Thyroid Dysfunction In Critically Ill Patients In A Tertiary Care Hospital

by

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ABSTRACT

Background

Thyroid hormones play an important role in maintenance of body growth by modulating metabolism and immune system. Critical illness decreases 5'deiodenase activity, thereby decreasing T4 to T3 conversion and rT3 clearance. Increased metabolic clearance of T4 in critical illness further diverts T4 to form inactive isomer of rT3. Therefore, T3 decreases and rT3 increases. Thyroid dysfunction is associated with increased mortality of patients admitted to ICU. This study was done to evaluate prognostic value of free T3, total T3, TSH, free T4 and total T4 in ICU patients.

Aims and Objective:

1)Identify critically ill patients and grade them clinically according to Acute Physiology and Chronic Health Evaluation II (APACHE II) severity scale.
2)Evaluate thyroid function tests (TFTs) and to document outcome and relate APACHE II severity scale with TFTs.

Methods:

It is an observational prospective study conducted on 100 patients who were admitted to ICU/CCU of BLDEU's Sri B M Patil Medical College and Hospital with critical illness will be included in this study. Patients were selected on the basis of the inclusion and exclusion criteria. APACHE II score was calculated on the day of admission and total T3, Total T4, TSH, free T3 & free T4 were sent on the day of admission and outcome were noted and statistically analyzed. This study was conducted between December 2017 to August 2019.

Results:

In this study, out of 100 patients 45 patients (45%) had low free T3. Patients with low T3 had mean APACHE II score 24.9±6.9 and had higher rate of mortality.

Conclusion:

Non Thyroidal illness syndrome is a common occurrence in critically ill patients and low T3 level correlates with poor outcome in terms of mortality. Therefore, estimation

of T3 level in a critically ill patient may help in predicting the outcome.

KEY WORDS: Non Thyroidal Illness Syndrome (NTIS); Euthyroid Sick Syndrome (ESS); Critically Ill.

LIST OF ABBREVATIONS

NTIS	Non thyroidal illness syndrome
ESS	Euthyroid Sick Syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation II
TFT	Thyroid function test
T4	Thyroxine
T3	Triiodothyronine
MIT	Mono-iodotyrosine
DIT	Diiodotyrosine
TBG	Thyroxine-binding globulin
TTR	Transthyretin
TBPA	Thyroxine-binding prealbumin
MCT	Monocarboxylate transporter
OATP	Organic anion transporting polypeptide
HPT	Hypothalamus-pituitary-thyroid
TRH	Thyrotropin-releasing-hormone
PVN	Paraventricular nucleus
TSH	Thyroid stimulating hormone
hCG	Human chorionic gonadotropin
TR	Thyroid hormone receptor
D1	Deiodinase type 1
rT3	Reverse T3
T3S	Sulfated T3
TRE	Thyroid hormone responsive elements
CAR	Constitutive active androstane receptor
D2	Deiodinase type 2
D3	Deiodinase type 3
PPAR	Peroxisome proliferator activated receptor
T2	Di-iodothyronine
THR	Thyroid hormone receptor
FT3	Free T3
FT4	Free T4
MSH	Melanocyte-stimulating hormone
NYP	Neuropeptide Y
AGRP	Agouti-related protein
IL	Interleukin
TNF	Tumour necrosis factor

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INTRODUCTION

The endocrine response to critical illness is complex. The physiological rationale behind these changes are to help body maintain homeostasis and is associated with the morbidity and mortality of patients[1]. The care of a critically ill patient is very important and at the same time it is very challenging for a physician. Predicting the outcome of a critically ill patient is as important as patients care because, complete resolution of the underlying illness or cure is not possible in every case and the outcome of treatment may vary from each patient and it is the duty of the treating physician to answer the questions posed by the patients' attendants regarding the prognosis of a critically ill patient. At times it is a very challenging task for the physician to explain about the disease and its prognosis. Although various clinical parameters, laboratory investigations and imaging modalities may help in predicting the outcome of the disease, none of them alone has helped as a prognosticating tool. For this reason, various scoring systems (like APACHE II & III, SAPS II & III) were designed to provide a morbidity/mortality risk score for a patient admitted in medical emergency ward or medical ICU. Calculating a morbidity score of a patient is a complex task and time consuming or may even require a calculator for a physician. Hence there is need for a simplified approach in predicting the morbidity and mortality of a critically ill patient.

Several studies have convincingly shown that various biochemical changes occur in an acutely ill patient and that includes changes in the levels of thyroid hormones. Similarly, during critical illness, changes in circulating hormone levels are a common phenomenon. These alterations are correlated with the severity of morbidity and the outcomes of patients in ICUs. Thyroid hormones play a key role in the maintenance of body growth and in modulating metabolism and the immune system. Various

studies have found that thyroid dysfunction is associated with increased mortality in patients admitted to the ICU and medical emergency ward. Subsequent studies confirmed the association between non thyroidal illness syndrome (NTIS) and adverse outcomes in patients with sepsis, multiple trauma, acute respiratory distress syndrome, respiratory failure and mechanical ventilation, as well as in ICU and medical emergency ward patients admitted for other causes.

Although there are many western studies on non-thyroidal illness syndrome (NTIS) in critically ill patients, there are a very few Indian studies. Hence, there is a need to study the thyroid hormone levels in an acutely ill patient admitted in medical emergency ward and ICUs as an important tool in predicting the outcome of the patient.

AIMS AND OBJECTIVE

1)Identify critically ill patients and grade them clinically according to Acute Physiology and Chronic Health Evaluation II (APACHE II) severity scale.

2)Evaluate thyroid function tests (TFTs) and to document outcome and relate APACHE II severity scale with TFTs.

REVIEW OF LITERATURE

ANATOMY, DEVELOPMENT AND HISTOLOGY OF THYROID GLAND

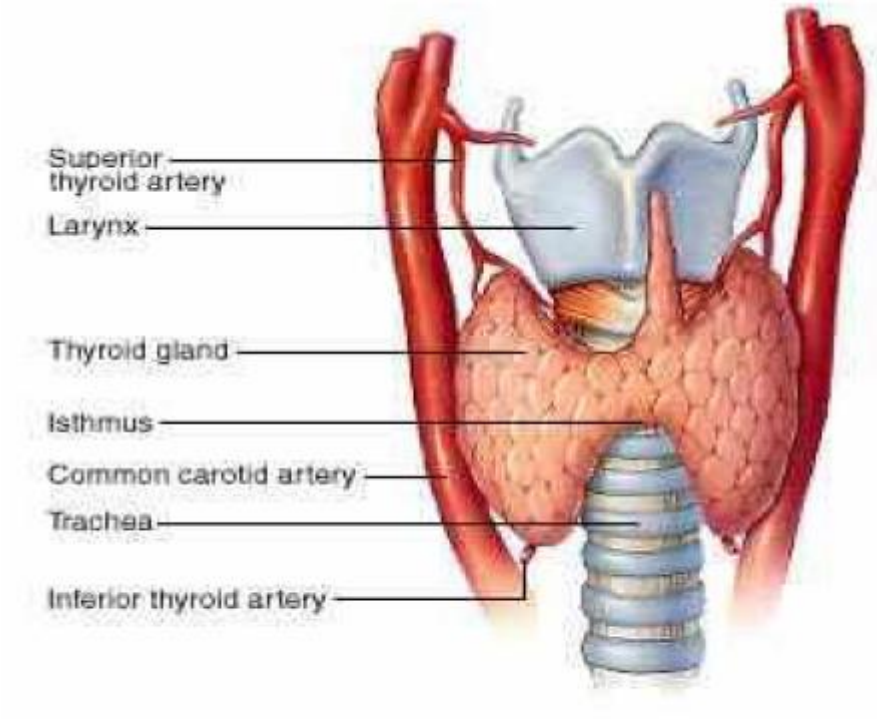


Figure 1: Anatomy of Thyroid gland

The word "thyroid" was derived from Greek (thyreos- shield, eidos-form). Thyroid gland weighs 15 to 20 gm. Normal thyroid gland (**Figure 1**) is made up of two lobes joined by a thin band of tissue, the isthmus. Right lobe is normally more vascular than left, and is often the larger. During the third week of gestation the thyroid gland develops from the floor of the primitive pharynx. The developing gland reaches its final location in the neck by migrating along the thyroglossal duct.

Histology

The gland is composed of closely packed spherical units called follicles. The interior of the follicle is filled with clear, proteinaceous colloid. The thyroid gland also contains parafollicular cells (C cells), source of calcitonin. The principal function of thyroid is production of the hormones thyroxin (T4), triiodothyronine (T3) and calcitonin.

PHYSIOLOGY OF THYROID HORMONE PRODUCTION AND METABOLISM

Iodine is first absorbed in the gut and undergoes "iodine trapping" by converting iodine to iodide and transporting it in the blood and then transferred into the thyroid cell. The iodide trapped is then oxidized to iodine and combined with residues of tyrosine to form mono-iodotyrosine (MIT) and Diiodotyrosine (DIT). T3 is formed by coupling of MIT and DIT, whereas T4 is formed by coupling of two DIT. "Thyroid peroxidise" catalyses oxidation, iodination and coupling reactions.

Thyroid hormones thus produced are bound and stored as thyroglobulin until secreted. There is twentyfold excess secretion of T4 than T3 from thyroid gland. "Plasma proteins, thyroxine-binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA), and albumin are bound to T3 and T4". The pool of circulating hormone is increased by plasma binding proteins, delays hormone clearance, and hormone delivery to selected tissue sites is modulated. TBG concentration is relatively low (1-2 mg/dL), 80% of bound hormones are carried by TBG because of its high affinity for thyroid hormones (T4 > T3). Albumin carries up to 10% of T4 and 30% of T3, but thyroid hormones have low affinity for albumin and has a higher plasma concentration (3.5g/dl). About 10% of T4 is carried by TTR but little T3. Serum thyroid hormone is 99% bound, and only 1% is available as free hormone for uptake by target tissues. The fraction of free T4 is smaller than free T3 because TBG has higher affinity forT4 compared to T3.

"Thyroid hormone has to be transported into the cells to be able to exert its effects. Several thyroid hormone transporters have been described. The efflux and the uptake of T3 and T4 is facilitated by Monocarboxylate transporter (MCT)-8 and MCT-10 and expressed in multiple tissues. T4 is preferentially transported by the organic anion transporting polypeptide (OATP)-1C1 which is mainly expressed in the brain"[2]

T3 binds to the thyroid hormone receptors in the nucleus once it is transported into the cell and exerts its effect on cellular gene-transcription. There is no direct effect on gene-transcription by the pro-hormone T4, but deiodinase converts it to active hormone T3. Alternatively, T4 and T3 can have direct non-genomic effects.

Table 1: Characteristics of circulating T4 and T3

Hormone Property	**T_4**	**T_3**
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	21×10^{-12}M	6×10^{-12}M
Serum half-life	7 days	0.75 days
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 g/d	32g/d
Intracellular hormone fraction	20%	70%
Relative metabolic potency	0.3	1

Regulation of the thyroid axis

The hypothalamus-pituitary-thyroid (HPT) axis regulates thyroid hormone production and secretion by the thyroid gland. Thyrotropin-releasing-hormone (TRH), synthesized in the paraventricular nucleus (PVN) of the hypothalamus, stimulates the anterior pituitary gland to produce and secrete a glycoprotein thyroid stimulating hormone (TSH). TSH in turn stimulates the thyroid gland to produce and release thyroid hormone. The HPT axis has a negative feedback mechanism, as hypothalamic TRH and pituitary TSH production are negatively regulated by T3 and T4.

TSH secreted by the thyrotrophic cells in the anterior pituitary, plays a pivotal role in control of thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. TSH is a 31-kDa hormone composed of alpha and beta subunits; the alpha subunit is common to the other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone, human chorionic gonadotropin (hCG)], whereas the TSH beta subunit

is unique to TSH.

“Thyroid hormones, acting predominantly through thyroid hormone receptor-beta (TR beta), inhibit TRH and TSH production. The ‘set-point’ in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs 15min after administration of exogenous TRH. Dopamine, glucocorticoids, and somatostatin suppress TSH but are not of major physiologic importance except when these agents are administered in pharmacologic doses. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH mediated stimulation of TSH”. TSH gene expression secretion and inhibition of TRH stimulation of TSH is quickly and directly suppressed by high thyroid hormone levels, indicating that thyroid hormones are the dominant regulator of TSH production.

Like other pituitary hormones, TSH displays diurnal rhythm and is released in a pulsatile manner; its maximum levels occur at night. However, these TSH excursions are modest in comparison to those of other pituitary hormones, in part, because TSH has a relatively long plasma half-life (50 minutes). Consequently, one value of TSH is enough for assessing its circulating level. TSH is measured using immunoradiometric assays that are highly sensitive and specific. These assays readily distinguish between normal and suppressed TSH values and TSH is extremely sensitive to the levels of thyroid hormones in circulation and can be used as a useful tool in detection of thyroid gland abnormalities[3].

DEIODINASES

T4 is converted to T3 by deiodination in the periphery. The selenoenzyme family of iodothyronine deiodinases, which consists of three deiodinases mediates deiodination of TH in various tissues.

Only about 13% of T3 is produced from thyroid gland and remaining 87% is formed from T4. “Both the inner (phenolic) ring and the outer (tyrosyl) ring of T4 can be deiodinated by

the deiodinases, ultimately leading to the formation of 3, 3'-di-iodothyronine (T2)"[4].

DEIODINASE TYPE 1

In the plasma membrane Deiodinase type 1 (D1) is localized and expressed in liver, kidney, thyroid and pituitary. The inner and the outer ring of T4 is de-iodinated by D1. D1 in liver was thought to be the major source of plasma T3 by deiodination of T4 for many years. "Recent studies, however, suggest that liver D1 is more important for thyroid hormone clearance during hyperthyroid circumstances, as the preferred substrate of D1 is not T4 (low affinity for T4), but reverse T3 (rT3), sulfated T3 (T3S) and T4S. T3 positively regulates via two thyroid hormone responsive elements (TRE) in the D1 promoter".

The constitutive active androstane receptor (CAR) can regulate liver D1 shown in recent reports, which helps in modulating hepatic energy metabolism[5].

DEIODINASE TYPE 2

Expression of type II deiodinase allows it to regulate T3 concentrations locally, a property that may be important in the context of levothyroxine (T4) replacement. Deiodinase type 2 (D2) is localized in the endoplasmic reticulum. D2 has a major role in the production of local T3 in the brain since D2 is expressed in brain. D2 is also expressed in pituitary, brown adipose tissue, placenta and although at remarkably low levels in skeletal muscle. In contrast to D1, outer ring deiodination occurs through D2 exclusively. T4 is the preferred substrate for D2. It has been postulated that under euthyroid conditions muscle D2 significantly contributes to serum T3 in humans[6].

