RESEARCH

# Thyroid hormone alterations in critically and non-critically ill patients with SARS-CoV-2 infection

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## Abstract

*Objective:* Following the evolution of COVID-19 pandemic, reports pointed on a high prevalence of thyroiditis-related thyrotoxicosis. Interpretation of thyroid tests during illness, however, is hampered by changes occurring in the context of non-thyroidal illness syndrome (NTIS). In order to elucidate these findings, we studied thyroid function in carefully selected cohorts of COVID-19 positive and negative patients.
*Design:* Cohort observational study.
*Methods:* We measured TSH, FT4, T3 within 24 h of admission in 196 patients without thyroid disease and/or confounding medications. In this study, 102 patients were SARS-CoV-2 positive; 41 admitted in the ICU, 46 in the ward and 15 outpatients. Controls consisted of 94 SARS-CoV-2 negative patients; 39 in the ICU and 55 in the ward. We designated the thyroid hormone patterns as consistent with NTIS, thyrotoxicosis and hypothyroidism.
*Results:* A NTIS pattern was encountered in 60% of ICU and 36% of ward patients, with similar frequencies between SARS-CoV-2 positive and negative patients (46.0% vs 46.8%, $P$ = NS). A thyrotoxicosis pattern was observed in 14.6% SARS-CoV-2 ICU patients vs 7.7% in ICU negative ($P$ = NS) and, overall in 8.8% of SARS-CoV-2 positive vs 7.4% of negative patients. In these patients, thyroglobulin levels were similar to those with normal thyroid function or NTIS. The hypothyroidism pattern was rare.
*Conclusions:* NTIS pattern is common and relates to the severity of disease rather than SARS-CoV-2 infection. A thyrotoxicosis pattern is less frequently observed with similar frequency between patients with and without COVID-19. It is suggested that thyroid hormone monitoring in COVID-19 should not differ from other critically ill patients.

**Key Words**
- thyroid
- COVID-19
- SARS-CoV-2
- critical illness

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## Introduction

With the emergence of the COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was soon realized that the disease affects not only the respiratory system but also multiple organs and systems of the body (1), the endocrine system being the less explored. The cellular infection takes place through the angiotensin-converting enzyme 2 (ACE2) receptor, making the tissues with increased expression of this receptor highly sensitive to SARS-CoV-2 (2). The thyroid gland has been shown to significantly express ACE2 (3), and its encoding mRNA (4), as well as the transmembrane protease serine 2 (TMPRSS2), an ubiquitous protease that cleaves the SPIKE protein subunit permitting internalization of the ACE2-viral complex (5), and it has been suggested that it may be a risk target of SARS-CoV-2. However, there is insufficient clinical data in COVID-19 patients and the significance, if any, of direct thyroid involvement remains uncertain (5). Pathological studies failed to show direct involvement of thyroid tissue (6). Reports describing patients with thyrotoxicosis attributed to SARS-CoV-2-related subacute thyroiditis (7, 8, 9, 10, 11, 12, 13) enforced the possibility that thyroiditis may be an underestimated manifestation of COVID-19. It is, therefore, important to evaluate the extent of thyroid involvement in COVID-19, especially in patients admitted to the hospital, since the presence of thyroiditis may aggravate the cardiovascular complications and arrhythmias already described in patients with SARS-CoV-2 infection (14) or lead to thyroid damage which requires prompt recognition and management.

Subsequent cohort studies in hospitalized patients admitted with COVID-19, either in the ICU or in special wards, reported an increased prevalence of lower than normal TSH levels, considered to indicate thyrotoxicosis (15, 16, 17, 18, 19, 20, 21), summarized in Table 1. A major, however, barrier when assessing severely or critically ill patients is the fact that these patients often display thyroid hormone alterations in the context of non-thyroidal illness syndrome (NTIS) (22). Therefore, we conducted an observational study of thyroid function in COVID-19 patients admitted in our hospital with either pneumonia not requiring mechanical ventilation or in the ICU, in comparison to patients with similar clinical severity admitted during the same period but who were SARS-CoV-2 negative. We also included a group of SARS-CoV-2 positive patients, either asymptomatic or oligo-symptomatic, who did not require hospitalization. In the patients with SARS-CoV-2 infection we also measured the levels of thyroglobulin as a marker of 'destructive' thyroiditis, anti-thyroid autoantibodies as well as interleukin-6 (IL-6) levels.

