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Thyroid Dysfunction and Critical Illness in Intensive Care Unit Patients of Aswan University Hospital

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ABSTRACT

Background: Thyroid hormones play an essential role in human metabolism. Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease.

Objective: This study was conducted to evaluate frequency of thyroid dysfunction in Intensive Care Unit patients of Aswan University Hospital and to correlate between thyroid dysfunction and susceptibility for mechanical ventilation. **Patients and methods:** This was a cross-sectional non randomized study was conducted at Internal Medicine Intensive Care Units and Surgical Intensive Care Unit of Aswan University Hospital on 200 patients who were eligible to inclusion/exclusion criteria of the study. Thyroid function test of TSH, FT3 and FT4 levels were investigated for all patients and were compared and correlated with the clinical data of those patients. **Results:** Thyroid function abnormalities are common in critically ill patients who didn't have abnormal thyroid functions before and more common in female patients than males. There was a correlation between abnormal thyroid functions in critically ill patients and their mortality and more in sick euthyroid syndrome patients. There was no relation between abnormal thyroid functions in critically ill patients and their increased susceptibility for mechanical ventilation.

Conclusions: Thyroid function abnormalities are common in ICU patients, reflecting the prognosis and affect the clinical outcome for those patients.

Keywords: Thyroid, Critical, Illness, ICU.

INTRODUCTION

Thyroid hormones play an essential role in human metabolism as they support anabolism, share in cardiovascular system function (increase myocardial contractility and cardiac output) by secreting triiodothyronine (T3) and thyroxine (T4). Thyroid stimulating hormone (TSH) which is secreted by the pituitary gland is adjusting serum levels of thyroid hormones [(1)].

Euthyroid sick syndrome (ESS) is described as abnormalities in circulating thyroid hormone levels without pre-existing hypothalamic pituitary or thyroid gland dysfunction in the setting of non-thyroidal Illness (NTI). It reverts back to normal after recovery from the NTI [(2)]. ESS is characterized by low triiodothyronine (T3), low or normal thyroxine (T4) and low or normal thyroid stimulating hormone (TSH). Three patterns are described in ESS; Type1 or low T3 syndrome (low T3 only), type 2 or low T4 syndrome (low T3 and T4) and type 3 or low TSH syndrome (low T3, T4, and TSH) [(3)]. Under normal circumstances 100% of T4 and 10-20% of T3 are directly secreted by the thyroid gland. 5`deiodinase is an enzyme causes peripheral monodeiodination of T4 transforming it to T3 and that step resulting in 80-90% of T3. This enzyme also increases the clearance of the inactive isomer reverses T3 (rT3), which is derived by the action of 5` deiodinase on T4 [(4)]. Critical illness decreases 5`deiodinase activity, thereby, decreasing T4 to T3 conversion and rT3 clearance. Increased metabolic clearance of T4 in critical illness further diverts T4 to form the inactive isomer rT3. Thus, T3 decreases and rT3 increases. Several mechanisms can contribute to the inhibition of 5`-monodeiodination and therefore to the low serum T3 concentration in critically ill patients with NTI [(5)]. Some authors have reported a relationship between hypothyroxinaemia and mortality in critically ill patients. Moreover, 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 sick euthyroid syndrome (SES) is still unclear [(6)].

AIM OF THE WORK

This study was conducted to evaluate frequency of thyroid dysfunction in Intensive Care Unit patients of Aswan University Hospital and if there is correlation between thyroid dysfunction and possible susciptibility for mechanical ventilation.

PATIENTS AND METHODS

This is a prospective observational cross-sectional non randomized hospital-based study. The study was conducted at Internal Medicine Intensive Care Units and Surgical Intensive Care Unit of Aswan University

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Hospital at the duration between 1-6-2017 to 30-1-2019 on 200 patients who are eligible to 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.
- Patient is not receiving any hormonal medications including insulin and thyroid replacing drugs.
- Patient is not receiving anti-thyroid medications.
- Mechanical ventilation: with or without.
- Fulfilling the ethical considerations.

Exclusion criteria:

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

PATIENTS AND METHODS

For all patients who are fullfilling 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 and 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 at ICU.
- Daily update for all clinical, laboratory and radiological changes.
- Severity assessment using APACHE II score.
- Venous blood samples for thyroid function tests (TSH, FT3, and FT4) will be collected after 24 hours ICU admission. The normal reference ranges for thyroid hormones are as following [7]:
  - TSH (0.4 - 4.5 mIU/L)
  - FT3 (4.0 - 8.0 pmol/L)
  - FT4 (10.0 - 24.0 pmol/L)

Any deviation from the normal range is considered to be abnormal:

- Hypothyroidism: high TSH with low FT3 and low FT4.
- Hyperthyroidism: low TSH with high FT3 and high FT4.
- Sick euthyroid syndrome (SES): low or normal TSH with low FT3 and low or normal FT4.