"Recent studies report that upregulation of D2 in skeletal muscle by bile acids via the G-protein coupled receptor TGR5, followed by an increase in mitochondrial activity, while agonists of peroxisome proliferator activated receptor (PPAR), which is an important metabolic regulator also increases D2 expression in skeletal muscle cells. Furthermore, Heemstra *et al* have shown that fasting and plasma insulin levels modulate muscle D2 mRNA expression. Thus, it appears that muscle D2 is involved in energy metabolism"[7].

DEIODINASE TYPE 3

The thyroid hormone inactivating enzyme is deiodinase type 3(D3)**.** The inner-ring de-iodination of T4 and T3 is catalyzed by D3. D3 is an important source for rT3. D3 is presenting the plasma membrane similar to D1. During embryonic development D3 plays an important role as it is highly expressed in placenta. Recent studies have shown that during bacterial and chemical inflammation D3 is expressed in activated infiltrating leukocytes and that lacking D3 impairs bacterial clearance capacity during infection[8].

During hypoxia in post-mortem liver biopsies of critically ill patients and during myocardial infarction D3 induction has been shown[9].

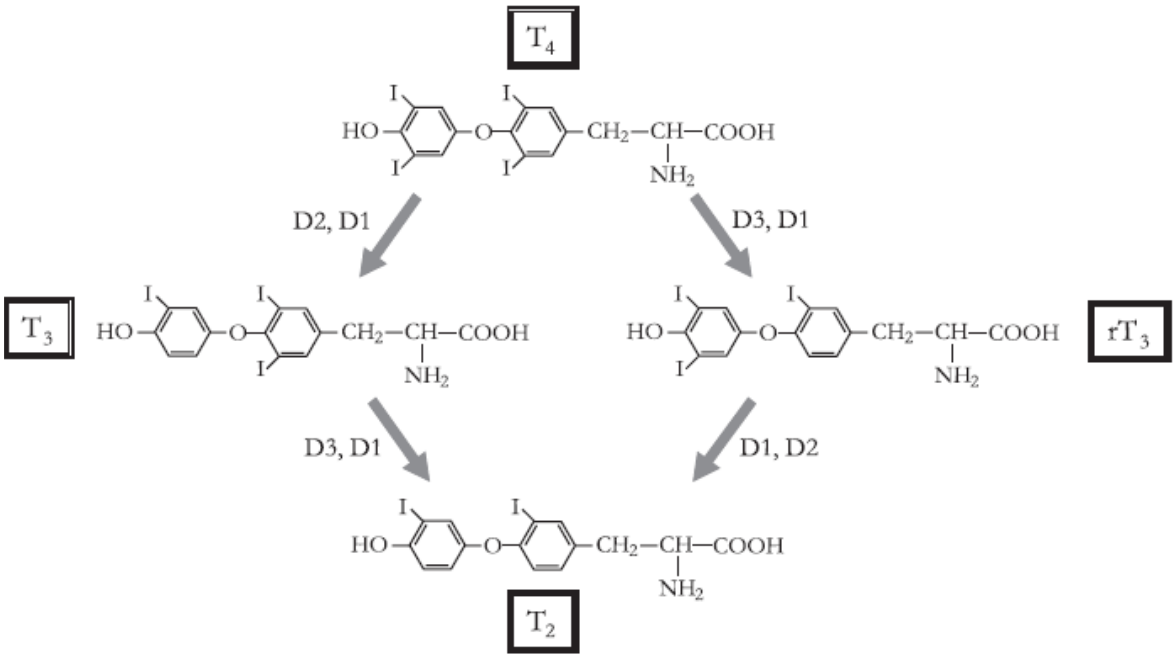


Figure 2: Overview of the deiodination of thyroxine (T4) into tri-iodothyronine (T3), reverse tri-iodothyronine (rT3) and di-iodothyronine (T2)

THYROID HORMONE RECEPTOR AND THYROID HORMONE ACTION

"The nuclear receptor family that modulate gene transcription are thyroid hormone receptors (TRs). The N-terminal activation function AF1 domain, the DNA binding domain, the hinge region and the C-terminal AF2 domain are the different domains of protein structure of thyroid hormone receptors (TRs)"[10]

TRα and TRβ gene encode thyroid hormone receptors. The TRα-gene may give rise to six isoforms: TRα1, TRα2, TRΔα1 and TRΔα2, p43 and p28 due to alternative splicing and alternative promoter usage.

The TRα1 isoform has a ligand binding domain, DNA binding domain and modulates gene-transcription which is a bonafide TR. The TRα2 isoform is not able to activate gene-transcription as it does not have a ligand binding domain. At the N-terminus, the TRΔα1 and TRΔα2 isoforms are truncated. TRα2, the short isoforms TRΔα1 and TRΔα2 functions are unknown at present, TRα1 and TRβ1 mediated transcriptional activation is inhibited by them. Mitochondrial activity is regulated by the truncated isoforms p28 and p43.TRβ1 and TRβ2 isoforms are encoded by TRβ gene. In contrast to the TRβ, TRβ-isoforms differ in the N-terminal region and arise only due to alternative promoter usage. bind T3 is bound by TRβ1 and TRβ2 and are able to modulate gene-transcription[11].

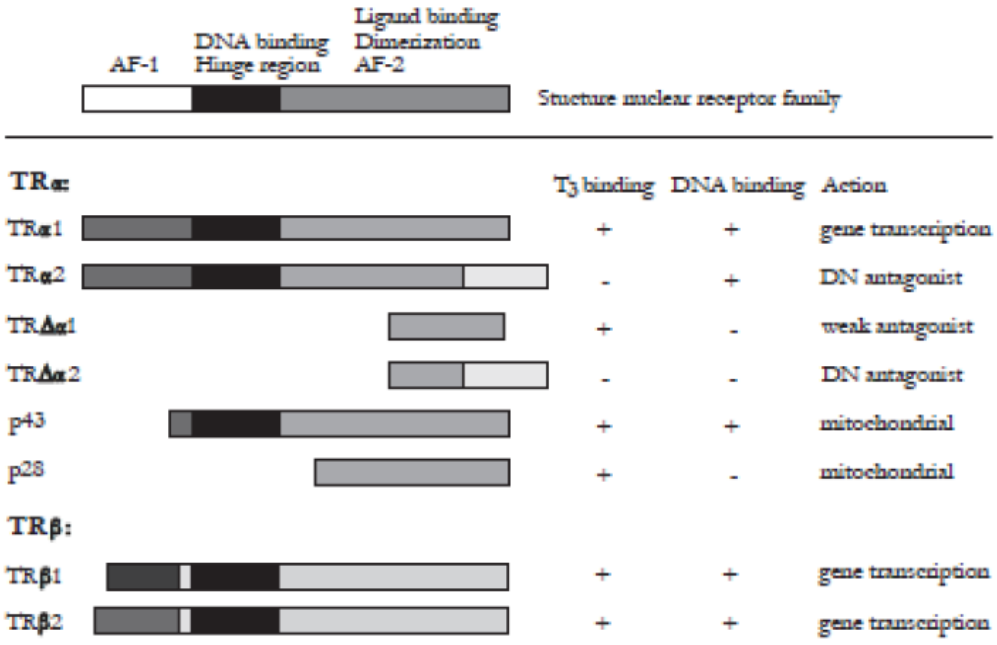


Figure 3: Schematic structure of the nuclear receptor family (upper panel) and overview of TR isoforms derived from the TRα (THRα) and TRβ (THRβ) gene (lower panel).

An overview of all described TR-isoforms is presented in **figure 3**. TRs are differentially expressed in different tissues. "Both TR-α and TR-β are expressed in most tissues, but their

relative expression levels vary among organs. TR-α is particularly abundant in brain, kidneys, gonads, skeletal muscle and heart, whereas TRβ expression is relatively high in the pituitary and liver".

The hormone-receptor complex then binds to DNA via zinc fingers and increases or in some cases decreases the expression of a variety of different genes that code for enzymes which regulate cell function.

NONTHYROIDAL ILLNESS SYNDROME(NTIS)

Introduction

Serum thyroid hormone level markedly changes in few hours after onset of acute illness. This is known as nonthyroidal illness or euthyroid sick syndrome or low T3 syndrome. Low levels of serum triiodothyronine(T3) is the most characteristic abnormality in mild illness. Serum T3 and thyroxine(T4) decreases as the severity of the illness increases. Starvation, sepsis, surgery, myocardial infarction, bypass surgery, and any severe illness will cause decrease in thyroid hormone levels[12,13]. Metabolic rate is decreased in hypothyroidism because of low levels of thyroid hormone. In NTIS and starvation, T3 levels are low in an attempt to save energy expenditure.

Low T3 states

Deiodination of T4 to T3 by type 1 iodothyronine deiodinase in the liver is inhibited because of carbohydrate deprivation, which inhibits generation of T3 and prevents metabolism of reverse T3(rT3). Basal metabolic rate is decreased during starvation, decrease in thyroid hormone is an adaptive response by body to spare calories and protein by inducing hypothyroidism. Patients with decreased T3 represent mildest form of NTIS, do not show clinical signs of hypothyroidism[14].

NTIS with low serum T4

As the severity of illness and starvation progresses, a complex syndrome with low T3 and low T4 develops. "Plikat et al. found 23% of admitted patients in ICU during 2-year period had low free T3, low free T4 and low or normal TSH, with increased risk of death. A high probability of death in NTIS with marked decrease in T3 and T4 which is correlated with

APACHE II score"[15].

Neuroendocrine changes in nonthyroidal illness

Acute illness

TSH level increases in response to low levels of T3 and T4 in primary hypothyroidism. But in acute illness in spite of decreased T3 and T4(in severe illness) levels, TSH remains within low to normal in nonthyroidal illness. This suggests an altered feedback setting at hypothalamus and/or pituitary. In acute phase illness physiological nocturnal surge is absent. "Cytokines are high in acute phase of critical illness. Injection of cytokines like IL-1, IL-6 and TNFα is at least partially able to mimic the thyrotropic alterations of the acute stress response. Cytokine antagonism fails to restore thyroid hormone levels".

In acute illness TSH response may be blunted because of high levels of endogenous cortisol. Endogenous thyroid hormone analogues like thyronamines and thyroacetic acids, contribute to the pathogenesis of nonthyroidal illness, by blunting the TSH response to low levels of thyroid hormones for binding to transport proteins, transmembrane transporters, deiodinases, and/or nuclear receptors[16].

THYROID HORMONE METABOLISM DURING ILLNESS

Significant changes may be induced in neuroendocrine systems due to acute illness. Due to acute stress, plasma cortisol levels rise rapidly because of the activation of the pituitary-adrenal axis. The extent of this rise is critical for survival and is related to the severity of the illness. Similarly, during acute illness changes occur in the hypothalamic–pituitary–thyroid (HPT) axis, which leads to low levels of total triiodothyronine (T3), and is called 'low T3 syndrome'.

'Euthyroid sick syndrome' was used for patients with low serum T3 but who are often clinically euthyroid. Thyroid hormone variation that occurs due to acute or chronic illness but there is no intrinsic abnormality in thyroid function such a condition is known 'Non-thyroidal illness syndrome (NTIS)'.

It's been debated if there in requirement of thyroid hormone replacement therapy during

illness where there is change in the HPT axis. It is either representative of an associated pathology or is an adaptive response to 'stress' to decrease metabolic rate.

"The mechanisms which arise due to the hormonal changes seen in the NTIS due to HPT axis modification are:

• Altered binding of thyroid hormone to circulating binding proteins

• Modified entry of thyroid hormone into tissue changes in thyroid hormone metabolism due to modified expression of the intracellular iodothyronine deiodinases and changes in thyroid hormone receptor (THR) expression or function".

TYPICAL CHANGES IN THYROID FUNTION TESTS IN ILLNESS

If a patient with co-existing illness, has undergone thyroid function test then the analysis of that becomes difficult, the variations in thyroid test which may be due to illness may mimic thyroid dysfunction. The most common finding in these patients is low T3, which is seen in even the minor forms of non-thyroidal illness (NTI). There may be abnormal T4 and TSH in patients with moderate to severe illness.

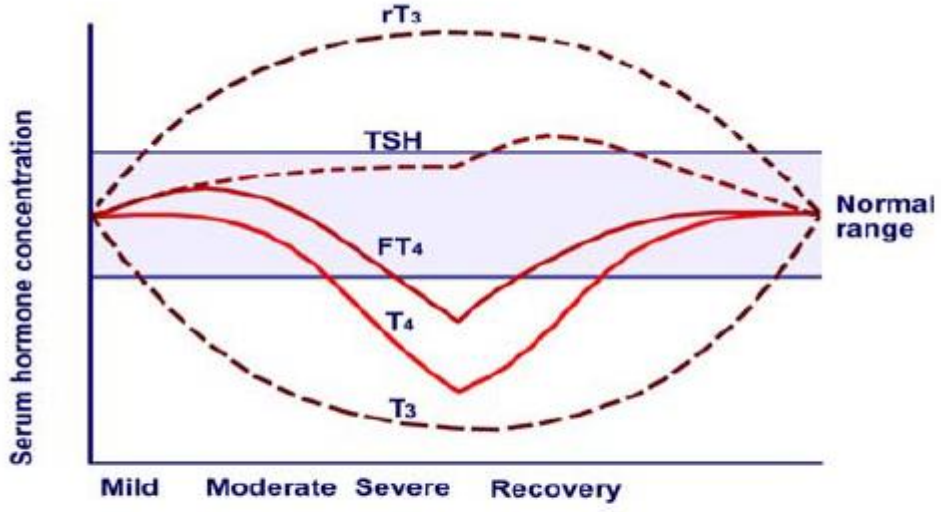


Figure 4: Changes in thyroid hormones during illness

"Although clinically serum TSH is considered as the most sensitive and specific thyroid function test, approximately 3% of patients can show TSH concentrations that are <0.1 mU/L

(typical TSH reference range 0.3–4.0 mU/L) in acute illness, the low TSH can be assigned to the NTIS or glucocorticoid or dopamine which causes TSH suppression in 75% patients"[17] There may be transient increase in TSH above the normal range during recovery from illness. Similarly, T4 can be high, normal or low in these patients. In the ICU, there is extremely high prevalence of abnormal thyroid function tests with low total T3 in more than 70% patients and low total T4 in around 50% [18].

