ORIGINAL ARTICLE

A LOOK AT THYROID FUNCTIONS AS A PREDICTOR ON PROGNOSIS OF CRITICALLY ILL PATIENTS IN INTENSIVE CARE UNITS FROM THE PERSPECTIVE OF COVID-19

Yoğun Bakım Ünitesindeki Kritik Hastaların Prognozunun Belirleyicisi Olarak Tiroid Fonksiyonlarına Covid-19 Perspektifinden Bir Bakış

Murat TÜMER[1], Nihal Deniz BULUT YÜKSEL[2], Banu KILIÇASLAN[3], Seda Banu AKINCI[3]

[1]VKV Amerikan Hospital,
Department of Anesthesiology and Reanimation,
İstanbul,
Türkiye.
[2]Department of Intensive Care,
Mersin State Hospital,
Mersin,
Türkiye.
[3]Hacettepe University,
Faculty of Medicine,
Department of Anesthesiology and Reanimation,
Ankara,
Türkiye.

Murat TÜMER, Dr.
(0000-0001-9132-9992)
Nihal Deniz BULUT YÜKSEL, Dr.
(0000-0002-3517-3919)
Banu KILIÇASLAN, Prof. Dr.
(0000-0003-3295-9999)
Seda Banu AKINCI, Prof. Dr.
(0000-0002-8538-6955)

İletişim:
Dr. Murat TÜMER
VKV Amerikan Hastanesi, Dept. of Anesthesiology and Intensive Care,
İstanbul-Türkiye

Geliş tarihi/Received:
Kabul tarihi/Accepted:
DOI: 10.16919/bozoktip.1416323

Bozok Tıp Derg 2024;14(1):113-119
Bozok Med J 2024;14(1):113-119

ABSTRACT

Objective: Thyroid gland can be affected both by cytokine storm and through angiotensin-converting enzyme 2 receptors. A worse prognosis has been described in patients with low fT3 levels. The aim of this study is to evaluate the prognostic significance of thyroid function during COVID-ICU hospitalization.
Material and Methods: After ethical approval, 100 COVID-19 patients followed in the ICU between March 2020 and April 2021 was admitted to study. Patients with previous thyroid disease were excluded from study. Free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels at ICU admission were evaluated. Clinical, demographic, laboratory, treatment, and outcome data were obtained from the patient's electronic hospital records. Mann Whitney U, Spearman correlation, binary logistic, and linear regression tests were used for statistical analysis.
Results: TSH was in 31 patients, fT3 was in 37 patients, and fT4 was in 54 patients, which were outside the normal ranges. fT3 were lower in non-survivors than the survivors (p=0.036). However, the fT3 level was not the independent factor for mortality rate in linear regression analysis (p=0.652). APACHE II and procalcitonin levels as independent predictors of mortality (p=0.017). fT3 remained an independent factor for the length of ICU stay (p=0.024) and the length of hospital stay (p=0.031).
Conclusion: fT3 is a prognostic indicator that can predict hospital and ICU length of stay in critically ill patients with Covid-19. In the future, a broader panel of validated biochemical markers, including fT3 levels, may become a simple tool for stratified management of patients with severe COVID-19.

Keywords: *COVID-19; Thyroid Function Tests, Intensive Care Unit; Critical Illness*

ÖZET

Amaç: Tiroid bezi hem sitokin fırtınası hem de anjiyotensin dönüştürücü enzim-2 reseptörleri aracılığıyla etkilenebilir. Düşük fT3 seviyelerine sahip hastalarda kötü bir prognoz tanımlanmıştır. Bu çalışmanın amacı, hastaların COVID-YBÜ yatışı sırasında tiroid fonksiyonunun prognostik önemini değerlendirmektir.
Gereç ve Yöntemler: Etik onayın ardından, Mart 2020 ile Nisan 2021 arasında YBU'da takip edilen 100 COVID-19 hastası çalışmaya alındı. Bilinen tiroid hastalığı olan hastalar çalışmadan çıkarıldı. YBÜ'ne kabulde serbest triiyodotironin (fT3), serbest tiroksin (fT4) ve tiroid simüle edici hormon (TSH) seviyeleri değerlendirildi. Klinik, demografik, laboratuvar, ve tedavi verileri elektronik hastane kayıtlarından elde edildi. İstatistiksel analiz için Mann Whitney U, Spearman korelasyon, ikili lojistik ve lineer regresyon testleri kullanıldı.
Bulgular: TSH 31 hastada, fT3 37 hastada ve fT4 54 hastada normal aralıkların dışında bulunuyordu. fT3 hayatta kalmayanlarda hayatta kalanlara göre daha düşüktü (p=0,036). Ancak, fT3 seviyesi, lineer regresyon analizinde mortalite oranı için bağımsız bir faktör değildi (p=0,652). APACHE II ve prokalsitonin seviyeleri mortalite için bağımsız prediktörler olarak saptandı (p=0,017). fT3, YBÜ kalış süresi (p=0,024) ve hastane kalış süresi (p=0,031) için bağımsız bir faktör olarak kaldı.
Sonuç: fT3, Covid-19'lu kritik hastalarda hastane ve YBÜ kalış süresini öngörebilen prognostik bir göstergedir. Gelecekte, fT3 seviyelerini içeren biyokimyasal belirteçlerin daha geniş bir paneli, şiddetli COVID-19 hastalarının tabalalı yönetimi için basit bir araç haline gelebilir.