## Patients and methods

This is a prospective observational study of 196 patients treated in Evangelismos General Hospital (a tertiary referral center in the nation's capital) from April 2020 to September 2020. The study was approved by the Scientific Council/ Ethics Board of the Evangelismos Hospital, Athens, Greece (No 170/April 24, 2020); written informed consent for the use of anonymized patients' data was obtained from the patients or their next of kin. Exclusion criteria were history of thyroid disease or use of thyroid function test-altering medications (glucocorticoids, amiodarone, dopamine, low molecular weight heparin, recent exposure to iodine, including iodine contrast material). We included 102 consecutive patients with confirmed SARS-CoV-2 infection (41 admitted in the ICU (ICU C+), 46 admitted in the ward (Ward C+), 15 patients were oligo- or asymptomatic and were treated as outpatients (Outpatient C+)). The control groups consisted of 94 patients who were admitted during the same period (39 admitted in the ICU (ICU NC) and 55 admitted in the ward (Ward NC) with respiratory infections not related to COVID-19).

Blood samples for measurement of total triiodothyronine (T3) (normal range 80–200 ng/dL), free thyroxine (FT4) (normal range 0.9–1.7 ng/dL), thyrotropin (TSH) (normal range 0.3–4.2 μU/mL), anti-thyroperoxidase (anti-TPO) (<34 U/mL), anti-thyroglobulin (anti-Tg) (<115 U/mL) autoantibodies and thyroglobulin (normal range <78 ng/mL) were taken within 24 h from admission (or diagnosis for the patients treated on an outpatient basis) and before administration of interferent medications (LMW heparin or glucocorticoids).

We defined the following thyroid hormone patterns as compatible with thyrotoxicosis: low TSH (<0.3 μU/mL) accompanied by high FT4 (>1.7 ng/dL) and/or high T3 (>200 ng/dL) (overt thyrotoxicosis) or low TSH accompanied by FT4 levels above the mid-range of the normal reference values (1.3 ng/dL) (subclinical thyrotoxicosis). We considered the following thyroid hormone patterns as indicating non-thyroidal illness syndrome (NTIS): isolated hypotriiodothyroninemia (only low T3); Low T3 (<80 ng/dL) and low FT4 (<0.9 ng/dL) and normal TSH; low T3, FT4 below the mid-range of the reference values and low TSH (23). The two latter patterns

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**Table 1** Prevalence of thyroid hormone abnormalities in patients with COVID-19 and controls in recently published studies.

| Month | Author | Design | *n* | Population | Groups | *n* | Low/suppressed TSH | NTIS | Overt and subclinical thyrotoxicosis | Overt and subclinical hypothyroidism | Other findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| July | Sun *et al.* | Retrospective | 336 | Unselected | COVID-19 + | 336 | NR | NR | NR | NR | Lower TSH levels in severe/ critical cases |
| July | Li *et al.* | Prospective | 96 | Non-critically ill | COVID-19 + | 40 | NR | NR | NR | NR | TSH levels lower than controls |
| | | | | | COVID-19 – | 57 | NR | NR | NR | NR | |
| July | Chen *et al.* | Retrospective | 50 | Unselected (12 critically ill) | COVID-19 + | 50 | 28 (56%) | 15 (30%) | 17 (34%) | - | TSH levels lower than controls |
| | | | | | COVID-19 – | 54 healthy/50 pneumonia patients | NR | NR | NR | NR | |
| August | Muller *et al.* | Mixed (COVID-19+ prospective, Controls: retrospective) | 204* | Both critically (85) and non-critically (41) ill | COVID-19 + (critically ill/non-critically ill) | 85/41 | 29 (34%) & 5 (12.2%) | NR | 13 (15.3%) & 1 (2.4%) | 3 (3.5%) & 4 (9.8%) | |
| | | | | | COVID-19 – (critically ill) | 78 | 7 (9%) | NR | 1 (1.3%) | 7 (9%) | |
| October | Lania *et al.* | Retrospective | 287 | Non-critically ill all | COVID-19 + | 287 | 58 (20.2%) | NR | 58 (20.2%) | 15/ (5.2%) | |
| November | Lui *et al.* | Prospective | 191 | Unselected (84.3% mild, 12.6% moderate, 3.1% severe) | COVID-19 + | 191 | 11 (5.8%) | 12 (6.3%) | 14 (7.3%)** | 1 (0.5%) | |
| November | Khoo *et al.* | Prospective | 456 | Unselected (40 critically ill) | COVID-19 + | 334 | 18 (5.4%) | NR | 18 (5.4%)*** | 19 (5.7%) | |
| | | | | | COVID-19 – | 122 | 8 (6.6%) | NR | 8 (6.6%)*** | 7 (5.7%) | |

*After excluding those with known thyroid disease. **Including patients with raised FT4 but normal TSH. ***All subclinical.
NR, not reported.

