İstanbul Med J 2023; 24(3): 272–8
DOI: 10.4274/imj.galenos.2023.82783

Evaluation of Thyroid Functions and Its Relationship with Disease Status and Mortality in Hospitalized Patients with COVID-19

Müge Bilge[1], Işıl Kibar Akıllı[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonary Diseases, İstanbul, Turkey

ABSTRACT

Introduction: Hospitalized coronavirus disease-2019 (COVID-19) individuals were studied in terms of their thyroid functioning with respect to their disease severity and mortality rate.

Methods: The thyroid function tests of 781 in patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pneumonia outside the intensive care units were examined as part of this retrospective investigation, which was conducted in a single center. Data from the patients were categorized as deceased or discharged. Based on their diagnostic categories, the patients were grouped according to their thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) values. TSH, fT4, and fT3 levels were assessed within 24 h after admission.

Results: Of the 781 patients who had COVID-19 of, 726 were discharged and 55 died. When compared to the discharged group, deceased patients exhibited lower than normal TSH and fT3 levels ($p<0.001$; for both). Notwithstanding, there was no significant difference between deceased and discharged patients regarding fT4 values. 115 (14.7%) patients had thyroid dysfunction (16 patients had elevated TSH, 99 had TSH levels below the reference value) and 154 (19.7%) patients had non-thyroidal illness (NTI). The individual effect of thyroid function tests on patient death was investigated using the log rank test, and fT3 levels were found to be significant for predicting mortality.

Conclusion: Our findings imply that thyroid function tests, especially in severe patients, may have prognostic significance. Lower fT3 and TSH levels may be associated with systemic inflammation, which could be a prognostic value associated with the disease state and mortality rate. fT3 was shown to be an independent risk factor for death. As a result, approximately 15% of the patients were observed to have thyroid dysfunction and 19.7% were NTI, which were all linked to severe disease status.

Keywords: COVID-19 pneumonia, thyroid function tests, mortality

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) epidemic, also named the "coronavirus disease-2019 (COVID-19) pandemic," has been linked to an elevated fatality rate throughout the world. Previously, SARS-CoV-1 brought about a SARS in late 2002 with a mortality rate of 9.6% (1). Although SARS-CoV-2 infection has been notified to have a relatively lower fatality rate of around 1-3% (2), it is believed to directly affect numerous endocrine glands, including the thyroid. Examination of changes in thyroid structure and function has been reported only in a few studies that rely on clinical assessments of blood samples from SARS patients. In postmortem studies, the thyroid glands of five SARS-CoV-1-effected patients were observed to show serious damage to their follicular epithelium and parafollicular cells. The follicular structure was entirely affected in the form of follicular distortion and collapse (3). In other postmortem studies, the existence of the precursors of the virus in follicular cells of the thyroid and pituitary gland has been demonstrated. Staining results indicated a decrease in the thyroid stimulating hormone (TSH) in the anterior pituitary gland (4,5), although a case series of three COVID-19 patients who received thyroid biopsy did not show any pathological thyroid illness (6).

SARS causes central hypothyroidism in survivors. Among 61 patients who recovered from SARS-CoV-1 with no previous endocrine disease, four (6.6%) had primary hypothyroidism diagnosis (7).

SARS-CoV-2 infects tissues in humans via entry into cells using the angiotensin-converting enzyme 2 (ACE2) receptor, sharing evolutionary similarities with SARS-CoV-1 (8,9). As a result, SARS-CoV-2 entrance into thyroid cells may be caused by the highly expressed ACE2 receptor in the thyroid tissue (10).

Address for Correspondence: Müge Bilge MD, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
Phone: +90 533 733 54 67 **E-mail:** mugebilge@yahoo.com **ORCID ID:** orcid.org/0000-0001-7965-3407

Cite this article as: Bilge M, Kibar Akıllı I. Evaluation of Thyroid Functions and Its Relationship with Disease Status and Mortality in Hospitalized Patients with COVID-19. İstanbul Med J 2023; 24(3): 272-8.

