ROLE OF THYROID BIOMARKERS IN ASSOCIATION WITH SOFA SCORE IN PREDICTING THE PROGNOSIS OF POST-OPERATIVE CRITICALLY ILL PATIENTS

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BACKGROUND
Thyroid hormone alterations in critically ill patients are very common and may add to the severity of disease and the outcomes of patients in Intensive Care Unit (ICU). This observational study was conducted to detect the thyroid biomarkers as independent predictors of ICU mortality to predict prognosis more accurately in post-operative critically ill ICU patients with sepsis.

This study also tries to determine any association between the thyroid biomarkers and SOFA (sepsis-related organ failure assessment) score.

MATERIALS AND METHODS
This is a prospective observational study. We investigated free triiodothyronine (FT3), free thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) in low SOFA score patients (LSS; n= 21, SOFA= 0 - 6) and in high SOFA score patients (HSS; n= 82, SOFA > 6). The serum levels of FT3, FT4 and TSH were correlated with SOFA score. Further, prognosis on fifth day of ICU admission was defined on the basis of SOFA score, FT3, FT4 and TSH.

RESULTS
The serum levels of FT3 (p= 0.004), FT4 (p= 0.025) and TSH (p > 0.05) decreased in HSS than LSS. A negative correlation was observed between thyroid biomarkers and SOFA score (> 6). Patients who deteriorated on the fifth day of ICU admission had significantly high SOFA score (p= 2.15E-06) and significantly low FT3 (p= 3.17E-10), FT4 (p= 4.06E-05) and TSH (p= 2.21E-05) on first day of ICU admission than those who improved on fifth day.

CONCLUSION
Thyroid biomarkers, specifically low FT3 might be an efficient biomarker or risk factor in evaluating prognosis of the post-operative critically ill patients.

KEY WORDS
Critically Ill Patients, Sepsis, Thyroid Hormone, Triiodothyronine, Thyroxine, Thyroid Stimulating Hormone, SOFA Score.

parameters such as hyperglycaemia, hyperprolactinaemia, procalcitonin (PCT), brain natriuretic peptide (BNP) etc. suggesting the inclusion of the thyroid profile in the scoring system, which are used to predict the mortality of the ICU patients.15-17

Sequential organ failure assessment or sepsis-related organ failure assessment score (SOFA score) is used to predict the severity of the critically ill patients admitted in ICU. SOFA score was developed to quantify the severity of patient’s illness based on the degree of organ dysfunction data on six organ failures, i.e. haematologic-platelets count, hepatic-serum bilirubin, renal-serum creatinine, cardiovascular- mean arterial pressure (MAP), central nervous system (CNS)- Glasgow coma score (GCS), respiratory-PaO2/FIO2. Although, there is no direct conversion of SOFA score to mortality, a rough estimate of mortality risk may be made.18-20 The mortality risk is > 25% if SOFA score is > 9 and > 50% if SOFA score is > 13.20

Sequential assessment of organ dysfunction during the first few days of ICU admission is a good indicator of prognosis. Both the mean and highest SOFA scores are particularly useful predictors of outcome. Regardless of the initial score, an increase in SOFA score during the first 48 h in the ICU predicts a mortality rate of at least 50%.21,22 Vosylius et al showed that cumulative SOFA scores were better in discriminating the outcome compared to a single organ dysfunction scores.23

Low level of thyroid hormone is correlated with severity of illness along with SOFA in various studies.24-28 Therefore, this observational study was intended to detect the thyroid biomarkers (FT3, FT4 and TSH) as independent predictors of ICU mortality in unslected post-operative patients. This study may be helpful in adding one more parameter to define the prognosis of these critically ill post-operative patients with sepsis along with SOFA, APACHE II and others.

MATERIALS AND METHODS

Ethics

The prospective observational study design was approved by the Ethics Review Committee of Santosh University, Ghaziabad, Uttar Pradesh and Baba Raghav Das (BRD) Medical College, Gorakhpur, Uttar Pradesh. All procedures were performed in accordance to the tenets of Helsinki Declaration. The study was explained to each subject and informed consent was obtained from each participant.

