Research Article

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Does COVID-19 affect thyroid more than non-COVID-19 infections? A retrospective study

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Abstract

Objectives: To evaluate the thyroid hormone levels and infection markers in COVID-19 patients and compare them to those in non-COVID-19 patients with infection in a large retrospective dataset.

Methods: In this study, thyroid-stimulating hormone (TSH), thyroid hormones (free T3 and free T4), and several infection markers were reviewed. The study group was divided into three groups that had no thyroid-related disorders: control patients (Group 0; n=7,981), COVID-19 patients (Group 1; n=222), and non-COVID-19 patients with infection (Group 2; n=477). The data were assessed for correlation and group comparisons.

Results: There was a reduction in median (25th–75th percentile) fT3 levels in COVID-19 patients 4.17 pmol/L (3.46–4.85) compared to non-COVID-19 patients with infection 4.65 pmol/L (4.12–5.15), p<0.0001. We detected a negative correlation between fT3 and neutrophil-to-lymphocyte ratio (NLR) in Group 1 (r=−0.534) and Group 2 (r=−0.346) (p<0.0001), indicating a relatively stronger link between fT3 and NLR in COVID-19 patients than non-COVID-19 patients with infection. Additionally, the fT3 levels remained significantly different between study groups when the model was adjusted for age, gender, and infection markers.

Conclusions: COVID-19 and non-COVID-19 infections are associated with low fT3 levels, which likely represent the suppression of the hypothalamic-pituitary-thyroid axis from non-thyroidal illness syndrome.

Keywords: COVID-19; thyroid hormones; neutrophil-to-lymphocyte ratio; free T3; infection

Introduction

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As of September 2023, the number of patients infected with SARS-CoV-2 has exceeded 770 million globally [2].

The SARS-CoV-2 infection has been shown to involve respiratory, circulatory, immune, hepatic, renal, and hematological systems. The multisystem involvement is partly due to the expression of angiotensin-converting enzyme 2 (ACE2) receptors on endothelial cells, a cellular entry point for SARS-CoV-2 [3, 4].

ACE2 is also expressed in the thyroid gland, making it a potential target for SARS-CoV-2 [5, 6]. Pathological changes in the thyroid gland have been described for SARS-CoV-1, which was responsible for the previous coronavirus outbreak [7]. Several researchers addressed thyroid dysfunction due to SARS-CoV-2 infection [8, 9]. One of the retrospective analyses that included patients with thyroid dysfunction showed worse biochemical and inflammatory profiles [8]. A viral effect on thyroid cells and an indirect effect of the systemic inflammatory immune response are the two mechanisms

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that account for abnormal TSH and/or thyroid hormone levels in COVID-19 patients [10].

Several studies examined the relationship between SARS-CoV-2 infection and abnormalities in thyroid hormone levels [8, 11–14]. We hypothesized that SARS-CoV-2 infection would alter thyroid hormone levels more than other infections. The main objective of this retrospective study was to evaluate the thyroid hormone function and infection markers in COVID-19 patients and non-COVID-19 patients with infection and compare them to the control subjects.

Materials and methods

Study population

This study included data from 11,737 patients admitted to 14 different Acibadem Healthcare Group laboratories between 2017 and 2021. Only patients with records of thyroid function test results measured within two days after admission were included and patients under 15 years, patients with a record of malignancies and with information on inflammatory disease and/or related laboratory tests were excluded from the study. All the patients were initially divided into three groups: control (Group 0, n=10,782), COVID-19 patients (Group 1, n=234), and non-COVID-19 patients with infection (Group 2, n=721). Group 0 (control patients) included patients' data from medical check-ups or conditions other than infection. At least 72 % of the control patients had medical records before 2019. For Group 1, a COVID-19-positive case was defined by a confirmed SARS-CoV-2 infection by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of pharyngeal and nasal swab specimens. The inclusion of subjects in Group 1 was based on the COVID-19 guidelines of the Ministry of Health of the Republic of Turkey. Briefly, patients with symptoms such as fever, muscle/joint pain, cough, and sore throat as well as a respiratory rate of <30/min and SpO_2 >90 on room air with mild-to-moderate pneumonia findings on lung X-ray and/or CT scan were included in Group 1. To eliminate COVID-19 patients in Group 2 and only include non-COVID-19 infections, the retrospective data of the subjects between 2017 and 2019 were included in the dataset. Most Group 2 had upper respiratory tract infection (33.1 %) and urinary tract infection (29.3 %). The rest of this group had lower respiratory tract infection (19.2 %), gastroenteritis (4.1 %), skin and soft tissue infection (3.8 %), genital tract infection (3.6 %), bacteremia (2.8 %), fluid (pericarditis, peritonitis) (1.5 %), catheter (1.5 %), and other (1.1 %) types of infections.