- Respiratory parameters of the patient will be recorded regularly including:
  - respiratory rate
  - chest auscultation
  - Sao2
  - PO2

To correlate the respiratory parameters with the laboratory result of thyroid function and if there is a relation between thyroid function and the need of the patient for mechanical ventilation.

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

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

Ethical considerations:

The study was approved by the Ethics Board of Aswan University.

The confidentiality of all participants admitted to this study was protected to the fullest extent possible. The study participants were not be identified by name in any report or publication resulting from data collected in this study. Ethical aspects whether substantial or procedural were implicated in this study.

Before participants are admitted in this study, the purpose and nature of the study as well as the risks were explained to the patients or their relatives (as patients of this study mostly will not be fully conscious). The participants' relatives agreed that he/she will have the investigational nature of the study, its inherent risks and benefits, they have rights to terminate participation in this study without affecting patient's rights in having proper health care in the study site, whom to contact with questions regarding the study and they are freely given an informed consent to participate in this study. The signed informed consent form was a permanent part of the participant's study records and will be maintained in the same manner as other records.

Statistical methods

The collected data were revised, coded, tabulated and computed by using statistical package for social science (SPSS) version 23.0 for windows (SPSS Inc, Chicago, IL, USA). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. For descriptive statistics, mean and standard deviation (± SD) and for parametric

numerical data, percentage of non-numerical data. P-value: level of significance, > 0.05: non-significant (NS). P≤ 0.05: significant (S).

RESULTS

Table (1): Thyroid function tests & status among study patients

		Total patients	Medical ICU	Surgical ICU
TSH (mU/L)	**Mean ± SD**	4.7 ± 1.1	4.9 ± 1.2	4.2 ± 1.05
FT3 (mU/L)	**Mean ± SD**	4.6 ± 1.01	4.6 ± 1.05	4.5 ± 1.02
FT4 (ng/dL)	**Mean ± SD**	13.3 ± 3.25	13.4 ± 3.14	12.8 ± 2.9
		Total patients	**Medical ICU**	**Surgical ICU**
Total patients		200	135	65
Normal		117	76	41
Abnormal	**Total**	83	59	24
	Hyper-thyroidim	7	6	1
	Hypo-thyroidism	34	24	10
	SES	42	29	13

Regarding thyroid function tests, TSH ranged from 0.01 – 52.7 with mean of 4.7 in total study patients, from 0.01 – 52.7 with mean of 4.9 in medical ICU patients and from 0.12 – 38.5 with mean of 4.2 in surgical ICU patients. FT3 ranged from 1.12 – 13.6 with mean of 4.6 in total study patients, from 1.13 – 13.2 with mean of 4.6 in medical ICU patients and from 1.12 – 13.6 with mean of 4.5 in surgical ICU patients.

FT4 ranged from 2.12 – 35.6 with mean of 13.3 in total study patients, from 2.12 – 35.6 with mean of 13.4 in medical ICU patients and from 2.12 – 32.7 with mean of 12.8 in surgical ICU patients (Table 1).

Regarding thyroid function status, the commonest result of thyroid function among ICU patients who were known not to have previous history of any thyroid disease was normal thyroid function.

Among total study patients, normal thyroid status was found in 58.5% while abnormal thyroid status was in 41.5% subdivided as hyperthyroidism in 3.5%, hypothyroidism in 17% and SES in 21%. Among medical ICU patients normal thyroid status was in 56.3% while abnormal thyroid status was in 43.7% subdivided as hyperthyroidism in 4.4%, hypothyroidism in 17.8% and SES in 21.5%. Among surgical ICU patients normal thyroid status was in 63.1% while abnormal thyroid status was in 36.9% subdivided as hyperthyroidism in 1.5%, hypothyroidism in 15.4% and SES in 20% (Figure 1).