Study Samples

The prospective observational study design was conducted on post-surgery critically ill patients admitted in the ICU under Department of Anaesthesia at BRD Medical College, Gorakhpur. A total of 103 post-operative critically ill subjects with sepsis were recruited in the study. Sepsis was defined by the presence of any two conditions among 1) Temperature >38°C or <36°C, 2) Heart rate > 90 beats/min, 3) White blood cell count > 12,000 or < 4,000 cells/mm² and 4) Respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg. SOFA score was recorded and sample was collected on the first day of admission to ICU. Prognosis of the patients was recorded on the 5th day of ICU admission.

Exclusion Criteria

Young patients (< 18 years) were not included in the study. Subjects were excluded from the study if they were under any hormonal therapy or taking amiodarone or had a previous history of thyroid diseases such as hyperthyroidism, hypothyroidism and thyroid tumours. Patients were also excluded if thyroid nodule was observed by physical examination when admitted to the ICU. Patients were excluded if they died or were discharged from the ICU within 4 hours of admission. Pregnant women and women receiving oral contraceptive or hormonal replacement therapy were excluded from the study. Participants were not recruited if there was inability to give consent or do not comply with the study protocol.

Limitations

Since the calculated sample size was too high and thereby not feasible to include in this limited period of study, we had to limit the sample size for convenience.

Sample Collection

Five mL of blood sample was drawn in the vacutainer on first day of ICU admission. The blood was clotted and centrifuged (Remi Laboratory Instruments, Mumbai, Maharashtra, India) for 10 minutes at 1500 rpm to collect serum for estimation of biomarkers.

Biomarker Estimation

ARCHITECT free T3, ARCHITECT free T4 and ARCHITECT TSH (ARCHITECT System, Abbott Diagnostics, Illinois, USA) were used for the quantitative determination of FT3, FT4 and TSH, respectively, in serum. These kits are based on chemiluminescent microparticle immunoassay.

Biostatistical Analyses

Data analysed by using GraphPad Prism version 5. P-value ≤ 0.05 was considered for statistical significance. P-value ≤ 0.001 was considered for high statistical significance. Tests: Fisher’s Exact test, unpaired t-test, SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) and Epi Info™ 6.0 (Centres for Disease Control, Atlanta, Georgia, USA) software were used for statistical analysis. Statistical power for biomarker study was calculated by Simple Interactive Statistical Analysis (SISA) online tool (http://www.quantitativeskills.com/sisa/calculations/power.htm). The power for all the significant biomarkers was ≥95%. Further, the biochemical parameters were expressed as mean ± SE (Standard Error), whereas the significance in levels were analysed using SPSS 16.0. A p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Clinical Characteristics

Table 1 highlights the clinical characteristics of the two study groups, i.e. LSS and HSS. Age and gender differed among the two groups. Hence, the biochemical data was adjusted with these factors as confounding. The average age of LSS was 27.71 ± 9.69 and for HSS 40.21 ± 17.3 (p=0.041). In LSS 9.5% patients were male and 90.5% were female, while in HSS 42.7% patients were male and 57.3% were female (p=0.005).
The average SOFA score in LSS was 5.9 ± 0.44 and it was 10.51 ± 2.48 in HSS (p= 0.0001; Table 1).

The Study Samples were divided into Two Groups based on the SOFA Score as following
1. Group 1 or low SOFA score group (LSS; n= 21, where ‘n’ is number of subjects): Patients with SOFA score 0 - 6; this was the reference group of our study.
2. Group 2 or high SOFA score group (HSS; n= 82): Patients with SOFA score ≥ 7.

Biomarker Serum Levels
Serum level of FT3 at 1.73 ± 0.31 pg/mL was reduced significantly in HSS than the level 2.03 ± 0.22 pg/mL in LSS (p= 0.004; Figure 1a). Similarly, serum level of FT4 at 0.94±0.23 ng/dL was reduced significantly in HSS than the level 1.14 ± 0.20 ng/dL in LSS (p= 0.025; Figure 1b). Further, serum level of TSH at 1.84 ± 1.16 µIU/mL in HSS than the level 2.54 ± 0.54 µIU/mL in LSS (p= 0.167; Figure 1c).

