

Thyroid Function Abnormalities and Outcomes in Hospitalized Patients with COVID-19 Infection: A Cross-Sectional Study

Authors

Deepika Patel¹ , Dukhabandhu Naik¹ , Sadishkumar Kamalanathan¹, Kadhiraivan Tamilarasu², Jayaprakash Sahoo¹, Ayan Roy³, Chandhana Merugu¹, Varun Suryadevara¹

Affiliations

- 1 Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
- 2 Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
- 3 Endocrinology and Metabolism, All India Institute of Medical Sciences – Kalyani, Kalyani, India

Key words

SARS-CoV2, low FT3 syndrome, mortality, sick euthyroid syndrome, thyroiditis

received 07.10.2022

accepted after revision 10.01.2023

Bibliography

Horm Metab Res 2023; 55: 169–175

DOI 10.1055/a-2014-4634

ISSN 0018-5043

© 2023, Thieme. All rights reserved.

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. Dukhabandhu Naik
Endocrinology, Jawaharlal Institute of Postgraduate Medical
Education and Research
605006 Puducherry
India
Tel.: +91-9843671306
drnaik2000@gmail.com

ABSTRACT

Thyroid gland can be affected by the COVID-19 infection. The pattern of thyroid function abnormality reported in COVID-19 is variable; in addition, some drugs used in COVID-19 patients like glucocorticoids and heparin can affect the thyroid function tests (TFT). We conducted an observational, cross-sectional study of thyroid function abnormalities with thyroid autoimmune profile in COVID-19 patients with varying severity from November 2020 to June 2021. Serum FT4, FT3, TSH, anti-TPO, and anti-Tg antibodies were measured before the initiation of treatment with steroids and anti-coagulants. A total of 271 COVID-19 patients were included in the study, of which 27 were asymptomatic and remaining 158, 39, and 47 were classified to mild, moderate and severe categories, respectively, according to MoHFW, India criteria. Their mean age was 49 ± 17 years and 64.9% were males. Abnormal TFT was present in 37.2% (101/271) patients. Low FT3, low FT4, and low TSH were present in 21.03%, 15.9% and 4.5% of patients, respectively. Pattern corresponding to sick euthyroid syndrome was the most common. Both mean FT3 and FT3/FT4 ratio decreased with increasing severity of COVID-19 illness ($p=0.001$). In multivariate analysis, low FT3 was associated with increased risk of mortality (OR 12.36, 95% CI: 1.23–124.19; $p=0.033$). Thyroid autoantibodies were positive in 58 (27.14%) patients; but it was not associated with any thyroid dysfunction. Thyroid function abnormality is common among COVID-19 patients. Both low FT3 and FT3/FT4 ratio are indicators of disease severity while low FT3 is a prognostic marker of COVID-19 associated mortality.

Introduction

The pandemic of the coronavirus disease 2019 (COVID-19) has taken a heavy toll on human health and life worldwide. So far, more than 550 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [1]. The leading cause of mortality and morbidity was due to COVID-19 pneumonia with acute respiratory distress syndrome [2–4]. The SARS-CoV2 virus enters the host cell via binding to the angiotensin-converting enzyme 2 receptors (ACE2 receptors) through its spike protein [5]. The ACE-2 receptor is abundantly expressed in several endocrine organs, including the thyroid [6].

The involvement of the thyroid gland was first documented in the form of subacute thyroiditis in a COVID-19 survivor [7]. Subsequently, other thyroid function test (TFT) abnormalities corresponding to sick euthyroid syndrome (SES), subclinical and overt thyrotoxicosis were reported among COVID-19 patients [8–13]. The “Low T3 syndrome” aspect of sick euthyroid syndrome is typically seen in intensive care unit (ICU) patients [14, 15]. However, low T3 syndrome has been reported even in mild to moderate COVID-19 infection [16–18]. In COVID-19 infection, the low T3 level has been shown to be associated with severity of illness and increased risk of mortality [19–22]. One of the earlier studies by

Chen et al. showed a lower TSH in 56% of cases with COVID-19 [11]. However, most patients were on steroids during the assessment of thyroid function. It is pertinent to note that both glucocorticoid and heparin used for the treatment of COVID-19 infection can interfere with thyroid function [23–25].