Initially, all the groups (Group 0, Group 1, and Group 2) included patients with hypothyroidism (n=658, n=0, and n=37, respectively), thyrotoxicosis (hyperthyroidism) (n=186, n=0, and n=8, respectively), thyroiditis (n=1,042, n=5, and n=99, respectively) as well as euthyroid patients (n=915, n=7, and n=100, respectively) and patients with no diagnosis of thyroid disorder (n=7,981, n=222, and n=477, respectively). Hypothyroidism was defined based on the International Classification of Diseases 10th revision (ICD-10) codes E02 and E03. Thyrotoxicosis (hyperthyroidism) was defined as E05. Thyroiditis was defined as E06 (thyroiditis), E060 (acute thyroiditis), E061 (subacute thyroiditis), E062 (chronic thyroiditis), and E063 (autoimmune thyroiditis). All the codes above for thyroiditis are grouped. Other thyroid-related conditions were grouped as euthyroid. To have homogenous groups of patients regarding thyroid function in control, COVID-19, and non-COVID-19 with infection groups, we performed all the statistical analyses on patients with no diagnosis of thyroid disorders (n=8,680). This study was approved by the Ministry of Health of the Republic of Turkey and the Ethics Committee of Acibadem University (ATADEK 2021-09/43).

Thyroid function tests and infection markers

Free T3 (fT3), free T4 (fT4), and TSH from serum samples were determined by electro-chemiluminescence immunoassay (ECLIA) using Elecsys 2010 (Roche Diagnostics, Germany). For the infection markers, C-reactive protein (mg/L) was measured by an immunoturbidimetric method using ADVIA Chemistry XPT (Siemens Healthineers, Germany); neutrophil (%), lymphocyte (%), and leukocyte (10^9/L) measurements were conducted by fluorescence flow cytometry (Sysmex XN 3000, Germany). The data were collected using the same complete blood count device and the same thyroid hormone analyzer between 2017 and 2021. The detection limit of serum TSH is 150 mIU/L, and the reference interval for TSH in the adult population is 0.55–4.78 mIU/L. TSH's total coefficient of variation (CV) is <6.64 %. For serum fT4 and fT3, the reference intervals are 11.5–22.7 and 3.5–6.5 pmol/L, respectively, and total CV values are <4.58 and <4.05 %, respectively. The reference ranges for neutrophil (%), and lymphocyte (%) were 1.9–7.0 × 103/μL, and 1.3–3.76 × 103/μL, respectively. C-reactive protein levels below 0.5 mg/dL were considered the reference range for adults.

Statistical approaches

Continuous variables were presented by median (25th–75th percentiles). The Kolmogorov–Smirnov test was applied to assess data normality, and the Whitney U test was used to compare the data. Spearman rank correlations with no adjustment were performed to evaluate the correlation between variables. The correlation was considered absent when the Spearman's coefficient value was between 0 and 0.25 or 0 and −0.25 [15]. The relationship of adjusted values of log-transformed fT3 with Group 0, Group 1, and Group 2 was assessed using analysis of covariance (ANCOVA) after adjusting the model for age, gender, and log-transformed infection markers (CRP and NLR). ANCOVA analysis was followed by pairwise comparisons using the Bonferroni procedure. A p-value less than 0.05 was considered statistically significant. All the statistical analyses were performed using Analyse-it (v4.20.1) software and IBM SPSS 24.

Results

Clinical and demographic characteristics of the subjects

The initial patient cohort in Group 0, Group 1, and Group 2 included 11,737 patients in total. Among them, 5.92 % had hypothyroidism (n=695), 1.65 % had thyrotoxicosis (hyperthyroidism) (n=194), 9.76 % had thyroiditis (n=1,146), 8.71 % were euthyroid, and 73.95 % had no diagnosis of thyroid

Table 1: Comparison of the clinical and demographic characteristics of the subjects with median (25th–75th percentile) in control patients, COVID-19 patients, and patients with non-COVID-19 infection.

