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Prognostic Value of Thyroid Hormone Dysfunction and Age in Septicemic Post-Surgical Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Critical illness and sepsis are difficult to treat with increasing age because of the poor adaptive physiological system as age progresses. The study tries to identify prognostic markers among thyroid hormones for post-surgical critically ill subjects, who have sepsis, to improve the outcome of patients with increasing age.
Methods: Free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were estimated by ARCHITECT immunoassay kits in 127 post-surgical critically ill patients with sepsis. 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 age. Thyroid markers were significantly inversely correlated with age (for FT4 $r= -0.616$, $p<0.0001$ and for TSH $r= -0.453$, $p<0.0001$), with the strongest correlation between FT3 and age ($r=0.674$, $p<0.0001$). A positive correlation was observed between SOFA score and age ($r=0.577$, $p<0.0001$). FT3 decreases, SOFA and age increase from improved prognosis to worst prognosis ($p<0.0001$).
Conclusions: FT3 surfaced as a prominent prognostic marker that may be used in predicting the prognosis of post-surgical critically ill geriatric patients with sepsis.

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Keywords: Critical illness; sepsis; thyroid hormone; thyroid stimulating hormone; thyroxine; triiodothyronine; SOFA score.

1. INTRODUCTION

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 may lead to multiple organ failure as cascades of molecular events occur to release cytokines to tackle infection and inflammation [1].

Sepsis is similar to the systemic inflammatory response (SIRS), which is the body's defense response against trauma, surgery, malignancy, infections and more while sepsis is a defense response only against infection. Clinical features are selected for SIRS as markers, which are; temperature > 38 ℃ or 36 ℃, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or paCO2 < 32 torrs (4.3 kPa), WBC > 12000 cells/mm3, while in case of sepsis these responses are for infection and generally two or more SIRS criteria are related to sepsis. Severe sepsis is associated with organ dysfunction, including, but not limited to, lactic acidosis, liguria, hypoxemia, coagulation disorders, or an acute alteration in mental status. Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities is known as septic shock which is mostly fatal [1-3].

Sepsis is often accompanied by hypothyroidism, which occurs when the immune response generated against infection starts to act on the thyroid gland [4]. Low triiodothyronine (T3), low or normal serum levels of thyroxine (T4) and thyroid stimulating hormone (TSH) are often observed in critically ill patients; this condition is known as non-thyroidal illness (NTI) [5]. NTI has been reported in gastrointestinal and cardiovascular diseases, infectious diseases, burns, cancer, trauma and surgery across all ages and gender [6-12].

Hypothyroidism is characterized by high plasma TSH and low plasma T4, however, in case of critical illness absence of elevated TSH does not exclude hypothyroidism [13]. Thus, it is difficult to diagnose hypothyroidism from NTI in critically ill patients. Reduction in serum T3 levels was reported within 2 h after the start of abdominal surgery [7]. Serum T3 further decreases as the severity of the disease progresses [6,13]. Thus, has the potential to be a prognostic marker. Clinical presentation of hypothyroidism differs with age and gender [14]. However, it is well established that as age increases thyroid gland develops functional changes and thyroid disorders prevalence also increases as age increases although subclinical disturbances of thyroid function are more common in patients with higher age groups [15]. In a large sample of 83643 individuals, it was observed that as the age progresses FT3 decreases while TSH increases [16]. Low FT3 is more prevalent in females [16]. The presence of thyroid biomarkers dysfunction has a high prevalence in the geriatric population; it can be a significant cause for higher morbidity and mortality rates in geriatric that are critically ill [17,18]. Another study reported that in geriatric patients NTI is highly prevalent with acute surgical problems and associated with the worst prognosis [19]. In critically ill patients, especially with sepsis, severity increases with increasing age which is associated with a bad prognosis [20,21]. Moreover, with the increase in age comorbidities develop which can be another factor for the worst prognosis in geriatric patients [22] this was further supported by a study in which age-related comorbidities are responsible for the increase in complexity of management of colon carcinoma and it also affects the patient outcome [23]. Although not sufficient study has been done in critically ill patients in different age groups patients to see their thyroid profile pattern. We hypothesize that as with increasing age and severity the levels of thyroid biomarkers will decrease, these levels at the time of ICU admission may act as a potential prognostic biomarker in geriatric patients, which are at higher risk of mortality than younger patients.