Received: 22.06.2023
Accepted: 26.07.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.
Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

In COVID-19, both the pituitary and hypothalamic tissues indicate ACE2, which renders them possible viral targets (11). Nevertheless, these mechanisms are not yet clarified and the presence of a similar involvement due to SARS-CoV-2 impact either directly or indirectly on the thyroid gland is still unknown (12).

Knowledge regarding how SARS-CoV-2 infection affects the thyroid is fairly limited. Currently, there are few published case reports and studies, especially on thyrotoxicosis due to thyroiditis and non-thyroidal illness (NTI) associated with COVID-19 (13-15).

NTI is a physiological adaptation and/or a pathological response to an acute disease, exhibiting a reduced level of serum T3 and/or T4, although no increase in TSH secretion is observed. Even though its underlying mechanism has not yet been resolved, NTI seems to result from an interaction of physiological adaptation and pathological response to acute illness (16).

In our retrospective research, we investigated thyroid functions and their relationship with mortality in hospitalized COVID-19 patients and evaluated their potential prognostic significance.

Methods

We adopted a cross-sectional and retrospective design in our single-center study. Real-time polymerase chain reaction testing was performed on 1,509 patients who were later diagnosed with COVID-19 and were hospitalized due to COVID-19 pneumonia. These patients who were hospitalized between September 01, 2020 and December 31, 2020 were screened through the database of our hospital, level-3 pandemic, in İstanbul. Patients with known thyroid disease, those who were taking thyroid hormones or antithyroid medications, and those who received any previous head and neck area surgery were excluded from the study. Additionally, individuals with hematological malignancies, advanced carcinoma, rheumatic immune disease, endocrinological disease, organ transplantation, chronic infection disease (such as human immunodeficiency virus, hepatitis C virus and hepatitis B virus), end-stage renal failure and chronic dialysis patients, pregnancy or breastfeeding, and those without clinical features and laboratory values were not included in the study. Patients receiving glucocorticoids and amiodarone were also excluded from the study. All patients were older than 18 years and were not admitted to the intensive care unit (ICU). Seven hundred and eighty-one COVID-19 hospitalized patients enrolled in the study whose demographic data and comorbidity were documented. Upon admission to the hospital, all the patients underwent examinations related to COVID-19, which consisted of recording the respiration rate and initial oxygen saturation by pulse oximetry (SpO_2) to assess the level of oxygen requirement and the radiological status based on spiral computerized tomography (CT). The pulmonary involvement on the chest CT scan was identified as mild, moderate, and severe (17). Data were categorized as deceased and discharged patients. Patients were classified as having moderate and severe illness (18). Within 24 h of admission, blood samples from patients were taken from a peripheral vein. A Roche Cobas C 601 (Roche Diagnostic Limited, Switzerland) device was used to measure thyroid function tests. Individuals were classified into diagnostic categories with respect to their fT4, fT3 and TSH values. In our laboratory, the reference ranges of fT3, fT4 and TSH were 2.5-3.9 pg/mL, 0.61-1.12 ng/dL and 0.34-5.6 µIU/mL, respectively. Patients with NTI were characterized by low fT3 (<2.5 pg/mL) with normal/low TSH and fT4.

The Medical Research Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital accepted the research (approval number: 2021/127, date: 15.03.2021). We are dedicated to uphold the Declaration of Helsinki and safeguarding patients' privacy. All the cases included in the study were managed in accordance with the COVID-19 treatment plan of the Turkish Health Ministry (19). All patients provided written informed consent.

Statistical Analysis

Mean and standard deviations were used to express descriptive statistics. Deviation from normality was determined using percentage and median distribution. Normally distributed continuous variables and the categorical data were examined using the chi-square test and Student's t-test. Continuous variables having an abnormal distributions were assessed by Mann-Whitney U test. Statistical significance was validated for a $p<0.05$. Commercially available SPSS software v.21 Statistical Package for the Social Sciences Inc. (Chicago, IL, USA) was used in all statistical analyzes.