Parameter	All (n=35,321)	Group 0 control patients (n=33,802)	Group 1 COVID-19 patients (n=382)	p-Value[a]	Group 2 patients with non-COVID-19 infection (n=1,137)	p-Value[b]	p-Value[c]
Age, years	35.0 (26.0–47.0)	35.0 (26.0–47.0)	45.0 (37.0–56.0)	<0.0001	37.0 (28.0–48.0)	<0.0001	<0.0001
Gender, F/M	16,107/19,214	15,673/18,129	149/233	0.02	285/852	0.08	0.13
fT3, pmol/L	5.0 (4.52–5.51)	5.0 (4.54–5.52)	4.39 (3.60–4.99)	<0.0001	4.72 (4.24–5.30)	<0.0001	<0.0001
fT4, pmol/L	15.59 (14.09–17.32)	15.60 (14.10–17.33)	15.22 (13.49–17.25)	0.004	15.31 (13.84–17.18)	0.003	0.31
TSH, µU/mL	1.71 (1.13–2.53)	1.73 (1.15–2.54)	1.39 (0.66–2.27)	<0.0001	1.43 (0.86–2.20)	<0.0001	0.55
CRP, mg/dL	0.14 (0.08–0.27)	0.14 (0.08–0.26)	0.28 (0.13–1.42)	<0.0001	0.20 (0.10–0.44)	<0.0001	<0.0001
Neut, %	55.30 (49.0–61.40)	55.10 (48.90–61.10)	61.40 (53.90–70.98)	<0.0001	61.80 (53.10–73.90)	<0.0001	0.71
Lympho, %	33.10 (27.60–38.80)	33.20 (28.0–38.90)	28.0 (19.35–34.70)	<0.0001	26.80 (15.50–35.10)	<0.0001	0.92
Leuko, 10^9/L	6.41 (5.40–7.69)	6.39 (5.38–7.64)	6.83 (5.45–8.50)	<0.0001	7.21 (5.92–9.34)	<0.0001	<0.0001
NLR	1.67 (1.27–2.21)	1.66 (1.26–2.18)	2.21 (1.53–3.78)	<0.0001	2.29 (1.50–4.85)	<0.0001	0.97

F, female; M, male; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; CRP, C-reactive protein; Neut, neutrophils; Lymph, lymphocytes; Leuko, leukocytes; NLR, neutrophil-to-lymphocyte ratio. [a]p-Value between Group 1 and Group 0. [b]p-Value between Group 2 and Group 0; [c]p-Value between Group 1 and Group 2.

disorders (n=8,680). Supplementary Table 1 shows the demographic and clinical characteristics of the patients in the initial dataset.

To have a homogenous cohort regarding thyroid disorders, we excluded all the patients in Group 0, Group 1, and Group 2 diagnosed with thyroid disorders. All subsequent analyses were performed on the group above of patients with no thyroid disorders diagnosis (n=8,680). Among 8,680 patients, 5,407 were female (62.29 %), and 3,273 were male (37.71 %). Control group (Group 0; n=7,981), COVID-19 patients (Group 1; n=222), and non-COVID-19 patients with infection (Group 2; n=477) represented 91.95 , 2.56, and 5.50 % of the final patient population, respectively.

Regarding the study groups (Group 0, Group 1, and Group 2), the median age was determined as 41 (30.0–57.0), 48 (38.75–58.0), and 41 (32.0–60.0) years, respectively. There was a statistical difference between the median age of Group 1 and Group 0 and Group 1 and Group 2 (p<0.001) (Table 1).

For the infection markers, median CRP levels and leukocyte levels were found to be significantly increased in COVID-19 patients (Group 1) compared to control patients and non-COVID-19 patients with infection (Group 2) (p<0.0001) (Table 2). Both neutrophil and lymphocyte levels showed similar trends in Group 1 and Group 2 that were suggestive of infection. For median neutrophil and lymphocyte levels, there was a statistically significant difference between Group 1 and Group 0 and Group 2 and Group 0 (p<0.0001) (Table 2). This result was seen for NLR distributions in Group 0, Group 1, and Group 2. Although infection increased NLR in Group 1 and Group 2 Figure 1(A), there was no distinction in the density histogram for NLR in COVID-19 patients and non-COVID-19 patients with infection Figure 1(B).

