



## The role of thyroid hormones in assessing the survival of intensive care unit patients

### Uloga hormona tiroidne žlezde u proceni preživljavanja bolesnika u odeljenjima intenzivne nege

Daniela Bartolović\*, Snežana Jovičić†, Branka Terzić‡

University Clinical Center of Serbia, \*Center for Medical Biochemistry, †Center for Anesthesiology and Resuscitation, Belgrade, Serbia; ‡University of Belgrade, Faculty of Pharmacy, Department of Medical Biochemistry, Belgrade, Serbia

All authors have equal contributions to the manuscript.

#### Abstract

**Background/Aim.** Patients in intensive care units (ICUs) often exhibit disturbances in the concentration of thyroid hormones (THs), even if they had no previous thyroid disorders. The aim of the study was to determine whether there is a correlation between THs and the survival rate in the ICU and whether these hormones have predictive capability for mortality rate assessment. **Methods.** The study included 41 patients (23 women and 18 men) divided into two groups: survivors (70.7%) and non-survivors (29.3%). In peripheral blood samples taken within the first 24 hrs after ICU admission, TH levels were measured: triiodothyronine (T3), thyroxine (T4), free T3 (FT3), free T4 (FT4), and thyroid stimulating hormone (TSH), as well as procalcitonin (PCT). The Sequential Organ Failure Assessment Score (SOFAS) was calculated for each patient. **Results.** A statistically significant difference between the study groups (survivor vs. non-survivor patients,  $p < 0.05$ ) was found for PCT, SOFAS, T3, T4, and FT4. The area under the receiver operating characteristic (ROC) curve (AUC) – (AUROC) for the SOFAS was 0.991 [95% confidence in-

terval (CI): 0.898–1.000,  $p < 0.001$ ], for T3 was 0.727 (95% CI: 0.566–0.854,  $p = 0.0097$ ), for T4 was 0.793 (95% CI: 0.638–0.903,  $p = 0.0008$ ), for FT3 was 0.707 (95% CI: 0.544–0.8389,  $p = 0.0299$ ), and for FT4 was 0.795 (95% CI: 0.640–0.904,  $p = 0.0005$ ). Compared to other parameters, T3 had higher sensitivity (91.67%), FT4 had higher specificity (93.10%), while SOFAS had both the highest sensitivity (91.67%) and specificity (96.55%) in relation to all other tested parameters. Multiple linear regression analysis showed that FT4 and T4 were significant predictors of survival time ( $\beta = -0.362$ ,  $p = 0.012$  and  $\beta = -0.356$ ,  $p = 0.014$ , respectively). **Conclusion.** Among all examined THs, only FT4 and T4 showed strong predictive potential for assessing mortality in ICU patients. This study has highlighted the significance of assessing THs levels in critically ill patients. This is crucial because it opens the possibility of implementing specific therapies to rectify issues stemming from hormonal deficiencies.

#### Key words:

intensive care units; mortality; organ dysfunction scores; thyroid hormones; treatment outcome.

#### Apstrakt

**Uvod/Cilj.** Bolesnici u odeljenjima intenzivne nege (OIN) često imaju poremećaj u koncentraciji tiroidnih hormona (TH), čak i u slučajevima kada nisu prethodno imali poremećaj funkcije tiroidne žlezde. Cilj rada bio je da se utvrdi da li postoji korelacija između TH i stepena preživljavanja u OIN, kao i da li ovi hormoni imaju prediktivni značaj u proceni smrtnosti bolesnika. **Metode.** U studiji je učestvovalo 41 bolesnika (23 žene i 18 muškaraca) koji su bili podeljeni u dve grupe: grupu preživelih (70.7%) i grupu preminulih (29.3%). U uzorcima

periferne krvi koji su uzimani u toku prva 24 sata od prijema u OIN određivani su nivoi TH: trijodtironin (T3), tiroksin (T4), slobodan T3 (*free* T3 – FT3), slobodan T4 (FT4) i tiroid-stimulirajući hormon (TSH), kao i prokalcitonin (PCT). Za svakog bolesnika izračunat je *Sequential Organ Failure Assessment Score* (SOFAS). **Rezultati.** Statistički značajna razlika između ispitivanih grupa (preživeli vs. preminuli,  $p < 0,05$ ) utvrđena je za parametre SOFAS, T3, T4 i FT4. Površina ispod *receiver operating characteristic* (ROC) krive [*area under the ROC curve* (AUC) – (AUROC)] iznosila je za SOFAS 0,991 [95% *confidence interval* (CI): 0,898–1,000,  $p < 0,001$ ], za T3 0,727 (95% CI:

