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Assessment of thyroid function and biochemical markers among COVID-19 Libyan patients

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Abstract

Background: There is a scarcity of data on thyroid function abnormality in coronavirus disease 2019 (COVID-19) outpatients in the world literature since previous studies were done on admitted patients.

Aim: The objective of this study was to assess thyroid function tests in Libyan outpatients with COVID-19 as well as the possible association between them and some routine hematological, inflammatory, and biochemical markers.

Methods: Laboratory results were retrospectively reviewed for a total number of 246 patients, where 214 patients with laboratory-confirmed COVID-19 and 32 non-COVID-19 patients were included in the study as a control group. The majority of the patients were females 179 (72.8%) and age range between 18 and 88 years old. They were registered in the outpatient department of COVID-19 at Zaweit-Dahmany Polyclinic in Tripoli, Libya between May and October 2021. Serum levels of thyroid-stimulating hormone, thyroid hormones (THs) [triiodothyronine (T3), thyroxine (T4), and free fractions], complete blood count, C-reactive protein (CRP), lactate dehydrogenase (LDH), liver function test, and renal function test were measured.

Results: Abnormal thyroid function was seen in 17.8% of 214 patients with COVID-19. Twelve patients had isolated low total or free triiodothyronine (FT3), suggestive of nonthyroidal illness syndrome, ten patients had hypothyroidism that was subclinical in six patients and overt in the remaining four patients. Three patients had hyperthyroidism. Thirteen patients had different isolated THs abnormalities. Low FT3 was associated with older age ($p = 0.035$), and it has a weak negative correlation with CRP (−0.335) and LDH (−0.245) ($p = 0.001$). The thyroid dysfunction (TD) group presented a statistically significant reduction in lymphocytes ($p = 0.000$), increased neutrophil ($p = 0.000$), increased CRP ($p = 0.000$), increased urea ($p = 0.014$), increased alkaline phosphatase ($p = 0.007$), a slight reduction in hematocrit ($p = 0.010$), low mean corpuscular volume ($p = 0.019$), and low mean corpuscular hemoglobin ($p = 0.019$) but no significant difference in hemoglobin, red blood cells, white blood cells, and platelet count when compared to euthyroid control.

Conclusion: Clinicians should be vigilant about the possible presence of thyroid function abnormalities among COVID-19 patients, especially elderly patients, and those with increased inflammatory markers.

Keywords: COVID-19, Thyroid dysfunction, Biochemical markers, Inflammatory markers, Hematological markers.

Introduction

Coronavirus disease-2019 (COVID-19) was first detected in Wuhan, China, by the end of 2019. Since then, the disease spread rapidly all over China and from there to the rest of the world. The causative agent of the disease was named a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (An *et al.*, 2020), and it was announced as a global pandemic by WHO on the 11th of March 2020 (Aloisio *et al.*, 2020).

On the 24th of March 2020, the first patient with COVID-19 was diagnosed in Libya, and after this, the number of patients increased continuously (Elhadi *et al.*, 2020).

COVID-19 is related to multi-organ involvement consisting of respiratory, immune, hematological, digestive, hepatic, and renal structures due to the widespread expression of Angiotensin-converting enzyme 2, (ACE-2) receptor and, transmembrane

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protease serine 2, (TMPRSS2) that is the practical access sites for SARS-CoV-2 (Wang *et al.*, 2021).

The virus additionally influences the endocrine system, for example, ACE2 and TMPRSS2 are more highly expressed in the thyroid gland than inside the lungs. It additionally has feasible mechanisms that might affect the thyroid gland and its hypothalamic-pituitary axis through direct virus contamination or oblique immune-inflammatory response (Scappaticcio *et al.*, 2020). The activation of the immune inflammatory response-mediated glandular harm through the formation of antibodies, as a result of humoral immune response, or cell-mediated damage to the thyroid gland, as a result of cellular immune response (Khoo *et al.*, 2021). Therefore, thyroid characteristic abnormalities may be a complication of COVID-19.

Numerous previous articles have defined the onset of thyroid disorder (TD) in normal thyroid among COVID-19 patients from subclinical to overt TD either hypo or hyperthyroidism in addition to nonthyroidal illness syndrome (NTIS) (Daraei *et al.*, 2020; Lania *et al.*, 2020; Giovanella *et al.*, 2021).

Few studies have mentioned an association between TD and inflammatory markers. Lui *et al.* (2021b) determined that a higher C-reactive protein (CRP) level, was independently linked to low free triiodothyronine (FT3). Wang *et al.* (2021) confirmed that the TD group had lower ranges of lymphocytes and higher ranges of leukocytes, neutrophils, CRP, and procalcitonin.

Ilera *et al.* (2021) reported that in hospitalized patients with COVID-19, thyroid hormones (THs) correlated with inflammatory parameters and worse clinical effects mainly, a low triiodothyronine/thyroxine (T3/T4) ratio, was correlated with severity and poor prognosis. Patients who were examined showed low T3 but high free thyroxine (FT4), higher ferritin, lower albumin, and more severe disease. Moreover, it is wise on the part of healthcare providers to adopt a cautious approach when treating COVID-19 patients with altered thyroid levels as they can predict disease severity and correlate with biomarkers (Asghar *et al.*, 2021).