The abnormalities in thyroid function tests not only cause organic illness but can also cause acute psychiatric admissions. In these patients, there may be normal or increased TSH with increased T4, which suggests central activation of the HPT axis. In most of the cases, the thyroid function tests will normalize in 2 weeks of admission. In psychiatric patients there is decreased TSH, with a normal free T4 (FT4).

With reference to serum FT4 and free T3 (FT3), it is complicated during illness by change in free hormone levels according to the analytical methods. In moderate severity illness there is increase in FT4 in reference methods, while routine diagnostic tests show subnormal results in the same samples which are less robust assays. Similarly, low FT3 prevalence in illness depends on the methodology[19].

CHANGES IN THE HYPOTHALAMIC-PITUITARY AXIS IN ORGANIC ILLNESS

"In illness and central hypothyroidism, even though circulating T3 is low, serum TSH is normal but can be suppressed. Both central hypothyroidism and critical illness result in a similar decline in the usual nocturnal surge and pulse amplitude of TSH, and in addition, TSH with impaired biological action may be produced in both conditions"

Using sensitive TSH assays, patients with low TSH levels because of NTIS have TSH level of >0.01mU/l, while all hyperthyroid patients have TSH values <0.01 mU/l. During illness there is 50% decrease in hypothalamic and pituitary T3 levels in spite of a low serum T3, which causes increase in TRH and TSH secretion under normal condition.

"During critical illness there is low TSH (or failure of TSH to rise in the presence of a low T3 and T4) which causes changes in the HPT axis set point because of central hypothyroidism. The synthesis of TSH and regulation of thyroid hormone synthesis is promoted by specific groups of TRH neurons which are situated in the paraventricular nucleus (PVN) of the hypothalamus, and such neurons appear to be the focus of the set point in the HPT axis"[20].

REGULATION OF HYPOTHALAMIC TRH PRODUCTION IN ILLNESS AND FASTING

Several factors mediate the effects of physiological stimuli on the TRH neurons of the PVN (paraventricular nucleus).

FASTING

The set point of the HPT axis is lowered during reduction in T3 levels in fasting. In fasting there is decrease in TRH in the PVN and it might be due to decrease in leptin. Two principal classes of neuroendocrine cells in the arcuate nucleus involves the action of leptin. "The neurons of the PVN that secrete TRH are innervated by neurons from the arcuate nucleus that contain a-melanocyte-stimulating hormone (α-MSH or MC1R), neuropeptide Y (NPY), agouti-related protein (AGRP) and the inhibitory neurotransmitter GABA". Both NPY and AGRP stimulate food intake. Recent work shows that during fasting the most critical part in the arcuate nucleus is the activation of NPY/AGRP neurons. "Hypothalamic T3 production triggers the production of mitochondrial uncoupling protein 2 which is catalyzed by D2" TRH gene expression is inhibited by NPY and AGRP, this is an action which is emphasized by ghrelin and prevented by leptin. In contrast, in the cells of the PVN, TRH gene expression is stimulated by α-MSH, and leptin enhances this effect. It is presumed that the provoking effects of α-MSH inhibits TRH gene expression by AGRP, whereas the inhibitory effect of NPY occurs by reducing cAMP. "During fasting, when leptin decreases, the set point for

feedback inhibition of the TRH gene by thyroid hormone is reduced by increase in AGRP and NPY production and the inhibition of α-MSH production"[21].

"The changes found during NTIS show a decline in T3 and TRH in the PVN which is similar to animals deprived of food, and by giving leptin these changes can be reverted or it can be reversed by introducing hypothalamic arcuate nucleus lesion"[22].

In an individual patient it becomes difficult to separate the effects of starvation from systemic illness as malnutrition is a component of many acute and chronic illnesses.

SEPSIS AND TRAUMA

"In the PVN there is an inhibitory feedback on TRH production by T3, but TRH neurons has inability to produce T3 from T4 and as such appear unable to directly sense circulating T4. The tanycyte is a unique glial cell type that lines the floor of the third ventricle having processes that extend deep into the hypothalamus"[20]. Tanycytes are an important source of T3 which are situated in the mediobasal hypothalamus, it gives feedback regulation to the TRH neuron situated in the PVN.

Tanycyte D2 is increased during sepsis and trauma, which is hypothesized to lead to an increased generation of T3 from T4. "T4 is extracted from portal capillaries, blood vessels in the arcuate nucleus or the CSF (in the third ventricle) by tanycyte processes. The T3 can then be released back into the CSF or the bloodstream. TRH neurons may take up T3 via diffusion from the CSF, by axonal terminals of the TRH neurons present in the median eminence, or the release of T3 into the arcuate nucleus may influence the activity of arcuate neurons that project into the PVN"[23].

Recent studies in rodents show how central hypothyroidism is produced by tanycytes in sepsis by changing the set point of HPT axis and downregulation of TRH production. Increased conversion of T4 to T3 occurs in infection which is D2 mediated, and local tissue hyperthyroidism occurs due to diminished D3-mediated catabolism of T3, which in turn

exerts a negative feedback control on TRH synthesis in hypophysiotropic neurons. In a rabbit model of prolonged critical illness, there is an increase in hypothalamic D2 expression and decrease in TRH in the PVN, but it is not yet clear if this mechanism works in humans or not. "The negative feedback regulation is exerted on TSH release by the thyrotroph in the pituitary by cytokines which are produced locally. TSH release is impaired by directly acting on the pituitary thyrotroph by pro-inflammatory cytokines which are produced peripherally by patients with sepsis, trauma and autoimmune disease. TSH in plasma is suppressed by potent Interleukin (IL)-6, but similar effect can also be seen by other cytokines, including TNF-α and interferon-γ". TSH is suppressed by stress and drugs like glucocorticoids and dopaminergic drugs[24].

THYROID HORMONE METABOLISM IN ILLNESS

"T4 for peripheral tissues is provided by thyroid gland, the differential tissue expression of the iodothyronine deiodinases in the extra-thyroidal tissues occurs because of fine regulation of the thyroid hormone. These enzymes metabolize T4 to biologically active T3, or bio-inactive reverse T3 (rT3) and T2". It is now clear that the illness modifies expression of these deiodinases and results in tissue-specific modifications to thyroid status in illness and these modifications can be highly organ specific.

ILLNESS

Data concerning the potential role of the deiodinases in the pathogenesis of NTIS is conflicting. "The commonly accepted view was that in illness due to a reduction in both hepatic/renal D1 activity and skeletal muscle D2 activity there is decrease in extra-thyroidal conversion of T4 to T3. In addition to these changes, T2 production is increased because of increased catabolism of T3 and increased production of rT3 from T4 due to increase in hepatic and skeletal muscle D3 activity"[25,26].

It was argued that together these modifications to deiodinase expression could be the major

contributors to the low T3 concentrations associated with the NTIS. In NTIS, the trigger for these changes in deiodinase expression has been ascribed to an increase in serum glucocorticoids and pro-inflammatory cytokines[27].

It has been suggested that "in acute illness there is swift fall in T3 which is either due to impaired thyroidal production of T3 (due to central hypothyroidism) and/or acute phase response which leads to decrease in serum thyroid hormone-binding proteins. An important role of thyroidal potassium channels for the maintenance of adequate thyroid hormone production has very recently been described"[28].

SELENIUM STATUS, DEIODINATION AND THE NTIS

"As plasma selenium levels are often low in sick patients, especially those with severe illness and sepsis, it has been suggested that the expression of the selenoenzymes D1, D2 and D3 may be limited by the low selenium supply in these patients, and that this represents a mechanism for the pathogenesis of the low T3 seem in the NTIS". There is little evidence to support this view; in fact, due to a switch to thyroidal production, plasma T3 is well maintained, while total T4 increases in selenium deficiency[29].

It seems more likely that in acute and chronically ill patients' selenium is low because of decreased concentrations of selenoproteins in plasma because of the acute phase response.

EFFECTS OF ILLNESS ON PLASMA THYROID HORMONES AND THYROID HORMONE BINDING PROTEINS

Thyroid hormones bind reversibly to thyroxine- binding globulin (TBG), transthyretin and albumin. During illness, acute phase proteins like transthyretin and TBG levels can fall markedly. In normal condition, unbound(free) hormone circulating in the plasma is <0.05%. "The free hormone hypothesis assumes that it is only this small 'free' hormone fraction that is able to enter the cell and interact with the nuclear THRs to confer biological action". Thus, the concentration of these binding proteins determine the levels of total T3 and total T4 in

plasma, while the free hormone concentrations is not dependent on concentration of binding protein.

In severe NTIS, because of 'acute phase response' the levels of the thyroid hormone-binding proteins often reduces; which arises from impaired synthesis, rapid breakdown and movement out of the plasma space[30].

For example, after a bypass surgery, there is reduction in TBG levels by 60% in 12 h. In acute illness reduction in these plasma binding proteins may lead to changes in plasma total T3 and total T4.

"In few patients with chronic illness, a desialylated form of TBG is synthesized by the liver, and this protein appears to have an affinity for thyroid hormone of approximately one-tenth of that of normal TBG (also known as slow TBG because of altered electrophoretic mobility); this also gives rise to a fall in the circulating levels of total thyroid hormone as a consequence of the diminished thyroid hormone binding capacity".

In sick patients, the serum binding capacity for thyroid hormone is reduced significantly, and it is likely that in hepatic and renal failure many substances are accumulated in the plasma that compete with thyroid hormone binding to plasma proteins. At therapeutic levels the binding of thyroid hormone to plasma proteins compete with drugs such as furosemide, diclofenac, carbamazepine and salicylate; which leads to a reduction in total T3 and total T4.

FREE THYROID HORMONE MEASUREMENTS IN NTIS

Equilibrium dialysis or ultrafiltration techniques are generally viewed as reference strategies for the estimation of free thyroid hormones in serum, albeit nor is totally agreeable except if the estimation framework has been well described. "When utilizing these dialysis techniques, it is important to limit interruption of the original equilibrium by keeping both sample dilution and the proportion of the volumes of dialyzing buffer and sample compartments as little as possible. In the event that these conditions are met, tests from patients with NTI

regularly show normal or increased FT4 in their serum and FT4 is seldom low". Conversely, the utilization of significant sample dilution before equilibrium dialysis results in decrease in FT4 estimated utilizing this technique[19].

Many routine assays which are used for the measurement of free thyroid hormone in serum, underestimate the 'true' free hormone concentration that is in the serum of patients with NTIS because they are prone to artefacts. "Samples with the lowest serum binding capacity for thyroid hormones (NTIS samples) are particularly prone to this effect. Unfortunately, the work which is published about the effects of NTIS on free thyroid hormones have used unsuitable methodology, and these methodological artefacts have resulted in a mass of literature that gives a misleading picture of the effects of illness on free thyroid hormone concentrations in blood. Indeed, FT4 may appear to be low, normal or raised even in the same sample depending on the assay method"[31].

The estimation of FT3 in serum has been much more challenging than for FT4 yet the estimation of the 'true' FT3 levels in disease is key to the impression of the 'thyroid status' of patients with NTI. In the literature its clear that during illness the reduction in serum total T3 is proportional to severity of illness.

Most routine methods for FT3 show that these concentrations tend to parallel the changes in serum total T3. "However, results from two studies that have utilized a 'reference' ultrafiltration method for FT3 analysis have concluded that illness results in only a modest fall in serum FT3.Using a commercial FT3 method that shows good agreement with the ultrafiltration reference method, it has been found that the percentage of patients in an intensive care unit who had aFT3 below the reference range was in the order of 27%, whilst 70–80% of patients had low total T3. In the same study, using a reliable assay for FT4, it was also found that whilst around 50% of patients had subnormal total T4 only around 2% had low FT4"[18].

These observations support the view that during acute NTIS, there is marked changes that occur in total thyroid hormone levels which is a result of the acute phase response that occurs due to changes in the serum binding capacity for thyroid hormones. While free hormones change during illness, these changes are of a more modest nature than that of total thyroid hormone.

"It should be noted that during diseases which causes hepatic inflammation, the plasma TBG levels (and thus the thyroid hormone binding capacity) increases transiently as a result of increased release from the liver; this produces an increase in TT4 during the acute phase of such inflammatory conditions"[32].

THYROID HORMONE UPTAKE BY TISSUE IN NTIS AND ROLE OF THYROID TRANSPORTERS

In NTIS, the changes in the circulating levels of thyroid hormones are commonly discussed, tissue thyroid status is governed by intracellular T3, especially which interacts with the THRs in the nucleus. Intracellular T3 and T4 is dependent not just on the capability of the cell to transport thyroid hormone but also on the local variation in the activity of different deiodinases. Clearly, deiodination of T4 cannot occur if the cellular uptake of thyroid hormone is impaired, which gives rise to reduced peripheral production of T3 and local tissue hypothyroidism.

ATP-dependent transport processes is involved in the cellular uptake of thyroid hormones. For the entry and exit of thyroid hormone from the cell, there is requirement of thyroid hormone transporters, and these transporters have different tissue distributions and ligand affinities. "Thyroid hormone transport proteins include Na-taurocholate co-transporting polypeptide, fatty acid translocase, multidrug resistance associated proteins, amino acid transporters, and members of the organic anion transporter polypeptide (OATP) and monocarboxylase transporter (MCT)families. The majority of the thyroid hormone transporters demonstrate a low specificity and an apparently low affinity for thyroid

hormone".

Only three key transporters like OATP1C1, MCT8 and MCT10 are identified. "Transport of T4 and rT3 occurs by OATP1C1 which is localized in the brain capillaries. MCT8 is found in the brain, hypothalamus, pituitary gland, liver, heart and placenta, skeletal muscle, kidney and MCT10 is found in the intestines, liver, kidney, skeletal muscle and placenta both transport T4 and T3"[33].

In NTIS, there is reduction in the transport of thyroid hormone into tissues, but it may not be due to a downregulation of the expression of thyroid hormone transporters; in fact, in acute and chronic illness the expression of these transporters seems to be increased. "Mebis (2009) found that an increase in MCT8 but not MCT10 gene expression occurs in the liver and skeletal muscle of patients in an intensive care unit with prolonged critical illness. The expression of the MCT8 gene demonstrated a strong inverse correlation with circulating TT3 and TT4"[34].

In contrast to the observations of Mebis, Rodriguez-Perez (2008) observed that in patients with septic shock, MCT8 expression was reduced in subcutaneous adipose tissue but was unchanged in skeletal muscle; liver was not investigated[35].

Current evidence in NTIS shows that there is no downregulation of thyroid hormone transporters, and there might be some other mechanisms during illness which is responsible for the reduced uptake of thyroid hormone. These mechanisms may include reduction of hepatic ATP. "NEFA and numerous substances that accumulate in the plasma of patients with renal or liver dysfunction inhibit cellular transport of T4 into cultured hepatocytes".