0,566–0,854,  $p = 0,0097$ ), za T4 0,793 (95% CI: 0,638–0,903,  $p = 0,0008$ ), za FT3 0,707 (95% CI: 0,544–0,8389,  $p = 0,0299$ ) i za FT4 0,795 (95% CI: 0,640–0,904,  $p = 0,0005$ ). U poređenju sa ostalim parametrima, T3 je imao višu osetljivost (91,67%), FT4 višu specifičnost (93,10%), dok je SOFAS imao istovremeno i najvišu osetljivost (91,67%) i specifičnost (96,55%) u odnosu na sve druge ispitivane parametre. Primenom multiple linearne regresione analize utvrđeno je da su FT4 i T4 bili značajni prediktori vremena preživljavanja bolesnika ( $\beta = -0,362$ ,  $p = 0,012$  i  $\beta = -0,356$ ,  $p = 0,014$ , redom). **Zaključak.** Među

svim ispitanim TH, pokazano je da FT4 i T4 imaju snažan prediktivni potencijal za procenu smrtnosti bolesnika u OIN. Ovom studijom je istaknut značaj određivanja nivoa TH kod kritično obolelih, što je ključno jer otvara mogućnost primene specifičnih terapija koje bi korigovale poremećaje nastale zbog deficita hormona.

**Ključne reči:**  
**intenzivna nega, odeljenja; mortalitet; skorovi, disfunkcija organa; tiroidna žlezda, hormoni; lečenje, ishod.**

## Introduction

Patients who are in intensive care units (ICUs) due to the severity of their health condition can develop serious metabolic disorders that lead to hyperglycemia, muscle weakness, and disturbances in the concentration of thyroid hormones (THs), even if they had no previous thyroid gland dysfunction<sup>1, 2</sup>. Non-thyroidal illness syndrome (NTIS) or euthyroid sick syndrome is a condition characterized by changes in THs levels that are not the result of pathological processes in the thyroid gland or hypothalamus<sup>3</sup>. The median prevalence rate of NTIS in patients who are in ICUs is 58%<sup>4</sup>. After recovery, THs levels generally return to reference values. As expected, the initial changes in TH concentration can be observed in triiodothyronine (T3), with a decrease in T3 levels and an increase in the concentration of reverse T3 (rT3). This condition is also referred to as low T3 syndrome. Decreased T3 concentration with a slight increase in rT3 is the most common disturbance in NTIS. Thyroxine (T4) levels remain within reference values until the disease progresses. The degree of T4 and T3 concentration decrease correlates with the severity of the underlying condition<sup>5-7</sup>.

Prolonged fasting or reduced carbohydrate intake leads to the inhibition of deiodinase D1 in the liver and the conversion of T4 to T3, resulting in decreased T3 production. On the other hand, the metabolism of rT3 is prevented<sup>8, 9</sup>. Since starvation causes a decrease in basal metabolism, the body adapts to hypothyroidism in order to conserve energy and proteins. Patients who only have a drop in T3, without a change in T4 concentration, have the mildest form of NTIS. As the disease progresses, a more complex syndrome characterized by a decrease in T4 levels develops<sup>10</sup>. Interpretation of obtained values for free T4 (FT4) in NTIS is challenging due to the influence of numerous factors on the assay itself (serum inhibitors, metabolites, free fatty acids). FT4 may be normal or slightly reduced but is usually elevated<sup>11, 12</sup>.

In addition to decreased T3 and T4 concentrations, normal or decreased thyroid stimulating hormone (TSH) levels are observed along with normal or increased rT3 levels. This low TSH level is likely due to disruptions at the hypothalamic level, inadequate secretion of thyrotropin-releasing hormone, and reduced glycosylation. In some hospitalized patients recovering from non-thyroidal illnesses,

a temporary increase in the serum TSH concentration is observed<sup>13, 14</sup>.

The aim of this study was to determine whether there is a correlation between THs levels and survival rates in ICU patients and whether these hormones have predictive significance in assessing patients' mortality.