Table 2: Spearman correlations for the relation of TSH, fT3, fT4, and several infection markers in control patients, COVID-19 patients, and patients with non-COVID-19 infection.

	Group 0 (control patients)			Group 1 (COVID-19 patients)			Group 2 (patients with non-COVID-19 infection)		
	fT3, pmol/L	fT4, pmol/L	TSH, µU/mL	fT3, pmol/L	fT4, pmol/L	TSH, µU/mL	fT3, pmol/L	fT4, pmol/L	TSH, µU/mL
CRP, mg/dL	−0.106	−0.071	−0.059	−0.424	−0.019[a]	−0.243	−0.171	0.010[a]	−0,087[b]
Neut, %	−0.181	−0.049	−0.155	−0.480	−0.030[a]	−0.358	−0.258	0.010[a]	−0.322
Lymph, %	0.160	0.041	0.148	0.479	0.019[a]	0.339	0.257	−0.005[a]	0.311
NLR	−0.172	−0.046	−0.153	−0.483	−0.023[a]	−0.347	−0.256	0.008[a]	−0.314
Leuko	0.030	0.033	−0.019	−0.013	0.192[a]	−0.128	−0.038	0.057[a]	−0.165

fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; CRP, C-reactive protein; Neut, Neutrophils; Lymph, Lymphocytes; Leuko, Leukocytes; NLR, Neutrophil-to-Lymphocyte ratio. p-Value <0.0001 for all the values except [a]and[b]. [a]p>0.05 [b]p<0.005.