Anahtar Kelimeler: *COVID-19; Tiroid Fonksiyon Testleri; Yoğun Bakım Ünitesi; Kritik Hastalık*

INTRODUCTION

The effect of COVID-19 on the thyroid gland is little known. It has been demonstrated in various publications that Angiotensin Converting Enzyme-2 (ACE2) and Transmembrane Protease Serine-2 (TMPRSS2), which are known to be key sites for COVID-19 during entry into the body, are highly expressed in the thyroid gland and are also more abundant in the lungs (1, 2). Data obtained during the previous coronavirus pandemic caused by SARS-related coronavirus, a member of the corona viridae family, have shown that SARS-CoV can damage thyroid cells and reduce the number of thyroid-stimulating hormone (TSH)-positive cells in the pituitary (3, 4). This result suggests that thyroid dysfunction may be a comorbidity in COVID-19 patients.

It is also a known fact that low triiodothyronine (T3) levels, also known as non-thyroid disease syndrome (NTI), also known as euthyroid patient syndrome, can be observed in critically ill patients (4). Therefore, several studies have attempted to assess the role of thyroid function in predicting the outcomes of COVID-19 in patients. Building on this conclusion, low free T3 (fT3) levels has been associated with multiple adverse events such as clinical lability, increased oxygen demand and prolonged hospital stay etc. in many studies, suggesting that low fT3 may have prognostic significance (4,5). However, there are few studies on whether fT3 has an independent prognostic value, especially in deaths due to COVID-19, and perhaps the possibility of it being a new predictor (5).

In this retrospective study, we aimed to describe changes in thyroid hormone levels, especially low fT3, which are considered to have prognostic value in patients hospitalized with COVID-19. We also investigated whether thyroid dysfunction was associated with mortality in COVID-19.

MATERIAL AND METHOD

This observational cohort study was approved by the Hacettepe University Ethics Committee of Non-Interventional Clinical Research (Approval Number: GO 21/617, Date: 04/05/2021). All patients 18 years or older admitted to Hacettepe University, Faculty of Medicine, Anesthesia Intensive Care Unit with a clinical suspicion of COVID-19 between March 01, 2020, and May 01, 2021, were included in this observational, retrospectively screening cohort study. Those who had positive COVID-19 polymerase chain reaction (PCR) tests, had thyroid hormone tests at ICU admission, had no history of thyroid disease, and did not use any medication (like glucocorticoids, dopamine agonists, somatostatin analogs) that would affect thyroid functions were included in the study.

Patients presenting with positive COVID-19 underwent a standard set of blood tests, including complete blood count, renal and liver function, albumin, C-reactive protein (CRP), procalcitonin, cortisol, and thyroid function. Clinical, demographic, laboratory, treatment, and outcome data were obtained from the patient's electronic hospital records. Preselected demographics and comorbidities of interest (age, sex, history of diabetes, hypertension, chronic kidney disease, cardiovascular disease, endocrine disease, current diagnosis of cancer, obstructive or restrictive pulmonary disease including asthma and chronic obstructive pulmonary disease) were recorded.

A COVID-19 diagnosis was a real-time reverse transcriptase polymerase chain reaction confirmation of infection from a nasopharyngeal swab. Free triiodothyronine (fT3, reference range: 3.8-6 pmol/L), free thyroxine (fT4, reference range: 7.86-14.41 pmol/L), and thyroid-stimulating hormone (TSH, reference range: 0.38-5.33 uIU/mL) levels were evaluated at admission. All data were obtained, independently recorded, and cross-checked by two physicians up to May 01, 2020.

