Bosphorus Medical Journal
Boğaziçi Tıp Dergisi

Original Article

DOI: 10.14744/bmj.2022.39358

Bosphorus Med J 2022;9(4):234–241

Investigation of the Relationship Between Thyroid Function Tests and COVID-19: A Retrospective Study

Tiroid Fonksiyon Testleri ile COVID-19 Arasındaki İlişkinin Araştırılması: Geriye Dönük Bir Çalışma

Hakan Aydın, Halil Doğan

ABSTRACT

Objectives: The coronavirus disease 2019 (COVID-19), causing a worldwide pandemic, affects various organs and systems. The effects of COVID-19 on the thyroid axis remain uncertain. Our aim is to examine the changes in thyroid function tests in patients with COVID-19 and to evaluate the effectiveness of these changes in predicting the prognosis.

Methods: This retrospective study was conducted in 1891 adult patients visited to the emergency department with suspected COVID-19. The diagnosis of COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction (rt-PCR), and patients were divided into two groups as those with and without COVID-19. COVID-19 patients were divided into groups according to their clinical severity and prognosis. The groups were compared in terms of free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH) levels.

Results: The rate of laboratory-confirmed COVID 19 patients was 54.7% in the patients included in the study. In COVID-19 patients, the hospitalization rate was 56.7%, the intensive care unit admission rate was 7.7%, and the in-hospital mortality rate was 5.4%. Most of the COVID-19 patients (60.1%) were euthyroid. Hyperthyroidism (overt 3.7%-1.3%, p=0.001; secondary 13.6–4.6%, p<0.001) and non-thyroid illness syndrome (NTIS) (18.9–3%, p<0.001) were more common in COVID-19 patients than in non-COVID19 patients. Patients with COVID-19 had lower TSH and FT3 levels and higher FT4 levels compared to those without COVID-19. Similarly, among COVID-19 patients, lower TSH and FT3 and higher FT4 levels were seen in deceased patients compared to survivors (p<0.001).

Conclusion: High FT4 levels combined with low TSH and FT3 levels may represent a type of NTIS that occurs in the acute phase of COVID-19. This pattern appears to be predictor of poor outcome of patients with COVID-19.

Keywords: Coronavirus disease 2019; free triiodothyronine; free thyroxine; non-thyroidal illness syndrome; thyrotropin.

ÖZET

Amaç: Dünya çapında bir pandemiye neden olan koronavirüs hastalığı (COVID-19), çeşitli organ ve sistemleri bozmaktadır. COVID-19'un tiroid ekseni üzerindeki etkileri belirsizliğini korumaktadır. Bu çalışmanın amacı, COVID-19 hastalarında tiroid fonksiyon testlerindeki değişiklikleri incelemek ve bu değişikliklerin prognozu öngörmedeki etkinliğini değerlendirmektir.

Yöntem: Bu retrospektif çalışma, COVID-19 şüphesiyle acil servise başvuran 1891 yetişkin hastada yürütüldü. COVID-19 tanısı revers transkriptaz-polimeraz zincir reaksiyonu (rt-PCR) ile doğrulandı ve hastalar COVID-19 olan ve olmayan olarak iki gruba ayrıldı. COVID-19 hastaları klinik şiddet ve prognozlarına göre gruplara ayrıldı. Gruplar serbest triiyodotironin (FT3), serbest tiroksin (FT4) ve tirotropin (TSH) düzeyleri açısından karşılaştırıldı.

Bulgular: Çalışmaya alınan hastaların %54.7'sinin COVID-19 olduğu laboratuvar testi ile doğrulandı. COVID-19 hastalarında hastaneye yatma oranı %56.7, yoğun bakım ünitesine kabul oranı %7,7 ve hastane içi ölüm oranı %5.4'tü. COVID-19 hastalarının çoğu (%60.1) ötiroiddi. COVID-19 olan hastalarda COVID-19 olmayan hastalara

Department of Emergency Medicine, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Türkiye

Cite this article as: Aydın H, Doğan H. Investigation of the Relationship Between Thyroid Function Tests and COVID-19: A Retrospective Study. Bosphorus Med J 2022;9(4):234–241.

