Correlation of thyroid hormones and age in predicting the outcome of critically ill surgical patients with sepsis

Abstract

Aim: Aged patients with critical illness and sepsis are difficult to treat because of their poor adaptive physiological system. The study tries to identify prognostic marker among thyroid hormones for aged post-surgical critically ill subjects, who have sepsis, to improve outcome of patients.

Methods: Free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were estimated by ARCHITECT immunoassay kits in 127 patients. Sequential Organ Failure Assessment (SOFA) score was recorded for each patient.

Results: The FT3, FT4 and TSH levels decreased and SOFA score increased with increasing average age. Thyroid markers inversely correlated with age ($p<0.001$), with strongest correlation between FT3 and age ($r=0.674$, $p=5.04E-18$). Positive correlation was observed between SOFA score and age ($p<0.001$). FT3 decreases, SOFA and age increases from improved prognosis to worst prognosis ($p<0.001$).

Conclusions: FT3 surfaced as a prominent prognostic marker that may be used in predicting prognosis of post-surgical critically ill elderly patients with sepsis.

Keywords: Critical illness; Sepsis; Thyroid hormone; Thyroid stimulating hormone; Thyroxine; Triiodothyronine

1. Introduction

Hypothyroidism has high prevalence in geriatric population, mostly in females; it can be a significant cause for higher morbidity and mortality rates in elderly that are critically ill [1, 2]. In India, the incidence of true hypothyroidism is 11% while in United States it is 4.6% and in United Kingdom only 2% elderly patients have true hypothyroidism [3, 4]. The most common cause of thyroid abnormalities in the aged patients is non-thyroidal illness (NTI), also known as euthyroid sick syndrome (ESS) [5]. NTI is generally defined by low serum levels of triiodothyronine (T3), low or normal serum levels of thyroxine (T4) and thyroid stimulating hormone (TSH) [6]. The prevalence of NTI is reported as 62.2% in hospitalized elderly patients [5]. In contrast, study from Tognini et al. found only 31.9% elderly patients representing NTI,

excluding patients admitted in intensive care unit (ICU) where the incidence is much higher. About 60–70% patients admitted to ICU had NTI, thus hospital mortality is well linked to NTI and is well documented [5, 7-9]. Nevertheless, controversy exists whether NTI is a maladaptive state, which induces damaging hypothyroidism10 and increases the mortality or it is an adaptive response to systemic illness by which it lowers tissue energy requirements [7, 11-14].

Alterations in thyroid function test in elderly hospitalized patients have association with morbidity and mortality. Low T4 and high TSH levels are associated with poor prognosis in critically ill old patients [6]. A 50% probability of death has been reported when serum T4 value is <4μg/dl [7, 10]. On the contrary, reports also suggest that low TSH and elevated free T4 (FT4) is associated with increased mortality rate [15-18]. Moreover, a low serum T3 is also associated with increased mortality during hospitalization in elderly patients. Some authors believe that low T3 can be used as predictor for morbidity and mortality in critically ill patients [5, 19]. However, it is still unclear that which of the thyroid parameters could truly predict the health outcome in elderly patients. On the other hand, the impact of true hypothyroidism present in critically ill patients is still uncertain and debatable; speculation is that it might be protective in the elderly [15].

Several outcome prediction models are being used in clinical practice like the Simplified Acute Physiology Score III [20], Acute Physiology and Chronic Health Evaluation IV Score [21], the Logistic Organ Dysfunction Score [22], and the Mortality Probability Model III [23]. These models are derived and validated on large groups of ICU patients. However, these require historical data and data after ICU admission for calculation. On the other hand, the Sequential Organ Failure Assessment (SOFA) score is a simple and objective score. It allows for calculation of the number and the severity of organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurological). SOFA score gives the freedom to measure the severity of dysfunction in individual or aggregate organ system dysfunction [24]. Since the SOFA score is an easy tool for prediction of mortality in elderly critically ill patients, we used this scoring system as a guideline for severity of illness.