To the best of our information, this is the first study on this subject within the Libyan population with COVID-19 patients and may be the first examination achieved on outpatients in the literature since previous studies had been all done on admitted patients. This study aimed to assess the effect of COVID-19 on TH levels and to correlate them with some hematological and biochemical markers in Libyan patients stricken by COVID-19.

Materials and Methods

Patients

All patients with laboratory-confirmed COVID-19, registered between May 12, 2021, and October 10, 2021, in the outpatient department of COVID-19 at Zaweit Al-Dahmani Polyclinic in Tripoli, Libya.

Inclusion and exclusion criteria

The inclusion criteria included: (1) confirmed COVID-19 diagnosis based on a positive PCR using RT-PCR; (2) age of ≥ 18 years, without sex limitation; (3) available information of thyroid function test (TFT) results, as a minimum one serum thyroid-stimulating hormone (TSH) measurement after COVID-19 analysis; and (4) also, non-COVID-19 patients with regular thyroid function have been recruited as a control group. Exclusion criteria covered: (1) previous clinical records of TD; (2) pregnancy; and (3) patients with incomplete records for key parameters.

Data collection

Demographic information of the covered patients had been collected from the laboratory scientific data. Preselected demographics and also some comorbidities of interest such as age, sex, and records of diabetes or hypertension were recorded. All COVID-19 patients were diagnosed according to presenting clinical and/or radiologic findings of COVID-19 and followed by a positive RT-PCR test for COVID-19.

Laboratory tests

Laboratory tests were conducted at the laboratory of Zaweit Al-Dahmani Polyclinic. Serum FT3, FT4, T3, T4, and TSH levels were tested using a Cobas e 411 analyzer® by Roche Electrochemiluminescence technology for immunoassay analysis. A complete blood count was done using the Sysmex XP-300™ Automated Hematology Analyzer. CRP, lactate dehydrogenase (LDH), liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), and renal function tests such as urea, creatinine (CRE), and uric acid (UA) were measured using the Roche Cobas Integra 400 plus analyzer.

Evaluation of the TH profile

TH results obtained from patients were classified according to the definitions given below:

- Overt thyrotoxicosis: low TSH level whereas the serum FT3 and/or FT4 are higher than the reference level.
- Overt hypothyroidism: high TSH level whereas serum FT4 and/or FT3 are lower than the reference level.
- Subclinical TD: the presence of low or high TSH levels whereas FT4 and FT3 within the reference level.
- NTIS: the presence of regular serum TSH, normal or high FT4, low T3, low FT3, or low serum TSH, FT4, FT3 (Güven and Gültekin, 2021).

Statistical analysis

Statistical analysis was performed using IBM® SPSS® version 20.0. The distribution of baseline characteristics across categories of the exposure variable was evaluated using nonparametric statistics, as determined by the one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean ± SD and were compared using *t*-tests. Variables

with skewed distribution are presented as median (25th, 75th percentile) and were compared using Mann–Whitney *U* tests. Categorical data were presented as numbers and percentages and were compared using chi-squared tests or Fisher exact tests as appropriate. Pearson or Spearman correlations were used to assess the relationship between continuous variables as appropriate. Differences were considered statistically significant when the *p*-value was <0.05.

Ethical approval

Not needed, as this was a retrospective study.

Results

A total number of 246 patients were included in this study; (214 COVID-19 patients and 32 non-COVID-19 patients), and the majority of the patients were females 179 (72.8%). Age of patients ranged between 18 and 88 years old, with a mean age of 46.3 ± 16.5 years (Fig. 1). Information about comorbidities was available in only 55 patients as follows: diabetes was present in 42 patients (76%), hypertension in 5 patients (9%), and diabetes with hypertension in 8 patients (15%).

Concerning the thyroid status, TSH was measured in all 214 patients with COVID-19, T3, and T4 in 212 patients (99.1%), while FT3, and FT4 in 145 patients (67.8%). Of some of the overall 214 patients with COVID-19, 38 patients (17.8%) showed one or greater abnormalities in thyroid function. The commonest abnormality in TFT was low FT3 and FT4 which were discovered in 9 patients (6.2%). The distribution of altered thyroid function parameters is given in Table 1. Abnormal TFTs were observed in 38 patients (17.8%) of them, 12 patients (5.6%) were NTIS, followed by 10 patients (4.7%) with hypothyroidism, of those, 4 patients had overt hypothyroidism, 3 patients had subclinical hypothyroidism, 2 patients had high TSH concentration with normal T3 and T4 concentration, and one patient had high TSH concentration with low T3 concentration and normal T4 concentration (FT3 and FT4 were missed). Hyperthyroidism was observed in 3 patients (1.4%). Of these, one patient had subclinical hyperthyroidism, while 2 patients had low TSH with high/or normal T4 and normal T3 concentrations (FT3 and FT4 were missed). One abnormality in thyroid function was observed in 13 (6.1%) patients including isolated high T3, T4, and FT4 in 2, 4, and 2 patients, respectively, and isolated mildly low FT4 in 5 patients (Fig. 2). TH abnormalities according to age and gender are presented in Tables 2 and 3.

