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RESEARCH

A new marker in determining the relationship between the clinical outcomes of patients with sepsis and thyroid function tests: free triiodothyronine to free thyroxine ratio

Sepsis hastalarının klinik sonuçları ile tiroid fonksiyon testleri arasındaki ilişkinin belirlenmesinde yeni bir belirteç: serbest triiyodotironinin serbest tiroksin oranı

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Abstract

Purpose: This study investigated the predictive value of thyroid hormones in septic patients.
Materials and Methods: Our study was conducted in patients with sepsis in intensive care unit (ICU). Free triiodothyronine (fT3) and free thyroxine (fT4) levels taken at the time of hospitalization and at the 48th hours were measured and the fT3 / fT4 ratio was calculated. Calculated fT3 and fT4 change between first and 48th hours.
Results: 192 patients with sepsis were included in the study. In non-survivor patients, first fT3 (1.60±0.57 ng/dL v.s. 2.01±0.41 ng/dL) and fT3 / fT4 ratio (1.34±0.88 v.s. 1.79±0.91) were found to be significantly lower than 48th hours fT3 (0.77±0.39 ng/dL v.s. 1.87±0.49 ng/dL) and fT3 / fT4 ratio (0.60±0.51 v.s. 1.66±1.21) survivors. It was found that the first fT3 levels (-0.83±0.45 v.s. -0.23±0.14) and fT3 / fT4 ratio (-0.73±0.62 v.s. -0.12±0.11) decreased significantly more at 48th hour in non-survivors than survivors. The 48th hours fT3 level and the change in fT3 between the first and 48th hour were found to be the most significant parameters for the mortality indicator.
Conclusion: fT3 / fT4 ratio has predictive value for mortality in patients with sepsis in ICU. In addition, fT3 was found to be an indicator for mortality predictivity both at admission and at 48th hours.
Keywords:. Free triiodothyronine/free thyroxine ratio, intensive care unit, sepsis, thyroxine, triiodothyronine

Öz

Amaç: Çalışmamızda septik hastalarda tiroid hormonlarının prediktif değerini araştırdık.
Gereç ve Yöntem: Çalışmamız yoğun bakım ünitesinde (YBÜ) yatan sepsis hastalarında yapıldı. Hastaneye yatış anında ve 48. saatte alınan serbest triiodotironin (sT3) ve serbest tiroksin (sT4) düzeyleri ölçüldü ve sT3/sT4 oranı hesaplandı. Birinci ve 48. saatler arasındaki sT3 ve sT4, değişikliği hesaplandı.
Bulgular: Çalışmaya 192 sepsis hastası dahil edildi. Kaybedilen hastalarda birinci sT3 (1.60±0.57 ng/dL vs 2.01±0.41 ng/dL) ve sT3/sT4 oranı (1.34±0.88 vs 1.79±0.91), 48. saatteki sT3 (0.77±0.39 ng/dL vs 1.87±0.49 ng/dL) ve sT3/sT4 oranından (0.60±0.51 vs 1.66±1.21) yaşayanlara göre anlamlı olarak düşük bulundu. İlk sT3 düzeylerinin (-0.83±0.45 vs -0.23±0.14) ve sT3/sT4 oranının 48. saatte (-0.73±0.62 vs -0.12±0.11) kaybedilenlerde yaşayanlarda göre anlamlı olarak daha fazla azaldığı saptandı. 48. saat sT3 düzeyi ve ilk ile 48. saat arasındaki sT3 değişiminin mortalite göstergesi için en anlamlı parametreler olduğu bulundu.
Sonuç: sT3/sT4 oranının YBÜ'deki sepsisli hastalarda mortalite için prediktif değere sahip olduğu gösterilmiştir. Ayrıca hem yatışta hem de 48. saatteki sT3 değerleri mortalite için anlamlı öngörücü göstergeler olduğu bulundu.
Anahtar kelimeler: Serbest triiyodotironin/serbest tiroksin oranı, yoğun bakım ünitesi, sepsis, tiroksin, triiyodotironin

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INTRODUCTION

Sepsis is the most common cause of intensive care unit (ICU) hospitalizations and its mortality is over 30%. Innate immune response can lead to cell and tissue damage that causes multiple organ failure in conditions such as sepsis. Due to inflammatory cytokinemia, there is a strong activation of the anterior pituitary and inactivation of the peripheral anabolic pathways in the neuroendocrine response of critical illness (ie sepsis). These initial adaptations seem to be adaptive and beneficial. In critical patients such as sepsis, hypothalamic-pituitary-thyroid axis (HPTA) and thyroid hormone (TH) metabolism are also affected. If the acute phase of the critical illness turns into chronic disease, it may result in target organ dysfunction, ICU dependency and mortality, mostly due to reduced stimulation in pituitary function[1].

