Original Article

Study of Non-Thyroidal Illness Syndrome and its Recovery in Critically Ill Patients at a Tertiary Care Centre in South India

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Abstract

Background and Objectives: Transient thyroid hormone alterations are common during critical illness and are termed non-thyroidal illness syndrome (NTIS). We studied the prevalence of NTIS in the ICU setting and its impact on predicting mortality and other outcomes and compared it to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. **Materials and Methods:** The study included 119 consecutive patients admitted with a critical illness. APACHE II score was calculated. Total T3, total T4, TSH, free T3, and free T4 were measured at admission and after six weeks of discharge. NTIS and euthyroid groups were studied for ICU, hospital stays, mortality, readmission, and recovery. Predictors of mortality were compared between survivors and non-survivors. **Results:** The mean age was 60.15 ± 14.50 years with M:F = 84 (71%):35 (29%). NTIS was observed in 84 (71%), low T3 being the most common abnormality in 53 (63%). The occurrence of NTIS was significantly higher among non-survivors (28/30, 93%) versus survivors (56/89, 63%) (P = 0.002). Non-survivors showed significantly lower T3, TSH, and FT3/FT4 ratios and higher readmissions. NTIS group showed significantly greater ICU stay (P = 0.02) and had higher readmission rates (P = 0.032). Baseline T3 had the greatest power to predict mortality. APACHE II score also correlated significantly with mortality (19.60 ± 10.58 vs 11.99 ± 6.80, $P < 0.001$). The area under the curve (0.677) for the T3 level was lower than the APACHE II score (0.760). After six weeks, 61% had recovered from NTIS. **Conclusions:** NTIS was common amongst critically ill patients (71.5%), which reversed in 61% at six weeks. Low T3 was the most common abnormality and independently predicted mortality. Free T3/free T4 also significantly predicted mortality. The correlation between thyroid dysfunction and the severity of primary illness makes it an additional attractive low-cost marker of mortality.

Keywords: Critically ill, free T3/free T4, high T4, low T3, non-thyroidal illness syndrome, thyroid hormones

Introduction

The phenomenon of transient alterations in thyroid hormones during critical illness is common and termed non-thyroidal illness syndrome (NTIS).[1] The prevalence of NTIS is reported as 70%–80% in all forms of critical illness.[2] The most common form of NTIS is low T3 syndrome with high levels of reverse T3, while combined low T3 and T4 represent a more severe form of NTIS. Rarely, NTIS with low T3, T4, and low TSH is observed along the continuum of severity of illness.[3] While multiple studies highlight a negative correlation between the severity of NTIS and poor prognosis of critical illness,[4-6] very few have studied the rate of recovery from NTIS.[7]

We conducted this prospective, observational study to evaluate thyroid hormone abnormalities in critically ill patients admitted to our hospital and their recovery at six weeks post-discharge.

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Aims and objectives

1. To study the frequency of NTIS in patients admitted to the critical care unit of our hospital
2. To observe the association between the severity of illness and the degree of thyroid dysfunction
3. To study whether thyroid dysfunction can be a predictor of the outcome
4. To study recovery from NTIS at six weeks post-discharge.

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Materials and Methods

Ours was a prospective, observational study conducted at Care Hospital, a tertiary care facility in Hyderabad, with 1000–1200 admissions per month and 50–60 daily ICU admissions, after approval from the Institutional Ethics Committee. A standard informed consent was obtained from the subject/their attendant, and the primary team was also involved in this stage.

The study recruited 119 consecutive adult critically ill patients with one or more organ dysfunctions between January 2021 and December 2021. The thyroid function tests were conducted within 24 h of admission in a fasting state at 8 AM.

The study excluded subjects with COVID-19 infection, intrinsic thyroid disease, patients on drugs altering thyroid functions, previous history of neck irradiation, pregnant and post-partum stage, and subjects on any hormonal therapy except for insulin and TSH more than 20 mIU/ml.

