

ORIGINAL ARTICLE

## Spectrum of thyroid dysfunctions among hospitalized patients with non-critically ill coronavirus disease 2019: A cross-sectional study

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### ABSTRACT

**Background:** Patients with coronavirus disease 2019 (COVID-19) particularly critically ill patients may present with various thyroid abnormalities. However, data regarding thyroid function tests (TFTs) among noncritical patients with COVID-19 are scarce. This study aimed to assess thyroid functions and their associations with the severity of illness among non-critically ill hospitalized patients with COVID-19.

**Methods:** This cross-sectional study assessed TFTs in 87 (aged 18-65 years) RT-PCR-confirmed COVID-19 patients admitted to a tertiary-care hospital in Bangladesh. Diagnosis of non-critical illness and severity (mild, moderate, and severe) were defined by WHO's interim guidance. Patients having known thyroid dysfunctions or taking drugs that may affect thyroid functions were excluded from the study. Serum TSH, FT4, and FT3 were measured by chemiluminescent immunoassay.

**Results:** Majority of the patients (72%) had normal thyroid function. Among the abnormalities, the highest frequency was isolated hyperthyroxinemia (12.6%) and the rest were subclinical hypothyroidism (6.9%), subclinical thyrotoxicosis (4.6%), thyrotoxicosis (2.3%), isolated tri-iodothyroninemia (1.1%), and hypothyroidism (1.1%). Serum TSH, FT4, and FT3 levels were similar across the spectrum of noncritical illness. No significant correlation was found between the inflammatory markers (C-reactive protein, ferritin, and D-dimer) and TSH levels.

**Conclusions:** More than one-fourth of non-critically ill hospitalized patients with COVID-19 presented with a spectrum of thyroid abnormalities with isolated hyperthyroxinemia being the most common. However, TFTs had no significant associations with the severity of illness among noncritically ill patients with COVID-19.

**Keywords:** coronavirus, COVID-19, thyroid function test, isolated hyperthyroxinemia

### INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a systemic viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its outbreak started in late 2019.<sup>1</sup> It mostly affects the respiratory system causing viral pneumonia and the spectrum of the disease ranges from mild, moderate to severe form, and there is also a critical form of illness.<sup>2</sup> Although the respiratory system shows majority of the manifestations, it has been observed over the past two and half years that it can affect many systems including the endocrine system.<sup>3</sup> The thyroid gland is reported to

be involved in COVID-19 owing to the presence of angiotensin-converting enzyme-2 (ACE-2) receptor expression combined with transmembrane protease serine 2 (TMPRESS2) in thyroid follicular cells thereby facilitating SARS-CoV-2 entry and replication inside the cell.<sup>4</sup> The reported prevalence of thyroid dysfunction varies between 13% to 64%, including thyrotoxicosis and hypothyroidism.<sup>5</sup> Thyrotoxicosis is mostly due to thyroiditis and there is a relapse or new onset of Graves' disease.<sup>6, 7</sup> The thyroid gland and the entire hypothalamic-pituitary-thyroid (HPT) axis were found to be affected resulting in central hypothyroidism induced by hypophysitis or hypothalamic dysfunction.<sup>8</sup>

## HIGHLIGHTS

1. More than one-fourth of non-critically ill hospitalized patients with COVID-19 may present with a spectrum of abnormal biochemical thyroid dysfunctions.
2. Isolated hyperthyroxinemia is the most common thyroid function abnormality.
3. Thyroid function tests have no significant associations with the severity of illness.