The best parameters for predicting mortality from thyroid function tests were obtained from the receiver operating characteristic curves and were later used in the Cox regression model. The possible factors determined by multivariate analyzes with backward selection were fed into the Cox regression model for identifying independent predictors of mortality. The univariate effects of age, gender, arterial hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, C-reactive protein (CRP), procalcitonin, albumin, fibrinogen, D-dimer, troponin I and free T3 (fT3) on death of patients were examined by the log rank test. The residual analysis (Schoenfeld and Martingale) was used to evaluate the proportional hazard assumption and model fit.

Results

Among 781 individuals who had COVID-19 of enrolled in this research, 726 were discharged and 55 died. When the demographic data and coexisting conditions of the patients were investigated, no difference in sex was found between the deceased and survivors. The deceased individuals were older than the discharged group. Hypertension, prior coronary artery disease, prior stroke, heart failure, and atrial fibrillation were significantly more frequent ($p<0.001$, $p=0.002$, $p=0.009$, $p=0.001$, $p=0.003$, respectively) among deceased patients than the discharged. SpO_2 values initially and with supplemental oxygen were significantly lower in deceased patients than in the discharged. Respiratory rate and need for oxygen supplementation were significantly higher in deceased patients. Lymphopenia and platelet counts were significantly lower, whereas neutrophil counts were significantly higher in the deceased group than in the discharged. Urea, creatinine, and aspartate transaminase levels were also significantly higher in deceased patients than in discharged patients. Additionally, deceased patients were associated with stronger inflammatory responses and exhibited poor prognostic laboratory test results, such as CRP, lactate dehydrogenase, D-dimer, fibrinogen, ferritin, and troponin I. Although calcium and albumin were significantly lower in the severe individuals, there was no difference in procalcitonin between groups. Regarding their CT results, the deceased group showed severe involvement compared with the discharged group. Among 781 patients with COVID-19 pneumonia, 53 (96.4%) were severe in deceased patients and 368 (50.7%) were severe in discharged patients (Table 1). TSH and fT3 values were significantly lower

Table 1. Evaluation of demographical and clinical data, laboratory, CT results, and disease status