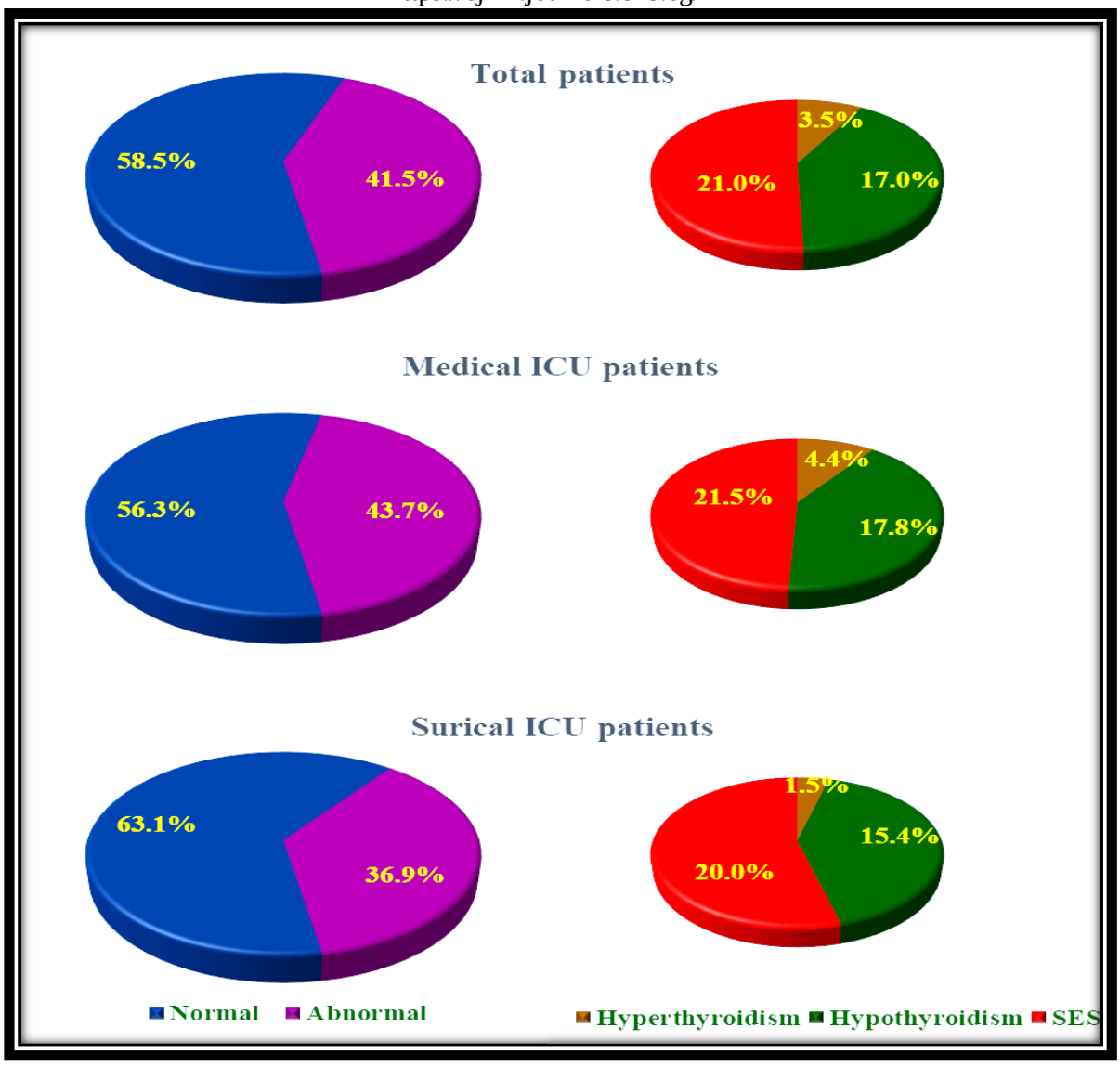


Figure (1): Thyroid function status among study patients.

Commonest thyroid function abnormalities in the study according to their frequency, SES was found in 50.6% of all abnormal thyroid function patients of the study. Hypothyroid was found in 41% of all abnormal thyroid function patients of the study. Hyperthyroid was found in 8.4% of all abnormal thyroid function patients of the study.

Commonest thyroid function abnormalities in each ICU according to their frequency: (1) Medical ICU: SES was found in 49.1% of its abnormal thyroid function patients. Hypothyroid was found in 40.7% of its abnormal thyroid function patients. Hyperthyroid was found in 10.2% of its abnormal thyroid function patients. (2) Surgical ICU: SES was found in 54.2% of its abnormal thyroid function patients. Hypothyroid was found in 41.7% of its abnormal thyroid function patients. Hyperthyroid was found in 4.2% of its abnormal thyroid function patients.

Table (2): Correlations between gender and thyroids function status among ICU patients.

