"A STUDY OF THYROID PROFILE AS A PREDICTOR OF MORTALITY AND MORBIDITY IN ICU ADMITTED PATIENTS – A ONE YEAR CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE HOSPITAL AND MRC"

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"A STUDY OF THYROID PROFILE AS A PREDICTOR OF MORTALITY AND MORBIDITY IN ICU ADMITTED PATIENTS – A ONE YEAR CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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ABSTRACT

Background: Thyroid hormones are the endocrine messengers that play a key role in normal development, growth, neural differentiation, modulating metabolism and immune system. In ICU admitted patients, a variety of hormonal changes secondary to alterations in the hypothalamic-anterior pituitary-peripheral hormone axes are observed which differ among acute and chronic illness. To further substantiate this view, we undertook a study among medical ICU patients to detect the independent predictors of ICU mortality and morbidity on the basis of Thyroid hormone levels.

Material and Method: Patients admitted in the ICU of KLES Dr. Prabhakar Kore Hospital for any reason from January 2021 to December 2021 were included in the study. After obtaining the informed consent, all baseline demographic and clinical characteristics were recorded. Fasting blood samples were collected from all patients immediately upon admission to the ICU. Patients were followed up till discharge or death, whichever occurred first. Samples were tested for free T3, free T4, and TSH. All data was entered in the Microsoft excel sheet and then imported to SPSS version 22 software for statistical analysis.

Results: A total of 115 adult patients admitted to the ICU of KLEs Dr Prabhakar Kore Hospital, Belagavi were included in the study. Patients belonged to the age group of 18 to 90 years with a median of 56 years and mean ± standard deviation (SD) age of 55.58 ± 15.21 years.In our study, mortality was significantly higher among patients with decreased free T3 levels (n=22, 84.6%; p=0.003).

Conclusion: The results of our study show a positive correlation between decreased free T3 levels and mortality among patients admitted in the ICU. Furthermore, patients with sepsis or septic shock and chronic liver diseases having lower free T3 levels were also at much higher risk of mortality. No significant association between free T4 and TSH levels and mortality was observed. The findings of our study highlight the importance of including thyroid profile tests in chronically ill patients to predict the prognosis of the patient.

Keywords: ICU, TSH, Free T3, Free T4.

LIST OF ABBREVIATIONS

T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
HPT	Hypothalamo Pituitary Thyroid
TRH	Thyrotropin Releasing Hormone
ICU	Intensive Care Unit
NTIS	Non Thyroidal Illness Syndrome
rT3	Reverse Triiodothyronine
fT3	Free Triiodothyronine
fT4	Free Thyroxine
TT3	Total Triiodothyronine
TT4	Total Thyroxine
CLD	Chronic Liver Disease

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INTRODUCTION

Thyroid hormones are the endocrine messengers that play a key role in normal development, growth, neural differentiation, modulating metabolism and immune system [1]. Upon its activation from prohormone thyroxine (T4) to the active form, triiodothyronine (T3), the thyroid hormone regulates a wide range of genes through highly regulated complex signaling pathway [2]. production and secretion of thyroid hormones is mainly modulated by the hypothalamic-pituitary-thyroid (HPT) axis. The regulation of thyroid hormones is done by negative feedback mechanism of circulating thyroid hormones. The thyroid stimulating hormone (TSH) secreted by the pituitary gland is considered an important biomarker of thyroid action in humans [3].

In critically ill patients, a variety of hormonal changes secondary to alterations in the hypothalamic-anterior pituitary-peripheral hormone axes are observed which differ among acute and chronic illness. The severity is related to higher morbidity and mortality. However, whether these endocrinal alterations are physiological adaptations or lead to further progression of the disease/illness is elusive [4,5]. In 1970s, changes in the thyroid hormones in critical patients without the preexisting thyroid diseases were first reported and these were termed as non-thyroidal illness syndrome or classic euthyroid syndrome. It was characterized by increased reverse T3 levels, significant decrease in the serum thyroid hormone levels which was positively correlated with morbidity and mortality while the TSH remains normal. While, mild illness was associated with decreased in serum T3 levels, increased duration of illness and severity was associated with drop in both serum T3 and T4 levels [6,7].

Although the severity of NITS is correlated to prognosis, the exact mechanism and causality of the syndrome is yet to be elucidated. It remains a matter of debate whether or to what extent these changes are adaptive or contributing to the metabolic support of the critically ill patient is a relatively new target of active research and little is as yet known about the effects of critical illness on metabolism. Previous studies have shown that alterations in the thyroid hormone levels can be considered an independent predictor of morbidity and mortality among critically ill patients admitted in the intensive care units (ICU), emphasizing the inclusion of thyroid profile in scoring system in those patients [8-11].

To further substantiate this view, we undertook a study among medical ICU patients to detect the independent predictors of ICU mortality and morbidity on the basis of Thyroid hormone levels.

AIM AND OBJECTIVE

AIM

- To evaluate relationship between thyroid hormone levels and prognosis of patients admitted in the ICU

OBJECTIVE

- To assess the role of Thyroid Function tests such as free T3, free T4 and TSH as a predictor of prognosis in patients admitted in ICU.

REVIEW OF LITERATURE

Thyroid hormones are the endocrine messengers, which along with insulin, growth hormone, glucocorticoids and other hormones are required for the normal growth and development of vertebrates. The production and secretion of thyroid hormone are regulated by series of conserved pathways known as 'hypothalamic-pituitary-thyroid axis'.Thehypothalamic-pituitary-thyroid (HPT) axis maintains the thyroid hormone homeostasis [12-14]. The secretion and regulation of thyroid hormone is depicted in figure 1.

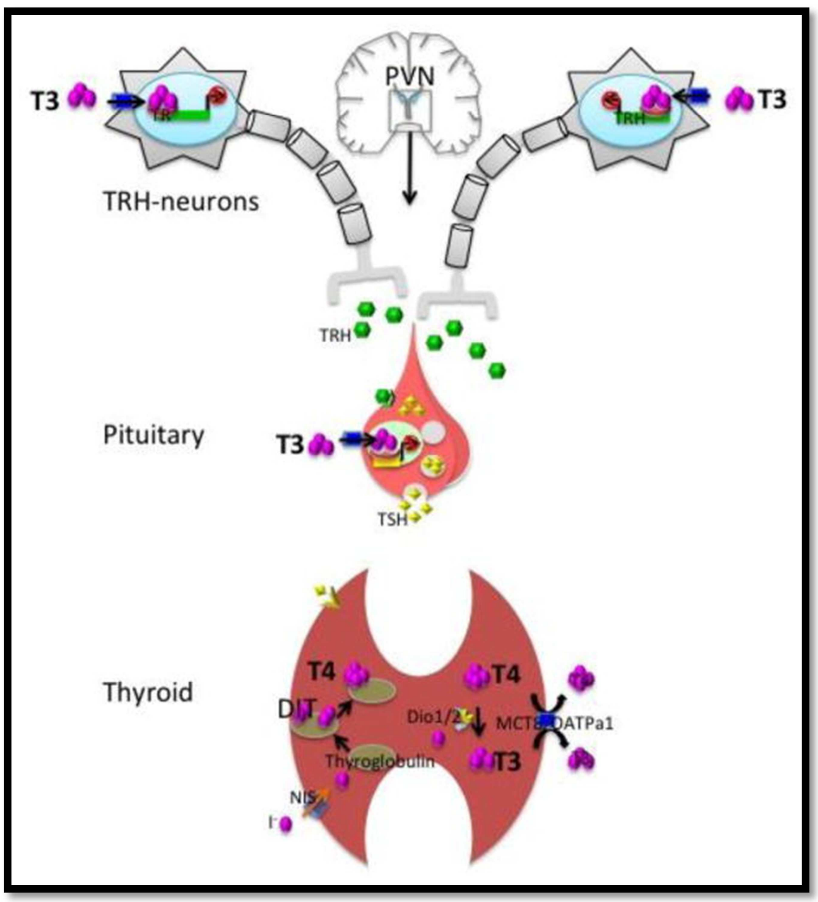

Figure 1: Secretion and regulation of thyroid hormones

In response to environmental and physiological stimuli, including low T3/T4 ratio thyrotropin-releasing hormone (TRH) neuronssecrete TRH from the paraventricular nucleus. Upon its release into the median eminence, TRH induces secretion of the TSH from the anterior pituitary. TSH further stimulates the release of thyroid hormones from the thyroid gland to the bloodstream. The circulating T4 and T3 with optimum T3/T4 ratio sends negative feedback to the TRH and TSH genes in the paraventricular nucleus, thereby regulating the production of TRH and TSH and maintaining normal circulating thyroid hormones (Figure 1) [12-14].

The synthesis of Thyroid hormone requires iodine uptake via sodium/iodide symporter, production and iodination of thyroglobulin by thyroid peroxidase enzyme. Proteolysis of thyroglobulin releases T4 and T3 with a ratio of 14:1. Most of the conversion from T4 to T3 is due to iodothyronine deiodinases type 1 and 2. More than 99.7% thyroid hormones are bound to plasma proteins and only a small amount is available as free T4 (fT4) and T3(fT3) forms. The free form is biologically active [15-17].

Factors affecting the thyroid function

Genetic factors account for approximately 65% of interindividual variations in the TSH and thyroid hormone levels. Other factors include, demographics such as age, sex, microorganisms, stress, concomitant medication use and other environmental factors including lifestyle and pollutants directly affect the production of thyroid hormones [18-21]. The factors affecting the thyroid function are depicted in figure 2.

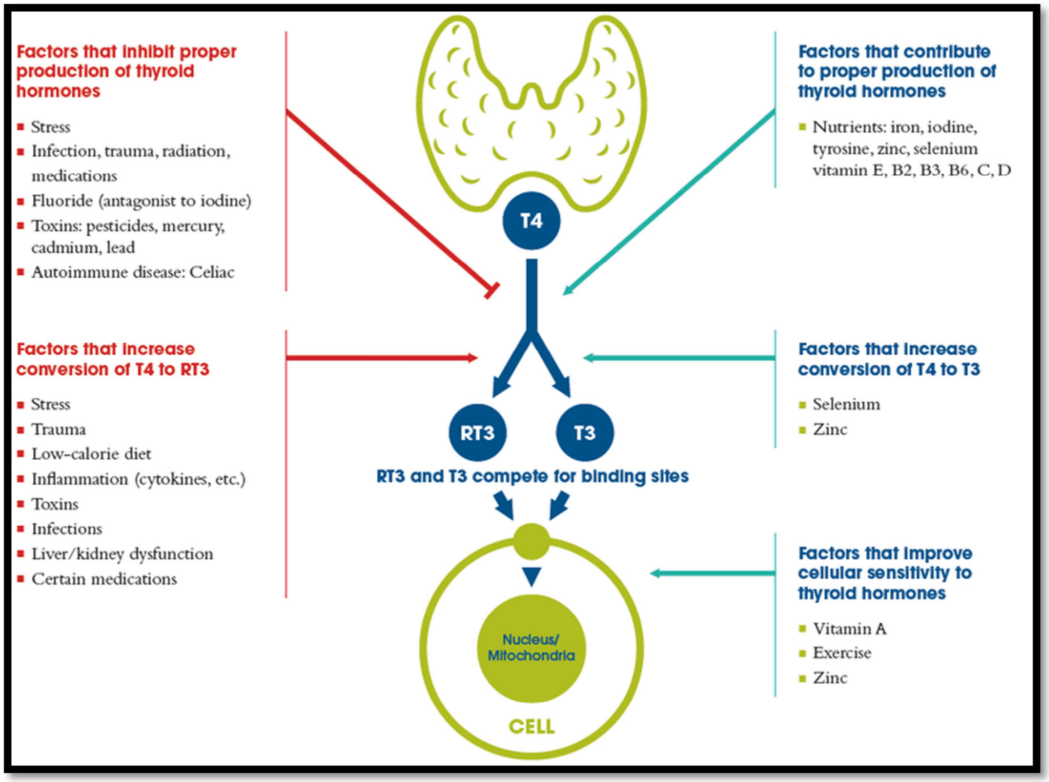

Figure 2: Factors affecting the thyroid function

Normal levels of thyroid hormones

Normal and optimal range of thyroid levels are shown in figure 3. [22, 23]

Name of Marker	Normal Range	Optimal Range
TSH	.35 to 5.0	1.8 to 3.0
Total T4 or TT4	6-12 ug/d	5.4-11.5 ug/dL
FTI	4.6-10.9 mg/dL	1.2-4.9 mg/dL
Free T4 or FT4	0.7-1.53 ng/dL	1.0-1.53 ng/dL
Resin T3 Uptake	24 - 39 md/dL	28 - 38 md/dl
Free T3 or FT3	260 - 480 pg/mL	300 - 450 pg/mL
TBG	15 - 30 ug/dl	18 - 27 ug/dl
TPO Antibody	<15	<15

Figure 3: Normal levels of thyroid hormones

Role of thyroid gland in normal growth

During the process of development, cellular proliferation and apoptosis is balanced by multihormonal mechanisms including T3. Based on animal studies, T3 is a liver mitogen that promotes hepatocytic proliferation after partial hepatectomy suggesting its role in development. T3 also has shown positive role in wound healing in variety of tissues [24,25]. Studies also report a role of T3 in branching morphogenesis and epithelial/mesenchymal differentiation of lungs and influences linear growth by stimulating DNA synthesis in osteoblasts and other cells [26].

Thyroid hormones in disease

Alterations in thyroid function is indicated by Variations in the TSH and thyroid hormone levels. During depression there is reduced TSH response to TRH stimulation resulting in decreased serum thyroid hormone levels. Moreover, there is reduced conversion of T4 to T3. Reduced thyroid hormone levels are also seen in patients with acute hepatitis, fulminant hepatitis and autoimmune liver disease. Medications such as dexamethasone and propranolol inhibit deiodinases resulting in reduced peripheral T3 and increased T4 levels. Similarly, T4 to T3 conversion is reduced in chronic renal failure resulting in decreased T3 and T4 levels; while reverse T3 remains normal. Decreased TSH and TSH response is noted in acute fasting in adults and in patients with anorexia nervosa and nutritional dwarfing. This results in decreased T3 and increased reverse T3 levels. In patients with obesity, thyroid hormone levels are normal [27].

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Endocrinal changes during critical illness

Critical illness refers to conditions that are life-threatening and require support of vital organ function for patient's survival. During critical illness, substantial changes in the plasma concentrations are reported in various studies which are characterized by decreased thyroid hormone levels and increased reverse T3 levels. Despite these changes the TSH levels are relatively normal. As these changes occur in patients without previous thyroid illness, these changes are called non-thyroidalillness syndrome(NTIS) orlow T3 syndrome or euthyroid syndrome [28, 29]. These changes are often seen in patients following acute stress due to myocardial infarction, surgery or in patients with chronic illness such as cardiovascular, gastrointestinal diseases, infectious diseases, burns, malignancy and trauma[30,31]. Previous studies have reported that serum T3 level or combination of T3 and T4 levels have high sensitivity and specificity in predicting mortality in patients with chronic diseases[33]. The decreased levels of T3 are correlated with severity of disease and is considered a marker of prognosis in chronic ill patients.

