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Association of Hormonal Changes with Disease Severity and Mortality in Critically-ill Patients

Yoğun Bakım Hastalarında Hormonal Değişimin Hastalık Ciddiyeti ve Mortalite ile İlişkisi

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Abstract

Purpose: Endocrine and metabolic changes, which may affect the prognosis and outcome, can occur in critically ill patients. In this prospective study, we aimed to evaluate the changes in the pituitary-adrenal-gonadal-thyroid axis in patients admitted to the adult intensive care unit on admission and 15 days later and also to evaluate whether these hormonal changes contribute to prognosis and mortality as well as to investigate the association between these hormonal changes and Acute Physiology and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores, length of hospitalization, and mortality.

Material and Method: One hundred and fifty seven patients were enrolled in this study. Severity of illness was assessed by APACHE II and SOFA scores. Blood samples were collected within the first 4 hours of intensive care unit admission and 15 days later for hormonal evaluation.

Results: Eighty-five patients were in survival (S), 72 were in the non-survival (NS) group. The median age, and baseline APACHE II, median APACHE II mortality and SOFA scores in NS group were significantly higher than in S group. According the baseline endocrine parameters, the predictive factors on mortality were age, baseline SOFA score and hospitalization length and also, 15 days after the admission, age and Δ TSH were found be the predictive factors in mortality.

Discussion: Our study revealed that none of the endocrine parameters contribute to mortality except Δ TSH. We assume that Δ TSH can be used together with APACHE II or SOFA scores in the prediction of prognosis in a tertiary mixed type intensive care unit.

Keywords: Critically ill patient, endocrine parameters, mortality

Öz

Amaç: Yoğun bakım hastalarında prognozu ve klinik sonuçları etkileyebilen metabolik ve endokrinolojik değişiklikler olabilmektedir. Biz bu prospektif çalışmamızda, erişkin yoğun bakım ünitesine kabul edilen hastalarda yoğun bakıma kabulde ve 15 gün sonra hipofiz-adrenal-gonad ve tiroid aksında değişiklik olup olmadığını ve bu değişikliklerin prognoz ve mortaliteye katkısı olup olmadığını değerlendirmeyi amaçladık. Ayrıca bu hormonal değişiklikler ile Akut Fizyoloji Skoru II (APACHE II), SOFA skorları, hastanede yatış süresi ve mortalite arasında ilişki olup olmadığını inceledik.

Gereç ve Yöntem: Çalışmaya 157 hasta dahil edildi. Hastalık ciddiyeti APACHE II ve SOFA skorları ile değerlendirildi. Hormonal değerlendirme için kan örnekleri yoğun bakıma kabulde ilk 4 saatde ve 15 gün sonra alındı.

Bulgular: Hastaların 85'i survival (S), 72'i non-survival (NS) gurubunda idi. NS gurubunda, yaş ortancası, bazal APACHE II skoru, APACHE II mortalite ortancası ve SOFA skorları S gurubundan anlamlı daha yüksek idi. Bazal endokrin parametrelerine göre mortalite üzerinde belirleyici faktörler yaş, bazal SOFA skoru, hastanede yatış süresi ve yoğun bakıma kabulden 15 gün sonra yaş ve Δ TSH'deki değişim idi.

Tartışma: Çalışmamız Δ TSH'deki değişim dışında endokrin parametrelerinin hiçbirinin mortaliteye katkısı olmadığını saptamıştır. Üçüncü basamak mikst tip yoğun bakım ünitesinde prognozun belirlenmesinde APACHE II veya SOFA skorları ile Δ TSH'deki değişimin kullanılabileceğini düşünmekteyiz.

Anahtar kelimeler: Yoğun bakım hastaları, endokrin parametreler, mortalite

Introduction

Critical illness is defined as any life-threatening condition requiring support of vital organ functions for survival (1). As it is important for critical care clinicians to accurately predict the outcome, several prognostic scoring systems have been developed to predict the severity of illness (2). The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring is widely used in grading the derangement in physiological homeostasis in individual patients as well as for prognostic calculations (3). Also sequential-related organ

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failure assessment (SOFA) score allows for repeated measurements of multiple organ dysfunction/failure and thereby functions as an index for determining either sequential deterioration or improvement of the pathological condition of the patient during treatment (3). Although APACHE II is the most commonly used tool in the prediction of mortality, it is insufficient to predict mortality in some group of patients (4). An alternative approach is to measure the response of the endocrine system to the physiological stress of critical illness (2). Patients with critical illness are in a state of physiological stress with changes in inflammatory pathways and tissue perfusion resulting in multiorgan dysfunction (5). The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in the endocrine regulation of metabolic and immunological homeostasis (6). Critical illness is characterized by changes in these systems, which have long been known to contribute to a high risk of morbidity and mortality (6).