Our aim was to assess thyroid function in surgical ICU patients that had sepsis and to determine the biomarker among the thyroid hormones that can predict clinical outcome in the elderly.

2. Material and Methods

2.1 Study samples

Ethics Committee of Santosh University, Ghaziabad, Uttar Pradesh, India and Institutional Human Ethics Committee of B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India approved the present prospective cohort study. Informed consent was obtained from each participant of the study. Procedures followed are in accordance with the ethical standards laid down by ICMR's Ethical guidelines for biomedical and health research on human participants (2017). The study was conducted in collaboration at Department of Pathology, in Critical Care Unit of Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh, from March 2016 to April 2018.

Post-surgical critically ill patients with sepsis were recruited in the study, consecutively. Emergency exploratory laparotomy was done for various intestinal perforations leading to sepsis for e.g. intestinal perforation, appendicular perforation, intestinal gangrene, blunt injury to abdomen leading to organic rapture, uterine perforation, and others in all the recruited patients. Key features of the critically ill patient are severe respiratory, cardiovascular or neurological derangement, often in combination, reflected in abnormal physiological observations. Patients were receiving heavy antibiotic combination isotropic support if needed and ventilatory support according to the requirement. The patients had some sort of infections/sepsis due to various reason. Surgical procedure was done to control the sepsis or to manage the source of infection. Clinical data including SOFA score for 127 post-surgical critically ill subjects with sepsis was recorded on the first day of admission to ICU after surgery under the Department of Anesthesia at BRD Medical College, Gorakhpur. Patients were followed for their complete stay at ICU.

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection with known or suspected infection with a change in Sequential Organ Failure Assessment (SOFA) score ≥ 2, or a modified "quick SOFA" for simpler use. Sepsis was confirmed when any two conditions among a) temperature >38ºC or <36ºC, b) respiratory rate >20 breaths/min or $PaCO_2$<32 mmHg c) heart rate >90 beats/min, and, d) white blood cells count >12,000 or <4,000 cells/mm^2 in the ICU was present. Infection was confirmed by haematological and other lab testing or testing of wounds and stitches for infection. Initial Sepsis definition and criteria was used for recruitment. Sepsis criteria were not updated to 2016 version in between of the study to maintain consistency of the study [25, 26]. The prognosis of the patients was recorded on the basis of SOFA scoring on the 5^{th} day of ICU admission for analysis to evaluate whether clinical parameters estimated on first day can predict early prognosis. This will facilitate the clinicians to modulate the treatment during early stay at ICU and improve the prognosis. Prognosis criteria was defined by SOFA, as reported by the physician.

Based on the age, four study groups were designed as follows:

1. Group 1 with patients of age 18-30 years (n=51); this group was considered as the reference group of our study.
2. Group 2 with patients of age 31-45 years (n=23).
3. Group 3with patients of age 46-60 years (n=20).
4. Group 4with patients of age 61-85 years (n=33).

2.1.1 Exclusion criteria

Patients under any hormonal therapy, patients taking amiodarone, patients with previous history of thyroid diseases and patients with thyroid nodule at the time of admission to ICU were excluded from the study. Patients were not included in the study if they died or were discharged from the ICU within 4 hours of admission, pregnant women and women consuming oral contraceptive or receiving hormonal replacement therapy or if there was inability to give consent.

2.2 Sample collection

Five ml of blood sample was drawn in the vacutainer on first day of ICU admission. Serum was collected by clotting the blood followed by centrifugation (Remi Laboratory Instruments, Mumbai, Maharashtra, India) for 10 minutes at 1500 rpm.

