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# EUTHYROID SICK SYNDROME: PREVALENCE AND PROGNOSIS IN ELDERLY PATIENTS WITH SEPSIS

## ÖTİROİD HASTA SENDROMU: SEPSİSLİ YAŞLI HASTALARDA SIKLIĞI VE PROGNOZU

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### ABSTRACT

**Objective:** Euthyroid sick syndrome (ESS) manifests by the decreased level of serum free thyroid hormones and with the normal or decreased secretion of thyroid-stimulating hormone. The study aims to identify the prevalence of ESS in elderly patients with sepsis and evaluate its possible effect on prognosis and mortality.

**Material and Methods:** Two hundred and three patients diagnosed with sepsis were prospectively evaluated. They were divided into two groups, a geriatric group (≥65 years), and a control group (<65 years). Patients with low free T3 (fT3) and/or free T4 (fT4) were considered to have euthyroid-sick syndrome. The demographic characteristics, comorbidities, laboratory results, hospitalization data, intensive care unit (ICU) duration, treatment outcomes, and mortality rates of the patients were recorded and compared.

**Results:** The incidence of ESS was significantly higher in the geriatric group (88.5% vs. 77.8%) (p=0.04). There was no difference between the groups in regard to mortality rate and ICU stay. However, 91.3% of deceased patients in the entire group and all deceased patients in the geriatric group were ESS (+) patients. The mean fT3 was significantly decreased in the deceased patients, and ICU patients (p=0.017). Additionally, the decreased levels of fT4 in both the entire group and the geriatric group were significantly associated with mortality and ICU stay (p-value: 0.020 and 0.019, respectively).

### ÖZET

**Amaç:** Ötiroid hasta sendromu (ÖHS), serum serbest tiroid hormonlarının azalması ve tiroid stimülan hormonun normal veya azalmış sekresyonu ile kendini gösterir. Bu çalışmada, sepsisli yaşlı hastalarda ÖHS prevalansının belirlenmesi ve prognoz ve mortalite üzerindeki olası etkisinin değerlendirilmesi amaçlandı.

**Gereç ve Yöntem:** Sepsis tanısı alan 203 hasta prospektif olarak değerlendirildi. Hastalar geriatrik grup (≥65 yaş) ve kontrol grubu (<65 yaş) olarak iki gruba ayrıldı. Serbest T3 (sT3) ve/veya serbest T4 (sT4)'ü düşük olan hastalar ötiroid hasta sendromu olduğu kabul edildi. Hastaların demografik özellikleri, komorbiditeleri, laboratuvar sonuçları, hastaneye yatış verileri, yoğun bakım ünitesi (YBÜ) ihtiyacı ve kalış süreleri, tedavi sonuçları ve mortalite oranları kaydedildi ve karşılaştırıldı.

**Bulgular:** Geriatrik grupta ÖHS insidansı anlamlı olarak daha yüksekti (%88,5 vs %77,8) (p=0,04). Gruplar arasında mortalite ve YBÜ ihtiyaçları açısından anlamlı fark saptanmadı. Bununla birlikte, tüm hastalarda ölen hastaların oranı %91,3 ve geriatrik gruptaki ölen hastaların ise tamamı ÖHS (+) hastalardı. Ölen hastalarda ve YBÜ hastalarında ortalama sT3 düzeyleri anlamlı olarak azalmıştı (p=0,017). Ek olarak, hem tüm grupta hem de geriatrik grupta azalmış sT4 seviyeleri mortalite ve yoğun bakım ihtiyaçları ile anlamlı olarak ilişkiliydi (p-değeri: sırasıyla 0,020 ve 0,019).

**Sonuç:** Sepsisli yaşlı hastalarda ÖHS prevalansının (%88,5) daha yüksek olduğu açıkça gösterilmiştir. Ek olarak, ÖHS (+) grubunda

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**Conclusions:** The higher prevalence of ESS (88.5%) in elderly patients with sepsis was clearly demonstrated. Additionally, approximately two-fold higher mortality and ICU stay risk was documented in the ESS (+) group. Thus, simply screening of ESS in septic elderly patients will certainly contribute to treatment decisions and early prediction of complicated clinical course and poor prognosis.

