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Does Euthyroid Sick Syndrome Have an Effect on the Outcome of Critically Ill Coronavirus Disease 2019 Patients?

ABSTRACT

Objective: Euthyroid sick syndrome (ESS) can be used as an outcome predictor in critically ill patients. Especially, plasma triiodothyronine is considered to have prognostic effects on intensive care unit (ICU) outcomes. In this study, we attempted to evaluate ESS existence and its effects on critically ill coronavirus disease 2019 (COVID-19) patients' mortality.

Methods: All patients who were admitted to the ICU with a diagnosis of COVID-19 between March 15, 2020, and June 1, 2021, were screened. Patients were grouped according to their thyroid hormone levels for ESS, and these groups were compared for their ICU outcomes.

Results: Ninety-one patients met the inclusion criteria with a median age of 68 [57-77] years, and 64 (70%) of them were male. The difference was not found between the groups according to acute physiology and chronic health evaluation II and sequential organ failure assessment scores ($P = .792$ and $P = .940$, respectively). The median admission PaO_2/FiO_2 ratio was 115 [82-187], and groups were similar according to PaO_2/FiO_2 ratio ($P = .827$). Totally 32 (35%) patients died in the ICU. In patients with ESS, 20 (35%) patients died, and in patients without ESS, 12 (35%) patients died. Mortality was not different between the 2 groups ($P = .98$). Moreover, in Kaplan–Meier's analyses, mortality was also similar ($P = .838$).

Conclusion: Patients' characteristics and mortality rates were found to be similar in critically ill COVID-19 patients with and without ESS in our study. In this respect, we could not reveal a relationship between ESS and increased mortality in critically ill COVID-19 patients.

Keywords: Intensive care unit, mortality, free triiodothyronine

Introduction

Coronavirus disease 2019 (COVID-19), which develops due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is not currently a pandemic, and its virulence is decreasing, but it is still taking place in our lives and is a reason for admission to the intensive care unit (ICU) in individuals with comorbidities and risk factors. Patients with COVID-19 show various clinical characteristics, from mild flu-like symptoms to acute respiratory distress syndrome. In this regard, searching for disease severity and mortality risk factors becomes more critical.

Different studies revealed the correlation with thyroid hormone levels, disease severity, and mortality.[1-5] Particularly, it was reported that a decline in serum triiodothyronine (T3) levels is inherent in higher mortality rates in patients with comorbidities like cardiac diseases, septic patients, and patients with chronic organ failure.[1,5-7] Variations in thyroid function tests are associated with an acute and critical illness, which was defined as euthyroid sick syndrome (ESS).[8] It is defined as a reduction of serum T3 levels as well as a reduction in serum thyroxine (T4) levels without an escalation in thyroid-stimulating hormone (TSH) levels, which is disclosed to be linked to the suppression of peripheral T4 deiodination. Euthyroid sick syndrome can be used as an outcome predictor in critically ill patients. In particular, serum T3 is considered to have a prognostic effect on ICU mortality.[1,9,10] Moreover, a lower than 2.7 pmol/L cutoff for free T3 (fT3) was proposed to be associated with an unfavorable outcome and a high risk of death in hospitalized SARS-CoV-2 patients.[11]

In our study, the primary aim was to assess the existence of ESS and its effects on the outcome of critically ill COVID-19 patients. The secondary purpose was to evaluate the link between thyroid hormone levels and ICU mortality.

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Materials and Methods

This retrospective observational study was conducted at a tertiary university hospital pandemic ICU. Approval from the Ankara University Research Ethics Committee was obtained (Decision no: 2022/460 and Date: August 31, 2022). Due to its retrospective design, informed consent was not obtained. The study was directed according to the Declaration of Helsinki.

All patients admitted to the ICU (designated as a pandemic ICU) between March 15, 2020, and June 1, 2021, were screened. We included adult patients (>18 years) with documented polymerase chain reaction (PCR)-positive COVID-19 infection and whose thyroid function tests were performed within the first 48 hours of ICU admission. Patients with underlying thyroid diseases (hypothyroidism or hyperthyroidism) with/without medication, pregnant patients, and patients with ICU length of stay (LOS) shorter than 24 hours were excluded from the study data.

Critically ill COVID-19 patients were specified as COVID-19-positive patients with respiratory failure with lower PaO_2/FiO_2 ratio and progressive lung lesions, which required high flow oxygen therapy and/or mechanical ventilation support, shock or other organ failure requiring intensive care therapy.