Some studies indicated that low thyroid stimulating hormone (TSH) (7), low total triiodothyronine (TT_3) (8), low thyroxine (T_4) (7,9), and high cortisol (10,11) levels are predictors of poor prognosis in cases of critical illness, while other studies showed no such correlations between TT_3, TSH, free T_4 (fT_4), or free T_3 (fT_3) levels and outcomes (12,13). In a study by Ilias et al. (14) in patients with trauma, the APACHE II score and hormonal parameters (DHEA-SO4 and TSH-age) were suitable for assessing survivals (S)/non-survivals (NS) as an endpoint and better than the APACHE II score alone in terms of predicting intensive care unit (ICU) survival or death. However, in the literature, there are several studies evaluating the endocrine changes in ICU patients at the time of admission, on day one and day 2 or 72 hours later, but not after 15 days. According to our knowledge, there is only one study which evaluated the patients on admission and also on the day of hospital discharge (15).

The aim of this prospective study was first to evaluate the changes in the pituitary-adrenal-gonadal-thyroid axis in patients hospitalized in the adult ICU on the day of admission and 15 days later. The second aim of our study was to evaluate whether these hormonal changes contribute to the prognosis and mortality and also the association of these hormonal changes with APACHE II and SOFA scores, length of hospitalization, and mortality.

Materials and Methods

Setting

The study has been approved by an institutional Ethics Committee of Yıldırım Beyazit University Faculty of Medicine (68/16.04.2014). Informed consent was obtained from the patients or from a first-degree relative if the patient was unconscious or too ill to communicate for consent. The study was conducted in a twenty-bed mixed type adult ICU in a major education and tertiary referral centre.

Patients

Patients who were hospitalized in the adult ICU between May 2014 and January 2015 were enrolled in this study. Since the endocrine tests could not be completed in 15 patients, a total of 157 patients were included in the study. Exclusion criteria were: age younger than 18 years; metabolic, or endocrine disease (except diabetes mellitus), resuscitation history before ICU admission, history of chronic alcohol usage, and concomitant treatment with amiodarone, dopamine agonists or antagonists, benzodiazepines, opioids, immunosuppressive drugs, antipsychotic agents, antidepressants, antiepileptic drugs, thyroid hormones, estrogens, and glucocorticoids. Hormone tests were made on the day of admission and 15 days later. For the patients discharged from ICU before the 15th day, blood samples were taken in the outpatient clinics.

Severity of illness was assessed by APACHE II and SOFA scores calculated 24 hours after admission to the ICU. The patients were followed until discharge from hospital or death to determine the hospital mortality rate. The diagnoses of patients admitted to the ICU are listed in Table 1.

Laboratory Parameters

Blood samples were collected within the first 4 h of ICU admission and after 15 days for measurement of sensitive TSH (sTSH), fT_3, fT_4, cortisol, adrenocorticotropic hormone (ACTH), estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), prolactin (PRL), growth hormone (GH), and insulin-like growth factor-I (IGF-I). For the patients who required glucocorticoid treatment in the follow-up, blood samples were taken after discontinuation of steroid therapy for at least 5 days.

Assays

The samples were subjected to the same assays using the same kits. The levels of sTSH, fT_3, and fT_4 were measured in all patients using chemiluminescence methods (Immulite 2000; Diagnostic Products Corporation, Los Angeles, CA and UniCel DxI 800; Beckman Coulter, Brea, CA). The normal ranges for sTSH, fT_3 and fT_4 were 0.4-4 µIU/mL, 1.57-4.71 pg/mL and 0.61-1.12 ng/dL, respectively. The serum levels of E2, FSH, LH, PRL, total T, cortisol, and ACTH were measured with specific electrochemiluminescence immunoassays (Elecsys 2010 Cobas, Roche Diagnostics, Mannheim, Germany). Serum GH was assessed by electrochemiluminescence immunoassay (hGH kit, Roche, Mannheim, Germany). The sensitivity of the method was 0.03 ng/mL. Serum total IGF-I was assessed by immunometric chemiluminescence assay (IMMULITE 2000, SIEMENS, Gwynedd, United Kingdom). Age-adjusted reference ranges were used for the evaluation of IGF-I levels.

Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distributions of discrete and continuous variables were normally or not was determined by the Kolmogorov-Smirnov test. Data were shown as mean ± standard deviation or median (min-max), where applicable. While, the mean differences between survivor and non-survivor groups were compared by Student's t-test, otherwise, the Mann-Whitney U test was applied for comparisons of the median values. Nominal data were analyzed by Pearson's chi-square test. Degrees of association between discrete and continuous variables were calculated by Spearman's correlation coefficient. While, the mean differences between baseline and 15th day measurements were compared by the paired samples t-test, otherwise, Wilcoxon signed-rank test was applied for comparisons of the median values.

Determining the best predictor(s) affecting mortality was evaluated by multiple logistic regression analysis Backward LR procedure. Any

variable whose univariable test had a p value of less than 0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Adjusted odds ratios and 95% confidence intervals for each independent variable were also calculated.

A p value of less than 0.05 was considered statistically significant. However, for all multiple comparisons, the Bonferroni adjustment was applied for controlling type I error.

Results

We evaluated 157 patients in this study. Eighty five patients (54.14%) were in the survival group (S), 72 patients (45.86%) were in the non-survival (NS) group. The mean age of the patients was 70.1±15.3 years. Demographic features and hospitalization rates, APACHE II and SOFA scores and APACHE II mortality rates of the patients are shown in Table 2. In the NS group, median age, baseline APACHE II score, median APACHE II mortality and SOFA scores were significantly higher than in the S group (p=0.011, p<0.001, p<0.001 and p<0.001, respectively). There was no significant difference between NS and S groups in regard to sex, body mass index and median hospitalization rates.

When we evaluated the hormonal status of the patients on the day of admission (baseline levels), median GH, E2 and cortisol levels were significantly higher in the NS group, whereas median FSH, LH and mean fT_3 and fT_4 levels were significantly lower than in the S group (p<0.05) (Table 3). In females, FSH levels were significantly higher in the S group, whereas E2 levels were significantly higher in NS group (Table 3). In the study group, there were 4 premenopausal women and no differences were found between pre- and post-menopausal women in FSH, LH and E2 levels. In males, LH levels were significantly higher in S group (Table 3).

After 15 days of hospitalization, median IGF-I and ACTH levels were significantly higher, whereas median cortisol was significantly lower compared to the baseline hormone levels measured on the day of admission (p<0.05) (Table 4). In females, FSH and LH levels were significantly lower compared to baseline levels, whereas LH levels were significantly higher in males (Table 4).

In the S and NS groups all endocrine parameters were evaluated on admission and 15 days after the admission to ICU. In the S group, median IGF-I and ACTH levels were significantly increased on the 15th day of admission compared to the baseline levels (p=0.007 and p=0.006, respectively), whereas median E2 levels were decreased (p=0.01). In the NS group, no significant changes were observed between the hormone levels measured on the day of admission and 15 days later. Compared with baseline levels, TSH and fT_3 levels were increased in the S group on the 15th day of admission whereas they were decreased in the NS group (p=0.011 and p=0.035, respectively) (Table 5). In females, FSH and LH levels were significantly lower on the 15th day in the NS group, and in males, LH levels were significantly higher on the 15th day in the S group.

We evaluated the correlation between baseline hormone levels and hospitalization length, baseline APACHE II and SOFA scores. We determined a negative correlation between LH and hospitalization length (r=-0.217, p=0.009). We also detected a positive correlation between APACHE II score and E2 and cortisol levels (r=0.378, p<0.001, and r=0.273, p=0.001) and a negative correlation between APACHE II score and fT_3 and TSH levels (r=-0.254, p=0.002, and r=-0.197, p=0.014). There was a positive correlation between SOFA score and GH, E2 and cortisol levels (r=0.207, p=0.011, r=0.486, p<0.001, r=0.184, p=0.024, respectively), whereas a negative correlation was found between SOFA score and FSH, sTSH, fT_3 and fT_4 levels (r=-0.282, p=0.001, r=-0.312, p<0.001, r=-0.389, p<0.001, r=-0.281, p<0.001).

Multiple logistic regression analysis revealed that the predictive factors of mortality were age, baseline SOFA score and hospitalization length [odds ratio (OR): 1.04, 95% confidence interval (CI): 1.00-1.08, p=0.031, OR: 1.29, 95% CI: 1.03-1.61, p=0.023, and OR: 1.01, 95% CI: 1.00-1.03, p=0.019, respectively].