Besides, severely unwell individuals have been described as having euthyroid sick syndrome (ESS) which is defined by low free triiodothyronine (FT<sub>3</sub>) and, less frequently, low free thyroxine (FT<sub>4</sub>), along with normal or low thyroid stimulating hormone (TSH).<sup>9</sup> The ESS has got some prognostic role in predicting the outcome of critically ill patients; in particular, low FT<sub>3</sub> is associated with poor outcomes.<sup>10</sup>

However, a study carried out on 334 COVID-19 patients for thyroid function abnormalities found that the majority (86.6%) were euthyroid. Another finding was that participants who were previously euthyroid but developed significantly low TSH and FT<sub>4</sub> after admission to the hospital eventually revert back to a euthyroid state after recovery.<sup>11</sup>

Numerous studies demonstrate that a significant proportion of COVID-19 patients without a history of thyroid disease have thyroid dysfunction. On the other hand, COVID-19 is associated with worsening of pre-existing thyroid diseases.<sup>12</sup> Moreover, one meta-analysis has shown that patients with thyroid abnormalities have been found to be associated with a significantly increased risk of higher disease severity, intensive care unit admission, mortality, and hospitalization.<sup>13</sup> However, data regarding thyroid function tests (TFTs) among noncritical patients with COVID-19 are scarce. Therefore, we have conducted this study to see thyroid hormone levels in COVID-19-infected patients who have been admitted to the COVID-19 unit of a tertiary care hospital with a noncritically ill status.

## METHODS

This cross-sectional study recruited reverse transcriptase polymerase chain reaction (RT-PCR) positive, non-critical, COVID-19 patients (age: 18 – 65 years)

from the COVID-19 unit of Bangabandhu Sheikh Mujib Medical University (BSMMU) from September 2021 to February 2022 on a consecutive basis. The sample size was calculated from the prevalence of thyroid dysfunctions (67.7%) of COVID-19 patients in a previous study, with a 10% margin of error (d) from the following formula,  $n = Z^2 p(1-p)/d^2$ . Considering limitations of collecting samples from COVID-19 positive patients, we took 10% margin of error as we thought it as the maximum acceptable error to give a satisfactory result. The minimum sample size was 85. We included 87 noncritical patients with COVID-19. Patients with known thyroid illness, chronic kidney diseases, chronic liver disease, malignancy, pregnancy, or any other diseases and drugs (eg. steroids, heparin, etc.) affecting the thyroid axis were excluded from the study. The critical COVID-19 patients according to World Health Organization's (WHO) interim guideline were also excluded from the study.<sup>2</sup> The patients were enrolled within 48 hours of admission before getting any steroids. A history of socio-demographic profiles and symptoms was taken and relevant physical examinations like height, weight, pulse, blood pressure, respiratory rate, and oxygen saturation were recorded in a semi-structured data sheet. Non-critical COVID-19 cases were discriminated into mild, moderate, and severe according to WHO interim guideline, 2020.<sup>2</sup> Patients' baseline investigations (complete blood count, C-reactive protein, serum D-dimer, serum-ferritin, etc.) conducted after hospital admission were also recorded in the data collection sheet.

A blood sample of 3 ml was drawn by venipuncture and serum was separated immediately for measurement of serum TSH, FT<sub>4</sub>, and FT<sub>3</sub> by chemiluminescent immunoassay (Advia. Centaur XP. Siemens, USA) in the Department of Microbiology and Immunology of BSMMU. The reference range for the normal levels of hormone assay was defined by the particular assay technique. Reference levels: Serum thyroid stimulating hormone,  $\mu\text{IU/mL}$  (0.35 – 5.5); serum free thyroxine,  $\text{ng/dL}$  (0.8 – 1.8); Serum free tri-iodothyronine,  $\text{pg/mL}$  (1.4 – 4.2).

Data were analyzed by SPSS version 22.0. They were expressed in median (inter-quartile range, IQR) or frequency (percent, %). There was missing data and the available numbers were mentioned within third