The demographic and laboratory results of the covered non-COVID-19 patients without TD as a control group and COVID-19 patients with TD are provided in Table 4. The mean age of non-COVID-19 patients without TD, and COVID-19 patients with TD was 43.25 ± 17.49 years, and 52.95 ± 15.88 years, respectively ($p = 0.146$). In both groups, most of the patients were females (68.8% and 81.6%, respectively; $p = 0.268$). The laboratory results showed that COVID-19 patients

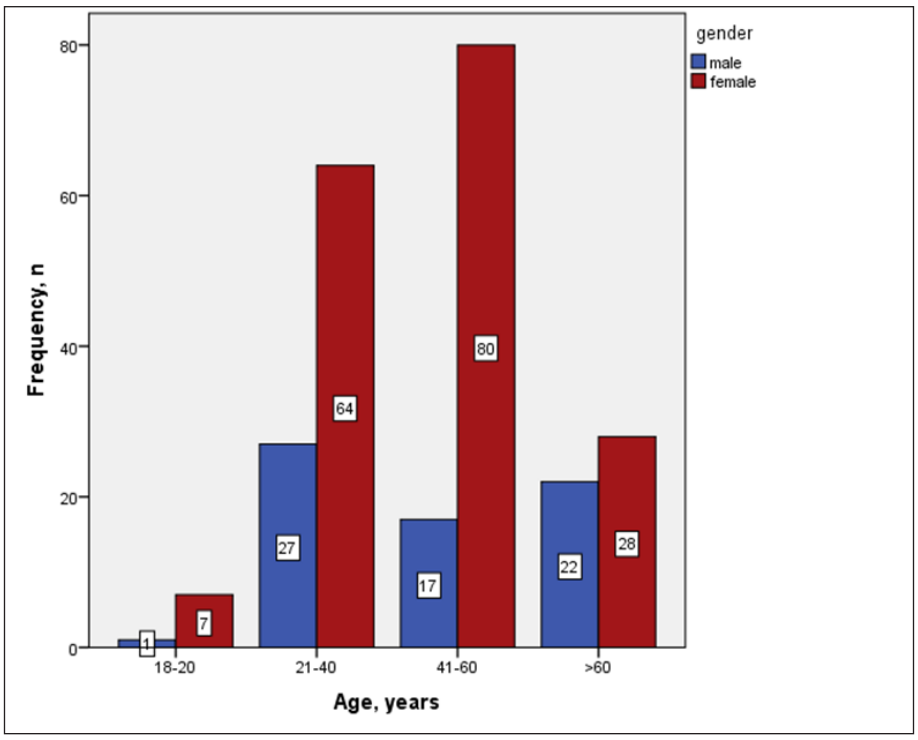

Fig. 1. Age and sex distribution of the study patients ($N = 246$).

Table 1. Distribution of various TFT values of COVID-19 patients in three groups (high, regular, low) together with their percent inside brackets $n = 214$.

Levels	TSH uiU/ml	T3 nmol/l	FT3 pmol/l	T4 nmol/l	FT4 pmol/l
Elevated	10 (4.7%)	2 (0.9%)	-	5 (2.4%)	3 (2.1%)
Normal	201 (93.9%)	199 (93.9%)	136 (93.8%)	206 (97.2%)	133 (91.7%)
Low	3 (1.4%)	11 (5.2%)	9 (6.2%)	1 (0.5%)	9 (6.2%)

TSH, thyroid-stimulating hormone; T3 triiodothyronine; FT3, free triiodothyronine; T4, thyroxin; FT4, free thyroxin.

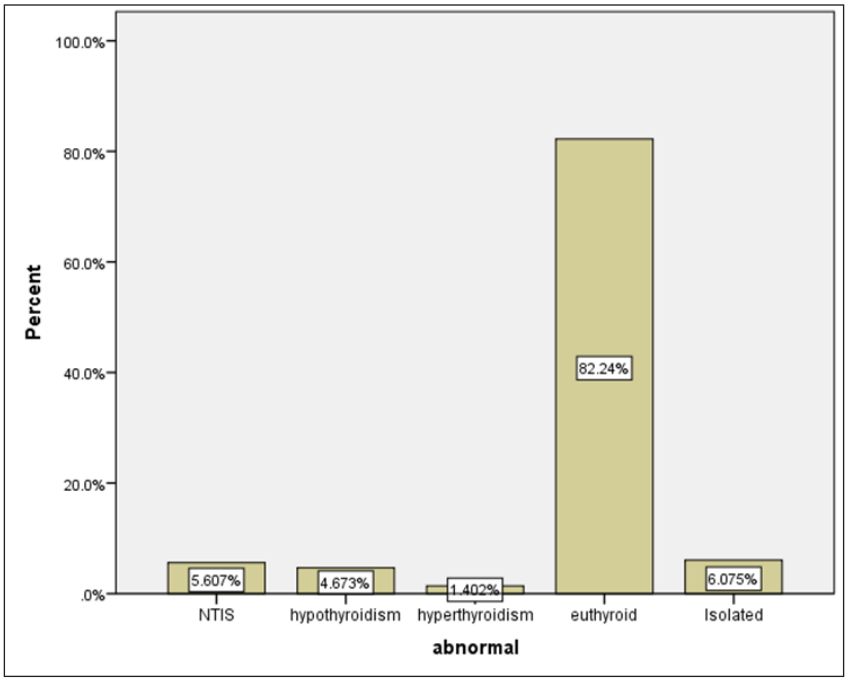

Fig. 2. TH abnormalities in COVID-19 patients ($n = 214$).