	Deceased (n=55)	Discharged (n=726)	p
Age (years)	71 (44-96); 71.18±10.88	60 (20-98); 59.89±14.97	<0.001
Gender (F/M) (%)	22/33; (40/60%)	316/410; (43.5/56.5%)	NS
Arterial hypertension on treatment	39 (70.9%)	327 (45%)	<0.001
Diabetes mellitus on treatment	25 (45.5%)	252 (34.7%)	NS
Dyslipidemia on treatment	5 (9%)	27 (3.7%)	NS
Prior coronary artery disease	16 (29%)	94 (12.9%)	0.002
Heart failure	9 (16.4%)	32 (4.4%)	0.001
Chronic atrial fibrillation	7 (12.7%)	23 (3.2%)	0.003
Prior stroke	6 (10.9%)	21 (2.9%)	0.009
COPD¶¶	2 (3.6%)	28 (3.9%)	NS
Asthma bronchial	4 (7.3%)	74 (10.2%)	NS
Baseline SpO_2 (%)	89 (87-93)	95 (94-99)	<0.001
O_2 support (L/per min)	15.67±9.9	3.32±5.4	<0.001
SpO_2¶	92.51±2.23	94.53±1.97	<0.001
The respiratory rate (per minute)	30.89±4.89	20.05±4.51	<0.001
Body temperature (°C)	37.03±0.64	37.02±0.69	NS
Systolic blood pressure (mmHg)	126.51±23.51	127.68±18.84	NS
Diastolic blood pressure (mmHg)	67.13±12.07	71.48±10.3	0.01
Heart rate (per minute)	85.95±16.39	84±14.14	NS
Neutrophil count	7.3±4.54	5.13±2.57	<0.001
Lymphocyte count	0.88±0.71	1.23±0.57	<0.001
Platelet count	214.15±103.58	249.59±107.01	0.01
Htc (%)	36.82±5.08	37.43±4.61	NS
Glucose (mg/dL)	165.92±74.42	150.94±68.2	NS
Urea (mg/dL)	66.74±38.61	38.88±25.27	<0.001
Creatinine (mg/dL)	1.37±1.45	0.95±0.82	0.001
AST (U/L)	51.33±26.61	42.19±29.22	0.02
ALT (IU/L)	39.05±28.57	41.87±39.28	NS
LDH (U/L)	497.80±232.85	327.85±161.75	<0.001
Sodium (mmol/L)	136.38±5.44	137.13±3.76	NS
Potassium(mmol/L)	4.23±0.6	4.16±0.5	NS
Magnesium (mg/dL)	2.01±0.32	2.01±0.28	NS
Calcium (mg/dL)	8.34±0.64	8.79±0.64	<0.001
C-reactive protein (mg/L)	152.01±76.68	96.86±73.46	<0.001
Procalcitonin (ng/mL)	1.04±3.31	1.03±10.70	NS
Albumin (g/dL)	32.42±5.27	36.28±5.32	<0.001
Ferritin (mcg/L)	816.03±754.84	431.66±472.61	<0.001
Troponin I (ng/mL)	67.22±245.2	14.62±58.08	<0.001
D-dimer (mcg FEU/mL)	1.09±1.11	0.77±1.17	0.04
Fibrinogen (mg/dL)	555.45±156.37	490.32±117.62	<0.001
Free T3 (pg/mL)	2.24±0.50	2.80±0.63	<0.001
Free T4 (ng/dL)	1.18±0.44	1.13±0.31	NS
TSH (µIU/mL)	1.18±2.15	1.65±2.64	<0.001
Thorax CT			<0.001
Mild involvement	3 (5.5%)	189 (26%)	
Moderate involvement	13 (23.6%)	339 (46.7%)	
Severe involvement	39 (70.9%)	198 (27.3%)	
Disease status			<0.001
Moderate	2 (3.6%)	358 (49.3%)	
Severe	53 (96.4%)	368 (50.7%)	
The duration of hospitalization (day)	13.85±8.89	11.40±6.64	0.01

¶: Under oxygen support; median, ¶¶: COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, F: Female, M: Male, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

in deceased patients than in discharged patients within the reference range. No significant difference in free T4 (fT4) value was found between the groups. TSH and fT3 distributions are shown in Figure 1, 2.

The univariate regression analysis demonstrated that gender, age, prior coronary artery disease, arterial hypertension diabetes mellitus, chronic obstructive pulmonary disease, albumin, CRP, fibrinogen, procalcitonin, troponin I, d-dimer, and fT3 were significantly associated with mortality. Cox multivariate regression analysis showed that fT3 was an independent risk factor for mortality (Table 2).

Among 781 patients with COVID-19 pneumonia, 154 (19.7%) were diagnosed with NTI. Only a small number of patients 16 (2%) had TSH levels above the reference value, 13 (1.6%) patients were subclinical with high TSH and normal fT4, 3 (0.4%) patients showed overt hypothyroidism with low fT4 and high TSH. In addition to that there were 99 (12.7%) patients whose TSH levels were below the reference value, 25 (3.2%) patients were subclinical with a low TSH and normal fT4, and 74 (9.5%) showed overt thyrotoxicosis with low TSH and high fT4.

