ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.58815
Nam Kem Med J 2024;12(1):17-26

Effect of Hypothalamic Adrenal Axis and Thyroid Function Alterations on Prognosis of Critically Ill COVID-19 Patients

Hipotalamik Adrenal Eksen ve Tiroid Fonksiyon Değişikliklerinin Kritik COVID-19 Hastalarının Prognozuna Etkisi

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ABSTRACT

Aim: The aim of this study was to evaluate the effect of changes in adrenal, and thyroid functions on the prognosis of Coronavirus disease-2019 (COVID-19) patients admitted to the intensive care unit (ICU).

Materials and Methods: This was a retrospective evaluation that included COVID-19 patients requiring ICU admission. Serum cortisol, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), free thyroxine (fT4) and triiodothyronine (fT3) levels were measured on admission and two more times during the hospitalization. Routine biochemistry, hemogram, C-reactive protein, procalcitonin, fibrinogen and D-dimer levels were also measured, along with hormones. All-cause mortality during ICU stay, inotropic drug and mechanical ventilation needs, and duration of hospitalization were recorded for each patient. Euthyroid sick syndrome (ESS) and hypocortisolism rates were determined. Deceased and surviving patients were compared in terms of hormone values, and logistic regression to determine independent associates of mortality was performed.

Results: Overall, 124 patients (58% male, mean age 70.7±11.3 years) were included. During the ICU stay, both fT3 and fT4, but not TSH, showed a statistically significant decrease compared to admission values. Serum cortisol and ACTH values increased compared to admission values, but this increase was not significant. ESS was present in 89.5% of the patients. Two-thirds of the patients died in ICU. Serum fT3 values were significantly lower among decedents compared to survivors. Hypocortisolism was detected in 20.1% of the patients. Only the fT3 level could independently and significantly predict all-cause mortality.

Conclusion: ESS was almost universal among critically ill COVID-19 patients. Serum fT3, but not other thyroid or adrenal hormones, could significantly predict all-cause mortality.

Keywords: Adrenal function, euthyroid sick syndrome, hypocortisolism, prognosis, thyroid function

ÖZ

Amaç: Bu çalışmanın amacı, yoğun bakım ünitesine (YBÜ) yatırılan Koronavirüs hastalığı-2019 (COVID-19) hastalarının adrenal ve tiroid fonksiyonlarındaki değişikliklerin prognoz üzerine etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışma YBÜ'ye kabul edilen COVID-19 hastalarını içeren retrospektif bir değerlendirmeydi. Serum kortizol, adrenokortikotropik hormon (ACTH), tiroid uyarıcı hormon (TSH), serbest tiroksin (sT4) ve triiyodotironin (sT3) düzeyleri ilk yatışta ve yatış sırasında iki kez daha ölçüldü. Hormonların yanı sıra rutin biyokimya, hemogram, C-reaktif protein, prokalsitonin, fibrinojen ve D-dimer seviyeleri de ölçüldü. Her hasta için YBÜ'de kalış süresi boyunca tüm nedenlere bağlı ölümler, inotropik ilaç ve mekanik ventilasyon ihtiyaçları ve hastanede kalış süreleri kaydedildi. Ötiroid hasta sendromu (ESS) ve hipokortizolizm oranlar belirlendi. Ölen ve yaşayan hastalar hormon değerleri açısından karşılaştırıldı ve mortalitenin bağımsız birlikteliklerini belirlemek için lojistik regresyon yapıldı.

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Received: 12.07.2023 **Accepted**: 07.01.2024

Bulgular: Genel olarak 124 hasta (%58 erkek, ortalama yaş 70,7±11,3 yıl) dahil edildi. YBÜ'de kalış süresi boyunca, hem fT3 hem de fT4, ancak TSH, yatış değerlerine göre istatistiksel olarak anlamlı bir düşüş gösterdi. Serum kortizol ve ACTH değerleri yatış değerlerine göre arttı, bu artış anlamlı değildi. Hastaların %89,5'inde ESS mevcuttu. Hastaların üçte ikisi YBÜ'de öldü. Serum fT3 değerleri, hayatta kalanlara kıyasla merhumlarda anlamlı derecede düşüktü. Hastaların %20,1'inde hipokortizolizm saptandı. Yalnızca fT3 düzeyi tüm nedenlere bağlı ölümleri bağımsız ve anlamlı bir şekilde öngörebilir.

Sonuç: ESS, kritik durumdaki COVID-19 hastaları arasında neredeyse evrenseldi. Serum fT3 tüm nedenlere bağlı ölümleri önemli ölçüde tahmin edebilir fakat diğer tiroid veya adrenal hormonları tahmin edemez.

