Thyroid dysfunction is associated with poor COVID-19 outcomes

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ABSTRACT

Objectives: We aimed to investigate the effects of the thyroid hormone level on the hospitalization rate and prognosis of COVID-19 patients.

Methods: Patients with a positive PCR test result and having their TSH, fT3, and fT4 values tested. The patients were classified according to their thyroids' functional status. The hospitalization rates in the hospital and intensive care unit and the mortality rate were evaluated.

Results: A total of 708 patients were included in the study. 225 (31.8%) patients were euthyroid. The rates of hospitalization to the intensive care unit ($p < 0.001$) and the clinic ($p < 0.001$) and also the mortality rate (0.012) were lower. 483 (68.2%) were classified as a euthyroid sick syndrome. In 305 (43.1%) patients, only the fT3 level was low, whereas in 47 (6.6%), both fT3 and fT4 were low, and in 131 (18.5%) patients, the fT3, fT4, and TSH levels were low. In patients with thyroid dysfunction, the levels of BUN, creatinine, D-dimer, neutrophil %, troponin T, CRP, procalcitonin, LDH were higher, and the aPTT was longer. In contrast, the leukocyte count and percentage were lower.

Conclusions: The intensive care hospitalization rate, the duration of hospitalization in the clinic, and the mortality rate were lower in euthyroid patients. ICU hospitalization and mortality rates were higher in patients in whom both fT3 and fT4 levels were low. Thyroid dysfunction is common in COVID-19 patients. The variations in serum TSH and T3 levels may significantly indicate disease severity in COVID-19.

Keywords: COVID-19; intensive care; euthyroid sick syndrome

Since the first coronavirus disease 2019 (COVID-19) cases due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in late 2019, COVID-19 has spread worldwide. As a result, in March 2020, a global pandemic was declared by the World Health Organization [1]. The virus infection is known to have a complex interaction with the thyroid gland and related inflammatory-immune responses. SARS-CoV-2 uses ACE2 jointly with transmembrane protease serine 2 (TMPRSS2) as the key molecular complex for infecting host cells. Surprisingly, in the thyroid gland, the expression levels of ACE2 and TMPRSS levels are higher than in the lungs [2].

In COVID-19 patients, thyroid dysfunction may be comorbidity. Besides, the low triiodothyronine (T3) status is considered as an indicator of the euthyroid sick syndrome (ESS) and observed in critical patients [3-5]. For this reason, alterations of thyroid functions during the coronavirus infection have

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drawn attention. Moreover, in observational studies, the thyroid hormone and TSH levels were lower in patients who died due to COVID-19 when compared to survivors [6, 7]. A cohort study conducted in China showed that in COVID-19 patients followed up in the hospital, the mortality rate was higher in the patients with thyroid dysfunction than those with no dysfunction [8]. Furthermore, investigators have reported that thyroid dysfunction was related to mortality among critical patients hospitalized in the intensive care unit [9, 10].

In euthyroid sick syndrome (ESS), low fT3, normal TSH, and normal fT4 were defined as ESS- mild disease, low fT3, normal/low TSH, and normal/low/high fT4 as ESS-moderate disease, low fT3,
low fT3, and low TSH as ESS-severe disease [11].
This retrospective study aimed to investigate the effects of thyroid hormone levels on COVID- 19 patients' hospitalization rates and prognosis.

METHODS

Study Design and Participants

The Local Ethics Committee (01.09.2021/ethics no.: 15 / 8) approved this study. Seven hundred eight patients with reverse-transcription polymerase chain reaction- (RT-PCR)-confirmed COVID-19 who were admitted to Our Hospital between April 2020 and December 2020 were enrolled. None of them had previous thyroid disease, used any thyroid medications, or had a pregnancy. Covid pcr positive patients were included in the study. Exclusion criteria were defined as using thyroid medication, having a history of thyroid disease, pregnancy and being under 18 years of age.

Data Collection

All patients were evaluated for thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4). In addition, the results for complete blood counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, creatinine, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, PT, aPTT, troponin T, and procalcitonin values were recorded from the laboratory information system.

The patients' age and gender distributions, hospitalization rates (%), duration of hospitalization in the clinics and ICU, and discharge status were evaluated.

The patients were divided into four groups: Euthyroid group, Group 1 - only low fT3; group 2 - low fT3 and low fT4; group 3 - low TSH, low fT3, and low fT4. It was determined as overt hyperthyroidism (low TSH, high fT3, and/or fT4) and overt hypothyroidism (elevated TSH and low fT4 and/or fT3). The patients' clinic and ICU hospitalization duration and discharge/exitus status were classified according to the groups.