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have been associated with more severe or prolonged disease (24). Overt hypothyroidism was defined as high TSH with low FT4 and subclinical hypothyroidism as high TSH with FT4 within the normal range. Isolated hyperthyroxinemia, a pattern that has been suggested to also indicate NTIS (25, 26), was defined as high FT4 with normal TSH. Mortality refers to in-hospital mortality.

### Assays

We measured total triiodothyronine (T3), free thyroxine (FT4), thyrotropin (TSH), anti-thyroperoxidase (anti-TPO), anti-thyroglobulin (anti-Tg) autoantibodies with electrochemiluminescence (Elecsys Systems, Roche Diagnostics, Mannheim, Germany). Thyroglobulin was measured only in the SARS-CoV-2 positive patients. In 33 SARS-CoV-2 positive patients (26 ICU C+ and 7 Ward C+) we also measured IL-6 levels, using an ELISA (Invitrogen, Thermo Fisher Scientific) on the Triturus automated analyzer (Grifols, Barcelona, Spain).

The presence of SARS-CoV- 2 was confirmed by RT-PCR from nasopharyngeal swab (NPS).

## Statistics

We used the SPSS statistical package, (IBM Corp. Released 2020. IBM SPSS Statistics for MC Os, Version 27.0 (IBM Corp and GraphPad Prism, version 8.0 (GraphPad Software)) Data are presented as the mean value ± S.D. of the mean. We checked normality with the Shapiro–Wilk test. For data without a normal distribution, we used non-parametric tests. Statistical analysis was done with Student's *t*-test or the Mann–Whitney *U* test, Pearson's or Spearman correlations, the Kruskal–Wallis test and the chi-square test. Statistical significance was set at $P=0.05$, with a Bonferroni correction where needed.

## Results

The mean age of all patients (66.3% males) was 59.3 ± 18.3 years. Demographic data, hormonal levels of the patients and mortality are shown in Table 2. COVID-19 asymptomatic patients were the youngest group. The Ward C+ were younger than patients admitted in the ward without COVID-19. The distribution of the hormonal levels is shown in Fig. 1. T3 and TSH levels were lower in the ICU patients, compared to ward patients (70.5 ± 31.9 vs 89.7 ± 42.0, $P$ = 0.001 and 0.95 ± 0.93 vs 1.66 ± 1.46, $P \leq 0.001$, respectively), but there was no difference between patients with or without COVID-19. FT4 levels were similar between ICU and ward patients (1.23 ± 0.32 vs 1.31 ± 0.51, $P$=NS); we observed, however, marginally higher FT4 levels in the ICU C+ group compared to ICU NC patients (1.3 ± 0.3 ng/dL vs 1.2 ± 0.3 ng/dL, $P=0.07$). Thyroid autoantibodies and thyroglobulin levels were measured only in the SARS-CoV2 positive patients. Positive thyroid autoantibodies were seen in 22.9% of ICU C+ patients, in 7.9% of Ward C+ patients and in 13.3% of the asymptomatic SARS-CoV-2 positive patients ($P$=NS); in particular, anti-thyroglobulin antibodies were positive in 2.4%, 4.3% and 6.7%, respectively ($P$=NS). In anti-Tg negative patients, thyroglobulin was 15.6 ± 15.8 ng/mL and lower in the SARS-CoV2 positive patients admitted in the ICU compared to SARS-CoV2 positive patients admitted in the ward (10.9 ± 1.9 ng/mL vs 19.5 ± 3.5 ng/mL, $P=0.02$). In SARS-CoV-2 patients, IL-6 was higher in the ICU patients compared to ward patients (134.7 ± 84.2 pg/mL vs 49.2 ± 69.5 pg/mL, $P=0.02$). A negative correlation between IL-6 and FT4 was noted, regardless of patient group (r=–0.41, $P=0.02$) as well as between IL-6 and thyroglobulin levels in anti-Tg negative patients (–0.44, $P=0.01$).

The associations between TSH levels and FT4 or T3 levels in the ICU and ward patients with and without

**Table 2** Demographic and hormonal data (IL-6 and thyroglobulin levels were measured only in COVID-19 positive patients).