Received: 21.09.2021
Revision: 07.03.2022
Accepted: 17.05.2022

Correspondence:
Dr. Hakan Aydın. Sağlık Bilimleri Üniversitesi, Bakırköy Dr. Sadi Konuk Eğitim Ve Araştırma Hastanesi, Acil Tıp Kliniği, İstanbul, Türkiye

Phone:
+90 212 414 71 71

e-mail:
drhakanaydin054@gmail.com

OPEN ACCESS

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

© Copyright 2022 by Bosphorus Medical Journal - Available online at http://www.bogazicitipdergisi.com

kıyasla hipertiroidi (aşikar %3.7-%1.3, p=0.001; ikincil %13.6-%4.6, p<0.001) ve tiroid dışı hastalık sendromu [non-Thyroid illness Syndrome (NTIS)] (%18.9-%3.0, p<0.001) görülmesi daha yaygındı. COVID-19'lu hastalarda, COVID-19 olmayanlara kıyasla daha düşük TSH ve FT3 düzeyleri ve daha yüksek FT4 düzeyleri vardı (p<0.001). Benzer şekilde COVID-19 hastaları arasında hayatta kalanlara kıyasla ölen hastalarda daha düşük TSH ve FT3 ve daha yüksek FT4 seviyeleri görüldü (p<0.001).

Sonuç: Düşük TSH ve FT3 düzeyleri ile birlikte yüksek FT4 seviyeleri COVID-19'un akut fazında ortaya çıkan bir NTIS tipini temsil edebilir. Bu model, COVID-19 hastalarında kötü sonlanımın bir göstergesi gibi görünmektedir.

Anahtar sözcükler: Tiroid dışı hastalık sendromu; COVID-19; TSH; FT3; FT4.

Since the first cases of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in China in late 2019, COVID-19 has spread rapidly worldwide, and a global pandemic was declared by the World Health Organization (WHO) in March 2020.[1] SARS-CoV-2 uses angiotensin-converting-enzyme 2 (ACE2) combined with the transmembrane protease serine 2 (TMPRSS2) as the key molecular complex to infect the host cells.[2,3] Moreover, ACE2 and TMPRSS2 expression levels are high in the thyroid gland and they are higher than in the lungs.[2,4]

Since the outbreak of the COVID-19 pandemic, several studies have examined the effects of SARS-CoV-2 infection on thyroid function.[5-10] The prevalence of thyroid dysfunction in COVID-19 patients varies widely (range 13% and 64%).[5-10] Thyroid disorders associated with COVID-19 may occur biochemically as thyrotoxicosis,[9,10] hypothyroidism,[9,10] as well as non-thyroidal illness syndrome (NTIS).[7,8]

NTIS or euthyroid sick syndrome is characterized by the decrease in T3 concentration associated with critical illness in individuals with a previously normal thyroid.[11] Because the first contact of a critically-ill patient with medical care usually occurs in the emergency department (ED), strong measures are necessary to aid the decision-making process regarding illness severity and risk of death.

Our aim was to investigate changes in thyroid function tests (TFT) in the first admission of COVID-19 patients to the ED and to examine whether these changes have prognostic significance.

Methods

This study was approved by the ethics committee of the research institution (Date: November 02, 2020, protocol number: 2020-458). The research was conducted ethically in accordance with the Declaration of the World Medical Association of Helsinki.

Setting and Study Population

This retrospective, single-center, and cross-sectional study was conducted in the ED of a tertiary education and research hospital in Istanbul between July 15 and October 15, 2020. During the study period, our hospital was declared a pandemic center by the Ministry of Health.

The population studied consists of adult (>18 years old) patients visiting to our hospital with the suspicion of COVID-19. SARS-CoV-2 infection was confirmed by reverse transcriptase–polymerase chain reaction (rt-PCR) of nasopharyngeal swab samples. Patients with the results of Rt-PCR, thyrotropin (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) tests were included in the study. We retrospectively evaluated the enrolment of 1891 consecutive patients after excluding patients with incomplete laboratory data, pregnancy, treatment with lithium, amiodarone, L-thyroxine, or anti-thyroid drugs, with known thyroid disease, and without evaluation of thyroid function. However, before blood sampling for thyroid function tests, none of our COVID-19 patients received heparin, glucocorticoids, dopamine/dobutamine, or iodinated contrasts. In addition, patients whose PCR results were negative for COVID-19 but those who were found to have pneumonia on thorax computed tomography were excluded from the study.