Pathogenesis of NTIS

Various hypothesis has been formulated to understand the pathogenesis of NTIS. Hypothalamic-pituitary-thyroid (HPT) axis feedback regulation and metabolism of thyroid hormone is the common mechanism leading to NTIS. During critical illness there is change in the thyroid hormone levels resulting in the HPT axis downregulation at hypothalamus and pituitary axis with a net resultant of lower serum thyroid hormone concentrations. However, the exact mechanism behind this is yet to be elucidated. Previous studies have briefly explained the mechanism and the same is depicted in figure 4.

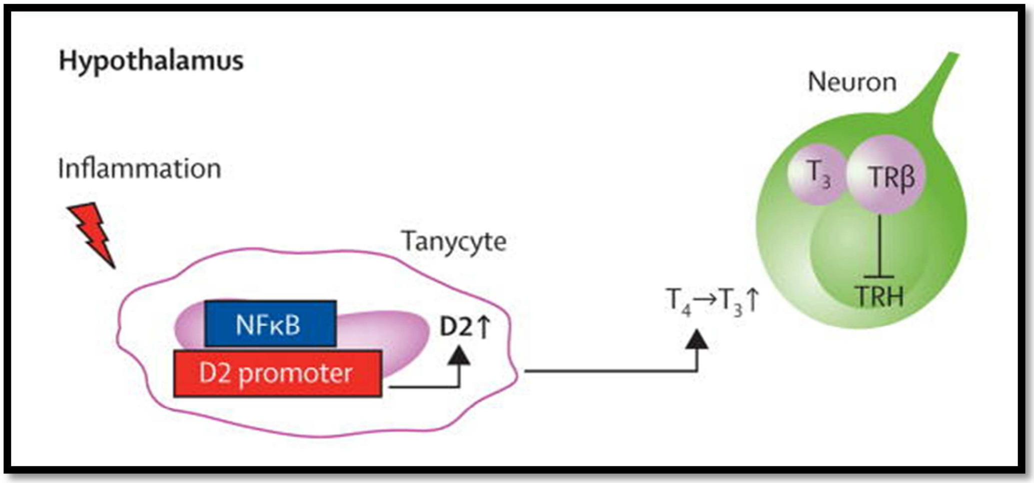


Figure 4: TRH regulation in hypothalamus in critical illness

NTIS induces changes in the enzymes Deiodinases type 1, 2 and 3 which regulates the thyroid hormones metabolism. Presence of inflammation in the body,causes activation of NFkB pathway in tancytes which express Deiodinase 2 essential for conversion of T4 to T3. Binding of NFkB to the tancytes increase the deiodinase expression and activity. The converted T3 enters the neurons which are adjacent to it and binds to TRβ in those neuronsand regulates the transcriptional activity of TRH and downregulation of Hupothalamo-pitutary-thyroid (HPT) axis during NTIS. There is also reported decrease in the Deiodinase 2 levels in liver linking to the pathogenesis of illness induced T3 and reverse T3 changes in circulation. Additionally, during critical illness there is substantial hypoxia or ischemia that results increased thyroid hormone catabolism via Deiodinase 3[33- 36]. Previous studies have shown an association between thyroid hormone metabolism and activation of pro-inflammatory cytokines during acute phase reaction. Most importantly, the activated cytokines secondary to inflammation play a role in pathogenesis of NTIS, suggesting NTIS is part of acute phase reaction [37].

NTIS and its effect on different organs

Thyroid hormones are required for growth and development and functioning of several organs in the body. During NTIS there is an overall downregulation of the metabolism in the organism to conserve energy. Investigations have suggested correlation between specific cells such as granulocyte, macrophages, lung epithelial cells, skeletal muscles and thyroid hormones signaling during critical illness. Thyroid hormones target cells and organs that respond to inflammation by increasing and decreasing the deiodinase expression and further cellular function [28,38,39]. Brief overview is shown in Figure 5.

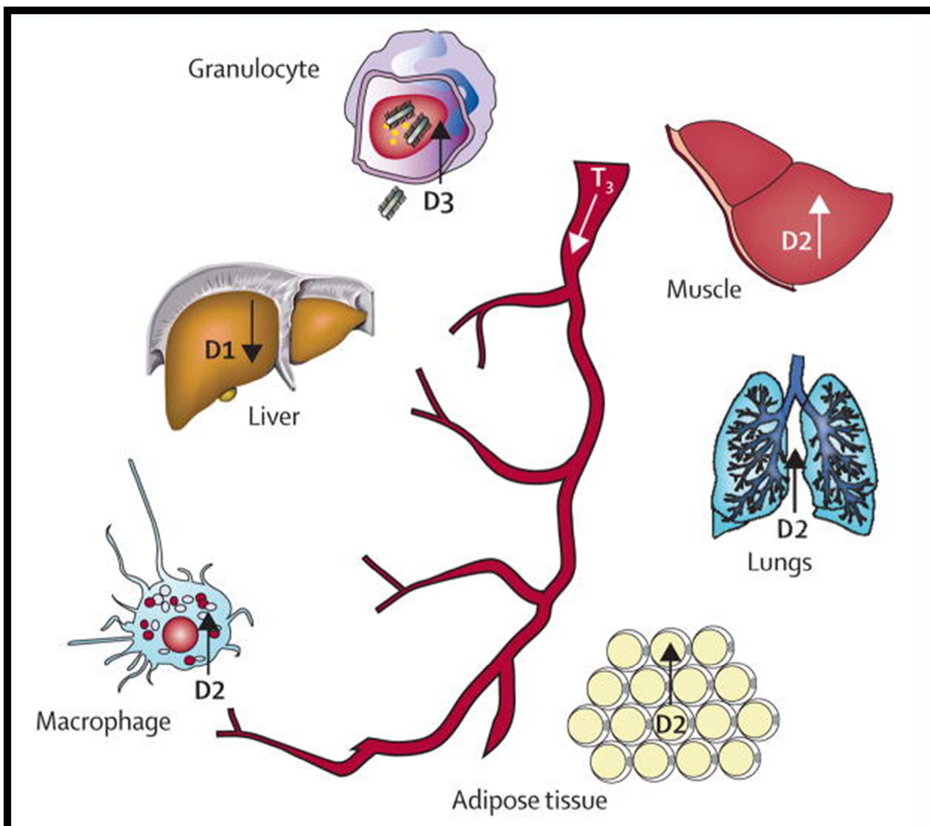


Figure 5: Effect on deiodinase activities in various tissues in NTIS.

Critical illness also occurs with decrease in appetite and poor parenteral and oral nutritional intake. The decreased food intake may imitate fasting state resulting in decreased serum hormone levels, reduced serum leptin and downregulation of thyrotropin releasing hormone (TRH), TSH. Moreoverm, there is decreased T4 to T3 and rT3 conversion resulting in development of NTIS [40, 41]. Overall, during critical illness there is alterations or adaptations in the HPT axis, and changes in the organ level and intrathyroidal changes with net result of decreased thyroid hormone concentrations.

Diagnosis and differential diagnosis of NTIS [42-44]

- NTIS is characterized by presence of very low free T3, low or normal free T4 or normal TSH with the absence of hypothyroidism features. When both T3 and T4 are very low the prognosis is poor.
- If elevated TSH is also present, overt primary hypothyroidism can be suspected. In these patients test for anti-thyroid peroxidase antibody should be performed. However, positive anti thyroid peroxidase antibody is although indicative of diagnosis, it does not prove hypothyroidism.
- Similarly, high TSH levels, high T3 to T4 ratio and low thyroid binding ratio and low rT3 could mean both hypothyroidism or NTIS.
- History of medication intake such as anticonvulsants and glucocorticoids can also lower free T4.
- Decreased TSH can also be seen in hyperthyroidism. However, decreased T3 and T4 levels are supportive of NTIS.

Related studies

den Brinker M, et al (2005) [45]conducted an observational cohort study to evaluate the role ofdisease severity, deiodination, sulfation, thyroid hormone binding, and dopamine use on thyroid function in euthyroid sick syndrome among 69 children with meningococcal sepsis admitted at paediatric ICU. Thyroid function were compared between survivors, both shock and sepsis and non-survivors. Among the 45 non-dopamine treated children, although there was no difference in the TSH levels, there was decreased total T3 to rT3 ratio and decreased T4 sulfate levels. Compared to shock survivors, non survivors had higher levels of TT3/rT3 ratios (0.30 vs. 0.71) correlating with short disease duration (r = -0.43). Compared to non-dopamine treated children, the 24 dopamine treated children had lower levels of TSH significantly (0.84 vs. 0.65), while other thyroid hormone levels were comparable. The authors concluded that children with meningococcal sepsis euthyroid sick syndrome. TT3/rT3 ratio and TT4 levels were predictive for mortality.

Suvarna JC, et al (2009) [46] carried out a study to evaluate the levels of thyroid hormones among critically-ill patients and assess the correlation between clinical outcome and disease severity. The levels of total serumT3, T4 and TSH were evaluated on admission and at the time of discharge or just before death. Compared to controls, Mean T3 levels was significantly low at admission and before death whereas mean T4 levels were low among patients and among those who died. Mean TSH levels were comparable. The authors reported than lower T3 and T4 levels increases the risk of mortality by 30 times and levels improved in patients who survive. Additionally, PRISM score at 24 hours and T4 levels were significant predictors of survival. The authors concluded that T3 levels reflect patient's clinical status and T4 levels predict survival.

Mingote E, et al (2012)[47] conducted a retrospective study to evaluate the association between thyroid profile and morbidity/mortality (MM) among hospitalized elderly patients. Between 2009 and 2010, data of a total of 2599 patients >60 years of age admitted to the hospital for various reasons were screened. In the study, high MM was defined as prolonged hospital stay, requirement of ICU or mortality in hospital and during follow up. Among then 7% patients, mostly women underwent thyroid function tests. Based on the thyroid values, patients were categorized into non thyroid illness, 61%; euthyroid, 25%; overt hyperthyroidism, 7%; overt hypothyroidism, 5% and subclinical hyper or hypothyroidism, 1%. Among these groups, patients with hypothyroid had the worst clinical outcome. Patients with high MM were significantly associated with increased TSH and low TT4 ($p<0.005$). While, lower TT4 values were strongly associated with short term MM (OR=2.0, 95%CI=1.1-3.6, $p<0.01$), higher TSH levels were associated with long term MM (OR=1.6, 95%CI 1.1-2.3, $p<0.05$). The authors concluded that TSH can be a useful tool to assess the MM in elderly hospitalized patients.

Wang F, et al (2012)[48] conducted a study to evaluate the prognostic value of thyroid indicators including fT3, total T3, T4, fT4, TSH and rT3 among 480 known thyroid patients admitted in ICU. Data including baseline characteristics, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and thyroid hormone levels, N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) levels were recorded at baseline. fT3 was superior at predicting ICU mortality with AUC of 0.762±0.028. Although the AUC was less than APACHE II score

(0.829±0.022), AUC was higher than NT-proBNP (0.724±0.030) and CRP levels (0.689±0.030). Based on multiple regression analysis, fT3 (P=0.001), APACHE II score (P<0.001), NT-proBP (P=0.017) and CRP levels (P=0.030) were independent predictors of ICU mortality. Moreover, combination of fT3 and APACHE II score were better predictors of mortality. The levels of Ft3 correlated to NT-proBNP levels (P<0.001) and CRP levels (P<0.001) levels. The authors concluded that among thyroid hormones fT3 is the only independent predictor of ICU mortality; the predictive ability increases with fT3 levels are used in combination with APACHE-II scores.

Galusova A, et al (2015)[49] carried out a study to evaluate the changes in neuroendocrine hormones among 24 critically ill polytrauma patients and association with morbidity. Blood levels of thyroid-stimulating hormone (TSH), total triiodothyronine (T3); free triiodothyronine (fT3), total thyroxine (T4), free thyroxine (fT4), growth hormone (GH), prolactin (PRL) and procalcitonin levels were assessed on day 1, 2, 3 and 7. At baseline, the TSH, T4, fT4 were normal in all patients whereas 20% and 33%, patients had low T3 and fT3 levels. At day 7, there was significant increase in TSH levels (p=0.07) and significant decrease in fT4 levels (p=0.03). The authors concluded polytrauma results in immediate dynamic hormonal response.

van der Jagt M, et al (2015)[50] carried out a retrospective cohort study among 29 comatose patients secondary to cardiac arrest to evaluate the prognostic role of pituitary-thyroid axis response to resuscitation from cardiac arrest before, during and after therapeutic hypothermia. Samples were collected before during and up to 48 h after a 24-h period of therapeutic hypothermia in the ICU. TSH levels and free T3 levels were comparable between survivors and non-survivors. Significant increase in the free T4 levels was observed among non survivors than survivors ($P = 0.001$). The thyroid hormone levels declined on both groups up to 72 h after start of 24 h hypothermia. The sensitivity analysis of free T4 showed a maximum AUC of 0.83 ($P = 0.003$) and an optimal cut off of ≥17.8 pmol/L to obtain 100 % specificity and positive predictive value for non-survival. The authors concluded that non-survivors following cardiac arrest, coma, and therapeutic hypothermia after successful resuscitation is associated with a transient increase in free T4, most probably due to inhibition of free T4 to T3 conversion.

In order to elucidate the TH metabolism during critical illness,Langouche L et al (2016)[51] conducted a cross sectional study among 83 critically ill patients admitted at intensive care unit of a University Hospital. A total of 38 demographically matched healthy volunteers were included as controls. Commercial assays and in-house developed immunoassays were used to analyse thyroid profile. Compared to the healthy controls, the serum 3-T1AM concentration and serum 3,5-T2 concentration were median 44% lower ($p < 0.0001$) and a 30% higher ($p = 0.01$), respectively among cases. Among patients with sepsis and non survivors there was significant increase in 3,5-T2 ($p \leq 0.01$), however the 3-T1AM ($p > 0.2$) concentrations were comparable with survivors and those without sepsis. According to the Multivariate linear regression analysis low serum 3-T1AM was positively correlated with the low serum T3 ($p < 0.001$). The authors suggested further studies to elucidate the role of 3-T1AM or 3,5-T2 in critical illness.

Quispe E Á, et al (**2016)**[52] conducted a study to compare theability of thyroid hormones, IL-6, IL-10, and albumin to predict mortality among critically ill patients.