In India, the incidence of true hypothyroidism is 11% while in the United States it is 4.6% and in the United Kingdom, only 2% of geriatric patients have true hypothyroidism [24,25]. The most common cause of thyroid abnormalities in aged patients is NTI, also known as euthyroid sick syndrome (ESS) [26]. The prevalence of NTI is reported as 62.2% in hospitalized geriatric patients [26]. In contrast, a study from Tognini et al found only 31.9% of geriatric 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 [26-29]. Nevertheless, controversy exists whether NTI is a maladaptive state, which induces damaging hypothyroidism [5] and increases mortality or it is an adaptive response to systemic illness by which it lowers tissue energy requirements [9,27,30-32].

Alterations in thyroid function tests in geriatric hospitalized patients have an association with morbidity and mortality. Low T4 and high TSH levels are associated with poor prognosis in critically ill old patients [24]. A 50% probability of death has been reported when serum T4 value is <4µg/dl [27,33]. On the contrary, reports also suggest that low TSH and elevated free T4 (FT4) is associated with increased mortality rate [34-37]. Moreover, a low serum T3 is also associated with increased mortality during hospitalization in geriatric patients. Some authors believe that low T3 can be used as a predictor for morbidity and mortality in critically ill patients [26,38]. However, it is still unclear that which of the thyroid parameters could truly predict the health outcome in geriatric 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 geriatric [34].

Several outcome prediction models are being used in clinical practice like the Simplified Acute Physiology Score III [39], Acute Physiology and Chronic Health Evaluation IV Score [40], the Logistic Organ Dysfunction Score [41], and the Mortality Probability Model III [42]. 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 SOFA score is a simple and objective score. It is the association between the 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 aggregated organ system dysfunction [43]. Since the SOFA score is an easy tool for the prediction of mortality in geriatric critically ill patients, the study uses this scoring system as a guideline for the severity of illness. Furthermore, the SOFA score was commonly used in the ICU of B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India for the prognosis of critically ill patients.

In spite of several studies on thyroid hormone dysfunction in sepsis affecting the prognosis of critically ill patients, controversies still exist. Thus, it becomes critical to evaluate thyroid markers as prognostic markers, especially in surgical patients suffering from septicemia, which is not evaluated before with respect to age. The aim of the study 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 outcomes in the geriatric. This study is the first to investigate thyroid markers as prognostic markers in geriatric post-operative surgical patients. Our study will further strengthen the fact that hypo functioning of the thyroid due to sepsis is quite common and will definitely affect the prognosis in geriatric patients.

2. MATERIALS AND METHODS

2.1 Study Samples

The study was conducted in collaboration at the Department of Pathology, in the 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 infection/sepsis due to various reasons. A 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. SOFA scoring was done as described by Vincent et al in 1996 [40]. Patients were followed for their complete stay at ICU.

Sepsis was confirmed when any two conditions among a) temperature >38ºC or <36ºC, b) respiratory rate >20 breaths/min or $PaCO_2$<32 mmHg) 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 hematological and other lab testing or testing of wounds and stitches for infection. Initial sepsis definition and criteria were used for recruitment. Sepsis criteria were not updated to the 2016 version in between of the study to maintain consistency of the study [44,45]. 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 the 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 were defined by SOFA, as reported by the physician.

Four study groups were divided on the basis of age as hypothyroidism is prevalent in aged patients [16, 46, 47]. Since the study was to determine the association of age with thyroid function in post-operative critically ill patients, we divided our subjects into the following group so that the correlation can be easily determined and discussed:

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

Individuals above 60 years of age were considered as geriatric patients, including young old, middle old and very old individuals [48]. Individuals of 18-30 years are young adults having a normal physiological function often referred to as emerging adulthood [49,50]. The individuals with ages 31 to 60 years were divided into the equal age range of 15 years i.e. into two groups namely, 31-45 and 46-60 years.

2.1.1 Inclusion criteria

Patients who went for surgery were included. Sepsis criteria were included to identify critically ill patients for this study. The age was between 18 and 85 years.

2.1.2 Exclusion criteria

Patients under any hormonal therapy, patients taking amiodarone, patients with a previous history of thyroid diseases and patients with thyroid nodules 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 contraceptives or receiving hormonal replacement therapy or if there was an inability to give consent.