## Methods

### Patients

From March to July 2016, 41 adult patients, 23 males and 18 females, had been admitted to an ICU at the Emergency Center of the University Clinical Center of Serbia (Belgrade, Serbia). Demographic data such as age and gender, length of stay at the ICU, and ICU mortality had been recorded for all patients. The research was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Ethics Committee of the University Clinical Center of Serbia (No. 68/4, from February 18, 2016). Each patient provided written consent to participate in the study.

Patients with known thyroid gland disorders (hypo- or hyperthyroidism) were excluded from this prospective study. In contrast, patients with cardiovascular disorders (12.2%), kidney dysfunction (7.3%), those who had undergone extensive surgical procedures (9.7%), and patients recovering from traffic accidents and other traumas (70.7%) were included in the study. T3, T4, FT3, FT4, and TSH were measured in serum samples. The concentration of procalcitonin (PCT) was determined for the purpose of daily monitoring of patients due to the possible occurrence of systemic infection (sepsis). The Sequential Organ Failure Assessment Score (SOFAS) was calculated for each patient according to Lambden et al.<sup>15</sup>.

The study included a total of 41 patients, comprising 23 males and 18 females. Patients were subsequently divided into two groups: survivors ( $n = 29$ ; 16 males and 13 females) and non-survivors ( $n = 12$ ; 7 males and 5 females).

### Laboratory analyses

Venous peripheral blood samples were collected within the first 24 hrs of admission, and THs levels and PCT concentration were determined in these samples. Blood was col-

lected in the morning in order to avoid daily variations in hormone concentration. T3, FT3, T4, FT4, TSH, and PCT concentrations were measured using an immunoassay analyzer Cobas e601 (Roche Diagnostics, Ltd. Switzerland), utilizing commercial electrochemiluminescent immune tests (ECLIA). Reference values were as follows: T4 = 66–181 nmol/L, FT4 = 12–22 pmol/L, T3 = 1.3–3.1 nmol/L, FT3 = 3.1–6.8 pmol/L, TSH = 0.270–4.20 mIU/L, and for PCT < 0.5 ng/mL. The PCT value < 0.5 ng/mL indicates a low risk for systemic infection, while PCT > 2.0 ng/mL indicates a high risk for systemic infection. Any deviation from these values was considered pathological (either elevation or decrease).

#### *SOFAS calculation*

The SOFAS was calculated for each patient during their stay in the ICU and was used to assess organ function or the degree of organ function impairment. It is based on the assessment and monitoring of hemostasis and the functioning of six organ systems: respiratory, cardiovascular, hepatic, renal, and neurological organ system. The SOFAS was calculated using an online calculator<sup>16</sup>, based on a formula that included the following data – partial pressure of oxygen (PaO<sub>2</sub>, kPa), fraction of inspired oxygen (FiO<sub>2</sub>, %), platelet count ( $\times 10^9$  /L), Glasgow Coma Scale (GCS, points), total bilirubin concentration (tBIL,  $\mu$ mol/L), serum creatinine concentration (sCRE,  $\mu$ mol/L), and hypotension status (value of mean arterial pressure or if on vasoactive agents support, at what concentration). The score ranged from 1 to 15, with higher scores indicating a higher likelihood of mortality. An increase in the SOFAS during the first 24–48 hrs indicates a probability of mortality ranging from 50% to 95%. A score less than 9 is associated with a mortality probability of approximately 33%, while a score of 11 or higher increases the probability to 95%<sup>17</sup>.

#### *Statistical analysis*

The Shapiro-Wilks test was used to check normality distribution. For parameters with a normal distribution, results were presented as mean  $\pm$  standard deviation, and Student's *t*-test was used for comparisons between groups. Parameters that did not have a normal distribution were presented as median and interquartile ranges (25<sup>th</sup>–75<sup>th</sup> percentile), and the comparison of these values between survivors and non-survivors was performed using the Mann-Whitney *U* test. The performance of THs levels and the SOFAS in predicting mortality in the ICU was assessed, and the following parameters were calculated: area under the curve (AUC) for the receiver operating characteristic (ROC) (AUROC) analysis, 95% confidence interval, cut-off values, sensitivity, and specificity. The association between ICU survival and the concentration of the studied hormones was determined using stepwise multiple linear regression (MLR) analysis, which was presented with  $\beta$  coefficients, *p*-values, and adjusted R<sup>2</sup> (coefficient of determination). The primary requirement for this analysis was that the parameters followed

a non-normal distribution. To meet this criterion, we applied logarithmic data transformation of variables with non-normal distribution in order to achieve normal distribution. Other variables with normal distribution were used as raw data. We calculated the power of the study using a *post-hoc* test and also *a priori* calculation by the G-power program (version 3.1.9.4, Kiel University, Germany).