**Keywords:** Sepsis, euthyroid sick syndrome, thyroid hormones

yaklaşık iki kat daha yüksek mortalite ve YBÜ kalış riski belgelenmiştir. Bu nedenle, sepsisi olan yaşlı hastalarda ÖHS'nin basitçe taranması, tedavi kararlarına ve karmaşık klinik seyrin erken tahminine ve kötü prognozun belirlenmesine kesinlikle katkıda bulunacaktır.

**Anahtar Kelimeler:** Sepsis, ötiroid hasta sendromu, tiroid hormonları

## INTRODUCTION

Sepsis is defined as a life-threatening acute organ dysfunction, secondary to infection. Sepsis is the result of an uncontrolled systemic inflammatory response which leads to high morbidity and mortality. Over than 19 million people are estimated to have developed sepsis, which is responsible for over 6 million deaths annually worldwide (1). While more than half of sepsis cases are documented in the elderly population due to the numerous risk factors such as comorbidities, the incidence of sepsis-related mortality dramatically increases with advanced age (2). There are several scoring systems to predict mortality in patients with sepsis. Currently, quick Sequential Organ Failure Assessment (SOFA) is the most commonly used scoring system for organ dysfunction (3).

Additionally, metabolic changes and hormonal alterations may occur during sepsis. Thyroid hormones are often more affected in this process. Euthyroid sick syndrome (ESS), also known as nonthyroidal illness syndrome (NTIS), manifests by the decreased levels of serum thyroid hormones [T3, free T3, and/or thyroxine (T4)], normal or decreased secretion of thyroid-stimulating hormone (TSH) with higher reverse T3 levels, and normal thyroid hormone function (4).

The prevalence of ESS has been documented as a prognostic risk factor particularly in patients with severe/critical diseases. ESS is also associated with prolonged ICU stay, end stage organ dysfunction, poor prognosis and mortality (5). The prevalence of ESS is significantly higher in geriatric patients particularly with comorbid chronic diseases or malignancies (6). However, the predictive value of thyroid hormone levels as a prognostic marker has yet been debated to date. Furthermore, the number of published data evaluating ESS in elderly patients with sepsis is limited. This study aims to identify the prevalence of ESS in elderly patients with sepsis and evaluate the possible effect on prognosis and mortality.

## MATERIALS AND METHODS

The present study was performed between March 2014 and February 2015 in the Department of Internal Medicine in Istanbul Faculty of Medicine with the approval of Clinical Research Ethics Committee (Date 21.06.2013, No: 12). Two hundred and three patients diagnosed with sepsis, according to the Surviving Sepsis Campaign Guidelines 2012 criteria, were prospectively evaluated. Written informed consent was obtained from the patients in the study. Patients with malignancies, chronic kidney failure, congestive heart failure, or thyroid dysfunction and patients using drugs that may affect thyroid hormone levels were excluded from the study. Patients were divided into two groups, the geriatric group age over 65 years and the control group aged between 18 to 65 years. The quick Sequential Organ Failure Assessment (qSOFA) scoring system was utilized in the evaluation of organ dysfunction. Patients with low free T3 and/or free T4 were considered to have ESS.

In addition, the demographic characteristics, detailed anamnesis, presence of comorbidities, physical examination findings, laboratory findings, hospitalization data, intensive care unit (ICU) stay, ICU duration, treatment follow-up outcomes, and mortality rate were recorded and compared.

The blood cell count analysis was performed from peripheral blood samples. Hematological parameters were analyzed using a hematology analyzer (Cell-Dyne 3700, Abbott, Abbott Park, IL, USA). Biochemical analysis was performed from serum samples by an electro-chemiluminescence immunoassay analyzer (Beckman Coulter Unicel DXI 800, Brea, CA, USA). The analysis of serum hormone levels was performed using an immunodiagnostic system (Siemens, Advia Centaur xp, Germany).

### Statistical analysis

Data were analyzed with SPSS for Windows (v21.0; IBM, Armonk, NY, USA) and presented with descriptive statistics. The normality of data distribution was identified with the Kolmogorov-Smirnov test. A comparison of the variables with normal distribution was made with a Student t test. Mann Whitney and Kruskal Wallis tests were used to compare non-normally distributed variables. The categorical variables were assessed using the Chi-Square test. The presence of correlation was analyzed

with Spearman's Rho or Pearson tests. Multivariable analysis was performed by logistic regression method. P-Values of <0.05 were considered statistically significant.