In addition, multiple logistic regression analysis showed that age and Δ TSH calculated at the 15th day of admission were found to be predictive for mortality (OR: 1.050, 95% CI: 1.00-1.09, p=0.023 and OR: 0.697, 95% CI: 0.49-0.97, p=0.037, respectively).

Discussion

Our study revealed that baseline endocrine parameters had no predictive effect whereas age, baseline SOFA score and hospitalization length was found predictive for mortality. Additionally, multiple logistic regression analysis showed that, when we considered the baseline and 15th day hormone results, age and Δ TSH were found to be the predictive factors of mortality.

In critical illness, activation of the HPA and the cortisol response are essential for survival (16). In the early phase, the cortisol level usually increases due to the increased secretion of CRH and ACTH directly or resistance to or negative feedback inhibition by cortisol (17,18). In previous studies, both high and low cortisol levels have been found to be associated with increased mortality (11,17,19,20,21). Plasma cortisol concentration was shown to be related to outcome in some studies (8,9,11) but not in others (10,22). In our study, the baseline cortisol level was found to be significantly higher in the NS group compared to that in the S group. When we consider all patients, ACTH was significantly higher on the 15th day of admission compared to the baseline levels whereas median cortisol level was lower. Activation of the HPA-axis would imply increased ACTH levels, yet published data on plasma ACTH concentrations in critically ill patients are scarce (23). Vassiliadi et al. (24) showed that, ACTH levels were decreased initially and raised significantly later on, mirroring the decline in cytokine levels. They stated that ACTH level probably is not the main determinant of cortisol levels during the early phase of critical illness. The authors

Table 1. The diagnoses of patients admitted to intensive care unit

Diagnosis	Patient number	
	n	%
Cardiovascular system	117	27.20
Pulmonary system	85	19.76
Neurological system	77	17.91
Urinary system	37	8.60
Trauma	22	5.11
Gastrointestinal system	17	3.95
Endocrine system	48	11.16
Inflammatory	8	1.86
Neoplasm	19	4.41

thought that the most suitable explanation was that during prolonged sepsis, cytokine levels subside and ACTH regains control to maintain cortisol at the appropriate levels, as supported by the finding that at this time point, ACTH levels were correlated with cortisol levels. Thus, in the chronic phase, ACTH takes over as a major adrenal stimulant. Also short half-life of ACTH and single measurement of ACTH may be insufficient to evaluate the HPA axis and all these factors may contribute the ACTH increase.

Changes in thyroid functions in critical illness are referred to as euthyroid sick syndrome or non-thyroidal illness syndrome (7,25,26). The most typical alterations are low plasma concentrations of T_3, low or normal plasma concentrations of T_4, or elevated plasma reverse T_3 (rT3) in the presence of normal thyrotropin (27). It is not clearly established whether this reflects an adaptation of the organism to illness or instead a potentially deleterious condition leading to hypothyroidism at tissue level (28). It is likely that the transient down regulation at all levels of the hypothalamic–pituitary–thyroid (HPT) axis (decreased TRH and TSH at the hypothalamic-pituitary level and a decreased T_3 due to altered peripheral deiodinase activity) is part of the neuro-endocrine adaptation to critical illness in an attempt to save energy (28). The magnitude of reduced T_3 indicates the severity of illness and is of prognostic importance (29,30,31,32). Plasma TSH concentration may be suppressed in the acute phase of critical illness and may increase to the hypothyroid range on recovery (3,26). It has been reported that TT_3 and TT_4 concentrations are lower in non-surviving than in surviving patients (2,8), and therefore, thyroid hormone dysfunction could affect the outcome and increase mortality in critical illness (3). In the chronic phase of critical illness, the pulsatile fraction of TSH release is markedly decreased and serum concentrations of T_4 and especially T_3 are low (33). Our study determined that baseline median fT_3 and fT_4 levels were significantly lower in the NS group than in the S group. In addition, we revealed that 15 days after ICU admission, TSH and fT_3 levels were significantly increased in the S group but not in the NS group compared to the baseline levels. Furthermore, we found a negative correlation between baseline fT_3 and sTSH levels and APACHE II score, and also a negative correlation between baseline fT_3, fT_4, and TSH levels and SOFA score. Ray et al. (26) found that TT_3 and TT_4 levels were significantly lower in NS than in S on admission and on day 1 but not on day 2 in critically ill patients and that cortisol concentrations were