	Normal	Abnormal	R	P-value
Total patients				
Total (200 patients)	117	83	0.396	0.000*
Male (114 patients)	86	28		
Female (86 patients)	31	55		
Medical ICU				
Total (135 patients)	76	59	0.357	0.000*
Male (73 patients)	53	20		
Female (62 patients)	23	39		
Surgical ICU				
Total (65 patients)	41	24	0.472	0.000*
Male (41 patients)	33	8		
Female (24 patients)	8	16		

R: Pearson correlation. p-value significant <0.05.

73.5% of patients with normal thyroid status were males while 66.3% of patients with abnormal thyroid status were females with a highly significant positive correlation between gender & thyroid function status in both medical & surgical ICU patients (P-value =0.000, both). This led also to a highly significant positive correlation between gender & thyroid function status in all ICU patients (P-value =0.000). 64% of total female patients of the study were found to have abnormal thyroid functions, while 24.6% of total male patients of the study were found to have abnormal thyroid functions.

66.3% of total abnormal thyroid function patients of the study were found to be females, while 33.7% of total abnormal thyroid function patients of the study were found to be males.

Those observations confirm the concept of thyroid dysfunction and diseases are common in females more than males.

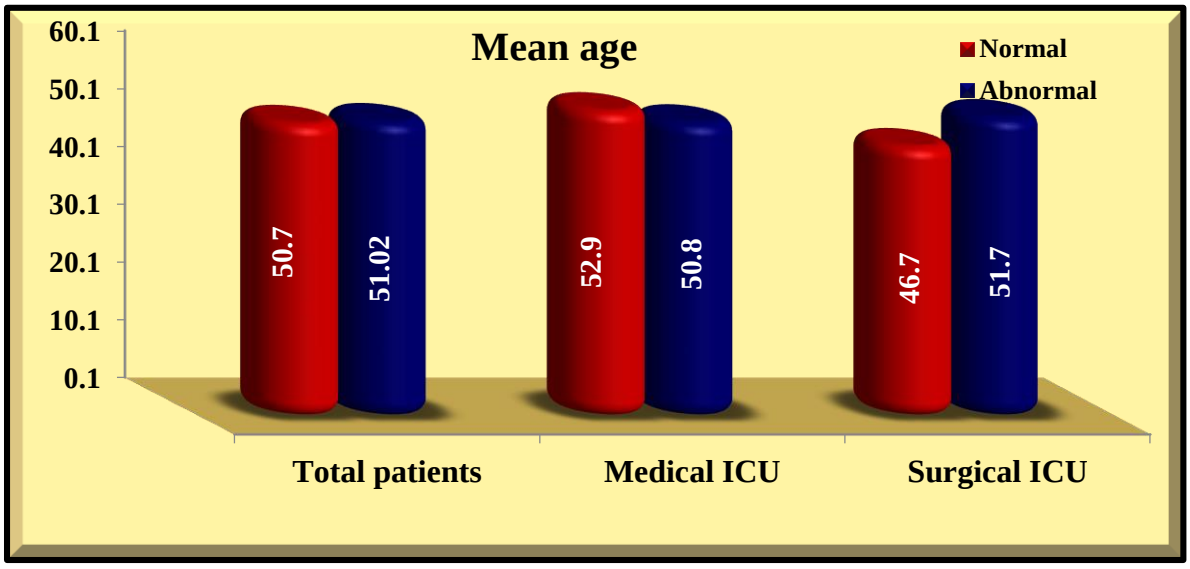


Figure (2): Age among study patients according to thyroid function status.