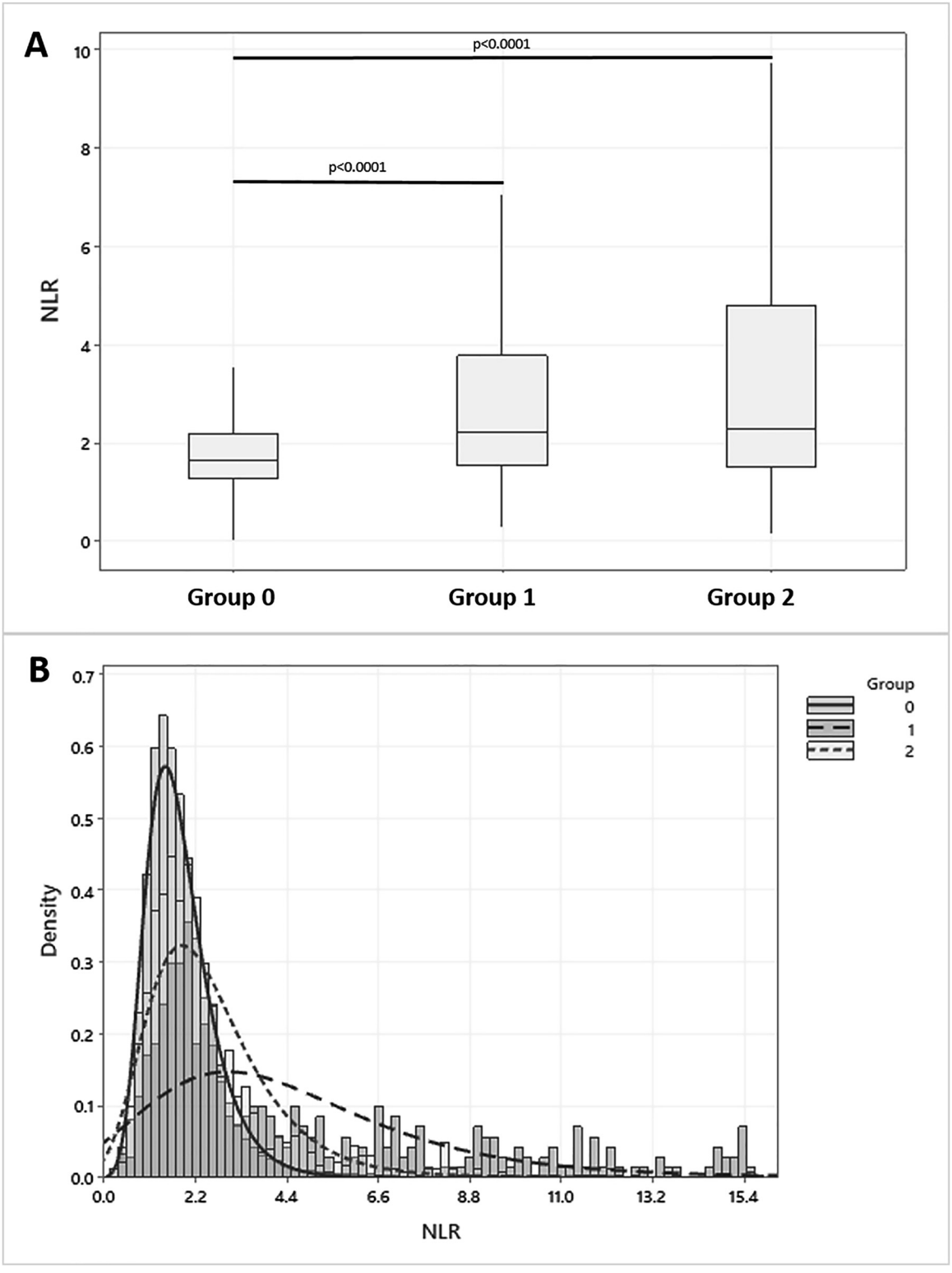

Figure 1: Neutrophil-to-lymphocyte ratio (NLR) in Group 0, Group 1, and Group 2. (A) Box-plot graph demonstrating median NLR in Group 0, Group 1, and Group 2. (B) Density histogram showing the distribution of NLR in Group 0, Group 1, and Group 2. Group 0: control patients, Group 1: COVID-19 patients, Group 2: non-COVID-19 patients with infection.

Comparison of thyroid hormone levels in COVID-19 patients and non-COVID-19 patients with infection

For thyroid function tests, median fT4 levels were found to be similar between COVID-19 patients (15.02 pmol/L [13.33–17.08]) and non-COVID-19 patients with infection (15.30 pmol/L [13.78–16.86]) ($p>0.05$). This was also the same when control patients (15.41 pmol/L [14.0–17.11]) were compared with COVID-19 patients and non-COVID-19 patients with infection ($p>0.05$). We detected similar results for TSH; median TSH levels were found to be similar in control patients (1.58 μU/mL [1.05–2.31]), COVID-19 patients (1.23 μU/mL [0.56–2.22]), and non-COVID-19 patients with infection (1.42 μU/mL [0.84–2.16]) ($p>0.05$).

Interestingly, the median fT3 in control patients was determined as 4.89 pmol/L (4.45–5.35), whereas there was a decrease in fT3 levels in infection; fT3 reduction of 14.93 % in COVID-19 patients and 4.91 % in non-COVID-19 patients with infection. Therefore, the reduction in fT3 levels was more pronounced in COVID-19 patients (4.16 pmol/L [3.46–4.85]) compared to non-COVID-19 patients with infection (4.65 pmol/L [4.12–5.15]) ($p<0.0001$) [Table 1, Figure 2(A)]. The density histogram showed a clear shift of fT3 levels in COVID-19 patients (Group 1) in Figure 2(B).

Relation between thyroid hormones and infection markers in COVID-19 patients and non-COVID-19 patients with infection

First, we assessed the correlation between TSH, thyroid hormones (fT3 and fT4), and infection markers (CRP and NLR) without any adjustments (Table 2). We did not find any correlation between fT4 and infection markers. The CRP and NLR markers showed negative correlations with TSH in COVID-19 patients (Group 1) ($r=-0.254$ and $r=-0.395$, respectively), whereas only NLR showed a negative correlation with TSH in patients with non-COVID-19 infection (Group 2) ($r=-0.298$, $p<0.0001$).

Interestingly, fT3 demonstrated significant correlations with several infection markers. A negative correlation was determined with NLR in Group 1 ($r=-0.534$, $p<0.0001$) and Group 2 ($r=-0.346$, $p<0.0001$), further indicating a stronger link between fT3 and NLR in COVID-19 patients than non-COVID-19 patients with infection (Figure 3). The control group had no correlation between fT3 and NLR ($r=-0.102$, $p<0.0001$).