2.2 Sample Collection

Five ml of blood sample was drawn in the vacutainer on the 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. These kits are based on chemiluminescent microparticle immunoassay.
The analytical specificity of the ARCHITECT Free T3 assay is ≤ 0.001% cross-reactivity T4 at 1,000,000 pg/mL (https://www.ilexmedical.com/files/PDF/FreeT3_ARC.pdf) and the mean analytical specificity of the ARCHITECT Free T4 assay is ≤ 0.0035% cross-reactivity T3 at 12,000 ng/dL in a sample containing 0.5 ng/dL of FT4 (https://www.ilexmedical.com/files/PDF/FreeT4_ARC.pdf). The analytical specificity of the ARCHITECT TSH assay is < 10% having cross-reactivity LH ≤ 500 mIU/mL, FSH ≤ 500 mIU/mL, hCG ≤ 200,000 mIU/Ml in the sample with TSH in the normal range (https://www.ilexmedical.com/files/PDF/TSH_ARC.pdf).

2.4 Statistical Analysis

The 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 the Simple Interactive Statistical Analysis (SISA) online tool (http://www.quantitativeskills.com/sisa/calculations/power.html). A 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.

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 1). The percentage of females was higher in the young groups of 18-30 years and 31-45 years, while the percentage of males was higher in the old groups of 46-60 years and 61-85 years (Table 1).

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 (Fig. 1A).

Group 1 has 82% female patients, Group 2 has 74% females, Group 3 has 20% females, Group 4 has 24% females (Table1). Although female patients were higher in number in the total sample size but the distribution of female patients was uneven in each group and was non-significant to establish any analysis. Hence, gender-wise analysis was not performed.

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±0.04pg/ml followed by 31-45 years at 1.78±0.05 pg/ml, 46-60 years at 1.52±0.10pg/ml and 61-85 years at 1.16±0.06pg/ml (Fig. 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 (Fig. 1C). The TSH levels in groups of age 18-30 years and 31-45 years were 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 (Fig. 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.

3.3 Correlations

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

Furthermore, the post operative critically ill patients were divided into four groups which were 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 the SOFA score (13.12±0.27) of the 'No change' group and the score increased in the 'Deteriorated' group from 15.67±0.60 to 17.00±0.59 ($p=0.04$). Among the deteriorated patients on the 5th day, five expired later during the follow-up of ICU. The trend in age, SOFA score, FT3, FT4 and TSH on the first day was investigated in these groups. Fig. 3 summarizes the observations among the prognosis groups.

The patients whose condition improved were mostly young (33.55±1.56 years) as compared to the 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.

Table 1. 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.