A total of 79 cases of mix acute critically ill patients without previous history of thyroid disease were included in the study. On admission to ICU, APACHE II scores and serum thyroid hormones, IL-6, IL-10, and albumin levels were recorded. Primary outcome was 28-day mortality. Compared to survivors at 28 days, non survivors were older, having higher APACHE II score (p=0.000), IL-6 (p<0.05), IL-10 (p=0.000) levels, and lower albumin levels (p=0.000). There was a negative correlation between Inflammatory markers including IL-6 and IL-10 and albumin (p=0.001) and FT3 (p < 0.05), however, a positive correlation was reported between lower albumin levels and FT3 (p<0.05). With an good AUC-ROC of 0.70-0.79, IL-10, albumin and APACHE II were independent predictors of mortality (p<0.05). However, FT3 serum levels were not predictors of mortality. The authors concluded that thyroid hormones assessed at admission did not have predictive value of prognosis in critically ill patients.

Gutch M, **et al (2018)**[53] conducted a study to find the relationship between the levels of thyroid hormones and outcome of patients in the ICU. A total of 270 patients with no previous thyroid disease, admitted to the ICU were included. Baseline characteristics, lactate, acute physiology and chronic health evaluation (APACHE-II) score, thyroid hormone levels were recorded. The mean (SD) age of the patients was 39 (18) years. Mortality rate was 30%. Compared to survivors, non-survivors had decreased levels of fT3 and fT4 levels. Predictive value of ICU mortality was highest with fT3 (AUC=0.990) followed by fT4 (AUC=0.917) and APACHE-II score (AUC=0.824). This was corroborated by the univariate logistic regression analysis which showed (β = 140.560) had the highest predictive potential for ICU mortality than APACHE-II scores (β = 0.776) and fT4 (β = 17.62). Further multivariate analysis showed mortality predictive potential is better with when fT3 is combined with APACHE-II ($R^2 = 0.652$) than APACHE-II alone ($R^2 = 0.286$). Authors concluded that FT3 alone or in combination with APACHE-II scores were better in predicting ICU-mortality in patients.

Foks M, et al (2019)[54] conducted a study to evaluate the predictive value of thyroid hormone in the prognosis of septic patients. A total of 49 patients diagnosed with sepsis, admitted to the ICU between2015 and 2017 were enrolled in the study. Primary and secondary endpoints were survival rate at the end of 30 days and death during the course of ICU stay, respectively. fT3, fT4 and TSH levels were measured from blood obtained at the time of initial epsis diagnosis. Compared to survivors, patients who died within 30 days had significantly lower fT4 levels (12.7 vs. 9.8 pmol; p=0.033), while TSH and fT3 levels were comparable. Among patients who died during the ICU stay, free T3 and free T4 levels were significantly lesser than those patients who survived. On the other hand, TSH levels were comparable between 2 groups. The authors concluded that based on the results of their study, free T3 and free T4 levels can be considered as potential new factors in sepsis prognosis.

Guo J, et al (2020)[55] conducted a prospective observational study at The Third Hospital of Hebei Medical University from February to November 2018 to evaluate the relationship between nonthyroidal illness syndrome (NTIS) characterized by low plasma T3 and prognostic indicators. They evaluated efficacy of freeT3 in predicting the 28-day mortality in patients admitted in an ICU by using specific cut off points. Based on the baseline low free T3 levels patients were categorised into NTIS (FT3 < 3.28) and non-NTIS groups. Of the 305 patients, 118 (38.7%) were diagnosed of NTIS. Compared to non-NTIS group, FT3 ($P < 0.001$) and FT4 ($P = 0.001$) were significantly lower, while the 28-day mortality rate ($P < 0.001$) and hospitalization expenses in ICU (*P* = 0.001) were significantly higher in the NTIS group. Based on the univariate analysis, factors associated with 28-day mortality included, age, NTIS, fT3, fT4, APACHEII, sequential organ failure score, duration of mechanical ventilation, creatinine, oxygenation index, white blood cells, albumin, and brain natriuretic peptide levels. The fT3 cut-off value of 2.88 pmol/L was beneficial in predicting 28-day mortality.

In a prospective observational study **da Silveira CD, et al (2021)**[56] evaluated the association of changes in thyroid hormone levels and mortality in 353 critically ill patients. Patients with known hypo or hyperthyroidism were not included in the study. Data on T4, fT4, T3, fT3, rT3, and TSH were collected from all ICU admitted patients within 48 hours of admission. The mean age of patients was 68.5 years. The mean±SD sequential organ failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) was 3.3 ± 2.9 and 17.1 ± 7.9, respectively. The rate of mortality was 17.6%. While rT3 levels werelow among survivors than non survivors (69.3 vs 59.2%, $p = 0.042$), T4 was significantly lower (4.8 vs 9.7%, $p = 0.045$). Mortality rates were high in elderly and in those with high SOFA and APACHE II ($p<0.05$) scores. The authors concluded that increased rT3 is an independent predictor of mortality.

Rao MJ et al (2022)[57] conducted a systematic review and meta-analysis to evaluate the relationship between thyroid hormones and TSH and clinical outcome among critically ill patients admitted in the ICU.All relevant articles from PubMed, Embase, and Cochrane databases were collected till July 122021. Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of studies. Based on the eligibility criteria, a total of 27 studies having 4970 participants were included. They reported significant lower levels of T3(13 studies), T4(11 studies), fT3 (14 studies) and fT4 (17 studies) among non survivors compared to survivors with a standardized mean difference [95% CI] of -0.78 [-1.36 to -0.20]; p = 0.008, -0.79 [-1.31 to -0.28]; p = 0.0002, -0.76 [-1.21 to -0.32]; p = 0.0008 and -0.60 [-0.99 to -0.22]; p = 0.002, respectively. Among the 20 studies for TSH, the TSH levels among survivors and non survivors were comparable [0.00 [-0.29 to 0.29]; p = 0.98]. The authors concluded that thyroid hormones can be used as a predictor of clinical outcome among critically ill patients admitted in ICUs.

MATERIALS AND METHODS

Source of Data: Patients admitted in the ICU of Department of General Medicine at KLES Dr. Prabhakar Kore Hospital, Belagavi

Study Design: A cross sectional study

Study Period: 1 year from January 2021 to December 2021.

Sample Size: Sample size was calculated using the formula as shown below

$$\mathbf{n} = \frac{z_{\alpha}^{2}\, P(1-P)}{d^{2}}$$

Where,

z^2 = standard normal variant at a 95% degree of confidence = 1.96

p = Expected proportion from population prevalence. Prevalence of critical illness in this population is 46%.

q = 100-p

d = margin of error = 20%

By imputing the values in the formula, a sample size of **115** was required for the study.

Sampling Method: Since it was a cross sectional study, all consecutive patients fulfilling the inclusion criteria were included in the study.

Selection Criteria

Inclusion criteria

- Both male and female patients aged above 18 years
- All patients admitted in the medical ICU at KLES Dr. Prabhakar Kore Hospital, Belagavi

Exclusion criteria

- Patients with history of thyroid disease
- Patients on drugs altering thyroid function
- Patients who are kept for observation in ICU in stable status

Methodology

Patients admitted in the ICU of KLES Dr. Prabhakar Kore Hospital for any reason from January 2021 to December 2021 were included in the study. After obtaining the informed consent, all baseline demographic and clinical characteristics were recorded. Fasting blood samples were collected from all patients immediately upon admission to the ICU. Patients were followed up till discharge or death, whichever occurred first. Samples were tested for free T3, free T4, and TSH. The following cut off values were considered normal in the study.

- TSH= 0.27 to 4.2 mIU/ml
- Free T3= 2.0 to 4.4 pg/ml
- Free T4= 0.93 to 1.7 ng/ml

Any value above or below was considered decreased and increased, respectively. The correlation between demographics, comorbidities, diagnosis and thyroid function tests and mortality was further analyzed.

Data collection: The following data were collected for the purpose of the study.

- Demographics such as age, gender
- Diagnosis
- Comorbidities
- Investigations such as Free T3, Free T4 and TSH levels
- Morbidity measured as length of hospital stay
- Mortality

Ethical considerations: Institutional ethical clearance was obtained prior to initiation of the study. The details of the study were explained to the patients and an informed consent was obtained from all patients

Data handling: The collected data were entered in Microsoft excel and the related records were stored safety with no access to other study personnel.

Statistical analysis: All data was entered in the Microsoft excel sheet and then imported to SPSS version 22 software for statistical analysis. Categorical variables were summarized as frequency and percentages. Continuous variables were presented as Mean and standard deviation or median (minimum, maximum) values. Chi-square test was used to check the association of outcome among categorical variables. P-value less than or equal to 0.05 indicates statistical significance.

RESULTS

A total of 115 adult patients admitted to the ICU of KLEs Dr. Prabhakar Kore Hospital, Belagavi were included in the study. Patients belonged to the age group of 18 to 90 years with a median of 56 years and mean ± standard deviation (SD) age of 55.58 ± 15.21 years. Descriptive statistics of age are described in table 1.

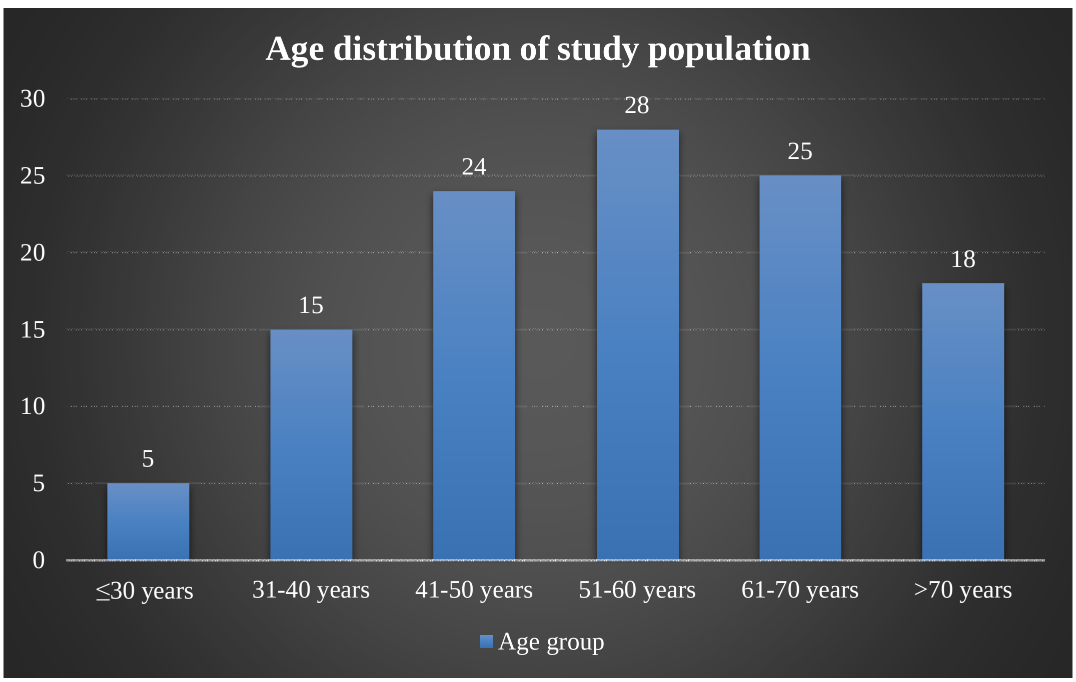
Table 1: Descriptive statistics of age in the study population

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
Age, years	115	55.58	15.21	56	18	90

Age distribution of study population is shown in Table 2, Graph 1. Majority of patients (n=28, 24.3%) belonged to the age group of 51-60 years followed by, 61-70 years (n=25, 21.7%) and 41-50 years (n=24, 20.9%).

Table 2: Age distribution of study population

Variable	Groups	Frequency N=115	Percentage %
Age groups	≤30 years	5	4.3
	31-40 years	15	13.0
	41-50 years	24	20.9
	51-60 years	28	24.3
	61-70 years	25	21.7
	>70 years	18	15.7
Total		**115**	**100**

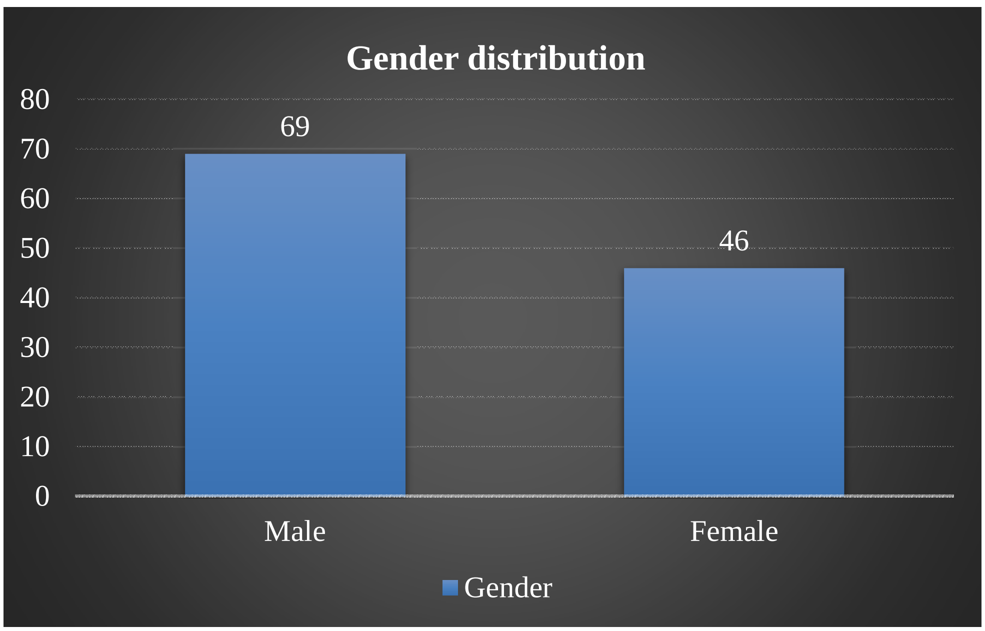


Graph -1, age distribution of study population.