Acute physiology and chronic health evaluation (APACHE) II score is a general assessment of disease severity based on the first 24 hours of ICU admission, worst physiologic measurements, age, and comorbidities. Higher scores are associated with higher mortality risk. The sequential organ failure assessment score (SOFA score) is based on 6 different organ system evaluation parameters, including respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. It is usually used to describe organ dysfunctions.

Age, gender, comorbid diseases, admission APACHE II and SOFA scores, invasive mechanical ventilation (IMV) requirement, administration of steroids, and immune modulatory treatments were recorded from medical records. Admission levels of TSH and serum T3 and T4 levels were recorded. The hospital LOS and ICU were recorded. We defined ESS as a reduction in the T3 level or fT3, a rise in thyroid hormone reverse T3 levels, and normal or decreased levels of T4/free T4 (fT4) and TSH.[8]

MAIN POINTS

- Euthyroid sick syndrome (ESS) existence can affect the outcome of critically ill coronavirus disease 2019 (COVID-19) patients.
- Although we found the incidence of ESS (62.6%) higher than the studies reported in the literature, we could not find a difference regarding mortality between groups.
- Current studies on COVID-19 patients with ESS demonstrated higher mortality rates than those without ESS, in contrast with our study findings.
- We did not observe differences in invasive mechanical ventilation, renal replacement therapy requirement, and medical therapies (need of immunosuppressive agents, steroids) in patients with or without ESS.
- These findings prompted us to consider whether racial differences influence the severity of the COVID-19 disease according to the state of ESS.

Serum TSH, fT3, and fT4 levels were assessed using a direct chemiluminescence immunoassay (Siemens, ADVIA Centaur XP Immunoassay system®, Tarrytown, NY, USA). Normal ranges in our laboratory for TSH, fT3, and fT4 are 0.38-5.33 mIU/mL, 3.99-6.71 pmol/L, and 7-22 pmol/L, respectively.

Groups were settled according to their thyroid hormone levels as patients with or without ESS. Groups were compared in terms of ICU outcomes. Regarding the secondary aim, patients were split into groups of survivors and nonsurvivors and examined according to their serum-free T3, fT4, and TSH levels.

Statistical Analysis

Analyses of the research were performed with the "Statistical Package for the Social Sciences for Windows, version 22.0 (IBM Corp.; Armonk, NY, USA)." Descriptive statistics are summarized as counts and percentages for categorical variables, mean, and standard deviations for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous or ordinal variables. The difference between the 2 groups was evaluated using the Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Pearson chi-square test and Fisher's exact test were used to compare categorical variables. A *P*-value below .05 was considered to be statistically significant.

Results

Severe acute respiratory syndrome coronavirus 2 RT-PCR was positive in 210 of 254 patients who were admitted to the ICU in the course of the study period. Of these patients, 91 met the inclusion criteria. The flow diagram of the study is presented in Figure 1.

The demographic and laboratory data of the patients with and without ESS are shown in Table 1. The median age of all the patients was 68 [57-77] years, and 64 (70.3%) were male. The median age of patients with ESS was 64 [55-74] years, and those without ESS were 72 [61-78] years. Age and gender were similar between the groups ($P = .061$ and $P = .322$, respectively).

The median APACHE II score was 16 [11-22], and the median admission SOFA score was 3 [2-5]. There was no difference between the groups according to the APACHE II and SOFA scores ($P = .792$ and $P = .940$, respectively). The median admission PaO_2/FiO_2 ratio was 115.8 [82.7-187.7], and the groups were similar according to PaO_2/FiO_2 ratio ($P = .827$).

Hypertension was the most common comorbidity, with a rate of 53 (58.2%). Hypertension was present in 29 (50.8%) patients with ESS and in 24 (70.5%) patients without ESS. Hypertension was similar between the groups ($P = .065$).

Forty-seven (51.6%) of the patients required IMV. Twenty-nine (50.8%) patients with ESS and 18 (52.9%) patients without ESS needed IMV. The IMV requirement was similar in both groups ($P = .849$). Renal replacement therapy was performed in 15 (16.4%) patients. Groups were similar according to renal replacement therapy requirement ($P = .817$).

