journal homepage: https://jablm.acclmp.com/

Journal of Applied Biochemistry & Laboratory Medicine (2022) 03 (1):7-14

Original Research article

Thyroid hormone abnormalities associated with severity of acute COVID-19

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Keywords:
COVID-19, Non-Thyroidal Illness syndrome, Interleukin 6

How to cite this article
Parul C , Kundan K , Saurabh J , Souvik M , Yashdeep G , Datta SK. Thyroid hormone abnormalities associated with severity of acute COVID-19. Journal of Applied Biochemistry &Laboratory Medicine 2022; 03 (1):7-14.
Access link for this article
https://jablm.acclmp.com/2022/03/01_7-14.pdf

ABSTRACT

Background:
COVID-19 may cause thyroid dysfunction (both thyrotoxicosis or hypothyroidism). However, the understanding of effect of COVID-19 on thyroid is still evolving due to limited data. Hence, we aimed to evaluate the prevalence of thyroid dysfunction in participants with COVID-19 and further studied correlation of thyroid tests with IL-6 levels and clinical parameters.

Methodology:
In this cross-sectional study, serum samples collected from RT-PCR confirmed COVID-19 cases were analyzed for levels of total thyroxine (TT4), total triiodothyronine (TT3) and Thyroid Stimulating hormone(TSH). Subgroups were made on basis of IL-6 levels and clinical details including admission to ICU, use of mechanical ventilator and mortality.

Results:
Overall, 54/105 cases (51.4%) had findings suggestive of Non thyroidal Illness syndrome (NTIS) and 17/105 (16.2%) were euthyroid. 15.2% participants had thyroid profile as seen in subclinical hypothyroidism or recovery from NTIS. Rest of the 17.2% participants had isolated derangement of either of the three TT3, TT4 or TSH. In the subgroup analysis, levels of TT3 and TT4 showed a negative correlation with serum concentration of IL-6. Subjects on ventilator support and those having mortality due to COVID-19 had significantly lower levels of TT3 and TT4 than their counterparts.

Conclusions:
An abnormality in thyroid profile may be seen in COVID-19 infection in cases with high levels of inflammatory markers and a severe disease. Majority of the cases included, presented with NTIS and a small percentage had other derangements in the thyroid profile. Therefore, long term implications of these derangements in need to be studied.

INTRODUCTION

Novel coronavirus disease 2019 (COVID- 19) is caused by a single stranded RNA virus. It is also termed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as it has got a high sequence similarity (~80%) with the gene of SARS-CoV. It is a matter of great concern being highly contagious causing rapid community transmission, having high virulence, and sustained surface viability. It is a serious viral infection with new manifestations being recognized and reported frequently. The spectrum of presentation of COVID-19 varies from asymptomatic cases, to mild flu-like symptoms, including high fever, to severe respiratory illness. Critical cases may go into rapid respiratory deterioration, septic shock that may lead to multiple organ failure. Manifestations of multiple organs or systems are being reported, such as cardiovascular, urinary, gastrointestinal and endocrine system. [1] Worldwide research is focused on better understanding of its characteristics and associated complications. Its effect on thyroid hormones is unclear and has not been studied widely. Pathogenesis of COVID-19 is due to entry of SARS-CoV-2 via respiratory system and lodgment in lung parenchyma.

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The entry of the virus into cells relies on binding to ACE2 receptor followed priming of the viral spike protein, by the transmembrane serine protease TMPRSS2, which is necessary for the viral RNA to enter the cell. Apart from pneumocytes the virus can interact with ACE2 expressed in other tissues. Expression of these receptors in the thyroid gland [2,3] is even more than in the lungs. [4] Other than effects due to direct invasion, there is a role of acute immune response leading to high levels of inflammatory cytokines specially IL-6 leading to thyroid dysfunction. These cytokines cause alterations in the regulation of hypothalamus- pituitary-thyroid (HPT) hormones axis, production, transport, activity and metabolism of thyroid hormones. [5,6] Hence, it is important to evaluate thyroid dysfunction in COVID-19. Therefore, we aimed to study the thyroid function profile in subjects with COVID -19 and correlation of these thyroid tests with IL-6 levels and clinical parameters.

