

# Thyroid Dysfunction in COVID-19

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## Abstract

**Objective:** The aim of this study was to evaluate thyroid dysfunction in COVID-19 and study its association with disease severity in COVID-19. **Methods:** Patients with confirmed COVID-19 infection who were admitted to dedicated COVID hospital were recruited over 3 months period. Those with pre-existing thyroid disease were excluded. The thyroid function tests were performed and correlated with interleukin-6 levels. **Results:** A total of 164 patients (14 children) with mean(SD) age 53.85 (19.54) years were recruited. The proportion of patients with mild, moderate and severe disease were 22 (13.4%), 78 (47.6%) and 64 (39.0%), respectively, among which 12 (54.5%), 56 (71.8%) and 43 (67.2%) patients had thyroid dysfunction, respectively;  $P = 0.309$ . Eighty eight (53.7%) had sick euthyroid (84 had low ft3 only), 14 had overt hypothyroidism and 9 had thyroiditis. Median (IQR) levels of serum ft3 showed significant decline from mild category [4.54 (3.81, 5.27)], to moderate [3.95 (3.67, 4.24)] and severe category [3.56 (3.22, 3.89)];  $P = 0.011$ . Low ft3 had significant risk [odds ratio (95% CI)] of death [2.634 (1.01, 6.87);  $P = 0.031$ ] and elevated IL-6 [2.575 (1.084, 6.118);  $P = 0.021$ ]. **Conclusion:** Sick euthyroid was seen in the majority of patients hospitalized with COVID. Low ft3 was associated with death and increased inflammation, suggesting poor prognosis.

**Keywords:** Hypothyroidism, IL-6, inflammatory marker, sick euthyroid, thyroiditis

## INTRODUCTION

Thyroid gland is the largest endocrine gland in the body which can get directly affected during systemic illnesses including viral infections. The state of sick euthyroid syndrome or low T3 syndrome describes thyroid dysfunction associated with systemic illnesses and is characterized by low T3 levels with normal TSH levels. This results from both central and peripherally mediated processes to decrease the catabolism in the body during an acute illness.<sup>[1,2]</sup> Overall, this condition is considered as an adaptive response of the body during acute illness, however, becomes pathological if prolonged. Most studies have reported an association between low T3 and poorer outcomes, highlighting it to be a worrisome condition.<sup>[3]</sup> In addition, subacute thyroiditis is also reported after a viral infection.<sup>[1]</sup>

Both sick euthyroid and subacute thyroiditis were documented in patients with severe acute respiratory syndrome (SARS) epidemic which occurred in 2002.<sup>[4,5]</sup> Coronavirus 2 (SARS-CoV-2) can invade the human tissue cells through the cell receptor of angiotensin-converting enzyme 2 (ACE2). The thyroid gland tissue shows high ACE2 expression, which has been associated with immune signatures making the thyroid

gland a possible target of SARS-CoV-2.<sup>[5]</sup> Few studies among COVID-19 patients have shown an association of thyroid dysfunction with clinical severity and poorer outcomes.<sup>[6]</sup>

The varied manifestations of thyroid dysfunction make it necessary to evaluate the thyroid hormonal profile in children and adults hospitalized with COVID-19. The objectives of this study were to estimate the proportion of thyroid dysfunction in hospitalized patients with COVID-19 infection; and to study the correlation between TSH, ft3, and ft4 with inflammatory disease markers.

## METHODS

This was a cross-sectional analytical study, conducted in the department of Pediatrics, Medicine and Biochemistry

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at a tertiary level hospital which was a dedicated COVID hospital during the pandemic. The study was conducted from September 2020 to December 2020 after informed consent from the participants/guardians. The study was approved by Institutional Ethics Committee.

Both children (age >12 months) and adults with COVID-19 infection diagnosed on RT-PCR on a nasopharyngeal or oropharyngeal swab, and with symptoms of COVID-19 like fever, malaise, myalgia, shortness of breath, difficulty breathing, anosmia, diarrhea or vomiting were enrolled. Any subject with pre-existing thyroid disorder (irrespective of medication intake) was excluded.

