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Original Research Article

Assessment of prognostic value of FT3, FT4 and TSH among critically ill patients

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ABSTRACT

Background: Thyroid dysfunction is found to be associated with increased morbidity and mortality rates in intensive care unit (ICU) admitted patients. Critically ill patients who were admitted to ICU showed free triiodothyronine (FT3) levels to be an independent and important predictor of mortality. Decreased levels of free thyroxine (T4) and thyroid stimulating hormone (TSH) showed an indication of worsening of disease and poor prognosis. The most common thyroid hormonal change reported in critically ill patients is reduced serum T3 level. The aim of this study was assessment and prognostic value of thyroid function values among critically ill patients.
Methods: The prospective observational study was conducted at department of medicine, at tertiary care hospital of Kanpur, India on 100 critically ill patients admitted who were more than 18 years of age. Patients with history s/o previous thyroid illness and documented thyroid disease, and clinically evident thyroid enlargement were excluded from the study.
Results: 50 (50.0%) of 100 patients were males and 50 (50.0%) were females. A total 44.0% mortality was reported with 57±11.96 years of mean age of non-survivors. Only FT3 of thyroid functions have shown statistically highly significant differences ($p<0.01$).
Conclusions: In our study patient admitted in ICU, FT3 was the strongest predictor of ICU mortality in comparison to all other important parameters included in our study.

Keywords: Thyroid dysfunction, Critically ill patients, Mortality, Intensive care unit

INTRODUCTION

The thyroid is an important gland involved in the metabolism, growth, development, and maintenance of the internal environment. Alteration in the levels of thyroid hormones is the most common phenomenon observed in any critical illness.[1] Such alteration in thyroid hormone levels during any critical illness is described as 'euthyroid sick syndrome' or 'nonthyroidal illness syndrome'. It is characterized by low levels of free and total triiodothyronine (T3) and high levels of reverse T3 (rT3) low to normal range.[2] The severity of illness correlates well with the reduction in total serum T3 level. The major cause of these hormonal changes is the release of cytokines such as IL-6. The most common hormone pattern in sick euthyroid syndrome (SES) is a decrease in T3 levels (low survivors and T3 syndrome) with normal level of T4 and TSH. Low T3 is an important contributor of mortality in critically ill patients. T4 and TSH did not vary between non-survivors.

The predominant changes in acute stress are lower circulating thyroid hormones indicating hypogonadism and hypercortisolism. Some studies have reported that the low thyroid hormones are independent predictors of mortality in patients who were critically ill and admitted to intensive care units (ICU). A similar study conducted previously involving pediatric ICU patients had shown

that low T3 is a 4-good mortality predictor, and the risk is enhanced 30 times in case it is associated with low T4.[3]

Low T3 syndrome has found to be emerging as most crucial independent predictor of short-term survival. The inflammatory cytokine is the result of mediation of imbalance between the activity of type I and type II deiodinase. The decrease in hypothalamus and pituitary sensibilities to thyroid hormones is mediated by the stress induced hormones and cytokine respectively.[4] Hypothyroxinemia with normal TSH levels was found in 22% of the patients which was associated with a higher mortality [thyroxine (T4) level of less than 3.0 micrograms/dL, 84% mortality; T4 levels of 30 to 5.0 micrograms/dL, 50% mortality; and T4 levels was found to be greater than 5.0 micrograms/dl, 15% mortality]. There exists a high correlational value between low T4 levels and mortality.[5]

In the light of these facts this current this study was conducted in order to assess prognostic values of FT3, FT4 and TSH among critically ill patients.

METHODS

Current descriptive prospective observational study was conducted out at department of medicine, at GVSM hospital of Kanpur, India during January 2020 to December 2020 on 100 critically ill adult patients after taking the consent were studied. The study was approved from institutional Ethical committee.

Inclusion criteria

All critically ill patients admitted to ICU of the hospital.

Exclusion criteria

Patients who have not given consent, patients with history s/o previous thyroid illness and documented thyroid disease and patients with clinically evident thyroid enlargement.