Anahtar Kelimeler: Adrenal fonksiyon, ötiroid hasta sendromu, hipokortizolizm, prognoz, tiroid fonksiyonu

INTRODUCTION

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), the etiologic agent of Coronavirus disease-2019 (COVID-19), might cause endocrine dysfunction on a wide range, including pituitary, thyroid, adrenal, gonadal, and pancreatic abnormalities[1]. Among these, perhaps thyroid hormone dysfunction, in the form of euthyroid sick syndrome (ESS), is the most common abnormality.

It has been reported that COVID-19 might cause thyroid dysfunction due to direct or indirect effects of the SARS-CoV-2 virus on the thyroid gland. This might be in the form of the ESS owing to severe systemic disease or may take the form of acute inflammation due to autoimmune reaction[2]. Several case reports demonstrated the development of subacute thyroiditis after COVID-19[3-5]. COVID-19 was also speculated as a trigger for autoimmunity and resultant Graves' disease in some patients, as well[6]. Several studies evaluated ESS and its severity on the prognosis of patients with COVID-19. These studies showed an increased prevalence of impaired thyroid function and an association between ESS and COVID-19 severity and level of inflammatory parameters[7-9].

Critical illness places great physical stress on the organism, and systemic availability of cortisol is a coping strategy with this stress. Several randomized studies produced conflicting results with respect to the impact of so-called relative adrenal failure-later renamed critical illness-related corticosteroid insufficiency-on clinical outcomes in patients with sepsis[10]. Subsequent research revealed the cause of increased systemic availability of cortisol, which was not due to increased adrenal secretion but rather owing to decreased degradation in the liver and kidney and less binding to cortisol-binding proteins in plasma[11]. Because of increased hospital and intensive care unit (ICU) admission rates of COVID-19 patients and dire outcomes for some, several investigators also evaluated the role of baseline levels of adrenocorticotropic hormone (ACTH) and cortisol on clinical outcomes and mortality in COVID-19 patients. Kanczkowski et al.[12], in their autopsy study, found that though not causing overt adrenal insufficiency, adrenal glands are a frequent target of SARS-CoV-2 and ensuing inflammation in deceased COVID-19 patients. A few case reports described cases of new-onset primary adrenal insufficiency following COVID-19[13-15]. Moreover, Mao et al.[16] found the level of serum cortisol significantly lower in ICU patients with COVID-19 compared to ICU patients without COVID-19. A very recent meta-analysis investigated the effect of serum cortisol levels on the prognosis of COVID-19 patients. The authors found significantly higher levels of serum cortisol in patients with severe COVID-19 compared to patients with moderate and mild COVID-19 patients[17]. Several treatment options were tried in COVID-19 patients with the hope of reducing mortality. Corticosteroids were one of the most promising among these potential treatment candidates. A meta-analysis by Boppana et al.[18] included 6 randomized controlled trials on 7 thousand patients with COVID-19 who were treated with corticosteroids and sought to answer whether corticosteroids were beneficial in reducing mortality. The analysis revealed that the use of systemic corticosteroids was associated with a reduction in all-cause mortality in patients with COVID-19 who required oxygen therapy or mechanical ventilation.

To the best of our knowledge, no study in the literature evaluated the combined power of thyroid and adrenal axes in the prediction of adverse clinical outcomes in patients with COVID-19. Thus, we aimed to evaluate the predictive ability of thyroid function along with serum cortisol and ACTH levels on clinical outcomes in COVID-19 patients who required ICU admission.

MATERIALS AND METHODS

Patients and Setting

This is a retrospective study that aims to evaluate the prognostic effects of admission serum cortisol level and thyroid function tests on the prognosis of patients admitted to a COVID-19 intensive care unit. The study was carried out in a teaching and research hospital in Karaman, Turkey. All patients who were admitted to the ICU due to COVID-19 were screened for eligibility for the study between March 11, 2020, and December 31, 2020. All patients had either a positive SARS-CoV-2 polymerase chain reaction (PCR) test from nasal swabs and/or a compatible chest computed tomography (CT) along with COVID-19 contact history. Exclusion criteria included the use of thyroid hormone therapy, the presence of

hypothalamic-pituitary gland dysfunction history, having the history of radiotherapy or chemotherapy in the last 6 months, the presence of thyroid surgery history and incomplete evaluation of thyroid gland function examination at admission (İndividuals with a history of thyroid disease were included in the study only if they lacked a history of active medication use or surgical intervention). Of the 95 patients who were excluded, the following reasons were ascertained: Being transfer from another service (n=5), having hypothyroidism (n=25), hyperthyroidism (n=7), change of thyroid gland revealed by chest CT scan (n=10), and nodular goiter (n=9), undergoing thyroidectomy (n=6) and radioiodine therapy (n=2), having multihormonal pituitary insufficiency (n=1), and lack of thyroid function test (n=30).

Approval was granted by the Ethics Committee of Karamanoğlu Mehmetbey University (date: 07/12/2020, no: 02-2020/04). This study was performed in line with the principles of the Declaration of Helsinki.