Methods:

This cross sectional study was carried out at a tertiary care hospital, Delhi, India. Serum samples from 105 confirmed COVID-19 positive subjects admitted to the COVID ward were collected and sent to the laboratory for thyroid function tests and IL-6 levels. Inclusion criteria: Adult subjects who were positive by RT-PCR on nasal and pharyngeal swab specimens were included in the study. Their serum samples were collected within 3 days of COVID positivity. The results of their laboratory investigations and clinical details were noted. Exclusion criteria: Subjects who were tested COVID negative or having previous history of abnormal thyroid function tests, recent surgery or any other prolonged illness were excluded on the basis of their clinical details and previous reports.

Serum total thyroxine (TT4), total triiodothyronine (TT3), Thyroid Stimulating hormone (TSH) and interleukin-6 (IL-6) levels were measured by chemiluminescence using Beckman Coulter Unicel DxI 800 Access Immunoassay system (Beckman Coulter, Brea, CA, USA). Routine quality control was done as per accepted guidelines. Any deviation from normal reference range was considered as abnormal thyroid results. The samples were sub-grouped on the basis of (i) IL-6 levels (pg/mL) into three categories (IL-6 <15; IL-6=15 to 1500; IL-6>1500); On the basis of clinical details during illness due to COVID-19 as (ii) admitted to ICU or not; (iii) used ventilator support or not; and on the basis of (iv) outcome as survival or death.

Ethical approval for the study was obtained by institutional ethical committee (Ref no. IECPG-111/24.02.2021).

Statistical Methods

Data was analyzed in SPSS version 20. Graphs were plotted on Minitab version19. Levels of serum TT3, TT4 and TSH were compared amongst the subgroups. Since the data for most of the parameters was non parametric, Mann Whitney U test or Kruskal Wallis test was done for intergroup comparison.

Results:

The demographic details of the subjects included in the study showed that the average age of the subjects was 59 ±16 years. The male: female ratio was 1.79 (66 males and 39 females). Supplemental Table 1 shows median and range of serum IL-6 levels and thyroid parameters in the study subjects. On the basis of values of TT3, TT4 and TSH the samples were grouped into clinical categories as shown in Table 1. It was seen that 54 cases out of 105 (51.4%) had findings as seen in non-thyroidal illness syndrome (NTIS) and 17 out of 105 (16.2%) were euthyroid. Next category that included 16 out of 105 (15.2%) cases was of those recovering from NTIS or having subclinical hypothyroidism. 9.6% participants had high levels of serum TT3, 3.8% had low serum TT4. Hyperthyroidism with low TSH and high TT3 and TT4 levels was seen in 2.9% and the remaining cases 0.9% had isolated low TSH levels indicating subclinical hyperthyroidism.

On doing the subgroup analysis (Supplemental Table 2) it was seen that levels of TT3 and TT4 were significantly different between the subgroups of different IL-6 levels (p-value=0.001 for both). The levels of these hormones decreased as the levels of IL-6 increased. Those on ventilator support and those who died due to COVID had significantly lower levels of TT3 and TT4 than those who did not use ventilator support and those who survived respectively. There was no significant difference in the levels of TSH in these sub-groups. The levels of all three hormones were not significantly different among those admitted to ICU and those not admitted to ICU. The box plots showing the distribution of the values of TT3, TT4 and TSH within all the subgroups is as shown in figure 1-4.

Table 1: Clinical categories of cases on basis of levels of thyroid hormones

Clinical category of cases on basis of thyroid profile	**Euthyroid**	**NTIS**	**Hyperthyroid**	**Low TT4**	**High TT3**	**Subclinical Hyperthyroidism**	**Recovery/ Subclinical hypothyroidism**
Number (Percent)	**17 (16.2%)**	**54 (51.4%)**	**3 (2.9%)**	**4 (3.8%)**	**10 (9.6%)**	**1 (0.9%)**	**16 (15.2%)**
Serum TT3	N	L	H	N	H	N	L/N
Serum TT4	N	L/N	N/H	L	N	N	L/N

Serum TSH	N	L/N	L	N	N	L	H

*N: Normal; L: Low; H: High

Fig 1a-1c – Box plots showing the distribution of the values of TT3, TT4 and TSH in subgroups of IL-6 in pg/mL: 1. IL-6<15; 2. IL-6:15-1500; 3. IL-6>1500.