2.3 Biomarker estimation

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

2.4 Statistical analysis

Sample size was calculated by Cochran formula. The biochemical parameters were expressed as mean±SE (standard error). General linear model (GLM), univariate analysis, was performed to calculate significance using Statistical Package for Social Sciences version 16.0 (SPSS 16.0; IBM Inc., Armonk, NY, USA). A p-value of ≤0.05 was considered statistically significant. Statistical power for biomarker estimation was performed by Simple Interactive Statistical Analysis (SISA) online tool (http://www.quantitativeskills.com/sisa/calculations/power.html). Partial correlation test using SPSS

16.0 was applied to ascertain any correlation between age and thyroid hormones/SOFA score. Bonferroni's correction was applied for multiple comparison correction; the p-value cut off after Bonferroni's correction was ≤0.05/number of statistical tests performed.

Table I: Clinical characterization of the study groups.

Study groups	**Age, years**	**Gender**	
		Male	**Female**
Group 1 **18-30 years (n=51)**	24.2±3.2	9 (18%)	42 (82%)
Group 2 **31-45 years (n=23)**	37.3±4.0	6 (26%)	17 (74%)
Group 3 **46-60 years (n=20)**	56.8±4.6	16 (80%)	4 (20%)
Group 4 **61-85 years (n=33)**	68.8±5.0	25 (76%)	8 (24%)

The age is represented as mean ± standard deviation and gender is represented as number of samples (percentage). 'n' represents Number of samples.

3. Results

3.1 Clinical characteristics

The study groups were designed based on the age of the study subjects from young to old. Hence, the average age increases from Group 1 to Group 4 (Table I). The percentage of females was higher in the young groups of 18-30 years and 31-45 years, while percentage of males was higher in the old groups of 46-60 years and 61-85 years (Table I).

3.2 Biomarkers serum levels

The SOFA score was highest in the old age group of 61-85 years at 15.21±0.68 followed by 46-60 years at 11.50±0.85, 31-45 years at 9.52±0.47 and 18-30 years at 8.47±0.36 (Figure 1a).

The three thyroid markers i.e. FT3, FT4 and TSH were highest in the young and lowest in the old patients. The FT3 was highest in the young age group of 18-30 years at 1.92±0.04 pg/ml followed by 31-45 years at 1.78±0.05 pg/ml, 46-60 years at 1.52±0.10 pg/ml and 61-85 years at 1.16±0.06 pg/ml (Figure 1b). Similarly, FT4 was highest in the young age group of 18-30 years at 1.08±0.03 ng/dl followed by 31-45 years at 0.98±0.04 ng/dl, 46-60 years at 0.82±0.05 ng/dl and 61-85 years at 0.67±0.02 ng/dl (Figure 1c). The TSH levels in groups of age 18-30 years and 31-45 years was similar at 2.27±0.12 μIU/ml and 2.26±0.22 μIU/ml, respectively. These were followed by TSH levels in groups of age 46-60 years at 1.56±0.22 μIU/ml and 61-85 years at 0.92±0.16 μIU/ml (Figure 1d). The power for the significant observations between group 1 and group 2 was <95%, while the power was ≥95% when group 3 or group 4 was compared to group 1. The power was >95% for TSH in comparison between group 1 and group 3.