It was recorded that 76 (83.6%) patients were treated with steroids and 10 (10.9%) patients with anakinra. In patients with ESS, 49 (85.9%) patients were treated with steroids, and 4 (7%) patients with anakinra. In patients without ESS, 27 (79.4%) patients were treated

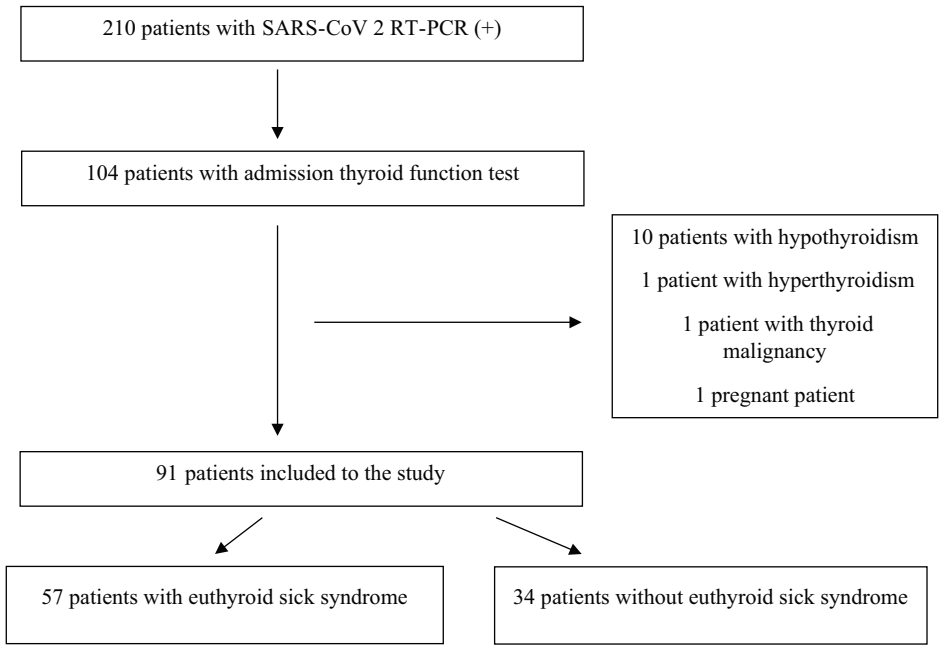

Figure 1. Flow diagram of the study. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction.

Table 1. Characteristics, Management, Thyroid Hormone Levels, and Outcome of Patients With and Without Euthyroid Sick Syndrome

	Total (n = 91)	With ESS (n = 57)	Without ESS (n = 34)	*P*
Age* (years)	68 [57-77]	64 [55-74]	72 [61-78]	.061
Male** (n, %)	64 (70.3)	38 (66.6)	26 (76.4)	.322
APACHE II score*	16 [11-22]	16 [11-24.5]	16 [13-20]	.792
SOFA score*	3 [2-5]	3 [2-5.5]	3 [2-4]	.940
PaO_2/FiO_2* ratio (%)	115.8 [82.7-187.7]	115.8 [83.8-191.2]	116.5 [68.6-157.2]	.827
Comorbidities**				
Hypertension (n, %)	53 (58.2)	29 (50.8)	24 (70.5)	.065
Diabetes mellitus (n, %)	35 (38.4)	23 (40.3)	12 (35.2)	.631
Coronary artery disease (n, %)	35 (38.4)	20 (35)	15 (44.1)	.392
Chronic obstructive pulmonary disease (n, %)	16 (17.5)	7 (12.2)	9 (26.4)	.085
Chronic heart failure (n, %)	13 (14.2)	9 (15.7)	4 (11.7)	.930
Malignancy (n, %)	10 (10.9)	9 (15.7)	1 (2.9)	.058
Immunosuppression (n,%)	10 (10.9)	7 (12.2)	3 (8.8)	.610
Chronic renal failure (n, %)	7 (7.6)	3 (5.2)	4 (11.7)	.260
Invasive mechanical ventilation** (n, %)	47 (51.6)	29 (50.8)	18 (52.9)	.849
Renal replacement therapy** (n, %)	15 (16.4)	9 (15.7)	6 (17.6)	.817
Steroid therapy** (n, %)	76 (83.5)	49 (85.9)	27 (79.4)	.415
IL-1 antagonist therapy** (n, %)	10 (10.9)	4 (7)	6 (17.6)	.115
fT3 (pmol/L)	2.90 [2.4-3.6]	2.54 [2.1-2.8]	3.65 [3.2-4.1]	< .001
fT4 (pmol/L)	15.30 [12.8-18.5]	16.30 [13.7-18.9]	13.34 [11.8-15.5]	.010
TSH (mIU/mL)	0.45 [0.23-0.96]	0.33 [0.11-0.79]	0.61 [0.34-1.10]	.012
Length of ICU stay* (days)	12 [7-25]	11 [5.5-21.5]	13 [7-26]	.607
Length of hospital stay* (days)	19 [11-30]	16 [10-29]	24.5 [13-35.5]	.343
ICU mortality** (n, %)	32 (35.1)	20 (35)	12 (35.2)	.984
Hospital mortality**(n, %)	40 (43.9)	23 (40.3)	17 (50)	.370