## RESULTS

Two hundred and three patients with sepsis were included in the study, and of these, 93 were female (45.8%). The mean age was 63.49±18.03 years (ranged=18-94 years) in our sample group. Of the patients, 122 (60.1%) were in the geriatric group and 81 (39.9%) were in the control group. The most common infection source was pneumonia with a rate of 61.6% (n=125) in both groups (geriatric 68% vs. control 51.9%) and followed by urosepsis (12.8%, n=26), cholangitis (4.4%, n=9), necrotic pancreatitis (3%, n=6), empyema (2%, n=4), febrile neutropenia (2%, n=4), cellulite (2%, n=4), abscess (2%, n=4), and pyelonephritis (1.5%, n=3).

The comparison of the clinical and laboratory characteristics of the study participants is presented in Table 1. The mean values of neutrophile, hemoglobin, hematocrit, fasting blood glucose (FBG), and blood urea nitrogen (BUN) were found statistically higher in the geriatric group compared to the control group. Similarly, the mean values of TSH and erythrocyte sedimentation rate (ESR) were significantly lower in the geriatric group than the control group. Additionally, no statistically significant difference was observed regarding fever, respiratory rate

**Table 1:** Comparison of the baseline clinical and laboratory characteristics of the groups

| | Control group | Geriatric group | p-value* |
|---|---|---|---|
| **Body temperature (°C)** | 38.31±0.90 | 38.37±1.03 | 0.219 |
| **Respiratory rate** | 24.74±3.95 | 25.40±4.29 | 0.200 |
| **Heart rate** | 111.27±14.57 | 108.30±12.50 | 0.092 |
| **FB Glucose (mg/dL)** | 122.50±54.74 | 146.27±75.27 | **0.017*** |
| **Hemoglobin (g/L)** | 9.71±2.58 | 10.34±2.15 | **0.017*** |
| **Hematocrit (%)** | 29.34±2.58 | 31.56±6.64 | **0.029*** |
| **Platelet (x10$^9$/L )** | 207.6±190.0 | 222.9±121.2 | 0.051 |
| **WBC (10$^6$/uL)** | 12.80±12.89 | 13.81±7.14 | 0.082 |
| **Neutrophile (x10$^9$/L )** | 10.53±11.61 | 11.55±6.91 | **0.044*** |
| **Lymphocyte (x10$^9$/L )** | 1.208±1.272 | 1.319±1.501 | 0.117 |
| **BUN (mg/dL)** | 28.06±24.56 | 34.86±25.81 | **0.003*** |
| **Creatinine (mg/dL)** | 1.98±2.09 | 1.75±1.51 | 0.194 |
| **AST (U/L)** | 39.37±73.21 | 39.05±69.56 | 0.095 |
| **ALT (U/L)** | 36.13±86.63 | 35.82±80.91 | 0.657 |
| **GGT (IU/L)** | 84.08±90.69 | 82.88±119.5 | 0.117 |
| **ALP (IU/L)** | 140.59±137.8 | 125.2±119.5 | 0.121 |
| **CRP (mg/dl)** | 244.2±141.1 | 208.5±127.8 | 0.094 |
| **Procalcitonin (ng/mL)** | 13.07±31.39 | 9.10±18.56 | 0.522 |
| **ESR (mm/h)** | 88.81±34.05 | 73.63±34.04 | **0.002*** |
| **Albumin (g/dL )** | 2.94±0.67 | 3.01±0.58 | 0.388 |
| **Total bilirubin (mg/L)** | 1.79±4.61 | 1.23±3.59 | 0.523 |
| **Direct bilirubin (mg/L)** | 2.02±7.72 | 0.81±2.70 | 0.666 |
| **TSH (uIU/mL)** | 1.90±1.52 | 1.51±1.74 | **0.005*** |
| **fT4 (ng/dL)** | 15.01±4.31 | 14.53±4.14 | 0.432 |
| **fT3 (ng/dL)** | 2.38±0.98 | 2.28±0.79 | 0.449 |

*: p<0.05 statistically significant, FB: Fasting blood, WBC: White blood cell, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, TSH: Thyroid-stimulating hormone, fT4: Free thyroxin, fT3: Free triiodotyronine

(min.), heart rate, leukocyte, lymphocyte, platelet count, creatinine, liver function test aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total/direct bilirubin levels, C-reactive protein (CRP), and procalcitonin (PCT) as well as fT3 and fT4 levels between the groups (Table 1).