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 23 (SPSS, Inc., Chicago, IL). The values that were normally distributed were presented as mean ± standard deviation. Ordinal data were expressed as median (min-max). Categorical data were shown as the number of cases and percentages. To compare the data in two groups, the chi-square and Mann-Whitney U tests were used as statistical methods, where applicable. The Spearman correlation test was used to test whether there is a relationship between the data. Binary logistic and linear regression tests were used for independent predictor analysis. A p-value < 0.05 was considered statistically significant.

Bozok Tıp Derg 2023;14(1):113-119
Bozok Med J 2023;14(1):113-119

RESULTS

A total of 166 moderate-to-critical patients with COVID-19 (with positive PCR tests on admission) between March 2020 and April 2021 were included in this study. Twenty-three patients were excluded because of thyroid disease or using drugs that may cause thyroid dysfunction (28 patients), and 15 patients whose thyroid function tests were not performed at the time of admission to the ICU. Eventually, 100 patients (35 female, 65 male) with COVID-19, including 57 survivors and 43 non-survivors, were enrolled in the final analysis.

More than half of the patients were admitted to the ICU from the emergency department (54 cases -data was not shown). The most common indication for admission was respiratory failure (74 cases), and comorbidities were hypertension (49 cases), diabetes (21 cases), cardiac disease (25 cases), chronic pulmonary disease (26 cases), and malignancies (21 cases). The 43 deaths of median (IQR) age was 73 (19-89) years, and 31 (47.7%) of them were men. The non-survivors were older (73 (19-89); p=0.002) and had a higher proportion of preexisting cardiac disease, diabetes, and malignancies (p>0.05) and also higher APACHE II (18 (8-36); p<0.0001) score than survivors. Respiratory rate (p>0.05) was higher and the peripheral oxygen saturation (p>0.05) was lower in the non-survivors. Laboratory testing showed that the non-survivors had a lower lymphocyte count (p: 0.053), higher levels of C reactive protein (CRP) (p: 0.001), procalcitonin (p < 0.0001) and cortisol (p: 0.058) (Table 1).

The most used antiviral agent in the treatment was favipiravir (86 cases). Forty-two patients had steroid therapy before admission to ICU. During follow-up in ICU, 80 patients had low doses of steroid therapy (less than 7.5 mg/day), and 12 patients had high doses of steroid therapy (more than 40 mg/day) (Table 1).

Fifty-five patients need mechanical ventilation (MV) therapy. Of these patients, 69% (38 cases) were survivor and 31% (17 cases) were non-survivor (p <0.0001). The median length of MV was 11 (1-78) days. The median length of ICU stay was 11 (1-98) days, and the total hospitalization time was 16 (2-108) days.

Considering the thyroid function tests of the patients, TSH was in 31 patients, fT3 was in 37 patients, and fT4 was in 54 patients, which were outside the normal ranges (Table 2). Thyroid function parameters were similar according to TSH serum levels (0.65 (0.1-16.7) vs. 0.6 (0.02-6.54) µIU/mL, p=0.751) between the survivors and non-survivors. In addition, fT4 levels were not significantly different between the two groups (14.6 (6.2-29.3) vs. 15.6 (8.4-45.2) pmol/L, p=0.679) (Table 1). However, fT3 levels were significantly lower in non-survivors than in the survivors (3.8 (1.98-5.55) vs. 3.4 (2.2-5.7) pmol/L, p=0.036) (Table 1).

Concordantly, a low fT3 state (defined as fT3 < 3.1 pmol/L) accounted for a higher proportion in the non-survivors than in the survivors (72.7% vs. 11.2%, p= .001). The mortality rate was 43%. There was a statistically significant relationship between fT3 levels (t(61)= 2.14, p=0.036) and mortality rate. However, the fT3 level was not the independent factor for mortality rate in linear regression analysis (B=0.444, β= -0.019, p=0.652) (Table 3). The ICU 28-day mortality rate was 34%. There was no significant relationship between the thyroid hormone levels and ICU 28-day mortality. Although there was a statistically significant relationship between mortality and advanced age, APACHE II scores, CRP and procalcitonin levels (p= 0,001; p=0.0001; p=0,001, p=0.0001), linear regression analysis revealed only APACHE II and procalcitonin levels as independent predictors of mortality (B=0.349, β=0.505, p=0.004 and B=2.142, β=0.038, p=0.017) (Table 3).