Further, there have been studies on occurrence of SARS-CoV2 related thyroiditis in hospitalised patients characterised by low TSH and elevated FT4 levels [13]. However, none of them had clinical features of thyrotoxicosis or neck pain typical of subacute thyroiditis. Few studies also measured the thyroid autoantibodies in acute COVID-19 infected patients [16, 17, 26]. The presence of anti-thyroid antibodies probably had some association with thyroid dysfunction. The prevalence and pattern of thyroid dysfunction abnormalities is not uniform across the studies. Moreover, number of studies related to TFT abnormalities in COVID-19 infection are limited from Indian subcontinent. Hence, we undertook this cross-sectional study to look at the abnormalities in TFT and thyroid autoantibodies before the initiation of interfering drugs like glucocorticoids and heparin in subjects with COVID-19 infection.

Patients and Methods

This observational cross-sectional study was done in the department of Endocrinology of a tertiary care centre in India from November 2020 to June 2021. The study began after the approval of the Institution Ethics Committee (JIP/IEC/2020/271) and getting written informed consent from all the patients. A total of 271 hospitalised adult (> 18 years) patients with COVID-19 infection were included. COVID-19 was diagnosed by either by real-time reverse transcriptase-polymerase chain reaction assay or rapid antigen test. Patients were excluded if they were: 1) already a known case of thyroid disorders 2) on treatment with drugs interfering with thyroid function; 3) started on glucocorticoid, other immunomodulators or low molecular weight heparin before the measurement of thyroid function; and 4) pregnant or lactating mother.

Patients with COVID-19 were classified into four categories (asymptomatic, mild, moderate, and severe) according to the Ministry of Health and Family Welfare (MoHFW), India criteria [27]. At baseline patient's demographic and clinical data were collected including age, gender, duration of symptoms, severity of symptoms, associated comorbidities like type 2 diabetes mellitus (T2DM), hypertension, coronary artery disease (CAD), chronic kidney disease (CKD), cerebrovascular accident (CVA), current medications, and any history suggestive of thyroiditis. Three ml of blood was collected from the study participants during hospitalisation before initiation of steroids and anti-coagulants. All blood samples were collected within 24 hours of hospitalisation. The baseline hematological and biochemical investigations were done as part of the routine care for hospitalised patients with COVID-19 infection were collected. Information on patient outcomes (recovered or dead) were also collected from the hospital database.

The blood samples were processed for serum thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-Tg Ab). All these investigations were performed in chemiluminescent immunoassay autoanalyser (Advia Centaur XP, Siemens Healthcare Diagnostics Inc, USA). The normal range of

TSH for the assay was 0.35–5.5 mIU/l, while its range of detection for TSH was 0.01–150 μ U/ml (mIU/l). The FT4 assay could measure concentrations up to 155 pmol/l (12 ng/dl) with a minimum detectable concentration (analytical sensitivity) of 1.3 pmol/l (0.1 ng/dl). The normal range of FT4 for the assay was 11.46–22.65 pmol/l (0.89–1.76 ng/dl). The FT3 assay could measure concentrations up to 30.7 pmol/l (20 pg/ml), with a minimum detectable concentration of 0.3 pmol/l (0.2 pg/ml). The normal range of FT3 for the assay was 3.53 to 6.45 pmol/l (2.3–4.2 pg/ml).

The anti-TPO Ab assay could measure concentrations up to 1300 U/ml with a minimum detectable concentration of 15 U/ml. A value of 60 U/ml and above indicated anti-TPO Ab positivity. The anti-Tg Ab assay could measure concentrations up to 500 U/ml with a minimum detectable concentration of 30 U/ml. A value of 60 U/ml and above indicated anti-Tg Ab positivity. If either or both of anti-TPO Ab and anti-Tg Abs were positive, then the patient was considered to have thyroid autoimmunity in this study.