According to the *post-hoc* analysis, for the five main parameters (SOFAS, T3, T4, FT3, FT4) measured in our study, we obtained different numbers of subjects for the two groups. Subsequently, to calculate the power of the study, we calculated the average number of patients for each of the two groups, the survivor and non-survivor group, which resulted in 28 and 14 patients, respectively, with a total of 42 patients. This number of patients yielded a study power of 0.854. Since we had a total of 41 patients (29 in the survivor group and 12 non-survivor group patients), we assumed that this number would provide a study power higher than 0.800, which was the basic requirement for study adequacy.

To analyze the survival rates in both groups of patients, we employed the Kaplan-Meier analysis and the log-rank test. A probability level of *p* less than 0.05 indicated a statistically significant difference for all implemented analyses. Complete statistical analysis was performed using MedCalc version 18.9 (MedCalc Software Ltd, Ostend, Belgium).

## **Results**

The characteristics of the study groups are presented in Table 1. The average length of stay in the ICU was approximately four days. The average age among survivors was 59.8  $\pm$  15.5 years, while among the non-survivors, it was 67.5  $\pm$  15.4 years. There was no statistically significant difference in age between these two groups of patients. The average age among surviving males was 56.6  $\pm$  14.9 years, while among non-surviving males, it was 72.4  $\pm$  12.2 years. There was no statistically significant difference between these two groups of patients. The average age among surviving females was 64.2  $\pm$  8.6 years, but among non-surviving females, it was 60.6  $\pm$  7.7 years. There was also no significant difference between these two groups of female patients. The SOFAS was significantly higher in the group of non-surviving patients (*p* < 0.001), who were also slightly older than the group of survivors. Statistically significant differences were observed between the T3, T4, FT4, and PCT values for the examined groups of patients. For other THs (FT3 and TSH), no statistically significant differences were observed between the obtained values (Table 1).

For the monitored parameters, the AUC value, sensitivity, specificity, and their cut-off values were calculated. FT4 and T4 showed the highest diagnostic accuracy in ICU patients' mortality prediction based on their AUC values. However, the AUC values for FT4 and T4 were lower than the AUC values for the SOFAS but higher than those for T3, FT3, and TSH (Table 2, Figure 1). Table 2 provides the data regarding the diagnostic accuracy of the examined variables in the prediction of ICU patients' mortality rate.

**Table 1**

Demographic and clinical characteristics of the patients				
Variables	All patients n=41	Survivors n=29	Non-survivors n=12	<i>p</i> -value
Gender (n)				
male/female	23/18	16/13	7/5	0.854
Age (years) <sup>a</sup>	62.1 ± 15.7	59.8 ± 15.5	67.5 ± 15.4	0.155
males	61.2 ± 18.6	56.6 ± 14.9	72.4 ± 12.2	0.057
females	63.2 ± 10.7	64.2 ± 8.6	60.6 ± 7.7	0.541
Principal diagnosis leading to ICU admission (%)				
cardiovascular disorders	12.2	4.9	7.3	
kidney dysfunction	7.3	2.4	4.9	
extensive surgical procedures	9.7	4.9	4.9	
traffic accidents and other traumas	70.7	58.5	12.2	
SOFAS (points) <sup>b</sup>	6 (5–9)	5 (3–6)	12 (11–12)	< <b>0.001</b>
Intensive care unit stay (days) <sup>b</sup>	4 (3–5)	4 (3–5)	3 (2–5)	0.108
T3 (nmol/L) <sup>b</sup>	0.89 (0.76–1.11)	0.95 (0.74–1.32)	0.74 (0.52–1.02)	<b>0.024</b>
T4 (nmol/L) <sup>a</sup>	76.8 ± 25.6	84.0 ± 21.7	59.3 ± 26.6	<b>0.004</b>
FT3 (pmol/L) <sup>a</sup>	3.08 ± 1.24	3.28 ± 1.14	2.62 ± 1.41	0.123
FT4 (pmol/L) <sup>b</sup>	15.4 (14.0–17.9)	17.2 (14.4–20.0)	12.6 (10.6–16.4)	<b>0.003</b>
TSH (mIU/L) <sup>b</sup>	1.47 (1.11–2.08)	1.56 (0.98–2.59)	1.11 (0.74–2.46)	0.566
PCT (ng/mL) <sup>b</sup>	0.75 (0.25–5.40)	0.52 (0.16–1.05)	4.46 (2.39–38.43)	< <b>0.001</b>

SOFAS – Sequential Organ Failure Assessment Score; T3 – triiodothyronine; T4 – thyroxine; FT3 – free T3; FT4 – free T4; TSH – thyroid-stimulating hormone; PCT – procalcitonin.