The median length of ICU stay was 11 (1-98) days. There was a weak correlation between the fT3 level and the length of ICU stay (r=-0.245, p=0.053) (Table 3). When CRP, procalcitonin, age, APACHE II, and T3 levels were entered as independent variables into linear logistic regression analysis of the length of ICU stay as the dependent variable, the fT3 level remained an independent factor for the length of ICU stay (B= -6.147, β= -0.293, p=0.024). The median length of hospital stay was 16 (2-108) days. A statistically significant but low rate correlations were found between the fT3 level and the length of hospital stay (r=-0.283, p=0.024). When the T3 level and the APACHE II scores were entered as independent variables into linear logistic regression analysis of the length of hospital stay as the dependent variable, the T3 level remained the only statistically significant independent variable.Linear regression analysis revealed fT3 level

Bozok Tıp Derg 2023;14(1):113-119
Bozok Med J 2023;14(1):113-119

Table 1. Clinical and laboratory characteristics in patients with COVID-19

Characteristics	Total (n = 100)	Survivor (n = 57)	Non-survivor (n = 43)	*P*-value
Age (years)	67 (19 - 95)	59 (21-95)	73 (19-89)	***0.002****
Gender, n (%)				
Male	65 %	34 (52%)	31 (48%)	0.212
Female	35 %	23 (66%)	12 (34%)	
BMI, median (IQR)	26.2 (15.6-39.1)	26.4 (19.5-38.1)	24.8 (15.6-39.1)	0.506
Comorbidities, n (%)				
Hypertension	49 %	25 (51%)	24 (49%)	0.313
Diabetes	21 %	8 (38%)	13 (62%)	0.081
Cardiac disease	25 %	10 (40%)	15 (60%)	0.063
Chronic pulmonary disease	26 %	13 (50%)	13 (50%)	0.491
Renal Disease	6 %	2 (33%)	4 (67%)	0.398
Hepatic Disease	2 %	1 (50%)	1 (50%)	1.000
Neurologic Disorders	16 %	7 (44%)	9 (56%)	0.279
Malignancy	21 %	10 (48%)	11 (52%)	0.458
APACHE II, median (IQR)	13 (3-36)	11 (3-25)	18 (8-36)	***<0.001****
ICU admission indications, n (%)				
Respiratory failure	74 %	41 (55 %)	33 (45 %)	0.546
Neurologic	11 %	8 (73 %)	3 (27 %)	
Gastroenterological	3 %	2 (67 %)	1 (33 %)	
Postoperative	4 %	3 (75 %)	1 (25 %)	
Others	8 %	3 (38 %)	5 (63 %)	
Laboratory findings				
Lymphocyte count ($x10^9$/L), median (IQR)	0.64 (0.12-12.5)	0.7 (0.12-12.5)	0.6 (0.13-1.6)	0.053
CRP, median (IQR), mg/L	10.1 (0.34-56.6)	8.6 (0.46-37)	13.8 (0.34-56.5)	***0.001****
Cortisol, median (IQR),	17.5 (1.8-133.4)	12 (1.82-65)	19.7 (2.15-133)	0.058
Procalcitonin, median (IQR), mcg/L	0.23 (0.02-90)	0.1 (0.02-90)	0.93 (0.05-64.8)	***<0.001****
Respiratory rate, median (IQR), b.p.m	28 (15-48)	18 (18-47)	30 (15-48)	0.334
Peripheral oxygen saturation, median (IQR), %	93 (62-100)	94 (72-100)	92 (62-100)	0.139
Heart rate, median (IQR), b.p.m	91 (35-160)	90 (58-136)	99 (35-160)	***0.015***[¤]
Thyroid function, median (IQR)				
TSH (µIU/mL)	0.6 (0.02-16.7)	0.65 (0.1-16.7)	0.6 (0.02-6.54)	0.617
FT3 (pmol/L)	3.6 (1.98-5.7)	3.8 (1.98-5.55)	3.4 (2.2-5.7)	***0.036****
FT4 (pmol/L)	14.8 (6.22-45.25)	14.6 (6.2-29.3)	15.6 (8.4-45.2)	0.262
FT3/FT4 ratio	0.22 (0.06-0.77)	0.24 (0.12-0.77)	0.2 (0.06-0.39)	***0.035****
Steroid therapy, (n %)				
Low dose (7.5 mg/day)	80 %	42 (52.5 %)	38 (47.5 %)	0.081
High dose (40 mg/day)	12 %	7 (58 %)	5 (41.6 %)	1.000
Other medical therapies, (n %)				
Favipiravir	86 %	55.8 %	44.1 %	0.633
Remdesivir	6 %	16.7 %	83 %	0.233
Hydroxychloroquine	2 %	50 %	50 %	0.1
Azithromycin	2 %	100 %	-	0.505
Convalescent Plasma	12 %	41.7 %	58.3 %	0.353
Tocilizumab	5 %	20 %	80 %	0.162
Anakinra	1 %	100 %	-	0.430
Mechanical ventilation, (n %)	55 %	38 (69 %)	17 (31%)	***<0.001****
Duration of mechanical ventilation, median (IQR), day	11 (1-78)	6 (1-78)	12 (1-48)	0.401
Length of ICU stay, median (IQR), day	11 (1-98)	9 (1-98)	13 (1-61)	0.052
Hospitalization time, median (IQR), day	16 (2-108)	15 (4-108)	17 (2-95)	0.689