Definition of various thyroid abnormalities

Euthyroid state was defined as a state with FT3, FT4, and TSH in the normal range. FT3 < 3.53 pmol/l, FT4 < 11.46 pmol/l, and TSH < 0.35 mIU/l were described as low FT3, low FT4, and low TSH, respectively. Isolated low FT3 was defined as FT3 below the normal range with FT4 and TSH being normal. Similarly, isolated low FT4 and isolated low TSH were defined when FT4 and TSH were below the normal range with the other thyroid parameters being normal. SES was defined as a state with thyroid profile corresponding to either isolated low FT3, low FT4 or low TSH or a combination of any of these patterns, that is, either low FT3 or low FT4 with low/normal/elevated TSH < 10 mIU/l, or low FT3 with low FT4 with low/normal/elevated TSH < 10 mIU/l. Subclinical hypothyroidism (SCH) was defined as elevated TSH above the upper limit of the normal range > 5.5 mIU/l with normal FT4. Overt hypothyroidism was defined as TSH > 10 mIU/l with low FT4. Thyrotoxicosis was defined as FT4 above normal range with suppressed TSH. FT3/FT4 ratio was calculated with units using pmol/l.

Statistical analysis

The normality of data was checked with the Shapiro–Wilk test. Data were presented as mean \pm SD (standard deviation), or median with interquartile range (IQR) for continuous variables, and number with percentage for categorical variables. Between-group comparisons were performed with the *t*-test and the Mann–Whitney U-test for continuous variables, and the chi-squared or Fisher exact tests for categorical variables as appropriate. ANOVA and Kruskal–Wallis tests were used to determine the difference among more than two groups. Multivariable logistic regression analysis was used to identify the variables independently associated with mortality. Variables with statistical significance (*p*-value < 0.2) in the univariate analysis were included in multivariable regression analysis. *p*-Values < 0.05 were considered as statistically significant in the adjusted analysis. All statistical analyses were performed with IBM SPSS version 26.

Results

A total of 271 patients fulfilling the inclusion and exclusion criteria were recruited in the study. ► **Table 1** represents the baseline clinical characteristics of the study participants. The mean age of the study population was 49 (± 17) years. There were 176 males (64.9%) and 95 females (35.1%) in the study. Fever, cough, and sore throat were the main presenting complaints in 72%, 51%, and 11% patients, respectively. T2DM was the most common comorbidity, present in 39.5%, followed by hypertension (30.6%). According to the MoHFW criteria, 27 (10.0%) patients were asymptomatic patients and the remaining 158 (58.3%), 39 (14.4%), 47 (17.3%) patients had mild, moderate and severe COVID-19 infection, respectively. A total of 250 (92.2%) patients recovered from the illness and were discharged, whereas 21 (7.8%) patients died during hospitalisation.

The thyroid profile and pattern of thyroid function abnormality in the patients are shown in the ► **Table 2**. The mean FT3, FT4 and median TSH of the study population were, 4.14 ± 0.75 pmol/l, 13.64 ± 2.7 pmol/l, and 0.92 (1.52–2.59) mIU/l, respectively. The mean FT3 level and FT3/FT4 ratio reduced with increasing severity of illness (p -value < 0.001 and $p = 0.016$, respectively). Low FT3 was

► **Table 1** Baseline clinical characteristics of the study participants.