SHOULD THYROID HORMONE REPLACEMENT BE GIVEN IN NTIS?

Controversy surrounds whether thyroid hormone should be replaced in the NTIS or not. There are only few clinical trials which helps to determine whether thyroid hormone replacement is helpful or not, and if it is helpful then which preparation should be used (T3 or

T4). These changes are due to a physiological variation, if any efforts are made to restore thyroid levels then it can lead to adverse outcome.

In a trial on ICU patients assigned to T4 or a placebo for 2 weeks, no improvement in survival was seen[36,37]. There was no improvement seen in patients with burns who were treated with T3.

A more novel approach to replacement in critically ill patients has been suggested by Van den Berghe et al. (2002). "They used a continuous infusion of TRH together with a GH secretagogue and successfully restored both thyroid hormone and TSH concentration and found improvements in catabolic parameters"[38].

Given that thyroid hormones have significant effects on cardiac function, the consequence of thyroid hormone replacement on cardiac patients has been studied in a number of settings including surgery, heart failure and transplant. In fact, many conferences in the US and Canada have recommended that T3 be included in a panel of hormones that are aimed at cardiac resuscitation, when the ejection fraction is <45%. "Short-term studies involving T4 andT3 treatment in heart failure patients also show promise, with one of the observed benefits being increased cardiac output. No studies have so far looked at its long-term use in these patients"[39].

CHANGES IN THYROID FUNCTION TESTS DURING RECOVERY FROM ILLNESS

When a patient improves from illness, abnormalities in serum TSH and thyroid hormone concentrations eventually resolve. In few patients, however, TSH concentrations may increase rapidly above the reference range in recovery phase. In patients who are admitted, increase in TSH level may be due to recovery from NTIS, and hence lifelong replacement of T4 should not be started. "Prospective studies on critically ill patients with burns, sepsis and acute renal failure showed that the rise in TSH during recovery consistently preceded the rise

in T3and T4 suggesting that this TSH rise is essential in some patients to return thyroid hormone homoeostasis to normal during recovery"[40].

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II(APACHE) SCORE

APACHE score was first presented by Knaus et al in 1981. APACHE score was designed to measure the severity of disease for adult patients admitted to intensive care units[41]. It has not been validated for use in children or young people aged under 16.

It is applied within 24 hours of admission of a patient to an intensive care unit (ICU)- a score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of mortality. APACHE II score can be used to describe the morbidity and mortality of a patient when comparing the outcome with other patients.

The point score is calculated from a patient's age and 12 routine physiological measurements:

1. Temperature (rectal)
2. Mean arterial pressure
3. Heart rate
4. Respiratory rate
5. AaDO2 or PaO2 (depending on FiO2)
6. pH arterial
7. Sodium (serum)
8. Potassium (serum)
9. Creatinine
10. Haematocrit
11. White blood cell count
12. Glasgow Coma Scale

These were measured during the first 24 hours after admission and utilized in addition to information about previous health status (recent surgery, history of severe organ insufficiency, immunocompromised state) and baseline demographics such as age.

The score is not recalculated during the stay. If a patient is discharged from the ICU and readmitted, a new APACHE II score is calculated.

Patient's predicted mortality is calculated using APACHE II score in combination with the principal diagnosis at admission.

Table 2: APACHE II score:

Physiologic Variable	High Abnormal Range						Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature (rectal °C)	>41	39-40.9		38.538.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49	
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39	
Respiratory Rate	≥50	35-49		24-34	12-24	10-11	6-9		≤5	
Oxygenation: A-a DO_2 or P_aO_2 (mmHg) FiO_2 > 0.5 record A-a DO_2 FiO_2 < 0.5 record P_aO_2	≥500	350-499	200-349		< 200 P_aO_2 > 70	P_aO_2 61-70		P_aO_2 55-60	P_aO_2 < 55	
Arterial pH (preferred) Serum HCO_3 (venous mEq/l) **(not preferred, may use if no ABGs)**	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160-171	155-159	150-154	130-149		120-129	111-119	≤110	
Serum Potassium (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2-3.4	1.4-1.9		0.6-1.4		<0.6			
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
White Blood Count (total/mm^3) (in 100s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
Total Acute Physiology Score (sum of above 12 points)										
Age points (years) ≤44= 0; 45 – 54 = 2; 55 – 64 = 3; 65 – 74 = 5; ≥75 = 6										
Chronic Health Points (see below)										
Total APACHE II Score (Add together points from A + B + C)										

Chronic Health Points: If the patient has a history of severe organ system insuffiency or is immunocompromised as defined below, assign points as follows:
2 points for nonoperative or emergency postoperative patients
2 points for elective postoperative patients
Liver insufficiency: Biopsy proven cirrhosis; Documented portal hypertension; Episodes of past upper GI bleeding attributed to portal hypertension; Prior episodes of hepatic failure / encephalopathy / coma. *Cardiovascular*: New York Heart Association Class IV Heart Failure. *Respiratory*: Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties; Documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40 mmHg), or respirator dependency. *Renal*: Receiving chronic dialysis. *Immunosuppression*: The patient has received therapy that suppresses resistance to infection e.g. immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS.

Table 5. Acute Physiology and Chronic Health Evaluation II (APACHE-II) Worksheet Adapted from *Crit Care Med* 13(10): 818-829. (Knaus, Draper et al. 1985)

METHODOLOGY

Source of Data

The results of tests done on blood samples of subjects who are critically ill, getting admitted to medical emergency ward and CCU/ICU between November 2017 to August 2019.

Method of collection of data

After obtaining written informed consent from patients or their legal guardian, who fulfil the inclusion criteria, details of the patients will be recorded on a pretested structured pro forma which include the demographic details, detailed case history, and APACHE II score.

Study design:

It is a prospective observational study.

Sample size:

With 95% confidence level and margin of error of ±10%, a sample size of 81 subjects will allow the study to assess the thyroid dysfunction in critically ill patients with finite population correction.

By using the formula:

$$n = \frac{z^2 p(1-p)}{d^2}$$

where

Z= z statistic at 5% level of significance

d is margin of error

p is anticipated prevalence rate

Sample size: 100

Duration of study: November 2017 to August 2019

Inclusion criteria

Critically ill patients admitted to medical emergency ward and CCU/ICU.

EXCLUSION CRITERIA

1. Age younger than 18 years.

2. Thyroid swelling detected by physical examination at the time of admission or previous history of thyroid diseases.

3. Patients on hormonal therapy or taking drugs which affect thyroid function (e.g. amiodarone) except insulin.

4. Pregnancy within past 6 months.

5. Patients with a history of ICU admission within previous 6 months.

METHOD OF STUDY

Patients admitted to medical emergency and CCU/ICU were explained about the study and written informed consent was taken. The relevant and required information was collected and the outcome of the patient (Survived/Died) was recorded.

Detailed history, clinical examination and the following investigations were carried out:

1. Complete Blood Count
2. Urine Routine
3. Serum urea, serum creatinine, serum electrolytes
4. Thyroid assay - T3, T4, TSH, free T3, free T4
5. Arterial Blood Gas analysis

The thyroid hormone assay (TSH, T3 and T4) was done by Chemiluminescence Immuno Assay (CLIA) using ADVIA Centaur equipment. FT3 and FT4 were measured by Enzyme Linked Immuno Sorbent Assay (ELISA) using Accubind ELISA kits.

Table: Reference range for serum thyroid hormones

Total T3	0.8 – 1.6 ng/ml
Total T4	4.2 – 12.0 µg/dL
TSH	0.4-6.0mIU/Ml
Free T3	4-7.4pmol/L
Free T4	9-23pmol/L

APACHE II score (Acute Physiology And Chronic Health Evaluation Score) was estimated for all subjects and also the predicted mortality in order to know the severity of the subject's illness was calculated.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance. ROC analysis for Sensitivity-specificity was done to check relative efficiency.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23.0. and Microsoft office 2007.

RESULTS

Population characteristics

Among the 100 subjects chosen for the study, 66 subjects were males (66%) and remaining 34 subjects were females (34%). Majority of the subjects were in the age group more than 50 years (60%).

TABLE 4: Distribution of cases according to age

AGE(Years)	N	%
≤20	3	3
21-30	14	14
31-40	8	8
41-50	15	15
51-60	21	21
61-70	18	18
>70	21	21
Total	100	100

Minimum age was 18 years and maximum was 87 years in our study.

	RANGE	MEAN±SD
AGE(Years)	18-87	53.9±18.6

FIGURE 5: Distribution of cases according to age

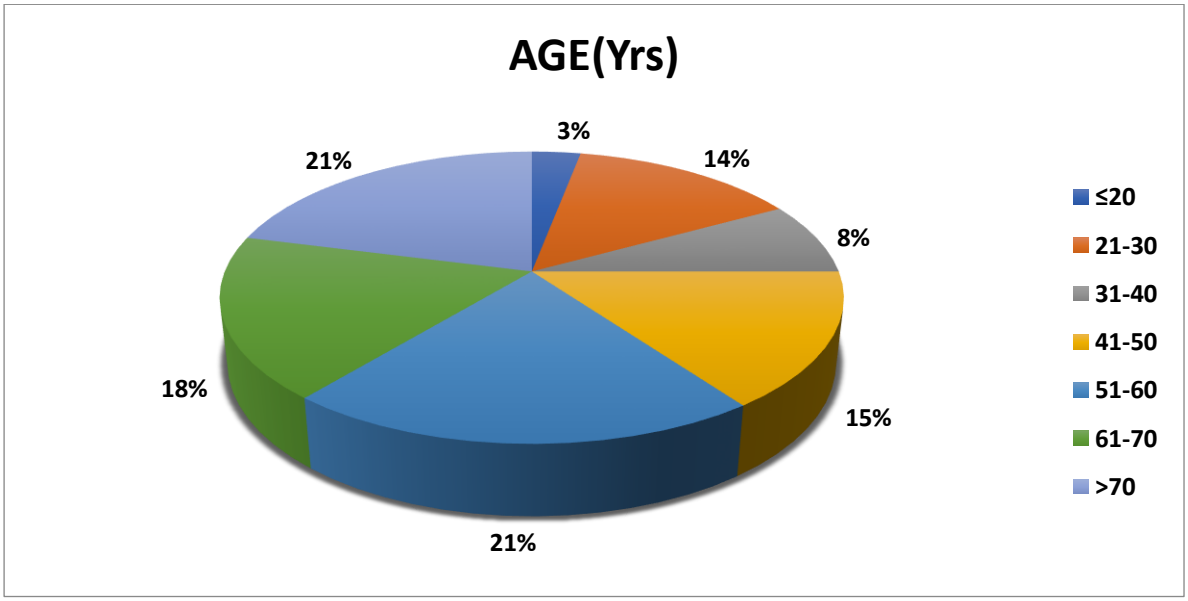


TABLE 5: Distribution of cases according to sex

SEX	N	%
FEMALE	34	34
MALE	66	66
Total	100	100

FIGURE 6: Distribution of cases according to sex

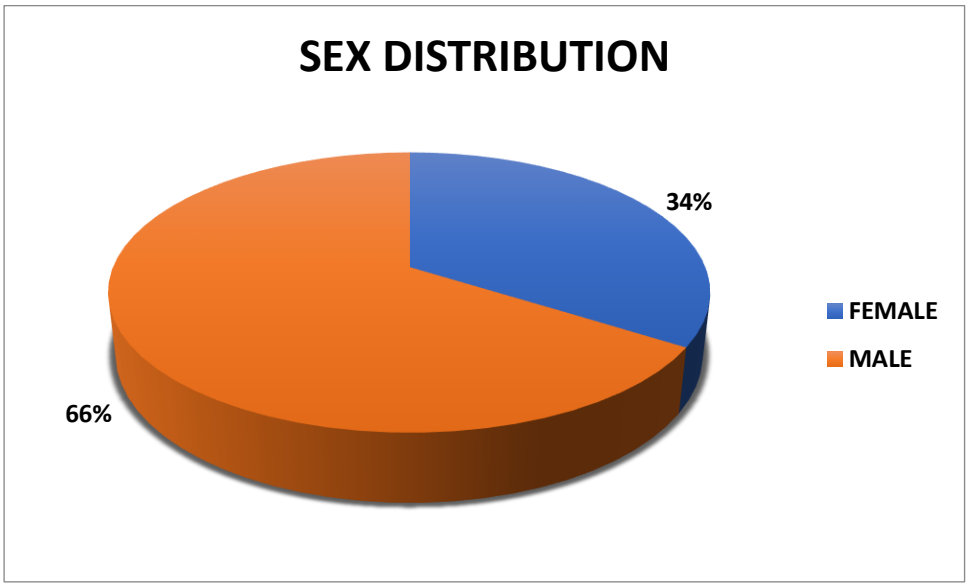


TABLE 6: Distribution of cases according to age and sex
This table show the distribution of male and female patients according to different age group.