Patients with elevated TSH were observed to be younger and had better clinical status with a lower mortality rate compared with the suppressed TSH and NTI patients. Patients with suppressed TSH levels had an average age of 65 years and had severe clinical status requiring ICU support with a mortality rate of 17.2%. Similar to those in the suppressed TSH patients, average age, clinical status, and mortality rate were higher in NTI patients. Among the 154 (22 deceased/132 discharged) NTI patients, 67 (43.5%) were moderate and 87 (56.5%) were severe, with a mortality rate of 14.3% (Table 3).

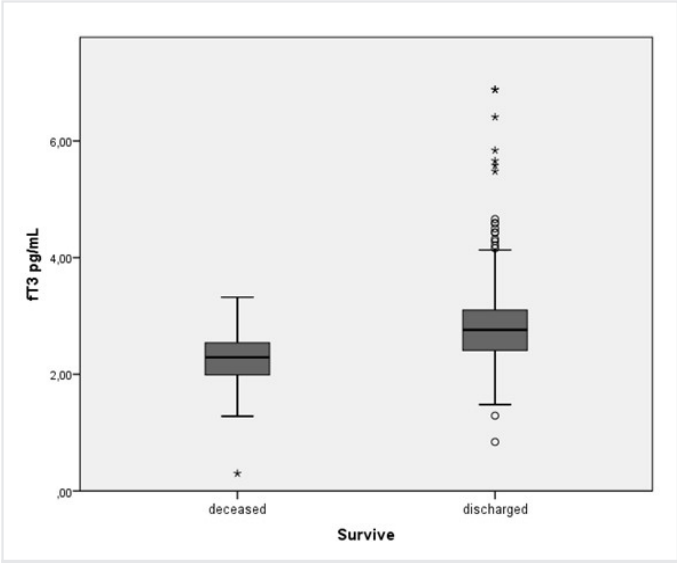

Figure 1. Deceased patients show significantly lower fT3 levels than the discharged (2.24±0.50 vs. 2.80±0.63 pg mL, p=0.001)

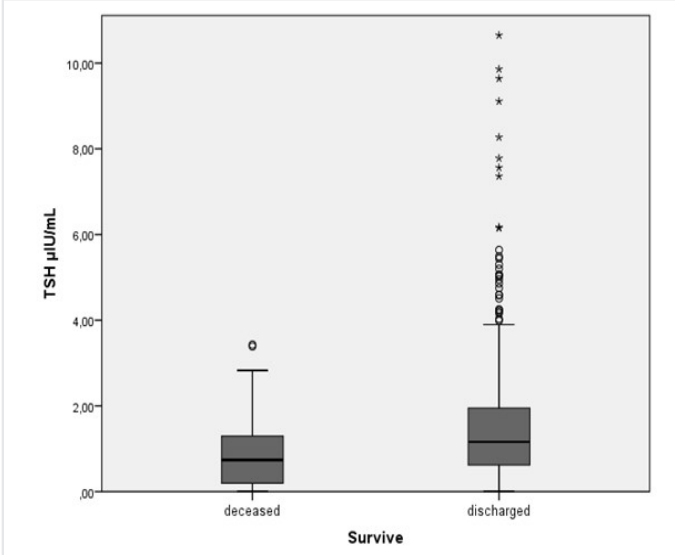

Figure 2. Deceased patients show significantly lower TSH levels than the discharged (1.18±2.15 vs. 1.65±2.64 µIU mL, p=0.001)
TSH: Thyroid stimulating hormone

Table 2. Univariate log-rank and multivariate Cox regression analysis of the risk factors associated with mortality in patients with COVID-19