Parameter	Total (n = 271)
Age (years)	49 \pm 17
Male gender	176 (64.9%)
Duration of symptoms (days)	7 \pm 3 days
Clinical presentation at admission	
Fever (n)	195 (72.0%)
Cough (n)	137 (50.6%)
Sore throat (n)	29 (10.7%)
Severity of COVID -19 at admission	
Asymptomatic (n)	27 (10.0%)
Mild (n)	158 (58.3%)
Moderate (n)	39 (14.4%)
Severe (n)	47 (17.3%)
Comorbidities in COVID -19 infected patients	
T2DM (n)*	107 (39.5%)
HTN (n)†	83 (30.6%)
CAD (n)‡	18 (6.6%)
CKD (n)§	3 (1.1%)
CVA (n)¶	2 (0.74%)
Other comorbidity (n)	30 (11%)
Clinical course and Outcomes	
Recovered (n)	250 (92.2%)
Died (n)	21 (7.8%)

Data are expressed as mean \pm SD or number (%), as appropriate. * Type-2 diabetes mellitus (T2DM). † Hypertension (HT). ‡ Coronary artery disease (CAD). § Chronic kidney disease (CKD). ¶ Cerebrovascular accident (CVA).

detected in total 21% (57/271) patients, whereas in patients with severe infection, 80.9% (38/47) patients had low FT3 ($p < 0.001$). Isolated low FT3, isolated low FT4, and isolated low TSH were present in 14.8%, 9.6%, and 1.9% patients, respectively. With increasing severity of illness, the proportion of patients with isolated low FT3 increased from 3.7% in asymptomatic patients to 4.4%, 20.5%, and 51.5% of patients with mild, moderate and severe categories of illness, respectively ($p < 0.001$). Among severe category patients, the prevalence of combination of low FT3 and low FT4 was most common, being seen in 12.8% (6/47) while that of low FT3 with low TSH was present in 10.6% (5/47).

Abnormal TFT was found in 101 (37.2%) patients. Among those with abnormal TFT 32.8%, 4.05%, 1.5%, and 0.37% had SES, subclinical hypothyroidism, overt hypothyroidism, and thyroiditis, respectively. Thyroid autoimmunity was present in 58 (21.6%) patients. A greater number of patients in the severe group had abnormal TFT compared to the other 3 groups ($p < 0.001$). We also found abnormal TFTs in 40.7% (11/27) of patients who were asymptomatic at the time of taking the samples and the majority had only mild reduction in FT4 level. SES was most prevalent in the severe category.

We also did a comparison between those with thyroid autoimmunity positive ($n = 58$) and those without ($n = 213$). The FT4 levels (12.61 ± 1.67 vs. 13.38 ± 2.4 pmol/l, $p = 0.012$) were lower and prevalence of overt hypothyroidism (6.9% vs. 0%, $p < 0.001$) higher in those who were positive for anti-thyroid antibodies. The age and distribution among the two groups were comparable. Severity of COVID-19 illness, prevalence of abnormal TFT, SES, and death also did not differ between the groups.

► **Table 3** shows comparison of various parameters between survivors and non-survivors. Those who died had more prevalence of diabetes (66.7% vs. 37.2%, p -value = 0.008). Both abnormal TFT (81% vs. 33.2%, $p = < 0.001$) and low FT3 (76.2% vs. 16.4%, $p < 0.001$) were prevalent in those who did not survive. Also, those who died had lower FT3 levels (3.26 ± 0.49 vs. 4.22 ± 0.72) pmol/l, higher FT4 levels (14.16 ± 3.73 vs. 13.64 ± 2.57) pmol/l and lower FT3/FT4 ratios (0.2 ± 0.04 vs. 0.27 ± 0.7). Multivariate linear regression analysis showed that low FT3, that is, $FT3 < 3.53$ pmol/l (OR 12.36, 95% CI: 1.23–124.19; $p = 0.033$) was significantly associated with occurrence of death.

Discussion

Our study was a cross-sectional design with a prospective analysis of TFT and thyroid autoantibodies in patients hospitalised due to COVID-19 infection. We collected TFT samples before treatment initiation with glucocorticoids, heparin, and other immunomodulators. A total of 271 study participants were included with all spectra of COVID-19 illness. We had 27 asymptomatic (10%), 158 mild (58.3%), 39 moderate (14.4%), and 47 severe (17.3%) category patients in our study.