The rate of septic shock development was more frequent in geriatric patients in comparison to the control group (32.1% vs. 17.2% p=0.014). ESS developed in a total of 171 (84.2%) patients, 108 of which (88.5%) were in the geriatric group and 63 (77.8%) were in the control group. The incidence of ESS was significantly higher in geriatric group (p=0.04) than controls. There was no statistically significant difference between the control and geriatric groups in terms of mortality (12.3% vs. 10.7%) and ICU stay (24.7% vs. 18.0%) (p=0.435). There was also no statistically significant difference between the groups regarding qSOFA score (p=0.310) (Figure 1) (Table 2). The rate of septic shock was significantly higher (33.8% vs. 18.1%) in patients who developed mortality (p=0.013). Age and gender did not differ with mortality (p=0.180 and p=0.331, respectively).

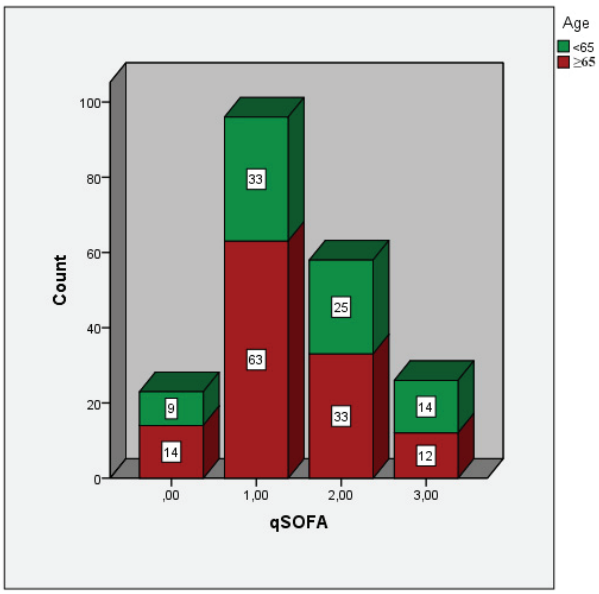


**Figure 1:** Distribution of the qSOFA score between the groups

**Table 2:** Comparison of the clinical characteristics between the groups

| | Control group n (%) | Geriatric group n (%) | p-value |
|---|---|---|---|
| **Septic shock** | 26 (32.1%) | 21 (17.2%) | **0.014*** |
| **ICU** | 20 (24.7%) | 22 (18.0%) | 0.251 |
| **Mortality** | 10 (12.3%) | 13 (10.7%) | 0.435 |
| **ESS** | 63 (77.8%) | 108 (88.5%) | **0.004*** |
| **qSOFA score** | | | |
| **0** | 9 (11.1%) | 14 (11.5%) | |
| **1** | 33 (40.7%) | 63 (51.6%) | 0.310 |
| **2** | 25 (30.9%) | 33 (27.0%) | |
| **3** | 14 (17.3%) | 12 (9.8%) | |

*: p<0.05 statistically significant, ICU: Intensive Care Unit, ICU: Intensive Care Unit, ESS: Euthyroid Sick Syndrome, qSOFA: quick Sequential Organ Failure Assessment