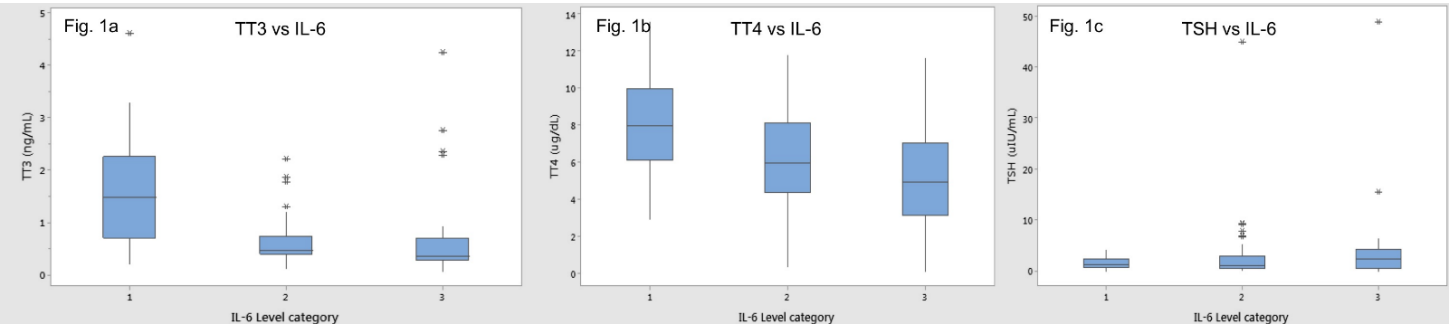


Fig 2a-2c - Box plots showing the distribution of the values of TT3, TT4 and TSH in subgroups on the basis of 0: Not admitted to ICU; 1. Admitted to ICU.

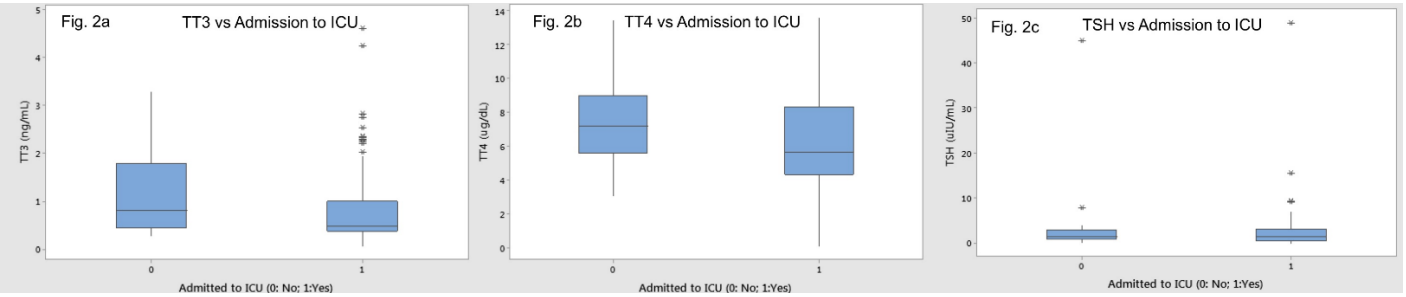


Fig 3a-3c - Box plots showing the distribution of the values of TT3, TT4 and TSH in subgroups on the basis of 0: Not on ventilator support; 1: on ventilator support.