The demographic details of the patients were recorded at admission. The severity of COVID infection was assessed using the National early warning score (NEWS) which scored the following: respiratory rate, oxygen saturation and need of oxygen, systolic blood pressure, heart rate, consciousness and temperature. The maximum score was 10 and score of 0-4, 5-7 and >7 was graded as mild, moderate and severe, respectively.<sup>[7,8]</sup> All patients were managed as per national guidelines for management of COVID-19.<sup>[9]</sup> Patient's outcome as discharge or death was recorded.

A blood sample was collected coinciding with the timing of routine blood sampling in first 24 hours of hospitalization. The serum was separated and processed the same day for serum-free thyroxine (fT4), free triiodothyronine (fT3), thyroid-stimulating hormone (TSH) and inflammatory markers. The thyroid profile was assayed on fully automated integrated clinical chemistry and immunoassay analyzer- Vitros 5600 (Johnson and Johnson, USA) using commercially available assay kits. The normal ranges of these were TSH: 0.465- 4.68 mIU/L, fT3: 4.3-8.1 pmol/L and fT4 12-22 pmol/L. Among inflammatory markers, interleukin-6 was measured depending on the availability of the kit where a value of <7 pg/mL was considered as normal and a three times elevation was considered raised.

Thyroid dysfunction was defined as central hypothyroidism with low fT4 and low TSH values; sick euthyroid if low fT3 with/without low fT4 and normal TSH; thyroiditis with elevated fT3 and/or fT4 with suppressed TSH; subclinical hypothyroidism with normal fT4/fT3 and elevated TSH (5-10 mIU/L) and overt hypothyroidism if low fT4/fT3 with elevated TSH >10 mIU/L. Patients who were detected with overt hypothyroidism were treated with oral thyroxine as per standard treatment protocol. Patients with clinical and biochemical evidence of subacute thyroiditis were continued on steroids which were being administered as part of treatment for COVID-19.

### Sample size

Considering an odds ratio of 4.9 based on earlier study,<sup>[10]</sup> for occurrence of severe COVID among those with thyroid dysfunction than those with normal thyroid function with an alpha error as 5% and power 80%, a total of 145 patients were required.

### Statistical analysis

Data were collected and analyzed using SPSS version 23. The continuous data (TSH, fT3, fT4, CRP, IL6) were represented as mean (standard deviation)/median (IQR) and were compared between three disease severity groups using ANOVA with Bonferroni (Post-hoc) analysis. Student's *t*-test and Mann-Whitney *U* test was used to compare fT3/fT4 and TSH, respectively between those with normal or raised IL-6 levels. Categorical variables (proportions) were analyzed using the Chi-square test. Correlation between IL-6 and thyroid hormones was measured using Spearman's correlation coefficient (*r*) for non-parametric data. A *P* value of <0.05 was taken as significant.

### RESULTS

A total of 185 (14 children) subjects were screened during the study period out of which 10 had a pre-existing thyroid disorder, 9 had incomplete laboratory reports, and 2 had incomplete clinical details that were excluded to finally enroll 164 subjects. The mean (SD) age was 53.85 (19.54) years with 107 (63.7%) males. The proportion of patients with mild, moderate, and severe COVID disease was 22 (13.4%), 78 (47.6%), and 64 (39.0%), respectively.

Table 1 shows the thyroid profile of enrolled patients of which 111 (67.7%) had abnormal thyroid profile (11/14 children). Eighty eight (53.7%) had sick euthyroid with median (IQR) fT3 levels 3.04 (2.5, 3.54) nmol/L, fT4 15.05 (11.75, 18.38) nmol/L and TSH 1.02 (0.497, 2.048) IU/L. Eight four (95.5%) of those with sick euthyroid had low fT3 only, while only 4 (4.5%) had isolated low fT4. Fourteen (8.53%) patients were detected with hypothyroidism (9 overt, 5 subclinical) with mean (SD) fT4 13.57 (4.0) pmol/L and TSH 8.39 (2.46) mIU/mL. Nine (5.5%) had thyroiditis with median (IQR) fT4 levels of 26.5 (24.1, 30.9) pmol/L and TSH 0.44 (0.09, 2.41) mIU/mL. No patient reported neck pain or discomfort during hospitalization.