In the present study, the mean creatinine and blood urea nitrogen (BUN) values were significantly higher in ESS (+) group than the mean values in ESS (-) group (p=0.010 and p=0.011, respectively). In addition, the mean albumin, fT3, and fT4 values were significantly lower in ESS (+) group than the mean values in the ESS (-) group (p<0.001, p<0.000 and p<0.000, respectively) (Table 3). There was no statistically significant difference according to the septic shock rates, mortality, malignancy, ICU stay, gender, and qSOFA score between the ESS (+) and (-) groups (Table 4). There was also no statistically significant difference according to the mortality (p=0.187), ICU stay (p=0.172), gender (p=0.302), and qSOFA score (p=0.132) between the ESS (+) and (-) groups within only the elderly patients. Both 91.3% of all patients (n=23/21) who died in the entire sample group and all patients (n=13) who died in the geriatric group (≥65 years) were ESS (+) patients. The mean fT3 levels were significantly decreased in non-survived and ICU patients (2.42 vs. 2.11 ng/dL) (p=0.017) (Figure 2). Additionally, decreased levels of fT4 in both the entire group (15.19 vs. 13.72 ng/dL) and the geriatric group (15.09 vs. 13.15 ng/dL) were significantly associated with mortality and ICU stay (p=0.020 and p=0.019, respectively) (Figure 3). TSH levels were not significantly associated with mortality or ICU stay (p=0.255). In addition, the increased levels of procalcitonin in both the entire group (8.93 vs. 24.41 ng/mL) and the geriatric group (7.04 vs. 26.31 ng/mL) were significantly associated with mortality (p<0.001 and p=0.006, respectively). In addition, the increased levels of PCT were significantly associated with mortality in ESS (+) patients both in the control group (8.56 vs. 28.69 ng/mL) and geriatric group (12.48 vs. 16.50 ng/mL) (p=0.001 and p=0.01, respectively).

In multivariable analysis, higher qSOFA scores (B:3.08, p<0.001, odds ratio [OR]: 21.8, 95% confidence interval [CI]: 9-52), higher PCT levels (B: 0.03, p=0.004, OR: 1.03, 95 % CI: 1.01-1.06), the presence of hypotension (B: 3.4, p<0.001, OR: 30.8, 95% CI: 6.6-143) in entire group, higher qSOFA scores (B:2.04, p<0.001, OR: 7.7, 95% CI: 3.5-17), and lower fT4 levels (B:-0.13, p=0.034, OR: 0.87, 95% CI: 0.77-0.99) were independently associated with mortality in patients with geriatric population.

**Table 3:** Comparison of the baseline clinical and laboratory characteristics between euthyroid-sick syndrome (ESS) (-) and (+) groups

| | ESS (-) | ESS (+) | p-value* |
|---|---|---|---|
| **Age** | 59.25±19.89 | 64.28±17.61 | 0.185 |
| **Body temperature (°C)** | 38.37±1.08 | 38.34±0.96 | 0.360 |
| **Respiratory rate** | 25.28±3.83 | 25.11±4.23 | 0.914 |
| **Heart rate** | 109.46±12.18 | 109.49±13.66 | 0.817 |
| **FB glucose (mg/dL)** | 126.37±40.58 | 138.74±72.66 | 0.727 |
| **Hemoglobin (g/L)** | 10.67±3.20 | 9.98±2.14 | 0.378 |
| **Hematocrit (%)** | 32.58±9.37 | 30.31±6.58 | 0.199 |
| **Platelet (x10$^9$/L )** | 193.9±124.9 | 221.0±156.7 | 0.564 |
| **WBC (10$^6$/uL)** | 13.21±11.40 | 13.45±9.54 | 0.675 |
| **Neutrophile (x10$^9$/L )** | 10.56±9.735 | 11.25±8.970 | 0.538 |
| **Lymphocyte (x10$^9$/L )** | 1.248±0.924 | 1.280±1.488 | 0.826 |
| **BUN (mg/dL)** | 23.65±20.82 | 33.74±26.00 | **0.011*** |
| **Creatinine (mg/dL)** | 1.29±1.35 | 1.95±1.81 | **0.010*** |
| **AST (U/L)** | 31.37±37.83 | 40.64±75.44 | 0.747 |
| **ALT (U/L)** | 30.40±35.84 | 36.98±89.16 | 0.883 |
| **GGT (IU/L)** | 83.31±122.1 | 83.37±106.4 | 0.868 |
| **ALP (IU/L)** | 115.2±76.57 | 134.40±134.3 | 0.933 |
| **CRP (mg/dl)** | 199.0±117.8 | 227.2±136.7 | 0.315 |
| **Procalcitonin (ng/mL)** | 7.74±13.2 | 11.23±26.0 | 0.324 |
| **ESR (mm/h)** | 71.43±39.60 | 81.23±33.69 | 0.260 |
| **Albumin (g/dL )** | 3.32±0.68 | 2.92±0.58 | **0.001*** |
| **Total bilirubin (mg/L)** | 1.14±2.04 | 1.51±4.30 | 0.612 |
| **Direct bilirubin (mg/L)** | 0.78±1.82 | 1.39±5.75 | 0.283 |
| **TSH (uIU/mL)** | 1.28±1.09 | 1.73±1.74 | 0.300 |
| **fT4 (ng/dL)** | 18.12±3.47 | 14.08±4.03 | **<0.001** |
| **fT3 (ng/dL)** | 3.59±0.56 | 2.08±0.70 | **<0.001** |