All patients meeting the inclusion criteria had a detailed clinical history, including diabetes mellitus, hypertension, coronary artery disease, cerebrovascular accidents, chronic kidney disease, chronic liver disease, cancer, and previous drug intake, and a structured physical examination was also conducted.

During the initial assessment, Acute Physiology and Chronic Health Evaluation II (APACHE II) score were measured within 24 h of admission, which is the current standard to prognosticate mortality and morbidity across different populations.[8,9] with a maximum score of 71.

Biochemical measurements

Fasting venous blood samples were collected on the morning of admission for the following thyroid function tests - total T3, total T4, TSH, free T3, and free T4. To determine serum-free T3, T3, T4, and TSH, a direct chemiluminescence immunoassay was used on a fully automated Beckman Coulter analyser, and an electrochemiluminescence immunoassay was used for free T4 on an e601 Roche analyser. Assay reference ranges in our laboratory are as follows: Free T3 (2.3–4.2 pg/ml), Free T4 (0.93–1.7 ng/dl), Total T3 (0.6–2.1 ng/dl), Total T4 (5–12 ug/dl), and Serum TSH (0.3–5.0 µIU/ml). A ratio of free T3/free T4 was calculated. Patients were tested for SARS CoV by RT PCR and thoracic HRCT to exclude COVID-19. Additional relevant investigations related to the primary conditions were also done concurrently.

According to the thyroid function test results, the study subjects were categorised into two groups.

Group A: NTIS.

Group B: euthyroid critically ill patients.

AQ12 Figure 1 illustrates the study design.

Statistical analysis

Statistical analysis was conducted by the SPSS software version 23. We used Student's t-tests to compare groups with continuously distributed data. For the non-normally distributed data, appropriate non-parametric tests were performed with the Wilcoxon test. A Chi-squared test was used to compare categorical data between groups. Fisher's Exact Test was applied in cases where the expected frequency in the contingency tables was <5 or >25%. A linear correlation between two continuous variables was investigated with Pearson's correlation (if the data were normally distributed) and Spearman's correlation (if the data were not normally distributed). A *P* value of <0.05 was considered statistically significant.