The diagnosis and treatment of these patients were performed in line with the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidelines published by the National Health Commission of Türkiye.[12]

Classification of Patients

Clinical classification of the patients was performed according to the WHO's COVID-19 clinical management: Living guidance.[1]

Mild disease: Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.

Moderate disease: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) but no signs of severe pneumonia, including SpO2 ≥90% on room air.

Severe disease: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 <90% on room air.

Data Collection

Patients meeting the inclusion and exclusion criteria were consecutively included in the study. Demographic data (age, gender, and comorbidity diseases), symptoms and onset time of symptoms, radiological imaging, rt-PCR results, treatment in the hospital or intensive care unit (ICU), and prognosis were recorded for the study by recording electronic medicine and/or interviewing patients. Thoracic CT was performed in 79% of all patients (90.8% [n=933] of COVID-19 patients, 64.9% [n=560] of non-COVID-19 patients). All thorax CT images were examined by radiologists who were blinded to rt-PCR results, and positive or negative radiology findings were decided with consensus.

Biochemical Assays

The FT3, FT4, and TSH serum levels were assayed using a Chemiluminescent Microparticle Immunoassay, using an immunoassay analyzer (Beckman Coulter DxI 680, Beckman Coulter Inc., CA, USA). All analytes were measured at the time of the visit to the ED. In our laboratory, the reference ranges of TSH, FT4, and FT3 were 0.34–5.6 μIU/mL, 0.61–1.12 ng/dL, and 2.5–3.9 pg/mL, respectively.

Description of Diseases

Patients were classified into diagnostic categories according to the pattern of results falling below, within, or above the reference ranges indicated above.

Overt hyperthyroidism was defined by low TSH values and serum FT3 and/or FT4 above the reference ranges.[13] Overt hypothyroidism was defined by high TSH values and serum FT4 and/or FT3 below the reference ranges.[14] Subclinical thyroid dysfunction was defined when TSH was either low or high accompanied by FT4 and FT3 in the reference ranges.[13,14] Secondary thyroid dysfunction was defined as low or high FT4 accompanied by TSH in the reference ranges.[6] NTIS was defined as low serum FT3 level accompanied by normal-low serum TSH levels.[11]

Statistical Analysis

All the statistical analyses were carried out by using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). The data's normality analyses were conducted using histograms and the Kolmogorov–Smirnov test. Continuous variables were highly skewed distributions, so standard parametric methods could not be applied. Continuous variables were presented as the median (25% to 75% interquartile range (IQR)) and categorical variables were presented as counts and percentages. Mann-Whitney U test was used to compare continuous groups, and the chi-square test or Fischer´s exact test were used to compare categorical groups. The areas under the receiver operating characteristic (AUROC) curves for the ability of TSH, FT3, and FT4 to predict in-hospital mortality and ICU admission were analyzed. The best FT3, FT4, and TSH cut-off points for predicting in-hospital mortality and ICU admission were determined by the Youden index. A p-value of <0.05 was considered statistically significant.

Results

Our study included 1891 consecutive adult patients who met the inclusion and exclusion criteria. The median age of the patients was 45 (IQR 32–58). About 54.7% (n=1035) of the patients were male. About 29.1% (n=550) of all patients had at least one comorbidity disease and the most common comorbidities were hypertension (15.8%) and diabetes (14%).

The rt-PCR result was positive in 54.4% (n=1028) of the patients. Most patients were euthyroid (72%), and the rate of euthyroidism was lower in COVID-19 patients compared to non-COVID-19 patients (86.1% vs. 60.1%, p<0.001).

4% of the COVID-19 patients had overt thyroid dysfunction (38 with hyperthyroid and 3 with hypothyroidism), 4.8% of them had subclinical thyroid dysfunction (25 with hyperthyroid and 24 with hypothyroidism), 14.1% of them had secondary thyroid dysfunction (140 with hyperthyroid and 40 hypothyroidism), and 18.9% of them (n=194) had NTIS. There was a statistically significant difference in the proportion of patients with hyperthyroidism (overt 3.7% vs. 1.3%, p=0.001; secondary 13.6% vs 4.6%, p<0.001) or NTIS (18.9% vs 3%, p<0.001) between the group with and without COVID-19 (Table 1).