Bozok Tıp Derg 2023;14(1):113-119
Bozok Med J 2023;14(1):113-119

Table 1 Explanation: Data are expressed as median (interquartile range), or n (%), as appropriate. P-value was calculated for the comparison between survivors and non-survivors (*p < 0.05) Abbreviations: COVID-19, coronavirus disease 2019; ICU: Intensive Care Unit; FT3: free triiodothyronine (reference range: 3.8-6 pmol/L); FT4: free thyroxine (reference range: 7.86-14.41 pmol/L); TSH: thyroid-stimulating hormone (reference range: 0.38-5.33 uIU/mL), CRP: C reactive protein. APACHE II: Acute Physiology and Chronic Health Evaluation

Table 2. Thyroid hormone levels of patients.

	fT3 (n)	**fT4 (n)**	**TSH (n)**
Normal Levels	24 (% 39)	43 (% 44,3)	68 (% 67)
Low Levels	37 (% 61)	1	29 (% 29)
High Levels	0	53 (% 51,41)	2

fT3: free triiodothyronine (reference range: 3.8-6 pmol/L), **fT4:** free thyroxine (reference range: 7.86-14.41 pmol/L),
TSH: thyroid-stimulating hormone (reference range: 0.38-5.33 uIU/mL)

Table 3. Independent predictor analysis for mortality, length of the hospital and ICU stay.

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	***P* value**	**Correlation Coefficient (rho)**	***P* value**
	B	**Std. Error**	Beta				
Dependent Variable: Length of the Hospital Stay							
(Constant)	64,142	21,002		3,054	0,004		
fT3 (pmol/L)	***-7,227***	***3,265***	***-0,281***	***-2,214***	***0,031****	***-0.284***	***0.024****
Age (years)	-0,162	0,201	-0,130	-0,806	0,424	0.185	0.065
APACHE II	-0,05	0,476	-0,017	-0,105	0,917	0.207	0.05
CRP (mg/L)	0,097	0,373	0,038	0,261	0,795	0.149	0.14
Procalcitonin (mcg/L)	-0,080	0,206	-0,052	-0,389	0,699	0.138	0.172
Dependent Variable: Length of the ICU stay							
(Constant)	33.805	17.137		1.973	0.054		
fT3 (pmol/L)	***-6.147***	***2.653***	***-0.293***	***-2.317***	***0.024****	-0.245	0.053
Age (years)	0.092	0.164	0.090	0.558	0.579	***0.262***	***0.009****
APACHE II	-0.212	0.388	-0.089	-0.545	0.588	***0.303***	***0.004****
CRP (mg/L)	0.147	0.304	0.071	0.484	0.630	***0.217***	***0.03****
Procalcitonin (mcg/L)	-0.107	0.168	-0.085	-0.638	0.526	***0.290***	***0.003****
Dependent Variable: Mortality							
(Constant)	-7.696	2.521		-637	0.002		
fT3 (pmol/L)	0.444	0.986	-0.019	-0.129	0.652	***-0.311***	***0.013****
Age (years)	0.048	0.041	0.135	1.040	0.243	***0.318***	***0.001****
APACHE II	***0.349***	***0.123***	***0.505***	***4.474***	***0.004****	***0.468***	***< 0.0001****
CRP (mg/L)	-0.135	0.198	0.205	1.815	0.494	***0.319***	***0.001****
Procalcitonin (mcg/L)	***2.142***	***0.899***	***0.038***	***0.345***	***0.017****	***0.587***	***< 0.0001****