*: p<0.05 statistically significant, FB: Fasting blood, WBC: White blood cell, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, TSH: Thyroid-stimulating hormone, fT4: Free thyroxin, fT3: Free triiodotyronine

**Table 4:** Comparison of the clinical characteristics between euthyroid-sick syndrome (ESS) groups

| | ESS (-) n (%) | ESS (+) n (%) | p-value |
|---|---|---|---|
| **Age** | | | |
| **<65 years** | 18 (56.3%) | 63 (36.8%) | **0.004*** |
| **≥65 years** | 14 (43.8%) | 108 (63.2%) | |
| **Septic shock** | 6 (18.8%) | 41 (24.0%) | 0.520 |
| **ICU** | 4 (12.5%) | 38 (22.2%) | 0.188 |
| **Mortality** | 2 (6.3%) | 21 (12.3%) | 0.214 |
| **Gender** | | | |
| **Female** | 17 (53.1%) | 76 (44.4%) | 0.366 |
| **Male** | 15 (46.9%) | 95 (55.65) | |
| **qSOFA Score** | | | |
| **0** | 5 (15.6%) | 18 (10.55) | |
| **1** | 17 (53.1%) | 79 (46.2%) | 0.520 |
| **2** | 6 (18.8%) | 52 (30.4%) | |
| **3** | 4 (12.5%) | 22 (12.9%) | |

*: p<0.05 statistically significant, ICU: Intensive Care Unit, ICU: Intensive Care Unit, ESS: Euthyroid Sick Syndrome, qSOFA: quick Sequential Organ Failure Assessment

