

# **The Prognostic Impact of Thyroid Hormonal Disorders and Thyroid Nodule According to the Clinical Severity of Coronavirus Disease 2019 (COVID-19): Results of Single Center Pandemic Hospital**

## **Abstract**

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause thyroid hormonal disorders. In addition, tracheal compression by thyroid nodules can aggravate hypoxia in critically-ill patients. No studies have investigated the effect of thyroid nodules on the prognosis of patients with COVID-19. In this study, we investigated the effect of thyroid hormonal disorders and thyroid nodules on the prognosis of patients with COVID-19.

**Material and Methods:** This prospective study was conducted at the Şırnak State Hospital (Pandemic hospital in Turkey) between 15 March and 15 August 2020. We evaluated thyroid hormonal disorder and thyroid nodules in 125 patients who were admitted to the non-intensive care unit (non-ICU) due to mild COVID-19 pneumonia (group 1) and 125 critically-ill patients who were admitted to the ICU (group 2).

**Results:** Thyroid stimulating hormone levels (TSH) were not significantly different between groups 1 and 2 ; however, group 2 patients had significantly lower levels of free thyroxine (FT4) and free triiodothyronine (FT3) as compared to group 1 ( $p = 0.005$ ,  $p < 0.0001$ , respectively). FT3 level showed a negative correlation with length of hospital stay and C-reactive protein level ( $\rho: -0.216$ ,  $p: 0.001$ ;  $\rho: -0.383$ ,  $p < 0.0001$ ). Overt thyroid disorder was observed in 13 patients [2 patients in group 1 (both with overt thyrotoxicosis) and 11 patients in group 2 (3 overt hypothyroidism, 8 overt thyrotoxicosis) ( $p = 0.01$ )]. Thyroid nodules sized  $\geq 1$  cm were found in 9 patients (7 %) in group 1 and 32 patients (26%) in group 2 ( $p < 0.0001$ ).

**Conclusion:** Overt thyroid hormonal disorders were more common in critically-ill COVID-19 patients. FT3 level at hospital admission is a potential prognostic marker of COVID-19 patients. Thyroid nodules may be associated with severe COVID-19 disease.

**Keywords:** COVID-19, thyroid disorders, thyroid nodule, intensive care unit, mortality

**What is already known about this topic?**

In many scientific articles, COVID-19 was thought to affect thyroid hormones. But scientific studies had not been done.

**What does this article add?**

With this study, it was revealed that thyroid hormones are affected by COVID-19 in the intensive care unit. In addition, thyroid nodules have been shown for the first time to be a poor prognostic factor for COVID-19.

## **1. Introduction**

In the final months of 2019, a novel virus emerged in Wuhan, China, which subsequently resulted in an international pandemic. In February 2020, the World Health Organization named the virus as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) and the associated disease as Coronavirus Disease-2019 (COVID-19) (1). Initial cases of COVID-19 in Turkey were reported after March 11, 2020; subsequently, cases were reported from across the country.

According to the Ministry of Health of the Republic of Turkey, a total of 337,147 cases of COVID-19 infection and 8,895 deaths have been reported in Turkey as of October 12, 2020.

According to a report by the Chinese Center for Disease Control and Prevention which included approximately 44,500 confirmed infections, the estimated distribution of disease severity was as follows: mild disease (no or mild pneumonia), 81%; severe disease (e.g., presence of dyspnea, hypoxia, or >50 % lung involvement on imaging within 24 to 48 hours), 14%; critical disease (e.g., presence of respiratory failure, shock, or multiorgan dysfunction), 5 % (2).

SARS-CoV-2 can affect the thyroid gland both through the angiotensin converting enzyme (ACE-2) receptors and due to the cytokine storm that occurs in the disease (3). Thyroid hormonal disorders that may occur in critically-ill patients hospitalized in the intensive care unit (ICU) may cause aggravation of the underlying clinical picture. In addition, tracheal compression causing by the existing thyroid nodules may aggravate hypoxia due to acute respiratory syndrome.

To the best of our knowledge, no studies have specifically investigated thyroid hormone disorders and thyroid nodules in critically ill COVID-19 patients admitted to the ICU. In this study, we aimed to compare the thyroid hormone dynamics and the presence of thyroid nodules in patients with mild COVID-19 pneumonia admitted to the non-ICU and patients with critical condition admitted to the ICU.