Biochemical Analysis

The parameters of AST, ALT, creatinine, and LDH were analyzed with Roche Cobas 8000 c 702. In addition, the parameters of PT, INR, APTT were measured with Coagulation Analyzer Cobas T711. The troponin T level was measured with sandwich principle Roche Cobas 8000-e801. The procalcitonin levels were measured with Sandwich Roche Cobas 800-e801 (ECLIA). CRP levels were measured with Particle-enhanced immunoturbidimetric assay-c702 (ECLIA). The D-dimer level was measured with particle-enhanced turbidimetric immunoassay - Roche Cobas T711. Ferritin values were measured with sandwich principle electrochemiluminescence- C801 (ECLIA). Complete blood counts were measured with Sysmex XN1000. TSH, free thyroxine (fT4), and fT3 were evaluated at admission before the administration of in-hospital medications using the sandwich principle electrochemiluminescence- e 801 (ECLIA) (Roche, Mannheim, Germany). The reference range for TSH was 0.27–4.20 mIU/L, for fT3 2.04–4.44 ng/L, and for fT4 0.93–1.71 ng/dl.

Statistical Analysis

The study's statistical analysis was performed using the JASP 0.14.1 and RStudio 1.0.959 software packages. Descriptive statistics for qualitative variables in the study were given as frequency and percentage, and quantitative variables as the mean, standard deviation, median, minimum, and maximum values. In addition, the conformity of the study's quantitative variables with a normal distribution was analyzed with the Shapiro Wilk test. The Mann-Whitney U test was used for independent two-group comparisons of quantitative variables not having a normal distribution; the Kruskal Wallis test compared three or more groups. The Mann Whitney U test with the Bonferroni correction was used for two-subgroup comparisons of variables with significant inter-group differences. For qualitative variables' inter-group comparisons, Pearson's Chi-square test was used. In the study's statistical analysis, the results with a p-value below 0.05 were considered statistically significant.

Table 1. Distribution of Euthyroid and ESS groups

	n	%	Age (Mean ± SD)	Male (n, %)
Euthyroid	225	31.8	62.01 ± 15.6	132 (58.7%)
Group 1	305	43.1	63.75 ± 14.78	176 (57.7%)
Group 2	47	6.6	62.51 ± 14.11	28 (59.6%)
Group 3	131	18.5	63.66 ± 13.88	76 (58.0%)
Total	708	100	63.10 ± 14.84	412 (58.2%)

RESULTS

Patients hospitalized in the our hospital between April 2020 and December 2020 were screened. Seven hundred eight patients with a positive PCR test and who were tested for TSH, fT3, fT4 were included in the study. Of 708 patients, 412 (58.2%) were male, and 296 (41.8%) were female. Six hundred three patients were discharged from the hospital, whereas 105 died. The number and percentage distributions of the groups are presented in Table 1.

Of 708 patients, 225 were in Euthyroid group. In 305 (43.1%) patients, only the fT3 value was low.

In 47 (6.6%) patients, both fT3 and fT4 values were low, and in 11 (18.5%), fT3, fT4, and TSH levels were low. Overt hypothyroidism was present in 11 patients, whereas overt hyperthyroidism in 30 patients.

Comparison of Euthyroid and ESS groups regarding the laboratory parameters

No statistically significant difference was deter-

Table 2. The mean, minimum, and maximum values of the parameters

	Euthyroid	Mild disease	Moderate disease	Severe disease	*p*
Alt	23 (7-3113)	22 (5-303)	27 (5-111)	23 (5-251)	0.608
Ast	28 (10-1927)	32 (6-378)	30 (8-271)	30 (11-219)	0.376
BUN	13.7 (3.6-139.2)	16.5 (4.7-109.1)	19.10 (7.9-78.4)	16.10 (6.2-70)	< 0.001
Creatinine	0.91 (0.44-3.02)	0.96 (0.41-3.64)	1.11 (0.42-2.04)	0.93 (0.53-3.99)	0.001
Hgb	13.4 (5.6-18.4)	13.1 (5.2-17.7)	13.3 (8.4-16.5)	13 (9.1-18.2)	0.052
Wbc	6.75 (1.38-450.40)	7.13 (0.92-58.91)	7.23 (2.70-20.07)	7.07 (1.61-27.74)	0.610
Leu	1.21 (0.17-298.57)	1.17 (0.20-48.77)	1.19 (0.47-2.96)	0.98 (0.15-3.13)	0.007
Leu %	18.5 (2.1-88.5)	17.9 (2.2-84.8)	16.3 (4.9-39.6)	14.5 (2.4-50.9)	0.004
Neu	4.53 (0.66-24.99)	5.19 (0.65-39.45)	5.05 (1.71-17.64)	4.96 (1.23-25.91)	0.304
Neu %	71.8 (2.3-97)	73.7 (10.7-96.3)	75.5 (52-93.6)	77.1 (43.1-93.7)	0.001
Plt	215 (22-724)	220 (52-697)	217 (57-483)	217 (72-620)	0.607
Ldh	250 (74-1343)	298 (98-1226)	305 (0.03-1352)	315 (138-767)	< 0.001
Prc	0.08 (0.02-13)	0.10 (0.02-81.59)	0.10 (0.02-16.50)	0.11 (0.02-5.59)	0.007
Crp	32.1 (0.2-313.5)	63.2 (0.8-497.8)	66 (3.8-345.5)	64.1 (1.8-324.3)	< 0.001
D-Dimer	0.46 (0.20-20.50)	0.54 (0.20-20.80)	0.58 (0.20-15.30)	0.63 (0.20-8.78)	0.028
Ferritin	294.5 (3-16931)	395 (14-4293)	284 (59-4745)	374.5 (5-6838)	0.005
Pt	9.07 (7.45-15.60)	9.09 (7.68-19.10)	9 (8.04-13.60)	9.05 (7.48-12.80)	0.664
INR	1.01 (0.84-1.70)	1.02 (0.86-2.05)	1.01 (0.91-1.47)	1.02 (0.85-1.41)	0.670
aPtt	30.5 (15-53.9)	31.40 (17.8-56.6)	31.6 (18.5-66.4)	31 (16.3-45.8)	0.046
Trop T	7.20 (3-6650)	12.75 (3-430.3)	15.7 (3-464)	11.3 (3-285)	< 0.001
TSH	1.17 (0.27-16.80)	0.64 (0.27-19.80)	1.49 (0.29-97.20)	0.15 (0.03-0.26)	< 0.001