In our study, majority of the study population comprised of males (n=69, 60%), followed by females (n=46, 40%). Male to female ratio was 3:2. Gender distribution is summarized in Table 3 and graph 2

Table 3: Gender distribution of study population

Variable		Frequency N=115	Percentage %
Gender	Male	69	60
	Female	46	40
Total		**115**	**100**



Graph 2: Frequency distribution of gender in the study population

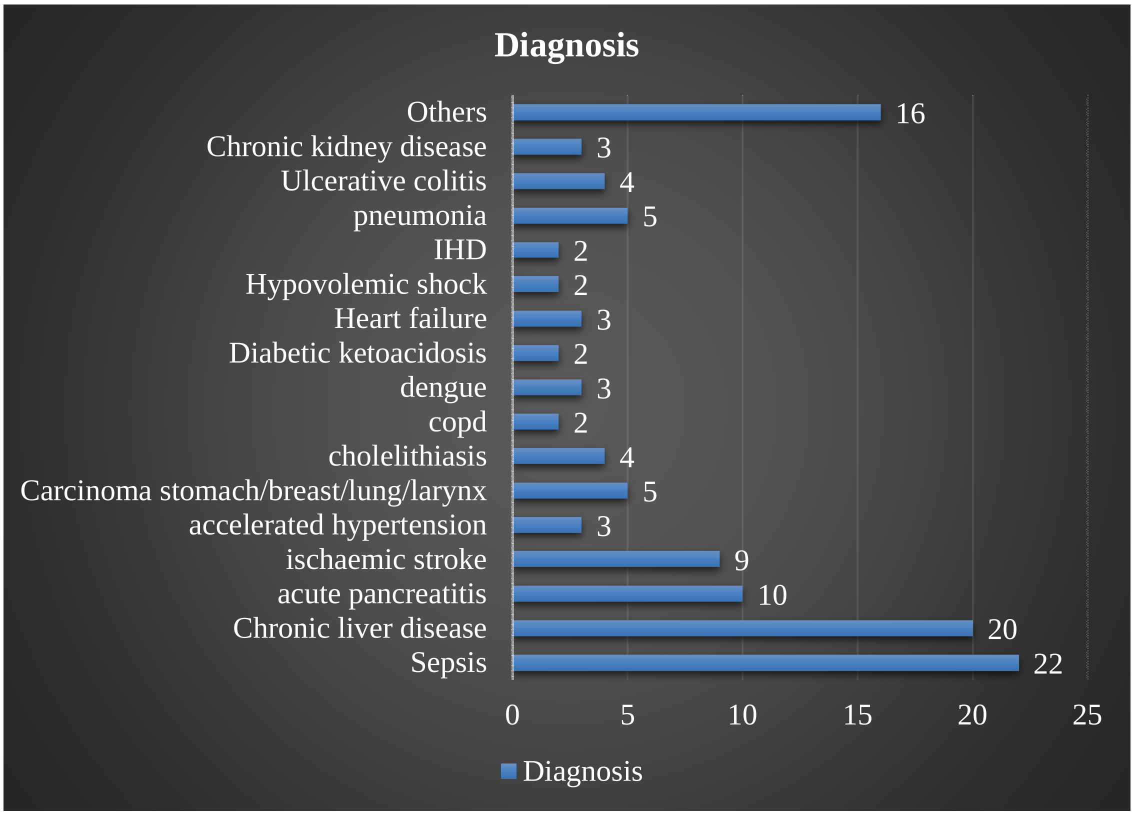
Table 4 and Graph 3 summarizes the distribution of diagnosis for admission among the study population. The most common diagnosis was sepsis/septic shock (n=22, 19.1%) followed by chronic liver disease (n=20, 17.4%) acute pancreatitis (n=10, 8.7%), ischaemic stroke (n=9, 3%. Accelerated hypertension, adenocarcinoma stomach, cholelithiasis, chronic obstructive pulmonary disease (COPD), dengue.

Diabetic ketoacidosis, heart failure, hypovolemic shock, IHD, pneumonia, ulcerative colitis, chronic kidney disease comprised of <5%, each of the diagnosis. 19/115 (16.5%) were categorized as other diagnosis which consisted of myasthenia gravis, alcoholic hepatitis, hypoglycaemia, cancer of larynx, breast and lung, multiple myeloma, tubercular meningitis, asthma, cor pulmonale, Hellp syndrome, drug overdose, Chron's disease, hypercalcemia and pyelonephritis.

Table 4: Distribution of patients based on diagnosis

Variable	**Groups**	**Frequency N=115**	**Percentage %**
Diagnosis	Sepsis/Septic shock	22	19.1
	Chronic liver disease	20	17.4
	acute pancreatitis	10	8.7
	ischaemic stroke	9	7.8
	accelerated hypertension	3	2.6
	Carcinoma stomach/breast/lung/larynx	5	4.3
	cholelithiasis	4	3.5
	COPD	2	1.7
	dengue	3	2.6
	Diabetic ketoacidosis	2	1.7
	Heart failure	3	2.6
	Hypovolemic shock	2	1.7
	IHD	2	1.7
	pneumonia	5	4.3
	Ulcerative colitis	4	3.5

	Chronic kidney disease	3	2.6
	Others	16	13.9
Total		**115**	**100**

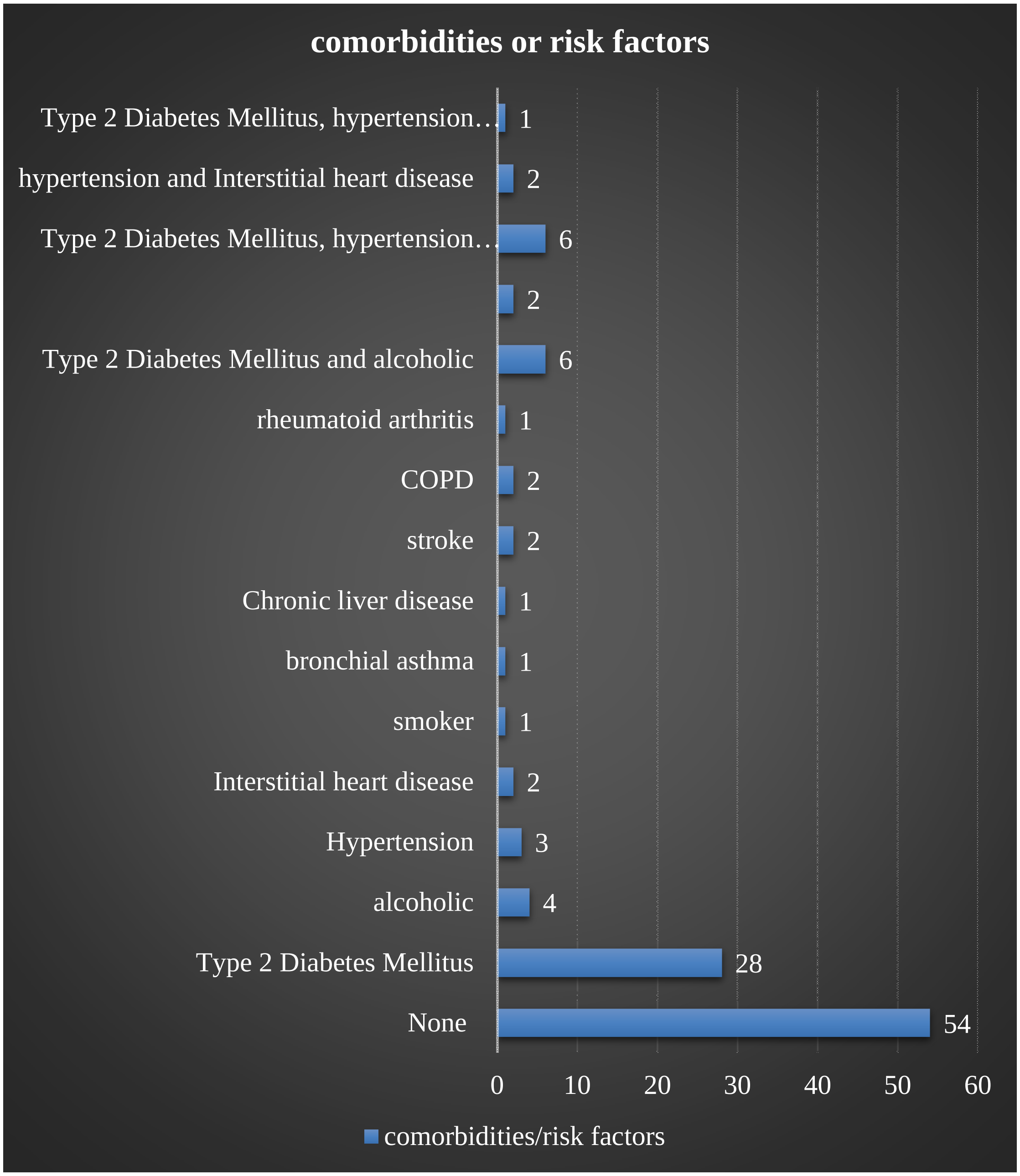


Graph 3: Bar diagram showing distribution of patients based on diagnosis

Among 115 patients, 54 (47%) patients did not have any comorbidities or associated risk factors. Type 2 Diabetes Mellitus was the most common comorbidity seen in 43 patients (37.4%), either alone or in combination with other comorbidities. The other common comorbidities occurring alone or in combination with others were hypertension, consumption of alcohol, interstitial heart disease, stroke, smoking, COPD and rheumatoid arthritis. Frequency distribution of comorbidities or risk factors are summarized in table 5 and Graph 4.

Table 5: Distribution of comorbidities/risk in study population

Variable	Groups	Frequency N=115	Percentage %
Comorbidities /risk factor	None	54	47.0
	Type 2 Diabetes Mellitus	28	24.3
	Alcoholic	4	3.5
	Hypertension	3	2.6
	Interstitial heart disease	2	1.7
	Smoker	1	.9
	bronchial asthma	1	.9
	Chronic liver disease	1	.9
	Stroke	2	1.7
	COPD	2	1.7
	rheumatoid arthritis	1	.9
	Type 2 Diabetes Mellitus and alcoholic	6	5.2
	Type 2 Diabetes Mellitus and hypertension	2	1.7
	Type 2 Diabetes Mellitus, hypertension and Interstitial heart disease	6	5.2
	hypertension and Interstitial heart disease	2	1.7
	Type 2 Diabetes Mellitus, hypertension and stroke	1	0.9
Total		**115**	**100**



Graph 4: Bar diagram showing distribution of patients based on comorbidities

Among 115 patients, TSH levels ranged from 0.01 to 9.43 with the mean ± SD of 1.98±1.72 and median of 1.46 (Table 6).

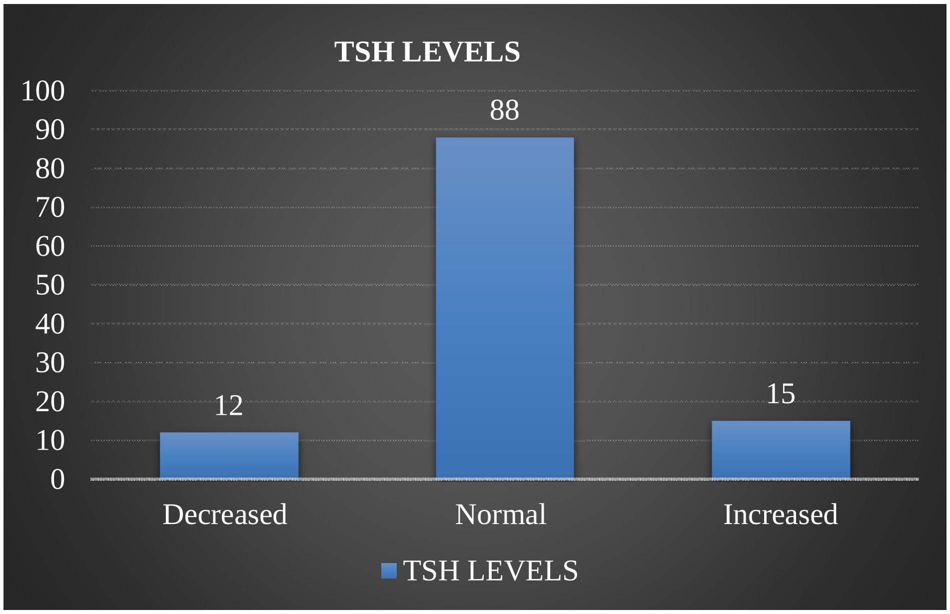
Table 6: Descriptive statistics of TSH levels among study population

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
TSH,	115	1.98	1.72	1.46	0.01	9.43

Distribution of patients based on TSH levels is summarized in Table 7 and Graph 5. In our study, 88 (76.5%) patients had normal TSH levels of 0.27 to 4.2. Decreased TSH levels (<0.27) was seen in 12 (10.4%) patients and increased levels (>4.2) were seen in 15 (13%) patients.

Table 7: Distribution of patients based on TSH levels

Variable		Frequency N=115	Percentage %
TSH	**Decreased (<0.27)**	12	10.4
	Normal (0.27-4.2)	88	76.5
	Increased (>4.2)	15	13.0
Total		**115**	**100**



Graph 5: Bar diagram showing distribution of patients based on TSH levels

In our study, free T3 levels ranged from 0.52 to 5.12 with the mean ± SD of 2.03±0.79 and median of 1.87 (Table 8).

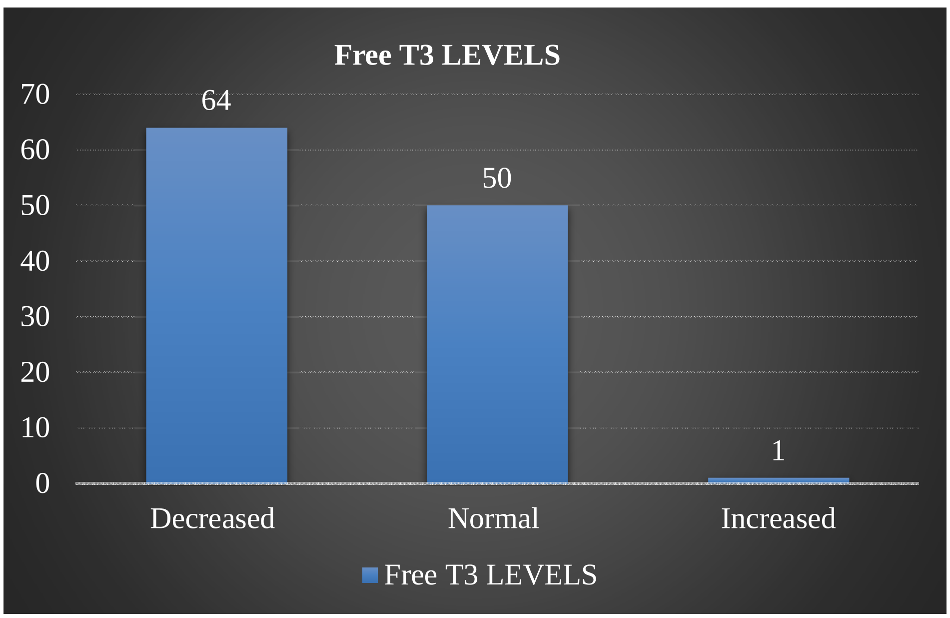
Table 8: Descriptive statistics of free T3 levels among study population

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
Free T3	115	2.03	0.79	1.87	0.52	5.12

Distribution of patients based on free T3 levels is summarized in Table 9 and Graph 6. Out of 115 patients, 50 (43.5%) patients had normal free T3 levels of 2.0 to 4.4. Decreased free T3 levels (<2.0) was seen in 64 (55.7%) patients and only 1(0.9%) patient had increased free T3 level (>4.4).