AGE(Years)	MALE		FEMALE		p value
	N	%	N	%	
≤20	2	3.0%	1	2.9%	0.732
21-30	10	15.2%	4	11.8%	
31-40	5	7.6%	3	8.8%	
41-50	11	16.7%	4	11.8%	
51-60	11	16.7%	10	29.4%	
61-70	14	21.2%	4	11.8%	
>70	13	19.7%	8	23.5%	
Total	66	100.0%	34	100.0%	

FIGURE 7: Distribution of cases according to age and sex

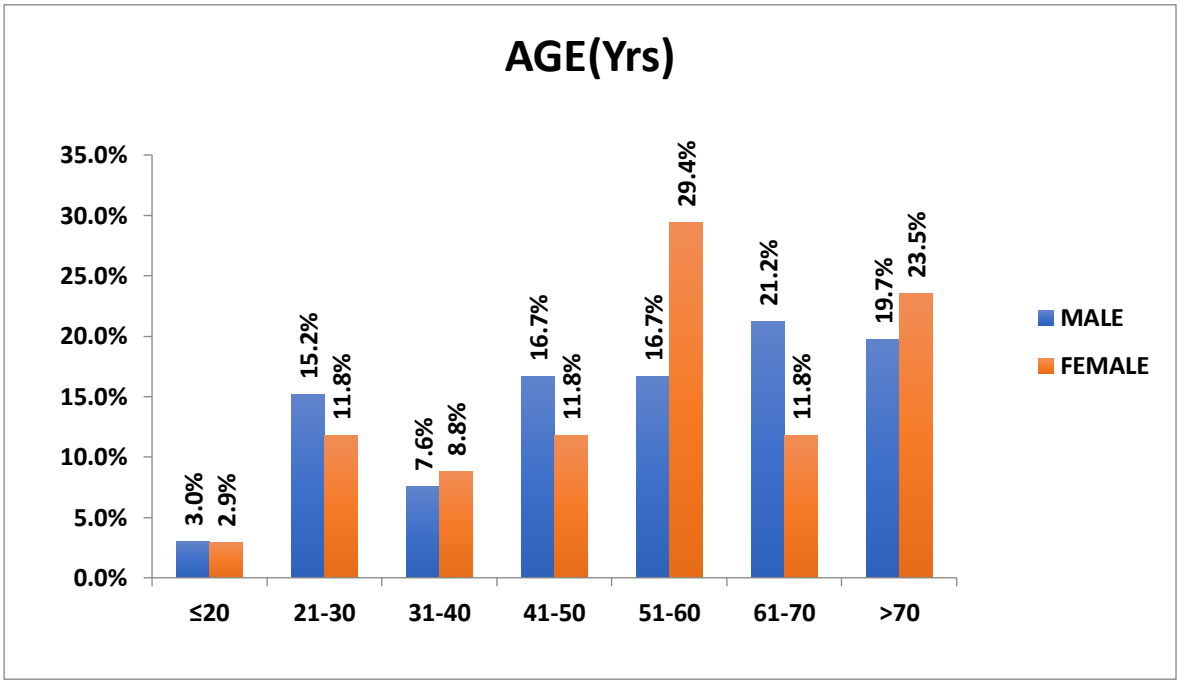


TABLE 7: Mean study parameters between died and survivors

This table shows relation between APACHE II score and mortality in all the cases of studied groups, there was significant statistical differences between died and survived groups as regarding APACHE II score (p value <0.001)

Parameters	DIED		SURVIVED		p value
	Mean	SD	Mean	SD	
APACHE II	25.9	7.2	18.0	6.4	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The table below shows relation between thyroid profile and mortality in all the cases of studied groups, there was significant statistical difference between died and survived groups as regarding total T3 (P < 0.001), while there were non-significant statistical differences as regarding total T4, TSH, FT3 and FT4.

Parameters	DIED		SURVIVED		p value
	Mean	SD	Mean	SD	
TOTAL T3	0.6	0.3	1.0	0.3	<0.001*
TOTAL T4	6.0	2.5	6.5	3.3	0.446
TSH	1.5	2.1	3.4	12.7	0.38
FREE T4	18.1	4.5	17.0	4.5	0.239
FREE T3	4.7	1.4	5.5	2.3	0.103

Note: * significant at 5% level of significance (p<0.05)

FIGURE 8: Mean study parameters between died and survivors

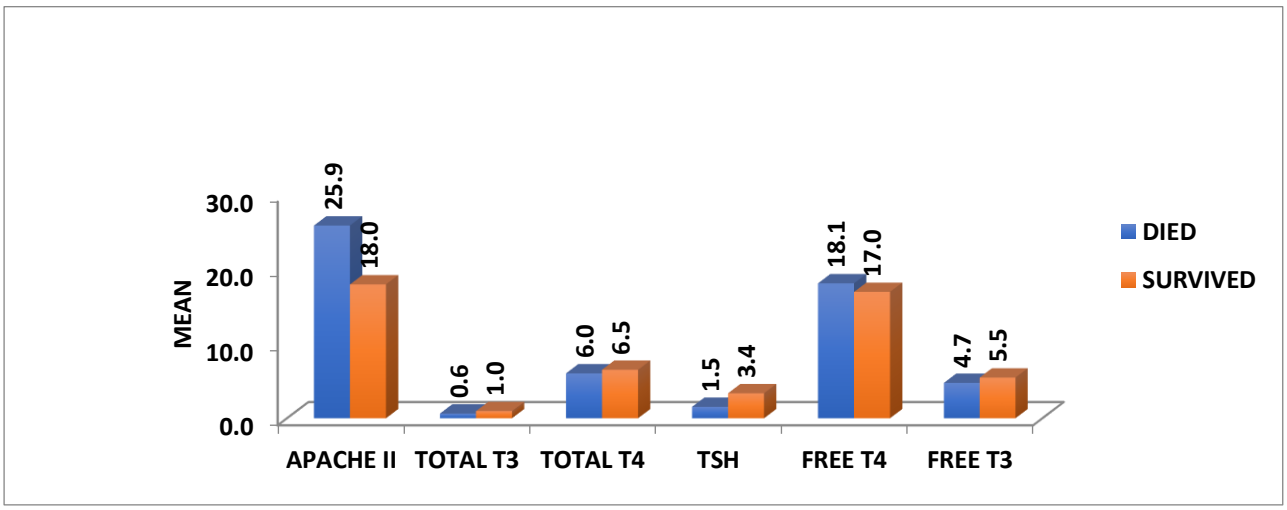


TABLE 8: Cases requiring ventilator between died and survivors

Among the 100 patients in our study, 56 patients required ventilator support, of that 33 patients died(P<0.001) which is statistically significant, and 23 patients survived. In our study, 44 patients did not require ventilator support, of which 5 patients died and 39 patients survived.

ON VENTILATOR	SURVIVED		DIED		p value
	N	%	N	%	
NO	39	65.0%	5	13.2%	<0.001*
YES	23	35.0%	33	86.8%	
Total	62	100.0%	38	100.0%	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 9: Cases requiring ventilation between died and survivors

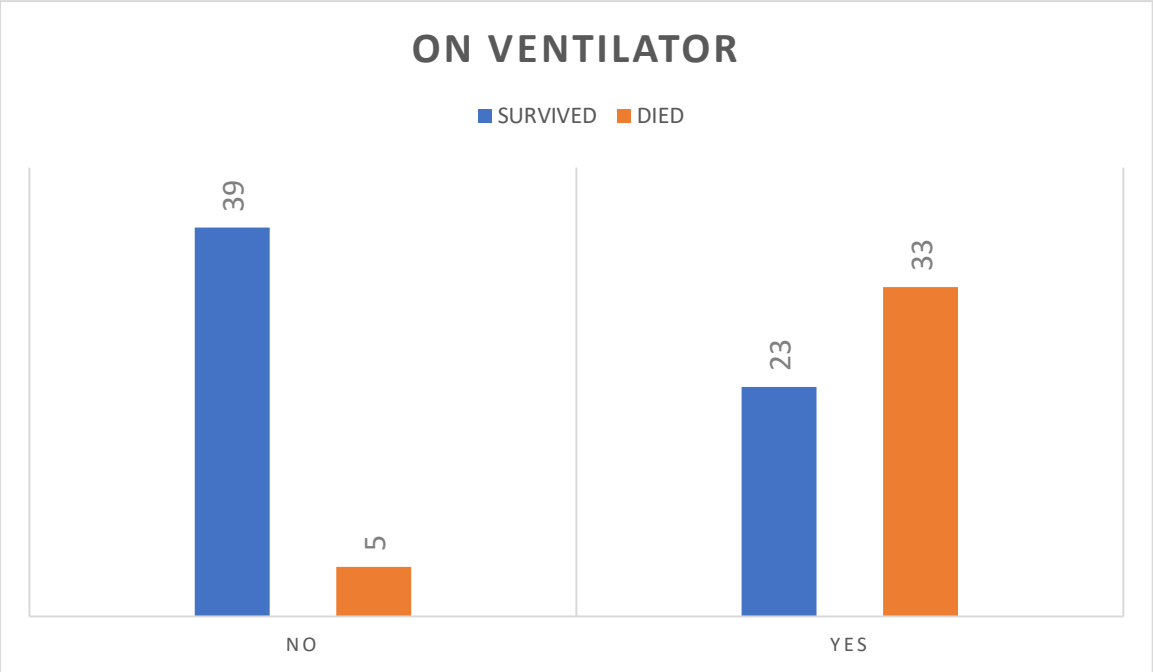


TABLE 9: Distribution of cases according to total T3

Among the 100 patients in our study, 45 patients had low T3 levels and 2 patients had high T3 levels.

TOTAL T3	N	%
LOW	45	45
NORMAL	53	53
HIGH	2	2
Total	100	100

FIGURE 10: Distribution of cases according to total T3

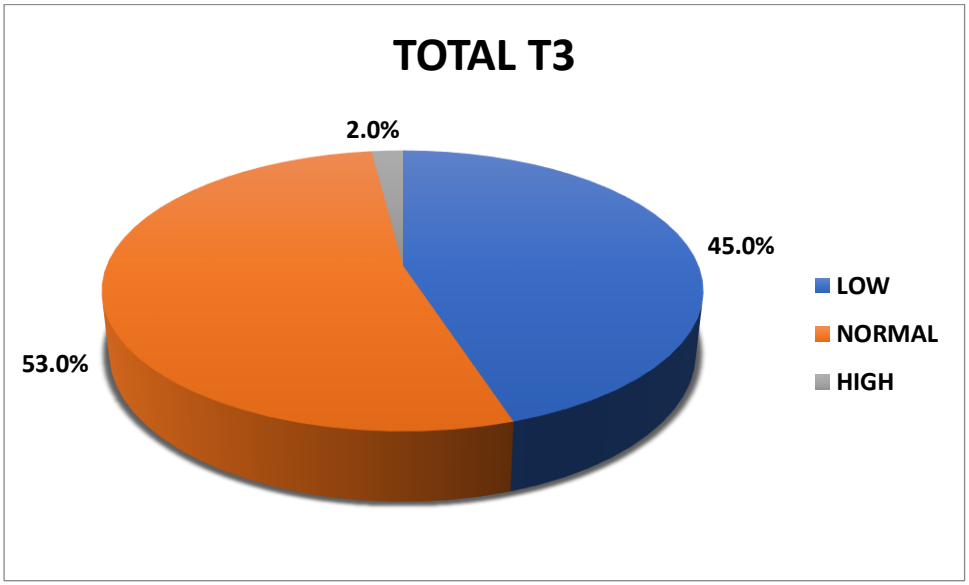


TABLE 10: Distribution of cases according to total T4
Among 100 patients, 15 patients had low T4 levels and 1 patient had high T4 level.

TOTAL T4	N	%
LOW	15	15
NORMAL	84	84
HIGH	1	1
Total	100	100

FIGURE 11: Distribution of cases according to total T4

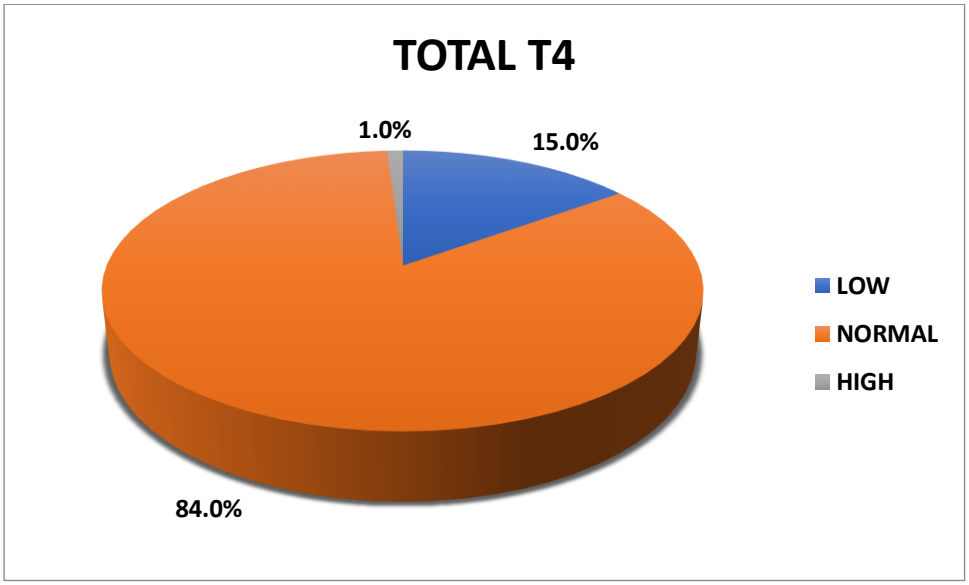


TABLE 11: Distribution of cases according to TSH
Among 100 patients, 20 patients had low TSH levels and 6 had high TSH levels.

TSH	N	%
LOW	20	20
NORMAL	74	74
HIGH	6	6
Total	100	100

FIGURE 12: Distribution of cases according to TSH

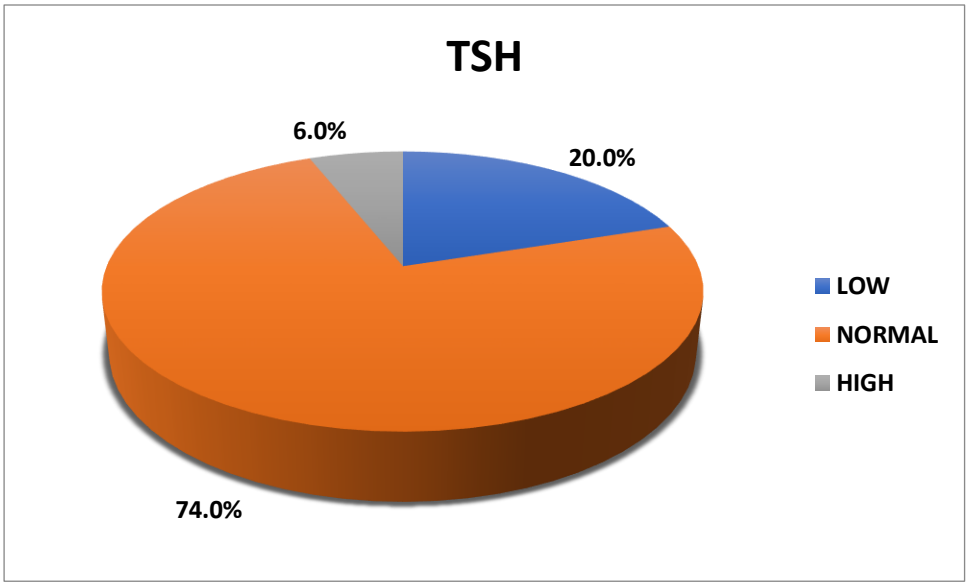


TABLE 12: Distribution of cases according to free T4

In our study, 12 patients had high free T4 levels and 2 patients had low freeT4 levels.