## **2. Material and Methods**

### **2.1. Population and Study Design**

Between 15 March and 15 August 2020, 125 patients who were hospitalized in the non-ICU at the Şırnak State Hospital (pandemic hospital in Turkey) due to mild COVID-19 pneumonia

and 125 critically ill patients admitted to the ICU due to COVID-19 pneumonia (dyspnea, hypoxia, respiratory failure, shock, or multiorgan dysfunction) were included in the study.

Patients with mild symptoms in the non-ICU were categorized as group 1, while patients with critical condition in the ICU were categorized as group 2. Patients in the ICU were further divided into two subgroups, survivor (n = 88) and deceased (n = 37).

Length of hospital stay was defined as the interval between the first hospitalization and the day of discharge from the hospital.

This prospective study was approved by the Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (Diyarbakır, Turkey) (September 11, 2020, number: 546).

## **2.2. Laboratory Analysis**

The diagnosis of COVID-19 was based on positive results of real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test of nasopharyngeal and oropharyngeal swabs or the presence of strong clinical and radiological signs of COVID-19 even if the nasopharyngeal swab result was negative.

In Group 1, fasting blood samples of patients were obtained at 07.00–08.00 Hrs on the first morning of their hospitalization. Complete blood count, glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, ferritin, C-reactive protein (CRP), D-dimer, thyroid stimulating hormone (TSH), free T4 (FT4), free T3 (FT3), antithyroid peroxidase (Anti-TPO), anti-thyroglobulin (Anti-Tg) levels were measured.

In group 2, blood samples for the above-mentioned investigations were obtained at 07.00–08.00 Hrs on the first morning of their admission to the ICU.

Hormone levels were analyzed using the Cobas 6000 analyzer (Roche Diagnostics, Germany).

### **2.2.3. Evaluation of Thyroid Hormone Profile**

Thyroid hormone results obtained from patients were classified according to the definitions given below.

**Overt thyrotoxicosis** was defined as low TSH level and serum FT3 and/or FT4 above the respective reference range.

**Overt hypothyroidism** was defined as high TSH level and serum FT4 and/or FT3 below the respective reference range.

**Subclinical thyroid dysfunction** was defined as presence of low or high TSH levels accompanied by FT4 and FT3 within the respective reference range.

**Non-thyroidal illness syndrome (NTIS)** was defined as presence of normal serum TSH, normal or high FT4, low FT3 or low serum TSH, FT4, FT3.

Other pituitary hormone levels (prolactin, ACTH, cortisol) were assessed to differentiate NTIS from central hypothyroidism. A distinction was made from central hypothyroidism as the other pituitary hormone levels were found to be normal or high.

Thyroid ultrasonography to assess the presence of subacute thyroiditis was performed in all patients with thyrotoxicosis.

### **2.3. Chest Computed Tomography (CT) Imaging and Thyroid Nodule Evaluation**

All thoracic CT studies were performed using 16-slice CT scanner (Alexion 16, Toshiba Medical Systems, Japan). The acquisition parameters included detector row configurations of 0.625 mm and section thicknesses of 3 mm. Iodine contrast agents were not used for chest CT imaging.

Non-contrast chest CT images with suspicion of pneumonia were examined. Thyroid gland was examined in chest CT cervical sections. Patients with incidentally detected nodule  $\geq 1$  cm in the thyroid gland were classified as '**nodule positive**'. Figure 1 shows a representative non-contrast chest CT image of a patient in Group 2 showing a nodule in the thyroid gland.

### **2.4. Exclusion Criteria**

Patients with previously known pituitary disorders, thyroid disorders, diabetes mellitus, kidney and liver disease were excluded from the study. Patients who were taking thyroid hormone therapy (levothyroxine or antithyroid drug), amiodarone, dopamine, dobutamine, corticosteroid, furosemide, nonsteroidal anti-inflammatory drugs (NSAIDs), heparin, anticonvulsants, metformin, or immunotherapy and those who were pregnant were excluded from the study. Apart from this, all patients over the age of 18 were included in the study.

### **2.5. Statistical analysis**

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows 18.0 program. Categorical variables are presented as frequency (percentage) while continuous variables are presented as median (interquartile range). Between-group differences with respect to categorical variables were assessed using the Chi-squared test, while those with respect to nonparametric continuous variables were assessed using the Mann-Whitney test. Spearman's correlation test was used to assess the correlation between two variables. P values  $< 0.05$  were considered indicative of statistical significance.