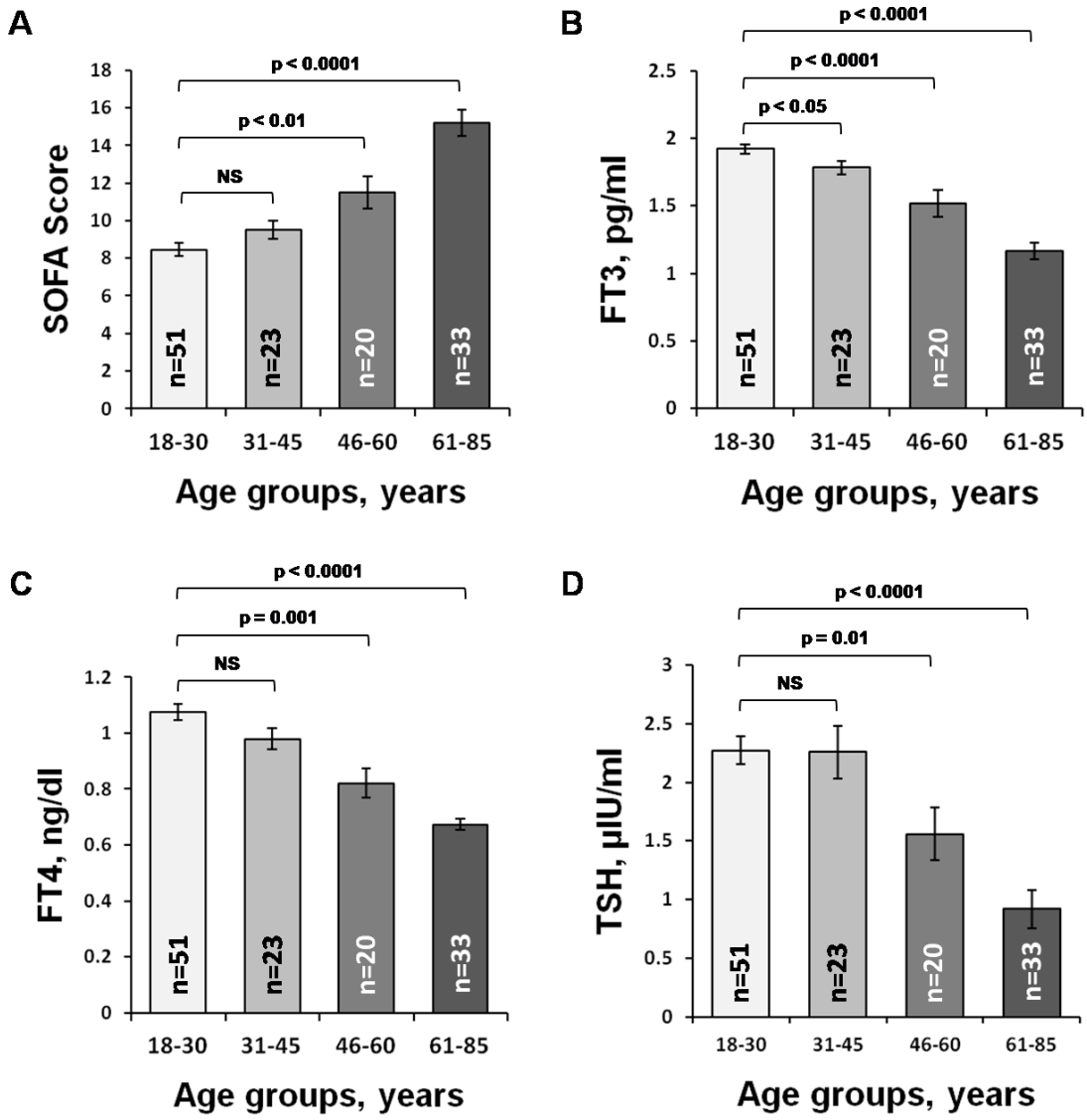


Figure 1: SOFA score and thyroid markers in the four study groups. A: SOFA score, B: FT3, C: FT4 and D: TSH. SPSS 16.0 was used to perform general linear model and obtain p-value after adjustment with gender.

3.3 Correlations

A positive correlation was observed between SOFA score and age of the post-operative critically ill patients (Figure 2a). Inverse correlations were observed between the thyroid biomarkers and age of the post-surgical critically ill patients. The strongest inverse correlation among the thyroid biomarkers was noticed between FT3 and age (Figure 2b) followed by FT4 and age (Figure 2c) and least between TSH and age (Figure 2d).

Furthermore, the post operative critically ill patients were divided into four groups which was based on the prognosis on the fifth day of ICU admission. These groups were (1) Improved (n=80), patients whose condition improved, (2) No change (n=24), patients with a static condition, (3) Deteriorated (n=15), patients whose health declined and (4) Expired (n=8), patients who died due to complications. In the 'Improved' group, the SOFA score reduced from 8.40±0.25 to 4.49±0.20 ($p<0.05$), there was no change in SOFA score (13.12±0.27) of 'No change' group and the score increased in 'Deteriorated' group from 15.67±0.60 to 17.00±0.59 ($p=0.04$). Among the deteriorated patients on 5th day, five expired later during the follow-up of ICU. Trend in age, SOFA score, FT3, FT4 and TSH on first day was investigated in these groups. Figure 3 summarizes the observations among the prognosis groups.