with TD had higher CRP ($p = 0.000$), urea ($p = 0.014$), alkaline phosphatase (ALP) ($p = 0.007$), neutrophil ($p = 0.000$), and had lower lymphocyte ($p = 0.000$), lower hematocrit (HCT) ($p = 0.010$), lower mean corpuscular volume (MCV) ($p = 0.019$), lower mean corpuscular hemoglobin (MCH) ($p = 0.019$) when compared to non-COVID-19 patients without TD.

Comparison between COVID-19 patients with normal FT3 and low FT3

When comparing COVID-19 patients with normal FT3 with those having low FT3 as shown in Table 5, patients with low FT3 additionally had lower T3 ($p = 0.000$) than those with normal FT3, and there has been no vast difference in the TSH ($p = 0.57$), T4 ($p = 0.570$), and FT4 ($p = 0.856$) among patients with normal FT3 and low FT3. regarding demographic characteristics, FT3 was a significant age difference ($p = 0.0.5$), patients with low FT3 have been drastically older as compared to patients with regular FT3, even as there was no sizable difference in FT3 according to sex ($p = 0.445$) between patients with regular FT3 and low FT3. The laboratory results confirmed that COVID-19 patients with low FT3 had drastically lower hemoglobin (Hb) ($p = 0.046$).

Comparison between COVID-19 patients with normal FT4 and low FT4

The comparison between COVID-19 patients with normal FT4 and those having low FT4 is presented in Table 6. Patients with low FT4 had higher TSH as expected ($p = 0.009$), lower T4 ($p = 0.000$), and FT3 ($p = 0.023$) than those with normal FT4. Regarding demographic characteristics, there was no significant difference in FT4 according to age ($p = 0.938$), and sex ($p = 0.277$) between patients with normal and low FT4. The laboratory results showed that COVID-19 patients with low FT4 had significantly higher LDH ($p = 0.039$).

Correlation of descriptive biochemical markers in all patients with thyroid profile

THs were shown to have a longitudinal relationship with other baseline hematological, some inflammatory biomarkers, and biochemical markers (Table 7).

Table 2. TH abnormalities with age among COVID-19 patients.

Abnormal		Age				Total
		18–20	21–40	41–60	>60	
NTIS	Count	0	1	5	6	12
	% within abnormal	0.0%	8.3%	41.7%	50.0%	
hypothyroidism	Count	0	3	5	2	10
	% within abnormal	0.0%	30.0%	50.0%	20.0%	
hyperthyroidism	Count	0	1	2	0	3
	% within abnormal	0.0%	33.3%	66.7%	0.0%	
euthyroid	Count	6	67	71	32	176
	% within abnormal	3.4%	38.1%	40.3%	18.2%	
TD	Count	0	4	7	2	13
	% within abnormal	0.0%	30.8%	53.8%	15.4%	
Total	Count	6	76	90	42	214
	% within abnormal	2.8%	35.5%	42.1%	19.6%	

Table 3. TH abnormalities according to gender among COVID-19 patients.

Abnormal		Gender		Total
		Male	Female	
NTIS	Count	3	9	12
	% within abnormal	25.0%	75.0%	
hypothyroidism	Count	1	9	10
	% within abnormal	10.0%	90.0%	
hyperthyroidism	Count	1	2	3
	% within abnormal	33.3%	66.7%	
euthyroid	Count	50	126	176
	% within abnormal	28.4%	71.6%	
TD	Count	2	11	13
	% within abnormal	15.4%	84.6%	
Total	Count	57	157	214
	% within abnormal	26.6%	73.4%	

CRP was positively correlated with T4 (r = 0.262, p < 0.001), while negatively correlated with FT3 (r = −0.335, p < 0.001). LDH was found to be negatively correlated with both FT3 (r = −0.254, p < 0.001) and FT4 (r = −0.326, p < 0.001). Urea was shown to be negatively correlated with T4 (r = −0.187, p < 0.001). DBIL was negatively correlated with TSH (r = −0.142, p < 0.05), while positively correlated with FT4 (r = 0.187, p < 0.05).

Lymphocytes were found to be positively correlated with TSH (r = 0.176, p < 0.001), while negatively correlated with both T4 (r = −0.208, p < 0.001) and FT4 (r = −0.191, p < 0.001). Neutrophil count was negatively correlated with TSH (r = −0.154, p < 0.05), while positively correlated with T4 (r = 0.156, p < 0.05).

Furthermore, red blood cells (RBC) were positively correlated with both FT3 (r = 0.259, p < 0.001) and FT4 (r = 0.245, p < 0.001), Also Hb was positively correlated with both FT3 (r = 0.291, p < 0.001) and FT4 (r = 0.206, p < 0.001), whereas HCT and platelets were positively correlated with FT4 (r = 0.321, p < 0.001), (r = 0.156, p < 0.05), respectively.