Data Collection

Age, sex, and comorbid medical conditions were recorded for each patient. Laboratory evaluations at ICU admission included complete blood count and differential, serum urea, creatinine, uric acid, lactate dehydrogenase, C-reactive protein (CRP), procalcitonin, and ferritin (daily COVID-19 sampling as part of hospital protocol). Serum levels of cortisol, ACTH, free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels were measured both on admission and thereafter two times during hospitalization (weekly COVID-19 sampling as part of hospital protocol). Initial laboratory examinations were taken before patients received any treatment. Serum TSH and thyroid hormones, ACTH, and cortisol measurements were performed with the chemiluminescence method via an autoanalyzer (Advia Centaur XP, Siemens). All study laboratory measurements were performed again during the course of the hospitalization (second and third measurements in addition to admission (first measurement) values).

The ESS was described as having a decreased serum fT3 with normal or low TSH levels[7]. The normal reference values for fT3 at our laboratory were 2.7-4.3 pg/mL. Hypocortisolism was defined as having a serum morning cortisol value below 10 µg/dL[19].

The patient outcomes (discharge or exitus) were obtained from patient charts. The length of ICU stay was determined for each study participant. Patients who were administered pulse prednisone as a part of the COVID-19 treatment regimen and who were receiving thyroid hormone or drugs containing steroids were also recorded. Pulse steroid was given to 46.0% of the patients as mentioned in the national COVID-19 treatment guidelines. All patients received the same glucocorticoid agent. The patients were treated with pulse steroid treatment with an intermediate-acting glucocorticoid in the form of 250 mg methylprednisolone for the first 3 days and 1 mg/kg methylprednisolone for the next 7 days. Data regarding intubation and mechanical ventilation and positive inotropic use were also gathered.

Statistical Analysis

The Statistical Package for the Social Sciences 25.0 software package (IBM, Armonk, NY, USA) was used to analyze the data of the study. A probability value of $p<0.05$ was considered statistically significant, and two-tailed p-values were used for all statistics.

To determine whether the continuous variables were normally distributed, the Shapiro-Wilks test, histogram, and Q-Q plot were used for continuous variables. Continuous variables were expressed as mean±standard deviation or median (minimum-maximum) depending on the distribution of the variable. Categorical variables were reported as numbers and percentages. To compare the categorical variables between the groups, the chi-square test and Fisher's exact test were used. The Mann-Whitney U test and the independent t-test were employed to compare two-group comparisons for numeric variables. The correlation was displayed with the Spearman correlation and the point biserial correlation test. Repeated measured ANOVA or the Friedman test with post-hoc Durbin-Conover test were used to analyze repeated measurements of the variables.

We performed univariate and multivariate logistic regression analyses to determine the independent associates of mortality. According to the univariate logistic regression, among those with a p value less than 0.050, only the variables that had clinical significance were included in the multivariate logistic regression analysis test. We did not include CRP in the regression model because its confidence intervals crossed 1.000.

RESULTS

Baseline Clinicodemographic Features and Laboratory Values

In total, 124 patients (58.1% males) with COVID-19 who required ICU admission were included in the study. The mean age was 70.7±11.3 years. The most prevalent chronic medical comorbidity was hypertension (63.7%), followed by type 2 diabetes mellitus. The majority of the patients (75%) had a positive PCR test for SARS-CoV-2. During the course of the hospitalization, 74.2% of the patients required tracheal intubation and mechanical ventilatory support. Approximately half of all patients required the administration of positive

inotropic agents to support blood pressure. Pulse steroid was given to 46.0% of the patients as part of the national COVID-19 treatment guidelines. Table 1 summarizes the baseline clinicodemographic features of all study patients. Admission and repeat laboratory values for hemogram, routine biochemistry, free thyroxine, free triiodothyronine, TSH, ACTH, and cortisol values are shown in Table 2. All controls were created one week apart. Controls were performed on 124 patients upon admission to intensive care (1st), 103 patients after 1 week (2nd), and 57 patients after 2 weeks (3rd).

Sixty-seven patients (54%) were not given pulse steroids during their hospitalization. In relation to patients who were administered pulse steroid treatment, clinical outcomes (length of ICU stay, rates of mechanical ventilation and inotropic drug use, and mortality) were comparable in both groups.

Thyroid and Adrenal Function

During the course of the ICU stay, both fT3 and fT4 showed a gradual decrease from their corresponding admission values. And these trends were statistically significant. Serum TSH did not significantly change during ICU stay. Although repeat values of serum cortisol and ACTH values increased in all patients compared to admission values, these increases were not statistically significant (Table 2).