In our study of patients with COVID-19, we found a 37.3% (101/271) prevalence of abnormal TFT. The proportion of patients with abnormal TFT was highest (85.1%) in those with severe illness. However, unlike other critical illnesses, TFT abnormalities are well documented in mild to moderate COVID-19 illness. Previous studies found a varying prevalence of abnormal TFT (13–70%) in COVID-

► **Table 2** Thyroid hormone profile and pattern of thyroid function abnormality in COVID-19 patients.

Parameter	Total (n = 271)	Asymptomatic (n = 27)	Mild (n = 158)	Moderate (n = 39)	Severe (n = 47)	p-Value
FT3 (pmol/l)	4.14 ± 0.75	4.52 ± 0.64	4.39 ± 0.67	3.95 ± 0.55	3.29 ± 0.39	< 0.001
FT4 (pmol/l)	13.64 ± 2.7	12.74 ± 2.19	13.51 ± 2.57	14.67 ± 2.7	13.9 ± 3.35	0.056
FT3/FT4 ratio	2.64 ± 0.66	3.08 ± 0.77	2.81 ± 0.57	2.31 ± 0.44	2.09 ± 0.59	0.016
TSH (mIU/l)	0.92 (1.52–2.59)	1.88 (1.19–2.8)	1.59 (0.99–2.58)	1.35 (0.63–1.85)	1.3 (0.61–2.75)	0.16
Low FT3 (n)	57 (21.0%)	2 (7.4%)	9 (5.7%)	8 (20.5%)	38 (80.9%)	< 0.001
Low FT4 (n)	43 (15.9%)	8 (29.6%)	22 (13.9%)	4 (10.3%)	9 (19.2%)	0.107
Low TSH (n)	12 (4.5%)	1 (3.7%)	3 (1.9%)	1 (2.6%)	7 (14.9%)	0.016
Abnormal TFT (n)	101 (37.2%)	11 (40.7%)	36 (22.8%)	14 (35.9%)	40 (85.1%)	< 0.001
Sick euthyroid syndrome (n)	89 (32.8%)	10 (37.0%)	29 (18.4%)	12 (30.8%)	38 (80.9)	< 0.001
Positive thyroid antibodies (n)	58 (21.4%)	6 (22.2%)	36 (22.8%)	10 (27.0%)	6 (12.8%)	0.399

Data are expressed as mean ± SD, median (IQR) or number (%), as appropriate.

19 illness [16, 18]. Our study profile is similar to the study by Lui et al. TFT abnormality in their study was 13.1% and majority of patients had mild to moderate illness [16]. In a retrospective study, Chen et al. [11] found a 64% (32/50) prevalence of abnormal TFT in COVID-19 pneumonia patients; low TSH was found in 56%. However, 62% of patients received glucocorticoids. The THYROCOV study by Lania et al. showed a prevalence of 25.43% (85/287) in non-intensive care unit (ICU) patients, of which 20.2% had thyrotoxicosis and several patients were on heparin during assessment of thyroid function. FT3 and FT4 were assessed only in patients with TSH abnormality [12]. In a multicentric study from UK, Khoo et al. found a prevalence of abnormal TFT (TSH and FT4) as 13.4% in 334 COVID-19 patients; however, FT3 was not estimated in their study. All samples were taken within 48 hours of admission [28]. The variable prevalence pattern can be partly related to the varying sample size, severity of illness, blood sampling after initiation of interference drugs such as glucocorticoid and heparin and selectively performing certain TFT parameters (FT4 and FT3) [29]. TFT abnormalities have been well documented even in mild to moderate categories of cases [16, 30]. A retrospective study by Wang et al. from China compared the TFT abnormalities between severe and mild-moderate cases, the proportion of patients with thyroid dysfunction was 74.6% in severe cases and 23.8% in mild-moderate cases [17]. Similarly, studies by Sen et al. and Kumar et al. also documented higher TFT abnormalities in severe cases [31, 32]. Few studies also documented higher prevalence of thyroid dysfunction in COVID-19 patients compared to healthy control and non-COVID-19 pneumonia patients [11, 16, 28].