| | ICU | | | WARD | | | OUTPATIENTS |
|---|---|---|---|---|---|---|---|
| | COVID-19 ($n=41$) | Non-COVID-19 ($n=39$) | *P* | COVID-19 ($n=46$) | Non-COVID-19 ($n=55$) | *P* | COVID-19 ($n=15$) |
| Age (years) | 63.0 ± 10.2 | 56.7 ± 20.0 | *NS* | 53.8 ± 17.4 | 69.3 ± 17.8 | *<0.001* | 38.9 ± 11.4 |
| Females/males | 8/33 (80.5%) | 15/24 (61.5%) | *NS* | 10/36 (78.3%) | 23/32 (54.5%) | *NS* | 8/7 (46.7%) |
| T3 (ng/dL), NR: 80–200 | 74.8 ± 35.1 | 65.9 ± 27.7 | *NS* | 88.9 ± 24.6 | 90.5 ± 53.6 | *NS* | 117.6 ± 28.1 |
| FT4 (ng/dL), NR: 0.9–1.7 | 1.3 ± 0.3 | 1.2 ± 0.3 | *0.07* | 1.3 ± 0.2 | 1.4 ± 0.7 | *NS* | 1.5 ± 0.2 |
| TSH (μU/mL), NR: 0.3–4.2 | 0.9 ± 0.8 | 1.0 ± 1.0 | *NS* | 1.3 ± 0.9 | 2.0 ± 1.8 | *NS* | 1.6 ± 1.1 |
| IL-6 (pg/mL) | 134.7 ± 84.2 | – | – | 49.2 ± 69.5 | – | – | – |
| Thyroglobulin[a] (ng/mL) | 11.3 ± 10.9 | – | – | 20.5 ± 19.5 | – | – | 14.9 ± 14.4 |
| Mortality | 29.7% | 35.9% | *NS* | 4.7% | 8.5% | *NS* | 0% |

[a]Measured only in anti-Tg negative patients

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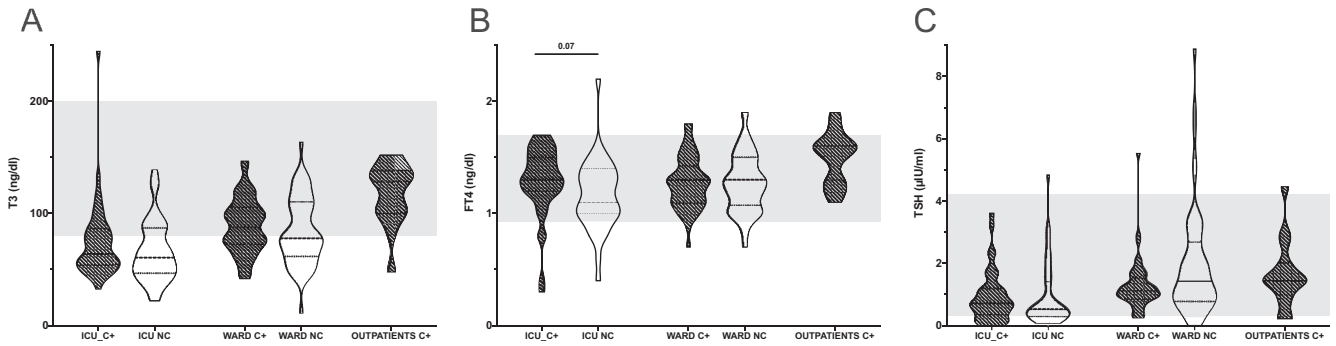


**Figure 1**
Violin plots depicting the distribution of T3 (A), FT4 (B) and TSH (C) in the various groups (ICU C+, patients admitted in the ICU with COVID-19; ICU NC, patients admitted in the ICU without COVID-19; Ward C+, patients admitted in the ward with COVID-19; Ward NC, patients admitted in the ward without COVID-19; Outpatients C+, patients with COVID-19 treated as outpatients). The shaded area indicates the normal range.

SARS-CoV-2 infection is shown in Fig. 2. Low TSH was observed in 20% of ICU patients (19.5% of ICU C+ and 20.5% of ICU NC), 7.9% of the ward patients (6.5% of Ward C+ and 9.1% of Ward NC) and in 13.3% of the Outpatient C+ patients. In 38.3% of the patients with low TSH the concurrent levels of FT4 and/or T3 were indicative of NTIS rather than thyrotoxicosis. Specifically, we identified the following thyroid function patterns (Table 3).