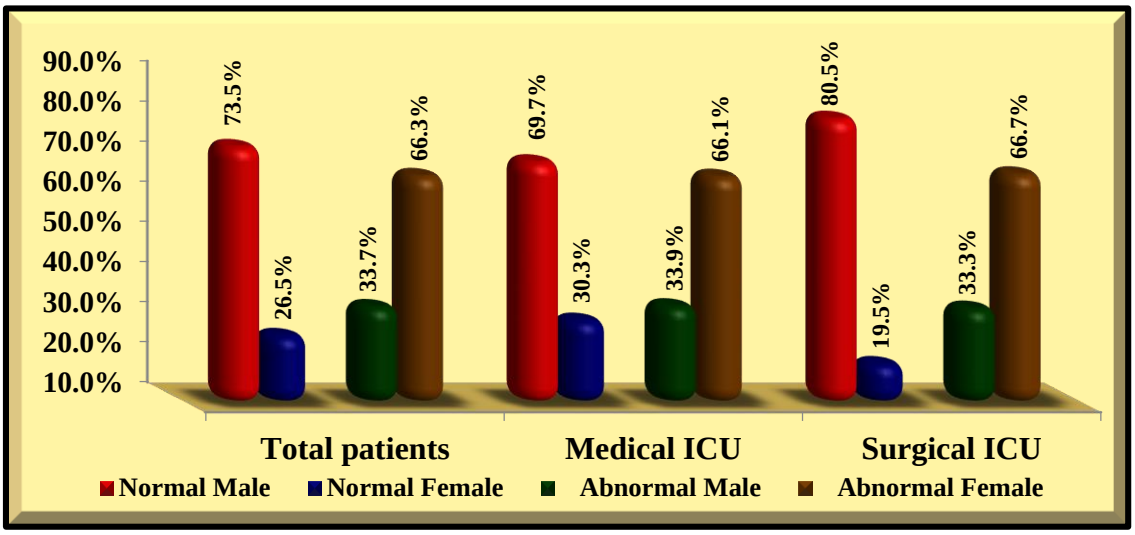


Figure (3): Gender among study patients according to thyroid function status.

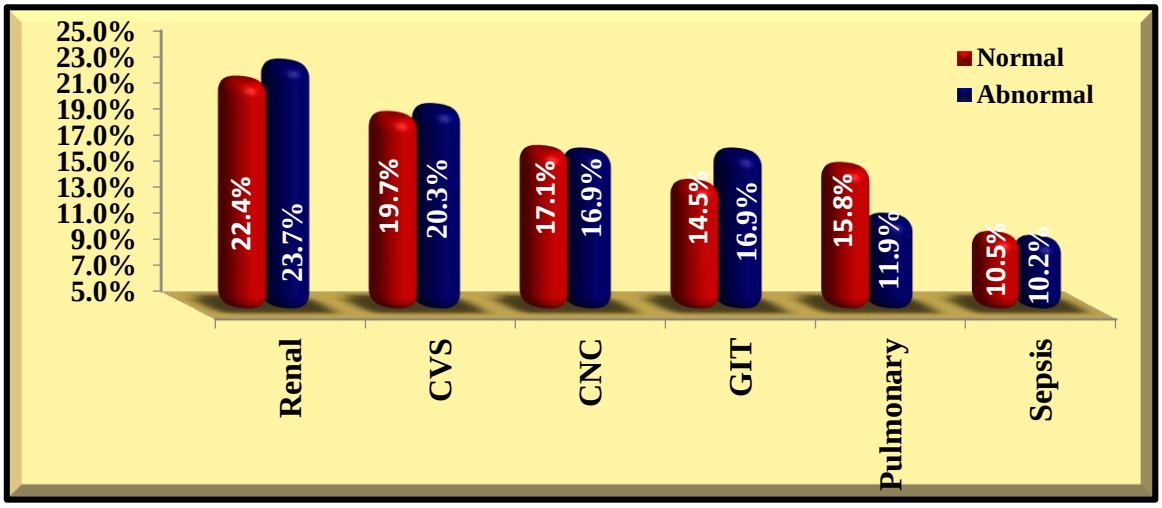


Figure (4): Frequency of thyroid function in medical ICU patients in each diagnosis.