Table 2. Demographic and clinical features of the all patients, survival and non-survival groups

Variables	All patients (n=157)	Survival (n=85)	Non-survival (n=72)	p
Age (year)	70.1±15.3	67.3±15.8	73.5±14.1	0.011
Sex				0.240
Male	88 (56.1%)	44 (51.8%)	44 (61.1%)	
Female	69 (43.9%)	41 (48.2%)	28 (38.9%)	
BMI (kg/m^2)	26.9±6.8	26.8±7.5	27.1±5.8	0.874
Hospitalization time (day)	14 (2-180)	13 (2-126)	19 (2-180)	0.056
Baseline APACHE II score	19.9±6.8	17.0±5.0	23.5±6.9	<0.001
APACHE II mortality	0.37 (0.04-0.95)	0.23 (0.08-0.81)	0.46 (0.04-0.95)	<0.001
Baseline SOFA score	5 (0-20)	3 (0-11)	7 (1-20)	<0.001

BMI: Body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential-related organ failure assessment

Table 3. Baseline (admission to the intensive care unit) hormonal evaluation of the patients between survival and non-survival groups

Variables	Survivals		Non-survivals		p
	n		n		
IGF-I (ng/mL)	80	64.6 (23.6-274.0)	66	51.7 (14.3-147.0)	0.053
Growth hormone (ng/mL)	81	1.0 (0.08-7.1)	69	1.8 (0.2-19.6)	0.002
FSH (mIU/mL)	70	6.5 (0.1-77.7)	59	3.7 (0.3-54.5)	0.011
Female	35	9.71 (0.363-77.67)	21	2.58 (0.303-51.14)	0.026
Male	35	5.74 (0.1-36.71)	38	4.47 (0.518-54.48)	0.305
LH (mIU/mL)	70	5.0 (0.1-58.4)	59	2.5 (0.1-62.9)	0.039
Female	35	3.61 (0.1-58.36)	21	0.86 (0.1-58.3)	0.219
Male	35	6.22 (0.1-27.12)	38	3.41 (0.1-62.87)	0.021
Testosterone (ng/mL)	35	0.63 (0.067-4.04)	38	0.4 (0.025-1.64)	0.112
Estradiol (pg/mL)	35	31.4 (5-463.1)	21	73.6 (6.07-511.8)	0.011
sTSH (uIU/mL)	83	1.3 (0.05-73.2)	70	1.0 (0.02-77.9)	0.175
fT_3 (pg/mL)	82	1.64±0.56	68	1.39±0.56	0.007
fT_4 (ng/dL)	82	1.22±0.35	66	1.01±0.34	<0.001
PRL (ng/mL)	77	30.6 (0.3-313.8)	69	34.0 (0.6-412.2)	0.511
ACTH (pg/mL)	66	17.2 (1.0-74.1)	52	17.3 (1.0-205.2)	0.151
Cortisol (ug/dL)	82	18.9 (1.1-58.5)	69	23.7 (0.9-63.4)	0.006

ICU: Intensive care unit, IGF-I: Insulin-like growth factor-I, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, sTSH: Sensitive thyroid-stimulating hormone, fT_3: Free triiodothyronine, fT_4: Free thyroxine, PRL: Prolactin, ACTH: Adrenocorticotropic hormone

higher in NS on admission and on day 1 but not on day 2. They also reported that TSH, fT_3, and fT_4 levels did not differ significantly between S and NS at any time point. They showed that only TT_4 and cortisol were independent predictors of outcome (26).

GH secretion increases in response to acute stress, and the level of its peripheral effector molecule, IGF-I, also decreases (33). In the chronic or prolonged phase of critical illness, pulsatile secretion of GH is suppressed, while the non-pulsatile fraction remains elevated (33). When we consider all patients, we observed that GH level did not change significantly on the 0th and 15th days of admission. There was not any difference in the delta change of GH between NS and S groups.

PRL, an immune enhancing and stress hormone, is known to be increased in response to acute stress (16,33,34). The pulsatile fraction of PRL is suppressed with prolongation of illness (33), and these changes have been suggested to contribute to the immunosuppression related to prolonged critical illness. However, we found no relationship between PRL levels and the other parameters.