Next, we adjusted the model for age, gender, and infection markers (CRP and NLR) using ANCOVA analysis to assess log-transformed fT3 (95 % CI) levels in study groups. Based on the model, fT3 levels in Group 0, Group 1, and Group 2 were determined as 0.686 (0.684–0.687), 0.626 (0.617–0.636), and 0.672 (0.665–0.678), respectively. The fT3 levels remained significantly different between study groups when the model was adjusted for age, gender, and log-transformed CRP and NLR values (Table 3).

Discussion

During the COVID-19 outbreak, several studies stated thyroid dysfunction in COVID-19 patients [8, 11–17]. This study aimed to assess the thyroid function and infection markers in COVID-19 patients and compare it to the thyroid function in non-COVID-19 patients with infection in a retrospective dataset. This study showed that COVID-19 and non-COVID-19 infections are associated with low fT3 levels with a potential effect on the hypothalamic-pituitary-thyroid axis.

Regardless of COVID-19, the presence of infection showed alterations in thyroid function. Considering the thyroid hormone variations in HIV-infected patients or the effects of fT4 on infection-related mortality in peritoneal dialysis patients [18, 19], it can be expected that fT4 will change with the varying infection conditions. Interestingly, we found no difference in fT4 and TSH levels between COVID-19 patients and non-COVID-19 patients with infection. The reason why there were no differences in TSH and fT4 levels between COVID-19 patients and non-COVID-19 patients with infection might be due to the mild-to-moderate COVID-19 patients dominating Group 1. The most prominent alteration during illness is the decrease in T3 levels, whereas serum T4 and TSH levels may decrease in severe illnesses [20]. For instance, mortality was associated with low fT4 and TSH levels in COVID-19 [21]. In our study, only fT3 demonstrated a significant decrease in patients diagnosed with COVID-19 compared to patients diagnosed with non-COVID-19 infection and control ones. Our result showed a significant reduction in fT3 levels in COVID-19 patients when the model was adjusted for age, gender, and infection markers. Additionally, a considerably low but significant decrease in fT3 levels in non-COVID-19 patients with infection highlighted the impact of infection on thyroid function. Of course, the types and severity of infections in Group 2 should be evaluated in a prospective cohort study to further understand the mechanism behind the lower fT3 levels in COVID-19 patients than in non-COVID-19 patients with infection. Still, the lower levels of TSH and total T3 in COVID-19 patients than those of the non-COVID-19 pneumonia patients might propose a specific role of Sars-CoV-2 infection in thyroid functioning [17]. Our results likely