Biomarker Correlations
The serum levels of FT3, FT4 and TSH were correlated with SOFA score. The serum levels of FT3, FT4 and TSH decreased with increase in SOFA score. Remarkable decrease in FT3 was observed after 12 SOFA scores, while in FT4 and TSH a remarkable decrease was observed after 11 SOFA scores (Figure 2a, 2b and 2c).

Figure 1. Serum Levels of (a) FT3 (b) FT4 and (c) TSH in LSS and HSS
The data are presented as mean ± SE. SPSS 16.0 was used to perform GLM and obtain p-value after adjustment with age and gender. A p-value of ≤ 0.05 was considered significant. Representations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; LSS, low SOFA score group; HSS, high SOFA score group; p, p-value; n, Number of samples.

Figure 2. Correlation between SOFA Score and (a) FT3 (b) FT4 and (c) TSH in LSS and HSS
The data are presented as mean ± SE. SPSS 16.0 was used to perform GLM and obtain p-value after adjustment with age and gender. A p-value of ≤ 0.05 was considered significant, *p≤0.05 when compared to LSS i.e. patients with 0-6 SOFA score. Representations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; SOFA score, sepsis-related organ failure assessment score; LSS, low SOFA score group; HSS, high SOFA score group.

Figure 3. Trend of (a) SOFA Score, (b) FT3, (c) FT4 and (d) TSH among Patients with different Prognosis
The data are presented as mean ± SE. SPSS 16.0 was used to perform GLM and obtain p-value after adjustment with age and gender. A p-value of ≤ 0.05 was considered significant.

Table 1. Clinical Characteristics of the Two Groups

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>LSS (n=21)</th>
<th>HSS (n=82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>27.7±9.69</td>
<td>40.2±17.26</td>
<td>0.040</td>
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<tr>
<td>Gender</td>
<td>M=2 (9.5%)</td>
<td>M=35 (42.7%)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>F=19 (90.5%)</td>
<td>F=47 (57.3%)</td>
<td></td>
</tr>
<tr>
<td>SOFA Score</td>
<td>5.9±0.44</td>
<td>10.5±2.48</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The data are presented as mean ± standard deviation except gender, which is represented as number of samples (percentage). P-values were calculated using the Epi Info™ 6.0. A p-value of ≤ 0.05 was considered significant. Representations: n, Number of samples; M, Male; F, Female; SOFA score, Sepsis-related organ failure assessment score.
Representations: SOFA score, sepsis-related organ failure assessment score; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; LSS, low SOFA score group; HSS, high SOFA score group; p, p-value; n, number of samples.

DISCUSSION

Thyroid dysfunction in critically ill patients is the most common observation. However, whether thyroid dysfunction can be considered as a risk factor to predict patient’s outcome is still debatable. Various studies have reported that non-survivors had very low thyroid biomarkers as compared to the survivors.27-29 Although, most of the studies suggest definite association between thyroid dysfunction and worse outcome in sepsis, the findings are inconsistent and need further investigation.30

In our study we observed the average serum FT3 level 1.73 ± 0.31 pg/mL in HSS group, while it was 2.03 ± 0.22 pg/mL in LSS group, though both the reading are in normal range; however, in HSS group it was significantly on lower side (p = 0.004; Figure 1a). About 22 patients (26.8% patients), in total 82 subjects in HSS group were having FT3 value below normal. FT4 was also significantly on lower side in HSS group, 0.94 ± 0.23 ng/dL as compared to LSS group where the average FT4 was 1.14 ± 0.20 ng/dL (p = 0.025; Figure 1b). However, 17 patients (20.7% patients) in HSS group showed FT4 level below normal. Further, the average TSH was 2.54 ± 0.54 µIU/mL in LSS group and 1.84 ± 1.16 µIU/mL in HSS group, though this change is insignificant (p=0.167; Figure 1c) but the value in HSS group is on lower side. Among HSS, 13 patients (15.85%) even have got the value below the lower limit of normal range i.e. 0.35 µIU/mL.