TH plays a role in many metabolic events such as cardiovascular system, neurological system, immune system, bone development, energy expenditure, regulation of glucose, lipid, and coagulation homeostasis[2-5]. In septic patients, reduction in triiodothyronine (T3) and thyroxine (T4) levels play a key role in adaptation to sepsis. The reason for this reduction is the transformation from T4 to excessively inactive reverse T3 (rT3) and the dysfunction of the HPTA by inflammatory cytokines[3]. Changes in TH during this critical illness are called euthyroid sick syndrome (ESS) or non thyroidal illness[6]. This change in TH in critical sepsis patients can provide information about clinical results. In the studies, it was concluded that there is a relationship between clinical results and free / total T3 (fT3 / TT3), free / total T4 (fT4 / TT4) and thyroid-stimulating hormone (TSH) levels[3,6].

Thyroid function can be affected by malnutrition, sepsis, and major injuries. As a result, the thyroid dysfunction is commonly seen in critically ill patients. Especially low T3, T4 and TSH levels have been recognized to be the predictor for poor prognosis in many diseases such as sepsis, chronic lymphocytic leukemia, chronic hemodialysis, COVID-19 and stress cardiomyopathy. The effect of thyroid hormone supplementation on poor clinical outcomes for low thyroid hormone levels in critically ill patients is unknown. The clinical benefit of thyroid hormone supplementation has not been fully demonstrated[7,8]. On the contrary, some studies have reported that TH concentrations are not associated with clinical outcomes[9,10]. The relationship between TH and clinical outcomes in sepsis is still unclear.

fT3 / fT4 ratio has been shown to be effective in differential diagnosis of primary thyroid diseases[4,11]. However, there is no data on whether there is a relationship between the clinical outcomes of critically ill patients with sepsis and the fT3 / fT4 ratio. fT3 / fT4 ratio may be a new marker for predicting clinical outcomes in patients with sepsis. Thus, fT3 / fT4 ratio can add new information to the literature by predicting the results of sepsis. According to the hypothesis of our study, fT3 / fT4 ratio is a useful indicator in determining the clinical outcomes of patients with sepsis. The aim of our study is to evaluate the possible relationship between fT3, fT4, TSH, fT3 / fT4 ratio and their changes during hospitalization with clinical outcomes in patients with sepsis hospitalized in ICU.

MATERIALS AND METHODS

Study design

Our ICU III. level is an adult ICU and all patients ≥18 years of age are followed up. Our study was carried out prospectively in patients hospitalized for sepsis in Department of Anesthesiology and Clinical of Critical Care in Ankara Numune Training and Research Hospital between January 1, 2021 and December 31, 2021. Ethical approval was obtained from the local ethics committee (Ankara Numune Training and Research Hospital Clinical Research Ethics Committee, date and number: 07.12.2017 and E-17-1412) before the study. Verbal and written consent was obtained from each case or legal representative before the study. The data were obtained from the hospital's electronic patient registry and patient files. All data collected during this study were kept confidential in terms of the reliability of the records and the confidentiality and privacy of the patients included in the study and were not shared anywhere. The study procedure was performed by four physicians in our study. During the study process, the authors acted in accordance with the Helsinki Declaration principles.

Procedure

Patients hospitalized in ICU due to primary sepsis diagnosis were included in the study. Patients who were hospitalized for ICU other than sepsis (trauma, intoxication, neurological and metabolic disorders,

myocardial infarction, etc.), had thyroid disease at the first examination, and died within the first 48th hour were excluded from the study. The patients were diagnosed with sepsis according to the "Third International Consensus Definitions" criteria with clinical and laboratory findings[12]. Patients with sepsis were treated in accordance with the "International Guidelines for Management of Sepsis and Septic Shock" guideline[13].