Table 9: Distribution of patients based on free T3 levels

Variable		Frequency N=115	Percentage %
Free T3	**Decreased (<2.0)**	64	55.7
	Normal (2.0-4.4)	50	43.5
	Increased (>4.4)	1	0.9
Total		**115**	**100**



Graph 6: Bar diagram showing distribution of patients based on free T3 levels

In our study, free T4 levels ranged from 0.12 to 3.82 with the mean ± SD of 1.27±0.45 and median of 1.28 (Table 10).

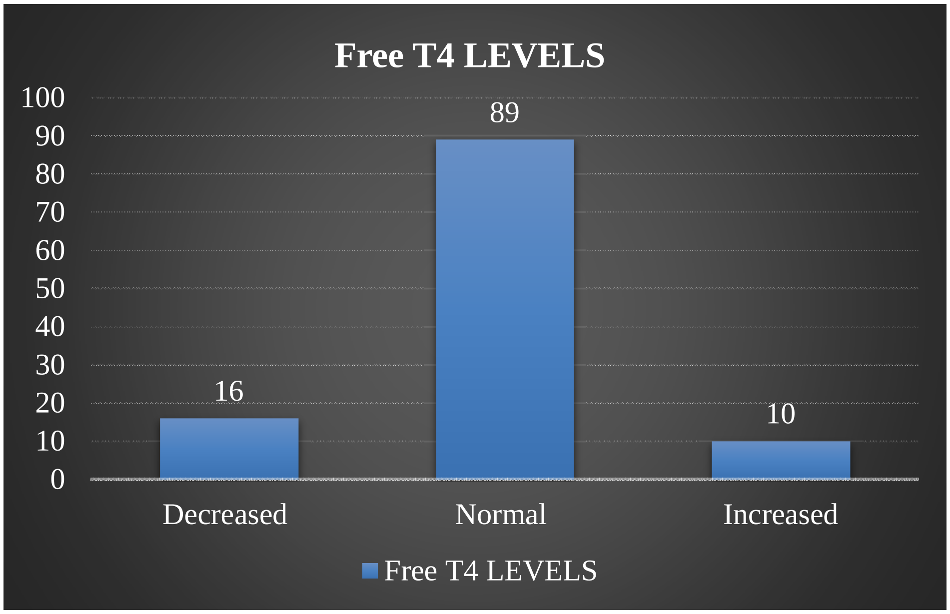
Table 10: Descriptive statistics of free T3 levels among study population

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
Free T4	115	1.27	0.45	1.28	0.12	3.82

Distribution of patients based on free T4 levels is summarized in Table 11 and Graph 7. Out of 115 patients, 89 (77.4%) patients had normal free T4 levels of 0.93 to 1.7. Decreased free T4 levels (<0.93) was seen in 16 (13.9%) patients and 10(8.7%) patients had increased free T4 level (>1.7).

Table 11: Distribution of patients based on free T4 levels

Variable		Frequency N=115	Percentage %
Free T4	**Decreased (<0.93)**	16	13.9
	Normal (0.93-1.7)	89	77.4
	Increased (>1.7)	10	8.7
Total		**115**	**100**



Graph 7: Bar diagram showing distribution of patients based on free T4 levels

We assessed morbidity as number of hospitalization days. The hospitalization days ranged from 1 to 30 days with a mean ± SD of 6.43±5.26 days and median of 5 days. The details are summarized in Table 12.

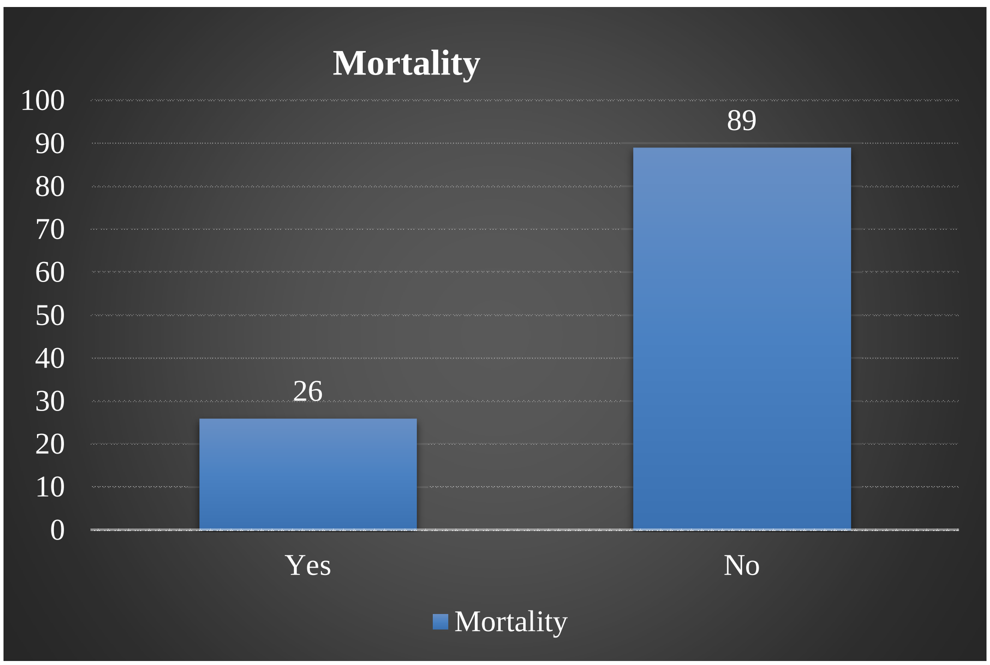
Table 12: Descriptive statistics of morbidity in the study population

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
Morbidity, days	115	6.43	5.26	5	1	30

Details of mortality are presented in Table 13 and Graph 8. In our study, out of 115 patients, mortality was reported in 26(22.6%) patients.

Table 13: Distribution of mortality among study population

Variable		Frequency N=115	Percentage %
Mortality	Yes	26	22.6
	No	89	77.4
Total		**115**	**100**

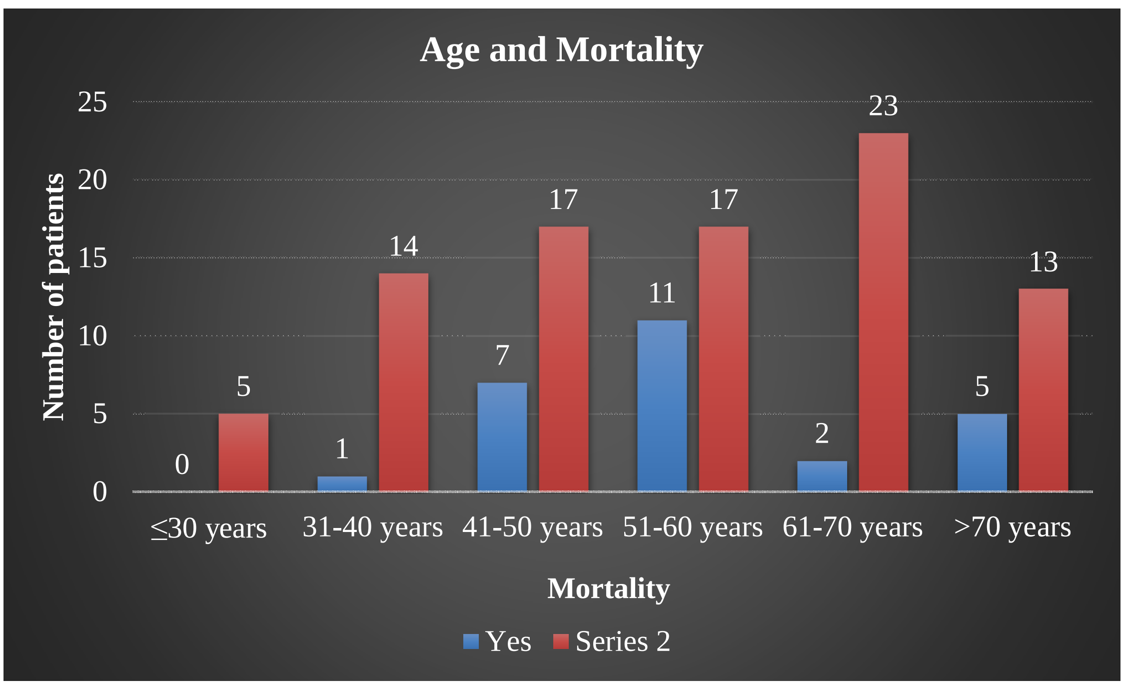


Graph 8: Bar diagram showing distribution of patients based on mortality

In our study, frequency of mortality was high among patients in the age group of 51-60 years (n=11, 423%) followed by 41 to 50 years (n=7, 26.9%). Age was significantly associated with mortality (p=0.035). The association of age and mortality is summarized in table 14 and graph 9

Table 14: Association of age and mortality

Variable	Groups	Mortality		P value
		Yes	No	
Age groups	≤30 years	0 (0.0%)	5(5.6%)	0.035
	31-40 years	1(3.8%)	14(15.7%%)	
	41-50 years	7(26.9%)	17(19.1%)	
	51-60 years	11(42.3%)	17(19.1%)	
	61-70 years	2(7.7%)	23(25.3%)	
	>70 years	5(19.2%)	13(14.6%)	
Total		**26(100%)**	**89(100%)**	

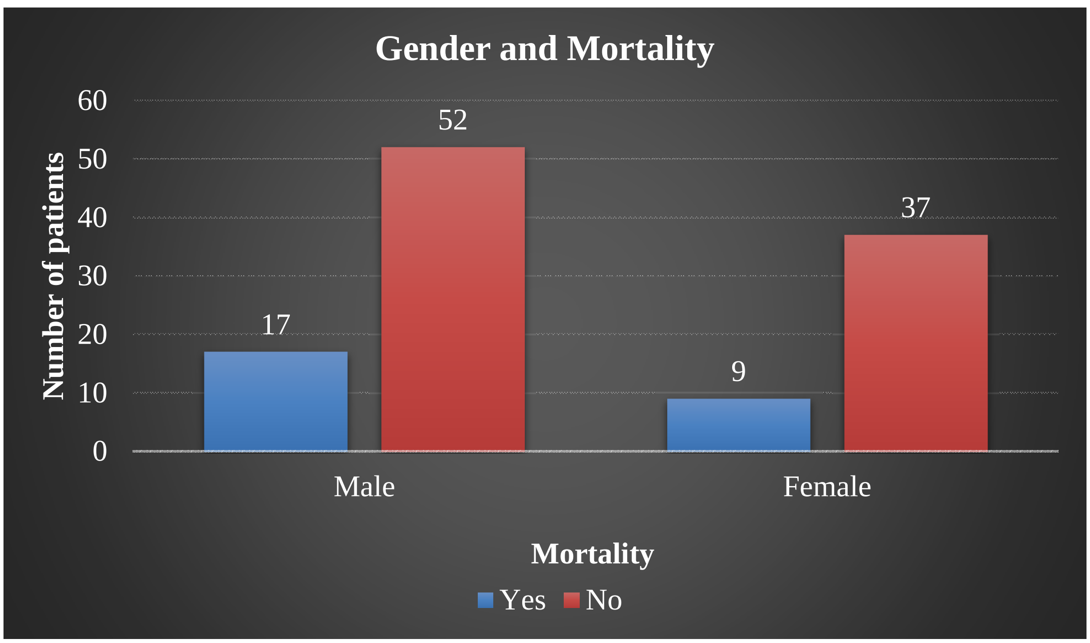


Graph 9: Comparison of mortality among different age groups

In our study, no significant difference in mortality between males and females was observed (p=0.524). Comparison of mortality among gender is summarized in Table 15 and Graph 10.

Table 15: Association of Gender and mortality

Variable	Groups	Mortality		P value
		Yes	No	
Gender	Male	17 (65.4%)	52(58.4%)	**0.524**
	Female	9(34.6%)	37(41.6%)	
Total		**26(100%)**	**89(100%)**	

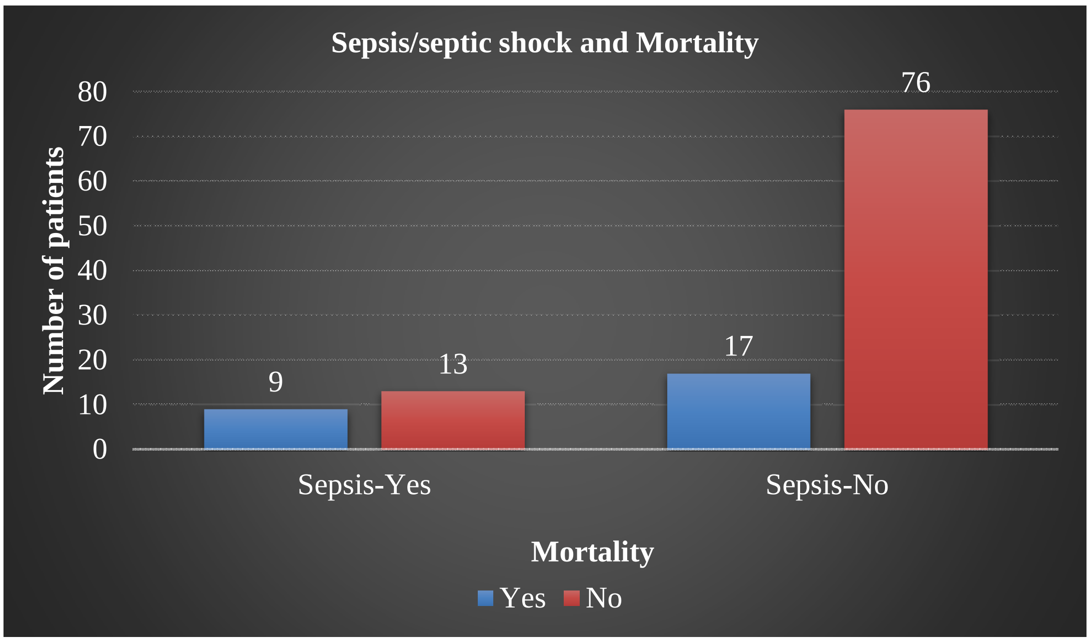


Graph 10: Comparison of mortality among gender

Comparison of sepsis/septic shock and its association with mortality is summarized in table 16 and Graph 11. In our study 22 out of 115 patients had sepsis/septic shock. Among these patients, mortality was reported in 9 patients and 13 patients survived. The difference was statistically significant (p=0.022).