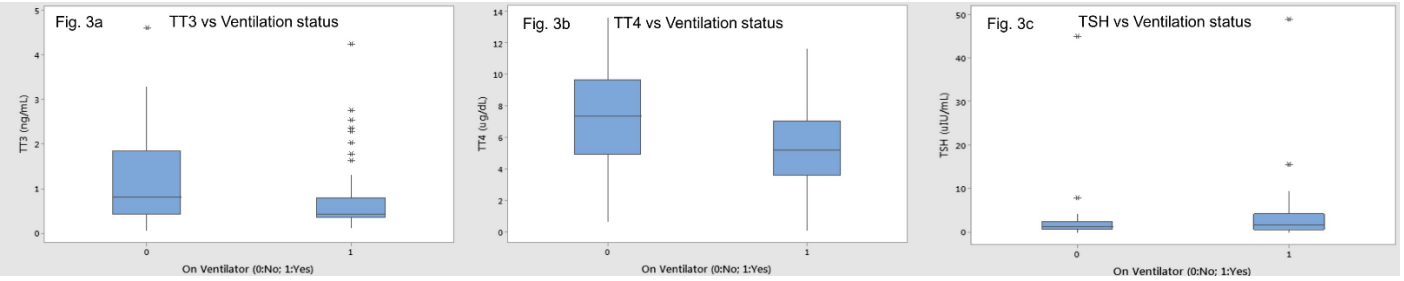
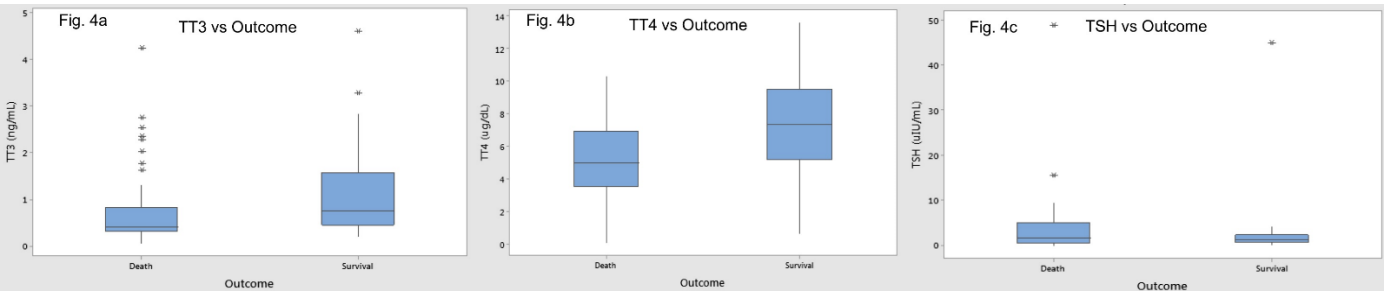


Fig 4a-4c - Box plots showing the distribution of the values of TT3, TT4 and TSH in subgroups on the basis of outcome death and survival of the cases under study.



The percentage of samples having these derangements within each subgroup was calculated and is as shown in table 2. It was seen that 58 out of 75 subjects (77.3%) having IL-6 levels >15pg/mL, had low levels of TT3. With very high values of IL-6 > 1500, 75.9% subjects for TT3, 62.1% for TT4 and 17.2% subjects for TSH had lower than normal results. Higher number of those admitted to ICU and on ventilator support had lower levels of TT3 and TT4 than those not admitted to ICU and not requiring ventilator for mechanical ventilation respectively. TSH was normal in majority of the cases within each subgroup. Also those who died due to COVID had lower levels of TT3 and TT4 than those who survived.

Table 2: Number and percentage of subjects with low, normal or high levels of serum TT3, TT4 and TSH levels in each subgroup n is the total number of samples in each subgroup.

TT3(0.8-2.0 ng/mL)	**Low**	**Normal**	**High**
Total (n=105)	67(63.8%)	23(21.9%)	15(14.3%)
IL-6 <15 pg/mL (n=30)	9(30%)	11(36.7%)	10(33.3%)
IL-6 15-1500 pg/mL (n=46)	36(78.3%)	9(19.5%)	1 (2.2%)
IL-6 >1500 pg/mL (n=29)	22(75.9%)	3(10.3%)	4(13.8%)
Not admitted to ICU (n=22)	11 (50%)	8 (36.4%)	3(13.6%)
Admitted to ICU (n=83)	56 (67.5%)	15 (18.1%)	12 (14.4%)
Not on ventilator (n=48)	24 (50%)	15 (31.2%)	9 (18.8%)
On Ventilator (n=57)	43 (75.5%)	8 (14%)	6 (10.5%)
Death (n=51)	38 (74.5%)	7 (13.7%)	6 (11.8%)
Survival (n=54)	29 (53.7%)	16 (29.6%)	9 (16.7%)
TT4(5.1-14.1 µg/dL)	**Low**	**Normal**	**High**
Total (n=105)	40(38.1%)	65(61.9%)	0
IL-6 <15 pg/mL (n=30)	5(16.7%)	25(83.3%)	0
IL-6 15-1500 pg/mL (n=46)	17(37%)	29(63%)	0
IL-6 >1500 pg/mL (n=29)	18(62.1%)	11(37.9%)	0
Not admitted to ICU (n=22)	5 (22.7%)	17 (77.3%)	0
Admitted to ICU (n=83)	35 (42.2%)	48 (57.8%)	0

