed with **Bello *et al.* [7], Wang *et al.* [9], and Tas *et al.* [12],** Low FT3 levels have been hypothesized. To promote the feeding-resistant catabolic state of prolonged critical illness [13]. In contrast, some studies showed that there was no association between FT3 levels and adverse outcomes of ICU patients [8].

CONCLUSION

The goal of thyroid function tests in the ICU should mainly be the identification of previously unrecognized thyroid dysfunction that would require therapeutic intervention. When hypothyroidism is suspected clinically in an ICU patient (e.g. hypothermia, bradycardia, respiratory acidosis, pleural effusions, failure to wean), and the evaluation suggests central hypothyroidism, one should consider, that the probability of euthyroid sick syndrome is much higher than the pituitary or hypothalamic disease. If hyperthyroidism is suspected (e.g. tachyarrhythmias, widened pulse pressure, respiratory alkalosis, high-output heart failure) and low TSH is detected, true hyperthyroidism, is unlikely unless the TSH is suppressed fully on a third-generation assay and the free T4 is elevated or at least in the upper limits of the normal range.

Mortality increased with patients had abnormal thyroid functions which indicate that thyroid functions can expect poor prognosis of ICU patients. FT3 was found the most sensitive among thyroid function in the detection of the prognosis of the critical illness. We recommend adding FT3 to the APACHE II score as one of mortality prediction in ICU.

REFERENCES

1. **Van den Berghe G (2003):** Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin North Am., 32:385–410.
2. **Marx C, Petros S, Bornstein SR *et al.* (2003):** Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: Diverse time course of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol. Crit Care Med., 31:1382–1388.
3. **Schuetz P, Müller B, Nusbaumer C *et al.* (2009):** Circulating levels of GH predict mortality and complement prognostic scores in critically ill medical patients. Eur J Endocrinol., 160:157–63.
4. **Slag MF, Morley JE, Elson MK *et al.* (1981):** Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA., 245:43–5.
5. **McIver B, Gorman CA (1997):** Euthyroid sick syndrome: An overview. Thyroid, 7:125–32.
6. **De Groot LJ (1999):** Dangerous dogmas in medicine: The nonthyroidal illness syndrome. J Clin Endocrinol Metab., 84:151–64.
7. **Bello G, Pennisi MA, Montini L *et al.* (2009):** Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. Chest, 135:1448–54.
8. **Ray DC, Macduff A, Drummond GB *et al.* (2002):** Endocrine measurements in survivors and non-survivors from critical illness. Intensive Care Med., 28:1301–8.
9. **Wang F, Pan W, Wang H *et al.* (2012):** Relationship between thyroid function and ICU mortality: A prospective observational study. Critical Care, 16: 11.
10. **Chinga-Alayo E, Villena J, Evans AT *et al.* (2005):** Thyroid hormone levels improve the prediction of mortality among patients admitted to the intensive care unit. Intensive Care Medicine, 31(10): 1356-1361.
11. **Tognini S, Marchini F, Dardano A *et al.* (2009):** Non-thyroidal illness syndrome and short-term survival in a hospitalized older population. Age and Ageing, 39(1): 46-50.
12. **Tas A, Tetiker T, Beyazit Y *et al.* (2012):** Thyroid hormone levels as a predictor of mortality in intensive care patients: A comparative prospective study. Wiener Klinische Wochenschrift, 124(5-6): 154-159.
13. **Gangemi EN, Garino F, Berchialla P *et al.* (2008):** Low triiodothyronine serum levels as a predictor of poor prognosis in burn patients. Burns, 34(6): 817-824.
14. **Angelousi AG., Karageorgopoulos DE, Kapaskelis AM *et al.* (2011):** Association between thyroid function tests at baseline and the outcome of patients with sepsis or septic shock: a systematic review. European Journal of Endocrinology, 164(2): 147-155.
15. **Joosten KFM, De Kleijn ED, Westerterp M *et al.* (2000):** Endocrine and metabolic responses in children with meningococcal sepsis: striking differences between survivors and nonsurvivors. The Journal of Clinical Endocrinology & Metabolism, 85(10): 3746-3753.
16. **Rothwell PM, Lawler PG (1995):** Prediction of outcome in intensive care patients using endocrine parameters. Critical Care Medicine, 23(1): 78-83.