Discussion

In this study, most COVID-19 patients were euthyroid (82.24%), normal range of TSH levels was observed in (93.9%) of COVID-19 patients, with TD being reported in 17.8%, this is consistent with the results obtained

Table 4. Comparison between non-COVID-19 patients without thyroid dysfunction, and COVID-19 patients with thyroid dysfunction.

Variable	Non-COVID-19 patients without TD (*n* = 32)	COVID-19 patients with TD (*n* = 38)	*p*-value
TSH uIU/ml	1.58 (1.17–2.36)	1.66 (0.88–5.22)	0.505
T3 nmol/l	1.81 ± 0.31	1.69 ± 0.66	**0.029**
T4 nmol/l	117.72 ± 23.86	113.62 ± 44.63	**0.014**
FT3 pmol/l	4.68 ± 0.71	3.60 ± 1.15	**0.022**
FT4 pmol/l	16.10 ± 2.25	14.60 ± 4.65	**0.012**
Age	43 ± 17.49	53 ± 15.88	0.146
Female	22 (68.8)	31 (81.6)	0.268
CRP mg/l	3.31 (0.99–8.24)	4.24 (1.95–8.79)	**0.000**
LDH U/l	201.86 ± 65.95	268.24 ± 86.92	0.163
Urea mg/dl	22.04 ± 5.89	27.51 ± 10.43	**0.014**
CRE mg/dl	0.73 ± 0.19	0.76 ± 0.31	0.156
ALT U/l	16.40 ± 11.05	15.18 ± 9.42	0.964
AST U/l	15.85 (13–19.25)	16.7 (14.15–19.83)	0.756
ALP U/l	72.38 ± 15.65	76.46 ± 27.40	**0.007**
TBIL mg/dl	0.40 ± 0.25	0.42 ± 0.23	0.993
DBIL mg/dl	0.18 ± 0.92	0.186 ± 0.87	0.667
UA mg/dl	4.93 ± 1.74	5.04 ± 1.66	0.684
WBC × 10^3/µl	6.44 ± 1.46	7.00 ± 1.73	0.170
LYM %	34.78 ± 4.44	30.16 ± 10.75	**0.000**
NEUT %	55.58 ± 4.96	60.54 ± 10.41	**0.000**
RBC × 10^6/µl	4.54 ± 0.40	4.37 ± 0.53	0.385
Hb g/dl	13.50 ± 1.31	12.13 ± 1.58	0.413
HCT %	37 (35.2–40.5)	36.15 (33.95-39.80)	**0.010**
MCV fl	84.69 ± 4.34	81.69 ± 10.86	**0.019**
MCH pg	29.41 ± 1.89	27.95 ± 3.31	**0.019**
PLT × 10^3/µl	249 ± 63.28	267 ± 86.89	0.118

p-values <0.05 was considered statistically significant indicated in bold. Data are presented as mean ± SD, median (IQR), and number (%) as appropriate. Abbreviations: TD, thyroid dysfunction; TSH, thyroid-stimulating hormone; T3 triiodothyronine; FT3, free triiodothyronine; T4, thyroxin; FT4, free thyroxin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALT, alanine aminotransferase AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL; direct bilirubin; CRE, creatinine; UA, uric acid; WBC, white blood cell; LYM, lymphocyte; NEUT, neutrophil; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelets.

by other studies (Giovanella *et al.*, 2021; Lui *et al.*, 2021b). Giovanella *et al.* (2021) demonstrated that the prevalence of TD in COVID-19 patients largely varies between 13% and 64% of COVID-19 patients.

Among outpatients with COVID-19 infection; 12 patients had NTIS, 10 had hypothyroidism, 3 had hyperthyroidism, and in another 13 patients at least one abnormality in thyroid function was detected (isolated THs abnormalities).

The results of this study showed that (12/214, 5.6%) of COVID-19 patients had decreased total T3 and/or FT3 levels with normal total and FT4 levels and normal TSH levels observed, suggesting the presence of a component of NTIS. Also, one of them had low FT3 and high FT4 levels, showing that this form could be a combination of NTI and thyrotoxicosis, in line with the previous report by Chen *et al.* (2021), Khoo *et al.* (2021), and Lui *et al.* (2021b).

In severe illness, both acute and chronic NTIS can arise in euthyroid patients. The preliminary position of NTIS appears to be para-physiological, adaptive, and protective, which lowers metabolic expenditure. despite the fact that it can be harmful and slow down the

Table 5. Comparison between COVID-19 patients with normal FT3 and low FT3.