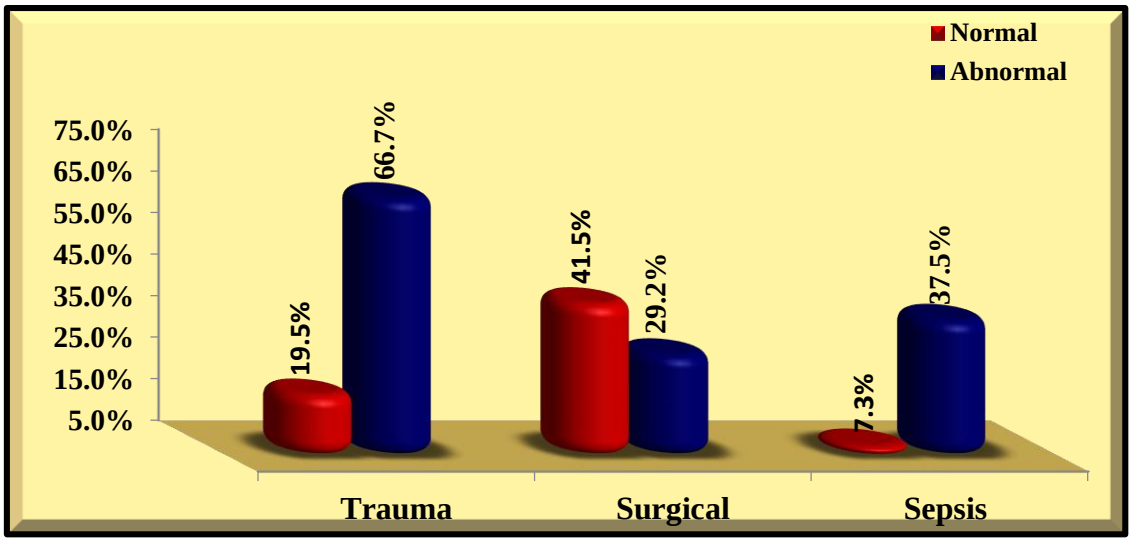


Figure (5): Frequency of thyroid function in surgical ICU patients in each diagnosis**.**

Table (3): Baseline characteristics of the patients stratified by thyroid function status.

	Normal	Abnormal	Hyperthyroidism	Hypothyroidism	SES
Total patients					
Age					
Mean ± SD	50.7 ± 14.6	51.02 ±	39.6 ± 13.8	52.0 ± 14.2	50.7 ± 14.6
Gender no					
Total (200	117	83	7	34	42
Male (114	86	28	1	12	15
Female (86	31	55	6	22	27
Medical ICU					
Age					
Mean ± SD	52.9 ±	50.8 ± 14.2	38.2 ± 14.6	51.8 ± 14.0	52.5 ± 13.4
Gender no					
Total (135	76	59	6	24	29
Male (73 patients)	53	20	1	9	10
Female (62	23	39	5	15	19
Diagnosis no					
Renal 31	17	14	1	5	8
CVS 27	15	12	2	3	7
CNS 23	13	10	1	6	3
GIT 21	11	10	1	4	5
Pulmonary 19	12	7	1	3	3
Sepsis14	8	6	0	3	3
Surgical ICU					
Age					
Mean ± SD	46.7 ±	51.7 ± 15.0	48.0	50.8 ± 16.5	46.7 ± 14.5
Gender no					
Total (65	42	24	1	10	13
Male (41 patients)	33	8	0	3	5
Female (24	8	16	1	7	8
Diagnosis no					
Trauma 29	21	8	0	2	6
Surgical 24	17	7	1	3	3
Sepsis 12	3	9	0	4	5

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). This 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 was 29.9%, which meant that abnormal thyroid function in critically ill patient who has no previous history of thyroid disease indicates poor prognosis of this patient.

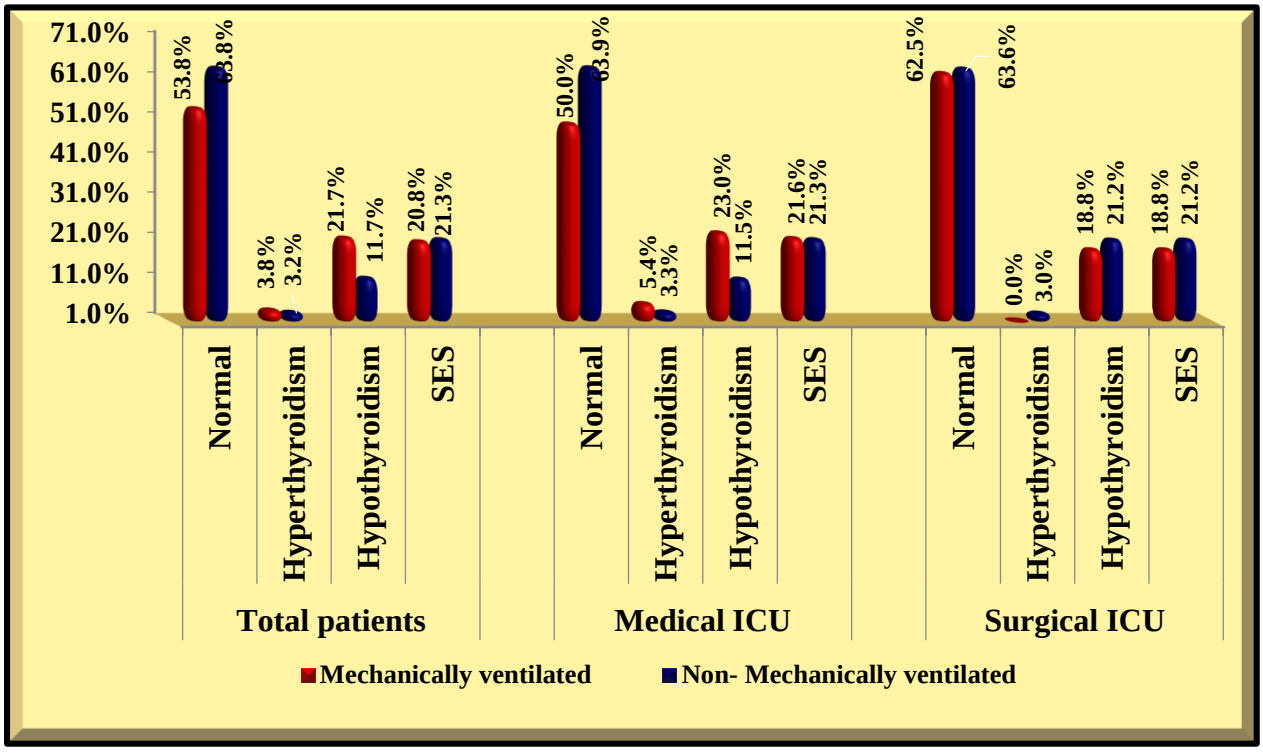
Mortality among different types of thyroid abnormalities in total patients of the study: 57.1% of total SES patients. 47% of total hypothyroid patients. 14.35% of total hyperthyroid patients. Which showed that SES patients had highest mortality frequency compared to other thyroid abnormalities, which meant that SES had the worst prognosis for the critically ill patient in the ICU.