SES was reported to be the most common thyroid abnormality in COVID-19 infected patients [8, 9, 33, 34]. Low T3 with normal or low TSH with or without low FT4 is the most common pattern of SES. The causes of SES in COVID-19 infection are multifactorial which includes direct invasion of thyroid cells by SAR-CoV-2 virus, suppression of TSH due to excess release of inflammatory cytokines and nonspecific adaptive response [35, 36]. The plasma concentra-

tion of T3 is reduced markedly due to decreased type-1 deiodinase (D1) activity and increased activity of D3; low FT3:FT4 ratio is an indirect indicator of deiodinase activity [15]. In our study, the FT3:FT4 ratio was significantly lower in severe cases. In COVID-19 illness, the markers of inflammation Interleukin-6 (IL-6), C-reactive protein (CPR), and lactate dehydrogenase (LDH) are markedly elevated, and these are associated with severity of COVID infection and thyroid dysfunction [10, 37]. Presence of lymphopenia was also found to be associated with severity of COVID-19 infection and abnormal TFT [38, 39].

In our study, SES is the most prevalent pattern (32.8%) of abnormal TFT and 80.9% of severe patients had SES compared to 18.4% in mild cases. Isolated low FT3 was detected in 14.8%. A study by Das et al. assessed the TFT in 84 patients, of which 35 had moderate to severe infection. Majority of their study patients had low T3 but the proportion of patients with SES was higher among moderate to severe disease [40]. Similarly, Ahn et al. analysed the TFT in 119 COVID-19 patients, of which 87 had severe to critical illness [41]. The level of TSH and T3 was found to be significantly lower in severely ill patients. SES is also found to be higher among ICU patients. Baldelli et al. analysed the TFT in COVID-19 ICU patients compared with COVID-19 pneumonia patients and healthy controls. ICU patients showed significantly lowered TSH and FT3 level [34]. A retrospective study by Gao et al. from China also showed that FT3 concentration was significantly lower in severe COVID-19 patients compared to the non-severe cases [42]. SES was also the most common TFT abnormality in mild and moderate COVID-19 illness [16, 18]. A prospective study by Sparano et al. from Italy assessing TFT in 506 patients found 57% of patients having SES (low FT3) at the time of admission [18]. SES (low FT3) at admission has also been described as an independent predictor of severity of illness [40]. The other patterns of SES reported are isolated low T3 (or FT3), with normal TSH and T4 (or FT4). In our study, isolated low FT3 was detected in 14.8%. In the study by Lui et al. 5.2% patients had isolated low FT3 [16].

► **Table 3** Comparison of various parameters between survivors and non-survivors.

	Survivors (n = 250)	Non-survivors (n = 21)	p-Value
Age	48.5 ± 16.7	66.7 ± 13.8	0.284
Male (n)	162 (64.8%)	14 (66.7%)	0.863
T2DM* (n)	93 (37.2%)	14 (66.7%)	0.008
Duration of symptoms (days)	7.1 ± 3.0	7.2 ± 2.9	0.731
Abnormal TFT (n)	83 (33.2%)	17 (81.0%)	0.000
ft3 (pmol/l)	4.22 (± 0.72)	3.26 (± 0.49)	0.039
FT3 by reference range (pmol/l)			
< 3.53 (n, %)	41 (16.4%)	16 (76.2%)	0.000
3.53–6.45 (n, %)	209 (83.6%)	5 (23.8%)	
> 6.45 (n, %)	none	none	
FT4 (pmol/l)	13.64 ± 2.57	14.16 ± 3.73	0.013
FT4 by reference range (pmol/l)			
< 11.46	37 (14.8%)	6 (28.6%)	0.001
14.46–22.65	213 (85.2%)	14 (66.7%)	
> 22.65		1 (4.8%)	
TSH (0.35–4.2 mIU/l)	1.56 (0.93–2.6)	1.30 (0.69–2.45)	0.367
TSH by reference range (mIU/l)			
< 0.35	10 (4.0%)	2 (9.5%)	0.275
0.35–5.5	223 (89.9%)	19 (90.5%)	
> 5.5	15 (6.0%)	0 (0%)	
AIT†	54 (21.8%)	4 (19%)	0.770
FT3/FT4 ratio	0.27 ± 0.07	0.2 ± 0.04	0.015

Data are expressed as mean ± SD, median (IQR) or number (%), as appropriate. * Type-2 diabetes mellitus (T2DM).† Auto-immune thyroiditis.