Patients' age, gender, number of comorbid conditions (diabetes mellitus, hypertension, malignancy / immunodeficiency, respiratory system disease, heart disease, renal disease, central nervous system disease, etc.), acute physiology and chronic health evaluation (APACHE) II score, sepsis-related organ failure assessment (SOFA) score, duration of mechanical ventilation (MV), hospital stay, bacteremia presence, C-reactive protein (CRP), white blood cell (WBC), thyroid function tests (TFT) and mortality data recording was obtained. The APACHE II score was made up of 12 physiological and two disease-related variables collected within the first 24 hours of ICU admission. SOFA score was a quantitative scoring index that dynamically describes sepsis-related organ dysfunction, including respiratory system, coagulation system, liver function, cardiovascular system, central nervous system, and renal function[14,15].

Determination of serum levels of CRP, WBC and blood culture

Venous blood samples were collected from patients with sepsis during their admission to ICU. WBC from blood taken in tubes containing ethylenediamine tetra-acetic acid and CRP from serum samples were studied. WBC was measured by a twice-daily calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, Abbott Park, IL, USA). Serum CRP levels were measured with a high sensitive immuno-turbidimetric assay (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Bacteremia was identified with the BACTEC FX automatic blood culture detection system (Becton Dickinson, Sparks, MD, USA).

Determination of thyroid function tests

After venous blood was taken within the 1st hour of hospitalization and at the 48th hours, serum samples were separated by centrifugation at 1200 rpm for 15 minutes. fT3, fT4 and TSH levels were studied in serum samples. In order to determine TH levels, the UniCel DxI 800 auto analyzer (Beckman Coulter, Inc., Fullerton, U.S.A.) was performed by immune enzymatic route.

After fT3 and fT4 values were obtained, the fT3 / fT4 ratio was calculated by dividing fT3 by fT4. ΔfT3 was defined as change in the levels of fT3 between the 1st and 48th hours, ΔfT4 was defined as change in the levels of fT4 between the 1st and 48th hour, Δ TSH was defined as change in the levels of TSH between the 1st and 48th hours, ΔfT3 / fT4 ratio was defined as change in the levels of fT3 / fT4 ratio calculated between the 1st and 48th hours. Our institutional reference values are 2.6-4.32 pg / mL for fT3, 0.61-1.2 ng / dL for fT4 and 0.38-5.33 mIU / mL for TSH. Laboratory parameters, demographic and clinical characteristics were compared between survivor and non-survivor patients with sepsis.

Statistical analysis

For statistical analysis, Statistical Package for Social Sciences (SPSS) software 17.0 (IBM SPSS, Chicago, IL) was used. T-test and / or Mann-Whitney's U-test were used to compare non-parametric continuous variables in independent samples between groups, and chi-square test or Fisher's exact test for categorical variables. Results are given as mean and standard deviation and / or median (range) for continuous variables.

Categorical variables were expressed as frequency and percentage distribution. Diagnostic screening tests to determine the cutoff for fT3, fT3 / fT4 ratio, ΔfT3 and ΔfT3 / fT4 ratio and receiver operating characteristic (ROC) curve analysis were performed. A p value of <0.05 was considered statistically significant.

Area under the curve (AUC), sensitivity, specificity and cut-off values were determined by ROC analysis. AUC was defined as high accuracy if > 0.9, moderate accuracy if 0.7-0.9, and low accuracy if <0.7[16]. The sample size calculated at a power of 90% and a significance level of 5% by using G*Power software (version 3.1.9.4, Kiel University, Kiel, Germany), was approximately 72 patients per group, with an effect size of 0.80 for statistical significance.

RESULTS

During the study period, 708 patients were followed in our ICU. According to exclusion criteria, 516 patients (without sepsis: 449, thyroid disease: 24, died within the first 48th hour: 43) were excluded from the

study. 192 diagnosed sepsis patients were included in the study. Of the patients included in the study, 80 (41.6%) patients died, 112 (58.4%) patients were discharged (Figure 1).