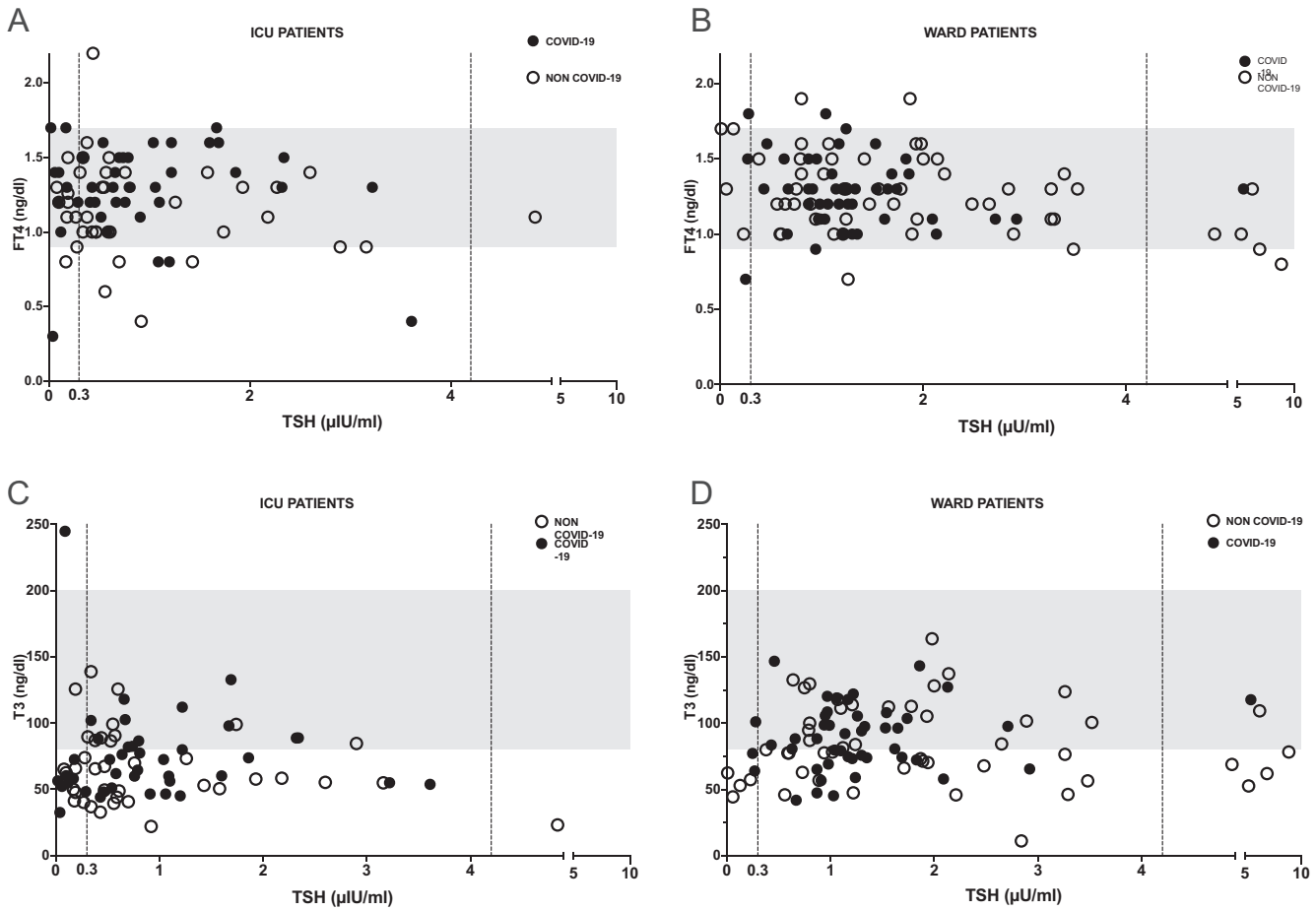


**Figure 2**
Relationship between TSH and FT4 levels in ICU patients (A) and ward patients (B) and between TSH and T3 levels in ICU patients (C) and ward patients (D). COVID-19 positive patients are shown with black circles, COVID-19 negative patients with open circles. The shaded area indicates the normal range.

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**Table 3** Thyroid hormone patterns among groups.

| Definitions | Thyroid hormone patterns | ICU ($n = 80$) | | Ward ($n = 101$) | | Outpatients ($n = 15$) |
|---|---|---|---|---|---|---|
| | | COVID-19 ($n = 41$) | Non-COVID-19 ($n = 39$) | COVID-19 ($n = 46$) | Non-COVID-19 ($n = 55$) | COVID-19 ($n = 15$) |
| Normal (41.3%) | | 12 (29.3%) | 9 (23.1%) | 25 (54.3%) | 25 (45.5%) | 10 (66.7%) |
| Non-thyroidal illness syndrome (43.4%) | | 23 (56.1%) | 26 (66.7%) | 18 (39.1%) | 21 (38.2%) | 3 (20%) |
| | Only Low T3 (34.2%) | 18 (43.9%) | 16 (41.0%) | 16 (34.8%) | 17 (30.9%) | 0 |
| | Low T3 and low FT4 and normal TSH (4.1%) | 3 (7.3%) | 4 (10.3%) | 0 | 1 (1.8%) | 0 |
| | Low T3, low/low-normal FT4 and low TSH (5.1%) | 2 (4.9%) | 5 (12.8%) | 1 (2.2%) | 1 (1.8%) | 1 (6.7%) |
| | High FT4, low/normal T3 and normal TSH (4.6%) | 0 | 1 (2.6%) | 1 (2.2%) | 2 (3.6%) | 2 (13.3%) |
| Thyrotoxicosis (8.2%) | | 6 (14.6%) | 3 (7.7%) | 2 (4.3%) | 4 (7.3%) | 1 (6.7%) |
| Overt thyrotoxicosis (1.5%) | High FT4 and/or high T3 and low TSH | 1 (2.4%) | 0 | 1 (2.2%) | 1 (1.8%) | 0 |
| Subclinical thyrotoxicosis (6.6%) | High-normal FT4 and low TSH | 5 (12.5%) | 3 (7.7%) | 1 (2.2%) | 3 (5.5%) | 1 (6.7%) |
| Hypothyroidism (4.1%) | | | | | | |
| Overt hypothyroidism (0.5%) | High TSH and low FT4 | 0 | 0 | 0 | 1 (1.8%) | 0 |
| Subclinical hypothyroidism (3.6%) | High TSH and normal FT4 | 0 | 1 (2.6%) | 1 (2.2%) | 4 (7.3%) | 1 (6.7%) |