Other abnormalities found in our study were subclinical hypothyroidism in 4.05% (11/271), overt hypothyroidism in 1.5% (4/271) and atypical thyroiditis (one patient). Thyroid autoantibodies were positive in all patients with overt hypothyroidism and five patients with subclinical hypothyroidism suggestive of Hashimoto's thyroiditis. A prospective study by Hashemipour et al. included 131 hospitalised patients with COVID-19 of which 6.9% had subclinical/overt hypothyroidism, and another 6.9% had subclinical/overt thyrotoxicosis [43]. Similarly, the studies by Lania et al. and Daraei et al. from Iran reported 5% and 5.4%, respectively, of hospitalised COVID-19 patients having subclinical/overt hypothyroidism [12, 44].

The subclinical thyrotoxicosis in COVID-19 infection is typically characterised by low TSH with elevated FT4 above the upper limit of normal and with normal FT3. It is commonly due to atypical thyroiditis and has been documented by several studies on COVID-19 illness. The first case of sub-acute thyroiditis was reported by Brancatella et al. in mild case of COVID-19 two weeks after recovery [7].

In the THYROCOV study in Italy, 20.2% of patients had biochemical features suggestive of atypical thyroiditis [12]. Das et al. also found that 14.3% of COVID-19 patients had atypical thyroiditis [40]. Muller et al. also reported that 15% of patients admitted to ICU had atypical thyroiditis [13]. However, most studies assessed TFT in patients who had already received glucocorticoid and heparin [13]. Few studies also report low TSH, not typical of thyroiditis [45]. A study by Chen et al. showed that 56% of COVID-19 patients had low TSH. The high proportion of patients with low TSH is likely contributed by the inclusion of patients on treatment with glucocorticoids [11].

In our study, we also analysed the thyroid autoantibodies along with thyroid function. Thyroid autoimmunity status did not affect the proportion of patients with abnormal TFT or SES and did not vary with the severity of illness. Lui et al. also reported a similar finding that thyroid autoimmunity did not predict thyroid dysfunction in COVID-19 infection [26].

Thyroid functional abnormalities (SES), especially low serum FT3, have been associated with severity and poor prognosis in COVID-19 illness [37, 46]. In our study on multivariate regression analysis, we found that low FT3 was associated with increase in mortality (OR 12.36, 95% CI: 1.23–124.19; p = 0.033). A prospective study from Turkey compared the TFT and outcomes between 125 mild COVID-19 pneumonia and 125 critically ill ICU patients. ICU patients had significantly lower FT3 and FT4 and the non survivors had significantly low FT3 level at the time of admission [47]. A study from Poland by Swistek et al. found that SES is associated with longer duration of hospitalisation, more need for invasive ventilation and increased mortality [9]. A meta-analysis by Llamas et al. found that low FT3 is an important predictor of all-cause mortality in COVID-19 patients [48]. Even in patients with mild to moderate COVID-19 illness, SES (low T3) is an important early predictor of outcome [16, 18]. Few studies used different tertiles of FT3 to prognosticate the COVID-19 patients and it was found that patients with lower tertile had more mortality and required more mechanical ventilation and ICU admission [22]. Zhang et al. reported that even the presence of thyroid dysfunction per se can be associated with increased risk of mortality [49]. A study by Okoye et al. primarily analysed the data in elderly patients (95 COVID-19 pneumonia and 81 non-COVID-19 pneumonia). There was no significant difference in the prevalence of SES between the groups (66.3% vs. 67.9%). SES was also not associated with increased mortality in this study [50]. A study by Gong et al. described low TSH as an independent predictor of 90 mortality among COVID-19 patients [33].