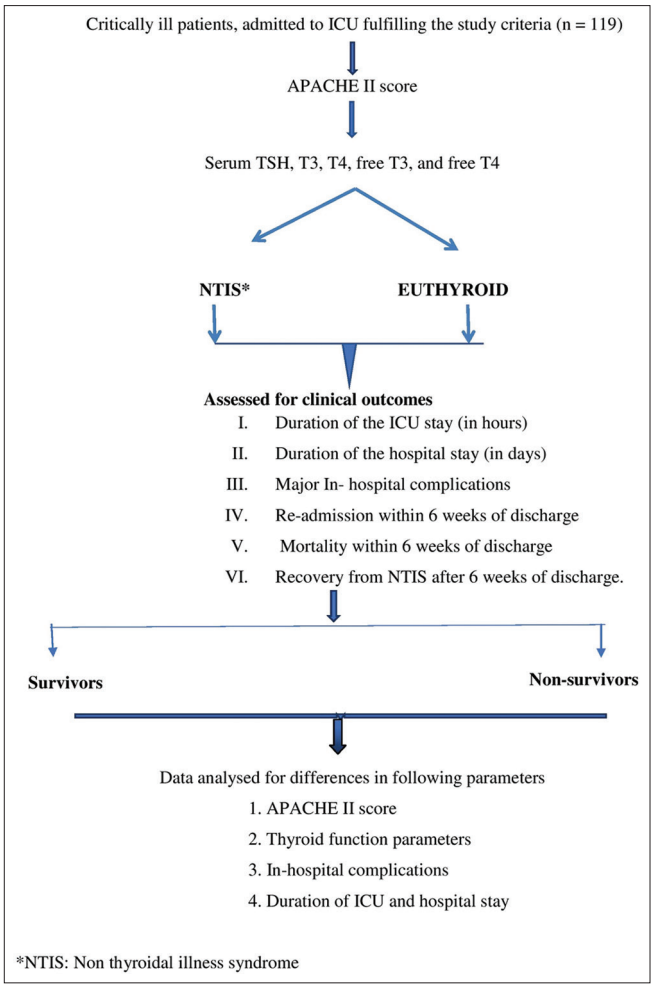

Figure 1: Illustrates the study design

Results

Baseline characteristics

A total of 119 patients were eligible for enrolment in this study. The mean age of the study population was 60.15 ± 14.5 (range, 20–94) years. Male and female were 84 (71%) and 35 (29%). Cardiology (43%) and neurology (36%) departments accounted for most admissions. Additionally, patients were admitted to nephrology (6%), infections/toxicology/haematology (6%), gastroenterology (5%), and pulmonology (4%). In total, 62 (52%) subjects had Type 2 diabetes mellitus, and 78 (65%) subjects had hypertension. CAD history was present in 34, and 21 had undergone interventions (PTCA/CABG) for the same.

Prevalence of NTIS

Of the 119 patients, 84 (71.5%) had thyroid dysfunction, and 35 (28.5%) were euthyroid. A median (interquartile range) duration of ICU stay was significantly longer at 118 (72–174) h for NTIS, compared to 72 (48–133) h for the euthyroid group. The most common abnormality in NTIS was low T3, seen in 53 of 84 (63%). NTIS was significantly higher in patients with pre-existing DM ($P = 0.01$) and previous cardiovascular events (MI/CVA) ($P = 0.015$). Pre-existing hypertension didn't show any increased association with NTIS. Figure 2 depicts the overall spectrum of NTIS.

Relationship between thyroid function tests and APACHE II score

The APACHE II scores ranged from 2 to 61, with a mean of 13.91 ± 8.54. The APACHE II score was higher (14.88 ± 7.56) in the NTIS group than in the euthyroid group (11.57 ± 10.28, $P = 0.004$). In addition, we examined the relationship between the APACHE II score and specific thyroid indices. The APACHE II score exhibited a statistically significant moderate negative correlation with baseline T3 ($r = -0.35$, $P < 0.01$) [Figure 3a] and as well as free T3 ($r = -0.36$, $P < 0.01$). A higher APACHE II score showed a weaker, though significant association with lower TSH ($r = -0.18$, $P = 0.047$) and free T3/free T4 ($r = -0.21$, $P = 0.023$) [Figure 3b].

Comparison of baseline parameters amongst survivors versus non-survivors

In the study of 119 patients, 89 (75%) were survivors, and 30 (25%) were non-survivors. Patients with primary neurological illness had the highest mortality of 60%, followed by 17% in those with cardiovascular disease. Non-survivors had higher APACHE II scores versus survivors (19.60 ± 10.58 vs 11.99 ± 6.80 $P < 0.001$). NTIS was observed more frequently in non-survivors 28 (93%), compared to survivors 56 (63%) ($P = 0.002$). Table 1 shows all the parameter analyses of survivors and non-survivors.

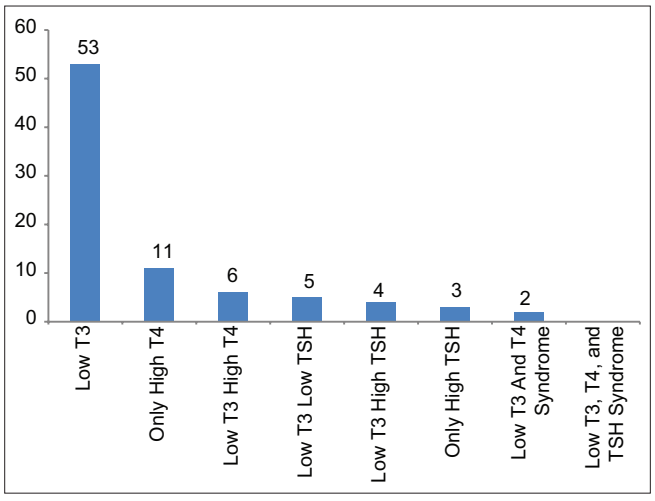

Figure 2: Spectrum of non-thyroidal illness syndrome ($n = 84$)