Variable	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.044	1.022-1.066	**<0.001**	1.027	0.999-1.057	0.058
Gender	0.911	0.529-1.567	0.736			
Arterial hypertension	2.043	1.139-3.667	**0.017**	1.159	0.501-2.683	0.730
Diabetes mellitus	1.283	0.753-2.186	0.360			
Prior coronary artery disease	1.897	1.055-3.412	**0.032**	1.349	0.618-2.944	0.451
Chronic obstructive pulmonary disease	0.797	0.193-3.289	0.754			
C-reactive protein	1.003	1.001-1.006	**0.008**	0.998	0.993-1.002	0.341
Procalcitonin	1.001	0.976-1.027	0.911			
Albumin	0.924	0.874-0.977	**0.006**	0.936	0.874-1.001	0.055
Troponin I	1.001	0.999-1.002	0.260			
D-dimer	0.962	0.814-1.136	0.645			
Fibrinogen	1.002	1.000-1.004	**0.015**	1.002	0.999-1.004	0.135
Free T3	0.212	0.115-0.390	**<0.001**	0.397	0.201-0.793	**0.008**

COVID-19: Coronavirus disease-2019, HR: Hazard ratio, CI: Confidence interval

Table 3. Thyroid function abnormalities among all patients

	Elevated TSH, µIU/mL >5.6, (n=16)	Supressed TSH, µIU/mL <0,374, (n=99)	NTI TSH, µIU/mL <5.6 and (n=154)
Subclinical/overt	13 (1.6%)/3 (0.4%)	25 (3.2%)/74 (9.5%)	154 (19.7%)
FT4, ng/dL (0.61-1.12)			(FT4 <1.12)
Age	60.5±4.02 (20-85)	64.55±14.73 (37-96)	66.27±15.4 (27-103)
Sex			
Female	10 (62.5%)	41 (41.4%)	83 (53.9%)
Male	6 (37.5%)	58 (58.6%)	71 (46.1%)
The duration of hospitalization (day)	12.69±1.08	14.42±9.72	12.28±7.65
Disease severity			
Moderate	8 (50%)	23 (23.2%)	67 (43.5%)
Severe	8 (50%)	76 (76.8%)	87 (56.5%)
Mortality	1 (6.3%)	17 (17.2%)	22 (14.3%)

NTI: Nonthyroidal illness syndrome, TSH: Thyroid stimulating hormone

Among all deceased patients, one had elevated TSH and 17 had suppressed TSH. Eleven of the suppressed TSH patients showed overt thyrotoxicosis. Moreover, among the deceased patients 22 suffered from NTI.

Discussion

There are few studies in the literature focusing on the evaluation of thyroid function or thyroid pathology on COVID-19. In addition to their scarcity, the results reported in these studies show a certain sense of ambiguity, which may be attributed to thyrotoxicosis or NTI. Evidence shows that there are various effects of SARS-CoV-2 on the thyroid system (11,15).

In our study, we examined the acute impacts of COVID-19 on thyroid function in the largest cohort of patients. Individuals with suppressed TSH levels had severe clinical status and high mortality. More than half of the overt thyrotoxicosis patients having lowered TSH levels and ICU support had severe clinical status with a mortality rate of 17.2%. The mortality rate of NTI patients was 14.3%.

Identification of the thyroid state is important because thyrotoxicosis is believed to arise from several different conditions. Also, tests such as thyroid autoantibodies, ultrasonography, or scintigraphy could not be applied to our patients, most of whom were in severe status due to pandemic conditions.

Several studies reported lower levels of TSH and fT3 within the reference range in patients with COVID-19 (14,15,20-23). Only Chen et al. (20) reported that thyroid function did not predict SARS-CoV-2 infection or progression leading to respiratory failure. Other studies also concluded that thyroid dysfunctions were correlated with COVID-19 severity. They demonstrated the link between thyroid dysfunction and prognosis as they suggested that thyroid dysfunction was associated with a higher mortality and a prolonged hospitalization in individuals with SARS CoV-2 (14,21-24).