Normal ranges; FT4 0.9–1.7 ng/dL (low < 0.9 ng/dL, low-normal <1.3 ng/dL, high-normal>1.3 ng/dL, high > 1.7 ng/dL), T3 80–200 ng/dL (low < 80 ng/dL, high > 200 ng/dL), TSH 0.3–4.2 μIU/mL (low<0.3 μIU/mL, high> 4.2 μIU/mL).

## NTIS patterns

The prevalence of hypotriiodothyroninemia (low T3) levels was significant higher in ICU patients (70.0%) compared to ward patients (45.5%) and outpatients (6.7%), $P < 0.001$. The proportion was comparable between ICU C+ and ICU NC patients (68.3% vs 71.8%, respectively) and between Ward C+ and Ward NC patients (41.3% vs 49.1%). As expected, isolated low T3 was the most frequently encountered abnormality, whereas patters consistent with more severe disease, such as low FT4 levels and/or low TSH levels where observed mainly in the ICU patients. In a few patients FT4 levels slightly above the normal range with normal TSH were encountered. Thyroglobulin levels in these patients were 16.0 ± 12.7 ng/mL.

## Thyrotoxicosis

Thyroid hormone abnormalities consistent with either overt or subclinical thyrotoxicosis were seen in 11.3% of the ICU patients (14.6% in the COVID-19 positive patients and 7.7% of the non-COVID-19 patients, $P$=NS) and 6.0% of the ward patients (4.4% in the COVID-19 positive patients and 7.3% of the non-COVID-19 patients, $P$=NS). Overt thyrotoxicosis was observed in 2.4% of ICU C+ patients and 2.2% of Ward C+ patients, in none of the ICU NC, 1.8% of the Ward NC and none of the Outpatient C+ groups (all $P$=NS). Overall, both overt and subclinical thyrotoxicosis was observed in 8.8% of all SARS-CoV-2 positive patients and 7.4% of the SARS-CoV2 negative patients. Of note, in SARS-CoV-2 positive patients with negative anti-Tg, high thyroglobulin (100 ng/mL) was observed in only one patient with low T3 but normal FT4 and TSH levels. There was no difference in thyroglobulin levels between SARS-CoV-2 positive patients with low and those with higher TSH (11.7 ± 3.5 ng/mL vs 16.4 ± 2.0 ng/mL, $P$=NS). Thyroglobulin levels in SARS-CoV-2 positive patients with either overt or subclinical hyperthyroidism were not different to those with normal thyroid function

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test or those with patterns compatible with NTIS (14.5 ± 12.6 ng/mL vs 13.6 ± 11.9 ng/mL vs 18.3 ± 20.3 ng/mL, respectively, $P$ = NS).

### Hypothyroidism

Of note hypothyroidism (overt or subclinical) was infrequent.

### Outcome of thyroid function tests in patients with a thyrotoxicosis pattern

One patient with overt thyrotoxicosis from the Ward NC group was subsequently diagnosed with toxic multinodular goiter and was started on thiamazole. In 8 (2 overt and 6 subclinical) of the remaining 15 patients with a thyrotoxicosis pattern thyroid function tests during follow up were available. In these patients, TSH levels increased (from 0.13 ± 0.08 μU/mL to 1.70 ± 1.59 μU/mL, $P < 0.01$), FT4 levels decreased (from 1.47 ± 0.23 ng/dL to 1.09 ± 0.23 ng/dL, $P < 0.01$) and T3 levels remained unchanged (95.73 ± 65.65 ng/dL to 66.24 ± 18.93 ng/dL, $P$ = 0.25).