Recovery of NTIS six weeks post-discharge

Of the 84 subjects with NTIS, 28 had succumbed to the illness. Follow-up thyroid function tests were done in 46 of the 56 surviving NTIS patients. Of the 46 subjects, complete recovery of NTIS was seen in 28 (61%). NTIS persisted in 18 (39%), and they were advised to repeat thyroid function tests after three months. A total of 53 of 119 patients (44%) had low T3 levels at baseline; of these 53 patients, 14 were non-survivors. On follow-up at six weeks, 23/35 (65.7%) of patients with low T3 had normalised, while 12/35 (34.3%) had persistent low T3. In patients with high T4, 5/11 recovered, and 4/11 persisted in having elevated T4. There was a statistically significant difference between the dynamics of T3 and T4 during illness and on follow-up ($P = 0.001$). An elevation in TSH in four subjects who had normal TSH at baseline. We observed that 6/12 (50%) patients with low free T3 had recovered. At six weeks, the recovery of low free T4 and high free T4 was observed in 1/2 (50%) and 2/8 (25%) of subjects, respectively. Figure 4 illustrates the spectrum of NTIS and its recovery.

Variables as indicators for predicting mortality

Receiver operating characteristic (ROC) curves were constructed for the assessment of each parameter as a predictor of ICU mortality, and then the area under the curve (AUC) for each indicator was calculated. The AUC, optimal cut-off value, sensitivity, and specificity of each indicator are presented in Table 2. In the study subjects, the following baseline parameters significantly predicted mortality outcomes: APACHE II score, total T3, TSH, and FT3/FT4. Among the thyroid hormone indicators, total T3 had the greatest power for predicting ICU mortality, as suggested by the largest AUC of 0.677 [Figure 5]. However, this was lesser than the APACHE II score (0.760).

Summary of trends of ROC AQ7

The best parameter in terms of AUROC: APACHE II score.

The best parameter in terms of sensitivity: Total T3.

Table 1: Summary of the baseline parameters between survivors ($n=89$) and non-survivors ($n=30$)

Baseline parameters	Survivors $n=89$	Non-survivors $n=30$	*P*
APACHE II***	11.99±6.80	19.60±10.58	<0.001[1]
T3 (ng/dL)***	0.58±0.22	0.46±0.20	0.004[1]
T4 (ug/dL)	9.75±2.82	9.50±3.91	0.783[1]
TSH (IU/mL)***	2.23±1.66	1.75±2.27	0.005[1]
FT3 (pg/mL)	2.68±0.54	2.48±0.49	0.065[4]
FT4 (ng/dL)	1.36±0.36	1.42±0.35	0.103[1]
FT3/FT4***	2.10±0.67	1.88±0.77	0.034[1]
NTIS***	56 (62.9%)	28 (93.3%)	0.002[2]
Euthyroid	33 (37.1%)	2 (6.7%)	
ICU stay (h)	128.66±117.51	190.23±188.68	0.073
Duration of hospital stay	8.06±5.08	9.60±9.02	0.749
Readmission (six weeks)***	5 (5.7%)	8 (57.1%)	<0.001[3]