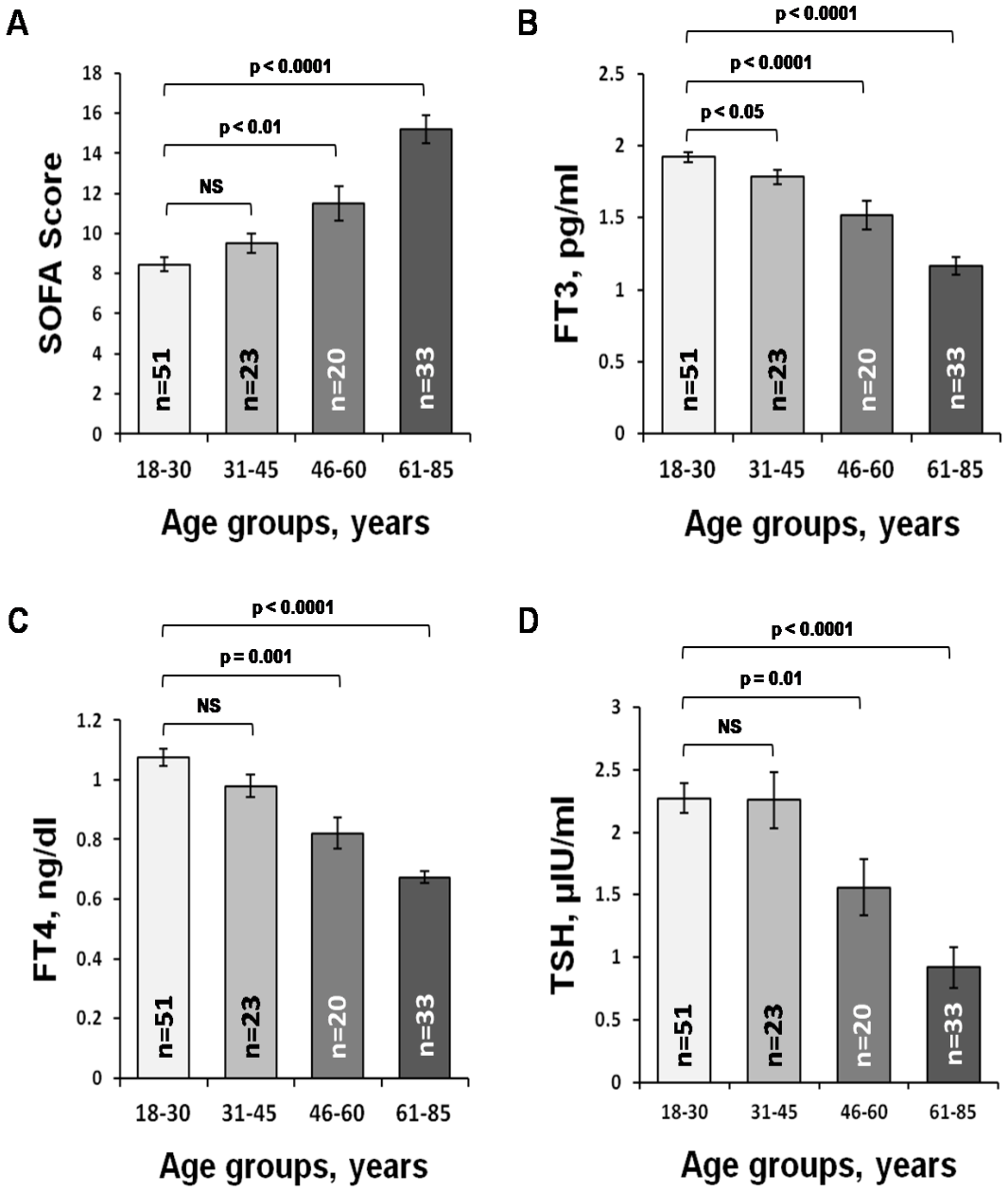


Fig. 1. SOFA score and thyroid markers in the four study groups; A: SOFA score, B: FT3, C: FT4 and D: TSH. SPSS 16.0 was used to perform general linear model and obtain p-value after adjustment with gender