Chen et al. (21) in a retrospective study found lower T3 and TSH levels in 18% of the patients, together with a correlation to severe disease. In another study, Lania et al. (13) similarly identified overt thyrotoxicosis in 10.8% of their cohort of 287 individuals with SARS-CoV-2 who were managed without ICU, although they measured thyroid hormones in only 25% of their patients. Similarly, we found lower TSH and fT3 levels in 12.7% of the patients, with a positive correlation to the severity of COVID-19 infection. Similar to our results, a further study by Gao et al. (23) showed that fT3 levels at baseline (but not fT4 or TSH) acted as independent predictors of mortality in their cohort of patients. We observed a decrease in both fT3 and TSH levels, which were positively related to mortality in a larger group of patients. Additionally, fT3 and TSH levels in deceased patients were significantly lower than those in discharged patients.

On the other hand, current observational research by Khoo et al. (25) provided the acute effects of COVID-19 on thyroid function in the largest known cohort of patients so far. Their results showed that a major group of patients were euthyroid, while only a small group was subclinical hypothyroid (5.1%) or overt hypothyroid (0.6%). Eight patients were suspected of secondary hypothyroidism (2.4%). Neither subclinical nor overt thyrotoxicosis was observed in the diagnosis of their patients. The authors determined that in their cohort there was no evidence of a COVID-19-associated overt thyroid dysfunction, but their results were more indicative of a NTI syndrome (25).

Recently, data obtained from case reports and small clinical studies indicate that NTI is characterized by a reduction in T3 levels associated with adverse conditions, which may lead to mortality, especially in severe COVID-19 patients (16,26-28).

We tried to demonstrate the relationship between mortality and thyroid function, which implied its prognostic significance. We also studied the relationship between the duration of hospitalization and death rates in a large study group of COVID-19 individuals with non-mild status and having no prior thyroid disease. As a result, thyroid dysfunction was observed in approximately 15% of the patients and was associated with severe clinical condition. In addition, the fT3 level was suggested to be an independent prognostic indicator of mortality. As shown in some previous studies, these findings indicate an association of COVID-19 and thyroid with destructive or autoimmune mechanisms.

COVID-19 disease may have a direct effect on thyroid function. Low normal FT3 and low normal TSH levels may be associated with systemic inflammation and bearing a prognostic significance associated with disease state and mortality. These findings may also be indicative of NTI, which is a probable reason for the changes in thyroid function. A minor decrease in TSH with normal fT4 levels with low-normal fT3 levels was observed in NTI patients. As against the widely accepted thyrotoxicosis argument, this fact may be attributed to an alteration in thyroid hormone metabolism and/or pituitary responsiveness.

In our study, the relationship between mortality and thyroid function, especially around 15% overt thyroid dysfunction and 20% NTI, and its prognostic significance was demonstrated. We showed that fT3 was an independent risk factor for mortality. Our results show the suggestibility of thyroid function tests to be considered, at least in severe patients, even if not in all cases. On the other hand, further studies are needed to investigate the long-term effects of SARS-CoV-2 on thyroid function.

Study Limitations

The fundamental limitations of our study are its retrospective character and its unbalanced female dominance over male subjects (16/781) having overt or subclinical hypothyroidism. Because tests such as thyroid autoantibodies, ultrasonography or scintigraphy could not be performed due to pandemic conditions, we could not study whether patients had chronic thyroiditis, such as Hashimoto's. Furthermore, severe patients had various comorbidities and were also under a commonly prescribed medication. This might have caused some drug interactions as an effect of displacement of the thyroid hormone from the binding proteins such as furosemide, metformin, and salicylates (29).

Thyroid hormones can also alter dynamically with the advance or resolution of the underlying primary disorder. Finally, the potential role of thyroid hormones in COVID-19 needs to be investigated further, although the cost-effectiveness and diagnostic value of serum TSH measurement in hospitalized patients are still controversial (30).

Conclusion

In our study, the relationship between mortality and thyroid function was investigated in COVID-19 patients. Our results suggest that thyroid function tests, especially in severe patients, may have prognostic significance because fT3 is an independent risk factor for mortality. The presence of suppressed TSH in an average of 10-15% of the patients supports the triggering of possible destructive and autoimmune mechanisms and/or pituitary responsiveness. NTI is an independent factor that may influence the changes in thyroid function leading to a severity in patients with COVID-19 pneumonia. Moreover, the presence of suppressed TSH levels and overt thyrotoxicosis in 17 of 55 patients who died indicate the importance of evaluating thyroid functions as etiologic factors in severely ill patients.