***Significant at $P<0.05$

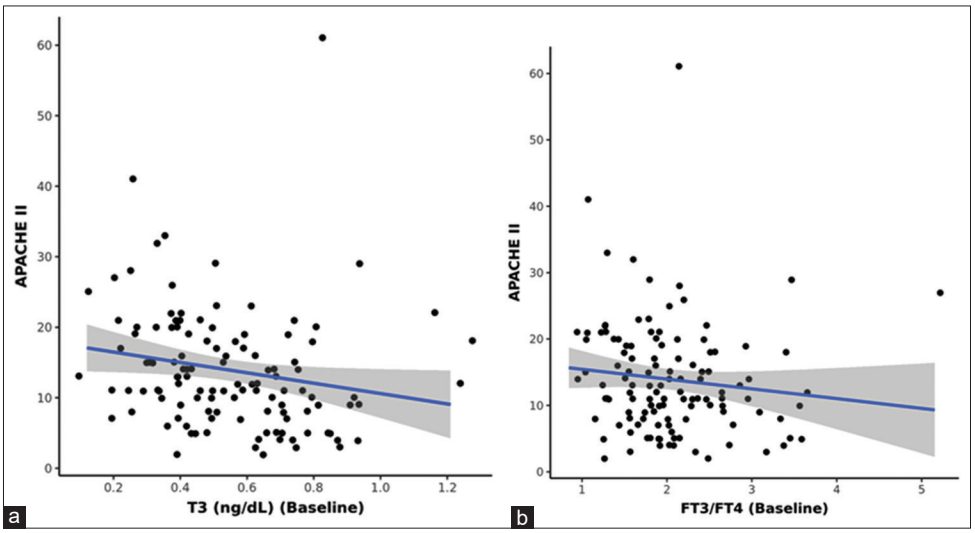

Figure 3: (a+b): Scatter plot depicting the correlation between the baseline values of total T3 (a) and free T3/free T4 with Acute Physiology and Chronic Health Evaluation II (APACHE II) score (b)

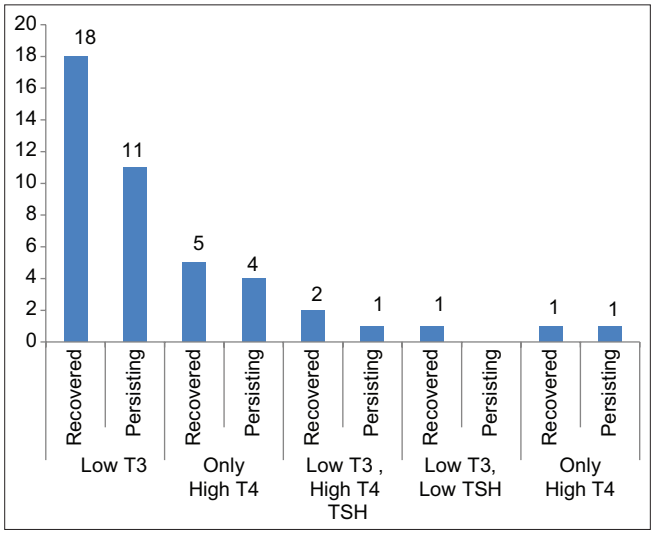

Figure 4: Recovery of non-thyroidal illness syndrome at six weeks post-discharge

The best parameter in terms of specificity: TSH.

The best parameter in terms of positive predictive value: TSH.

The best parameter in terms of negative predictive value: T3.

The best parameter in terms of diagnostic accuracy: TSH.

Discussion

The hormonal changes observed in NTIS follow a pattern. Low T3 is the initial and the most common abnormality. There is an initial rise in TSH and TT4/fT4 followed by another surge of TSH during recovery with normalisation of TT4/fT4. Most patients eventually recover, with the changes varying according to the severity of the illness and the course of the disease.

We reported the prevalence of NTIS as 71.5% in critically ill ICU patients, spread across age groups of 18–94 years, an observation similar to the study by Girvent *et al.*[11] and others.[7,8] About 61% of the subjects with NTIS recovered from NTIS at six weeks post-discharge. Most study subjects had primary cardiac (42.9%) or neurological (36.1%) illnesses, comparable to other studies.[5,12]

Among the 119 study participants, there were 30 non-survivors and 89 survivors. Only two of the non-survivors were euthyroid, and 28 belonged to the NTIS group. Low T3 levels were found in 25 (83.3%) of 30 non-survivors and 45 (50.6%) of 89 survivors. The presence of low T3 was a significant and independent predictor of mortality. Similar results have been reported in other studies.[5,7]

Among the various patterns of NTIS, low T3 was the most common abnormality found. Approximately 43% of those with low T3 also had low free T3. This can be attributed to changes in the TBG and a defect in peripheral deiodination.