## Discussion

Our study, along with the studies reported in Table 1, examined the prevalence of thyroid function abnormalities in critically and non-critically ill patients with COVID-19, a clinical setting that is different from published cases of COVID-19-related typical subacute thyroiditis. The main finding from this observational study, is that thyroid hormone abnormalities are encountered in a significant proportion of patients, both critically and non-critically ill, irrespective of underlying SARS-CoV-2 infection. The most common abnormality was that of non-thyroidal illness syndrome (NTIS). In particular, patterns associated with thyrotoxicosis were observed in 8.2% of the whole cohort. Although the prevalence of thyrotoxicosis in SARS-CoV-2 positive patients admitted in the ICU was almost twice that in the SARS-CoV-2 negative ICU patients, the difference was not statistically significant. The rates of thyrotoxicosis were similar between non-critically ill patients with and without COVID-19. Of note, we did not find evidence of destructive thyroiditis in patients with thyroid function tests suggestive of thyrotoxicosis.

In our cohort, the prevalence of thyroid hormone abnormalities increased with increasing disease severity. Thus, more than 2/3 of outpatients had normal thyroid function tests compared to half of the non-critically ill hospitalized patients and less than 1/3 of the patients admitted in the ICU. Non-thyroidal illness syndrome patterns were the most frequently observed alteration, occurring in more than half of the patients in the ICU and about 1/3 of the patients in the ward. These percentages are similar to those reported previously in critically and severely ill patients (23, 25). When comparing, however, patients with and those without SARS-CoV-2 infection we did not find significant differences in the prevalence of thyroid hormone abnormalities, indicating that the most important factor is the severity of illness. This is in agreement with previous reports on COVID-19 patients (15, 17, 19) who observed an inverse relationship between TSH and T3 levels and clinical severity. Two of these studies (15, 17), however, did not include control groups and reported only on the mean hormone levels with no description of the prevalence of specific patterns. Chen *et al.* (19) reported a significant (56%) proportion of subnormal TSH levels, compared to controls, in patients with COVID-19. It should be noted that more than half of these patients were on corticosteroids, known to lower TSH levels (27). In fact, the prevalence of low TSH levels in subsequent studies is considerably lower, ranging between 5.4% and 34%, being higher in the more severe cases (Table 1). Two recent studies (20, 21) reported thyroid hormone alterations compatible with NTIS in around 15% of the patients; these studies included mostly non-critically ill patients, explaining the lower incidence of NTIS compared to our observations. Non-thyroidal illness syndrome represents a constellation of thyroid function abnormalities including not only low T3 levels but often, usually in more severe or prolonged cases, low T4/FT4 levels and low TSH levels (23, 28). Moreover, several of the commonly used medications in the ICU, such as glucocorticoids, dopamine or heparin, may affect or interfere with the thyroid function tests (27). Therefore, the interpretation of thyroid hormones during illness and the differentiation of NTIS from primary thyroid disorders can frequently be challenging (29). Of special interest is the postulation that the new coronavirus SARS-CoV-2 may cause thyroiditis. Several reports described patients with SARS-CoV-2 infection and transient thyrotoxicosis attributed to subacute thyroiditis (7, 8, 9, 10, 11, 12, 13). So far, two cohort studies (16, 18) have focused specifically on this presumption. In the study by Muller *et al.* (18) they reported a rate of thyrotoxicosis among critically ill patients with COVID-19 of 15.3%, similar to what we observed (14.6%). However, in this study, the rate of thyrotoxicosis among critically ill patients without COVID-19 was

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substantially low (1.3%), as well as among non-critically ill patients with COVID-19 (2.4%), compared to our observations (7.7% and 4.3%, respectively). The reason for this difference is not obvious. It should be noted, however, that Muller *et al*. used a historical control group, whereas we included confirmed SARS-CoV-2 negative patients who were admitted and evaluated during the same period with our SARS-CoV-2 positive patients. In the study by Lania *et al.* (16) the reported rate of thyrotoxicosis was even higher (20.2%). This study included only non-critically ill SARS-CoV-2 positive patients with 74.6% of them having normal TSH values; in fact, FT4 and T3 were only measured in the subgroup of 73 patients with abnormal TSH. Also, there was no control group. The authors considered a low TSH value as indicative of thyrotoxicosis; overt when FT4 levels were above the reference range and subclinical when FT4 levels were within the reference range. Thus, one difference from our study is that we did not classify all patients with low TSH values (19.5% in the ICU patients and 6.5% in the ward patients) as having thyrotoxicosis but stratified patients with low TSH levels and FT4 levels that were lower than the mid-range level in the NTIS group. In this line, we observed a negative correlation between FT4 and IL-6 levels, possibly due to more severe NTIS with more pronounced inflammatory response and more severe disease (30). Another possible confounding factor is the timing of blood sampling. We aimed at assessing thyroid function at the time of admission and excluded patients who were already on possible interfering medications (glucocorticoids, amiodarone and heparin) whereas in the study by Lania *et al.* 51.7% of the patients with thyrotoxicosis were on thromboprophylaxis with low-molecular-weight heparin, known to cause an artifact that increases FT4 levels (27), before assessment of thyroid function. In a recent study by Khoo *et al.* (20), none of the patients presented with overt thyrotoxicosis, whereas a pattern suggestive of subclinical thyrotoxicosis was observed with similar frequency between COVID-19 positive and COVID-19 negative patients (Table 1), in agreement with our results. Of note, the authors interpret their results more in the context of NTIS rather than thyrotoxicosis. Regional differences in nutritional iodine sufficiency/deficiency (31, 32, 33, 34, 35) or the (possible) seasonality of thyroiditis/subacute thyroditis (36, 37, 38, 39, 40) may also account for the disparities among studies.