*p < 0.05: The Spearman correlation test was used to test whether there is a relationship between the data.**p < 0.05: Binary logistic (mortality) and linear regression (Length of the Hospital and ICU stay) tests were used for independent predictor analysis. Abbreviations:
ICU: Intensive Care Unit; FT3: free triiodothyronine, CRP: C reactive protein, APACHE II: Acute Physiology and Chronic Health Evaluation

as the independent predictor for the length of hospital stay (B= -7.227, β=-0.281, p=0.031) (Table 3).

DISCUSSION

In this study, in which we wanted to show that thyroid function and especially low T3 levels play a predictive role in the prognosis of patients treated with Covid-19 in the intensive care unit, we found that low T3 levels are an independent variable in terms of ICU and hospital length of stay. However, APACHE II and procalcitonin levels were found to be significant predictors of mortality.

The effects of Covid-19 on endocrine systems have been of interest since the beginning of the pandemic. Euthyroid disease has been the most commonly diagnosed thyroid disease during Covid-19 (6). The prognostic importance of euthroid sick disease in ICU patients was confirmed in a study, which aimed to show that low fT3 levels have an important predictive role in severe COVID-19 disease (7). This study concluded that intensive care unit (ICU) patients had a higher rate of euthyroid sick syndrome in non-survivors. In the study by Llamas et al. evaluating a sub-cohort with thyroid function available during hospitalization, low fT3 values were associated with a risk ratio (RR) of death of 8.07 (95%CI 2.87; 22.72) (8). However, the RR in this study was calculated from only three studies and these were calculated for a non-homogeneous sample (9-11). Nevertheless, the prognostic value of T3 levels has been confirmed by different statistical analyses and concluded to be more successful than other biochemical markers such as CRP levels. Looking at the literature in general, it is seen that the analysis of the studies mostly in non-mild infections or without critical stratification according to disease severity. The euthroid sick disease diagnosis rate ranges from 5.9-8 % in non-critically ill patients to 16.5-100% in those with more severe disease (9,11-14). The disease severity of our patients was moderate to critical. In a study of 367 COVID-19 patients, Lui et al found that only 7.4% of patients had low T3, which was more likely to be associated with the mild form of COVID-19 (15). This study suggests that low T3 levels are rare in a mild-to-moderate population, while suggesting an association between low T3 levels and the risk of clinical deterioration, even without an increased risk of death (15). In our study, low fT3 status (defined as FT3 < 3.1 pmol/L) was more common in non-survivors than in survivors (72.7% vs. 11.2%).

The fact that studies were conducted in different geographical settings may also lead to differences in results. Among studies conducted in the East, there are several studies associated with low fT3 in COVID-19 populations (16-22). But in fact, most of the available European series show that thyrotoxicosis is more prominent, mostly in cases of severe infections or in critical settings (16, 18-21).

Regarding low T3 values, there are two Italian studies showing a high association with severe disease (16, 17). This study by Baldelli et al. (n = 84) reported a diagnosis rate of 43% and 78% in non-critical and critical patients, respectively (17). In our patients, there were no patients with high fT3 levels, while 61% (37 patients) had low fT3 levels. Another Italian study by Campri et al. confirmed the presence of low fT3 in 18 % of cases, but only half of these cases did not have ongoing intervention medications (e.g. corticosteroids) (17). Almost all of our patients were taking steroid-type medications.

In summary, the present results suggest that low fT3 levels are a reliable prognostic factor for length of hospital and ICU stay, given a large sample of COVID-19 patients in a critical setting. However, APACHE II and procalcitonin are still the most important prognostic factors for mortality. Since the majority of COVID-19 patients have mild or no symptoms at the onset of infection and an early radiologic examination may also be negative, a single early drop in fT3 levels may be serve as an important warning for medium- to long-term prognosis (23,24).

Although the single center of the study is a disadvantage in terms of the number of patients, the clinical uniformity and standardization of the patient population makes our results meaningful.

When comparing literature studies, it should be kept in mind that different results may be obtained because the studies were conducted in different geographical regions and during different periods of COVID-19 waves. Retrospective design can be considered as a limitation of the study.