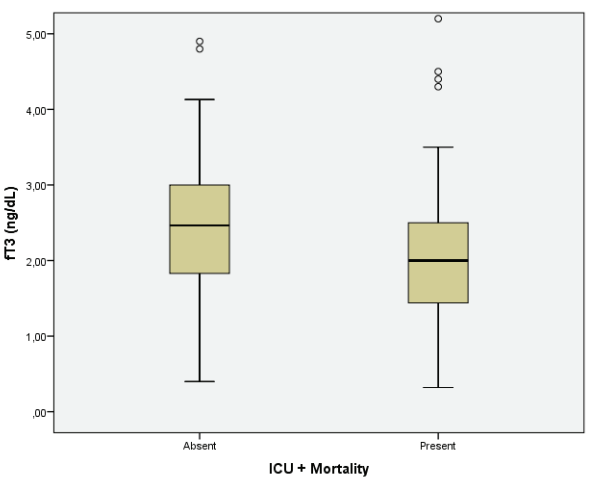


**Figure 2:** Alteration of the mean fT3 levels in accordance with mortality and ICU stay

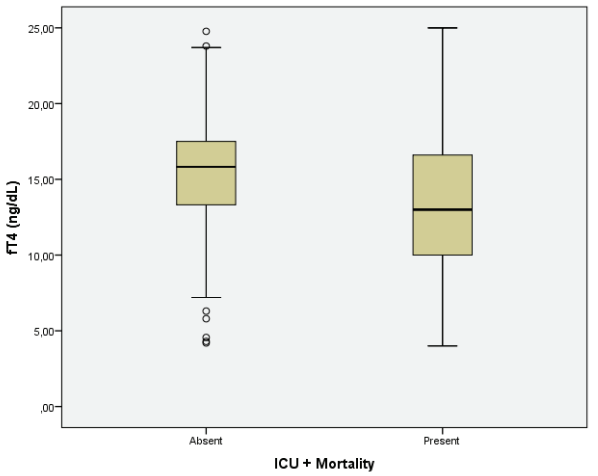


**Figure 3:** Alteration of the mean fT4 levels in accordance with mortality and ICU stay

## DISCUSSION

In our study, the incidence of ESS was significantly higher in the geriatric group, but there was no statistically significant difference between the control and geriatric groups in terms of mortality and ICU stay. Mean fT3 levels, decreased levels of fT4, and increased levels of PCT were significantly associated with mortality and ICU stay. Elderly patients are known to be more prone to develop sepsis than the younger population due to several risk factors, such as comorbidities, invasive interventions, malnutrition, and immune system disorders. Moreover, sepsis typically occurs with more severe clinical course and potentially increased mortality risk in older patients (7). Respiratory tract infections are documented to be the most common origins of sepsis in the published data (8). Cheng et al. reported respiratory tract infections as the most common source of sepsis in their both sample groups (35.5% and 55.0%, respectively) which involves elderly (n=4414) and non-elderly (n=2673) patients (9). Supporting this, the most frequent infection source was pneumonia, with a rate of 61.6% in both groups (geriatric 68% vs. control 51.9%), in the present study.

It has been documented that blood glucose levels increase even in non-diabetic patients diagnosed with sepsis. Furthermore, blood glucose levels and glucose variability were significantly associated with sepsis severity (10). Sim et al. reported significantly increased glucose levels in highly elderly ICU patients and increased glucose levels associated with higher mortality rate (11). Researchers noted that high glucose levels have a predictive value for mortality in elderly patients (11). In addition, increased platelet, neutrophile, and BUN levels have been associated with poor prognosis and mortality in elderly patients with sepsis and septic shock in various studies (12, 13). Arihan et al. reported higher baseline mean BUN levels in older patients (70±12 years vs 62±14 years), and the researchers associated higher BUN levels with multi-organ failure and long-term mortality in their study, which included 4176 critically ill patients involved 544 sepsis patients (13). Consistent with this, the mean neutrophile, fasting blood glucose, and BUN values were found statistically higher in the geriatric group than the mean values in the control group in our study.

Euthyroid sick syndrome prevalence has been reported to have increased by aging particularly in critically ill elderly patients. Moreover, ESS has been associated with poor prognosis, the development of complications, severity of disease, and mortality in older subjects, particularly in critically ill geriatric patients (14). Poliniet al. reported an ESS prevalence of 31.9% in 808 critically ill geriatric patients. Researchers also stated ESS as a significant independent risk factor for mortality ($p<0.0001$) (6). Similarly, Zhu et al. reported a 37.3% ESS prevalence in 83 patients aged over 60 years, and researchers concluded that the prevalence of ESS increases with aging (15). Furthermore, it has been documented that the increase of ESS prevalence through sepsis ranges between 60% to 70% in the published data. Padhi et al. reported an ESS prevalence of 67% in 360 ICU patients with sepsis (16). Similarly, Neamtu et al. reported a 63% ESS prevalence in 65 children with sepsis (17). Supporting this in our study, the total ESS prevalence was 84.2%, 108 of which (88.5%) were in the geriatric group and 63 (77.8%) were in the control group. The incidence of ESS was significantly higher in the geriatric group, but there was also no statistically significant difference according to the mortality, ICU stay, gender, and qSOFA score between the ESS (+) and (-) groups within only the elderly patients.

Despite the prognostic value of ESS being well-documented in the published data, there is a limited amount of data with controversial results which evaluated ESS in sepsis-patients. Moreover, to our knowledge, there is no study available in the published data which evaluated ESS in elderly patients diagnosed only with sepsis. Ergan et al. significantly associated ESS with increased non-invasive ventilation failure rate ($p=0.04$) and mortality ($p=0.02$) in a study conducted with 44 elderly patients (≥65 years) with chronic obstructive pulmonary disease (18). In the present study, qSOFA scores, the presence of hypotension, and PCT levels were all significantly associated with mortality in both entire group and geriatric population. Similarly, these variables are also shown as important predictors of mortality in patients with septic shock in published data (5).