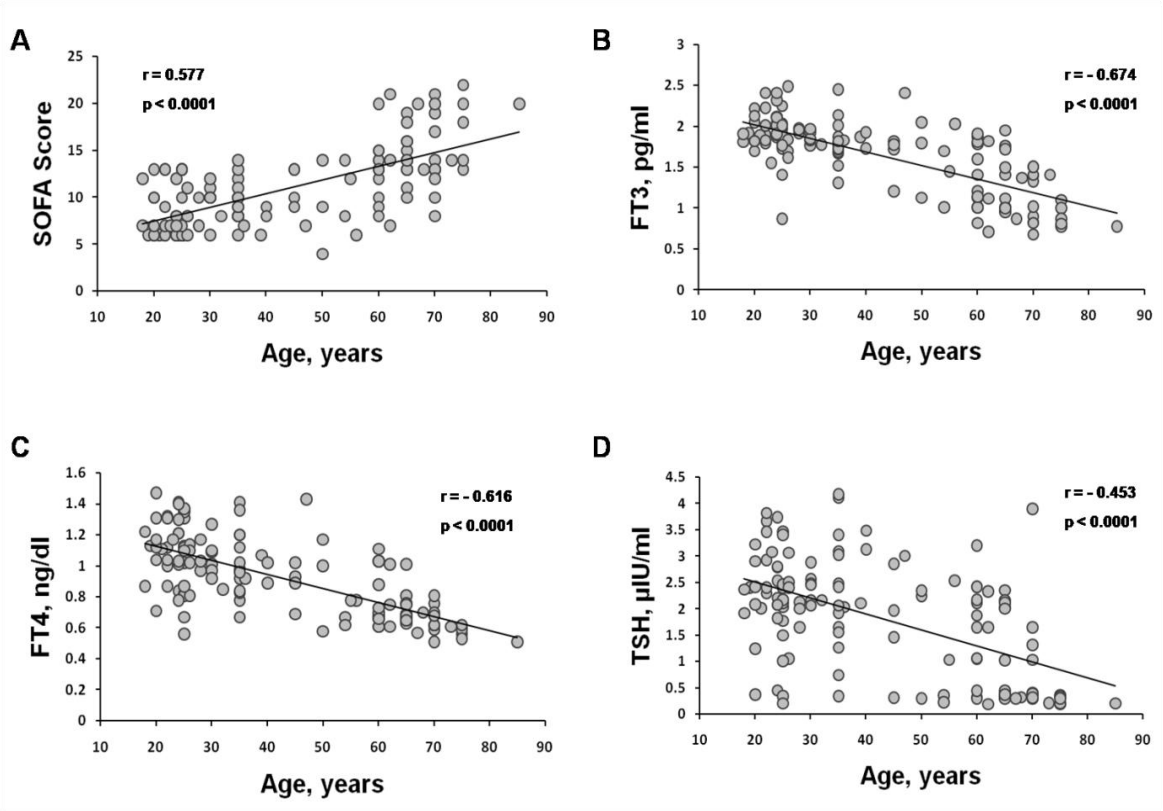


Fig. 2. Correlation of SOFA score and thyroid biomarkers with age in the total study subjects. A: SOFA score, B: FT3, C: FT4 and D: TSH. Partial correlation was performed using SPSS 16.0, and the significance was maintained at p≤0.05/4=0.01. P-values were obtained after adjusting with gender

4. DISCUSSION

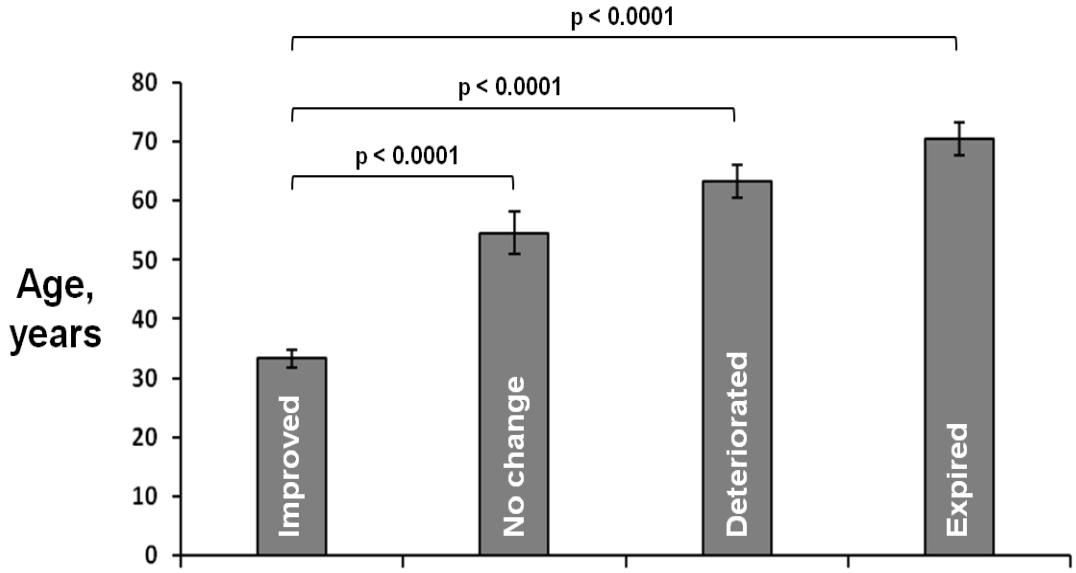
Critically ill patients and their management have always been a challenge for clinicians. Geriatric patients are even more difficult to manage because of their poor adaptive physiological system including the immune system. To improve the outcome in geriatric patients various research is being done worldwide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

The study was aimed to study prognostic markers in geriatric patients, hence age was considered to define groups of the study. The patients included in the present study were between 18-85 years of age, of which geriatric patients were 33i.e. 26%. We found the highest SOFA score in higher age group 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 geriatric patients, organ function deteriorates more rapidly after sepsis due to a maladaptive physiological system. The same amount of insult to the body produces more harm in geriatric than young adults. Previous studies have also reported that SOFA is high among the geriatric [51].

Generally, with increasing age the incidence of subclinical hypothyroidism increases, i.e. T3 & T4 levels decrease and TSH levels increase. Thus, patients with no history of thyroid dysfunction or use of medication that influence thyroid hormones were included. It was observed that FT3 and FT4 were low in elder patients in the present study. However, between the two, FT3 was much lower in geriatric patients crossing the lower limit of the normal range

(1.71-3.71 pg/ml) in many patients. The decrease in FT3wasvery significant when compared with 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 a normal range. With this result, it can be said that there is a 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 geriatric age group patients in comparison with younger group 1 critically ill patients but most of them are within normal limits. Further, in all the groups TSH was within the normal range but it was towards a lower limit in geriatric patients.