FREE T4	N	%
LOW	2	2
NORMAL	86	86
HIGH	12	12
Total	100	100.0

FIGURE 13: Distribution of cases according to free T4

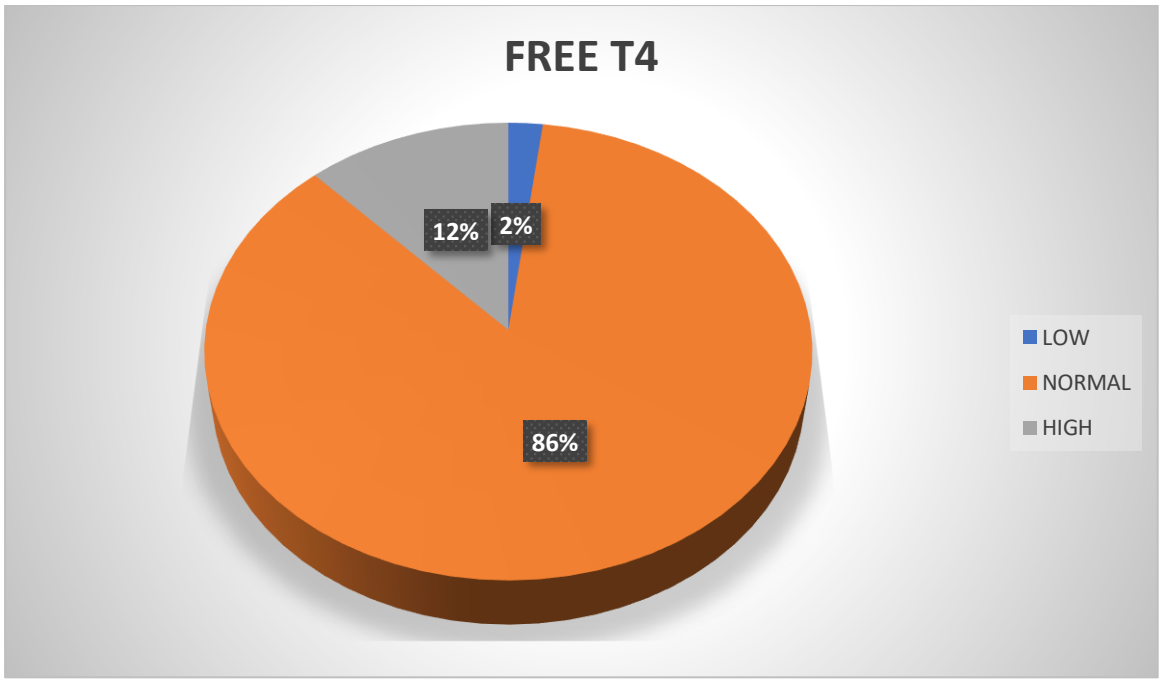


TABLE 13: Distribution of cases according to free T3

In our study, 17 patients had low free T3 levels and 7 patients had high free T3 levels.

FREE T3	N	%
LOW	17	17
NORMAL	76	76
HIGH	7	7
Total	100	100.0

FIGURE 14: Distribution of cases according to free T3

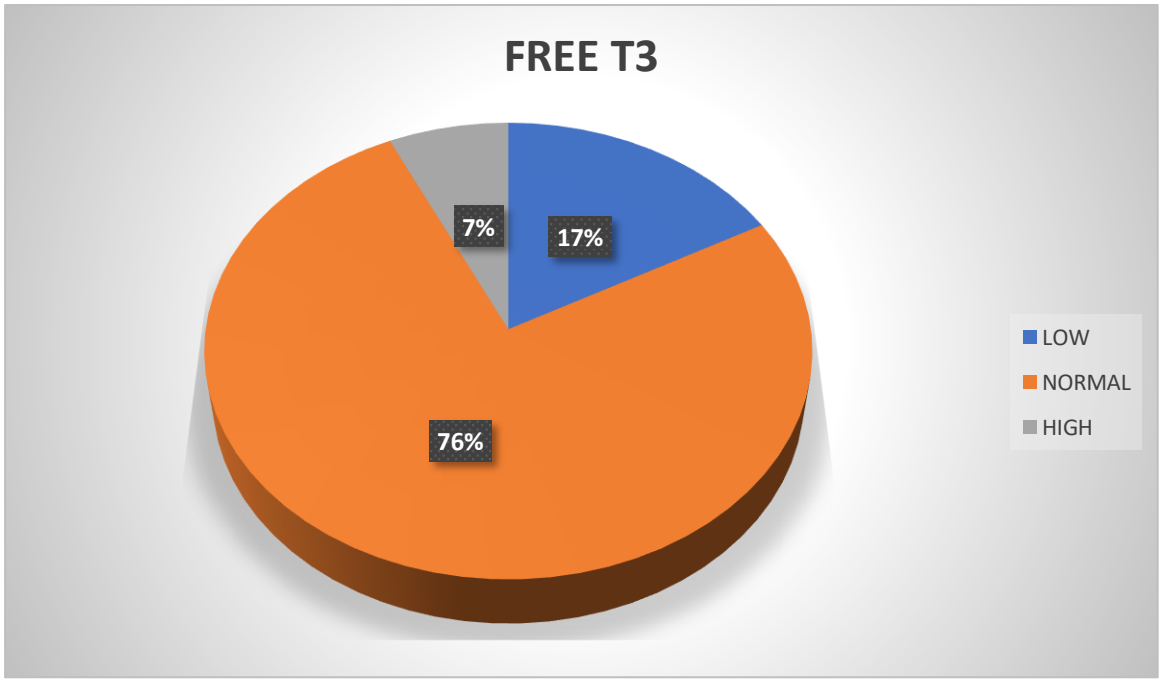


TABLE 14: Mortality according to total T3

In our study, among the 100 patients, 45 patients had low T3, of that 30 patients died(78.9%)

p value of <0.001 which is statistically significant.

TOTAL T3	DIED		SURVIVED		p value
	N	%	N	%	
LOW	30	78.9%	15	24.2%	<0.001*
NORMAL	7	18.4%	46	74.2%	
HIGH	1	2.6%	1	1.6%	
Total	38	100.0%	62	100.0%	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 15: Mortality according to total T3

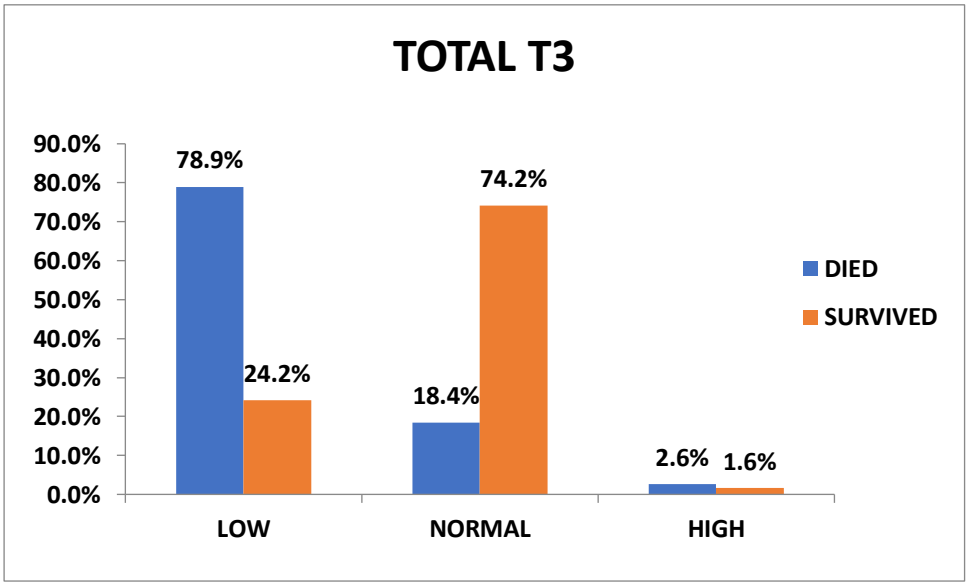


TABLE 15: Mortality according to total T4

Among 100 patients, 15 patients had low T4,6 patients died (15.8%) and 9 survived (14.5%), but it was not statistically significant (p value 0.727).

TOTAL T4	DIED		SURVIVED		p value
	N	%	N	%	
LOW	6	15.8%	9	14.5%	0.727
NORMAL	32	84.2%	52	83.9%	
HIGH	0	0.0%	1	1.6%	
Total	38	100.0%	62	100.0%	

FIGURE 16: Mortality according to total T4

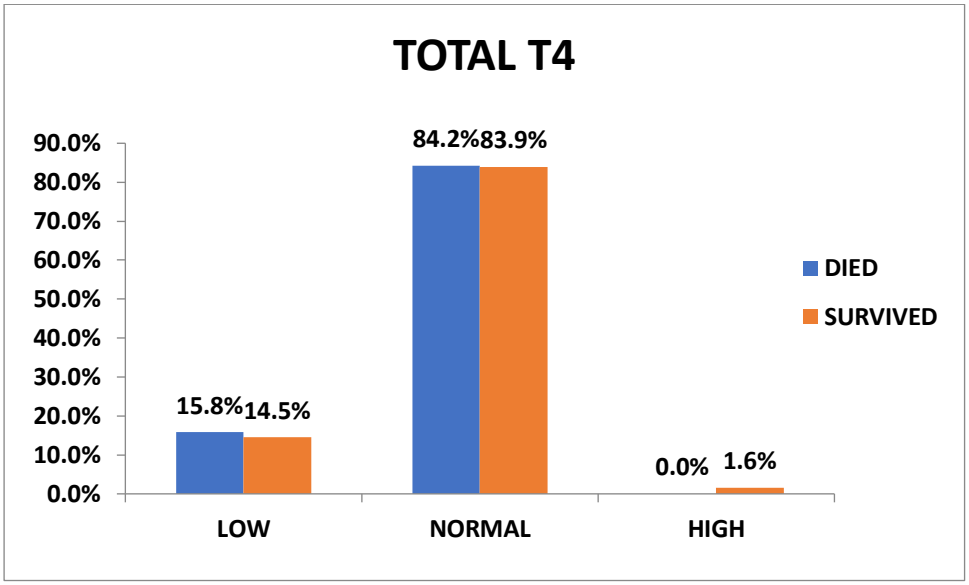


TABLE 16: Mortality according to TSH

Among 100 patients in our study, 26 patients had low/high TSH but it was not statistically significant (p value 0.216).

TSH	DIED		SURVIVED		p value
	N	%	N	%	
LOW	11	28.9%	9	14.5%	0.216
NORMAL	25	65.8%	49	79.0%	
HIGH	2	5.3%	4	6.5%	
Total	38	100.0%	62	100.0%	

FIGURE 17: MORTALITY ACCORDING TO TSH

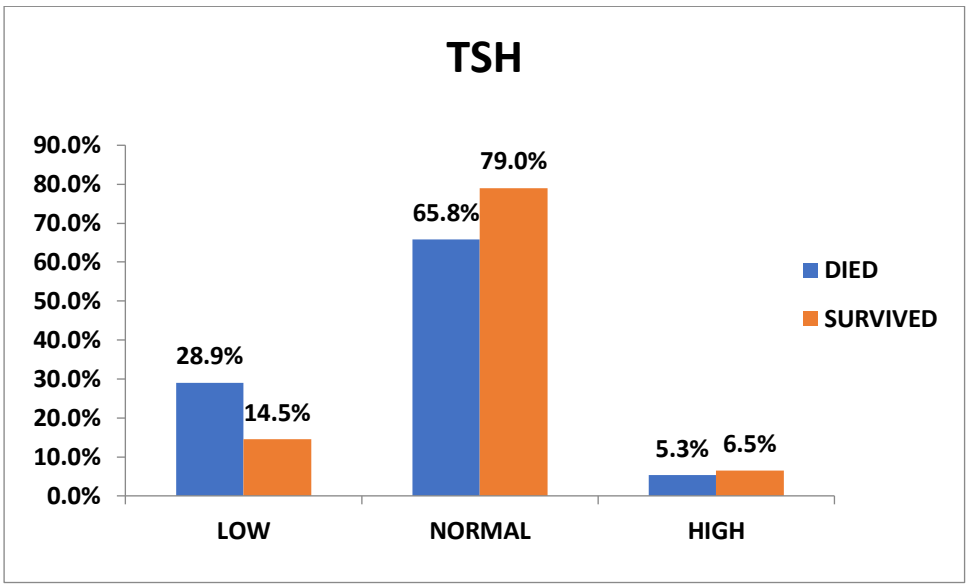


TABLE 17: Mortality according to free T4

In our study 12 patients had high free T4 and 2 patients had low free T4 but it was not statistically significant (p value 0.365).

FREE T4	DIED		SURVIVED		p value
	N	%	N	%	
LOW	0	0.0%	2	3.2%	0.371
NORMAL	32	84.2%	54	87.1%	
HIGH	6	15.8%	6	9.7%	
Total	38	100.0%	62	100.0%	

FIGURE 18: Mortality according to free T4

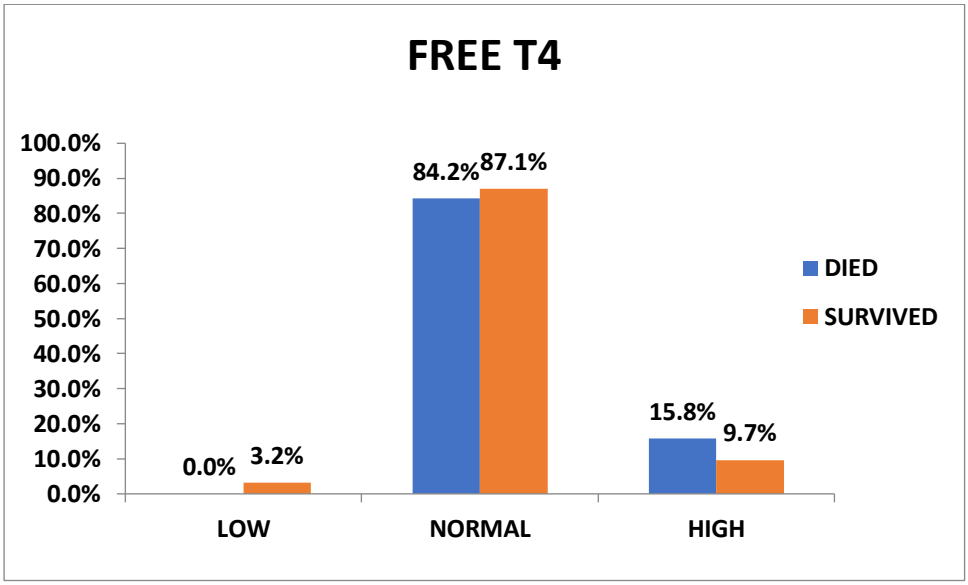


TABLE 18: Mortality according to free T3

In our study, 17 patients had low free T3, of that 11 patients died (31.4%) and 6 patients survived (10.3%) which is statistically significant (p value 0.038).