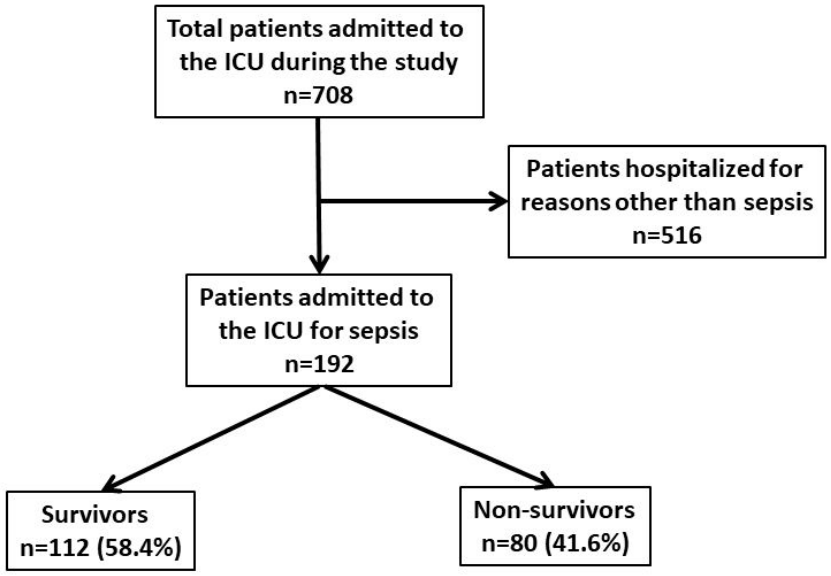

Figure 1. Flow chart of study patients

Table 1. Comparison of demographic and clinical features between survivors and non-survivors

Variables	Survivors (n=112)	Non-survivors (n=80)	P value
Age, (years), [a]	74.1±14.2	75.8±11.2	0.359
Male gender, n (%)	56 (50)	32 (40)	0.110
Comorbid disease, [b]	2 (0-5)	3 (0-6)	<0.001*
APACHE II score, [b]	20 (8-33)	23 (11-47)	<0.001*
SOFA score, [b]	7 (3-15)	9 (6-22)	<0.001*
Duration of MV, (days), [b]	5 (2-40)	6 (2-44)	0.841
Hospital stay, (days), [b]	14 (4-45)	19 (5-49)	<0.001*
Bacteremia, n (%)	22 (19.6)	45 (56.2)	<0.001*
White blood cell, ($x10^3/\mu L$) [a]	13.3±6.6	14.6±11.4	0.345
C-reactive protein, (mg/L) [a]	64.3±25.2	134.4±43.7	<0.001*

[a] mean ± standard deviation, [b] median (range), *Statistically significant p values are highlighted.
APACHE II: acute physiology and chronic health evaluation score, SOFA: sepsis-related organ failure assessment score, MV: mechanical ventilation

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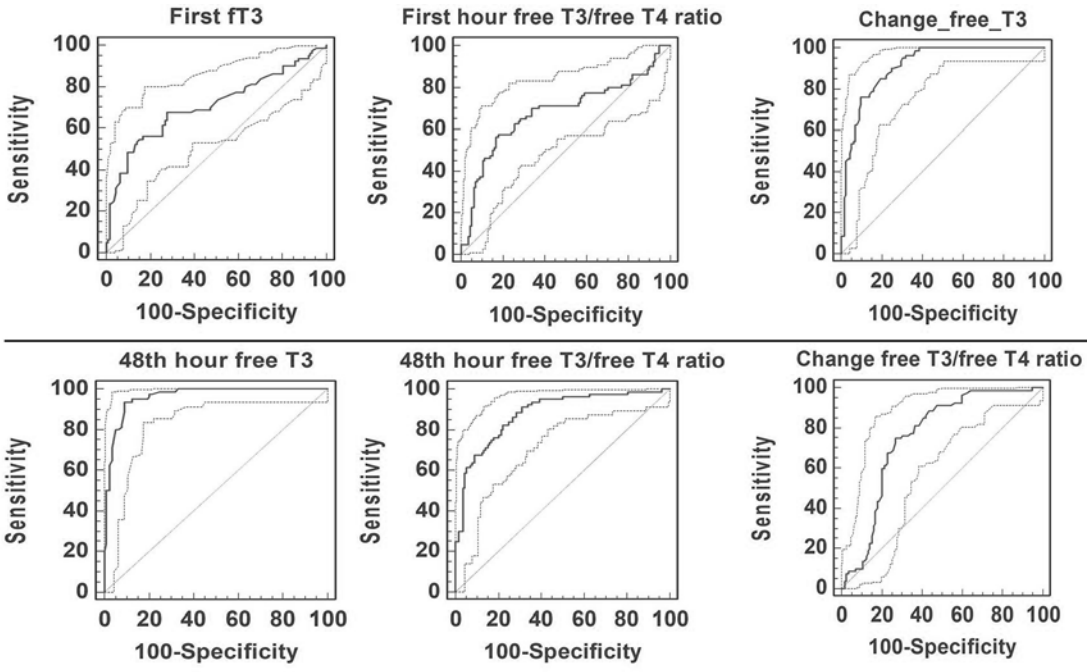
Table 2. Comparison of thyroid function test between survivors and non-survivors