Table 1. Demographic and clinical features of the whole study cohort

	Patients (n=124)
Age (years)	70.7±11.3
Sex	
Male	72 (58.1%)
Female	52 (41.9%)
Comorbidities	
Hypertension	79 (63.7%)
Diabetes mellitus	40 (32.3%)
Coronary artery disease	25 (20.2%)
Pulmonary disease	21 (16.9%)
Cerebrovascular disease	19 (15.3%)
Valvular heart disease	15 (12.1%)
Thyroid disease	15 (12.1%)
Chronic kidney disease	10 (8.1%)
Dyslipidemia	6 (4.8%)
Malignancy	6 (4.8%)
Pulse steroid administration	57 (46.0%)
Inotropic drug administration	68 (54.8%)
PCR test positivity	93 (75.0%)
Need for mechanical ventilation	92 (74.2%)
Length of hospital stay (days)	8 (1-60)
Outcome	
Survivors	42 (33.9%)
Decedents	82 (66.1%)

PCR: Polymerase chain reaction

When admission laboratory values were evaluated in the whole cohort of patients, 89.5% of the patients had ESS. This rate was maintained during the course of the hospitalization [ESS (2nd)=93.2%, ESS (3rd)=93.0%] (Table 3).

We also assessed ESS frequency among deceased and survivors who were not given pulse steroid treatment. The ESS frequency was similar at all measurement points during the hospitalization between survivors and deceased patients (Table 3).

Although admission values were comparable, repeat values of serum TSH were significantly lower in patients who were administered pulse steroid compared to patients who were not. On the other hand, fT3 and fT4 measurements were not different. All ACTH measurements, including admission value, were consistently and significantly lower in patients who were administered pulse steroids compared to patients who were not. Similarly, baseline and repeat serum cortisol values were significantly lower in patients who were treated with pulse steroids (Table 4).

Hypocortisolism (serum cortisol value below 10 µg/dL) was present in 25 (20.1%) patients. Inotropic medications were given to 14 (56%) patients with hypocortisolism. The coexistence of ESS and hypocortisolism was evident in 24 (19.4%) patients. The frequency of hypocortisolism in survivors and decedents was 21.4% and 19.5%, respectively. Mortality rate was not different between patients with and without hypocortisolism. In addition, serum fT3 levels were also comparable between patients with and without hypocortisolism. In a cohort of 25 patients with hypocortisolism, 22 received pulse steroid therapy, while 3 did not. Among the 22 patients who received pulse steroid therapy, 15 (68.2%) experienced an adverse outcome (exitus). Of the 3 patients who did not receive pulse steroid therapy, 2 (66.7%) had an adverse outcome. Statistical analysis using the Fisher's Exact test indicated no significant difference in mortality between these two groups (p=0.704).

Patient Survival and Associated Factors

Two-third of all patients died during ICU stay. When compared, survivors and decedents had comparable age and comorbid disease distribution. As expectedly, mechanical ventilation requirement and inotropic drug administration were significantly more frequent among the deceased compared to survivors. The mean admission serum fT3 and T4 levels were comparable between the survivor and deceased groups. However, repeat values taken during the course of the

Table 2. Comparison of laboratory parameters (on admission, second, and third) of the whole study cohort

	On admission (1st) (n=124)	Second (2nd) (n=103)	Third (3rd) (n=57)	p value
WBC count (K/uL)	12.76±6.01	13.31±7.59	13.15±6.00	0.516
Hemoglobin (g/dL)	12.2±2.43	11.48±2.12	11.17±2.20	**0.001***
Hematocrit (%)	36.91±6.65	35.61±6.53	34.22±7.61	**0.001****
Lymphocyte count (K/µL)	0.84±0.48	0.88±0.48	1.05±0.93	0.077
Platelet count (K/µL)	230.5 (25.0-597)	252.7±121.7	251.3±119	0.266
Ferritin (ng/mL)	420 (13-2000)	489 (53-2000)	525 (65-2000)	**0.002†**
D-dimer (mg/L)	2528 (401-9999)	2398 (306-9999)	2257 (931-9999)	0.824
LDH (U/L)	562.9±371.5	459.3±221.1	469.6±372.1	0.325
Fibrinogen (g/L)	4.77±1.46	4.80±1.37	5.10±1.39	0.154
Free triiodothyronine (pg/mL)	1.44 (0.52-6.0)	1.33±0.37	1.27±0.43	**0.003††**
Free thyroxine (ng/dL)	1.13±0.36	1.05±0.36	0.96±0.37	**0.003≠**
TSH (mU/L)	0.64 (0.01-39.8)	0.44 (0.01-20.13)	0.76 (0.02-33.14)	0.166
ACTH (pg/mL)	9.77 (1.0-166.5)	10.58 (1.58-74.34)	11.17 (1.0-69.0)	0.374
Cortisol (µg/dL)	22.57±17.78	18.10±13.08	18.81±12.19	0.123
Triglyceride (mg/dL)	161.6±82.3	162.4±84.4	147.7±67.5	0.577
Uric acid (mg/dL)	6.35±2.94	4.81±2.62	4.54±2.39	**<0.001≠≠**
CRP (mg/L)	164.1±96.2	124.3±79.2	149.7±83.5	**0.004ϕ**
Procalcitonin (µg/L)	0.57 (0.03-100)	0.40 (0.01-49.05)	0.52 (0.01-75.0)	0.390
Urea (mg/dL)	64.5 (10.6-301)	77.0 (23.0-315)	114.6±77.2	**0.011ΦΦ**
Creatinine (mg/dL)	1.19 (0.58-7.70)	1.03 (0.52-8.60)	1.09 (0.52-6.84)	0.197

All controls were created one week apart.