Generalized depression of thyroid gland function in critically ill surgical patients was observed and the depression further enhanced with age. The patients with deranged thyroid function were having NTI.A positive correlation between SOFA and age was observed, which is in line with the previous report [51]. Further, inverse correlations were observed between thyroid hormone levels and the age of the patients, with the strongest inverse correlation for FT3.



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

Fig. 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

Patients with low FT3 o rFT4 in advanced 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 [52]. NTI was observed in critically ill patients and it was a major determinant of the prognosis of geriatric patients besides SOFA score. The surviving patients had near to normal thyroid function test values 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 geriatric patients and it is associated with long-term mortality [53]. Most of the non-survivors had very low levels of FT3 suggesting that FT3 might be most commonly associated with the worst prognosis in geriatric patients. With these observations, it is evident that FT3can be a suitable biomarker in geriatric critical patients.

The non-survivor patients were mostly geriatric with high SOFA scores and low FT3, FT4 and TSH. An association of high mortality with low FT3, low FT4 and higher than normal TSH has been reported [5]. Many authors have observed that the geriatric population with sub-clinical hypothyroidism or NTI when suffering from a medical or surgical illness they becomes more critical and their prognosis worsens. NTI has also been linked with mortality in cardiac diseases, stroke and kidney failure [54-56]. In the present study, SOFA score and thyroid function test indicate that geriatric patients are more critical and require intensive care management. They should be given enough space in ICU. Unfortunately, these patients are not given enough consideration for ICU admission in developing countries [51]. Gender-specific treatment strategy and prognostic markers is also of interest in the case of sepsis as males have increased cytokine release capacity [57]. Further, females are more prone to develop thyroid problems with age.

Nevertheless, the present 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, a larger sample size is vital to validate the observations of this study. Further, to establish FT3 as a strong prognostic marker a wider multi-centric study is required. Further, the patients were only followed in the ICU and not followed after shifting to the ward. Further, true hypothyroidism was not observed in the study.

5. CONCLUSION

Post-operative critically ill geriatric 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 the age of the patients. The geriatric patients had high SOFA scores. Thus, thyroid biomarkers especially FT3along with SOFA score seem to be a nice tool in predicting the prognosis of critically ill geriatric patients. Including FT3 as an early prognostic marker will improve the in-time treatment of geriatric and critically ill patients with sepsis.

6. LIMITATIONS

There are a few limitations of the study. Gender-specific and disease-specific grouping was not done in this study. T3 supplementation and its effect were not studied. Further, patients were not followed up after their discharge from ICU. Studies on a much larger sample size should be done to establish results for clinical use.

DISCLAIMER

The products used for this research are commonly and predominantly used 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 the personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

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. The 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).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis Crit Care Med. 1992;20(6):864-74.
2. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Crit Care. 2006;10(2):R42. DOI: 10.1186/cc4854.
3. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4): 1250-6. DOI:10.1097/01.CCM.0000050454.01978.3B.
4. Luo B, Yu Z, Li Y. Thyroid hormone disorders and sepsis. Biomed Mater Eng. 2017;28(s1):S237-S241. DOI: 10.3233/BME-171646.
5. Mingote E, Meroño T, Rujelman R, Marquez A, Fossati P, Gurfinkiel M, Schnitman M, Brites F, Faingold C, Brenta G. High TSH and low T4 as prognostic markers in older patients. Hormones (Athens). 2012;11(3):350-5. DOI: 10.14310/horm.2002.1364.
6. Wiersinga WM, van den Berghe G. Nonthyroidal illness syndrome. In: Braverman LE, Cooper DS, editors. Werner & Ingbar's the thyroid: a fundamental and clinical text. 10. Philadelphia: Lippincott Williams and Wilkins. 2013;203–17.
7. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNFalpha in nonthyroidal illness syndrome induced by abdominal surgery. J Clin Endocrinol Metab. 2001;86(9):4198-205. DOI: 10.1210/jcem.86.9.7795.
8. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf). 1993;39(5):499-518. DOI: 10.1111/j.1365-2265.1993.tb02401.x.
9. Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. J Clin Endocrinol Metab. 2005;90(8):4559-65. DOI: 10.1210/jc.2005-0535.
10. Bello G, Pennisi MA, Montini L, Silva S, Maviglia R, Cavallaro F, Bianchi A, De Marinis L, Antonelli M. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. Chest. 2009;135(6):1448-1454. DOI: 10.1378/chest.08-1816.
11. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev. 2011;32(5):670-93. DOI: 10.1210/er.2011-0007.
12. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal Illness Syndrome Across the Ages. J Endocr Soc. 2019;3(12):2313-2325. DOI: 10.1210/js.2019-00325.
13. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3(10):816-25. DOI: 10.1016/S2213-8587(15)00225-9.
14. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390(10101):1550-1562. doi: 10.1016/S0140-6736(17)30703-1.
15. Gesing A. The thyroid gland and the process of aging. Thyroid Res. 2015; 8(Suppl 1): A8. doi: 10.1186/1756-6614-8-S1-A8.
16. Chen X, Zheng X, Ding Z, Su Y, Wang S, Cui B, Xie Z. Relationship of gender and age on thyroid hormone parameters in a large Chinese population. Arch Endocrinol Metab. 2020;64(1):52-58. DOI: 10.20945/2359-3997000000179
17. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and