APACHE, acute physiology and chronic health evaluation score; ESS, euthyroid sick syndrome; FT3, free triiodothyronine; FT4, free thyroxine; ICU, intensive care unit; IL, interleukin; n, number; %, ratio; SOFA, sequential organ failure assessment score; TSH, thyroid-stimulating hormone.
*median [quartiles]. **n (%).

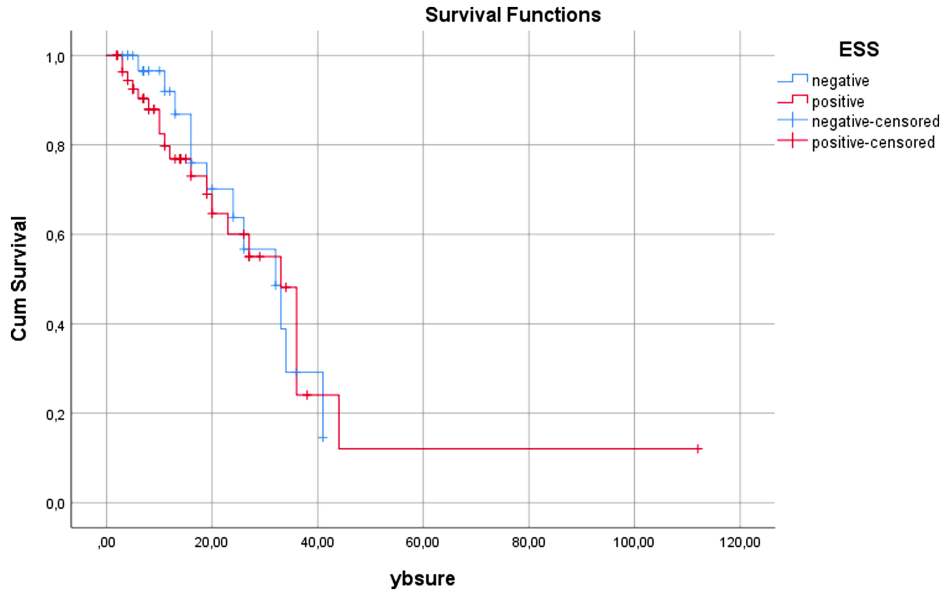

Figure 2. Kaplan–Meier graph of patients with or without euthyroid sick syndrome. ESS, euthyroid sick syndrome.

with steroids, and 6 (17.6%) patients with anakinra. Treatment practices were similar in all groups.

Median ICU LOS was 12 [7-25] days, and hospital LOS was 19 [11-30] days. The ICU and hospital stay lengths were similar in both groups ($P = .607$ and $P = .343$, respectively).

Totally 32 (35.1%) patients died in the ICU. In patients with ESS, 20 (35%) patients died, and in patients without ESS, 12 (35.2%) patients died. Mortality was similar between groups ($P = .984$). In Kaplan–Meier analyses, mortality was also similar ($P = .838$, Figure 2).

The groups were similar when patients were compared according to their fT3, fT4, and TSH levels as survivor and nonsurvivor ($P = .24$, $P = .30$, and $P = .24$, respectively) (Figure 3).

Discussion

This study revealed ESS incidence and whether ESS was a prognostic indicator of mortality in critically ill COVID-19 patients. We noted the incidence of ESS (62.6%) higher than the studies reported in the literature. Although the ESS incidence was higher than in the previous studies, we could not find a difference regarding mortality between groups.