*Post-hoc significant difference: Hemoglobin (1st) vs. hemoglobin (2nd), hemoglobin (1st) vs. hemoglobin (3rd).

**Post-hoc significant difference: Hematocrit (1st) vs. hematocrit (2nd), hematocrit (1st) vs. hematocrit (3rd).

†Post-hoc significant difference: ferritin (1st) vs. ferritin (3rd).

††Post-hoc significant difference: triiodothyronine (1st) vs. triiodothyronine (2nd), triiodothyronine (1st) vs. triiodothyronine (3rd).

≠Post-hoc significant difference: thyroxine (1st) vs. thyroxine (2nd), thyroxine (1st) vs. thyroxine (3rd).

≠≠Post-hoc significant difference: uric acid (1st) vs. uric acid (2nd), uric acid (1st) vs. uric acid (3rd).

ϕPost-hoc significant difference: CRP (1st) vs. CRP (2nd).

ΦΦPost-hoc significant difference: Urea (1st) vs. Urea (3rd).

ACTH: Adrenocorticotropic hormone, CRP: C-reactive protein, LDH: Lactate dehydrogenase, TSH: Thyroid-stimulating hormone, WBC: White blood cell

hospitalization were significantly lower in deceased patients compared to survivors (Table 5). On the other hand, serum TSH values at all time points were lower among deceased compared to survivors. However, only the second repeat TSH value difference reached statistical significance. There was no significant difference in serum basal cortisol and ACTH values between decedents and survivors except for second repeat serum cortisol values. Figure 1 shows changes of serum fT3 level throughout ICU stay in survivor and decedent groups.

In addition, deceased patients had significantly higher serum CRP and procalcitonin values compared to survivors.

We performed univariate and multivariate logistic regression analyses to evaluate independent predictors of mortality. In multivariate analysis, only serum fT3 level appeared as a significant predictor of all-cause mortality (Table 6). Age, comorbid conditions, serum cortisol, ACTH values, and inflammatory markers were not independent associates of mortality.

DISCUSSION

The salient findings of the present study were as follows: (1) ESS was very common among COVID-19 patients admitted to ICU (2). Serum fT3 level was comparable on admission; however, it remained significantly lower during ICU stay in decedents compared to survivors (3). Serum fT3 was the sole predictor of all-cause mortality among several factors, including inflammatory markers, kidney function, and comorbid conditions (4). One-five of our patients had hypocortisolism. However, hypocortisolism rates, serum cortisol, and ACTH levels were comparable between the decedents and survivors (5). Serum ACTH and cortisol levels were significantly different throughout the ICU stay between patients who were given and not given pulse steroids. Values

Table 3. Frequency of ESS in the whole cohort and patients who did not receive pulse steroid throughout ICU stay in the survivor and decedent groups

	Euthyroid sick syndrome	TFT not showing a specific pattern	p value
Whole cohort			
On admission (1st) (n=124)			
Survivors	36 (85.7%)	6 (14.3%)	0.361
Decedents	75 (91.5%)	7 (8.5%)	
Second (2nd) (n=103)			
Survivors	36 (92.3%)	3 (7.7%)	>0.999
Decedents	60 (93.8%)	4 (6.2%)	
Third (3rd) (n=57)			
Survivors	20 (95.2%)	1 (4.8%)	>0.999
Decedents	33 (91.7%)	3 (8.3%)	
Patients who did not receive pulse steroid			
On admission (1st) (n=67)			
Survivors	22 (84.6%)	4 (15.4%)	0.727
Decedents	36 (87.8%)	5 (12.2%)	
Second (2nd) (n=53)			
Survivors	21 (87.5%)	3 (12.5%)	0.649
Decedents	27 (93.1%)	2 (6.9%)	
Third (3rd) (n=29)			
Survivors	11 (100%)	0	0.512
Decedents	16 (88.9%)	2 (11.1%)	

P values belong to comparisons in which the frequency of ESS was compared between decedents and survivors.

ESS: Euthyroid sick syndrome, ICU: Intensive care unit

apart from admission might reflect the effects of pulse steroid administration on the hypothalamic adrenal axis (6). Coexistence of ESS and hypocortisolism was evident in 24 (19.4%) patients. However, this cooccurrence did not pose a mortality disadvantage.