<sup>a</sup>mean ± standard deviation; <sup>b</sup>median and interquartile range (25<sup>th</sup>–75<sup>th</sup> percentile).

Student's *t*-test or Mann-Whitney *U* test was applied for continuous variables;  $\chi^2$  test was applied for categorical variables.

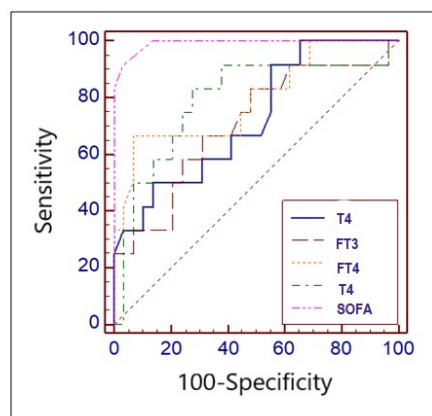
**Bolded values are statistically significant differences between groups.**

**Table 2****Diagnostic accuracy of the variables for mortality rate prediction estimated by ROC curve**

Parameter	AUC	SE	95% CI	<i>p</i> -value	Cut-off value	Sensitivity	Specificity
T3	0.727	0.088	0.566–0.854	0.010	1.11	91.7	44.8
T4	0.793	0.087	0.638–0.903	0.001	76	83.3	72.4
FT3	0.707	0.095	0.544–0.838	0.030	2.77	66.7	69.0
FT4	0.795	0.085	0.640–0.904	0.001	13.4	66.7	93.1
TSH	0.557	0.107	0.394–0.712	0.593	1.15	58.3	69.0
SOFAS	0.991	0.009	0.898–1.000	< 0.001	9	91.7	96.6

ROC – receiver operating characteristic; AUC – area under the curve; SE – standard error; CI – confidence interval.

For other abbreviations, see Table 1.



**Fig. 1 – Receiver operating characteristic analysis of thyroid hormone status and SOFAS in ICU patients' mortality rate prediction.**  
For abbreviations, see Table 1.

Among several thyroid gland-related parameters measured in this study, FT4 ( $\beta = -0.362$ ,  $p = 0.012$ ) and T4 ( $\beta = -0.356$ ,  $p = 0.014$ ) were the significant predictors of

survival time. Additionally, the adjusted  $R^2$  (0.285) revealed that nearly 30% (28.5%) of survival times' variability was determined by the selected model of parameters (Table 3).

The Kaplan-Meier curves and log-rank analysis revealed a significant difference in survival rates when comparing the T4 and SOFAS parameters. Notably, the curves generated for the terciles of the T4 and SOFAS values exhibited a significant difference (log-rank test,  $p < 0.05$ ). This indicates that only T4 and the SOFAS exert a significant influence on survival in the ICU. There

was no statistical significance detected for other parameters (Table 4).

Based on the median survival time for SOFAS and T4, similar values were obtained in the number of days of survival (Table 5, Figures 2 and 3). These results confirm the importance of determining T4 in the assessment of patient survival in the ICU.

Table 3

**Stepwise multiple linear regression analysis  
of Intensive care unit patients' survival time prediction**

	$R^2 = 0.321$	
	Adjusted $R^2 = 0.285$	
	$\beta$ value	$p$ -value
FT4 <sup>a</sup>	-0.362	<b>0.012</b>
T4	-0.356	<b>0.014</b>
T3 <sup>a</sup>	-0.071	0.676
TSH <sup>a</sup>	-0.008	0.954
FT3	-0.027	0.855

$\beta$  – coefficient of multiple linear regression analysis;  $R^2$  – coefficient of determination in multiple linear regression analysis.

<sup>a</sup>log<sub>10</sub>-transformed data. Bolded values are statistically significant.

For abbreviations, see Table 1.