In COVID-19 patients, the hospitalization rate was 56.7%, and the intensive care unit admission rate was 7.7%. The median length of hospital stay of hospitalized COVID-19 patients was 9 (IQR:6-14) days. The in-hospital mortality rate of COVID-19

Table 1. Demographic, clinical, and laboratory data of the patients included in the study

	NON-COVID19 n=863 (45.6%)	COVID19 n=1028 (54.4%)	p
Age, years	37 (28–50)	51 (39–65)	<0.001
Gender (F/M)	409/454	447/581	0.089
Arterial hypertension	67 (7.8)	232 (22.6)	<0.001
Diabetes mellitus	64 (7.4)	201 (19.6)	<0.001
COPD or asthma	19 (2.2)	88 (8.6)	<0.001
Cardiovascular disease	27 (3.1)	91 (8.9)	<0.001
Chronic kidney disease	5 (0.6)	19 (1.8)	0.014
Prior stroke	6 (0.7)	15 (1.5)	0.114
Active cancer	2 (0.2)	23 (2.2)	<0.001
TSH, µIU/mL	1.55 (0.99–2.36)	1.29 (0.77–2.08)	<0.001
FT3, pg/mL	3.28 (2.97–3.55)	2.93 (2.61–3.26)	<0.001
FT4, ng/dL	0.87 (0.79–0.96)	0.94 (0.81–1.10)	<0.001
Euthyroid	743 (86.1)	618 (60.1)	<0.001
Overt hyperthyroidism	11 (1.3)	38 (3.7)	0.001
Overt hypothyroidism	1 (0.1)	3 (0.3)	0.407
Sc thyroid dysfunction	34 (3.9)	49 (4.8)	0.382
Sec hyperthyroidism	40 (4.6)	140 (13.6)	<0.001
Sec hypothyroidism	10 (1.2)	5 (0.5)	0.101
NITS	26 (3.0)	194 (18.9)	<0.001

Categorical data were presented as numbers (percentages). Continuous data were presented as median and interquartile range (25th-75th), COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease 2019, F: Female, M: Male, NITS: Non-thyroidal illness syndrome, SC: Subclinical, Sec: Secondary, TSH: Thyrotropin, FT3: Free Triiodothyronine, FT4: Free thyroxine.

patients was 5.4% (n=55). Among the COVID-19 patients, the rate of euthyroidism was higher in the survivor group than in the non-survivor group (18.2% vs. 62.5%, p<0.001). However, overt hyperthyroidism (14.5% vs. 3.1%, p<0.001) and NTIS (67.3% vs. 16.1%, p<0.001) were more common in the survivors' group compared to non-survivors (Table 2).

The group of COVID-19 patients had lower median TSH (1.29 µIU/mL [0.77-2.09] vs. 1.54 µIU/mL [0.99-2.36]) and FT3 (2.93 pg/mL [2.61-3.27] vs. 3.28 pg/mL [2.97-3.55]) levels and higher median FT4 levels (0.94 ng/dL [0.81-1.10] vs. 0.87 ng/dL [0.79-0.96]) compared to the group of patients without COVID-19 (p<0.001).

Similarly, among COVID-19 patients, lower median TSH and FT3 values and higher median FT4 levels were seen in non-survivors patients compared to survivors (Table 3).

In our study, the areas under the ROC curves (AUCs) for FT3 were 0.811 (95% CI 0.785–0.834) to predict in-hospital mortality and 0.731(95% CI 0.703–0.758) to predict ICU admission, and these values were superior to those for serum FT4 and TSH. The best FT3 cut-off points for predicting in-hospital mortality and ICU admission were FT3≤2,55 pg/mL (Fig. 1).

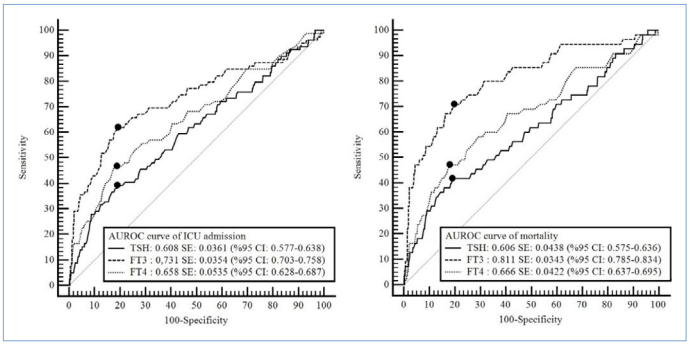

Figure 1. The areas under the receiver operating characteristic curves for TSH, FT3 and FT4 for in-hospital mortality **(a)** and ICU admission **(b)**. Cut-off points: TSH (A≤0.66 µIU/mL 95% Confidence interval (CI) ≤0.56 to ≤2.59; B≤0.67 µIU/mL %95CI ≤0.42 to ≤1.9739), FT3 (A≤2.55 pg/ml %95CI ≤2.42 to ≤2.86; B ≤2.55 pg/ml %95CI ≤2.49 to ≤2.87), FT4 (A>1.13 ng/dL %95CI >1.03 to >1.33; B>1.12 ng/dl %95CI >0.84 to >1.16).