A study by Świstek et al.[20] found that ESS was present in 38.1% of COVID-19 patients, with higher levels of inflammatory markers and mechanical ventilation need. The study found that ESS increased the risk of death by 3.1 times. ESS was also found to be a prognostic factor even in mild cases. Sparano et al.[21] found that the frequency of ESS was 57% among hospitalized COVID-19 patients. Serum fT3 level was found to be inversely related to inflammatory markers and an independent associate of mortality.

Although it might be associated with *de novo* development of Graves' disease and subacute thyroiditis, ESS remains the most common thyroid pathology in COVID-19 patients with serum fT3 levels significantly lower than non-severe patients[22]. ESS is an independent predictor of all-cause mortality in these

Table 4. Comparison of clinical features and admission laboratory data between groups stratified according to pulse steroid administration

	Pulse steroid administration		p value
	Not given (n=67)	Given (n=57)	
Age (years)	71.9±11.4	69.4±11.2	0.218
Sex			
Male	38 (56.7%)	34 (59.6%)	0.883
Female	29 (43.3%)	23 (40.4%)	
Comorbidities			
Diabetes mellitus	24 (35.8%)	16 (28.1%)	0.467
Thyroid disease	9 (13.4%)	6 (10.5%)	0.827
Hypertension	44 (65.7%)	35 (61.4%)	0.760
Dyslipidemia	4 (6.0%)	2 (3.5%)	0.686
Valvular heart disease	11 (16.4%)	4 (7.0%)	0.186
Coronary artery disease	14 (20.9%)	11 (19.3%)	>0.999
Malignancy	5 (7.5%)	1 (1.8%)	0.217
Cerebrovascular disease	13 (19.4%)	6 (10.5%)	0.264
Pulmonary disease	9 (13.4%)	12 (21.1%)	0.375
Chronic kidney disease	6 (9.0%)	4 (7.0%)	0.752
Inotropic drug administration	36 (53.7%)	32 (56.1%)	0.930
Need of mechanical ventilation	46 (68.7%)	46 (80.75)	0.186
Length of hospital stay (day)	10.8±9.3	13.4±13.8	0.219
Outcome			
Survivors	26 (38.8%)	16 (28.1%)	0.285
Decedents	41 (61.2%)	41 (71.9%)	
TSH (1st)	0.66 (0.01-39.8)	0.54 (0.05-3.39)	0.287
TSH (2nd)	0.56 (0.01-20.13)	0.33 (0.04-2.8)	**0.035**
TSH (3rd)	1.28 (0.03-33.14)	0.70 (0.02-1.96)	**0.022**
ACTH (1st)	13.74 (1.61-77.8)	5.85 (1.00-166.5)	**<0.001**
ACTH (2nd)	14.41 (2.05-68.0)	6.52 (1.58-74.34)	**0.002**
ACTH (3rd)	14.56 (3.07-69.0)	8.43 (1.0-31.46)	**0.008**
Cortisol (1st)	26.33±12.90	18.14±21.48	**0.014**
Cortisol (2nd)	20.96±11.74	15.06±13.85	**0.022**
Cortisol (3rd)	22.01±12.36	15.48±11.27	**0.042**

ACTH: Adrenocorticotropic hormone, TSH: Thyroid-stimulating hormone

patients[23]. Apparently, as the severity of COVID-19 increases, the frequency of ESS also increases[24]. In our cohort of patients, the frequency of ESS on admission was 89.5%. Different from the studies published to date, we also evaluated thyroid function during the course of the ICU stay. In our patients, the rate of ESS never descended below 90% during ICU stay. However, the frequency of ESS on admission was not statistically significant between the decedents and survivors. The patients who died in ICU had significantly lower fT3 levels compared to survivors. Serum fT4 values were significantly lower in decedents during hospitalization compared to survivors, and serum fT3 was found to be an independent and significant predictor of all-cause mortality.

During the critical illness, cortisol secretion normally increases as a stress response[24]. However, in some critically ill patients, this increase is not sufficient to meet the needs of the body.

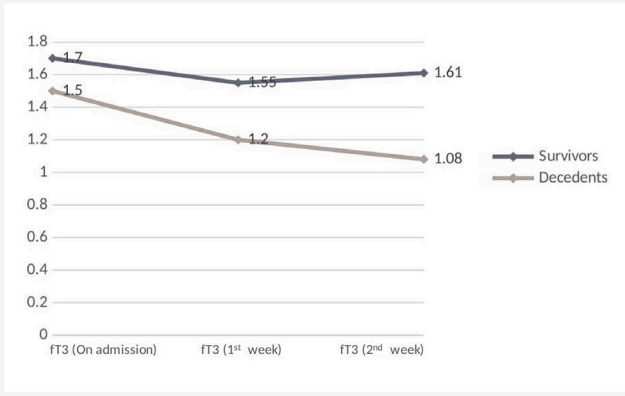

Figure 1. Changes of serum fT3 level throughout ICU stay in the survivor and decedent groups