Variable	Normal FT3 (*n* = 136)	Low FT3 (*n* = 9)	*p*-value
TSH uIU/ml	1.61 (1.07–2.43)	1.19 (0.43–1.79)	0.57
T3 nmol/l	1.83 ± 0.41	1.27 ± 0.378	**0.000**
T4 nmol/l	114.12 ± 25.48	108.56 ± 46.07	0.570
FT3 pmol/l	4.61 ± 0.70	2.17 ± 0.82	**0.000**
FT4 pmol/l	15.77 ± 2.49	15.60 ± 6.29	0.856
Age	46 ± 17.44	59 ± 12.47	**0.035**
Female	97 (92.4%)	8 (7.6%)	0.445
CRP mg/l	3.36 (1.13–6.74)	10.05 (1.84–24.82)	0.227
LDH U/l	220(173–293)	227 (164–281)	0.712
Urea mg/dl	23.07 (18.79–31.53)	22.95 (21.91–32)	0.925
CRE mg/dl	0.67 (0.57–0.79)	0.66 (0.60–0.79)	0.809
ALT U/l	12.45 (9.5–18.25)	13.2 (11.48–29.75)	0.358
AST U/l	15.90 (13–18.5)	17.6 (14.45–36.18)	0.261
ALP U/l	76.10 ± 26.73	70.32 ± 20.13	0.604
TBIL mg/dl	0.38 (0.29–0.59)	0.36 (0.25–0.50)	0.507
DBIL mg/dl	0.18 (0.14–0.26)	0.16 (0.12–0.26)	0.663
UA mg/dl	4.76 ± 1.46	5.48 ± 1.70	0.249
WBC × 10^3/µl	7.33 ± 2.41	7.72 ± 2.10	0.639
LYM %	32.51 ± 10.17	26.30 ± 12.30	0.081
NEUT %	58.75 ± 10.73	64.54 ± 11.58	0.121
RBC × 10^6/µl	4.57 ± 0.51	4.38 ± 0.55	0.287
Hb g/dl	12.87 ± 1.80	11.63 ± 1.33	**0.046**
HCT %	37.84 ± 4.41	40.20 ± 17.11	0.248
MCV fl	84 (80.7–87)	79.1 (74.25–88.1)	0.322
MCH pg	28.8 (27.1–30)	27.8 (23.25–30.85)	0.547
PLT × 10^3/µl	273 (221–311)	251 (214.5–390.5)	0.776

Significant *p*-values are indicated in bold. Data are presented as mean ± SD, median (IQR), and number (%) as appropriate. Abbreviations; TSH, thyroid-stimulating hormone; T3 triiodothyronine; FT3, free triiodothyronine; T4, thyroxin; FT4, free thyroxin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALT, alanine aminotransferase AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL; direct bilirubin; CRE, creatinine; UA, uric acid; WBC, white blood cell; LYM, lymphocyte; NEUT, neutrophil; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelets.

recovery process like different homeostatic responses of the body (Fliers *et al.*, 2015).

This research verified that low FT3 and occasionally, a reduction of TSH levels in COVID-19 patients, defined as NTIS, may be explained either by targeting the thyroid gland by SARS-CoV-2 through access to the follicular thyroid cells that express the ACE-2 receptor as SARS-CoV-2 cell access receptor (Rotondi *et al.*, 2021) or particular and direct harm to the pituitary TSH-secreting cells by the SARS-CoV-2 (Chen *et al.*, 2021).

The results of this study indicated that COVID-19 patients with low FT3 were significantly older, also FT3 levels were negatively correlated with higher levels of inflammatory markers including CRP, and LDH, in agreement with the results of other studies (Zou *et al.*, 2020; Güven and Gültekin, 2021; Lui *et al.*, 2021a, 2021b;). These findings might reflect that low FT3, whether FT4 and TSH were normal or reduced, may have prognostic relevance as it was associated with worsening clinical severity of COVID-19 (Gao *et al.*, 2021).

The current study also found that 4.7% (10/214) of COVID-19 patients had hypothyroidism, approximately 50% of patients were around 50 years and older, and more than two-thirds were females. These results follow the THYROCOV study conducted in Italy which found that 5.2% (15/287) of non-ICU COVID-19 patients had hypothyroidism (Lania *et al.*, 2020). Our results also agree with the results of a study

Table 6. Comparison between COVID-19 patients with normal FT4 and low FT4.

Variable	Normal FT4 (*n* = 136)	Low FT4 (*n* = 9)	*p*-value
TSH uIU/ml	1.59 (1.04–2.35)	3.24 (1.56–29.75)	**0.009**
T3 nmol/l	1.81 ± 0.43	1.56 ± 0.30	0.081
T4 nmol/l	115.77 ± 25.08	77.98 ± 26.39	**0.000**
FT3 pmol/l	4.51 ± 0.89	3.81 ± 0.84	**0.023**
FT4 pmol/l	16 ± 2.14	10.09 ± 3.30	**0.000**
Age	47 ± 17.77	47 ± 14.20	0.938
Female	94 (89.5%)	8 (7.6%)	0.277
CRP mg/l	3.26 (1.13–7.06)	4.32 (2.09–6.10)	0.723
LDH U/l	218 (167.5–288.5)	304 (232–338)	**0.039**
Urea mg/dl	23.07 (18.78–31.05)	26.5 (20.66–32.94)	0.648
CRE mg/dl	0.67 (0.57–0.79)	0.64 (0.58–0.79)	0.827
ALT U/l	12.6 (9.53–18.78)	16.2 (8.7–20.4)	0.775
AST U/l	15.9 (13–18.8)	18.2 (16.4–20.2)	0.260
ALP U/l	75.57 ± 25.55	84 ± 38.97	0.412
TBIL mg/dl	0.46 ± 0.25	0.34 ± 0.45	0.246
DBIL mg/dl	0.18 (0.138–0.26)	014 (0.12–0.16)	0.056
UA mg/dl	4.80 ± 1.47	4.99 ± 1.34	0.739
WBC × 10^3/µl	7.43 ± 2.45	6.39 ± 0.91	0.207
LYM %	32.07 ± 10.15	38.13 ± 11.97	0.086
NEUT %	59.217 ± 10.62	53.31 ± 12.94	0.139
RBC × 10^6/µl	4.58 ± 0.50	4.31 ± 0.74	0.127
Hb g/dl	12.87 ± 1.76	11.87 ± 2.22	0.107
HCT %	37.86 ± 4.24	35.37 ± 5.95	0.099
MCV fL	84 (80.36–87.08)	82.1 (74.45–87.4)	0.440
MCH pg	28.9 (27.03–30.1)	27.5 (26.35–29.05)	0.239
PLT × 10^3/µl	272.5 (222.25–322.25)	244 (186–334)	0.479