An informed consent of participation in the study was taken by the patients or their significant others where appropriate. A total 100 consecutive patients admitted to medical ICU irrespective of the underlying diagnosis. Information on demographic profile, age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, respiratory rate (RR) was collected.

The patients were categorised in two groups: Survivors (one who were discharged from hospital) and Non-survivors (patients who died due to their illness inside hospital).

The blood samples were immediately collected on admission to ICU from all the studied patients, which went further for hormone analyses. SOFA score used to determine severity of illness. It was calculated from all patients along with their thyroid hormone profile.

Thyroid Function

After the admission of patients in ICU, their fasting blood samples were collected and obtained from all the eligible patients, which was further subjected to hormone analysis of thyroid gland (TSH, FT3, and FT4) along other useful investigations. The samples obtained were assayed by using solid-phase chemiluminescence immunoassay technique. The normal count values for TSH, FT3 and FT4 are 0.3-4.5 µIU/l, 3.5-6.5pmol/l, and 11.5-23 pmol/l respectively. The TSH assessment was not held again even during ICU stay or at their discharge time.[2] On a similar basis, the hormonal assays test was not repeated for another time in the ICU or in case of prior to discharge of the survivors.

Statistical analysis

Data was analysed using Statistical Package of Social Sciences (SPSS, version 23.0) software and expressed in form of mean±standard deviation. Inter group and intra group comparisons were done using Independent Sample T test/ un-paired t test for comparison of mean values. We used receiver operating characteristic (ROC) curves to assess and evaluate the performance of variables in predicting mortality; area under the curve, i.e., AUC was calculated from the ROC curve. Association between variables was considered statistically significant if p-value was <0.05.

RESULTS

Total of 100 (50 males and 50 females) patients admitted in MICU of PG department of medicine during the study period, mean age of all patients was 54.81±14.37 years (ranged 18-85 years). 50.0% were male patients whereas 50.0% female patients (Table 1).

Table 1: Demographic of all studied patients.

Variables		N=100
Age (in years)		54.81±14.37
Gender	Male (%)	50 (50.0)
	Female (%)	50 (50.0)

In clinical profile thyroid function test, mean TSH, FT3 and FT4 was 2.70±1.46 µIU/l, 3.03±1.72 (pmol/l) and 13.16±4.08 (pmol/l) respectively. Mean SOFA score and hospital stay was 9.51±2.35 and 11.70±3.32 days respectively as depicted in Table 2. We have observed that there were 56 (56.0%) survivors and 44 (44.0%) non-survivors; the mean age of survivors (52.38±15.68) was lower than that of the non-survivors (57±11.96). It does not show any statistical significance difference (p>0.05). The non-survivors had a lower systolic blood pressure, i.e., SBP, diastolic blood pressure, i.e., DBP as compared to survivors. SBP and DBP show statistically significant

difference (p<0.05). Pulse was significant (p<0.05) whereas respiratory rate was found statistically non-significant (p>0.05) (Table 3).

Mean TSH in survivor 2.82±1.62µIU/l was more than non-survivors 2.53±1.23 µIU/l. Mean value of FT3 in survivor 3.56±1.67 pmol/l is higher than non-survivor 2.34±1.54 pmol/l. Mean value of FT4 in survivor 13.82±3.00 pmol/l is higher than in non-survivor 12.34±5.05 pmol/l. Only FT3 of thyroid functions have shown statistically highly significant differences (p<0.01) (Table 4).

Table 2: Clinical profile of all studied patients.

Thyroid function	**TSH (µIU/L)**	**2.70±1.46**
	FT3 (pmol/L)	3.03±1.72
	FT4 (pmol/L)	13.16±4.08
Systolic blood pressure (SBP) (mmHg)		105.20±16.81
Diastolic blood pressure (DBP) (mmHg)		69.25±8.12
Pulse (per min)		88.98±11.85
Respiratory rate (RR)		19.31±2.32

Table 3: Hematological parameter of studied patients.

Variables	Survivor (N=56) Mean±SD	Non- survivor (N=44) Mean±SD	P value
Systolic blood pressure (mmHg)	110.80±15.60	-	<0.001
Diastolic blood pressure (mmHg)	73.68±7.38	63.61±4.92	<0.001
Pulse (per min)	91.54±12.24	85.73±10.59	0.014
Respiratory rate (RR)	19.18±2.18	19.48±2.31	0.509

Independent sample T test/ unpaired t test.