Studies showed that in the acute illness or stress, sex steroid hormone levels (E2 in females and T in males) are associated with inappropriately low gonadotropin levels consistent with a transient suppression of the hypothalamic-pituitary-gonadal axis in both men and women (35). While serum T levels are decreased after surgery or during critical illness, the levels of estrone and E2 remain constant or rise in both males and postmenopausal females (36). The decreases in T levels in critical illness or after surgery may be due to several factors, including suppressed gonadotropin-releasing hormone (GnRH) secretion, which results in decreased testicular response to gonadotrophins in some patients (36). Normally, when serum T level is decreased, a negative feedback of sex hormones on the hypothalamic-pituitary axis is lost and secretion of gonadotropin increases (15). Moreover, administrating the GnRH to healthy subjects stimulates the anterior pituitary gonadotropes, resulting in high serum FSH and LH levels (15). These natural responses might be either absent or decreased in critically ill patients. Spratt et al. (36) reported that increased serum estrogen concentrations in acute illness were caused mainly by increased peripheral aromatization due to increased expression of aromatase. The clinical impact of increased serum estrogen level in critical illness is not clear. Estrogens have acute non-reproductive physiological effects on cardiovascular functions, the immune system, and hepatic protein production (36). In our study, according to the baseline hormonal levels we found that median E2 levels were significantly increased, and median FSH and LH levels were significantly decreased in the NS group. Comparing the baseline and the 15th day levels, the E2 levels were significantly decreased on the 15th day in S group but not in NS group. Additionally, in females, E2 levels were significantly higher in NS group whereas the gonadotropins were lower. This suggests that estrogen is derived from the peripheral aromatization of adrenal androgens to estrogen. In our study, there were 4 premenopausal women and no differences were found between pre- and post-menopausal women in FSH, LH and E2 levels. One of the studies evaluating the gonadotropin levels in post-menopausal women during acute severe illness has been performed by Raj et al. (35). They found that LH and FSH levels were significantly lower among sick patients in comparison to healthy controls, however, E2 values were significantly higher among patients than in controls. Both FSH and LH hormones are produced by the same cells and are released in response to GnRH. Cytokines are the probable mediators of gonadotropin suppression in sick patients via their negative impact on GnRH pulses (35). Injection of interleukin-1α in primates caused suppression of gonadotropin secretion (37). Spratt et al. (38) reported that in postmenopausal women nadir serum FSH

Table 4. Hormonal parameters of the all patients in the baseline and 15 days after the admission to intensive care unit

Variables	n	Baseline	15th day	p	Δ change
IGF-I (ng/mL)	26	54.8 (25.0-248.0)	103.0 (25.0-330.0)	0.002	25.7 (-31.7-186.9)
Growth hormone (ng/mL)	71	1.16 (0.08-11.2)	1.05 (0.06-13.9)	0.906	-0.15 (-9.1-6.6)
FSH (mIU/mL)	76	4.8 (0.3-65.5)	4.3 (0.1-51.9)	0.707	-0.02 (-47.7-20.2)
Female	34	13.76 (0.303-77.6)	8.05 (0.062-51.95)	0.02	-2.41 (-42.42-20.22)
Male	42	7.52 (0.1-54.48)	6.97 (0.27-33.3)	0.1	0.85 (-47.73-13.62)
LH (mIU/mL)	76	3.0 (0.1-62.9)	3.5 (0.1-85.3)	0.591	0.0 (-59.9-27.6)
Female	34	7.13 (0.1-58.36)	2.98 (0.1-21.89)	0.036	-0.32 (-36.4-12.85)
Male	42	7.68 (0.1-62.87)	9.19 (0.1-85.34)	0.005	0.90 (-59.89-27.65)
Testosterone (ng/mL)	42	0.77 (0.025-4.04)	1.08 (0.025-6.23)	0.09	0.07 (-1.59-5.42)
Estradiol (pg/mL)	34	95.4 (5-866.8)	71.92 (6-654.9)	0.126	-17.51 (-264.21-428.7)
sTSH (uIU/mL)	73	1.1 (0.02-77.9)	1.3 (0.02-67.4)	0.658	0.05 (-13.2-6.1)
fT_3 (pg/mL)	69	1.51±0.64	1.62±0.72	0.245	0.11±0.74
fT_4 (ng/dL)	70	1.08±0.36	1.11±0.49	0.505	0.03±0.43
PRL (ng/mL)	72	29.3 (0.3-412.2)	23.6 (3.2-235.9)	0.323	1.6 (-343.0-157.2)
ACTH (pg/mL)	50	15.7 (1.0-156.5)	37.7 (1.0-211.9)	<0.001	14.8 (-123.9-194.6)
Cortisol (ug/dL)	72	21.9 (0.9-63.4)	16.8 (2.5-63.4)	0.032	-1.9 (-39.4-34.9)