Table 4

**Log-rank survival analysis for patients in ICU**

Parameters	Chi-square value	$p$ -value
T3	2.921	0.232
T4	7.420	<b>0.024</b>
FT3	4.152	0.125
FT4	4.878	0.087
TSH	3.057	0.217
SOFAS	22.060	<b>&lt; 0.001</b>

For abbreviations, see Table 1.

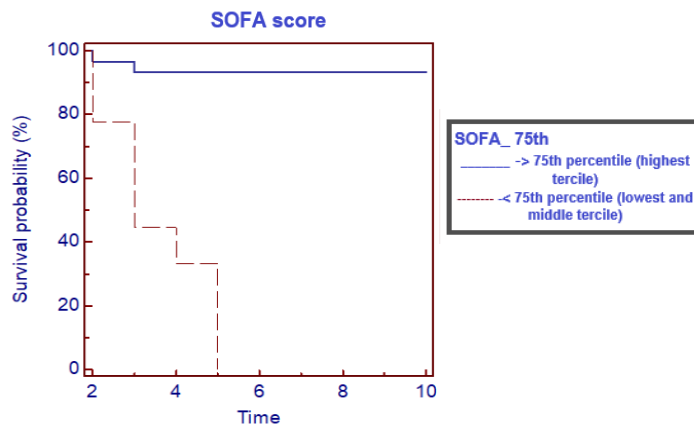
Bolded values are statistically significant.

Table 5

**Median for survival time**

Parameters	Median	95% CI
SOFAS (75 <sup>th</sup> percentile)	3.000	2.026–3.974
T4 (tercile)		
lowest	4.000	1.405–6.595
middle	5.000	2.962–7.038

For abbreviations, see Tables 1 and 2.



**Fig. 2 – Survival time depending on SOFAS.**

For abbreviation, see Table 1.

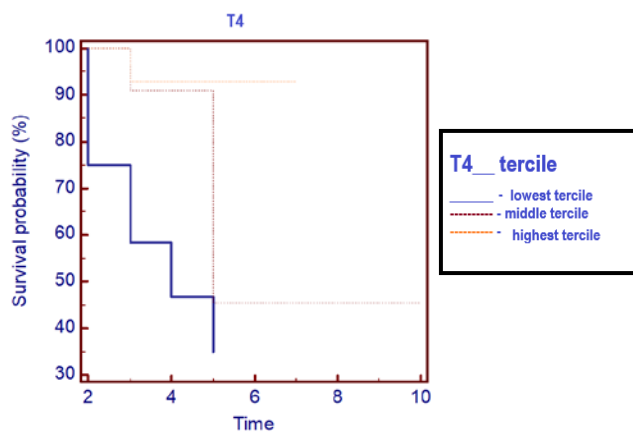


Fig. 3 – Survival time depending on the levels of thyroxine (T4).

## Discussion

Severe health conditions encountered in patients in ICUs are often accompanied by disturbances in the concentration of THs<sup>18, 19</sup>. Rarely are these disorders isolated. Instead, they are usually associated with other endocrine disorders (reduced levels of gonadotropins and sex hormones in the serum, along with elevated levels of adrenocorticotrophic hormone and cortisol)<sup>20–22</sup>. The total thyroxine levels are usually decreased in patients with NTIS during the first 24–48 hrs. Initial reductions occur due to decreased binding of hormones to transport proteins. The concentration of FT4 in serum generally remains in reference ranges until the disease becomes severe. Hypothalamic-pituitary suppression in the chronic phase of severe illness leads to reduced TSH secretion, decreased synthesis of T4 in the thyroid gland, and, consequently, reduced FT4 in circulation, all of which indicate a poor disease outcome<sup>23</sup>. In euthyroid sick syndrome, TSH levels are usually within reference values until the disease progresses, at which point TSH levels decrease. Some hospitalized patients experience transient increases in serum TSH levels during recovery from non-thyroidal illness. Some of these patients will have transient hypothyroidism after recovery. Patients with very high TSH levels during non-thyroidal illness and hospitalization will have permanent hypothyroidism after recovery<sup>24</sup>.

The 41 seriously ill adult patients were admitted to ICU in the Emergency Center of Serbia. According to the outcome of the disease, the patients were subsequently divided into two groups: survivors and non-survivors. The average length of stay in the ICU was four days. There was no statistically significant difference in age between these two groups of patients, but our results showed significantly higher SOFAS in the non-survivors group compared to survivors.