Table 4: Thyroid functions test of studied patients.

Variables	Survivor (N=56) Mean ±SD	Non-survivor (N=44) Mean ±SD	P value
TSH (µIU/L)	2.82±1.62	2.53±1.23	0.324
FT3 (pmol/L)	3.56±1.67	2.34±1.54	<0.001
FT4 (pmol/L)	13.82±3.00	12.34±5.05	0.071
Sofa score	8.79±2.23	10.43±2.18	<0.001
Hospital stay (in days)	10.95±2.71	12.66±3.78	0.010

Table 5: Test result variable(s): mortality (non-survivor).

Test result variables	Area under the curve	Std. error a	Asymptotic sig. b	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
SOFA score	0.717	0.051	0.000	0.618	0.306
TSH	0.207	0.051	0.000	0.108	0.521
FT4	0.398	0.063	0.081	0.275	0.570
FT3	0.457	0.058	0.457	0.343	0.570

Note: The test result variable(s): SOFA Score, TSH, FT4, FT3 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. (a) Under the nonparametric assumption, (b) Null hypothesis: true area= 0.5.

In our findings mean sofa score test value was lower in survivors (8.79±2.23) than in non-survivor (10.43±2.18). Hospital stay in survivors (10.95±2.71 days) was lower than in non-survivors (12.66±3.78 days) (Table 4).

Out of 100 patients, 44 (44.0%) were found as positive in terms of mortality in our study. In our study, cut off values for TSH (µIU/l), FT3 (pmol/l), FT4 (pmol/l) and SOFA score of non-survivors patients were tabulated in table 6. The sensitivity, specificity and accuracy for mortality were 52.3%, 44.6% and 20.7% respectively in TSH (µIU/l); similarly, 54.5%, 10.7% and 45.7% for respectively in FT3 (pmol/l); similarly, 52.3%, 23.2% and 39.8% for respectively in FT4 (pmol/l) and for SOFA score these were 68.2%, 53.6% and 71.7% respectively (Table 6). On the basis of accuracy, SOFA score and FT3 were found to most prognostic factor for mortality in our study.

Table 6: Sensitivity, specificity, accuracy of the of non-survivors.

Variables	Cut off	Sensitivity (%)	Specificity (%)	Accuracy (%)
FT4 (pmol/l)	5.65	54.5	23.2	39.8
FT3 (pmol/l)	1.96	45.5	10.7	45.7
TSH (µIU/l)	2.52	52.3	44.6	20.7
SOFA score	8.50	68.2	53.6	71.7

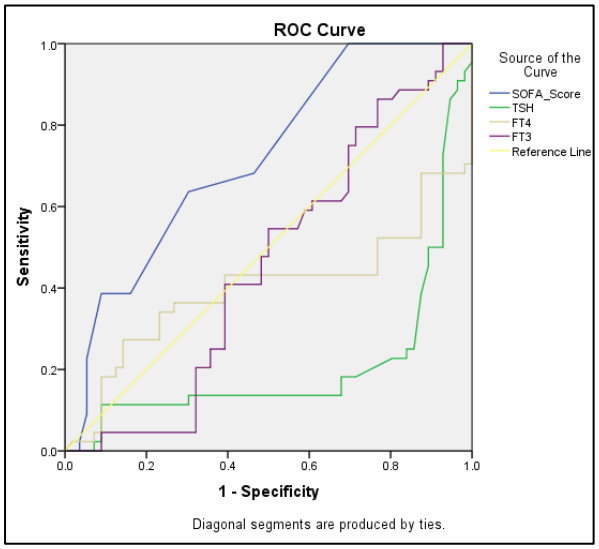

Figure 1: ROC.