The changes in thyroid hormone economy in post-surgical critically ill patients observed may be because of peripheral metabolism of the thyroid hormone, alterations in TSH regulation and alteration in binding of thyroid hormone to thyroid binding globulin. Acute inhibition of type-I 5'-deiodinase also play an important role in decreasing level of T3 in such patients.31-33 Role of some cytokines, notably tumour necrosis factor-α (TNF-α), interleukin 1 (IL-1) and IL-6 has also been observed by researchers.34 Therefore, thyroid dysfunction may be a general finding in critically ill patients irrespective of aetiology of the illness (medical or post-surgical).

When these biomarkers are correlated with SOFA score, it was found that FT3, FT4 and TSH start decreasing when SOFA score is > 11. However, FT3 decreases more remarkably when SOFA score is more than 12 (Figure 2a, 2b and 2c). So, it seems that there is definite negative correlation between thyroid hormones and SOFA score. Hosny et al and Türe et al also observed decreasing FT3 with increasing SOFA score in septic and Acute Respiratory Distress Syndrome (ARDS) patients, respectively.27,28 FT3 levels might have additive discriminatory power to age, SOFA and APACHE II scores in predicting short-term mortality in ARDS patients.28

Further, we observed the prognosis of the patients on fifth day. All the patients in LSS group improved. In HSS group, we noticed the patients who improved (n = 54) has less SOFA score as compared to the patients in which there was clinically no change (n= 20). The patients who further deteriorated (n = 8) had even higher SOFA score (Figure 3a). The FT3 was well within normal range in the patients who improved, and it is below normal in the patients who deteriorated (Figure 3b). The FT4 value was again below normal range in patients who deteriorated as compared to the patients who showed no sign of improvement, where FT4 value was slightly on higher side and the value was well within normal range in improved patients (Figure 3c). In the deteriorated patients, the TSH value was on lower side or below normal range. While in other patients whether they improved or in status quo had their TSH value within normal range (Figure 3d). So, the observations suggest that patients who had lower thyroid biomarkers value might deteriorate further with the same treatment protocol.

Low serum T3 levels have also been observed in muscle and liver during critical illness leading to higher mortality.35 Thyroid treatment might be helpful in improving the condition of the critically ill patients, but the studies have reported inconsistent finding. Young and Worthley in their clinical practical review noted abnormal thyroid function, which improves when patient’s general condition improves, so generally does not require thyroid supplementation.36 Further, Kumar et al observed marked suppression of FT3 with normal TSH in critically ill patients and they noticed improvement in their patients with intravenous levothyroxine treatment.37

In post-operative surgical patients thyroid dysfunction is often observed, especially when associated with septicaemia.28 Hence, it is obligatory to investigate that thyroid dysfunction might be a risk factor and whether controlling it would decrease the mortality rate in surgically ill patients. Bunevicius et al have shown that low T3 syndrome is a strong independent predictor of unfavourable clinical outcome and depressive symptoms in patients that went under brain tumour surgery.39 Therefore, the free T3 concentration might be considered as a prognostic biomarker in neurosurgical critically ill patients. To generalise the above finding, we performed our study in post-operative surgical patients including the post-operative neurosurgical patients. We observed that thyroid dysfunction, especially low FT3 levels can predict worse outcome in post-operative surgical patients with high SOFA score on the first day of admission to ICU. However, further study is required in a larger sample size and including patients with higher SOFA score than our study. Increasing the observation timeline to more than 5 days, i.e. until recovery or demise and determining thyroid biomarkers on successive days will further increase the significance of study.

Limitations

Since the calculated sample size was too high and thereby not feasible to include in this limited period of study, we had to limit the sample size for convenience.

CONCLUSION

After careful observations of our results, we concluded that there is definite correlation between thyroid biomarkers and SOFA score. Thyroid profile decreases with increase in SOFA score. These biomarkers, specifically FT3 might act as an effective tool in evaluating prognosis of the post-operative critically ill patients. However, more studies with large sample size should be done to establish this finding in clinical use.
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REFERENCES