Significant *p*-values are indicated in bold. Data are presented as mean ± SD, median (IQR), and number (%) as appropriate. Abbreviations: TSH, thyroid-stimulating hormone; T3 triiodothyronine; FT3, free triiodothyronine; T4, thyroxin; FT4, free thyroxin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALT, alanine aminotransferase AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL; direct bilirubin; CRE, creatinine; UA, uric acid; WBC, white blood cell; LYM, lymphocyte; NEUT, neutrophil; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelets.

of COVID-19 patients in Iran, where hypothyroidism was detected in 5.4% (21/390) of hospitalized patints with COVID-19 and approximately 90% of patients were 50 years or older (Daraei *et al.*, 2020), while another study found the frequency of hypothyroidism was 3.2% in ICU COVID-19 patients, the lower rate was likely to expand exclusion standards (patients with the previously recognized pituitary disorder, diabetes mellitus, kidney, and liver disease had been excluded in the study) (Güven and Gültekin, 2021).

In the study by Lania *et al.* (2020), hypothyroidism was subclinical in 13 patients and overt in the remaining two non-ICU patients with COVID-19, whereas, Daraei *et al.* (2020) study found hypothyroidism was subclinical in one ICU patient and overt in the three ICU COVID-19, patients. Among the outpatients, our study found hypothyroidism was subclinical in six patients and overt in four patients with COVID-19. These results may reflect the effects of SARS-CoV-2 on the thyroid gland that may induce hypothyroidism seen mainly as subclinical (Jaiswal *et al.*, 2021).

Noteworthy, the superiority of hyperthyroidism became low at 1.4% (3/214) in this study, suppressed TSH values have been discovered in three outpatients; none of these patients had low overall FT3 values, and certainly one of them, T4 values have been above the reference range suggesting thyrotoxicosis rather than NTI. In comparison, the findings of the study by Lania *et al.* (2020), reported thyrotoxicosis in approximately 20% of 287 COVID-19 patients and discovered an inverse

Table 7. Correlation of descriptive biochemical markers in all patients with thyroid profile ($N = 246$).

Laboratory investigation	TSH uIU/ml	T3 nmol/l	T4 nmol/l	FT3 pmol/l	FT4 pmol/l
CRP mg/l	−0.023	0.058	0.262**	−0.335**	0.044
LDH U/l	−0.073	−0.005	0.037	−0.254**	−0.326**
Urea mg/dl	−0.030	−0.055	−0.187**	−0.103	0.014
CRE mg/dl	−0.117	−0.085	−0.110	0.036	0.149
ALT U/l	−0.016	0.073	0.102	0.071	0.120
AST U/l	−0.011	−0.026	0.057	−0.071	0.024
ALP U/l	0.064	0.088	0.062	−0.138	0.095
TBIL mg/dl	−0.048	0.027	0.045	0.109	0.150
DBIL mg/dl	−0.0142*	0.040	0.074	0.080	0.187*
UA mg/dl	−0.024	0.032	−0.069	−0.036	0.035
WBC × 10^3/µl	0.039	0.038	−0.045	−0.026	0.018
LYM %	0.176**	0.000	−0.208**	0.131	−0.191*
NEUT %	−0.154*	0.018	0.156*	−0.124	0.146
RBC × 10^6/µl	−0.015	0.104	0.072	0.259**	0.245**
Hb g/dl	−0.051	0.077	0.030	0.291**	0.206**
HCT %	−0.065	0.077	0.035	0.082	0.321**
MCV fl	−0.037	−0.075	−0.067	−0.043	−0.088
MCH pg	−0.070	−0.031	−0.051	0.014	−0.004
PLT × 10^3/µl	0.072	0.039	0.121	−0.019	0.156*

*Significant p-value <0.05. **Significant p-value ≤0.001. Abbreviations: TSH, thyroid-stimulating hormone; T3 triiodothyronine; FT3, free triiodothyronine; T4, thyroxin; FT4, free thyroxin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALT, alanine aminotransferase AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL; direct bilirubin; CRE, creatinine; UA, uric acid; WBC, white blood cell; LYM, lymphocyte; NEUT, neutrophil; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelets.

correlation between serum TSH values and IL-6 levels, excessive mortality rate, and longer hospitalization. In another retrospective study of 50 patients, TSH was reduced in about 58% of COVID-19 patients, and an inverse link between serum TSH and T3 values with the severity of COVID-19 (Chen *et al.*, 2021).