DISCUSSION

The phenomenon of change in the thyroid hormone levels during the course of critical illness is known as euthyroid sick syndrome.[6,7] In the Indian context, very few studies throw light on such a crucial area which helps in determining a relationship between thyroid hormone levels and prognosis of Intensive care unit-admitted patients as performed by our study. A study by Kumar KV et al.[3] conducted on hundred ICU-admitted patients gives us the direction that low T3 was an important factor of prognosis in critically ill patients in relation to HbA1C, prolactin, T4 and TSH levels. Another study by Suresh M et al on hundred ICU-admitted patients further strengthens similar relationship between low T3 levels and criticality of ill patients.[8]

In the study of Gutch M et al, sample size was 90 patients admitted in a medical ICU. Mean age in their study was 38.99±18.32. Out of 90 patients, 46 (51.1%) patients were male in majority and 44 (48.9%) patients were female, in all studied cases mean TSH, FT3 and FT4 was 3.31±11.85 (µIU/l), 3.38±0.34 (pmol/l) and 14.95±1.30 (pmol/l) respectively.[2] Mean SBP and DBP was 104.56±20.45 and 63.29±13.61 respectively.

In the study of Kumar KH et al sample size was similar to our sample size i.e. 100.[3] Mean age in their study was 58.7±16.9. Mean hospital stay in their study was 7.05±5.2.

In another study relationship between thyroid function and ICU mortality: a prospective observation study Feilong Wang et al have taken a sample size of 480 patients.[9] Difference between sample sizes could be because of inclusion an exclusion criterion and due to geographical region differences. Furthermore, there are several factors which are responsible for gender differentiations like differences in hormone secretion by the two studied genders, their working traditions, the weight of their body, their eating schedules, their dietary habits or consumption of drugs which can account for the results.

Another study by Mishra A et al has taken a sample size of 338 critically ill patients, mean age in their study was 47.14±18.84; out of total patients, majority 206 (60.9%) patients were male and 132 (39.1%) patients were female.[10] In thyroid function test, mean TSH, FT3 and FT4 was 2.56±1.51UIU/m, 0.92±0.75 (pg/mL) and 0.96±0.68 (ng/mL) respectively.

In our study, 56 (56%) patients survived and 44 (44%) patients not survived. These out was similar to the study of Gutch M et al that 63 (70%) patients survived out of 90.[1] Another study by Feilong Wang et al reported were 388 (80.33%) survivors out of 480 patients.[9]

We observed greater age of non-survivors than survivor in our study, mean age of survivors was 52.38±15.68 years and mean age of non-survivors was 57.91±11.96 years ($p>0.05$). Similar observation was reported by Gutch M et al mean age of survivors was 36.94±17.96 years whereas mean age of non-survivors was 43.78±18.60 years.[2] Mishra A et al reported mean age of survivors and non-survivors was 47.06±19.06 years and 47.25±18.58 years respectively.[4] These differences could be attributed to the sample size and inclusion criteria of all studies.

In our study, even though 50 (50.0%) out of 100 sample of patients were males and 50 (50.0%) were females; the distribution of patient's gender among survivors and non-survivors was found to be statistically non-significant ($p>0.05$). Furthermore, 18 (40.9%) male patients did not survive and 26 (59.1%) female patients were also not survived. Another study of Mishra A et al 58.5% male patients were non-survivors and 41.5% female patients were also non-survivors.[4]

In present study, the non-survivors had a lower SBP and DBP as compared to survivors and it show statistically

significant differences ($p<0.05$). It was also observed that non-survivors had a lower pulse 85.73±10.59 per min and higher RR 19.48±2.31 per min as compared to survivors ($p>0.05$). Similar observation was reported by Gutch M et al i.e. mean SBP and DBP of survivors was more than non-survivors in their study.[4] Another study of Mishra A et al reported mean SBP in survivors was more than non-survivors and mean DBP of Survivors was also higher than non-survivors in respective study.[10]