Guo et al[7] noted 38.7% ESS incidence in ICU patients before the COVID-19 pandemic. Similarly, in a study from Poland, the frequency of ESS in hospitalized COVID-19 patients was reported as 38%.[3] On the other hand, Okoye et al[12] reported a 66.3% rate of ESS in geriatric COVID-19 patients. In our cohort, we evaluate the incidence of ESS at 62.6%. The first cohort included non-COVID ICU patients,

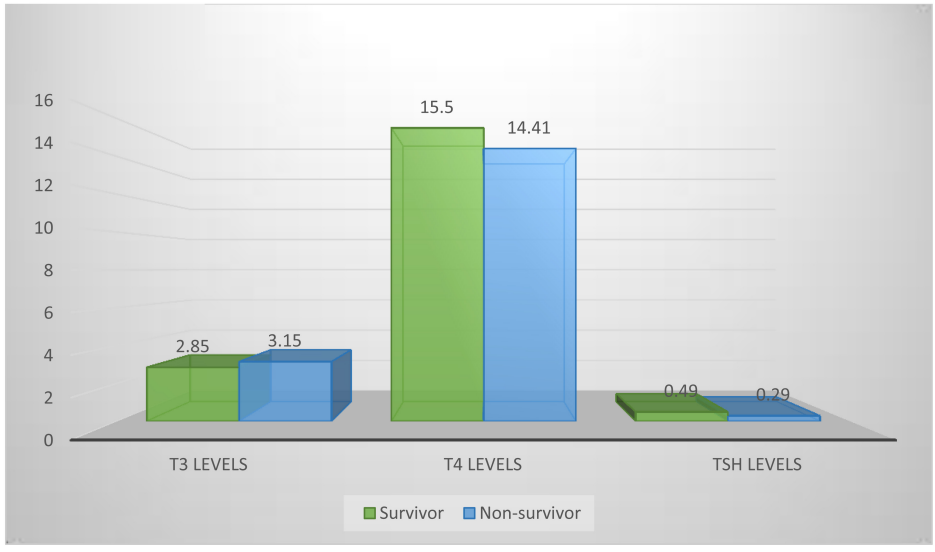

Figure 3. Serum free triiodothyronine, serum free thyroxine, and thyroid-stimulating hormone levels in survivors and nonsurvivors. T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

mostly with trauma and lower APACHE II scores, and the second one included all hospitalized COVID-19 patients; in contrast, our study consisted of only critically ill COVID-19 patients. The difference in ESS incidence might result from the special group of patients in our study population.

ESS has been extensively studied and accepted as a prognostic factor in critically ill patients.[13,14] Current studies on COVID-19 patients with ESS also demonstrated higher mortality rates than those without ESS. Świstek et al[3] reported a 34.1% vs. 11.3% mortality rate in COVID-19 patients with and without ESS, respectively. In another study, the mortality rate of this group of patients was recorded as 40%.[4] In contrast, there was no mortality difference between patients with and without ESS in our study.

Previous studies revealed that low levels of serum T3 were associated with increased mortality in critically ill patients.[2,4,10,15] In this respect, we evaluated patients in terms of FT3 levels, and the levels were similar between survivors and nonsurvivors.

After noticing the positive clinical effects of corticosteroids, we treated our patients with corticosteroids. In this regard, we compared patients with and without steroid treatment. We did not observe differences in ESS development or serum fT3 levels between patients with or without corticosteroid treatment. Gao et al[15] reported similar findings about the effects of steroid treatment on thyroid hormone levels.

To the best of our knowledge, there were no studies regarding the therapy of ESS due to COVID-19 infection. We did not observe differences in terms of IMV, renal replacement therapy requirement, and medical treatments (requirement of immunosuppressive agents, steroids) in patients with or without ESS.

There are also limitations in our study. We could not evaluate dynamic changes in thyroid function tests and thyroid antibodies because of being a retrospective study, and we did not assess all patients admitted to the ICU in the study period because of missing thyroid function tests. Although glucocorticoids can inhibit TSH secretion from the pituitary, we did not exclude the patients receiving steroid therapy because the 2 groups had similar treatment modalities, and most of the patient groups received steroid therapy (83.6%). Finally, some of our patients were treated with steroids before thyroid hormone sampling. Although there was no mortality difference between those treated with steroids or not, steroid treatment might change the results.

Our study found patients' characteristics and mortality rates similar in critically ill COVID-19 patients with and without ESS. In this respect, we could not reveal a relationship between ESS and increased mortality in critically ill COVID-19 patients.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara University, (Approval No: 200/460, Date: August 31,2022).

Informed Consent: Due to its retrospective design, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G.C., L.T.; Design – A.G.C., L.T.; Supervision – N.D.A.; Resources – O.N.; Materials – L.T.; Data Collection and/or Processing – O.N., L.T.; Analysis and/or Interpretation – A.G.C., O.N.; Literature Search – L.T., A.G.C.; Writing – L.T., A.G.C.; Critical Review – N.D.A.

Declaration of Interests: The authors have no conflict of interest to declare.

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