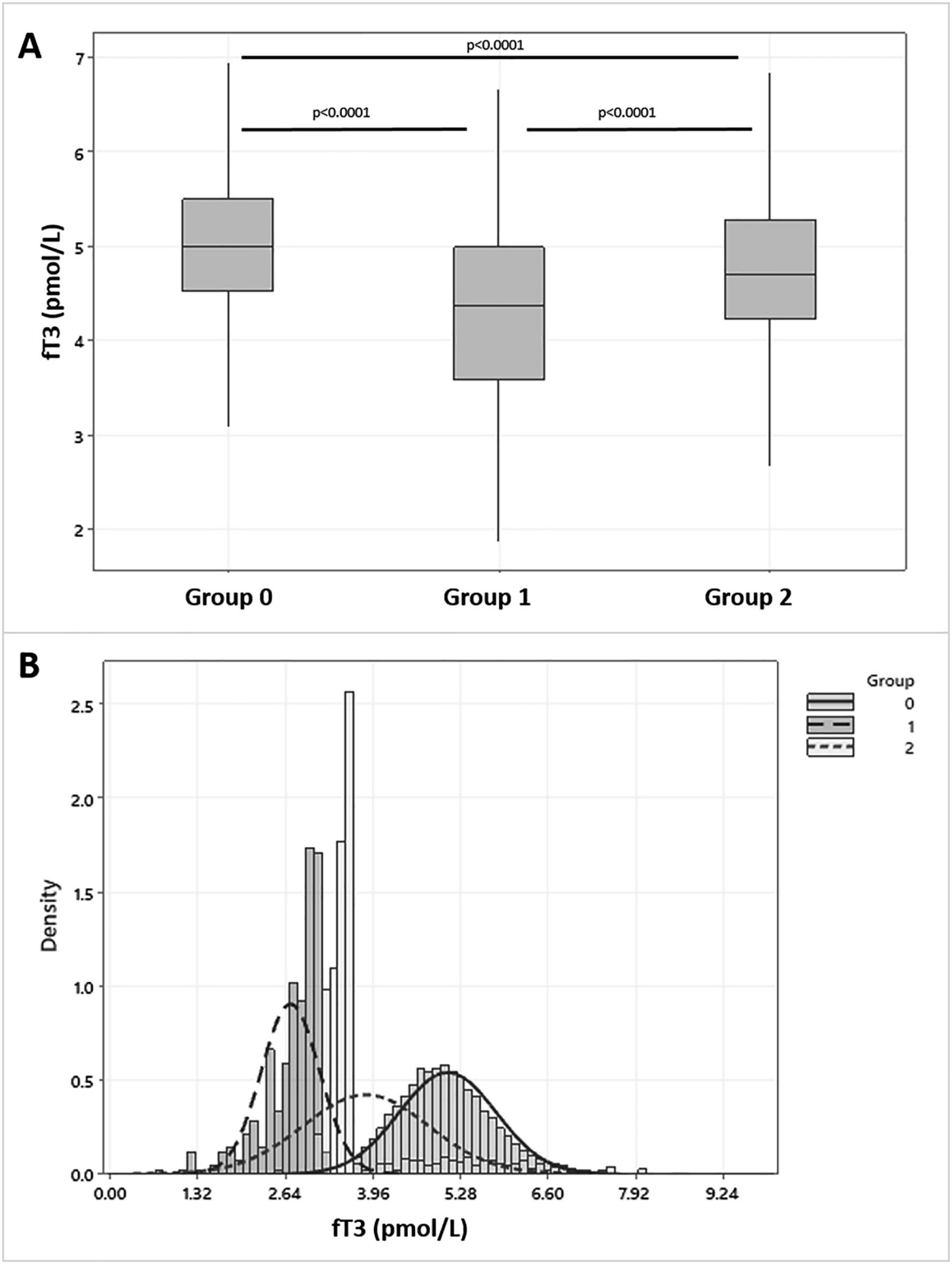

Figure 2: Free triiodothyronine (fT3) levels in Group 0, Group 1, and Group 2. (A) Box-plot graph demonstrating median fT3 in Group 0, Group 1, and Group 2. (B) Density histogram showing the distribution of fT3 in Group 0, Group 1, and Group 2. Group 0: control patients, Group 1: COVID-19 patients, Group 2: non-COVID-19 patients with infection.

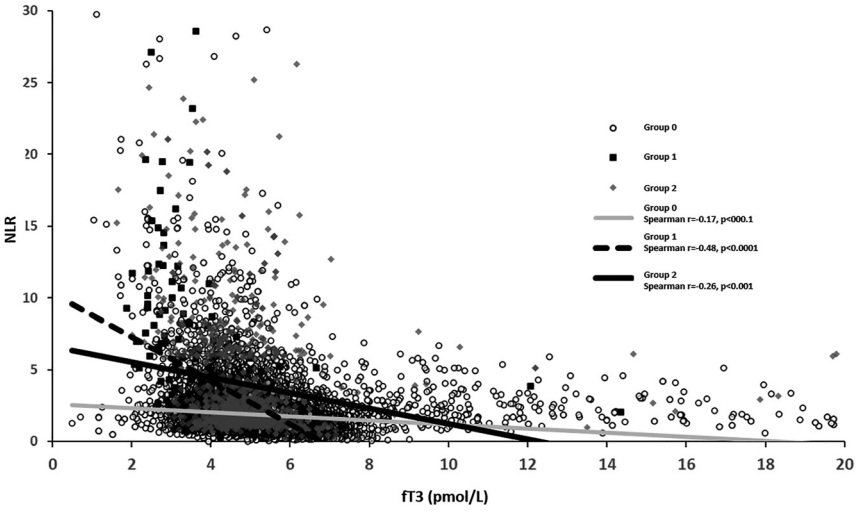

Figure 3: Correlation graph between fT3 (pmol/L) and NLR in Group 0, Group 1, and Group 2. Each data point indicates the value of the fT3 (pmol/L) and NLR in Group 0 (circle), Group 1 (square), and Group 2 (crystal). The grey, black dotted-line, and black line represents the regression lines for Group 0 (Spearman r=−0.17, p<0.001), Group 1 (r=−0.48, p<0.0001), and Group 2 (r=−0.26, p<0.001), respectively. Group 0: control patients, Group 1: COVID-19 patients, Group 2: non-COVID-19 patients with infection.