Hyperthyroidism was not common in this study which could be due to the clinical setting where most of the patients in our study were outpatients and the possibility of thyrotoxicosis may develop during or after the resolution of COVID-19 infection (Brancatella *et al.*, 2020; Ippolito *et al.*, 2020; Lania *et al.*, 2020; Ruggeri *et al.*, 2021) and difficult follow-up of these patients after their full recovery owing to the retrospective nature of this study.

Few studies have reported an association between TD and inflammatory markers, however very few have reported an association with different hematological and biochemical markers. Wang *et al.* (2021) confirmed that the TD group had lower counts of lymphocytes and higher leukocytes, neutrophils, CRP, and procalcitonin. They described TD as any abnormality in T3, T4, or TSH. Those findings, with this study finding, confirmed that COVID-19 patients with TD showed a statistically sizable reduction in lymphocytes and increased neutrophil, CRP, urea, and ALP in comparison to euthyroid control indicating that systemic infection might also affect deiodinase activity. Systemic inflammation; (represented through higher inflammatory markers), which is additionally associated with systemic tissue damage, ends in reduced deiodinase activity (Ilera *et al.*, 2021).

It has been reported that liver and kidney function abnormalities in COVID-19 patients either due to direct viral effect, indirect SARS-CoV-2 effect through abnormal systemic inflammatory-immune responses, or antiviral drugs that may have a toxic effect (Ciaccio and Agnello, 2020; Hwaiz *et al.*, 2021).

Our study found a weak correlation between TFT and other biochemical markers; TSH was negative and total FT4 was positively correlated with high serum DBIL concentration, whereas a weak inverse correlation was found between T4 and urea. In contrast, the study by Asghar *et al.* (2021) in the analysis of 54 COVID-19 patients, found a direct correlation between TSH and urea, and a nonsignificant correlation between T4 and

urea, whereas serum DBIL wasn't assessed. An inverse correlation has been observed between T4 levels and serum DBIL (Burmeister, 1995).

Currently, it is still unknown what mechanisms are precisely responsible for the association of TFT parameters and the biochemical markers and how both TSH and THs would possibly result in an increase in liver function. but, for hyperthyroidism and hypothyroidism, numerous pathways were proposed. It has been shown that as much as 72% of patients with hyperthyroidism and presumably ordinary liver function may also have an elevation of at least one hepatic enzyme, ALP elevations are most commonly found (Bal and Chawla, 2010). THs metabolism is influenced by factors aside from the thyroidal state. It has been reported that T4 became negatively related to growing serum bilirubin concentration. Inhibited transport of T4 in hepatocytes patients with elevated bilirubin has been shown in severe cases of COVID-19 (Burmeister, 1995). Similarly, FT4 can be increased when overall T4 is normal or low in hyperthyroidism because of a decreased concentration of TH-binding proteins (Bal and Chawla, 2010).

Moreover, previous studies found a negative correlation between T4 and urea. It has been observed that regulation of nitrogen metabolism and urea biosynthesis was increased in isolated hepatocytes of hypothyroid rats PORTALES (Marti *et al.*, 1988). Furthermore, it has been shown that patients with uremia had low T3 and T4 before hemodialysis, and had normal T3 and T4 after hemodialysis (Shamsadini *et al.*, 2006). These findings might suggest that THs increase catabolic activities and lead to increasing CRE and BUN concentration, which in turn switch off THs secretion by a feedback mechanism (Marti *et al.*, 1988; Shamsadini *et al.*, 2006).

Our study also showed that TD was slightly associated with lower hematological parameters. Given the small difference in HCT, MCV, and MCH levels among TD groups and a weak positive correlation with RBC, and Hb in all patients with thyroid profiles, the contribution of thyroid abnormalities to low Hb levels or anemia may be small. It remains to be assessed in a larger randomized controlled study to further clarify whether these results are considered clinically relevant and whether these should influence practice.

Our study had numerous boundaries that could cause possible bias First, the data collection was retrospective with an exceptionally small sample size.

Second, records about comorbidity and medication data were inaccessible to most patients. Eventually, lacked information on antibodies for thyroid autoimmunity.

Conclusion

In conclusion, in this study of outpatients with COVID-19 infection, alteration of thyroid characteristics was observed in 17.8% of the outpatients. Low FT3 and FT4 are the most common abnormalities seen in 6.2% of patients. Low FT3 is often seen in isolation, suggestive of NTIS. Low FT3 was associated with older age, and higher markers of infection consist of CRP and LDH. Both TSH and THs (T3, T4, and free fractions) correlated with a few biomarkers. Clinicians ought to be vigilant about the possible presence of thyroid function abnormalities among COVID-19 patients, particularly elderly patients, and those with elevated inflammatory markers.

Conflict of interest

The authors declare that there is no conflict of interest.

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