Variables	Survivors (n=112)	Non-survivors (n=80)	P value
First hour free T3, ng/dL [a]	2.01±0.41	1.60±0.57	<0.001*
First hour free T4, ng/dL [a]	1.41±0.93	1.69±1.11	0.071
First hour TSH, µIU/L [a]	2.83±5.89	6.35±6.02	0.112
First hour free T3/free T4 ratio [a]	1.79±0.91	1.34±0.88	0.001*
48th hours free T3, ng/dL [a]	1.87±0.49	0.77±0.39	<0.001*
48th hours free T4, ng/dL [a]	1.56±0.98	1.81±1.04	0.105
48th hours TSH, µIU/L [a]	3.52±3.01	5.9±5.11	0.284
48th hours free T3/free T4 ratio	1.66±1.21	0.60±0.51	<0.001*
Δ free T3, ng/dL [a]	-0.23±0.14	-0.83±0.45	<0.001*
Δ free T4, ng/dL [a]	0.15±0.10	0.14±0.12	0.738
Δ TSH, µIU/L [a]	-0.69±0.53	0.40±0.34	0.662
Δ free T3/free T4 ratio [a]	-0.12±0.11	-0.73±0.62	<0.001*

[a] mean ± standard deviation, *Statistically significant p values are highlighted.
T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; Δ free T3, change in the levels of free T3 between the 1st and 48th hour; Δ free T4, change in the levels of free T4 between the 1st and 48th hour; Δ TSH, change in the levels of TSH between the 1st and 48th hour; Δ free T3/free T4 ratio, change in the levels of free T3/free T4 ratio between the 1st and 48th hours.



Variables	AUC	95% Confidence interval	p values	Cutoff level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
First hour free T3, ng/dL	0.708	0.638-0.771	0.0001	≤1.62	75	84	72	73
48th hour free T3, ng/dL	0.962	0.924-0.984	0.0001	≤1.25	94	91	88	95
First hour free T3/free T4 ratio	0.712	0.645-0.779	0.0001	≤1.19	77	82	70	73
48th hour free T3/free T4 ratio	0.880	0.826-0.923	0.0001	≤0.86	83	78	73	86
Δ free T3, ng/dL	0.910	0.861-0.947	0.0001	≥-0.51	76	90	85	84
Δ free T3/free T4 ratio	0.755	0.688-0.814	0.0001	≥-0.32	75	73	68	80

AUC: area under the curve, PPV: positive predictive values, NPV: negative predictive values, ROC: receiver operating characteristic, triiodothyronine (T3) ve thyroxine (T4), Δ free T3, change in the levels of free T3 between the 1st and 48th hour, Δ free T3/free T4 ratio, change in the levels of free T3/free T4 ratio between the 1st and 48th hour.

Figure 2. ROC curve for fT3, fT3/fT4 ratio, ΔfT3 and ΔfT3/fT4 predicting mortality in patients with sepsis in intensive care unit.

Bacteremia rate in blood culture of all patients was 34.9% (67/192). Results in terms of age, male gender, duration of MV and WBC were found similar in non-survivor and survivor patients ($p > 0.05$). The number of comorbid diseases, hospital stay, bacteremia ratio, CRP levels, APACHE II and SOFA scores were found to be significantly higher in non-survivor patients compared to patients with survivor ($p < 0.05$) (Table 1).