Mechanical ventilation among patients of the study:

Table (4): Correlations between mechanical ventilation and thyroids function status among ICU patients

		Mechanically ventilated	Non- Mechanically ventilated	R	P-value
Total patients					
Total (200)		106	94	-0.102	0.151
Normal (117)		57	60		
Abnormal	**Total (83)**	49	34		
	Hyperthyroidism(7)	4	3		
	Hypothyroidism(34)	23	11		
	SES(42)	22	20		
Medical ICU					
Total (135)		74	61	-0.140	0.106
Normal (76)		37	39		
Abnormal	**Total (59)**	37	22		
	Hyperthyroidism(6)	4	2		
	Hypothyroidism(24)	17	7		
	SES (29)	16	13		
Surgical ICU					
Total		32	33	-0.012	0.926
Normal(41)		20	21		
Abnormal	**Total (24)**	12	12		
	Hyperthyroidism(1)	0	1		
	Hypothyroidism(10)	6	4		
	SES (13)	6	7		

Figure (6): Mechanical ventilation of the study patients according to thyroid function status.



Frequency of mechanical ventilation among thyroid function of all patients: 48.7% of normal thyroid function patients were mechanically ventilated. 59% of abnormal thyroid function patients were mechanically ventilated. Which meant that mechanical ventilation was higher in abnormal thyroid function patients and confirms the previous observation of abnormal thyroid function in ICU patient who had no previous thyroid illness indicates more poor prognosis compared with normal thyroid function patient. Among abnormal thyroid function, hypothyroid patients had the highest frequency percentage of mechanical ventilation with 67.6% of total hypothyroid patients, followed by hyperthyroid and SES patients who had frequency percentages of 57.1% and 52.4% of total hyperthyroid and SES patients respectively. This observation suggest the effect of hypothyroidism on hypoventilation. Though the frequency, but p-value (in comparison between the 2 groups of mechanically ventilated and non-mechanically ventilated patients) suggested no significant correlation between mechanical ventilation and thyroid function status among ICU patients.

DISCUSSION

Thyroid hormones play an essential part in human metabolism. Thyroid hormones support anabolism, intricate in cardiovascular system function (increase heart contractility and cardiac output) and reduce triiodothyronine/reverse triiodothyronine (T3/rT3) ratio, which frequently relates to normal or low thyroid stimulating hormone (TSH) and thyroxine (T4) levels [8]. Euthyroid sick syndrome (ESS) is considered when patients with non-thyroidal illness (NTI) demonstrate abnormal thyroid function. Among ICU patients, ESS or low-T3 syndrome is more common than true hypothyroidism [2].

With no previous intrinsic thyroid disease [9, 10, 11], ESS is the commonest endocrine change seen in critically ill patients [12]. It is described as abnormalities in circulating thyroid hormone levels without pre-existing hypothalamic pituitary or thyroid gland dysfunction in the setting of a Non-Thyroidal Illness (NTI) [13]. It reverts back to normal after recovery from the NTI. ESS is characterized by low T3, low or normal T4 and normal TSH. Three patterns are described in ESS; Type1 or low T3 syndrome (seen in moderately sick patients), type 2 or low T4 syndrome (low T3 and T4, seen in very sick patients and associated with poor prognosis) and type 3 or low TSH syndrome. These probably reflect different stages on a continuum and severity of illness [14].