FREE T3	DIED		SURVIVED		p value
	N	%	N	%	
LOW	11	28.9%	6	9.7%	0.044*
NORMAL	25	65.8%	51	82.3%	
HIGH	2	5.3%	5	8.1%	
Total	38	100.0%	62	100.0%	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 19: Mortality according to free T3

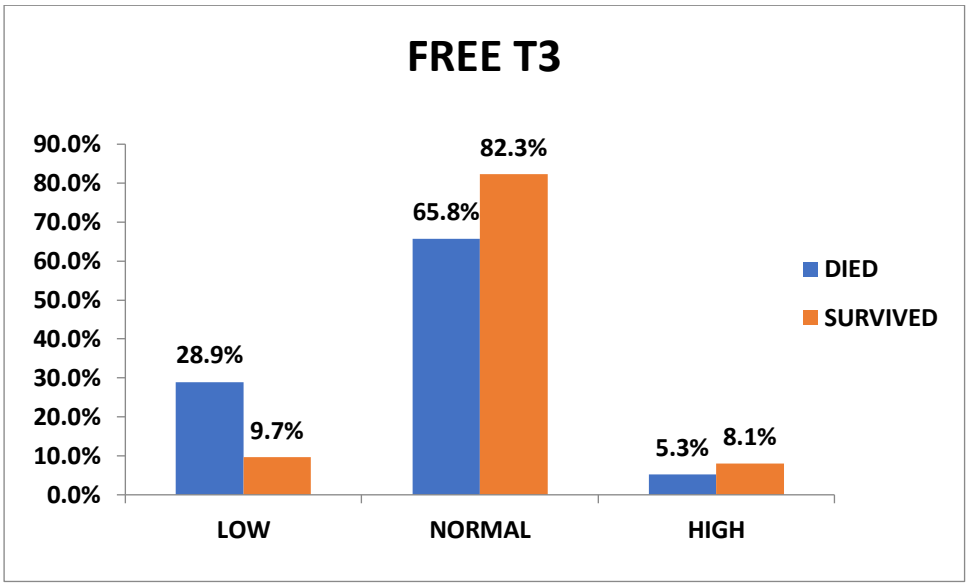


TABLE 19: Mean APACHE II by thyroid dysfunction

In our study, patients with low T3 had mean of 24.49 and SD of 7.10 with p<0.001 which is statistically significant. Patients with low FT3 had mean of 23.96 and SD of 7.80 with p<0.039 which is statistically significant.

MEAN APACHE II BY THYROID DYSFUNCTION	DYSFUNCTION		NORMAL		p value
	Mean	SD	Mean	SD	
TOTAL T3	24.49	7.10	17.85	6.92	<0.001*
TOTAL T4	18.00	8.23	21.54	7.54	0.093
TSH	20.77	7.95	21.04	7.70	0.878
FREE T4	22.14	7.27	20.92	8.00	0.596
FREE T3	23.96	7.50	20.12	7.80	0.039*

Note: * significant at 5% level of significance (p<0.05)

FIGURE 20: Mean APACHE II by thyroid dysfunction

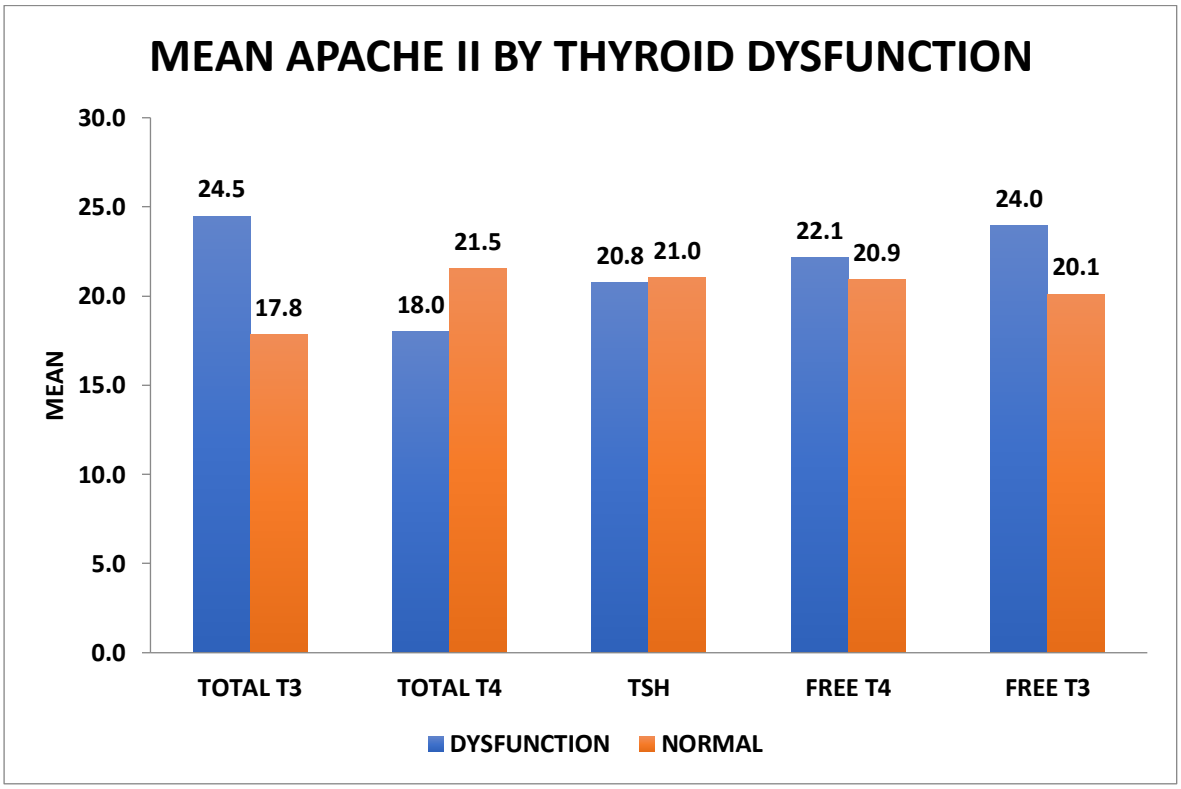


TABLE 20: Mean predicted mortality % by thyroid dysfunction

In our study, patients with deranged total T3 had a mean predicted mortality % of 47.3($p<0.001$) statistically significant and with normal T3 had 25.7. patients with deranged free T3 had mean predicted mortality % 47.8(p 0.003) statistically significant.

MEAN PREDICTED MORTALITY % BY THYROID DYSFUNCTION	DYSFUNCTION		NORMAL		p value
	Mean	SD	Mean	SD	
TOTAL T3	47.3	21.7	25.7	18.7	<0.001*
TOTAL T4	25.4	16.2	37.9	23.4	0.043*
TSH	37.7	19.8	35.2	23.8	0.64
FREE T4	39.3	23.5	35.7	22.7	0.597
FREE T3	47.8	21.3	32.3	21.9	0.003*

Note: * significant at 5% level of significance ($p<0.05$)

FIGURE 21: Mean predicted mortality % by thyroid dysfunction

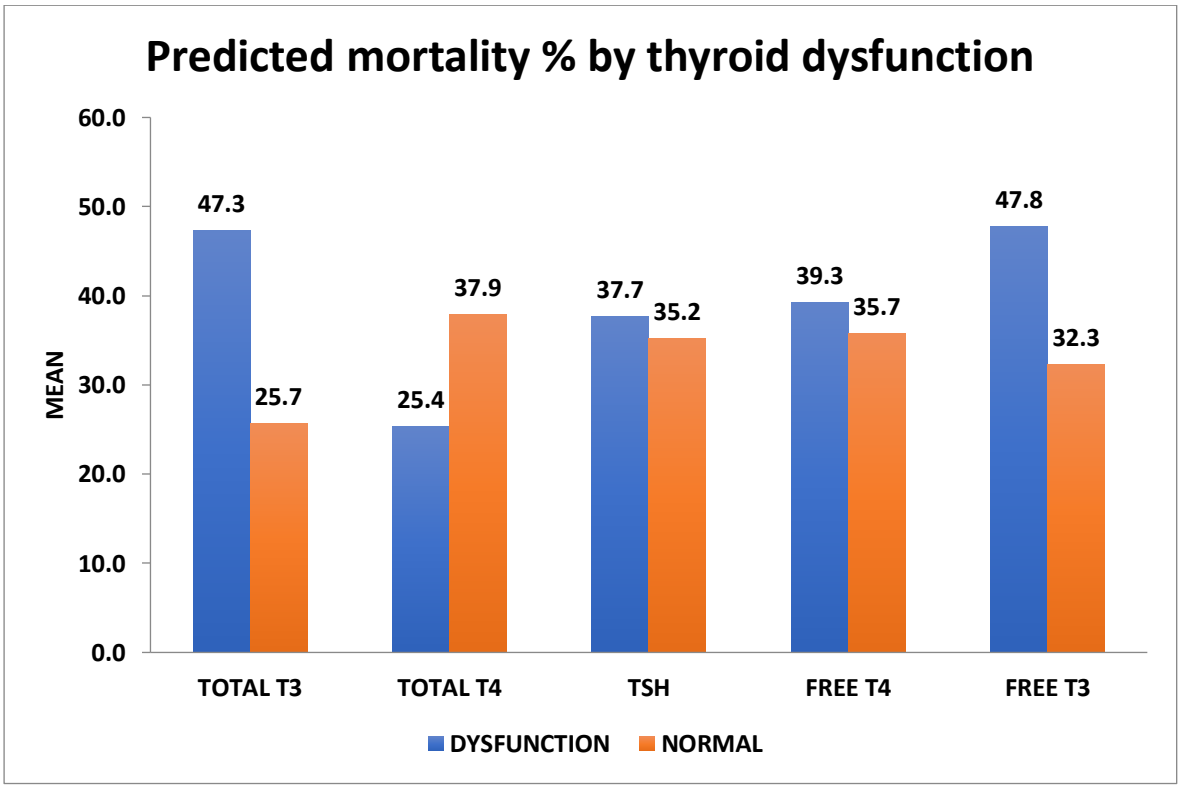


TABLE 21: Distribution of cases according to system involved

SYSTEM INVOLVED	N	%
RS	27	27
CNS	21	21
CVS	15	15
ENDOCRINE	11	11
POISONING/TOXINS/BITE	11	11
RENAL	5	5
GI/HEPATOBILIARY	5	5
NEOPLASM	2	2
SEPSIS	2	2
HANGING	1	1
Total	100	100

FIGURE 22: Distribution of cases according to system involved

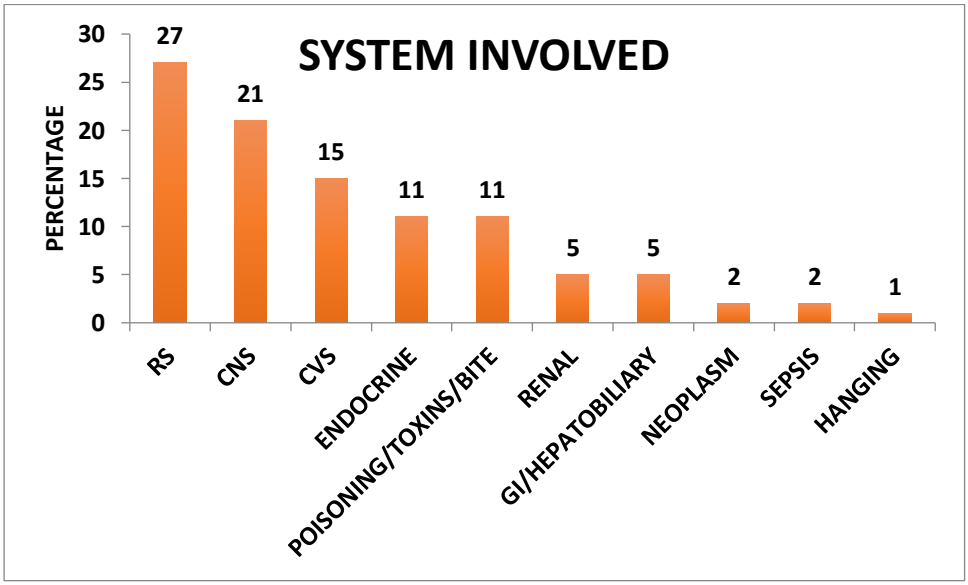


TABLE 22: Receiver operating characteristic (ROC) analysis of thyroid parameters and APACHE II in the prediction of mortality

This table shows that by ROC curve analysis, the best cut off value for predicting mortality was TT3 with Area Under Curve (AUC) 0.825 (95% CI 0.736-0.913) and (p< 0.001) which is statistically significant. Patients with values below these cut off values were at higher risk of mortality.