CONCLUSION

In conclusion, our study particularly highlights the concept that low fT3 is a prognostic indicator that can predict hospital and ICU length of stay in critically ill patients with Covid-19. In the future, a broader panel of validated biochemical markers, including fT3 levels, may be able to select patients requiring specialized care at an earlier stage, thereby enabling a more rational use of medical resources.

Acknowledgement

There is no conflict of interest between the authors. There is no funding for this study.

KAYNAKLAR

1. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2020; 21:1–13.

2. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020; 9(1):45

3. Ippolito S, Dentali F. Tanda ML. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. J Endocrinol Invest. 2020; 43 (8):1171–2.

4. Wei L, Sun S, Xu CH, Zhang J, Xu Y, Zhu H, et al. Pathology of the thyroid in severe acute respiratory syndrome. Hum Pathol. 2007; 38(1): 95–102.

5. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab. 2021;106(2): e926–e935.

6. Lisco G, De Tullio A, Stragapede A, Solimando AG, Albanese F, Capobianco M, et al. COVID-19 and the endocrine system: a comprehensive review on the theme. J Clin Med 2021, 10(13):2920.

7. Llamas M, Garo ML, Giovanella L. Low free-T3 serum levels and prognosis of COVID-19: systematic review and meta-analysis. Clin Chem Lab Med 2021; 59(12): 1906–13

8. Campi I, Bulgarelli I, Dubini A, Perego GB, Tortorici E, Torlasco C, et al. The spectrum of thyroid function tests during hospitalization for SARS COV-2 infection. Eur J Endocrinol 2021; 184(5):699–709.

9. Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concen- trations in severely or critically ill patients with COVID-19. J Endocrinol Invest 2021; 44(5):1031–40.

10. Schwarz Y, Percik R, Oberman B, Yaffe D, Zimlichman E, Tirosh A. Sick euthyroid syndrome on presentation of patients with COVID-19: a potential marker for disease severity. Endocr Pract 2021; 27 (2):101–9.

11. Lang S, Liu Y, Qu X, Lu R, Fu W, Zhang W, et al Association between thyroid function and prognosis of COVID-19: a retrospective observational study. Endocr Res 2021; 170-7.

12. Güven M, Gültekin H. The prognostic impact of thyroid disorders on the clinical severity of COVID-19: Results of single centre pandemic hospital. Int J Clin Pract. 2021; 75(6): e14129.

13. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. Front Endocrinol 2020; (Lausanne) 11:566439

14. Das L, Dutta P, Walia R, Mukherjee S, Suri V, Puri GD, et al. Spectrum of endocrine dys- function and association with disease severity in patients with COVID-19: Insights from a cross-sectional, observational study. Front Endocrinol (Lausanne) 2021; 12:645787.

15. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity. Clin Endocrinol (Oxf) 2021; 95(3): 469-77.

16. Baldelli R, Nicastri E, Petrosillo N, Marchioni L, Gubbiotti A, Sperduti I, et al. Thyroid dysfunction in COVID-19 patients. J Endocrinol Invest. 2021; 44:2735–9.

17. Campi I, Bulgarelli I, Dubini A, Perego GB, Tortorici E, Torlasco C, et al. The spectrum of thyroid function tests during hospitalization for SARS COV-2 infection. Eur J Endocrinol 2021; 184(5): 699–709.

18. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 2020; 8(9):739–41.

19. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYR- COV study. Eur J Endocrinol 2020; 183(4):381–7.

20. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G, et al. Is Subacute Thyroiditis an Underestimated Manifestation of SARS-CoV-2 Infection? Insights From a Case Series. J Clin Endocrinol Metab 2020; 105(10):dgaa537.

21. Ruggeri RM, Campennì A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS- COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Athens) 2021; 20(1): 219–21.

22. Ippolito S, Dentali F, Tanda ML. SARS-CoV-2: a poten- tial trigger for subacute thyroiditis? Insights from a case report. J Endocrinol Invest 2020; 43(8):1171–2.

23. Rodrigues JCL, Hare SS, Edey A, Devaraj A, Jacob J, Johnstone A, et al. An update on COVID-19 for the radiologist - A British society of Thoracic Imaging statement. Clin Radiol 2020; 75(5):323–5.

24. Boelen A, Kwakkel J, Fliers E Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev 2011; 32(5):670–93.