The present study was conducted on 200 ICU patients in Aswan University hospital, 135 patients from the medical ICU and 65 patients from the surgical ICU to assess frequency of different patterns of thyroid dysfunctions and their impact on short-term outcome of mortality in ICU patients.

Out of all patients of the study, 64% of total female patients of the study were found to have abnormal thyroid functions, while 24.6% of total male patients of the study were found to have abnormal thyroid functions. 66.3% of total abnormal thyroid function patients of the study were found to be females, while 33.7% of total abnormal thyroid function patients of the study were found to be males. Those observations confirm the concept that thyroid dysfunction and diseases are common in females more than in males.

This preponderance of the female patients in the present study might be attributed to the fact that thyroid disorders being more common in females, which is more likely to raise physician's suspicion. This may be the reason for high screening rate in the female patients. Moreover, hormonal differences between the two genders, working traditions, body weight, meal schedules, dietary factors or ingestion of drugs among other factors may be responsible for the observed gender differentiation in this study.

In the current study we found that commonest thyroid function abnormalities according to their frequency: SES was found in 50.6% of all abnormal thyroid function patients of the study. Hypothyroid was found in 41% of all abnormal thyroid function patients of the study. Hyperthyroid was found in 8.4% of all abnormal thyroid function patients of the study. From results also we found that commonest thyroid function abnormalities in each ICU according to their frequency were as follows; **Medical ICU:** SES was found in 49.1% of its abnormal thyroid function patients, hypothyroid was found in 40.7% of its abnormal thyroid function patients and hyperthyroid was found in 10.2% of its abnormal thyroid function patients. **Surgical ICU:** SES was found in 54.2% of its abnormal thyroid function patients, hypothyroid was found in 41.7% of its abnormal thyroid function patients and hyperthyroid was found in 4.2% of its abnormal thyroid function patients. These results of our study are the same as of **Sahana *et al.*** [12] who had a study on endocrine changes in patients of the intensive care unit. They reported that NTIS was detected in 80% of the ICU patients, while **Tognini *et al.*** [7] reported lower prevalence of 31.9%.

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide selection of Non-Thyroidal Illness Syndrome (NTIS) without evidence of pre-existing thyroid or hypothalamic-pituitary disease. The most prominent alterations are low serum T3 and elevated rT3 leading to the general term "low T3 syndrome." TSH, T4, free T4 (fT4) and Free T4 Index (FTI). Also, they were affected in variable degrees based on the severity and duration of the NTIS. As the severity of the NTIS increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers [15].

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 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 [16].

Also in this study we assessed the frequency of the mechanical ventilation in ICU patients either with normal and abnormal thyroid function and we found that 48.7% of normal thyroid function patients were mechanically ventilated and 59% of abnormal thyroid function patients were mechanically ventilated. Which meant that mechanical ventilation was higher in abnormal thyroid function patients and confirmed the previous observation of abnormal thyroid function in ICU patients who had no

previous thyroid illness indicating poorer prognosis compared to normal thyroid function patient. Among abnormal thyroid function, hypothyroid patients had the highest frequency percentage of mechanical ventilation with 67.6% of total hypothyroid patients, followed by hyperthyroid and SES patients who had frequency percentages of 57.1% and 52.4% of total hyperthyroid and SES patients respectively. That observation suggest the effect of hypothyroidism on hypoventilation. However, in hypothyroidism we resulted that hypothyroidism was associated with respiratory failure, and it is one of the causes of ventilator dependence. Impairment of normal ventilator responses to hypercapnia and hypoxia, diaphragmatic and skeletal muscle dysfunction, pleural effusions and obstructive sleep apnea are assumed to be the major causes of respiratory failure in hypothyroidism[6]. Correction of hypothyroidism was reported to be beneficial in weaning these patients from MV [8, 13]. In our study, correlation between thyroid function abnormality and mechanical ventilation was found non-significant though hypothyroid patients required MV more than other patients with thyroid dysfunction.

CONCLUSION

Thyroid function abnormalities are common in critically ill patients who didn't have abnormal thyroid functions before. Abnormal thyroid functions during critical illness are common among females more than males. There is a correlation between abnormal thyroid functions in critically ill patients and their mortality and it is highest in sick euthyroid syndrome patients. There was insignificant correlation between thyroid function abnormalities and mechanical ventilation in critically ill patient.

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