Nutrition Examination Survey (NHANES 1999-2002). Thyroid. 2007;17(12):1211-23. doi: 10.1089/thy.2006.0235.
18. So M, MacIsaac RJ, Grossmann M. Hypothyroidism. Aust Fam Physician 2012;41:556-62.
19. Girvent M, Maestro S, Hernandez R, et al: Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation, Surgery. 1998;123:560–567. DOI: 10.1067/msy.1998.87238.
20. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006;34(1):15-21. DOI: 10.1097/01.ccm.0000194535.82812.ba.
21. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: An overview. World J Crit Care Med. 2012;1(1):23-30. Published 2012 Feb 4. DOI:10.5492/wjccm.v1.i1.23.
22. Piccirillo JF, Vlahiotis A, Barrett LB, Flood KL, Spitznagel EL, Steyerberg EW. The changing prevalence of comorbidity across the age spectrum. Crit Rev Oncol Hematol. 2008;67(2):124-132. DOI:10.1016/j.critrevonc.2008.01.013.
23. Yancik R, Wesley MN, Ries LA, Havlik RJ, Long S, Edwards BK, Yates JW. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer. 1998;82(11):2123-34.
24. Bagcchi S. Hypothyroidism in India: more to be done. Lancet Diabetes Endocrinol 2014;2:778. DOI:10.1016/S2213-8587(14)70208-6.
25. The Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. UK Guidelines for the Use of Thyroid Function Tests. 2006. Available:https://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf
26. Iglesias P, Muñoz A, Prado F, Guerrero MT, Macías MC, Ridruejo E, Tajada P, Díez JJ. Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome. Clin Endocrinol (Oxf). 2009;70(6):961-7. DOI: 10.1111/j.1365-2265.2008.03421.x.
27. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin North Am 2007;36:657-72. vi. DOI: 10.1016/j.ecl.2007.04.007.
28. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab 1997; 82:329-34. DOI: 10.1210/jcem.82.2.3745.
29. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M, Monzani F. Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing. 2010;39(1):46-50. DOI: 10.1093/ageing/afp197.
30. Dietrich JW, Stachon A, Antic B, Klein HH, Hering S. The AQUA-FONTIS study: protocol of a multidisciplinary, cross-sectional and prospective longitudinal study for developing standardized diagnostics and classification of non-thyroidal illness syndrome. BMC Endocr Disord 2008;8:13. DOI: 10.1186/1472-6823-8-13.
31. Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Schölmerich J, Wrede CE. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metabolism. 2007;56(2):239-44. DOI: 10.1016/j.metabol.2006.09.020.
32. Silberman H, Eisenberg D, Ryan J, Shofler R, Niland J, Kaptein E, Nicoloff J, Spencer C. The relation of thyroid indices in the critically ill patient to prognosis and nutritional factors. Surg Gynecol Obstet. 1988;166(3):223-8.
33. De Groot LJ. Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin 2006;22:57-86. vi. DOI: 10.1016/j.ccc.2005.10.001.
34. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004;292:2591-9. DOI: 10.1001/jama.292.21.2591.
35. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid function, activities of daily living and survival in extreme old age: the 'Leiden 85-plus Study'. Ned Tijdschr Geneeskd. 2006;150:90-6.
36. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly geriatric people from one low serum

thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861-5.
DOI: 10.1016/S0140-6736(01)06067-6.