The proportion of patients with abnormal thyroid profile across mild, moderate and severe disease severity categories were 12 (54.5%), 56 (71.8%) and 43 (67.2%), respectively; *P* = 0.309. The proportion of patients with sick euthyroid among mild, moderate and severe category were 8 (36.4%), 43 (55.1%) and 37 (57.8%); *P* = 0.213. Table 2 compares the thyroid function

**Table 1: Thyroid function tests in patients with COVID-19 (n=164)**

Parameter	Median (IQR)	Range (Minimum-Maximum)
Free tri-iodothyronine, pmol/L	3.69 (2.92, 4.73)	1.48-9.29
Free thyroxine, pmol/L	16.2 (13.05, 19.35)	5.81- 34.3
TSH, mIU/mL	1.335 (0.503, 2.945)	0.015-14.3
*Serum interleukin-6, pg/mL	5.05 (0.53, 21.68)	0.0-1399.70

\*n = 152

**Table 2: Thyroid profile according to NEWS category of disease severity**

Parameter	Mild: NEWS score 0-4 (n=22)	Moderate: NEWS score 5-7 (n=78)	Severe: NEWS score >7 (n=64)	P value
*Free tri-iodothyronine, pmol/L	4.54 (3.81, 5.27)	3.95 (3.67, 4.24)	3.56 (3.22, 3.89)	0.011
Free thyroxine, pmol/L	16.48 (14.37, 18.59)	16.83 (15.62, 18.04)	15.90 (14.74, 17.07)	0.549
TSH, mIU/mL	1.88 (1.04, 2.72)	2.37 (1.78, 2.96)	1.90 (1.34, 2.45)	0.442
**Serum interleukin-6, pg/mL	9.55 (0.42, 18.68)	17.32 (9.14, 25.50)	76.33 (19.66, 133.01)	0.040

Data expressed as mean (95% CI); \*n=16, 75 and 61 respectively; \*P<0.05 between group A and C on Post-Hoc tests

tests across disease severity categories. Patients with severe disease had higher but insignificant odds of low ft3 (1.859, 95% CI 0.949-3.64);  $P = 0.097$ . Low ft3 had significant risk [odds ratio (95% CI)] of death [2.634 (1.01, 6.87);  $P = 0.031$ ] and elevated IL-6 [2.575 (1.084, 6.118);  $P = 0.021$ ].

A comparison of age and thyroid function tests in patients with elevated and normal IL-6 is shown in Table 3. The correlation between IL-6 levels with ft4 was significant ( $r = 0.186$ ,  $P = 0.022$ ), with ft3 and TSH showed poor correlation ( $r = -0.03$ ;  $P = 0.76$ ; and  $r = 0.002$ ,  $P = 0.98$ ), respectively. The odds ratio (95% CI) for death in those with elevated IL-6 levels was 2.346 (1.01, 5.47);  $P = 0.041$ .

## DISCUSSION

The present study reported a significant proportion of sick euthyroid syndrome (predominantly low ft3) in patients with COVID-19 infection, which was similar across different disease severity categories of COVID. The low ft3 levels had a significantly higher risk of death and severe inflammation (raised IL-6 levels).