The patients whose condition improved were mostly young (33.55±1.56 years) as compared to no change group (52.58±3.56 years), deteriorated group (63.27±2.76 years) and expired group (70.50±2.82 years). An increasing trend in age was observed as we move from improved prognosis to worst prognosis. A clear increasing trend of SOFA score and decreasing trend of FT3 was observed as we move from improved prognosis to worst prognosis. Both, FT4 and TSH reveal decreasing trend with declining health. However, FT4 was similar in both deteriorated and expired patients, whereas TSH was high in expired patients than the deteriorated patients.

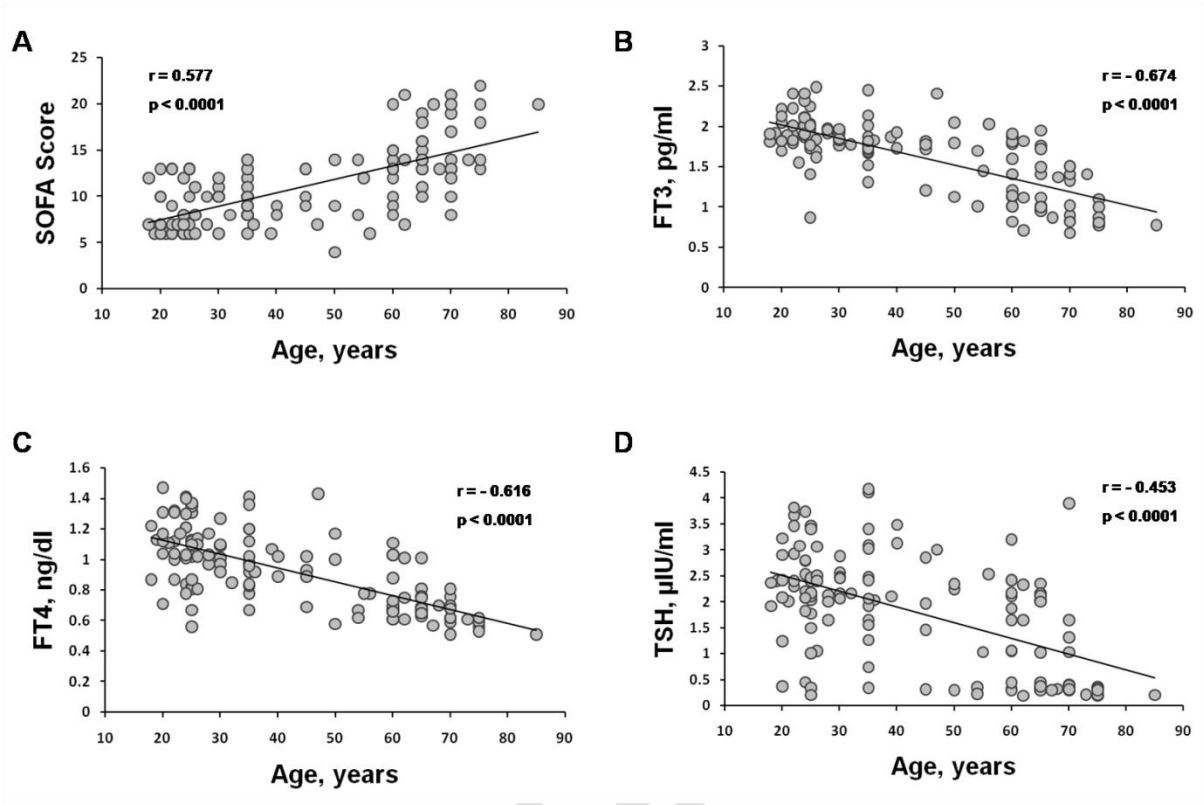
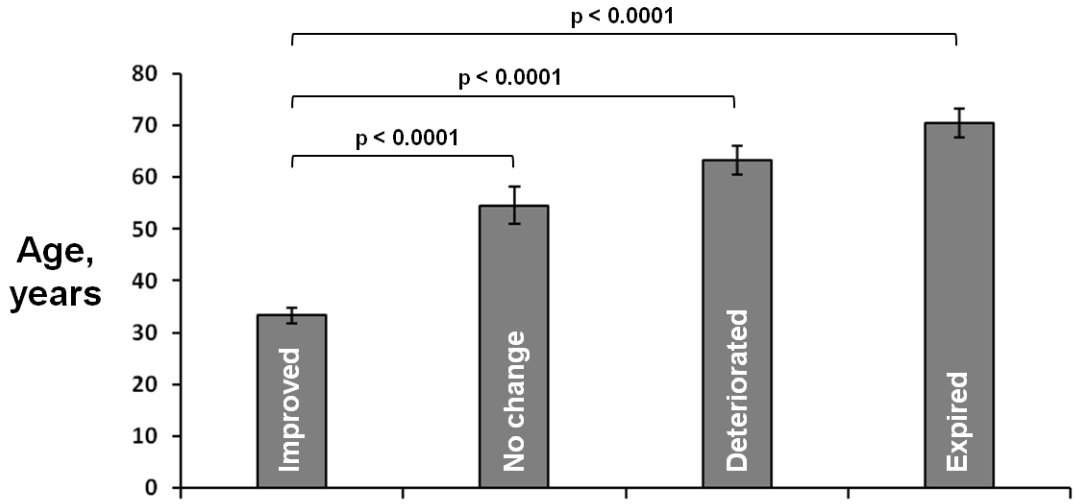