We have observed that mean TSH in survivor 2.82±1.62µIU/l was more than non-survivors 2.53±1.23 µIU/l. Mean value of FT3 in survivor 3.56±1.67 pmol/l is higher than non-survivor 2.34±1.54 pmol/l. Mean value of FT4 in survivor 13.82±3.00 pmol/l is higher than in non-survivor 12.34±5.05 pmol/l. Only FT3 of thyroid functions have shown statistically highly significant differences ($p<0.01$). As per the results found for critically ill patients, low fT3 (50%) was indicated the most common abnormality followed by high TSH (12.4%), low TSH (8.8%) and low FT4 (4.7%) concentration respectively. In the study of Gutch M et al mean TSH in survivor 3.69±13.99 µIU/l was more than non-survivors 2.41±3.58 µIU/l.[1] Mean value of FT3 in survivor 3.57±0.19 pmol/l is higher than non-survivor 2.94±0.15 pmol/l. Mean value of FT4 in survivor 15.60±0.42 pmol/l is higher than in non-survivor 13.44±1.40 pmol/l. In the study of Kumar KH et al mean value of T3 in non-survivor 49.1±32.7 ng/dL is lower than survivor 66.2±30.1 ng/dl and mean value of T4 in non-survivor 6.8±2.6 µg/dl is lower than in survivor 7.5±2.3 µg/dl.[2]

In the study of Feilong Wang et al TSH (IU/ml) in non-survivors 0.60 (IU/ml) was less than survivor 0.87 (IU/ml), mean value of FT3 in survivor 3.53±0.60 (pmol/l) was higher than non-survivor 2.95±0.57 (pmol/l).[4] Mean value of FT4 in survivor 15.80±3.29 (pmol/l) was higher than in non-survivor 14.48±3.66 (pmol/l). In the study of Mishra et al TSH (IU/ml) in non survivors 2.39±1.50 (UIU/ml) was less than survivor 2.68±1.51 (UIU/ml).[4] Mean value of FT3 in survivor 1.15±0.84 (pg/ml) was higher than non-survivor 0.60±0.43 (pg/ml). Mean value of FT4 in survivor 1.00±0.80 (ng/ml) was higher than in non-survivor 0.89±0.45 (ng/ml).

In our findings mean sofa score test value was higher in non-survivor (10.43±2.18) than in survivors (8.79±2.23). Hospital stay was higher in non-survivors (12.66±3.78) than in survivors (10.95±2.71). In the study of Mishra A et al sofa score test value was higher in non-survivor 12.18±3.40 than in survivors 9.67±2.36.[4] The sensitivity, specificity and accuracy for mortality were 54.5%, 44.6% and 20.7% respectively in TSH (µIU/l); similarly, 45.5%, 10.7% and 45.7% for respectively in FT3 (pmol/l); similarly, 52.3%, 23.2% and 39.8% for respectively in FT4 (pmol/l) and for SOFA score these were 68.2%, 53.6% and 71.7% respectively. FT3 level accounts for most of the ICU mortality among all the other thyroid function markers (T3, T4, TSH, FT3, and FT4) as per the calculations of the AUC from the ROC curve. Similar observation was reported by Gutch et al that FT3 levels were the strongest indicator of ICU mortality among all thyroid function markers (T3, T4, TSH, FT3, and fT4) by calculating the AUC from the ROC curve.[2]

Earlier held studies which were conducted in order to demonstrate any existing association between thyroid hormone levels and prognosis in critically ill patients showed inconsistent results.

Either they were not able to establish any association between FT3 and the observed adverse outcomes, or they came up associating TSH, and FT4. Such results may be attributed to either small sample sizes or different population included in various studies. However, a large-scale study having a sample size of 480, admitted to the ICU showed that FT3 was the most crucial predictor of ICU mortality rate among other indicators.[9]

The mechanisms involved in associating low T3 levels and poor prognosis of critically ill patients are yet to be clarified and needs further in-depth analysis. The low levels obtained on thyroid hormones during any critical illness might be viewed both in adaptive and maladaptive response.[2,12]

The undiagnosed thyroid disease present in patients before their admission to ICU was not ruled out. The clinical examination of the presence of thyroid nodule was only considered.

CONCLUSION

In the present study of ICU-admitted patients, it has been observed that FT3 was the most important predictor of ICU mortality rate in relation to other parameters studied by us. Furthermore, it can be concluded that FT3 levels and SOFA scores combined, provides us with a high probability for anticipating mortalities in ICU patients.

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