Not on ventilator (n=48)	13 (27.1%)	35 (72.9%)	0
On Ventilator (n=57)	27 (47.4%)	30 (52.6%)	0
Death (n=51)	27 (52.9%)	24 (47.1%)	0
Survival (n=54)	13 (24.1%)	41 (75.9%)	0
TSH(0.27-4.2 µIU/mL)	**Low**	**Normal**	**High**
Total (n=105)	11(10.5%)	78(74.3%)	16(15.2%)
IL-6 <15 pg/mL (n=30)	3 (10%)	27(90%)	0
IL-6 15-1500 pg/mL (n=46)	3(6.5%)	34 (73.9%)	9(19.6%)
IL-6 >1500 pg/mL (n=29)	5(17.2%)	17(58.6%)	7(24.2%)
Not admitted to ICU (n=22)	1 (4.5%)	19 (86.4%)	2 (9.1%)
Admitted to ICU (n=83)	10(12%)	59 (77.1%)	14(16.9%)
Not on ventilator (n=48)	5 (10.4%)	41 (85.4%)	2 (4.2%)
On Ventilator (n=57)	6 (10.5%)	37 (64.9%)	14 (24.6%)
Death (n=51)	7 (13.7%)	29 (56.9%)	15 (29.4%)
Survival (n=54)	4 (7.4%)	49 (90.7%)	1 (1.9%)

Discussion:

Infection with COVID-19 may be associated with derangements in thyroid profile. These cases may present with thyrotoxicosis or hypothyroidism or NTIS. [7,8] The pathogenesis seems to be multifactorial. Not enough literature is available to definitively determine of the outcome of thyroid dysfunction in COVID patients.

NTIS was the most commonly found presentation in our study subjects (51.4%) having low levels of serum TT3. As the levels of IL-6 increased, higher number of cases had low TT3 levels. On correlating with clinical severity in terms of use of ventilator support and mortality due to COVID-19, significantly lower TT3 levels were seen in cases on mechanical ventilation and those who died due to COVID. Serum TSH however, did not show any relation to the disease severity.

An over-active immune response due to acute infection leads to the release of pro-inflammatory cytokines, particularly IL-6 causing overt thyroid dysfunction. It leads to disruption of deiodases and thyroid transport proteins, impaired pituitary TSH secretion and ultimately deranged thyroid hormones T3 and T4. The decrease in T3 is mostly inversely proportional to IL-6, described as euthyroid sick syndrome where there is thyroid dysfunction in non- thyroid related conditions. [9,10] T4 may also reduce in these cases. However, despite low T3 and T4 levels, TSH is within normal range in mild to moderate NTI or may be slightly decreased in severe NTIS. In the recovery phase TSH may even rise. [11]

In a study undertaken in China on 50 patients with COVID- 19, similar to our study, a generalized decrease in TSH, TT3 levels and the degree of decrease correlated with their severity. Reversal of these hormonal changes occurred after recovery from COVID-19, a fact that highlights plausible acute/transitory effects of COVID-19 on HPT axis. [11] However, in 34%(17/50) patients only TSH was decreased indicating the effect of COVID-19 on TSH secreting cells via direct viral effect on pituitary, pro-inflammatory cytokines hormonal changes in pituitary endocrine feedback loops. Only TSH low was seen in 1 (0.9%) of our patients. Another factor in COVID patients that can suppress TSH secretion, even at physiological levels is cortisol. Chen *et al*. 2021 were unable to exclude exogenous glucocorticoids given as treatment to these patients as a factor influencing TSH. [12]