**TABLE 1** Characteristics of the study participants with thyroid status

Variables	Euthyroid status (n=62)		Abnormal thyroid status (n=25)		P*
	Number	Median (IQR) †	Number	Median (IQR) †	
Age, years	62	52.5 (28.0 – 60.5)	25	50.0 (40.0 – 57.5)	0.91
Sex‡					
Men	25	40.3	10	40	0.99
Women	37	59.7	15	60	
Body mass index, kg/m <sup>2</sup>	59	23.8 (20.3 – 26.0)	25	23.2 (20.7 – 26.5)	0.60
Severity of COVID-19‡	62	100	25	100	
Mild	38	61.3	13	52.0	
Moderate	20	32.3	6	24.0	0.10
Severe	4	6.5	6	24.0	
Neutrophil/lymphocyte ratio	54	3.4 (2.3 – 6.1)	20	3.42 (1.9 – 9.5)	0.94
Platelet/lymphocyte ratio	54	128.1 (92.8 – 197.9)	20	128.6 (84.4 – 194.6)	0.72
Serum C-reactive protein, mg/L	31	24.0 (7.8 – 72.0)	15	33.6 (12.0 – 124.0)	0.34
Serum D-dimer,	38	0.5 (0.1 – 3.1)	16	1.5 (0.4 – 5.1)	0.26
Serum ferritin	25	473.2 (129.3 – 641.2)	9	497.8 (205.7 – 757.6)	0.85

\*Mann-Whitney U test or Chi-square test was done as appropriate

†Interquartile range

‡Percentage

brackets. Associations between two groups were analyzed by Mann-Whitney U test and for more than two groups, Kruskal-Wallis test was done for quantitative values. Chi-square or Fisher's exact test was done as appropriate for qualitative variables. Spearman's correlation test was done to see the correlation of TSH with different clinical and biochemical variables. *P* values less than 0.05 was considered statistically significant.

## RESULTS

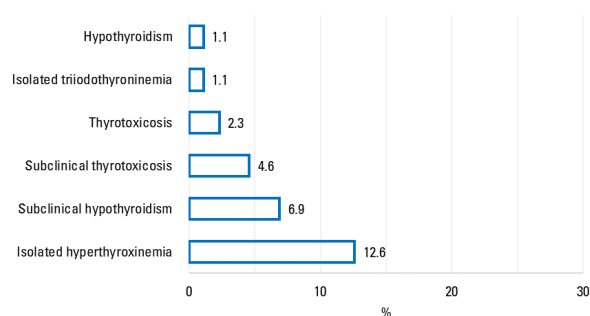
This study screened 87 non-critical COVID-19 patients aged (18-61 years) who were tested for thyroid hormone status after admission to the hospital. Of them, 52 (59.8%) were females. The median duration of COVID symptoms was 7 days (IQR: 4 – 10 days). A total of 25 (28.7%) of the study participants had abnormal thyroid status. All the characteristics including biochemical variables were statistically similar between the study groups (euthyroid vs. abnormal thyroid status) (**TABLE 1**).

Considering the laboratory cut-off values, 7 (8.0%), 13 (14.9%), and 3 (3.4%) had high and 6 (6.9%), 1 (1.1%), and 1 (1.1%) had low serum TSH, FT<sub>4</sub>, and FT<sub>3</sub> values, respectively in the study participants (**FIGURE 1**). Other participants had normal TSH, FT<sub>4</sub>, or FT<sub>3</sub> levels. A total of 62 (71.3%) of the study participants had euthyroid status (**FIGURE 2**).

**FIGURE 1** Thyroid function abnormalities in the study participants (n=

Among abnormal thyroid functions (n=25), the most common were isolated hyperthyroxinemia [11 (12.6%)], followed by subclinical hypothyroidism [6 (6.9%)], and subclinical thyrotoxicosis [4 (4.6%)], and less common were thyrotoxicosis [2 (2.3%)], isolated triiodothyroninemia [1 (1.1%)], and hypothyroidism [1 (1.1%)].

The serum levels of TSH, FT<sub>4</sub>, and FT<sub>3</sub> among three categories (mild, moderate, and severe) of COVID-19 patients had no significant differences (**TABLE 2**). Serum TSH negatively correlated with FT<sub>4</sub> (rs= -0.24, *P*=0.023) and FT<sub>3</sub> (rs= -0.042, *P*<0.001) in the study population. None of the other variables had any significant correlations with TSH, FT<sub>4</sub>, and FT<sub>3</sub> (**TABLE 3**).