In the non-survivor group, the first hour fT3, first fT3 / fT4 ratio, 48th hour fT3, 48th fT3 / fT4 ratio, ΔfT3 and ΔfT3 / fT4 ratio levels were found to be significantly lower than the survivor group ($p < 0.05$). Results were found similar in terms of first hour fT4, first hour TSH, 48th hour fT4, 48th hour TSH, ΔfT4 and ΔTSH in non-survivor and survivor groups ($p > 0.05$) (Table 2).

ROC analysis was implemented for first and 48th hour fT3, fT3 / fT4 ratio, ΔfT3 and ΔfT3 / fT4 for the prediction of mortality in patients with sepsis. The results were presented in Figure 2 as ROC curve, AUC, p value, cut-off levels, sensitivity, specificity, positive predictive value, and negative predictive value

DISCUSSION

Our study was the first to use the fT3/fT4 ratio parameter to predict mortality in sepsis. The first fT3, 48th hour fT3, and fT3 / fT4 ratio were found to be significantly lower in patients with mortality. In addition, ΔfT3 / fT4 ratio was found to be significantly higher in non-survivor patients than in survivor patients. In mortality prediction, first hour fT3, first hour fT3 / fT4 ratio, 48th hours fT3 / fT4 ratio, Δ free T3 / free T4 ratio AUC values are between 0.7-0.9 at moderate accuracy level, 48th hours fT3 and Δ fT3 AUC values > 0.9 and it was found that he had a high accuracy level for mortality[16]. In addition, higher APACHE II and SOFA scores are linked with increase mortality in more severe sepsis patients, as in our results[3,6,17,18]. CRP and the clinical scores are higher in non-survivor group than survivor group. Severe inflammation may affect TH. Thus, these results were due to severe inflammation, cytokineemia, and organ failure. Our study may reveal the importance of changes in TH during sepsis in terms of clinical outcomes[19].

In the early phase of sepsis, changes in TH are mainly peripheral mechanisms that result in reduced T4 to T3 conversion and low T3. In the late phase of sepsis, in addition to low T3 and T4, there is centrally induced hypothyroidism that causes normal or decreased TSH[4]. Some studies had shown a correlation between low T3 and T4 levels and clinical outcomes in critically ill patients[3,20]. In our study, while low fT3 was associated with mortality, fT4 and TSH levels were not found to be associated with clinical outcomes. The reason for this is due to the peripheral effect due to the fact that only fT3 is affected by TH taken in the acute phase of sepsis, but not fT4 and TSH[3]. In addition, different serological inflammatory markers such as TNF-a, IFN-γ and interleukin-6 can reduce the activity of 5'-deiodase in the liver, thyroid gland and liver. These inflammatory markers elevated in the acute period. It is known to reduce the conversion from fT4 to fT3 in the follow-up of the disease. Low fT3 is often observed in the initial stage of critical illness. This is a metabolic adaptive phenomenon related to the disease. Therefore, low fT3 and fT4 levels do not require treatment during critical illness[21].In our results, it was found to be significant for both first hour and 48th hour fT3 mortality indicators. Similar to our results, Wang et al. reported that the first fT3 AUC value was 0.762 and it was close to our first hour AUC value (0.708) and lower than the 48th hour AUC value (0.962), and it was observed that the predictive value of fT3 for mortality increased during follow-up[18]. Therefore, serial measurement of T3 in sepsis may possibly be a more effective parameter to evaluate the prognosis in sepsis[3].

As the sepsis clinic gets more severe, the rT3 levels will increase[5]. Detection of rT3 level in our study could not be done because of the laboratory of our institute does not analyze rT3 levels and its high cost. Instead, fT3 / fT4 ratio was used as the determinant of the conversion level of T4 to T3. The fT3 / fT4 ratio is a reflection of the conversion of T4 to T3 in 5'-deiodinase activity[20]. The relationship between T3 and T4 in healthy individuals is finely controlled that it can be buffered by systematic regulation of the T3 / T4 ratio[22]. In addition, fT3 / fT4 ratio is a simply calculated index that reflects the effects of thyroid function and hormones on tissues[23]. The fT3 / fT4 ratio has not been used previously to predict the clinical consequences of sepsis. In our results, first hour fT3 / fT4 ratio ≤1.19, 48th hour ≤0.86 and ≥0.32 change between first hour and 48th hours were found as significant parameters in predicting

mortality in sepsis for the first time in the literature. We evaluated fT3/fT4 ratio because it may reflect peripheral thyroxin deiodination degree instead of rT3 with lower costs. In this way, it has been shown that it can be used indirectly in the prediction of mortality by using fT3 / fT4 ratio, which is the indicator of the transformation from T4 to T3, without using high cost parameters such as rT3. However, in order to verify these results, rT3 level and fT3 / fT4 ratio should be evaluated together[24].