In another study by Wang W *et al*. 2021, low TT3 and TSH was found in COVID-19 patients compared to control. Within the group of COVID-19, 61.9% (52/84) patients presented with thyroid function abnormalities. Thyroid dysfunction in severe cases had higher proportion of thyroid derangement than mild or moderate cases. On comparison between COVID-19 and non-COVID-19 pneumonia patients TSH level was significantly lower in COVID-19 cases. [13]

In a cohort study of 456 patients with 334 participants having COVID-19, it was found that patients with COVID-19 had a lower TSH and free T4 at admission compared to those without COVID-19. On follow up of COVID-19 patients, low TSH was seen to recover to its baseline value at follow-up. They did not have any patients with overt thyrotoxicosis, not even in those admitted to intensive care unit using value of TSH < 0.30mU/L and FT4 > 23.0 pmol/L. [14]

In a study, TSH was raised in moderately and critically affected patients of COVID-19 (n=48) as compared to non-COVID-19 (n=28) patients. Also level of TT3 were raised significantly at follow-up in COVID-19 patients than non-COVID-19 patients. On doing a logistic regression it was seen that TT3, IL-6, and procalcitonin were independent risk factors for COVID-19. [15]

Both SARS CoV-1 and 2 use the receptors ACE2 and TMPRSS2 to enter and infect the host cells. Thyroid glands exhibit high mRNA expression in in both sexes. [16] Direct invasion of the virus into thyroid gland may lead to damage of the host cells. This ultimately causes a hyper-immune response leading to the release of pro-inflammatory cytokines and thus the 'cytokine storm'. In the acute phase due to raised cytokines like IL-6 there may be inflammatory destruction of thyroid gland or autoimmune thyroiditis leading to thyrotoxicosis. Evidence of destruction of thyroid follicles and presence of apoptosis in autopsy studies has been reported previously from SARS CoV. [17,18] Few cases of subacute thyroiditis following infection have been reported. [19,20] They present with overt thyrotoxicosis that may be followed by a hypothyroid and later a euthyroid phase. In a report of two cases, infection with COVID-19 has even been known to act as a trigger for new cases or for relapse of previous case of Grave's disease. [21]

Lania *et al.* 2020 reported TSH level below 0.33 mU/L in 20.2% cases and overt thyrotoxicosis in 10.8% of their cohort of 287 patients with COVID-19 who were treated outside intensive care. Serum TSH correlated inversely with higher IL-6 levels. [22] Muller et al. 2020 studied thyroid hormone derangements in COVID patients admitted to Intensive care unit. Overt thyrotoxicosis was reported in higher percentage of patients admitted to high dependency intensive care unit (15%) with COVID-19 as compared those admitted in low-intensity settings (2%). Out of 8 subjects who were followed, 2 developed hypothyroidism and 6 had suppressed levels of serum TSH. [19] In

contrast 4 out of 105 (3.8%) of our study subjects were having low TSH levels with high or normal TT3 and TT4.

Other than thyrotoxicosis, SARS-CoV virus can also produce low thyroid hormones due to either primary thyroid injury or secondary causes through an impaired hypothalamic pituitary thyroid axis leading to thyroid dysfunction. Huang et al. 2020 reported low normal T3, T4, and TSH in COVID-19 without clinically apparent hypothyroidism. [23] Chen T *et al*. 2019 studied 113 deceased and 161 recovered subjects with COVID -19. The deceased patients had significantly lower TSH and free T3 concentrations than in patients who recovered from COVID-19. [24] In another recent study, death and increased inflammation and thus poor prognosis in the hospitalized cases with COVID-19 was more commonly seen to be associated with having low free T3 levels. [8] Previous literature from SARS infection have studies reporting hypocortisolism and central hypothyroidism in survivors. In a study by Leow *et al*. 2005 SARS-CoV survivors were followed up for hormonal alterations 3 months after recovery and noted that 6.7% (4 in number) of the patients had developed biochemical hypothyroidism, one of which developed primary hypothyroidism and three central. The patient with primary hypothyroidism did not recover and required thyroxine replacement even at the end of the study. The other cases of thyroid dysfunction resolved between 3 and 9 months. [25] Similarly, another previous study reported central hypothyroidism due to hypophysitis caused by the cytokine storm. [26]