ICU: Intensive care unit, IGF-I: Insulin-like growth factor-I, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, sTSH: Sensitive thyroid-stimulating hormone, fT_3: Free triiodothyronine, fT_4: Free thyroxine, PRL: Prolactin, ACTH: Adrenocorticotropic hormone

but not LH levels during hospitalization were lower in patients with a APACHE II score of >15 than in patients with a APACHE score of <15. Thus, while both gonadotropins are suppressed in acute illness, the FSH level of suppression correlates with the severity of illness. Raj et al. (35) also observed that higher levels of E2 in critically ill post-menopausal women when compared to healthy postmenopausal controls despite the lower levels of gonadotropins in them. The authors suggested that the estrogen elevation was not under gonadotropin stimulation and was thus not of ovarian origin and the only other source of estrogen was that derived from the peripheral aromatization of adrenal androgens to estrogen (35). Raj et al. (35) also found that there was a negative correlation between the

Table 5. The endocrine measurements on the baseline and 15 days later admission to the intensive care unit between the survivals and non-survivals

Variables	n	Baseline	15th day	p†	Δ change	p‡
IGF-I						0.597
Survival	17	55.7 (25.0-248.0)	108.0 (25.0-330.0)	0.007	65.1 (-31.7-186.9)	
Non-survival	9	38.9 (25.0-88.6)	35.0 (25.0-240.0)	0.116	2.9 (-13.9-169.1)	
GH						0.355
Survival	35	1.0 (0.08-7.1)	0.8 (0.06-7.6)	0.623	0.04 (-4.0-6.6)	
Non-survival	36	1.6 (0.2-11.2)	1.4 (0.1-13.9)	0.535	-0.2 (-9.1-5.6)	
FSH						0.106
Survival	36	5.1 (0.4-65.5)	6.1 (0.2-51.9)	0.423	0.7 (-14.2-20.2)	
Non-survival	36	3.8 (0.3-54.5)	3.2 (0.1-42.5)	0.120	-0.2 (-47.7-6.1)	
LH						0.627
Survival	36	4.7 (0.1-31.5)	6.1 (0.1-28.5)	0.447	0.06 (-30.1-16.5)	
Non-survival	37	2.4 (0.1-62.9)	1.3 (0.1-85.3)	0.936	0.0 (-59.9-27.6)	
Testosterone						0.870
Survival	28	0.6 (0.03-2.2)	0.4 (0.03-6.2)	0.792	0.0 (-2.0-4.2)	
Non-survival	28	0.4 (0.03-1.5)	0.4 (0.03-2.2)	0.732	0.0 (-1.0-1.5)	
Estradiol						0.161
Survival	31	49.1 (5.0-463.1)	26.9 (5.0-231.0)	0.010	-13.0 (-264.2-89.3)	
Non-survival	32	49.1 (6.1-250.0)	38.0 (5.0-654.9)	0.751	-0.1 (-168.0-428.7)	
sTSH						0.011
Survival	35	1.1 (0.05-73.2)	1.9 (0.03-67.4)	0.039	0.3 (-5.8-6.1)	
Non-survival	38	1.1 (0.02-77.9)	1.1 (0.02-64.7)	0.157	-0.2 (-13.2-3.3)	
fT_3						0.035
Survival	34	1.56±0.65	1.85±0.76	0.033	0.29±0.77	
Non-survival	36	1.47±0.64	1.39±0.60	0.502	-0.08±0.67	
fT_4						0.522
Survival	34	1.15±0.33	1.21±0.52	0.439	0.06±0.51	
Non-survival	35	1.01±0.38	1.01±0.44	0.978	0.00±0.33	
PRL						0.389
Survival	35	30.4 (0.3-177.2)	20.1 (3.8-235.9)	0.169	1.9 (-59.6-157.2)	
Non-survival	37	29.1 (0.6-412.2)	23.9 (3.2-194.7)	0.958	-0,3 (-343.0-124.9)	
ACTH						0.776
Survival	29	16.6 (1.0-64.7)	33.9 (1.0-206.0)	0.006	13.3 (-46.6-193.1)	
Non-survival	21	13.6 (1.0-156.5)	41.8 (1.0-211.9)	0.039	15.3 (-123.9-194.6)	
Cortisol						0.437
Survival	37	20.2 (1.4-58.5)	14.8 (5.4-29.6)	0.028	-3.0 (-39.4-16.1)	
Non-survival	35	23.5 (0.9-63.4)	19.2 (2.5-63.4)	0.388	-0.6 (-37.0-34.9)	