Figure 2: Correlation of SOFA score and thyroid biomarkers with age in the total study subjects. A: SOFA score, B: FT3, C: FT4 and D: TSH. Partial correlation was performed using SPSS 16.0, and the significance was maintained at $p \leq 0.05/4 = 0.01$. P-values were obtained after adjusting with gender.



Clinical parameters	Prognosis on the 5th day			
	Improved (n=80)	No change (n=24)	Deteriorated (n=15)	Expired (n=8)
SOFA Score	8.39±0.25 Reference	13.12±0.27 p < 0.0001	15.67±0.60 p < 0.0001	20.25±0.41 p < 0.0001
FT3, pg/ml	1.91±0.03 Reference	1.40±0.07 p < 0.0001	1.05±0.04 p < 0.0001	0.79±0.02 p < 0.0001
FT4, ng/dl	1.07±0.03 Reference	0.75±0.03 p < 0.0001	0.62±0.01 p < 0.0001	0.61±0.03 p < 0.0001
TSH, µIU/ml	2.47±0.12 Reference	1.11±0.19 p < 0.0001	0.75±0.33 p < 0.0001	1.64±0.87 p = 0.069

Figure 3: Trend of SOFA score, FT3, FT4 and TSH with respect to age across the patients with different prognosis. SPSS 16.0 was used to perform general linear model and to calculate gender adjusted p-value.

4. Discussion

Critically ill patients and their management has always been a challenge for clinicians. Aged patients are even more difficult to treat because of their poor adaptive physiological system including the immune system. To improve the outcome of aged patients various research are being done all over the world regarding prognostic predictor and adopting treatment schedule accordingly. Thyroid hormones estimation in these patients is being extensively studied in recent years and most of them showed lack in thyroid hormones secretion, however to use this as prognostic tool is still debatable. This study is a step further towards the same with intention to characterize and understand critical illness with sepsis after surgery in elderly patients.