Table 16: Association of sepsis/Septic shock and mortality

Variable	Groups	Mortality		P value
		Yes	**No**	
Sepsis/Septic shock	Yes	9(34.6%)	13(14.6%)	**0.022**
	No	17 (65.4%)	76(85.4%)	
Total		**26(100%)**	**89(100%)**	

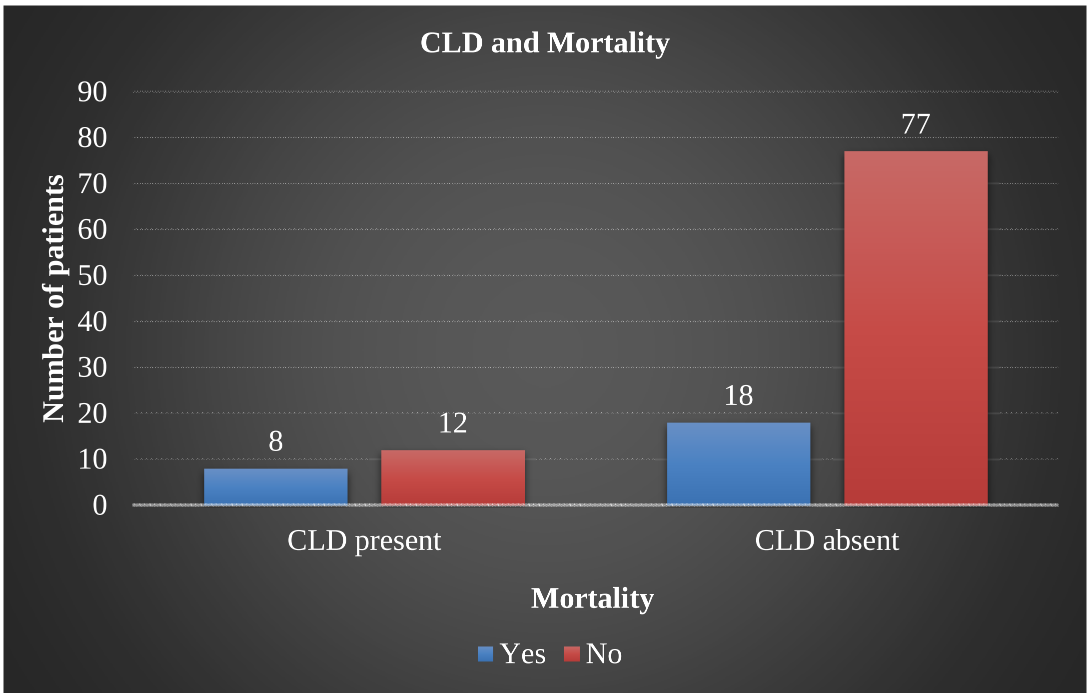


Graph 11: Comparison of mortality with presence and absence of sepsis/Septic shock

Comparison of chronic liver disease and its association with mortality is summarized in table 17 and Graph 12. In our study 20 out of 115 patients had chronic liver disease. Among these patients, mortality was reported in 8 patients and 12 patients survived. The difference was statistically significant (p=0.041).

Table 17: Association of chronic liver disease and mortality

Variable	Groups	Mortality		P value
		Yes	No	
Chronic liver disease	Present	8(30.8%)	12(13.5%)	**0.041**
	Absent	18 (69.2%)	77(86.5%)	
Total		**26(100%)**	**89(100%)**	

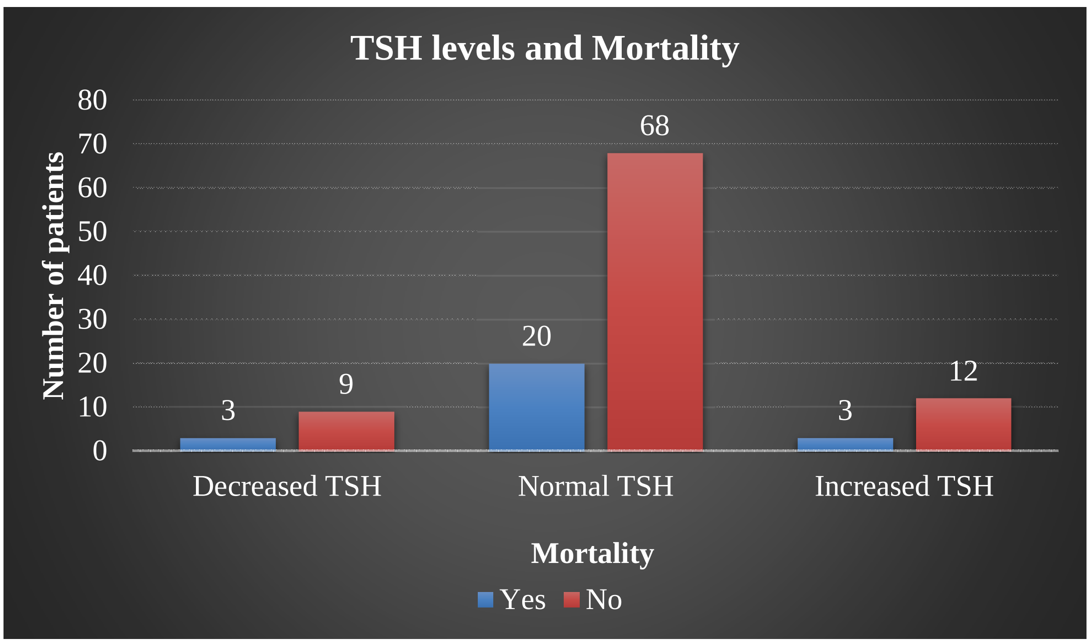


Graph 12: Comparison of mortality with presence and absence of chronic liver disease

Relationship between TSH levels and mortality among chronically ill patients is summarized in table 18 and Graph 13. No significant difference in the mortality rates between patients with decreased, normal and increased TSH levels were observed (p=0.952).

Table 18: Association of TSH levels and mortality

Variable	Groups	Mortality		P value
		Yes	No	
TSH levels	Decreased (<0.27)	3 (11.5%)	9(10.1%)	0.952
	Normal (0.27-4.2)	20(76.9%)	68(76.4%)	
	Increased (>4.2)	3(11.5%)	12(13.5%)	
Total		26(100%)	89(100%)	

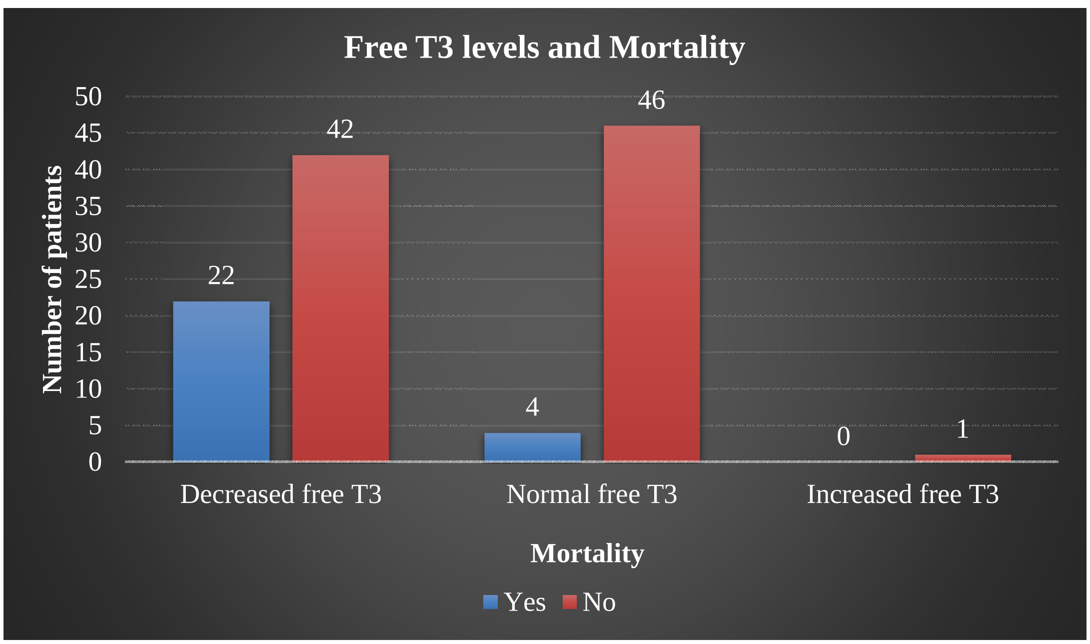


Graph 13: Comparison of mortality with TSH levels

Relationship between free T3 levels and mortality among chronically ill patients is summarized in table 19 and Graph 14. In our study, mortality was significantly higher among patients with decreased free T3 levels (n=22, 84.6%; p=0.003).

Table 19: Association of Free T3 levels and mortality

Variable	Groups	Mortality		P value
		Yes	No	
Free T3 levels	**Decreased (<2.0)**	22 (84.6%)	42(47.2%)	**0.003**
	Normal (2.0-4.4)	4(15.4%)	46(51.7%)	
	Increased (>4.4)	0(0.0%)	1(1.1%)	
Total		**26(100%)**	**89(100%)**	

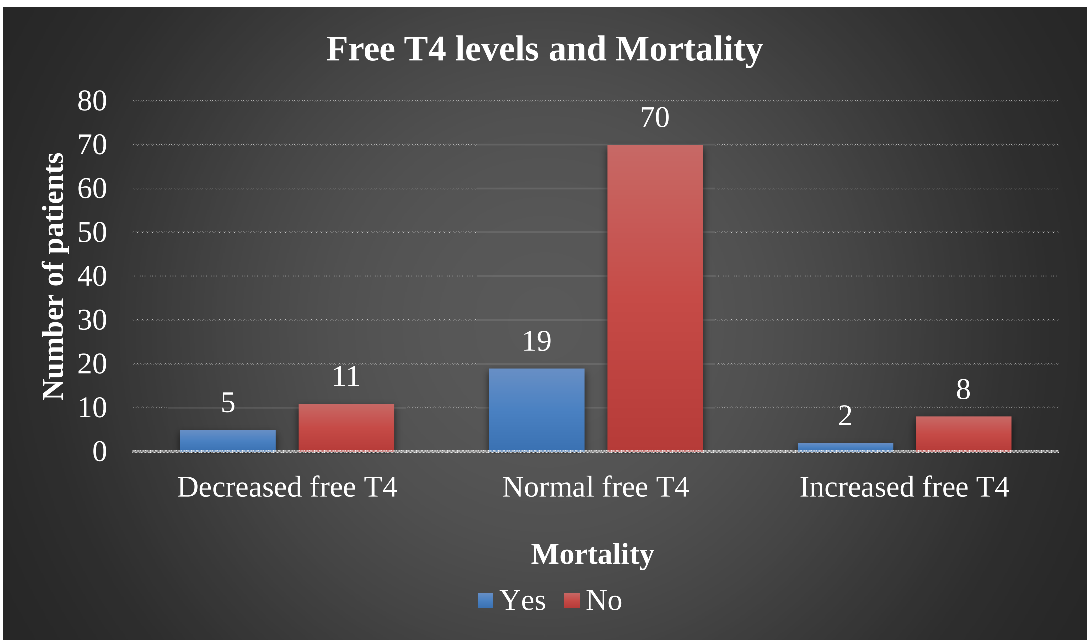


Graph 14: Comparison of mortality with Free T3 levels

Relationship between free T4 levels and mortality among chronically ill patients is summarized in table 20 and Graph 15. No significant difference in the mortality rates between patients with decreased, normal and increased free T4 levels were observed (p=0.669).

Table 20: Association of Free T4 levels and mortality

Variable	Groups	Mortality		P value
		Yes	No	
Free T4 levels	Decreased (<0.93)	5 (19.2%)	11(12.4%)	0.669
	Normal (0.93-1.7)	19(73.1%)	70(78.7%)	
	Increased (>1.7)	2(7.7%)	8(9.0%)	
Total		26(100%)	89(100%)	

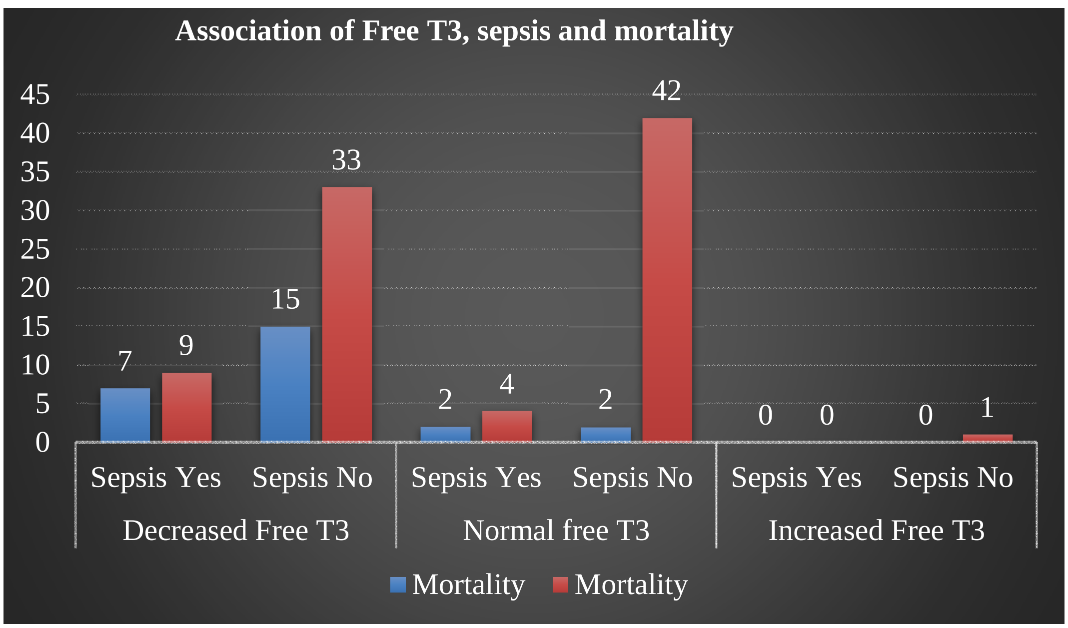


Graph 15: Comparison of mortality with Free T4 levels

Table 21 and Graph 16 summarizes the relationship between free T3 levels, sepsis/septic shock and mortality. In our study, patients with 7/22 patients with sepsis/septic shock had decreased free T3 levels and 2/22 with sepsis/septic shock had normal free T3 levels. Patients with sepsis and decreased free T3 were significantly associated with mortality (p=0.022).