### 3. Results

A total of 103 patients (82%) in group 1 and 99 patients (79%) in group 2 showed positive results of real-time RT-PCR test on oropharyngeal/nasopharyngeal swab. The median age of patients in groups 1 and 2 was 56 (interquartile range [IQR], 46–69; range, 21–92) years, and 74 (IQR, 66.5–83; range, 25–107) years, respectively ( $p < 0.0001$ ). The majority of patients in both groups were male (62% and 64%, respectively;  $p > 0.05$ ).

The median glucose level in groups 1 and 2 was 110 (IQR, 93–128) mg/dL and 139 (IQR, 113.5–189.5) mg/dL, respectively ( $p < 0.0001$ ). The median CRP level in groups 1 and 2 was 1.88 (IQR, 0.51–4.17) mg/dL and 12.73 (IQR, 7.21–17.59) mg/dL, respectively ( $p < 0.0001$ ).

One patient died during the follow-up period in group 1, as against 37 patients in group 2 ( $p < 0.0001$ ). The median length of hospital stay in groups 1 and 2 was 6 (IQR, 4–9) days and 13 (IQR, 8.5–19) days, respectively ( $p < 0.0001$ ). The demographic characteristics and laboratory results of patients in the two groups are summarized in Table 1.

There was no significant difference between male and female patients with respect to TSH, FT4, FT3, anti-TPO, and anti-Tg levels. Furthermore, none of these laboratory indices showed any correlation with age. There was no significant difference between group 1 and 2 with respect to TSH level ( $p > 0.05$ ). However, FT4 and FT3 levels in group 2 were significantly lower than those in group 1 ( $p = 0.005$  and  $p < 0.0001$ , respectively). CRP level showed a negative correlation with FT3 ( $\rho: -0.383$ ,  $p < 0.0001$ ) (Figure 2). FT4 level showed no correlation with length of hospital stay; however, FT3 level showed a negative correlation with length of hospital stay ( $\rho: -0.216$ ,  $p = 0.001$ ) (Figure 3).

Anti-Tg level, which was examined in terms of thyroid autoantibodies, was not different between the two groups; however, the anti-TPO level in group 2 was significantly higher than that in group 1 ( $p = 0.009$ ). Thyroid nodules were detected in 9 patients (7%) in group 1 as against 32 (26%) patients in group 2 ( $p < 0.0001$ ).

Overt thyroid disorder was observed in 13 patients in this study; these included 2 patients (both with overt thyrotoxicosis) in group 1 and 11 patients (3 with overt hypothyroidism and 8 with overt thyrotoxicosis) in group 2. Subclinical thyroid disorder was observed in 6 patients (all with subclinical thyrotoxicosis) in group 1 and 8 patients (1 subclinical hypothyroidism, 7 subclinical thyrotoxicosis) in group 2. While thyrotoxicosis was more common in ICU patients, the between-group difference in this respect was not statistically significant ( $p > 0.05$ ). Thyroid ultrasonography was performed in patients ( $n = 23$ ) with thyrotoxicosis. Thyroid nodules were detected in 15 patients with thyrotoxicosis (8 with overt thyrotoxicosis and 7 with subclinical thyrotoxicosis). Subacute thyroiditis was not detected in any of the patients with thyrotoxicosis.

None of the patients in group 1 had hypothyroidism; however, hypothyroidism was observed in 4 (3%) patients in group 2. Of these, three patients had overt hypothyroidism, while one patient had subclinical hypothyroidism. Central hypothyroidism was not detected in any of the patients included in the study. Anti-TPO and anti-Tg levels of the patients with overt hypothyroidism in group 2 were  $\geq 3$  times higher than the normal range and were consistent with autoimmune thyroiditis.

The number of patients with euthyroidism in groups 1 and 2 was 107 (86%) and 84 (67%), respectively ( $p = 0.001$ ). The number of patients with NTIS in groups 1 and 2 was 10 (8%) and 22 (18%), respectively ( $p = 0.023$ ). Table 2 shows the analysis of thyroid hormonal disorders in the two groups.

Among the patients admitted to the ICU, 88 patients survived while 37 patients died. The median age of survivors was 72.5 (IQR, 65.25–82.75) years, while that of patients who died was 80 (IQR, 69–83.5) years ( $p > 0.05$ ). Male accounted for 81% ( $n = 30$ ) of the patients who died in the ICU ( $p = 0.01$ ). There was no significant difference in TSH level between survivors and deceased patients; however, the deceased patients had significantly lower FT4 and FT3 levels as compared to survivors ( $p = 0.036$  and  $p = 0.012$ , respectively). The prevalence of thyroid nodules in the survivor group was 21% ( $n = 18$ ) as against 38% ( $n = 14$ )

in the deceased group ( $p = 0.042$ ). In the group with overt thyroid disorder, 9% (6 overt thyrotoxicosis, 2 overt hypothyroidism) were detected, 8% in the deceased group (2 overt thyrotoxicosis, 1 overt hypothyroidism). Clinical results of survivors and deceased patients in the ICU are given in Table 3.