ICU: Intensive care unit, IGF-I: Insulin-like growth factor-I, GH: Growth hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, sTSH: Sensitive thyroid-stimulating hormone, fT_3: Free triiodothyronine, fT_4: Free thyroxine, PRL: Prolactin, ACTH: Adrenocorticotropic hormone, †Comparements between the groups baseline and 15 days later, p value <0.025 were considered statistically significant according the bonferroni adjustment, ‡Between the groups, comparements the changes between baseline and 15 days later, p value <0.05 were considered statistically significant

severity of illness and FSH levels. In our study, we found a negative correlation between SOFA score and baseline FSH levels and a positive correlation between APACHE II score and baseline E2 levels, and also between SOFA score and baseline E2 levels.

We found that the overall mortality rate was 37% and overall APACHE II score and SOFA score were 19.9±6.8 and 5, respectively. Rothwell and Lawler (2) reported an overall mortality rate of 31% and overall APACHE II score of 19.8±8.6 in ICU patients. In our study, multiple logistic regression analysis indicated that age, baseline SOFA score and hospitalization length were the predictive factors of mortality. In addition, age and Δ TSH levels between baseline and 15th day of admission have found to be predictive factors of mortality. Rothwell and Lawler (2) found that cortisol, T4, and TSH concentrations were independent predictors of outcome. Türe et al. (3) suggested that in predicting the short-term mortality in acute respiratory distress *syndrome* patients admitted to ICU, fT_3 levels may have additive discriminatory power with age and APACHE II score. Jarek et al. (8) reported that baseline cortisol and T_3 levels collected from patients within 48 h of admission to the ICU were better discriminators of patient outcome than APACHE II score. In another study performed on 113 patients in the ICU (only 4 were admitted for trauma), the addition of TSH and TT_3 improved the prognostic value of APACHE II score (39). Variations in reported endocrine-based prediction of outcome may be related to the time of sampling, reliability and sensitivity of the assays used, and to differences in patient populations among studies (26). Such as, only medical patients in some studies (8), patients with multiple trauma in others (9), or both medical and surgical patients in others (2,7,12). In addition, the severity of illness varied among studies. In a study by Rothwell and Lawler (2), thyroid and adrenal responses to critical illness were of significantly greater prognostic value than APACHE II scores.

Combinations of endocrine parameters may provide better indices than measurement of a single hormone or an APACHE II-based score (2,9). However, our study revealed that none of the endocrine parameters contribute to the prognostic factor except Δ TSH. This may be due to the factors mentioned above. Also, we did not perform dynamic tests of thyroid and adrenal functions as these tests are difficult in critically ill patients and the results are subjective. This study was performed in a tertiary care center and referred patients had high APACHE II scores. Therefore, our patients may have been undergoing extreme hormonal changes at the time of admission to the ICU.

Conclusion

In conclusion, we think that Δ change in TSH can be used together with APACHE II or SOFA scores in the prediction of prognosis in tertiary mixed type ICU.

Ethics

Ethics Committee Approval: The study has been approved by an institutional Ethics Committee of Yıldırım Beyazıt University Faculty of Medicine (68/16.04.2014), Informed Consent: Informed consent was obtained from the patients or from a first-degree relative if the patient was unconscious or too ill to communicate consent.

Peer-review: Externally and İnternally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Bekir Çakır, Neslihan Çuhacı, Berna Öğmen, Concept: Bekir Çakır, Neslihan Çuhacı, Berna Öğmen, Design: Bekir Çakır, Neslihan Çuhacı, Berna Öğmen, Data Collection or Processing: Neslihan Çuhacı, Berna Öğmen, Cihan Doğer, Analysis or Interpretation: Neslihan Çuhacı, Burçak Polat, Reyhan Ersoy, Literature Search: Neslihan Çuhacı, Cihan Doğer, Burçak Polat, Seval İzdeş, Writing: Neslihan Çuhacı, Berna Öğmen, Seval İzdeş.

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