Discussion

COVID-19 is a serious disease facing the world that directly or indirectly affects multiple organs and systems. Thyroid dysfunction is quite common in patients with COVID-19 infection. In many studies, the prevalence of thyroid dysfunction in COVID-19 patients was found to be significantly higher compared to the control group.[6,7,9]

Table 2. The incidence of thyroid dysfunction diseases in COVID-19 patients

	Euthyroid	Overt hyper	Overt hypo	Sc thyroid dysfunction	Sec. hyper	Sec. hypo	NITS
Mild, n (%)	245 (79.3)	2 (0.6)	0	23 (7.4)	16 (5.2)	4 (1.3)	19 (6.1)
Moderate, n (%)	332 (59.1)	23 (4.0)	2 (0.4)	23 (4.0)	82 (14.6)	1 (0.2)	111 (19.7)
Severe/Critical, n (%)	41 (25.9)	13 (8.2)	1 (0.6)	3 (1.9)	42 (26.6)	0	64 (40.5)
p-value *	<0.001	0.004Ψ	0.541Ψ	0.035	<0.001	0.056Ψ	<0.001
p-value **	<0.001	<0.001	0.335Ψ	0.017	<0.001	0.306Ψ	<0.001
p-value ***	<0.001	0.036	0.526Ψ	0.234Ψ	<0.001	1.00Ψ	<0.001
Non-Pneumonıa, n (%)	177 (79.4)	2 (0.9)	0	16 (7.2)	10 (4.5)	1 (0.4)	17 (7.6)
Pneumonıa, n (%)	369 (51.9)	35 (4.9)	3 (0.4)	24 (3.4)	124 (17.4)	1 (0.1)	173 (24.3)
p-value	<0.001	0.006Ψ	1.00Ψ	0.014	<0.001	0.421Ψ	<0.001
Non-ICU adm., n (%)	599 (63.1)	27 (2.8)	3 (0.3)	49 (5.2)	130 (13.7)	5 (0.5)	149 (15.7)
ICU adm., n (%)	19 (24.1)	11 (13.9)	0	0	10 (12.7)	0	45 (57.0)
p-value	<0.001	<0.001	1.00Ψ	0.028Ψ	0.796	1.00Ψ	<0.001
Survivor, n (%)	608 (62.5)	30 (3.1)	3 (0.3)	49 (5.0)	135 (13.8)	5 (0.5)	157 (16.1)
Non-survivor, n (%)	10 (18.2)	8 (14.5)	0	0	5 (9.1)	0	37 (67.3)
p-value	<0.001	<0.001	1.00Ψ	0.105Ψ	0.314	1.00Ψ	<0.001

Chi-square tests were used to compare groups, ΨFischer's exact test was used when Chi-square was not suitable for use, *Compared between mild ill patients and moderate ill patients, **Compared between mild ill patients and severely or critically ill patients, ***Compared between moderate ill patients and severely or critically ill patients, Adm: Admitted, Hyper: Hyperthyroidism, Hypo: Hypothyroidism, ICU: Intensive care unit, NITS: Non-thyroidal illness syndrome, SC: Subclinical, Sec: Secondary.