Table 21: Association of Free T3, sepsis and mortality

Free T3	Sepsis	Mortality		P value
		Yes	No	
Decreased Free T3	**Yes**	7(43.8%)	9(56.2%)	0.022
	No	15(31.2%)	33(68.8%)	
Normal free T3	**Yes**	2(33.3%)	4(66.7%)	
	No	2(4.5%)	42(95.5%)	
Increased Free T3	**Yes**	0(0.0%)	0(0.0%)	
	No	0(0.0%)	1(100%)	

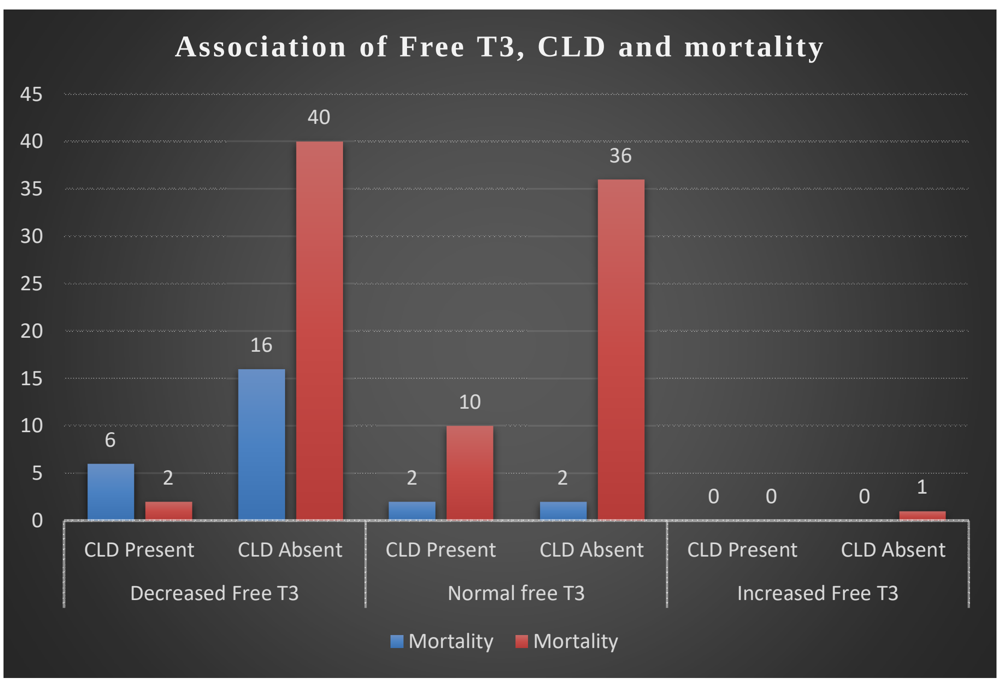


Graph 16: Comparison of free T3, sepsis and mortality

Table 22 and Graph 17 summarizes the relationship between free T3 levels, chronic liver disease and mortality. In our study, patients with 6/20 patients with chronic liver disease had decreased free T3 levels and 2/20 with chronic liver disease had normal free T3 levels. Patients with chronic liver disease and decreased free T3 were significantly associated with mortality (p=0.041).

Table 22: Association of Free T3, CLD and mortality

Free T3	CLD	Mortality		P value
		Yes	No	
Decreased Free T3	Present	6(75.0%)	2(25.0%)	0.041
	Absent	16(28.6%)	40(71.4%)	
Normal free T3	Present	2(16.7%)	10(83.3%)	
	Absent	2(5.3%)	36(94.7%)	
Increased Free T3	Present	0(0.0%)	0(0.0%)	
	Absent	0(0.0%)	1(100%)	



Graph 17: Comparison of free T3, CLD and mortality

DISCUSSION

Non-thyroidal illness syndrome or euthyroid sick syndrome is a condition characterized by decreased levels of plasma T3 and T4, increased rT3 without any changes in the TSH levels. Severity of the NTIS is positively correlated with outcome of patient. The alterations in thyroid hormone secretion and regulation during critical illness includes changes in thyroid hormone binding, peripheral uptake of the free thyroid hormones and alterations in the conversion of T4 to T3 due to changes in expression and activity of deiodinases. These changes are most commonly seen during acute illness as part of an adaptive and beneficial response. On the other hand, in patients who are with chronic illness admitted in the ICU are in a fully fed state and the mechanism of NTIS differs[58-60].

During prolonged illness, there is suppression of TRH expression resulting in reduced TSH and reduced thyroid hormones. Therefore, it is important to understand the changes on thyroid hormone levels in critically ill patients and to further evaluate the relationship between risk factors for alteration in thyroid hormones and mortality. In view of this, the present study was conducted to evaluate the relationship between thyroid hormone levels and prognosis of patients admitted in the ICU and to identify the risk factors of poor prognosis in the critically ill patients.

In our study, a total of 115 adult patients with critical illness were included. Patients belonged to the age group of 18 to 90 years with a median of 56 years and mean age of 55.58 years. The mean age in our study is much higher than 39 years reported by Gutch M, et al[53] and comparable to the mean age (54.81 years) reported by Giri R, et al[61]. Similar to a study by Mishra A, et al[62] (61% vs 39%), male to female ratio was 3:2 (60% males and 40% females) in our study.

In a study by Cao P, et al[63] among 41 patients, the most common diseases among ICU admitted patients were related to cardiovascular system followed by diseases related to digestive system, neoplasms, trauma and accidental injury, respiratory diseases and renal diseases. In a study by Sasi Sekhar, TVD et al,[64] common diagnosis or comorbidities included sepsis, acute renal failure, acute respiratory failure, diabetic ketoacidosis, congestive cardiac failure and stroke. In our study the most common diagnosis was sepsis/septic shock (19.1%) followed by chronic liver disease (17.4%) acute pancreatitis (8.7%) and ischemic stroke (3%).Type 2 Diabetes Mellitus was the most common comorbidity seen in 37.4%, either alone or in combination with other comorbidities.

In a study by Mishra A, et al[62] the mean ± SD of TSH free T3 and free T4 were 2.56±1.51, 0.92±0.75 and 0.96±0.68, respectively. In our study the TSH levels ranged from 0.01 to 9.43 with the mean ± SD of 1.98±1.72, Free T3 levels ranged from 0.52 to 5.12 with the mean ± SD of 2.03±0.79 and free T4 levels ranged from 0.12 to 3.82 with the mean ± SD of 1.27±0.45. The differences in the mean values could be attributed to the chronicity and severity of the disease and associated changes in the thyroid profile of the patient.

The hospitalization days ranged from 1 to 30 days with a mean ± SD of 6.43±5.26 days and median of 5 days. Mortality rate was 22.6%, which is lower than 30% reported by Gutch M et al.[53] According to Langouche L, et al[65] NTIS can present across all ages, however the severity correlates with the NTIS Phenotype. Age was a significant predictor of mortality in our study and mortality increased with increased age. The results are in accordance with Gutch M, et al[53] and Giri R, et al[61] who reported that non-survivors were older than survivors. On the contrary, Mishra A, et al[62] reported comparable age between survivors and non-survivors. The differences in age can be due to variations in the sample size and selection criteria of the study.

It is well known that NTIS is associated with lower levels of free T3 hormone and normal or low levels of free T4 hormone and normal TSH hormone levels. The reduction in thyroid hormones increase with disease severity. Low free T3 levels is a marker to predict the prognosis in ICU admitted patients. In a study population of 306 patients, Guo J et al,[66] reported NTIS among 39% of patients. Sripad DV, et al[67] reported, NTIS was significantly associated with mortality. In our study, 76.5% patients had normal TSH levels, 10.4% patients and 13% patients had decreased and increased levels of TSH, respectively. Out of 115 patients, 43.5% patients had normal free T3 levels, 55.7% had decreased free T3 levels and only 0.9% patients had increased free T3 levels. Out of 115 patients, 77.4% patients had normal free T4, 13.9% and 8.7% patients had decreased increased free T4 levels.

Various studies have used different cut off levels as optimal values of free T3. While Padhi R, et al[68] used 3.7 pmol/L as normal value, Gutch M, et al[53] used 3.7 pmol/L, Rothberger GD, et al[69] used 2.3 pg/mL and Guo J, et al[66] used 3.28 pmol/L as cut off value of free T3 levels. In our study, free T3 levels of 0.93 to 1.7 were considered normal. The optimal values used in various studies could differ based on study design, nature of the study and the institutional protocols. As, cut off values of different studies differ, therefore, the comparative evaluations between various studies should be interpreted with caution.

In a study by Guo J, et al,[66] patients with NTIS had decreased fT3, decreased fT4, higher 2 day mortality and higher associated hospital costs. Kumar KV et al,[70] reported that as compared to HbA1c, prolactin, T4 and TSH levels, decreased T3 levels was a predictor of prognosis among critically ill patients. This was further corroborated in another study by Suresh M, et al.[71] who found a strong correlation between decreased T3 levels and severity of illness. Gutch M, et al[53] reported significantly lower levels of free T3 and free T4 among nonsurvivors as compared to survivors. Mishra A, et al[62] reported frequency of patients with decreased free T3 levels were significantly higher among non survivors as compared to survivors (94% vs 73%) and higher odds of predicting mortality among patients admitted in ICU. Similarly, in our study, mortality was significantly higher among patients with decreased free T3 levels but not with decreased free T4 levels. Similar to the NTIS criteria, TSH levels were not correlated with mortality in our study.

Although as reported by previous studies and in our study lower free T3 levels were common in critically ill patients and is related to mortality. However, the exact mechanism or pathogenesis of NTIS and its relationship between prognoses of critical illness is yet to be elucidated. The decreased thyroid hormone levels are either considered an adaptive response or maladaptive response by previous researchers[72]. Further studies are warranted to evaluate the role of thyroid hormones as prognostic marker in critically ill patients along with research to further study the mechanism behind the lower thyroid levels in critically ill patients.

Low plasma T3 are often found in patients suffering from illnesses including infectious diseases, metabolic disorders, and systemic diseases including cardiovascular, pulmonary or gastrointestinal systems, burs trauma and major surgeries[72,73]. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host reaction to infection. There is an upward trend in sepsis prevalence and mortality worldwide. Sepsis causes hypoxia, which reduces the ability of cells to produce ATP. This process is also influenced by thyroid hormones. Some of the previous studies revealed association between the mortality rate in sepsis and thyroid hormone levels [54]. In another systematic review of nine studies, Angelousi AG, et al[74] reported that decreased thyroid functions at baseline in patients with sepsis or sepsis shock had worst outcome. Similarly, we observed overall higher risk of mortality among patients with sepsis/septic shock and the mortality was higher among patients with a combination of low free T3 levels and sepsis/septic shock.

Previous studies have reported that thyroid profile in patients with cirrhosis and liver disease resemble that of NTIS which is secondary to caloric deprivation. The low T3 is reflective of impairment of hepatic uptake and conversion of T4 to T3 secondary to decreased hepatocellular function or caloric deprivation[75-77]. Low free T4 and T3 are related to poor prognosis of patients with liver cirrhosis. Studies have also suggested that serum TSH levels significantly correlate to prognosis of HBV related acute on chronic liver failure patients and is a predictor of 30 and 90 day mortality in these patients[78]. In our study, presence of decreased free T3 and chronic liver disease significantly increased the risk of mortality. Moreover, sepsis or chronic liver disease significantly increased the risk of mortality in chronically ill patients.

Strengths of our study

Along with the thyroid profile we further evaluated the correlation between decreased free T3 levels in specific diseases and its association with mortality.

Limitations of the study

- Ours was a single centre retrospective, cross sectional study with a relatively smaller sample size which could limit the generalizability of the results. Further prospective studies with multicentre study designs are warranted to evaluate the role of thyroid hormones in the prognosis of critically ill patients.

- The distribution of disease types and comorbidities was diverse in our study and these patients were analysed together. Although correlation between sepsis and chronic liver disease and mortality were assessed individually, the sample size was less. Further studies should have population with balanced inclusion based on disease types.

- Other baseline clinical characteristics including vitals may also predict the prognosis in critically ill patients particularly shock or trauma patients, which corresponds to the drop in blood pressure[79-80]. Our study did not include other risk factors of NTIS

- The data collected were obtained on admission to the ICU and patient monitoring was not taken into consideration. Further prospective studies are warranted in this regard.

CONCLUSION

The results of our study show a positive correlation between decreased free T3 levels and mortality among admitted in the ICU. Furthermore, patients with sepsis or septic shock and chronic liver diseases having lower free T3 levels were also at much higher risk of mortality. No significant association between free T4 and TSH levels and mortality was observed. The findings of our study highlight the importance of including thyroid profile tests in chronically ill patients to predict the prognosis in terms of morbidity and mortality. This will further enable the doctors to modify the treatment strategy in such patients, as needed. We also suggest further prospective studies to evaluate the risk of mortality in individual diseases with concomitant low free T3 levels.

SUMMARY

The present cross-sectional study was conducted in the Department of General Medicine, KLES Dr. Prabhakar Kore Hospital, Belagavi. All patients aged above 18 years admitted in the ICU of KLES Dr. Prabhakar Kore Hospital for any reason from January 2021 to December 2021 were included in the study. Patients with history of thyroid disease, those on drugs altering thyroid function and those patients who were kept for observation in ICU in stable status were excluded.

The study was approved by the institutional ethics committee. After obtaining the informed consent, all baseline demographic and clinical characteristics were recorded. Fasting blood samples were collected from all patients immediately upon admission to the ICU. Patients were followed up till discharge or death, whichever occurred first. The correlation between demographics, comorbidities, diagnosis and thyroid function tests and mortality was further analyzed.

A total of 115 adult patients belonged to the age group of 18 to 90 years were included in the study. The mean ± SD age of patients was 55.58 ± 15.21 years. Majority of the study population comprised of males (60%) and male to female ratio was 3:2. Sepsis/septic shock (19.1%) was the most common diagnosis, followed by chronic liver disease (17.4%). Approximately half the population did not have any associated comorbidities or risk factors. Among the comorbidities, type 2 Diabetes Mellitus (37.4%) was reported either alone or in combination with other comorbidities.

In our study, TSH levels ranged from 0.01 to 9.43 with the mean ± SD of 1.98±1.72. Decreased and increased TSH levels were seen in 10.4% and 13% patients, respectively.

The free T3 levels ranged from 0.52 to 5.12 with the mean ± SD of 2.03±0.79. Decreased and increased free T3 levels were seen in 55.7% and 0.9% patients, respectively. The free T4 levels ranged from 0.12 to 3.82 with the mean ± SD of 1.27±0.45. Decreased and increased free T4 levels were seen in 13.9% and 8.7% patients, respectively.

The hospitalization days ranged from 1 to 30 days with a mean ± SD of 6.43±5.26 days. Mortality rate was 22.6%. Risk factors of mortality included age ($p=0.035$), diagnosis of sepsis/shock ($p=0.022$), history of chronic liver disease ($p=0.041$), decreased free T3 levels ($p=0.003$). No significant difference in the mortality was observed between sex, with TSH and T4 levels ($p<0.05$). Combination of sepsis and decreased free T3 ($p=0.022$) and chronic liver disease and decreased free T3 ($p=0.041$) had higher risk of mortality.