#Kruskal Wallis test

Table 3. The duration of hospitalization in Euthyroid and ESS groups (days)

	Euthyroid	Group 1	Group 2	Group 3	*p*
Duration of Hospitalization in ICU	9 (1-36)	10 (1-51)	19 (1-53)	11 (1-25)	0.126
Duration of Hospitalization in the Clinic	8 (1-31)	10 (1-47)	11 (2-60)	9.5 (1-44)	< 0.001
Duration of Total Hospitalization	9 (2-38)	12 (3-61)	16 (3-88)	12 (3-60)	< 0.001

#Kruskal Wallis test

mined among the groups regarding the values of ALT, AST, Hgb, WBC, PLT, PT, INR, and neutrophil count (p = 0,608, p = 0,376, p = 0,0,052, p = 0,610, p = 0,607, p p = 0,664, p = 0,670, p = 0,610). On the other hand, significant differences were present among the groups regarding other parameters as presented in the Table 2.

Comparison of Euthyroid and ESS groups regarding hospitalization duration in the clinic and ICU The average ICU hospitalization duration was nine days in Euthyroid patients, whereas ten days, 19 days, and 11 days in Groups 1, 2, and 3, respectively (p = 0.126). The hospitalization duration of Euthyroid patients in the clinic was significantly shorter than Groups 1, 2, and 3 (p = 0.001, p = 0.007, and p = 0.026). In Euthyroid patients, it was eight days on average, whereas in Groups 1, 2, and 3, 10 days, 11 days, and 9.5 days, respectively (p < 0.001). The total hospitalization duration of Euthyroid patients was significantly lower than Groups 1, 2, and 3. On average, it was determined as nine days in Euthyroid patients, whereas 12 days, 16 days, and 12 days in Groups 1, 2, and 3, respectively (p < 0.001). The duration of hospitalization in Euthyroid and ESS groups (days) in the Table 3.

Comparison of Euthyroid and ESS groups regarding hospitalization rates in the clinic and ICU, and the mortality rate

The ICU hospitalization rate of Euthyroid patients was 16.6% and significantly lower than the patients with TD. This ratio was 30.6%, 40.4%, and 31.3% in Groups 1, 2, and 3, respectively (p < 0.001). The rate of hospitalization in the clinic was 97.4% in Euthyroid patients, whereas 97.4%, 95.7%, and 99.2% in Groups 1, 2, and 3, respectively (p = 0.502). The mortality rate was 9.8% in Euthyroid patients and was lower than the patients with TD. This ratio was 16%, 27.7%, and 16% in Groups 1, 2, and 3, respectively (p < 0.001). The relationship between hospitalization and mortality rate in Euthyroid and ESS groups in the Table 4.

The relationship between hospitalization in the clinic, ICU, and mortality in the hypothyroid and hyperthyroid patients

The ICU hospitalization rate was 36.4% in the hypothyroid group, whereas 40% in the hyperthyroid group (p = 1.000). On the other hand, the mortality rate was 18.2% in the hypothyroid group, whereas

26.7 in the hyperthyroid group (p = 0.012). The relationship between hospitalization and mortality rate in Hypothyroid and Hyperthyroid patients in the Table 5.