Rarely, severely ill patients with hyperthyroidism may have a low serum T3 concentration, according to Moura Neto et al.<sup>25</sup>. In our study, T3 concentrations were in both groups below the reference values and significantly lower in the deceased participants compared to the survivors group. T4 concentration was also significantly lower in non-survival patients, which is also shown in a study led by Bartolovic et al.<sup>26</sup>. Economidou et al.<sup>27</sup> explained THs alterations

connected with critical illness as the adaptive physiological response to stress or as the maladaptive response which required specific treatment.

FT4 and T4 showed the highest diagnostic accuracy in ICU patients' mortality prediction based on their AUC values. However, the AUC values for FT4 and T4 were lower than the AUC values for the SOFAS but higher than those for T3, FT3, and TSH. Similar results were presented in the study by Praveen et al.<sup>28</sup>. According to the result from our MLR analysis, FT4 and T4 were the significant predictors of survival time ( $\beta = -0.362$ ,  $p = 0.012$ ;  $\beta = -0.356$ ,  $p = 0.014$ , respectively). Results of other published studies have shown a correlation between FT3, FT4, and the rate of mortality<sup>29</sup>. On the other hand, some studies have shown a correlation between the levels of T3, T4, FT4, and TSH and the rate of patient mortality<sup>30–32</sup>. In a study led by Wang et al.<sup>33</sup>, FT3 had the greatest power for predicting ICUs mortality rate, as suggested by the largest value of AUC ( $0.762 \pm 0.028$ ). Such differences in results may likely be a consequence of the small number of subjects or heterogeneous patient groups with different pathological processes. The variability in results regarding the predictive significance of THs may also be attributed to patients being in different disease phases, some in the acute and others in the chronic phase. Abnormalities in THs metabolism observed during the acute phase of illness are probably part of the systemic stress response, accompanying disturbances in the neuroendocrine system<sup>34, 35</sup>.

Based on power analysis, we believe that the number of participants in the two groups (29 in the survivors group and 12 in the non-survivors group, totaling 41 patients) was sufficient to achieve a study power that exceeded the level of 0.800 and to justify the inclusion of the patients already enrolled in the study<sup>36</sup>. In addition, it is important to emphasize that our data reflect a study conducted in an ICU with patients in life-threatening conditions. Therefore, in this context, the results could be precious as they directly apply to the critical care and management of these patients. When we talk about survival analysis, we should point out that only SOFAS and T4 values had an impact on survival in the ICU.

All patients had blood drawn within the first 24 hrs of admission to the ICU. Still, some patients were transferred to

the ICU from other departments or other hospital centers due to deteriorating conditions. Thus, it is very likely that their primary illness was already in the chronic phase, with fulminant acutisation, which affected thyroid gland function and led to a different hormone distribution.

#### *Limitations of the study*

While designing the study, we were aware of some limiting factors that could affect the final outcome. In the first place, we were faced with a smaller number of patients, both due to their state of consciousness and the impossibility of giving consent to participate in the study, as well as the fact that the patients who had thyroid disease and were on some of the therapies, were not included in the study. On the other hand, we had a limited number of laboratory tests for determining the concentration of THs, which additionally affected a smaller number of patients. During the study, we could not monitor the patients for a long period of time, both due to economic reasons and because patients do not stay long in ICUs but get transferred to another department or sent for home treatment. In the study, we presented the power of the study regardless of the small number of respondents and obtained satisfactory results in spite of that. Because of the patients' status complexity and the absence of Ethical Committee approval for any other patient data, we were unable to

provide additional data from the other health centers covering the period before ICU admission, which is certainly one of the prominent study limitations.

The results we obtained during this study should be considered preliminary data due to the small number of subjects, the heterogeneous nature of the patient group regarding their illnesses, and the inability to assess the disease phase at the time of ICU admission. Despite all of this, the number of patients was still sufficient for accurate analyses of the parameters with valid conclusions.

#### **Conclusion**

The results of this study are modest. Further research with a larger number of subjects may help resolve the existing dilemma. We intended to conduct a clinical study with the aim of contributing valuable insights into patient care and enhancing diagnostic capabilities of vital importance for the future. Results obtained in our study represent real-life data in critically ill patients, and because of that, were assumed with distinct value. In cases of significant thyroid hormone imbalances that can be addressed through specific therapy, the correction of these imbalances can lead to an enhancement in patients' overall condition and a reduction in the risk of life-threatening complications.

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