Table 3: Multiple regression model for thyroid measures adjusted for subjects with non-COVID-19 infection.

	Variables	β	p-Value	OR	95 % CI of OR	
					Lower	Upper
Group 0 (control patients)	Constant	0.12	0.96			
	fT4	−0.01	0.89	0.99	0.82	1.19
	fT3	1.03	0.007	2.81	1.32	5.95
	TSH	0.10	0.56	1.11	0.79	1.56
	Gender	−0.25	0.66	0.78	0.25	2.44
	Age	−0.01	0.58	0.99	0.96	1.02
Group 1 (COVID-19 patients)	Constant	−2.45	0.36			
	fT4	0.02	0.84	1.02	0.83	1.27
	fT3	0.85	0.04	2.44	1.01	5.45
	TSH	0.03	0.90	1.03	0.69	1.54
	Gender	−1.13	0.10	0.32	0.08	1.26
	Age	−0.01	0.62	0.99	0.95	1.03

represented a suppression of the hypothalamic-pituitary-thyroid (HPT) axis during infection, be it COVID-19 or non-COVID-19.

The alteration in fT3 in COVID-19 patients may represent non-thyroidal illness syndrome, where low fT3 is a classical indicator [9, 12, 22–24]. For example, a meta-analysis revealed that serum fT3 levels were consistently low in critically ill patients and non-survivors compared to sick non-critically patients and survived ones [25]. The results of our study regarding the reduction of fT3 in COVID-19 patients largely repeat the cited ones. However, we additionally showed that fT3 had a significant negative correlation with NLR and CRP. Moreover, this negative correlation indicated a more substantial relation in COVID-19 patients when COVID-19 patients and non-COVID-19 patients with infection were evaluated together. Similarly, high CRP values were independently associated with low T3 levels in COVID-19 subjects [12]. The NLR is an indicator of the systematic inflammatory response and is widely investigated in different conditions, including thyroid malignancies and COVID-19 [26–28]. For example, high levels of NLR might serve as a factor for prescribing a thorax CT in COVID-19 patients, which can affect patients' clinical management [29]. Recently, abnormal thyroid function, specifically T3 levels correlating with lymphocyte counts, was determined in patients with severe infections [30]. In our study, a relatively strong link between fT3 and NLR in COVID-19 patients (r=−0.534, p<0.0001) than in non-COVID-19 patients with infection (r=−0.346, p<0.0001) might indicate the multisystemic effects of SARS-COV-2 infection. Overall, it can be deduced that the degree of infection might affect thyroid measures. To this end, follow-up studies that include thyroid hormone measures and different biochemical and inflammation markers are valuable further to evaluate the effect of COVID-19 on thyroid function. A short-term follow-up (90 days; range: 30–120) study showed that thyroid function was normalized in 96.6 % of subjects with COVID-19-related thyrotoxicosis [14]. Still, ultrasonographic alterations detected in the short-term follow-up may lead to late-onset thyroid abnormalities [14]. In another supporting study, COVID-19 patients with thyroid dysfunction at hospital admission were recovered in recovery [31].

This work presented here was a retrospective data-mining study. Due to the lack of clinical markers like IL-6 and procalcitonin and clinical information such as comorbidities, prognosis, and mortality, the thyroid hormones and their association with inflammatory markers could not be extensively evaluated and represent the limitations of

this study. As for now, the results could at most support that infection impacts thyroid function, causing a pattern suggestive of non-thyroidal illness syndrome, similarly seen in COVID-19 and non-COVID-19 infections. There is a need for future longitudinal study designs to understand the variations in thyroid hormones and the inflammatory conditions in COVID-19, along with the clinical information.

Research ethics: This study was approved by the Ethics Committee of Acibadem University (ATADEK 2021-09/43).
Informed consent: In this retrospective study, all patient information was de-identified and patient consent was not required. Patient data will not be shared with third parties.
Author contributions: YU: Conceptualization, data curation, writing-original draft, writing-review and editing; MuhS: conceptualization, data curation, writing-review and editing; HK: data curation; MK: data curation, writing-review and editing; MusS: data curation, writing-review and editing AO: conceptualization, data curation, writing-review and editing;
Competing interests: Authors state no conflict of interest.
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