The patients included in the present study were between 18-85 years of age, of which geriatric patients were 33 i.e. 26%. We found highest SOFA score in geriatric patients (61-85 years) and lowest in young patients (18-30 years); the difference was highly significant. The increasing trend of SOFA score with the age further confirms that in elderly patient's organ function deteriorate more rapidly after the sepsis due to maladaptive physiological system. So, the same amount of insult to the body produces more harm in elderly than young adult. Previous studies have also reported that SOFA is high among the elderly [27].

Generally, with increasing age the incidence of subclinical hypothyroidism increases, i.e. T3 & T4 levels decrease and TSH levels increase. We also observed that FT3 and FT4 were low in elder patients. However, between the two, FT3 was much lower in geriatric patients crossing the lower limit of normal range (1.71-3.71 pg/ml) in many patients. The decrease in FT3 was very significant when compared with our reference group 1. The other two groups i.e. 31-45 years and 46-60 years too had significantly lower FT3 levels than group 1, but most of them were in normal range. With this result it can be said that there is definite decrease in serum FT3 level in critically ill patients and this trend is more in aged patients. FT4 too was found to be significantly low in elderly age group patients in comparison with younger group 1 critically ill patients but most of them are within normal limits. Further, in all our groups TSH was within normal range but it was towards lower limit in elderly patients.

Concisely, we observed a generalized depression of thyroid gland function in critically ill surgical patients and the depression further enhanced with age. All our patients who have deranged thyroid function were having NTI.A positive correlation between SOFA and age was observed, which is in line with previous report [27]. Further, inverse correlations were observed between thyroid hormone levels and age of the patients, with strongest inverse correlation for FT3.

Patients with low FT3 or FT4 in advance age were more critical, and most of them deteriorated or succumbed to their illness. However, younger patients improved by the same management protocol. It has been reported that in ICU patients with NTI had higher mortality than patients with true hypothyroidism [28]. We have observed the occurrence of NTI in critically ill patients and it was a major determinant of the prognosis of elderly patients besides SOFA score. We noticed that our surviving patients had almost normal thyroid function test reports as compared to non-survivors, where it was markedly deranged. Iglesias et al. in his seven years observational study showed that alternation in thyroid function is often found in hospitalized elderly patients and it is associated with long term mortality [29]. Most of our non-survivors had very low levels of FT3 suggesting that FT3 might be most commonly associated with the worst prognosis in the elderly patients. With these observations it is evident that FT3 can be a suitable biomarker in aged critical patients.

Over all our non-survivor patients were elderly with high SOFA score having very low FT3, low FT4 and low TSH. Although in a study association of high mortality with low FT3, low FT4 and higher than normal TSH has been reported [6]. Many authors have observed that geriatric population with sub-clinical hypothyroidism or NTI when suffer with medical or surgical illness they become more critical and their prognosis worsens. NTI has also been linked with mortality in cardiac diseases, stroke and kidney failure [30-32]. In our study, SOFA score and thyroid function test indicates that elderly age patients are more critical and require intensive care management. They should be given enough spaces in ICU. Unfortunately, these patients are not given enough consideration for ICU admission in developing countries [27].

Nevertheless, our study had some limitations such as the subject size and duration of the study. Although the subject size was pretty good to detect differences in the thyroid levels, we suggest studies in a larger sample size to validate our observations. Further, to establish FT3 as a strong prognostic marker a wider multi-centric and long duration study is required. Further, the patients were only followed in the ICU and not followed after shifting to the ward. We did not observe true hypothyroidism in our study case.

5. Conclusion

Post-operative critically ill elderly patients with sepsis have more deranged thyroid function in comparison to young adults. Low FT3 stands out as a probable prognostic marker. Further, a negative correlation exists between all the thyroid biomarkers and age of the patients. The old patients had high

SOFA score. Thus, thyroid biomarkers especially FT3along with SOFA score seems to be a nice tool in predicting prognosis of critically ill elderly patients. Including FT3 as an early prognostic marker will improve the in-time treatment of elderly and critically ill patients with sepsis.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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