**FIGURE 2** Thyroid status of hospitalized patients with noncritical COVID-19 (n=87)

## DISCUSSION

The present study encompassed non-critical COVID-19 patients without known thyroid illness from the COVID unit of a tertiary-level hospital. In the evaluation of

**TABLE 2** Thyroid function tests according to the severity of COVID-19 (n=87)

Thyroid function tests	Mild (n=51)	Moderate (n=26)	Severe (n=10)	P*
Serum thyroid stimulating hormone ( $\mu\text{IU/mL}$ )	1.9 (1.0 - 3.0)	1.2 (0.6 - 2.0)	1.2 (0.5 - 3.7)	0.10
Serum free thyroxine (ng/dL)	1.3 (1.2 - 1.6)	1.3 (1.1 - 1.5)	1.5 (1.1 - 1.7)	0.76
Serum free tri-iodothyronine (pg/mL)	3.0 (2.7 - 3.2)	3.0 (2.5 - 3.1)	3.0 (2.2 - 4.1)	0.82

\*Kruskal Wallis test; Results are median (interquartile range)

thyroid function, most of the study population had normal thyroid function. Abnormalities in thyroid function were found in 25 (28.7%) participants. Those were isolated hyperthyroxinemia, subclinical hypothyroidism, and subclinical thyrotoxicosis, and less common were thyrotoxicosis, isolated triiodothyroninemia, and hypothyroidism. There was no significant difference in thyroid function among mild, moderate, and severe groups.

Acute viral illness is associated with abnormalities in TFTs. Thyroiditis is the common presentation with elevated free thyroid hormones and suppressed TSH levels. However, autoimmune thyroid diseases may also flare up.<sup>15</sup> Similarly, several studies show thyroid dysfunctions following SARS-CoV-2 infection and our study also found a spectrum of different abnormalities in thyroid hormone levels. However, majority of the patients (72%) were found to be euthyroid. This is similar with studies by other researchers who also found that most of the patients (>80%) were euthyroid.

They found mild thyroid dysfunctions in smaller percentages (10% - 15%).<sup>10, 16</sup> This might be explained by the fact that thyroid dysfunction takes time to develop in the course of COVID-19 but it was tested early in this study.<sup>16</sup>

Among thyroid dysfunctions, the prevalence of thyrotoxicosis is reported to be common. A retrospective study evaluating 287 patients in Italy found 20.2 % had thyrotoxicosis though prevalence was found lower in other European countries (0.7%) and the USA (0.5%).<sup>17</sup> The prevalence of hyperthyroidism and subclinical hyperthyroidism in Bangladesh was less than one percent (regional study) for each in the general population.<sup>18</sup> We found relatively higher percentages of thyrotoxicosis and subclinical hyperthyroidism, 2.3% and 4.6%, respectively. We recruited the patients before

getting steroids; our patients did not receive heparin. Therefore, low TSH is not due to steroids or elevated FT4 not by heparin due to displacement of the thyroid hormone from the binding proteins. This suggests true thyroid dysfunctions in COVID-19 patients, not drug interference.<sup>19, 20</sup>

In our study, 12.6% of patients had hyperthyroxinemia, while isolated triiodothyroninemia was present in only one patient (1.1%). The finding of the higher percentage of compared hyperthyroxinemia to triiodothyroninemia

**TABLE 3** Correlation of serum thyroid stimulating hormone with clinical, hormone, and biochemical variables in the study participants

Determinants of 'r <sub>s</sub> '	Available number	r <sub>s</sub>	P*
Serum free thyroxine, ng/dL	87	- 0.24	0.023
Serum free tri-iodothyronine, pg/mL	87	- 0.42	<0.001
Age, years	87	- 0.01	0.98
Body mass index, kg/m <sup>2</sup>	84	0.07	0.55
Neutrophil/Lymphocyte ratio	74	- 0.04	0.71
Platelet/lymphocyte ratio	74	0.01	1.00
Serum C-reactive protein, mg/L	46	0.03	0.82
Serum D-dimer, mg/L	54	- 0.06	0.65
Serum ferritin, ng/dL	34	- 0.30	0.09

\*Spearman's correlation test was done

is suggestive of destructive thyroiditis though we could not do a thyroid scan or radioiodine uptake for confirmation. Additionally, we did not follow up on the patients to see spontaneous improvement or did not go for thyroid autoantibody testing for Graves' disease as clarifying the etiology of thyroid dysfunctions was beyond the scope of our study.