In addition, a large amount of serum T3 is generated by the deiodination of the outer ring of T4 in extra-thyroidal tissues, while the removal of an atom of iodine in the inner ring of T4 produces the inactive thyroid metabolite reverse T3 (3,3',5'-triiodothyronine or rT3). So fT3/fT4 ratio is an indicative of peripheral thyroxin deiodination degree, and frailty, functional status and mortality in elderly[22]. Arosio et al. described an age-dependent decrease in fT3 levels and fT3/fT4 ratio and an increase in fT4 and TSH levels associated with an impaired functional status and increased mortality in offspring[25]. Also, sepsis may decrease the fT3 level and fT3/fT4 ratio while increase the TSH level, in accordance with age-dependent manner[20]. In recent studies, it has been shown that the fT3/fT4 ratio can be an indicator of the prognosis of both cancer and cardiovascular diseases. In this respect, the fT3/fT4 ratio may be a promising parameter for the prognosis of critical diseases[26-29]. fT3/fT4 ratio may be a prognostic new marker in sepsis, which is among the critical diseases. For this purpose, we designed our study. In our study we showed that lower levels of fT3 and, fT3/fT4 ratio might be used in order to predict the clinical results. Additionally, we did not find any statistical significance between survivor and non-survivor groups, when we checked the levels of fT4, TSH and their daily changes in geriatrics patients with sepsis while there was statistically significance decrease in fT3 level and fT3/fT4 ratio. We speculated that this result had arisen because of the possibility that acute sepsis affected only thyroid gland but did not have any effect on pituitary gland[25,30].

This study has some limitations. Although we exclude those with thyroid nodules by palpation of the thyroid at the time of admission to ICU, some patients with thyroid disease and subclinical hypothyroidism that were not diagnosed before admission may be included in the study. Other comorbidities and medications could not be evaluated because of lack of information. Sepsis patients have limitations in terms of weight classification (sepsis, severe sepsis and septic shock) and the lack of data on drug use (amiodarone, propranolol, barbiturates, benzodiazepines, furosemide and dopamine) that may affect thyroid functions. Adjusting these potential contradictions in clinical practice is very difficult because many drug uses are involved. In addition, many drugs affect the thyroid binding globulin (TBG) concentration, or the ability of the TBG to bind, causing abnormal thyroid function tests. Conversely, fT3 and fT4 levels are not affected by these factors. Therefore, the main result of our study, that the fT3 and hence fT3 / fT4 ratio is the strongest and only independent predictor of ICU mortality among all thyroid indicators, is relatively reliable. Patients who died in the first 48 hours were excluded from the study and the ΔfT3, ΔfT4, and ΔfT3 / fT4 ratio of these patients could not be evaluated. In addition, the laboratory of our institute does not analyze rT3 and TBG levels. Therefore, fT3 / fT4 ratio, which are low cost, simple, easily accessible and quickly available, may be useful to clinicians for predictivity of the mortality in patients with sepsis.

In conclusion, determining the parameters that predict mortality in patients with sepsis in ICU can greatly help clinicians. The determining parameters for mortality should be quickly available, inexpensive and effective. To our knowledge, our study is the first study evaluating the fT3 / fT4 ratio for predicting mortality in septic patients in ICU. The low fT3 and fT3 / fT4 ratio at the time of hospitalization and the significant lowness of these parameters in the follow-up can be used to identify patients with mortality. Thus, fT3 / fT4 ratio may be new and useful for clinicians. Prospective studies that will be conducted in the future may be more helpful in evaluating the relationship of thyroid functions with the clinical outcomes in patients with sepsis.

Author Contributions: Concept/Design : EY; Data acquisition: EY; Data analysis and interpretation: CY, MK; Drafting manuscript: EC; Critical revision of manuscript: IOT; Final approval and accountability: EY, CY, MK, IOT; Technical or material support: EY, MK; Supervision: IOT; Securing funding (if available): n/a.
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Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
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