Available evidence suggests that TFT changes during COVID-19, but the relevant pathophysiological mechanisms have not been clarified. Several different hypotheses have been put forward in this regard.[15,16] The first hypothesis is that the virus directly invades the thyroid gland. This theory was confirmed in the SARS-CoV-1 study, which has a similar phylogenetic structure to SARS-CoV-2.[17] SARS-CoV-2 infects human tissues by entering cells through the ACE2 receptor.[2,3] Although ACE2 is highly expressed in thyroid tissues,[2,4] post-mortem studies on COVID-19 patients revealed no sig-

Table 3. Comparison of serum TSH, FT3, and FT4 among patients of COVID-19

	TSH, µIU/mL	FT3, pg/mL	FT4, ng/dL
Mild	1.39 (0.80–2.15)	3.14 (2.87–3.41)	0.86 (0.77–0.96)
Moderate	1.30 (0.80–2.14)	2.86 (2.59–3.19)	0.95 (0.83–1.10)
Severe/Critical	1.04 (0.61–1.81)	2.62 (2.32–3.01)	1.12 (0.93–1.30)
p-value *	0.518	<0.001	<0.001
p-value **	0.002	<0.001	<0.001
p-value ***	0.005	<0.001	<0.001
Non-Pneumonıa	1.32 (0.73–2.11)	3.12 (2.87–3.42)	0.86 (0.77–0.96)
Pneumonıa	1.25 (0.77–2.04)	2.83 (2.50–3.16)	0.98 (0.85–1.14)
p-value	0.905	<0.001	<0.001
Non-ICU adm.	1.30 (0.78–2.07)	2.94 (2.64–3.26)	0.94 (0.81–1.10)
ICU adm.	1.00 (0.41–1.76)	2.41 (2.09–2.89)	1.09 (0.87–1.29)
p-value	0.001	<0.001	<0.001
Survivor	1.29 (0.78–2.06)	2.94 (2.62–3.26)	0.94 (0.81–1.10)
Non-survivor	1.00 (1.40–1.86)	2.29 (2.03–2.67)	1.09 (0.88–1.31)
p-value	0.008	<0.001	<0.001

Data were presented as median and interquartile range (25th-75th), *Compared between mild ill patients and moderate ill patients, **Compared between mild ill patients and severely or critically ill patients, ***Compared between moderate ill patients and severely or critically ill patients, adm: admitted, TSH: Thyrotropin, FT3: Free Triiodothyronine, FT4: Free thyroxine, ICU: Intensive care unit.

nificant abnormalities in thyroid morphology and failed to detect SARS-CoV-2 in thyroid tissue.[18,19] There may also be other reasons that prevent the virus from entering thyroid follicular cells.

Another potential mechanism is that the direct suppressing effect of SARS-CoV-2 on the hypothalamic-pituitary-thyroid (HPT) causes a decreased level of serum TSH in COVID-19 patients.[20] It has been shown that there are significant decreases in both the number and immunoreactive density of TSH-positive cells in some SARS patients.[21] In our study, central hypothyroidism (low FT4 and low/normal TSH) was found in only 0.5% of COVID-19 patients. In the study by Chen et al.[7] central hypothyroidism (low FT4 with low/normal TSH) could be diagnosed in 2–6% of patients hospitalized for non-mild COVID-19. Reversal of these hormonal changes occurred after recovery from COVID-19, which is a fact that highlights plausible acute/transitory effects of COVID-19 on the HPT axis.[7] However; while low TSH, FT3, and also FT4 levels in central hypothyroidism were expected, some COVID-19 patients have unexpectedly increased FT4 levels, which is the main limitation of this hypothesis.

The third possible explanation may imply an underlying NTIS caused by critical illness.[22] The term NTIS describes the alterations in TFT observed during illness in individuals without pre-existing thyroid disease and intact HPT axis. The most typical alterations are low plasma concentrations of T3, low or normal plasma concentrations of T4, or increased plasma reverse-T3 in the presence of normal TSH.[11,22] NTIS can occur in a variety of acute or chronic systemic diseases including cardiovascular, respiratory, infectious diseases, and cancer.[9]

Severe and critical COVID-19 patients with NTIS were identified in two studies,[7,9] On the other hand, coronaviruses infection has a wide spectrum of clinical severity, ranging from asymptomatic cases and the common cold to more severe and even fatal respiratory tract infections.[23] In our study, laboratory data consistent with NTIS were also seen in mild and moderate COVID-19 patients. In addition, the incidence of NTIS increased as the severity of the disease increased in our study. Contrary to expectations, high FT4 values were observed in NTIS in 62 of our patients. This pattern (subnormal TSH, low FT3, and high FT4 levels) might represent a unique type of NTIS that occur during the acute phase of COVID-19. On the other hand, NTIS treatment with thyroid hormones is still controversial since there is no conclusive evidence of its effectiveness.[11,24] We would like to state that none of the COVID-19 patients included in our study were given anti-thyroid medication or triode hormone replacement during the follow-up and treatment process.