The mechanism of COVID-19-related thyroiditis remains largely unknown. It has been suggested that it is a form of subacute thyroiditis similar to that observed after other viral infections of the upper respiratory system. In fact, the reported clinical, biochemical and imaging features in the published case reports supported the notion that it is a form of 'subacute like' destructive thyroiditis, possibly caused by direct invasion of the thyroid tissue by the SARS-CoV-2 through the abundance of ACE2 receptors. In our patients with thyrotoxicosis, however, thyroglobulin levels were well within the normal range and comparable to the other patients, arguing against a 'destructive' mechanism of thyroiditis (41). In order to avoid potential interference in Tg measurement, we excluded patients with positive anti-Tg antibodies. Even low anti-Tg antibodies concentrations, however, may still affect the results of Tg measurement (42, 43). Recently, TgAbs of IgM class (44) have been detected in subacute thyroiditis and may serve as a diagnostic marker of destructive thyroiditis. Thyroid uptake and ultrasound would be more informative; these tests, however, were not performed due to practical constraints. Another hypothesis is that the activation of the immune system and the circulation of cytokines may trigger thyroiditis by yet unknown mechanism. Alternatively, based on data from the previous coronavirus pandemic caused by the SARS-associated coronavirus (SARS-CoV), involvement of the pituitary gland may be responsible for the low TSH, as part of central hypothyroidism (45).

Importantly, the course of 'thyrotoxicosis pattern' in our cohort, as well as in all previous studies, is quite mild, shot-lasting and self-limited. Besides, the current guidelines advocate the use of dexamethasone in most severely ill patients with COVID-19, which probably covers thyroiditis as well.

Our study provides a comprehensive description of all possible thyroid alterations in patients with and those without COVID-19 and several degrees of severity. Most previous studies included cohorts that were unselected for severity. We opted to examine severity subgroups separately. This, however, narrowed the number of the included subjects in each subgroup, and we cannot rule out the possibility that larger numbers would result in statistically significant differences in the incidence of thyroid disorders in COVID-19 positive subjects. A limitation of this study is that we focused on recording data on medications and comorbidities related to thyroid function, but we did not gather detailed data on the past medical history for all subgroups.

In the previously published studies, there is a great variation in the reported incidence of thyrotoxicosis ranging from 5.4 to 34%. As already discussed, this can be attributed to differences in the definitions of thyrotoxicosis, the hormonal tests performed (not all previous studies measured FT4 and T3, or FT3, levels to

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all subjects), the studied population (critical ill vs non-critically ill subjects), the timing of assessment with regards to the course of the disease. Also, medications that potentially interfere with thyroid hormone measurements were not an exclusion criterion for some studies.

We carefully selected our cohorts, attempting to avoid possible confounding factors (such as medications or pre-existing thyroid disorders) and measured TSH levels as well as FT4 and T3 levels in all patients, at variance to the previous studies that measured FT4 and T3 only in those with abnormal TSH levels (16, 18). Another strength of our study is the measurement of Tg levels, as a marker of thyroiditis (41) and, also, IL-6 levels. Given that thyroid hormone abnormalities are quite common and multifarious in ill patients, we included appropriate control groups in order to evaluate whether there is a specific impact of SARS-CoV-2 on thyroid function. Our results indicate that thyrotoxicosis affects a number of patients, although this is not limited only to SARS-CoV-2 infected patients. On the other hand, NTIS is common and relates to the severity of the illness. Thus, the routine evaluation of the thyroid function in hospitalized patients with COVID-19 may cause uncertainty or result in unnecessary investigations or treatment, and it should better be reserved for those patients with pertinent symptoms or signs.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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