#### **4. Discussion**

The majority of COVID-19 patients included in our study were men. The median age of non-ICU patients was significantly lower than that of ICU patients. The median age of patients who died in the ICU was higher than that of survivors. Studies have shown that advanced age and male sex are risk factors for COVID-19 (4,5). The disease severity and the associated mortality increases with increase in age. In a meta-analysis of 24 observational studies (combined  $n = 10,150$ ), the ICU mortality rate was found to be 41.6 (34.0–49.7) % (6). In a retrospective study conducted in Italy ( $n = 1591$ ), the mortality rate in ICU patients was found to be 26% (7). In our study, the mortality rate in the ICU (29.6%) was slightly lower as not all patients in the ICU were included in the study owing to the study protocol.

In patients with acute illness, hyperglycemia can be assumed to be an adaptive response that increases the patient's chances of survival. Numerous studies of both ICU and non-ICU inpatients have shown a strong association between stress hyperglycemia and adverse clinical outcomes, including mortality, morbidity, length of hospital stay, infections, and general complications (8,9,10). In this study, patients with diabetes were excluded; the early morning glucose level on the first day of admission in ICU patients was significantly higher than that in non-ICU patients.

Several studies have demonstrated the association of elevated inflammatory markers (CRP, ferritin) and D-dimer level with poor prognosis (11,12,13). Similar results were obtained in this study; inflammatory markers and D-dimer levels were observed to be higher in ICU patients. The CRP levels of patients who died in the ICU were higher than those of survivors. These results indicate that prompt evaluation of patients with high CRP levels at admission and early initiation of comprehensive treatment can help decrease the mortality rate.

Several studies have shown that Sars-Cov-2 uses ACE-2 as a receptor to enter the host cell (3,14,15). ACE-2 is expressed on arterial and venous endothelial cells of many organs, especially the thyroid gland. Autopsy studies performed in the previous viral coronavirus epidemic showed significant damage in the follicular and parafollicular cells of the thyroid

(16). In addition, the cytokine storm and high levels of inflammation due to COVID-19 may also disrupt the hypothalamic-pituitary-thyroid axis.

Considering that SARS-CoV-2 can induce organ damage through autoimmunity (17), there is a distinct possibility of the occurrence of autoimmune thyroid disorders. In this study, we found no significant difference in anti-Tg levels between patients in various groups and subgroups. Anti-TPO level in ICU patients was significantly higher than that in non-ICU patients. Three of the four hypothyroid patients seen in ICU were cases of overt autoimmune hypothyroidism. However, there was no significant difference in anti-TPO level between survivor and deceased subgroups of ICU patients. The high level of anti-TPO in the ICU may be due to the cytokine storm triggering autoimmunity due to COVID-19.

In our study, we found no significant difference in TSH levels between various groups and subgroups; however, FT4 and FT3 levels were significantly different between ICU and non-ICU patients, and between the survivors and the deceased subgroups of ICU patients. In a study of 162 patients admitted to the ICU, FT3 levels were found to be associated with poor outcomes (18). In another study of 116 critically ill patients without thyroid disease, only FT3 level showed a correlation with disease severity and was found to be an independent predictor of outcomes (19). In our study, FT4 level showed no correlation with CRP level, while FT3 level showed a negative correlation with CRP level. The observed negative correlation of FT3 with the length of hospital stay was consistent with the results of other studies; thus, FT3 level may be a prognostic marker that reflects the severity of COVID-19.

Low thyroid hormone levels can be observed in non-thyroidal systemic diseases, especially in critically ill patients admitted to the ICU. This phenomenon, also referred to as NTIS, is a potential protective mechanism against excessive tissue catabolism in severely ill patients (20). The typical hormonal profile in these patients is low or low-normal serum total T4, low T3 concentration, and low, low-normal, or normal TSH (21,22).