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ANNEXURE- I - CONSENT FORM

Dear Mr./Mrs./Dr. ______________________________, you are kindly requested to enroll yourself in a research study tilted ***"A STUDY ON THYROID PROFILE IN ICU ADMITTED PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC"*** being conducted by **Dr. ______________________,** a post graduate student in M.D. General Medicine and the study will be carried out under the direct supervision and guidance of **Dr.________________**, Professor and Unit Chief, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum.

You have been requested to participate in this as you fit into the laid out criteria for a study 'subject'/ participant.

Your participation in study is voluntary. During the study you will be undergoing few routine blood investigations. Your decision whether or not to participate in the study will not affect your treatment in any form. If you decide to participate you are free to withdraw at any time.

TITLE OF THE STUDY: "A STUDY ON THYROID PROFILE IN ICU ADMITTED PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC"

PURPOSE OF THE STUDY: To asses Thyroid Function tests in patients admitted in Medical ICU and analyse their correlation with Prognosis of the Patient.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, you will be clinically examined in detail and investigated for the below said investigations accordingly.

1) FREE T3.
2) FREE T4.
3) TSH.

RISKS AND BENEFITS: There are no potential risks involved in this study.

BENEFITS OF TAKING PART IN THIS RESEARCH: To Assess the levels of Thyroid hormones and their role in assessing the severity of morbidity and risk of mortality in ICU admitted patients.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY: Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES: Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY: All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

- In emergency to protect your rights AND welfare.
- If required by law.

AUTHORIZATION TO PUBLISH RESULT: The results of the study may be used to publish an article .When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION: No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION: In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS: You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for. In case of the queries during study or in future you may contact following persons,

		Dr. HARSHA HEGDE Head of Ethical Committee for research JNMC BELAGAVI

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered

Signature / Left Thumb print of the Participant or legally authorized representative Participant's name:……………………………...

Signature / Left thumb impression:……………………….. of the participant

Name of the legally authorized:……………………………...

Representative / guardian

Signature / Left thumb impression:……………………………...

Witness' name:…………………………...

Signature / Left thumb impression:……………………………...

Investigator's name and signature:……………………………...

Date:

Place:

ANNEXURE- II - PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION

COMPLAINTS AT PRESENTATION:

PAST HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

TREATMENT HISTORY:

GENERAL PHYSICAL EXAMINATION:

GENERAL CONDITION:

PALLOR- YES/NO

ICTERUS-YES/NO

LYMPHADENOPATHY-YES/NO

CYANOSIS- YES/NO

CLUBBING-YES/NO

EDEMA-YES/NO VITALS:

TEMPERATURE

PULSE

RESPIRATORY RATE

BLOOD PRESSURE

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

C.N.S.:

P.A.:

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

1) FREE T3.
2) FREE T4.
3) TSH

ANNEXURE III – MASTER CHART										
sl.no	**patient name**	**age**	**sex**	**diagnosis**	**past h/o**	**TSH**	**FREE T3**	**FREE T4**	**MORBIDITY**	**DEATH**
1	neelambika	68	f	sepsis secondary to cholecystitis	t2dm	3.26	1.82	0.8	2days	
2	mahaveer	52	m	sepsis secondary to urinary tract infection	t2dm	1.73	1.93	1.33	10 days	yes
3	malavva	60	f	sepsis secondary to cellulitis	t2dm	1.51	1.71	0.9	3days	yes
4	channabasangouda	59	m	sepsis secondary to pneumonia	t2dm	0.17	2.02	1.62	13 days	yes
5	mark	68	m	sepsis secondary to uti	t2dm	6.04	2.35	1.01	2 days	
6	dilipraj	52	m	sepsis secondary to uti	t2dm	5.31	2.33	1.32	2 days	
7	swati	44	f	septic shock	t2dm	3.59	0.52	1.31	4 days	
8	maya	52	f	sepsis secondary to acute pancreatitis	nil	4.74	2.68	1.14	2days	yes
9	ningappa	70	m	sepsis secondary to right leg cellulitis	t2dm	0.07	1.64	1.41	4 days	
10	kempavva	38	f	sepsis secodary to VZV	nil	1	0.79	1.32	9 days	yes
11	anushriya	71	f	sepsis secondary to pneumonia	t2dm	2.8	1.76	1.4	5days	
12	sambhaji	47	m	sepsis secondary topneumonia	nil	0.16	1.66	1.25	3days	
13	praveen	59	m	septic shock secondary topneumonia	nil	1.46	1.5	1.57	3days	
14	devamma	68	f	sepsis secondary to uti	t2dm	1.8	3.8	1.72	2days	
15	ammini	70	f	sepsis secondary to pneumoniae	t2dm	0.01	2.62	3.82	3 days	
16	veerayya	78	m	sepsis secondary to pyelonephritis	t2dm, htn	0.34	1.89	1.3	5 days	
17	sadashiv	83	m	sepsis secondary to pneumonia	ihd, htn	0.13	1.91	1.28	4 days	
18	sindu	60	f	sepsis secondary to pneumoniae	t2dm	0.95	1.87	1.03	4 days	
19	ramachandra	75	m	sepsis secondary to uti	t2dm	1.08	1.14	0.34	6 days	yes
20	saradha	69	f	sepsis secondary to aspiration pneumoniae	stroke, t2dm, htn	0.23	1.56	1.94	11 days	yes
21	anita	53	f	sepsis shock secondary to uti	t2dm	1.19	1.84	1.37	2 days	yes
22	manisha	45	f	sepsis secondary to cellulitis	t2dm	0.96	1.06	0.73	30 days	yes
23	jitan	37	m	chronic liver disease	nil	0.93	2.14	1.03	5days	
24	ravindragouda	52	m	chronic liver disease	t2dm, alcoholic	4.87	2.63	1.48	6days	
25	bebijan	73	f	hepatic encephalopathy	CLD	2.28	2.42	1.37	5days	
26	basavaraj	58	m	chronic liver disease	alcoholic	2.93	2.8	1.48	4 days	
27	sachin	42	m	chronic liver disease	nil	0.97	1.7	0.64	7 days	yes
28	somaling	46	m	chronic liver disease	alcoholic	0.08	2.4	0.96	5 days	
29	ashok	44	m	chronic liver disease	nil	0.35	2.56	1.5	4 days	
30	laxmikanth	50	m	chronic liver disease	nil	2.52	1.8	1.52	4 days	
31	vandana	42	f	chronic liver disease	nil	1.34	0.84	1	16 days	yes
32	ramesh	56	m	chronic liver disease	htn	3.4	1.42	1.43	17 days	yes
33	ramagond	54	m	chronic liver disease	nil	1.72	1.7	0.94	8 days	yes

34	shobha	56	f	chronic liver disease	nil	1.27	2.81	0.92	5 days	
35	basappa	52	m	chronic liver disease	nil	2.11	1.64	1.42	3 days	
36	sambhaji	70	m	chronic liver disease	nil	1.09	1.11	1.42	11 days	yes
37	appasab	55	m	chronic liver disease	nil	0.79	2.16	1.52	15 days	yes
38	nagappa	59	m	ugi bleed secondary to CLD	nil	1.93	1.7	1.14	5days	yes
39	clifford	54	m	CHRONIC LIVER DISEASE secondary to NAFLD	NIL	1.59	3.37	1.22	3 DAYS	
40	ramu	44	m	chronic liver disease	alcoholic	0.52	2.14	1.08	10days	
41	basavaraj	48	m	chronic liver disease	nil	0.02	2.12	1.66	9 days	YES
42	basavaraj	47	m	chronic liver disease	nil	0.58	2.36	1.6	12 days	
43	nagaraj	46	m	acute pancreatitis	nil	1.72	3.21	1.39	3 days	
44	gaurav	31	m	acute pancreatitis	nil	0.53	1.73	1.2	4 days	
45	appasaheb	61	m	acute on chronic pancreatitis	nil	2.71	1.75	1.46	10days	
46	bharathi	35	m	acute pancreatitis	nil	1.9	1.89	1.1	7days	
47	renuka	47	f	acute pancreatitis	nil	3.12	2.3	1.23	4 days	
48	mallappa	65	m	acute on chronic pancreatitis	t2dm	4.4	2.78	1.61	3 days	
49	vasu	38	m	acute pancreatitis	nil	4.08	2.35	1.69	4 days	
50	santosh	27	m	acute pancreatitis	nil	0.72	3.37	0.84	15 days	
51	anand	35	m	acute pancreatitis	nil	3.92	3.11	1.89	4 days	
52	appasaheb	44	m	acute onchronic pancreatitis	nil	0.37	1.2	1.17	13 days	
53	ganesh	35	m	ischaemic stroke	nil	1.52	1.79	0.93	9days	
54	sulbha	48	f	ischaemic stroke	t2dm	9.43	0.99	1.1	16days	
55	shamavva	75	f	ischaemic stroke	t2dm, htn	4.97	1.37	1.24	15 days	
56	nagaling	83	m	ischemic stroke	t2dm, htn	3.46	1.41	0.93	4 days	
57	gopibai	87	f	ischaemic stroke	t2dm, ihd, htn	0.97	1.47	2.22	3 days	
58	savita	68	f	ischaemic stroke	t2dm	0.42	1.35	1.39	8days	
59	malaprabha	56	f	ischaemic stroke	t2dm, htn	0.73	1.22	0.85	7 days	
60	purushotham	47	m	ischaemic stroke	t2dm	2.23	1.43	1.16	21 days	
61	pramod	65	m	ichaaemic stroke	ihd	0.08	2.03	1.59	2days	
62	shantavva	53	f	accelerated hypertension	htn	0.78	1.1	1.33	4 days	
63	ranaba	87	m	accelerated hypertension	htn	1.23	2.38	1.43	2 days	
64	shantavva	53	f	accelerated hypertension	ihd, htn	0.78	1.1	1.33	4days	
65	jayaram	55	m	adnocarcinoma stomach	nil	0.56	1.68	0.98	5days	yes
66	jamuna	44	f	adenocarcinoma stomach	nil	1.12	1.42	1.81	2 days	yes
67	fatima	50	f	choledocholithiasis	nil	1.44	1.33	1.19	5 days	
68	shialingavva	67	f	choledocholithiasis	nil	1.21	1.76	1.36	7 days	

69	chetana	18	f	cholelithiasis	nil	1.76	2.16	1.54	14 days	
70	durgappa	53	m	cholelithiasis	nil	3.62	3.87	1.25	2 days	
71	salim	67	m	copd	htn, IHD	0.44	2.1	1.3	6 days	
72	ishwar	68	m	copd	nil	1.76	1.64	0.73	6days	
73	dinesh	57	m	dengue shock syndrome	nil	0.09	2.05	1.55	7 days	
74	veerappa	31	m	dengue shock	nil	1.66	3.7	1.48	2days	
75	suraj	26	m	dengue fever	nil	5.53	3.17	1.44	2 days	
76	laxmi	62	f	diabetic ketoacidosis	t2dm	0.97	1.45	0.97	4 days	
77	shareefanbee	65	f	diabetic keto acidosis	t2dm	1.09	2.08	1.43	2 days	
78	satavva	70	f	heart failure with reduced ef	ihd, htn	0.79	1.49	1.1	5 days	
79	ravindranath	57	m	heart failure with reduced ef	ihd,htn	4.3	1.84	1.29	5 says	yes
80	shanta	75	f	heart failure with reduced ef	htn, ihd	0.98	3.07	2.01	4 days	
81	mala	35	f	hypovolemic shock	nil	4.57	2.64	1.1	3 days	
82	dhurjati	40	m	hypovolemic shock seconady to acute gastroenteritis	nil	3.4	3.43	1.11	6 days	
83	shankar	66	m	ihd	t2dm	0.08	5.12	0.6	4 days	
84	bindhumadhav	69	m	ihd	t2dm, htn	3.1	1.14	1.03	5 days	yes
85	shamavva	75	f	pneumonia	t2dm, htn	4.97	1.37	1.24	3days	
86	gangadhar	90	m	aspiration pneumonie	stroke, t2dm, htn	6.7	0.82	0.2	13 days	yes
87	deepika	59	f	covid 19 pneumonia	t2dm	4.37	1.03	0.52	6days	
88	gopal	32	m	covid 19 pneumonia	nil	3.01	2.47	1.25	6 days	
89	kasturibai	45	f	pneumonie	nil	2.02	1.98	1.38	6 days	
90	zakirhusen	47	m	ulcerative colitis	nil	0.89	1.86	1.11	10days	YES
91	panchappa	62	m	ulcerative colitis	nil	2.73	3.35	1.09	5days	
92	rajabee	49	f	ulcerative colitis	nil	3.35	1.39	0.12	3 days	
93	vinayak	40	m	ulcerative colitis	nil	0.77	2.1	1.09	3days	
94	omani	65	f	chronic kidney disease	t2dm	1.53	1.45	1.06	2 days	
95	suvarna	76	f	chronic kidney disease	t2dm	2.06	1.14	1.04	19 days	yes
96	iranna	62	m	chronic kidney disease	t2dm	0.76	2.02	2.05	3days	
97	mehabubsab	58	m	myaesthenia gravis	t2dm	0.2	2.46	1.7	2 days	
98	vasu	38	m	alcoholic hepatitis	alcoholic	2.13	1.7	1.42	24 days	
99	kenchamma	83	f	hypoglycemic episodes	t2dm, htn	3.1	3.47	1.04	1 day	
100	hanumant	74	m	larynx cancer	smoker	3.68	1.16	1.5	3 days	yes
101	prabhakar	79	m	tb meningitis	ihd	0.3	1.86	1.37	9days	yes
102	mahalingappa	72	m	acute severe asthma	bronchial asthama	0.68	1.99	1.04	4 days	
103	virupakshi	63	m	cor pulmonale	copd	1.34	3.08	1.83	5days	

104	priyadarshi	31	f	hellp syndrome	nil	0.22	2.55	1.46	3 days	
105	priyanka	27	f	clonazepam overdose	nil	5.29	3.88	1.29	2 days	
106	shivshankar	58	m	hypoxic ischamic encephalopathy	nil	1.99	1.75	1.16	25 days	
107	vijaykumar	73	m	multiple myeloma	nil	1.37	1.76	1.4	7days	
108	mallikarjun	48	m	crohns disease	nil	0.79	1.64	1.03	6days	
109	vinay kumar	26	m	drug overdose	nil	2.66	3.01	1.28	3 days	
110	shanmukh	45	m	methotrexate overdose	rheumatoid arthritis	0.32	1.1	1.51	6days	
111	shaila	47	f	ca lung	nil	0.86	2.9	1.18	4 days	
112	mumtaz	67	f	cor pulmonale	copd	0.42	2.04	2.36	3 days	
113	jyothi	38	f	ca. breast	nil	4.35	2.45	0.38	4 days	
114	padma	66	f	hypercalcemia in aki	rheumatoid arthritis	3.98	1.53	2.82	4days	
115	ramjansab	56	m	pyelonephritis	t2dm	0.39	2.19	0.84	5 days	