Many studies have reported a correlation between thyroid dysfunction and the clinical severity of COVID-19, in particular, the degree of the decrease in TSH levels and fT3 levels is positively correlated with the severity of the disease.[7,25] On the other hand, total T4 levels alone were not correlated with the severity of the disease.[7] In addition, studies have reported that both TSH and thyroid hormone levels returned to normal limits after recovery.[6,7]

Lui et al.[5] reported that the decrease in FT3 levels associated with systemic inflammation seemed to be associated with the clinical worsening of the patient, but TSH or FT4 levels were not associated with the severity of the disease. Although these studies provide useful information, they have limitations. For example, they have included incomplete data such as measuring thyroid hormones only when TSH was out of range,[9,10] or failed to exclude factors such as steroid treatment.[7]

It has known that glucocorticoids may disrupt thyroxine metabolism. It is also worth noting that iodine load from computed tomography scanning can also affect euthyroid status. However, most of the available studies have not clarified this. Medication and vaccination are important measures to prevent and control COVID-19. Many drugs are currently used to treat COVID-19. However, it is unclear whether these agents can affect the thyroid gland during anti-COVID-19 therapy. Therefore, TSH levels should be monitored to ensure the protection of euthyroidism.

Finally, apart from the direct viral effect on thyroid or pituitary cells, another potential mechanism that cannot be ignored is the indirect effects of the immune-mediated post-viral inflammatory reaction caused by SARS-Cov-2 infection.[17,26]

However, the effect of T3 on COVID-19 is questionable. T3 has some potential mechanisms for the treatment of COVID-19 such as increasing the tolerance of cells to hypoxia by inhibiting p38 mitogen-activated protein kinase activation, promoting tissue repair by regulating Akt activity, and inhibiting lung fibrosis by improving epithelial mitochondrial function.[27] Research has shown that as the critical disease increases its severity, fT3 levels continue to decrease gradually due to an adaptive reaction that arises to prevent the usage of excessive energy, even in mild-severity illnesses.[28,29] However, it is controversial whether low T3 syndrome

represents a protective or maladaptive response to long-term critical illness.[30] It has been found that low T3 syndrome in patients with long-term critical illness is caused by low expression of the TRH gene in the paraventricular nucleus and impairs the hypothalamic stimulation of thyrotropes.[31] Unlike an acute disease, low T3 level is associated with markers of muscle breakdown and bone loss, indicating a hypercatabolic maladaptive response in long-term disease.[32] Low T3 levels are ultimately important for patient follow-up, whether they are a direct or indirect effect of COVID-19 or a mechanism for the body's adaptation to critical illness.

In summary, as a critically ill patient's first contact with medical care often occurs in the ED, strong foresight is required to aid decision-making regarding outcomes, disease severity, and risk of death.

Therefore, rapid and reliable biomarkers are needed to determine diagnosis and prognosis in COVID-19 patients to optimize therapeutic potential. The aim of our study was to investigate the changes in TFT at the first visit to the ED of COVID-19 patients and to examine whether these changes have prognostic significance. To the best of our knowledge, this is the study with the largest number of patients focusing on the relationship between serum TFT levels and disease severity, critical illness, and mortality in COVID-19 patients. The results of our study show that TSH, FT3, and FT4 levels measured in the ED can help us predict outcomes, disease severity, and risk of death in COVID-19 patients. However, every test performed will have a cost and it is also not possible to perform these tests in every health center. Therefore, we do not recommend these tests for diagnostic or screening purposes in patients applying with the suspicion of COVID-19. However, we recommend that clinicians be more careful about the worsening of clinical status that may occur due to TFT changes in patients infected with SARS-CoV-2, especially in those with severe and critical illness, and in patients who are planned to be given drugs that may affect TFTs.

This study has several limitations. First, this study is a retrospective and single-center study. Second, the thyroid function was only accessed at admission. Third, the result of the endocrine-based test may be related to the timing of sampling. In addition, thyroid autoantibodies (thyroid peroxidase antibodies, thyroglobulin antibodies, and the TSH receptor) were not measured in the patients in the study. Finally, in our study, it was observed that the comorbidities stated in COVID-19 patients were higher than in patients without COVID-19. It is known that some of these comorbid diseases and some drugs used in their treatment cause deterioration in TFT.[33] However, patients using many drugs (heparin, glucocorticoids, amiodarone, and dopamine/dobutamine) that may affect TFT due to these comorbid diseases were excluded from the study.