ICU: Intensive care unit

Table 5. Comparison of clinical features and on admission laboratory data between groups stratified according to in-hospital mortality

	Survivors (n=42)	Decedents (n=82)	p value
Age (years)	68.4±11.8	71.9±11.0	0.114
Sex			0.669
Male	26 (61.9%)	46 (56.1%)	
Female	16 (38.1%)	36 (43.9%)	
Comorbidities			
Diabetes mellitus	15 (35.7%)	25 (30.5%)	0.699
Thyroid disease	4 (9.5%)	11 (13.4%)	0.735
Hypertension	27 (64.3%)	52 (63.4%)	>9.999
Dyslipidemia	4 (9.5%)	2 (2.4%)	0.178
Valvular heart disease	5 (11.9%)	10 (12.2%)	>9.999
Coronary artery disease	11 (26.2%)	14 (17.1%)	0.336
Malignancy	1 (2.45%)	5 (6.1%)	0.663
Cerebrovascular disease	8 (19.0%)	11 (13.4%)	0.575
Pulmonary disease	7 (16.7%)	14 (17.1%)	>9.999
Chronic kidney disease	3 (7.1%)	7 (8.5%)	>9.999
Pulse steroid administration	16 (38.1%)	41 (50.0%)	0.285
Inotropic drug administration	6 (14.3%)	62 (75.6%)	**<0.001**
Need of mechanical ventilation	10 (23.8%)	82 (100.0%)	**<0.001**
Length of hospital stay (day)	9 (2-60)	7.5 (1-55)	0.239
Free triiodothyronine (1st)	1.48 (0.68-6.0)	1.40 (0.52-3.46)	0.077
Free triiodothyronine (2nd)	1.55±0.37	1.20±0.31	**<0.001**
Free triiodothyronine (3rd)	1.61±0.34	1.08±0.36	**<0.001**
Free thyroxine (1st)	1.20±0.37	1.10±0.34	0.129
Free thyroxine (2nd)	1.16±0.33	0.99±0.37	**0.013**
Free thyroxine (3rd)	1.16±0.19	0.84±0.40	**<0.001**
TSH (1st)	0.84 (0.01-5.72)	0.54 (0.06-39.80)	0.214
TSH (2nd)	0.70 (0.05-15.74)	0.34 (0.01-20.13)	**0.017**

Table 5. Continued

	Survivors (n=42)	Decedents (n=82)	p value
TSH (3rd)	1.14 (0.05-3.02)	0.47 (0.02-33.14)	0.103
ACTH (1st)	9.79 (1.61-79.10)	9.76 (1.00-166.50)	0.782
ACTH (2nd)	14.23 (2.05-40.69)	9.93 (1.58-74.34)	0.446
ACTH (3rd)	11.48 (3.66-54.40)	10.93 (1.00-69.00)	0.418
Cortisol (1st)	19.27±10.67	24.26±20.35	0.076
Cortisol (2nd)	15.09±6.44	19.93±15.59	**0.031**
Cortisol (3rd)	18.63±9.02	18.91±13.82	0.925
CRP (1st)	138.3±83.5	178.4±99.9	**0.024**
CRP (2nd)	93.7±70.1	143.0±79.1	**0.001**
CRP (3rd)	122.2±77.9	165.8±83.4	0.053
Procalcitonin (1st)	0.30 (0.04-100.0)	0.84 (0.03-100.0)	**0.007**
Procalcitonin (2nd)	0.21 (0.01-6.10)	0.74 (0.08-49.05)	**<0.001**
Procalcitonin (3rd)	0.26 (0.01-75.0)	0.70 (0.06-44.25)	0.082

ACTH: Adrenocorticotropic hormone, CRP: C-reactive protein, LDH: Lactate dehydrogenase, TSH: Thyroid stimulating hormone, WBC: White blood cell

Table 6. Univariate and multivariate logistic regression analyses to determine independent predictors of in-hospital mortality in the whole cohort

	Univariate			Multivariate		
Parameters	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	1.028	0.994-1.063	0.107	-	-	-
Dyslipidemia	4.211	0.738-24.007	0.106	-	-	-
Ferritin	1.001	1.000-1.003	**0.033**	1.000	0.999-1.002	0.720
D-dimer	1.000	1.000-1.001	0.054	-	-	-
Free triiodothyronine	0.017	0.002-0.148	**<0.001**	0.959	0.929-0.989	**0.007**
Free thyroxine	0.057	0.008-0.412	**0.005**	0.994	0.965-1.024	0.708
Cortisol	1.035	0.996-1.074	0.077	--		-
Uric acid	1.194	0.928-1.535	0.167	-	-	-
CRP	1.005	1.000-1.009	**0.035**		--	-
Procalcitonin	1.631	1.087-2.446	**0.018**	0.152	0.742-6.827	2.251
Creatinine	2.010	1.102-3.665	**0.023**	0.747	0.423-1.853	0.886