Acknowledgements

The authors wish to thank Prof. Dr. Ahmet Ademoğlu and Biomedical Engineering Institute of Boğaziçi University for his help with statistical analyses and interpretation of data.

Ethics Committee Approval: The Medical Research Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital accepted the research (approval number: 2021/127, date: 15.03.2021). We are dedicated to uphold the Declaration of Helsinki and safeguarding patients' privacy.

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.B.; Concept - M.B.; Design - M.B.; Data Collection or Processing - M.B., I.K.A.; Analysis or Interpretation - M.B., I.K.A.; Literature Search - M.B., I.K.A.; Writing - M.B.

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

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

References

1. World Health Organization. Geneva (Switzerland): World Health Organization; 2003. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003 [Internet] Dec [cited 2020 Apr 1]. Available from: https://www.who.int/csr/sars/country/table2004_04_21/en/
2. Asselah T, Durantel D, Pasmant E, Lau G, Schinazi RF. COVID-19: Discovery, diagnostics and drug development. J Hepatol 2021; 74: 168-84.
3. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005; 202: 415-24.
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: 95-102.
5. 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.
6. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. Zhonghua Bing Li Xue Za Zhi 2020; 49: 411-7.
7. Leow MKS, Kwek DSK, Ng AWK, Ong KC, Kaw GJL, Lee LSU. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol 2005; 63: 197-202.
8. 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.
9. 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.
10. 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.
11. Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. J Endocrinol Invest 2020; 43: 1027-31.
12. Garg MK, Gopalakrishnan M, Yadav P, Misra S. Endocrine Involvement in COVID-19: Mechanisms, Clinical Features, and Implications for Care. Indian J Endocrinol Metab 2020; 24: 381-6.
13. 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.
14. 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.

15. 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.

16. Lee S, Farwell AP. Euthyroid Sick Syndrome. Compr Physiol 2016; 6: 1071-80.

17. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiol Cardiothorac Imaging 2020; 2: e200047.

18. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020; 133: 1087-95.

19. Republic of Turkey Ministry of Health. Covid-19 (SARS-CoV-2 Infection) Guide. Available @:covid-19rehberieriskinhastatedavisipdf.pdf (saglik.gov.tr), (Accessed 20/07/2020.)

20. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368: m1091. Erratum in: BMJ 2020; 368: m1295.

21. Chen M, Zhou W, Xu W. Thyroid Function Analysis in 50 Patients with COVID-19: A Retrospective Study. Thyroid 2021; 31: 8-11.

22. 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.

23. 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.

24. Zhang Y, Lin F, Tu W, Zhang J, Choudhry AA, Ahmed O, et al. Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19. Mol Cell Endocrinol 2021; 521: 111097.

25. 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.

26. 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: 101-9.

27. Laurino A, Gencarelli M, Buci L, Raimondi L. Commentary: Euthyroid Sick Syndrome in Patients With COVID-19. Front Endocrinol (Lausanne) 2021; 12: 633097.

28. Sen K, Sinha A, Sen S, Chakraborty S, Alam MS. Thyroid Function Test in COVID-19 Patients: A Cross-Sectional Study in a Tertiary Care Hospital. Indian J Endocrinol Metab 2020; 24: 532-6.

29. Cannarella R, Condorelli RA, Barbagallo F, Aversa A, Calogero AE, La Vignera S. TSH lowering effects of metformin: a possible mechanism of action. J Endocrinol Invest 2021; 44: 1547-50.

30. Bashkin A, Yaakobi E, Nodelman M, Ronen O. Is routine measurement of TSH in hospitalized patients necessary? Endocr Connect 2018; 7: 567-72.