Conclusion

The thyroid and HPT axis involvement must be considered when facing COVID-19. Our results showed that TFT, especially FT3 levels, have a reliable predictive effect on disease severity and prognosis in patients diagnosed with COVID-19 during an ED visit. In addition, the coexistence pattern of decreased TSH and FT3 levels and increased FT4 levels may represent a unique type of NTIS that occurs during the acute phase of COVID-19.

Disclosures

Ethics Committee Approval: This study was approved by the ethics committee of the research institution (Date: November 02, 2020, protocol number: 2020-458).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.A., H.D.; Design – H.A., H.D.; Supervision – H.A., H.D.; Materials – H.A., H.D.; Data collection &/or processing – H.A., H.D.; Analysis and/or interpretation – H.A., H.D.; Literature search – H.A., H.D.; Writing – H.A., H.D.; Critical review – H.A., H.D.

References

1. World Health Organization (2021). COVID-19 Clinical management: Living guidance, 25 January 2021. Available at: https://apps.who.int/iris/handle/10665/338882. Accessed Nov 14, 2022.
2. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 2020;181:1016–35.e19.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.e8.
4. 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;9:45.
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:e926–35.
6. Khoo B, Tan T, Clarke SA, Mills EG, Patel B, Modi M, et al. Thyroid function before, during, and after COVID-19. J Clin Endocrinol Metab 2021;106:e803–11.

7. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: A retrospective study. Thyroid 2021;31:8–11.
8. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, et al. Euthyroid sick syndrome in patients with COVID-19. Front Endocrinol (Lausanne) 2020;11:566439.
9. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 2020;8:739–41.
10. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: The THYRCOV study. Eur J Endocrinol 2020;183:381–7.
11. Van den Berghe G. Non-thyroidal illness in the ICU: A syndrome with different faces. Thyroid 2014;24:1456–65.
12. T.C. Ministry of Health. Covıd-19 (Sars-Cov-2 Enfeksiyonu) Rehberi (in Turkish). Available at: https://algoloji.org.tr/wp-content/uploads/2020/04/COVID-19_Rehberi-6.pdf. Accessed Mar 3, 2020.
13. Petretta M, Bonaduce D, Spinelli L, Vicario ML, Nuzzo V, Marciano F, et al. Cardiovascular haemodynamics and cardiac autonomic control in patients with subclinical and overt hyperthyroidism. Eur J Endocrinol 2001;145:691–6.
14. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: Who to treat and how. Drugs 2012;72:17–33.
15. Parolin M, Parisotto M, Zanchetta F, Sartorato P, De Menis E. Coronaviruses and endocrine system: A systematic review on evidence and shadows. Endocr Metab Immune Disord Drug Targets 2021;21:1242–51.
16. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord 2020;21:495–507.
17. 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;38:95–102.
18. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. Am J Clin Pathol 2020;153:725–33.
19. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: A case series. Lancet 2020;396:320–32.
20. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol (Oxf) 2005;63:197–202.
21. Wei L, Sun S, Zhang J, Zhu H, Xu Y, Ma Q, et al. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol 2010;88:723–30.
22. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol 2015;3:816–25.
23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
24. Lee S, Farwell AP. Euthyroid sick syndrome. Compr Physiol 2016;6:1071–80.
25. Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. J Endocrinol Invest 2021;44:1031–40.
26. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: The current evidence and treatment strategies. Front Immunol 2020;11:1708.
27. Yu G, Tzouvelekis A, Wang R, Herazo-Maya JD, Ibarra GH, Srivastava A, et al. Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function. Nat Med 2018;24:39–49.
28. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: An update. J Endocrinol 2010;205:1–13.
29. Akcay I, Okoh AK, Yalav O, Eray IC, Rencuzogullari A, Dalci K, et al. The prognostic value of pro-calcitonin, CRP and thyroid hormones in secondary peritonitis: A single-center prospective study. Ulus Travma Acil Cerrahi Derg 2014;20:343–52.
30. Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1–13.
31. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 1997;82:4032–6.
32. Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, et al. Neuroendocrinology of prolonged critical illness: Effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 1998;83:309–19.
33. Kökümer M, Şehirli AO. Drug-induced thyroid disorders. Clin Exp Health Sci 2015;5:191–6.