Another abnormality in the thyroid function of COVID-19 is due to non-thyroidal illness, the so-called ESS, which has been observed in several studies, particularly in severely or critically ill patients. The ESS is characterized by a combination of low FT<sub>3</sub> and low TSH and less frequently low FT<sub>4</sub>.<sup>8</sup> We found low FT<sub>3</sub> only in one patient. Moreover, there was a significant negative correlation of TSH with both FT<sub>4</sub> and FT<sub>3</sub> in severe COVID-19 patients that excluded the chance of ESS but favors thyrotoxicosis. Our study shows negative correlations of TSH with both FT<sub>4</sub> and FT<sub>3</sub> in the total study population and also a significant and negative correlation with FT<sub>4</sub> in moderate COVID-19. Thus, it further supports the occurrence of true thyrotoxicosis.

COVID-19 is also reported to be related to both primary and central hypothyroidism. There are study reports of the unmasking of chronic autoimmune thyroiditis (Hashimoto's thyroiditis) with primary hypothyroidism evidenced by the presence of autoimmune markers. The humoral effects related to the cytokine storm syndrome can lead to several effects on the HPT axis causing central hypothyroidism.<sup>17, 21, 22</sup> In our study, only one patient had primary hypothyroidism and 6.9% had subclinical hypothyroidism. Among 287 patients, 5.2% had hypothyroidism in a study conducted in Italy.<sup>17</sup> We cannot comment on the etiology of hypothyroidism as we did not check thyroid autoantibodies.

When we categorized the patients into mild, moderate, and severe groups, there were no significant differences in thyroid functions (TSH, FT<sub>4</sub>, FT<sub>3</sub>) in the three groups. Similarly, Lui et al. and Zhang et al. found that thyroid function did not vary according to the severity of COVID-19.<sup>21, 23</sup> However, a study done in neighboring India found a significant negative association with total T<sub>3</sub> and T<sub>4</sub> with the severity of noncritical COVID-19 patients.<sup>7</sup>

Although other researcher found a significant negative correlation between TSH and C-reactive protein, which became more pronounced between mild and moderate disease severity and less pronounced between moderate and severe disease severity, there was no significant correlation between TSH and the inflammatory marker C-reactive protein in any group of COVID-19 in our study.<sup>7</sup>

### **Limitations**

The limitations of our study were the lack of follow-up data, and we could not measure antibody status, thyroid uptake and scan to find out the etiology.

### **Conclusion**

More than one-fourth non-critical COVID-19 patients admitted to the hospital have thyroid dysfunction. These abnormalities do not vary among the severity of illness. Further evaluations and follow-ups are needed to confidently identify the thyroid dysfunction's etiology in noncritical COVID-19 patients.

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### **Author Contributions**

Conception and design: NS, HB, MSM, AAS, MAH, SMA. Acquisition, analysis, and interpretation of data: NS, HB, MSM, TA. Manuscript drafting and revising it critically: NS, HB, MSM, TA, AAS, MAH. Approval of the final version of the manuscript: NS, HB, MSM, TA, AAS, MAH. Guarantor accuracy and integrity of the work: AAS, MAH, SMA.

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### **Conflict of Interest**

The authors have no conflict of interest to declare.

### **Ethical Approval**

Institutional Review Board clearance was taken from Bangabandhu Sheikh Mujib Medical University (No. BSMMU/2021/557, Date: 21/09/2021). Before enrollment, informed written consent was taken from each participant. The study was conducted according to the declaration of Helsinki for medical research.

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