While the decreased level of thyroid hormones reported to have a predictive value for poor prognosis and

mortality in patients with sepsis or septic shock in some studies, other studies have not associated lower thyroid hormones with poor prognosis (19). Padhi et al. reported the overall mortality of 30%; non-ESS patients was reported as 13.4%, group ESS with low total T3 was 50.1%, and group ESS with low T3 with low thyroxine (T4) was 69.1% (p<0.001) in their study included 360 ICU patients with sepsis. Researchers concluded that low T3 and free T3 levels are significant prognostic factors for mortality (16). Brinker et al. documented ESS in 69 children with meningococcal sepsis. They reported that the TT3/rT3 ratio decreased with no increase in TSH level, and TT4 levels were negatively correlated with the severity of the disease. Researchers also concluded that both the TT3/rT3 ratio and TT4 levels had a predictive value for mortality (20). Similarly, Hagag et al. documented significantly lower free TT3 and free TT4 in 40 neonates with neonatal sepsis (21). In the present study, the increased prevalence of mortality (6.3% vs. 12.3%) and ICU stay (12.5% vs. 22.2%) was not found statistically significant between the ESS (+) and (-) groups. There was also no statistically significant difference found according to the mortality, ICU stay, and qSOFA score between the ESS (+) and (-) groups within only elderly patients. However, it is noteworthy that both 91.3% of all patients (n=23/21) who died in the entire sample group and all patients (n: 13) who died in the geriatric group were ESS (+) patients. Moreover, mean fT3 levels were significantly decreased in deceased and ICU patients (2.42 vs. 2.11 ng/dL) in the entire group. Additionally, the decreased fT4 levels in both the entire group (15.19 vs. 13.72 ng/dL) and the geriatric group (15.09 vs. 13.15 ng/dL) were independently associated with mortality and ICU stay.

The mean creatinine and BUN values were significantly higher in ESS (+) group. In addition, the mean values of albumin, fT3, and fT4 were significantly lower in ESS (+) group than the mean values in ESS (-) group in our sample group. Furthermore, higher levels of procalcitonin, increasing levels of which have been well-documented as a prognostic factor for mortality, in both the entire group (8.93 vs. 24.41 ng/mL) and the geriatric group (7.04 vs. 26.31 ng/mL) were significantly associated with mortality. In addition, increased levels of PCT were also significantly associated with mortality in ESS (+) patients both in the control group (8.56 vs. 28.69 ng/mL) and geriatric group (12.48 vs. 16.50 ng/mL). On the other hand, Arnau-Barrés et al. significantly associated lower albumin levels with mortality (Survivors:3.1 vs. Non-survivors:2.6 g/dl) (p<0.0001) in 235 patients diagnosed with sepsis or septic shock with a median age of 75 years. Researchers highlighted lower albumin levels (<2.6 g/dL) as a prognostic factor for mortality in elderly patients (22). In another study, Guo et al. evaluated the clinical characteristics of euthyroid sick syndrome in their sample group (n=305), which involved 118 (38.7%) ESS patients. Researchers reported that the albumin level was significantly lower in the ESS group than the levels in the non-ESS group (26.63±6.51 vs 30.13±7.13 g/L) (p<0.001). Additionally, the creatinine level was significantly higher in the ESS group than the creatinine level in the non-ESS group (120.3±165.8 vs 80.6±85.8 umol/L) (p=0.007).

There are a few limitations in our study. Since we included patients from different clinics in our hospital, the initial evaluation and the physical examination were performed by different clinicians, and this might have led to heterogenous results; however, we used a predefined protocol to minimize these disadvantages and missing data. Caution is needed when interpreting the final results because of the different groups of patients included in our study.

In conclusion, significantly higher ESS prevalence (88.5%) was clearly demonstrated in elderly patients diagnosed with sepsis in the present study. Additionally, approximately a two-fold higher mortality (6.3% vs. 12.3%) and ICU administration (12.5% vs. 22.2%) risk was documented in the ESS (+) group. Moreover, well-documented prognostic markers such as increased BUN, creatinine levels, and decreased albumin, fT3, fT4 levels were found in the ESS (+) group. Thus, simply screening for ESS in elderly patients with sepsis certainly will contribute to treatment decisions and early prediction of complex clinical course, poor prognosis, and mortality.

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