Hosmer and Lemeshow test p=0.844 (for multivariate regression).
OR: Odds ratio, CI: Confidence interval

When a disorder of the hypothalamic-pituitary-adrenal (HPA) axis is present and not appropriately treated with high doses of hydrocortisone, acute stress may induce a life-threatening adrenal crisis. In the absence of adrenal insufficiency, stress doses of hydrocortisone are also used to lessen the requirement for vasopressors in patients suffering from septic shock. Research on the HPA axis during critical illness have led to the realization that neither of these disorders can be classified as "critical illness-induced corticosteroid insufficiency" or CIRCI. Instead, these results advised adopting the term CIRCI for a syndrome that may develop in individuals who are critically sick for an extended period of time. Patients who rely on organ support for weeks may develop central adrenal insufficiency due to increased systemic glucocorticoid availability, suppressed circulating cortisol-binding proteins, and suppressed hepatic/renal cortisol metabolism. This negative feedback inhibition at the hypothalamus/pituitary is exacerbated by high levels of other glucocorticoid receptor ligands and drugs like opioids. The adrenal cortex may become physically and functionally damaged, leading to inadequate cortisol production and potentially contributing to persistent vasopressor demand and encephalopathy, impeding recovery[25]. Patients with adrenal crisis usually present with nonspecific symptoms and signs, including severe fatigue, weakness, myalgia, postural dizziness, nausea, vomiting, abdominal pain, and fever[26]. These symptoms are also common in an acute COVID-19 infection, and it might be difficult to differentiate between the features of acute adrenal crisis and acute COVID-19 infection. Since

adrenal insufficiency clinic and COVID-19 clinical findings can be confused with each other, we created a treatment plan for relative adrenal insufficiency by combining the cortisol cut-off value with clinical findings. Given the dynamic nature of the pituitary-adrenal axis, single measurements of serum cortisol cannot fully explain the adrenal reserve. Some studies accepted a serum cortisol level below 10 µg/dL as a hypocortisolism response to critical illness[19]. Das et al.[24] found that among patients with severe and mild COVID-19, hypocortisolism rates were 38.5% and 6.8%, respectively. In our study, the frequency of hypocortisolism was 20.1%, which was lower than the findings of Das et al.[24], because Das et al.[24] used 15 µg/dL as the cut-off value in their study, unlike the 10 µg/dL we used in our study. Patients with severe disease had significantly lower serum ACTH values compared to patients with mild COVID-19[24]. Another case-control study involving noncritical patients hospitalized for COVID-19 revealed that, compared to normal subjects, serum levels of ACTH were significantly lower, and cortisol was higher in COVID-19 patients[27]. A significant number of our patients received pulse steroid treatment as part of COVID-19 treatment guidelines. However, admission values reflected the steroid-naive status before pulse steroid administration. Hypocortisolism frequencies were comparable between the survivors and decedents. Moreover, neither serum cortisol nor serum ACTH values were independent predictors of all-cause mortality. There was no correlation between serum fT3 and cortisol values, either.

Study Limitations

Some limitations of the current study are worthy of mention. First, our sample size was not large, and this might have led to a failure to unravel subtle differences in thyroid hormone and adrenal hormone levels. Moreover, ESS was almost universal among our patients, and this precludes us from meaningfully comparing patients with and without ESS in terms of study outcomes. Second, pulse steroid administration in a significant portion of patients might affect adrenal axis evaluation during the hospitalization period. It might also have impacted the thyroid axis to some extent. However, several strengths of this study make our results contributive to the current literature. For the first time, we evaluated the combined prognostic impact of thyroid and adrenal axes on the prognosis of critically ill COVID-19 patients. Second, we also evaluated hormone values throughout the hospitalization but not at a single time point, as was the case in the previous studies in the literature.

CONCLUSION

In conclusion, ESS was prevalent in critically ill COVID-19 patients. One-five of all patients also had hypocortisolism. Although the frequencies of ESS and hypocortisolism were similar between survivors and decedents, patients who died during ICU stay had significantly lower levels of serum fT3. In addition, fT3, but not serum cortisol and ACTH levels, was an independent predictor of all-cause mortality.

Ethics

Ethics Committee Approval: Approval was granted by the Ethics Committee of Karamanoğlu Mehmetbey University (date: 07/12/2020, no: 02-2020/04).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.K., T.E., R.Y., Concept: M.K., S.K., N.K., Design: M.K., S.K., R.Y., Data Collection or Processing: T.E., R.Y., N.K., Analysis or Interpretation: S.K., T.E., N.K., Literature Search: M.K., T.E., R.Y., Writing: M.K., S.K., T.E., R.Y., N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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