In addition, 11/84 (14%) patients had high T4 levels and high free T4 levels. This reflects the initial surge in the hypothalamic-pituitary-thyroid axis, causing a mild increase in TSH, which in turn causes elevation of T4.[13,14] Later, T4 drops, reflecting the severity of the condition. Fatal outcomes were observed in patients who had lower levels of T3 and T4.

In our study, we observed fluctuations in TSH above and below the normal range. TSH levels ranged from a minimum of 0.003 mIU/ml to a maximum of 7.86 mIU/ml. The TSH surge occurs in the early phase and the recovery phase of the illness. We noted that four of the five patients with lower baseline TSH succumbed to their primary illness, reflecting the severity of the condition. Lower TSH levels are a marker that indicates a very severe form of illness.

Free T3 was described as an independent predictor of mortality in two studies by Gutch *et al.*[15] and another Chinese study.[12] However, we couldn't show a significant correlation between survivors and non-survivors for this parameter. However,

Table 2: Comparison of the diagnostic performance of various predictors in predicting outcome: Non-survivor versus survivor

Predictor	AUROC	95% CI	*P*	Sn	Sp	PPV	NPV	DA
APACHE II	0.760	0.659-0.861	<0.001	80%	62%	41%	90%	66%
T3 (ng/dL) (Baseline)	0.677	0.565-0.79	0.004	83%	56%	39%	91%	63%
T4 (ug/dL) (Baseline)	0.517	0.388-0.646	0.783	40%	74%	34%	79%	66%
TSH (IU/mL) (Baseline)	0.673	0.55-0.797	0.005	43%	90%	59%	82%	78%
FT3 (pg/mL) (Baseline)	0.614	0.499-0.73	0.062	67%	58%	35%	84%	60%
FT4 (ng/dL) (Baseline)	0.600	0.478-0.722	0.103	63%	64%	37%	84%	64%
FT3/FT4 (Baseline)	0.630	0.513-0.747	0.034	63%	68%	40%	85%	67%

AUROC=area under receiver operating characteristic curve, CI=confidence interval, *P*=*P* value, Sn=sensitivity, Sp=specificity, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

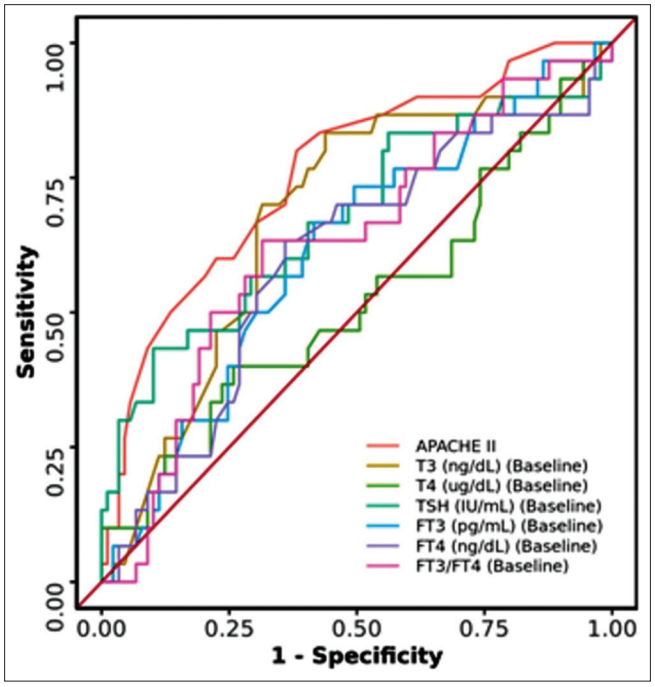

Figure 5: Receiver operating characteristic curves analysis showing diagnostic performance of various baseline parameters in predicting mortality outcome (n = 119)

the ratio of freeT3 to freeT4, which corresponds to the early changes in the dynamics of NTIS, was found to be a predictor of mortality. Similar observations were made by Pasqualetti *et al*.[16] who showed that decreased FT3/FT4 ratio, an indirect marker of peripheral thyroxin deiodination, was an independent risk factor for frailty and increased mortality in hospitalised older patients.