Parameters	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
TOTAL T3	0.825	0.045	<0.001*	0.736	0.913
TOTAL T4	0.518	0.061	0.772	0.398	0.638
TSH	0.561	0.062	0.323	0.439	0.683
FREE T4	0.432	0.063	0.272	0.308	0.555
FREE T3	0.597	0.062	0.119	0.475	0.719
APACHE II	0.791	0.047	<0.001*	0.699	0.882

Note: * significant at 5% level of significance (p<0.05)

FIGURE 23: ROC analysis of thyroid parameters and APACHE II in the prediction of mortality

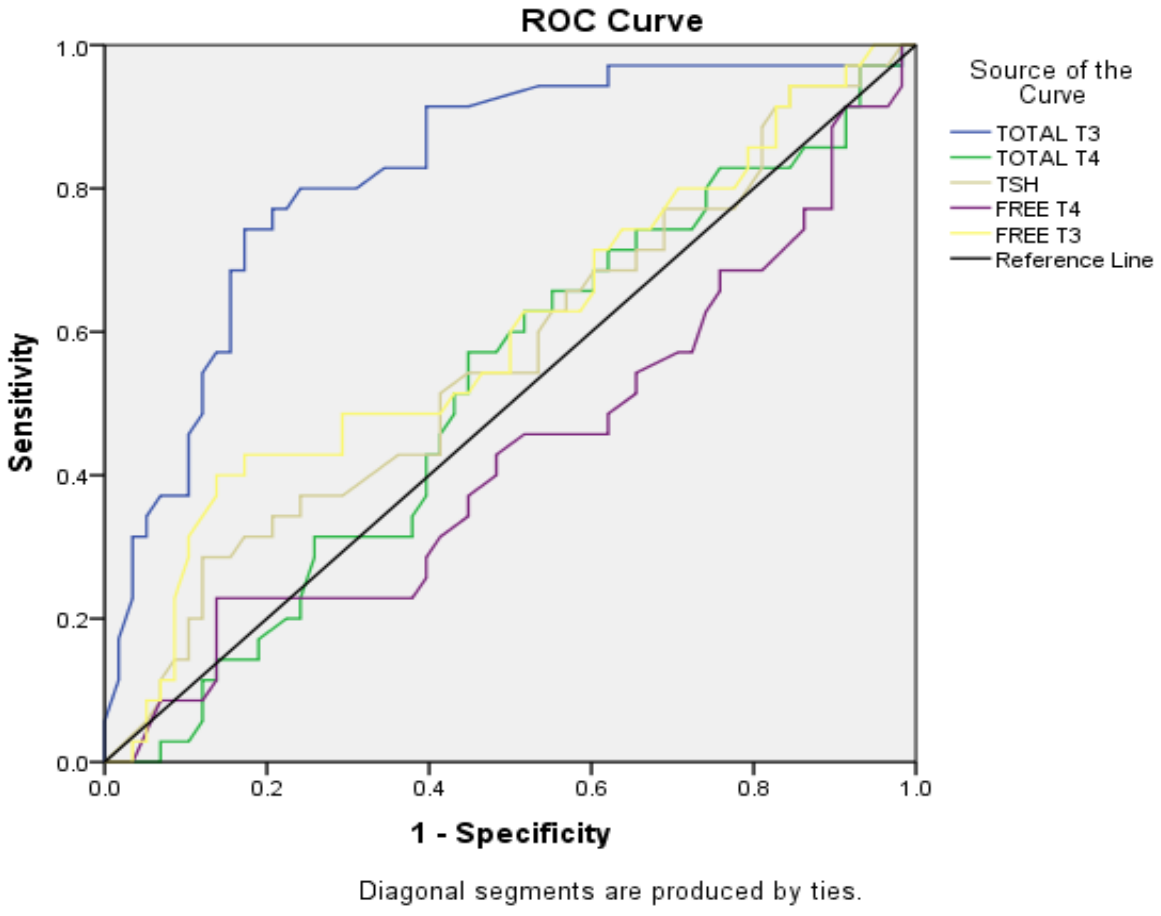


TABLE 23: ROC cut off values of thyroid parameters in the prediction of mortality

This table shows that by ROC curve analysis, the best cut off values for predicting mortality was TT3 of 0.77 with sensitivity 80% and specificity 76% (p< 0.001), TT4 of 6.36 with sensitivity 57% and specificity 55%. Patients with values below these cut off values were at higher risk of mortality.

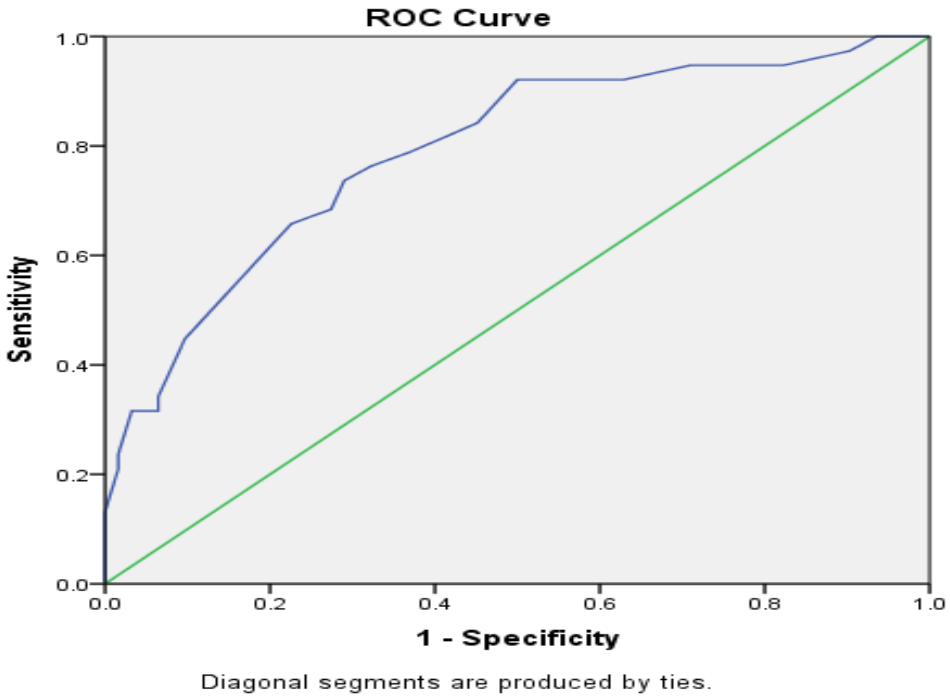
Parameters	Positive if Less than or equal to	Sensitivity	Specificity
TOTAL T3	0.77	80%	76%
TOTAL T4	6.36	57%	55%
TSH	0.98	54%	53%
FREE T4	16.48	46%	45%
FREE T3	4.84	54%	53%

TABLE 24: ROC cut off values of thyroid parameters in the prediction of mortality

This table shows that by ROC curve analysis, the best cut off value for predicting mortality for APACHE II score of 21.5 with sensitivity 74 % and specificity 71% (p < 0.001). Patients with values above these cut off values were at higher risk of mortality.

Parameters	Positive if more than or equal to	Sensitivity	Specificity
APACHE II	21.5	74%	71%

FIGURE: ROC cut off values of thyroid parameters in the prediction of mortality



DISCUSSION

In our study, we found that the levels of T3, FT3 and TSH levels were generally reduced in patients with NTIS. TT3 or FT3 levels were found to be better than TSH and T4 level (or FT4 level) for predicting ICU outcomes. The T3 or T4 levels are affected by the concentration of thyroxin-binding globulin (TBG) and the binding ability of TBG, which is affected by many health conditions like acute hepatic dysfunction and liver disease and by commonly used drugs in ICU like glucocorticoids, nonsteroidal anti-inflammatory drugs, furosemide and heparin. Conversely, FT3 levels are not affected by these factors. Thus FT3 may be better than T3 levels for predicting ICU outcomes.

In our study, 66% were males and remaining 34% were females. 60% subjects were in the age group of more than 50 years. Depending upon the changes in T3, T4, free T3, free T4 and TSH, thyroid hormone alterations were categorized into low T3, low T4, low TSH, high TSH, low FT3, high FT3 and high FT4. Majority of the subjects had low T3(45%), low FT3(18.3%). TSH was reduced in 20% and elevated in 6% patients.

In our study, patients with low total T3 had a mean predicted mortality % of 47.3($p<0.001$). Patients with low free T3 had mean predicted mortality % 47.8(p 0.003).

T3 and FT3 levels were significantly lower in non survivors compare to survivors (P value <0.001 and 0.038 respectively). Although TT4 and TSH were lower in non survivors than in survivors, it was statistically not significant (P values 0.727 and 0.216 respectively). Hence, estimation of T3 and FT3 levels in a critically ill patient may help in predicting the outcome. Low T3 level is associated with poor outcome in terms of mortality. Mortality rate was higher in subjects with thyroid dysfunction, than in the subjects without thyroid dysfunction.

A similar study was conducted in India at Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar by Zargar and it was noted that severity of illness correlated with decrease in T3 and T4. A low T3 and T4 with low or undetectable TSH were associated with increased

mortality. At the onset of acute illness low T3 was seen in 113 (29.6%, low T3 -low T4 in 50 (13.1%), high T4 in 28 (7.3%) lowT3-lowT4- low TSH in 10 (2.6%) and low T4 alone in 4 (1%) patients. T3 (mean) was significantly reduced at the onset of illness compared to that in the controls. Although serum TSH showed noticeable fall and rise in some individuals, no significant difference in mean TSH was observed during any period of illness compared to that in the controls[42].

In a similar study done by Feilong wang, at Shanghai, a total of 480 consecutive patients without known thyroid diseases were screened and followed up during their ICU stay. It was found that among the thyroid hormones, FT3 had the greatest power to predict ICU mortality, could independently predict primary outcome. 23 (4.79%), 53 (11.04%), 261 (54.38%) and 48(10.00%) patients had low T3, low T4, low FT3 and low FT4 levels, respectively, and 17 (3.54%) and 30 (6.25%) patients had high TSH and rT3 levels, respectively. A total of 91 patients (19.13%) died during their ICU stay. The levels of TT3, TT4, FT3, FT4, TSH and T3/rT3 were lower in non survivors than in survivors (all $P < 0.01$). Compared with survivors, Non survivors were older and had higher APACHE II scores (19.49 ± 6.85 vs 11.38 ± 5.60, $P< 0.0001$)[43].

In our study, low T3 was seen in critically ill patients because the conversion of T4 to T3 is inhibited by deiodinase.

CONCLUSION

- Low T3 and low free T3 levels were seen in 45% and 18.3% subjects respectively.
- Most common pattern of thyroid dysfunction was Low T3 (Low T3 syndrome).
- Mortality rate was higher in subjects with thyroid dysfunction than in subjects without thyroid dysfunction.
- T3 levels were lower in Non survivors than in Survivors (P values <0.001). No significant difference was noted in T4, free T3, free T4 and TSH levels among survivors and non survivors.

  Hence, in our study of critically ill patients, we had common occurrence of low T3 level correlates with poor outcome in terms of mortality, which was in accordance with the other studies conducted earlier.

  Therefore, estimation of T3 level in a critically ill patient may help in correlating the outcome.

SUMMARY

Care of a critically ill patient remains a major global healthcare concern, owing to high morbidity and mortality, despite the advances in medical therapeutics. Alterations in the thyroid hormone levels in an acutely ill patient (Non Thyroidal Illness Syndrome) correlates with the severity of morbidity and mortality of patients admitted to medical emergency ward and ICU. In critically ill patients there is no clear evidence to treat non thyroidal illness. This study was designed and conducted to evaluate the incidence of non thyroidal illness and whether these could correlate with mortality in critically ill patients.

100 patients admitted to CCU/ICU and medical emergency ward who met the inclusion and exclusion criteria were selected for the study after obtaining the written informed consent. Baseline clinical examination and biochemical parameters, including the APACHE II score were estimated within 24 hours. All patients were followed up during the hospital stay and outcome of the patient was recorded (survivors/died).

• Majority of the subjects were in the age group of more than 50years (60%). 66% were males and remaining 34% were females.

• Low T3 and low free T3 levels were seen in 45 (45%) and 17 (18.3%) subjects respectively. Most common patterns of thyroid dysfunction were low T3. Mortality rate was higher in subjects with thyroid dysfunction than in subjects without thyroid dysfunction.

• Patients with low total T3 had a mean predicted mortality % of 47.3 and with low free T3 had mean predicted mortality % 47.8. T3 levels was lower in Non survivors than Survivors (P values <0.001). Hence, low T3 level is associated with poor outcome in terms of mortality. Therefore, estimation of T3 levels in a critically ill patient may help in predicting the outcome.

LIMITATIONS OF THE STUDY

1. The inclusion of patients with undetected thyroid disease before ICU admission may be unavoidable, even though we evaluated patients by detailed history and clinical examination.

2. Thyroid hormones were estimated only at the time of admission and not after complete recovery from the present illness. Hence, these patients require long term follow up.

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ANNEXURE –II

INFORMED CONSENT FORM

TITLE OF THE PROJECT- THYROID DYSFUNCTION IN CRITICALLY ILL PATIENTS IN A TERTIARY CARE HOSPITAL

I) INFORMED PART

1) Purpose of research:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) Procedure:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) Risk and discomforts:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) Benefits:

I understand that my participation in this study will help the patient's survival and better outcome.

5) Confidentiality:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records but will be stored in the

investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) Request for more information:

I understand that I may ask more questions about the study at any time doctor is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the study which might influence my continued participation.

If during the study or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) Refusal or withdrawal of participation:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that doctor may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) Injury statement:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be

available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Date:

(Investigator)

II) STUDY SUBJECT CONSENT STATEMENT:

I confirm that doctor has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date:

_____ _____

Witness to signature Date:

APPENDIX –III

THYROID DYSFUNCTION IN CRITICALLY ILL PATIENTS IN A TERTIARY CARE HOSPITAL

SCHEME OF CASE TAKING

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Past Occupation:

Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past History:

History of immunization:

Personal History:

Diet/appetite:

Sleep:

Bladder and bowel habits:

Smoking/Tobacco chewing/Snuff Inhalation/alcohol:

Family History:

TB:

Asthma:

Malignancy:

DM:

HTN:

Treatment History:

General Physical Examination

Height:

Weight:

Body Mass Index:

Vitals

PR:

BP:

RR:

Temp:

Head to toe examination:

SYSTEMIC EXAMINATION:

Cardiovascular System:

Respiratory System:

Per abdomen:

Central Nervous System:

Glasgow Coma Scale (GCS):

a. Eye Movements:
b. Verbal Response:
c. Motor Response:

INVESTIGATIONS

Urine routine and microscopy	

Complete blood count:

Hemoglobin	gm. %
Total WBC counts	Cells/mm^3
Differential counts	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour
Hematocrit(%)	

Arterial blood gas analysis:

Parameters	Test values	Units
Ph		
PCO_2		mmHg
PO_2		mmHg
HCO_3		mmol/L
SBC		mmol/L
BEb		mmol/L
BEecf		mmol/L
TCO_2		mmol/L

SO_2C		**%**
RI		
FIO_2		**%**

Thyroid profile:

Thyroid stimulating hormone (TSH)	
Total thyroxine (T4)	
Free thyroxine (free T4)	
Total tri-iodo thyronine(T3)	
Free tri-iodo thyronine (free T3)	

Renal function test:

Urea	
Serum creatinine	
Serum sodium	
Serum potassium	
Serum chloride	
Uric acid	

FINAL DIAGNOSIS:

Acute Physiology And Chronic Health Evaluation (APACHE) II Score

Physiological Variable	Score
Temperature(ºCelsius)	
Mean arterial pressure(mmhg)	
Heart rate (beats per min)	
Respiratory rate (cycles per min)	
Oxygenation:A-aDO_2 or PaO_2 (mmhg) a. FiO2≥0.5 record A-aDO_2 b. FiO2<0.5 record only PaO_2	
Arterial pH	
Serum Sodium(mMol/L)	
Serum Potassium(mMol/L)	
Serum Creatinine(mg/100ml)	
Hematocrit (%)	
White Blood Cells(cells/mm3)	
Glasgow Coma Score (GCS)	
A.Total ACUTE PHYSIOLOGY SCORE(APS)	
B. Age points	
C. Chronic Health Points	
TOTAL APACHE II SCORE	