A recent meta-analysis among COVID-19 patients strongly predicted severe COVID-19 disease among those with thyroid abnormalities with OR (95% CI) of 2.46 (1.32, 4.66).<sup>[6]</sup> The present study also had an insignificantly higher proportion of thyroid dysfunction in moderate/severe disease than mild disease. However, a higher overall incidence of thyroid dysfunction was seen in this study as majority of patients had moderate to severe COVID-19, unlike earlier studies which had lower incidence among patients, majority of whom had mild disease.<sup>[11]</sup>

The ft3 levels were lowest in severe disease category in the present study as was also seen earlier in COVID-19 infection.<sup>[11-15]</sup> Persistent low T3 levels may have a deleterious effect on clinical recovery as seen among critically sick hospitalized children and adults.<sup>[1,16]</sup> Sick adults admitted in ICU showed increased risk of mortality with low T3 levels,<sup>[17-19]</sup> as also seen in the present study. However, most patients with low T3 including children recovered spontaneously without the need for thyroxine (LT4) supplementation.<sup>[18,19]</sup> No patient with COVID-19 and non-thyroid illness received thyroxine in the present study as also recommended by the Indian Endocrine society.<sup>[20]</sup>

A cytokine storm is implicated in thyroid disruption in illness. Mild disease states are usually associated with low ft3 with

normal ft4 and TSH, while moderate disease states are associated with low ft3, elevated ft4 and reverse T3 with normal or depressed TSH levels. Gradually, with an increase in severity of disease, the TSH pulsatility is lost to result in depressed ft3 and ft4 levels in the state of adaptability.<sup>[21]</sup> Cytokine storm also accompanies COVID-19 infection where a significant association between ft4 and IL-6 levels was seen in this study suggesting ft4 toxicosis in moderate to severe disease.<sup>[22,23]</sup> The levels of ft4 were not concomitantly low as ft3 in those with sick euthyroid syndrome in the present study, similar to an earlier report.<sup>[23]</sup> The patients with SARS-Cov2 thyroiditis had tested negative for thyroid autoantibodies with an increased risk of thrombo-embolic phenomenon earlier,<sup>[22]</sup> the details of which were however, not available in the present study.

An association between elevated inflammatory markers and thyroid dysfunction has been earlier reported.<sup>[23]</sup> Those with elevated CRP levels and elevated interleukin-6 levels were more likely to have more severe disease.<sup>[24-26]</sup> A higher inflammatory response has been reported in COVID-19 patients with thyroid dysfunction earlier,<sup>[15]</sup> as also observed in the present study.

The main drawback of the study was lack of follow-up of patients detected with thyroid abnormality. This was not possible as the hospital was only catering to inpatient services for COVID during the pandemic without any outpatient services. The objective information on need for mechanical ventilation, inotropes and other co-morbidities was not collected. Also, thyroid autoimmunity and reverse T3 could not be assessed in the affected patients. However, this study reports thyroid abnormality in a large sample with association to clinical severity and IL-6 as an inflammatory marker.

To conclude, thyroid dysfunction with sick euthyroid syndrome was seen in the majority of patients hospitalized with COVID-19 with a possible indolent ft4 thyrotoxicosis. Low ft3 levels predicted mortality suggesting the need to monitor thyroid function tests in patients with elevated IL-6 levels and severe COVID-19 infection.

## Ethics approval

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**Table 3: Comparison of variables based on serum IL-6 levels**

Parameter	IL-6 <21 pg/mL (n=113)	IL-6 ≥ 21 pg/mL (n=39)	P value
Age, years	54.89 (17.6)	61.36 (14.2)	0.036
<sup>ab</sup> Serum interleukin-6, pg/mL	2.2 (0.0, 6.15)	65.4 (32.7, 141.2)	<0.001
Free tri-iodothyronine, pmol/L	3.88 (1.28)	3.65 (1.26)	0.317
Free thyroxine, pmol/L	16.23 (4.67)	17.33 (5.9)	0.302
<sup>ab</sup> TSH, mIU/mL	1.51 (0.50, 3.22)	1.13 (0.58, 2.12)	0.606

Data expressed as mean (SD) or <sup>a</sup>median (IQR); <sup>b</sup>Mann–Whitney U test

### Conflicts of interest

There are no conflicts of interest.

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