37. Singer RB. Mortality in a complete 4-year follow up of 85-year-old residents of Leiden, classified by serum level of thyrotropin and thyroxine. J Insur Med. 2006;38:14-9.
38. Bossoni S, Cossi S, Marengoni A, De Martinis M, Calabrese P, Leonardi R, Giustina A, Romanelli G, Grassi V. Low T3 syndrome and outcome in elderly geriatric hospitalized geriatric patients. J Endocrinol Invest. 2002;25(10 Suppl):73-4.
39. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR; SAPS 3 Investigators. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med. 2005;31:1345-55.
DOI: 10.1007/s00134-005-2763-5.
40. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34:1297-310.
DOI:10.1097/01.CCM.0000215112.84523.F0.
41. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA. 1996;276(10):802-10.
DOI: 10.1001/jama.276.10.802.
42. Higgins TL, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). Crit Care Med. 2007;35:827-35.
DOI:10.1097/01.CCM.0000257337.63529.9F.
43. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707-10.
DOI: 10.1007/BF01709751.
44. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. Chest. 2016;149:1117-8.
DOI: 10.1016/j.chest.2016.02.653.
45. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.
DOI: 10.1001/jama.2016.0287.
46. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76-131.
DOI: 10.1210/er.2006-0043.
47. Gesing A. The thyroid gland and the process of aging. Thyroid Res. 2015 Jun 22;8(Suppl 1):A8. doi: 10.1186/1756-6614-8-S1-A8.
48. Forman DE, Berman AD, McCabe CH, Baim DS, Wei JY. PTCA in the elderly: the "young-old" versus the "old-old". J Am Geriatr Soc. 1992;40(1):19-22.
DOI: 10.1111/j.1532-5415.1992.tb01823.x.
49. Board on Children, Youth, and Families; Institute of Medicine; National Research Council. Improving the Health, Safety, and Well-Being of Young Adults: Workshop Summary. Washington (DC): National Academies Press (US); 2013. D, Background Paper: Pathways to Young Adulthood and Preventive Interventions Targeting Young Adults.
Available:https://www.ncbi.nlm.nih.gov/books/NBK202209/
50. Arnett JJ, Žukauskienė R, Sugimura K. The new life stage of emerging adulthood at ages 18-29 years: implications for mental health. Lancet Psychiatry. 2014 Dec;1(7):569-76.
DOI: 10.1016/S2215-0366(14)00080-7.
51. Gupta V, Karnik ND, Agrawal D. SOFA Score and Critically Ill Elderly geriatric Patients. J Assoc Physicians India. 2017;65:47-50.
52. Qari FA. Thyroid function status and its impact on clinical outcome in patients admitted to critical care. Pak J Med Sci. 2015;31:915-9.
DOI: 10.12669/pjms.314.7497.
53. Iglesias P, Ridruejo E, Muñoz A, Prado F, Macías MC, Guerrero MT, Tajada P,

García-Arévalo C, Díez JJ. Thyroid function tests and mortality in aged hospitalized patients: a 7-year prospective observational study. J Clin Endocrinol Metab. 2013;98(12):4683-90.
DOI: 10.1210/jc.2012-3849. Epub 2013 Oct 30.

54. Alevizaki M, Synetou M, Xynos K, Pappa T, Vemmos KN. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. Eur J Clin Invest. 2007;37:651-7.
DOI: 10.1111/j.1365-2362.2007.01839.x.

55. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, Ford I, Welsh P, Sattar N, Macfarlane PW, Mooijaart SP, Rodondi N, de Craen AJ; PROSPER Group. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. 2012;97(3):852-61.
DOI: 10.1210/jc.2011-1978.

56. Zoccali C, Mallamaci F. Thyroid function and clinical outcomes in kidney failure. Clin J Am Soc Nephrol. 2012;7:12-4.
DOI: 10.2215/CJN.12081111.

57. Albertsmeier M, Pratschke S, Chaudry I, Angele MK. Gender-Specific Effects on Immune Response and Cardiac Function after Trauma Hemorrhage and Sepsis. Viszeralmedizin. 2014;30(2):91-6.
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