Ours is a cross-sectional study done to observe the thyroid hormone levels in those affected with COVID-19. However, it had some limitations. The levels of free T3 and T4 in serum could not be measured. Drug history of drugs especially related to glucocorticoid intake that might influence thyroid profile was not available. These need to be correlated with clinical features of the cases to reach at a conclusion. Also we were not able to follow the subjects up to see whether these derangements were transient or permanent.

Conclusions:

An abnormality in thyroid profile may be seen in subjects with COVID-19 infection not having any prior history of thyroid dysfunction particularly at high levels of serum IL-6. Majority of these present with NTIS: T3 reduced, T4/ TSH Normal or reduced. Small percentage may have other thyroid dysfunction including hyperthyroidism or isolated TT3 or TT4 derangements. Significant lowering of TT3 and TT4 was seen to be related to higher IL-6 levels, requirement of ventilator support and mortality as outcome. A good clinical correlation and follow up of these patients for thyroid profile may thus be required to understand the long term implications of these derangements.

Supplemental Tables

Supplemental Table 1: Median and range of serum IL-6 levels and thyroid parameters in the study subjects

	Median	**Range**	**Normal reference ranges**
IL-6 (pg/mL)	500.5	0.6-1624	<15 pg/mL
TT3 (ng/mL)	0.57	0.06-4.61	0.8-2.0
TT4 (µg/dL)	6.18	0.11-13.56	5.1-14.1
TSH (µIU/mL)	1.51	0.05-49	0.27-4.2

Supplemental Table 2: Levels of serum TT3, TT4 and TSH within the subgroups and their comparison

IL-6 levels*	**IL-6 <15 (n=30) Median (Range)**	**IL-6:15-1500 (n=46) Median (Range)**	**IL-6>1500 (n=29) Median (Range)**		**P-value**
TT3 (ng/mL)	1.49 (0.21-4.6)	0.46 (0.13-2.2)	0.36(0.06-4.2)		0.001
TT4 (µg/dL)	7.96(2.9-13.5)	5.94(0.36-11.7)	4.92(0.11-11.6)		0.001
TSH (µIU/mL)	1.32(0.005-4.03)	1.18(0.17-44.98)	2.47(0.02-49)		0.359
Admission to ICU #	**Not admitted to ICU (n=22) Median (Range)**	**Admitted to ICU(n=83) Median (Range)**	**-**	**-**	**P-value**
TT3 (ng/mL)	0.81(0.28-3.29)	0.48(0.06-4.6)	-	-	0.123
TT4 (µg/dL)	7.17(3.09-13.4)	5.67(0.11-13.56)	-	-	0.059
TSH (µIU/mL)	1.53(0.14-44.98)	1.51(0.005-49)	-	-	0.582
Ventilator support #	**Not on ventilator (n=48) Median (Range)**	**On Ventilator (n=57) Median (Range)**	**-**	**-**	**P-value**
TT3 (ng/mL)	0.8(0.06-4.6)	0.43(0.13-4.25)	-	-	0.004
TT4 (µg/dL)	7.35(0.64-13.5)	5.2(0.11-11.6)	-	-	0.001
TSH (µIU/mL)	1.32(0.021-44.9)	1.72(0.005-49)	-	-	0.242
Outcome #	**Death (n=51) Median (Range)**	**Survival (n=54) Median (Range)**	**-**	**-**	**P-value**
TT3 (ng/mL)	0.42(0.06-42.5)	0.75(0.21-4.61)	-	-	0.001
TT4 (µg/dL)	4.9 (0.11-10.3)	7.3 (0.64-13.56)	-	-	0.001
TSH (µIU/mL)	1.73 (0.01-49)	1.37 (0.121-44.98)	-	-	0.296

*Kruskal Wallis test and #Mann Whitney U test done for intergroup comparison

Acknoledgement: Nil

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