The APACHE II score between survivors, 11.99 ± 6.80, and non-survivors, 19.60 ± 10.58, showed a higher prediction of mortality, which was similar to an Indian study.[15] APACHE II score was also higher in the NTIS group (14.88 ± 7.56) than in the euthyroid group (11.57 ± 10.28). Our study results are in concordance with the study by Wang *et al*.,[17] where the APACHE II scores were higher in patients with NTIS than in normal thyroid function. In addition, older age groups had higher APACHE II scores in our study.

The AUC by ROC analysis of T3 was observed to be 0.677. Baseline T3 with a cut-off ≤0.55 ng/dl had a sensitivity of 83%, making it the most sensitive of all thyroid function parameters for predicting mortality. Despite its statistical significance, it was regarded as a poor diagnostic test based on ROC analysis. It had the highest negative predictive value of the parameters studied. A study done by Gutch *et al*.[15] had an AUC ROC of 0.364 ± 0.065, which showed no discrimination. However, in a Chinese study,[12] TT3 was the most sensitive diagnostic parameter and showed an AUC ROC of 0.722 ± 0.33, making it a fair diagnostic test.

A cut-off of TSH ≤0.65 uIU/ml predicted mortality outcomes with a sensitivity of 43% and a specificity of 90%. It showed the highest specificity of the parameters studied. The AUC derived by ROC analysis for TSH was 0.673. Another study[12] demonstrated an AUC ROC of 0.603 ± 0.034, implying poor diagnostic ability. In the current study, we observed that the ratio of free T3 to free T4 significantly predicted mortality. With the AUC by ROC of 0.630, it showed poor diagnostic performance.

The AUC derived from ROC analysis of the APACHE II score was 0.760, which suggested a good diagnostic correlation with mortality. The cut-off value of ≥13 correlated with mortality with a sensitivity and specificity of 80% and 62%, respectively. This was the best parameter in terms of AUC ROC. A similar observation was noted[15] with an AUC of 0.824 ± 0.051 and a cut-off of ≥18.5. Another study (16) noted an AUC ROC analysis value of 0.829 ± 0.022. With the cut-off value of ≥15, they had sensitivity and specificity of 74% and 75%, respectively. AQ8 AQ9

We found in-hospital complications of acute kidney injury and rate of re-admissions significantly correlated with lower TT3 and FT3. Lower freeT3/freeT4 ratios were found to be associated with cardiac complications such as heart failure and cardiac arrest. Since these findings are novel and haven't been previously studied, there is a need for further research.

Conclusion

Among all parameters, low T3 was the most common form in NTIS. NTIS had a comparable predictive value for mortality

to the APACHE II score. The ratio of FT3/FT4 had a high predictive value for mortality. Recovery from NTIS was seen in 61% of patients. While thyroid functions are not routinely recommended for ICU patients, its correlation with the severity of primary illness makes it an additional attractive low-cost tool to predict ICU outcomes and mortality.

Limitations

1. As an integral part of patient management in the ICU, drug interference in thyroid function tests could not be eliminated, for example, dopamine, heparin, noradrenaline, furosemide, etc.
2. Longer follow-up is required in those with persisting NTIS after six weeks of discharge.
3. Thyroid function status done within 24 h may not correspond to the most severe phase of the illness.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/blood tests and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil

Conflicts of interest

There are no conflicts of interest.

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