DISCUSSION

Our study determined ESS in 483 (31.8%) of the 708 COVID-19 patients. Thyroid dysfunction was

Table 4. The relationship between hospitalization and mortality rate in Euthyroid and ESS groups

		Euthyroid n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	*p*
Hospitalization in ICU	No	186 (83.4)	211 (69.4)	28 (59.6)	90 (68.7)	< 0.001
	Yes	37 (16.6)	93 (30.6)	19 (40.4)	41 (31.3)	
Hospitalization in the Clinic	No	5 (2.2)	8 (2.6)	2 (4.3)	1 (0.8)	0.502
	Yes	218 (97.8)	296 (97.4)	45 (95.7)	130 (99.2)	
Final situation	Discharged	203 (90.2)	256 (84)	34 (72.3)	110 (84)	0.012
	Exitus	22 (9.8)	49 (16)	13 (27.7)	21 (16)	

#Kruskal Wallis test

Table 5. The relationship between hospitalization and mortality rate in Hypothyroid and Hyperthyroid patients

		Hypothyroid n (%)	Hyperthyroid n (%)	*p*
Hospitalization in ICU	No	7 (63.6)	18 (60.0)	
				1.000
	Yes	4 (36.4)	12 (40.0)	
Hospitalization in the Clinic	No	-	-	
	Yes	11 (100)	30 (100)	-
Final situation	Discharged	9 (81.8)	22 (73.3)	
				0.012
	Exitus	2 (18.2)	8 (26.7)	

Pearson's Chi-square test

associated with a longer duration of hospitalization and a higher mortality rate. In the study conducted by Zhang *et al*., 16.9% (n=71) of the COVID-19 patients had ESS, and it was associated with a high mortality rate. Besides, the neutrophil count, CRP, LDH, and CK were high, and the lymphocyte count was low [8]. In Gao *et al*.'s study involving 100 patients with severe COVID-19, thyroid functions were assessed, and a higher mortality rate was determined in those with a low fT3. [12]. In our study, hospitalization rates in both the ICU and the clinic and the mortality rate were higher in ESS patients. On the other hand, the mortality rate was 18.2% in the Hypothyroid group and was higher, 26.7% in the Hyperthyroid group.

The ICU hospitalization rate in Euthyroid patients was 16.6%, lower than in the patients with TD. This rate was 30.6%, 40.4%, and 31.3% in Groups 1, 2, and 3, respectively. In addition, the mortality rate was 9.8% in Euthyroid patients and was lower than in the patients with TD. This ratio was 16%, 27.7%, and 16% in Groups 1, 2, and 3, respectively.

The pathophysiology of ESS varies according to the type, severity, and stage of the disease. In the acute phase of the disease, the plasma concentration of T3 decreases rapidly, and the reverse T3 level increases. These alterations can be partially explained by decreased thyroid hormone-binding protein and albumin levels and reduced binding activity. Additionally, an acute change in T4's peripheral conversion due to reduced Type 1 deiodinase (D1) activity and increased Type 3 deiodinase (D3) activity can explain these changes. It is known that circulatory cytokines reduce D1

activity and increase D3 activity, leading to acute reduction of T3 levels in critical patients [13, 14]. In COVID-19, the disease's course and severity are closely related to the effects of various cytokines

such as interleukin-6 and tumor necrosis factor-alpha (15). In our study, the levels of inflammatory markers (CRP, procalcitonin, LDH) were higher in ESS patients than in Euthyroid patients. Elevations of inflammatory cytokine levels can suppress central TSH and 5'-deiodinase activity. ESS might have occurred in COVID-19 patients due to SARS-CoV-2 directly infecting the thyroid glandular cells.

In our study investigating the ESS subgroups, the higher mortality rate determined in the group with low fT3 and low fT4 (Group 2) suggests that the fT4 and fT3 levels being low together may indicate significance in mortality and ICU hospitalization. In our study, TD did not affect the duration of ICU hospitalization, whereas it led to prolongation of hospitalization in the clinic and the total length of stay in the hospital.

In a multi-center study in the U.S.A., Khoo *et al*. evaluated the thyroid functions of the COVID- 19 patients at admission and follow-up examinations. They reported that the TSH and fT4 levels were

relatively lower in COVID-19 patients than those without COVID-19 [16].

The study's main limitations were its retrospective nature, lack of a control group, lack of thyroid antibody measurements, absence of oxygen support and treatment modality status, lack of data collection on mechanical ventilation requirement, inotropes, and other comorbidities.

Our study may be representational due to the investigation of ESS subgroups. However, the effect mechanisms of TD on COVID-19 should be investigated thoroughly with large-scale studies in the future. On the other hand, should thyroid hormone replacement therapy be encouraged in the non-thyroidal illness syndrome? Studies related to its prognostic effect may also be conducted in the future.

CONCLUSION

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa City Hospital, Bursa, Turkey. (Decision number: 2021 15/8, date: 1.09.2021).

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