In a meta-analysis of 23 studies of patients with ischemic heart disease (combined n = 19310), NTIS was associated with higher risk of all-cause mortality (hazard ratio = 2.61; 95% confidence interval = 1.89–3.59) (23). In our study, there was a higher prevalence of NTIS in ICU patients. In this study, 24% of patients who died had NTIS. In conclusion, NTIS is a clinical syndrome associated with poor prognosis in COVID-19.

In the THYROCOV study conducted in Italy (n = 287), the frequency of thyrotoxicosis and hypothyroidism in non-ICU COVID-19 patients was 20.2% and 5.2%, respectively (24). In our total study population, the frequency of thyrotoxicosis and hypothyroidism was 9.2% and 2%, respectively. Among ICU patients, the frequency of thyrotoxicosis and hypothyroidism was 12% and 3.2%, respectively. The lower rates in our study were likely attributable to wider exclusion criteria (patients with previously known pituitary disorder, diabetes mellitus, kidney, and liver disease were not included in the study).

Overt thyroid hormone disorders were observed 6 times more frequently in ICU patients compared to non-ICU patients. Since the differential diagnosis of patients with thyrotoxicosis was not possible (thyroid scintigraphy could not be performed) and since thyrotoxicosis may worsen the cardiovascular status of critically ill patients, patients with overt thyrotoxicosis were administered short-term low-dose antithyroid medication (2.5 mg methimazole daily) until restoration of thyroid hormone levels within the normal reference range; subsequently, the drug was discontinued. No complications occurred in any of the patients treated with methimazole. Low-dose levothyroxine therapy was initiated in patients with overt hypothyroidism and their clinical condition was improved. On post-treatment clinical follow-up, serum TSH levels had decreased to the reference range.

Compression of the trachea by the enlarged thyroid nodules may cause obstructive symptoms. Patients with thyroid nodules may develop obstructive symptoms due to progressive compression of the trachea or sudden enlargement due to intranodular bleeding. Patients admitted to the ICU are vulnerable to mechanical trauma such as endotracheal intubation; the consequent bleeding into the nodule may compress the trachea. Tracheal compression caused by nodules may aggravate hypoxia caused by lung damage due to COVID-19. In a study of 96,278 patients (including patients in the age-group of 18–65 years) who were evaluated with ultrasound in Germany, the frequency of thyroid nodules over 1 cm in the community was found to be 11.9% (25). In another study in which 60,921 chest CT images were examined, the frequency of thyroid nodules was found to be 4.5%, regardless of the nodule diameter (26). To the best of our knowledge, this is the first study to investigate the relationship of thyroid nodules with COVID-19. In our study, the rate of detection of nodules sized  $\geq 1$  cm on non-contrast chest CT images of ICU patients diagnosed with COVID-19 was 26%. Significantly more nodules were detected in ICU patients than in non-ICU patients. Among the ICU patients, the rate of nodule detection was higher in deceased patients as compared to that in survivors. Representative non-contrast chest CT images of two ICU patients are

presented in Figure 4. In addition, both thyrotoxicosis and nodules were detected in 15 patients (8 with overt thyrotoxicosis, 7 with subclinical thyrotoxicosis).

In our study, thyroid nodules were found to be associated with poor clinical outcomes, as they aggravate hypoxia due to compression effect and cause thyrotoxicosis.

Some limitations of this study should be considered while interpreting the results. The study population comprised only of patients who were hospitalized due to COVID-19 pneumonia. Patients with non-COVID-19 pneumonia were not included in the study. Thus, we were not able to assess the impact of COVID-19 on thyroid function. Secondly, the frequency of thyroid hormone disorders and thyroid nodules may change with age. The age of patients in the two groups was not homogeneously distributed. This may have affected our results. However, the age distribution of the survivors and deceased patients in the intensive care unit was homogeneously distributed. In the study we hypothesized that the thyroid nodules can cause tracheal compression and aggravate hypoxia. However, we did not measure or compare the diameter of the tracheal opening between the various groups. Lastly, this was a single-center study. Larger multi-center studies are required to provide more definitive evidence .

## **5. Conclusion**

In this study, COVID-19 was found to affect the thyroid hormone metabolism. Thyroid hormone disorders may worsen the cardiovascular status. Therefore, rapid evaluation of free thyroid hormones and TSH at admission will facilitate early diagnosis and appropriate treatment. Low FT3 level at admission is another risk factor for severe cases and indicates a poor prognosis. Thyroid nodules may be among the comorbidities that pose a risk for COVID-19, since thyroid nodules can cause tracheal compression and the nodules may cause thyrotoxicosis.

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## **Conflict of Interest**

There are no conflicts of interest.

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