The major strength of our study is inclusion of a large sample size with a good proportion of patients from all severity of illness, including those with moderate and severe illnesses. Blood investigations for TFT and thyroid autoantibodies were taken before the patients started on treatments like glucocorticoids and heparin. This study has also few limitations; the data on markers of inflammation (CRP, ferritin, and d-dimer) and SARS-CoV2 viral load were not performed due to cost constraints, and the information on long term patient follow up is not available.

Conclusion

The current study showed that more than one-third of patients with COVID-19 infection can have abnormal TFT, more so in those with severe illness. The most common thyroid function abnormality was a sick euthyroid syndrome, irrespective of thyroid autoantibody status. A low FT3 level is an important predictor of both the disease severity and mortality.

Acknowledgements

The manuscript was presented as e poster in the Annual conference of Endocrine Society of India o held between 10th-12th Dec 2021, Bangalore, India

Funding Information

Jawaharlal Institute Of Postgraduate Medical Education and Research — <http://dx.doi.org/10.13039/501100009530>

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2022 Sep 13]. Available from: <https://covid19.who.int>
- [2] Zhu N, Zhang D, Wang W et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733
- [3] Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506
- [4] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020; 368: 473–474
- [5] Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181: 271–280
- [6] Rotondi M, Coperchini F, Ricci G et al. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. *J Endocrinol Invest* 2020; 44: 1085–1090
- [7] Brancatella A, Ricci D, Viola N et al. Subacute thyroiditis after Sars-COV-2 infection. *J Clin Endocrinol Metab* 2020; 105: 2367–2370
- [8] Lui DTW, Lee CH, Chow WS et al. Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity. *Clin Endocrinol (Oxf)* 2021; 95: 469–477
- [9] Świstek M, Broncel M, Gorzelak-Pabiś P et al. Euthyroid sick syndrome as a prognostic indicator of COVID-19 pulmonary involvement, associated with poorer disease prognosis and increased mortality. *Endocr Pract* 2022; 28: 494–501
- [10] Zou R, Wu C, Zhang S et al. Euthyroid sick syndrome in patients with COVID-19. *Front Endocrinol (Lausanne)* 2020; 11: 566439
- [11] Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. *Thyroid* 2020; 31: 8–11
- [12] Lania A, Sandri MT, Cellini M et al. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. *Eur J Endocrinol* 2020; 183: 381–387
- [13] Muller I, Cannavaro D, Dazzi D et al. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020; 8: 739–741
- [14] Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid* 2014; 24: 1456–1465
- [15] Fliers E, Bianco AC, Langouche L et al. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol* 2015; 3: 816–825
- [16] Lui DTW, Lee CH, Chow WS et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. *J Clin Endocrinol Metab* 2021; 106: e926–e935
- [17] Wang W, Su X, Ding Y et al. Thyroid function abnormalities in COVID-19 patients. *Front Endocrinol (Lausanne)* 2020; 11: 623792
- [18] Sparano C, Zago E, Morettini A et al. Euthyroid sick syndrome as an early surrogate marker of poor outcome in mild SARS-CoV-2 disease. *J Endocrinol Invest* 2022; 45: 837–847
- [19] Lang S, Liu Y, Qu X et al. Association between thyroid function and prognosis of COVID-19: a retrospective observational study. *Endocr Res* 2021; 46: 170–177
- [20] Deng J, Zhang S, Peng F et al. The association between FT3 with the outcome and inflammation/coagulopathy/fibrinolysis of COVID-19. *Front Endocrinol* 2022; 13: 877010
- [21] Beltrão FE, de L, Beltrão DC, de A, Cordeiro GC, de A et al. Thyroid hormone levels during hospital admission inform disease severity and mortality in COVID-19 patients. *Thyroid* 2021; 31: 1639–1649
- [22] Schwarz Y, Percik R, Oberman B et al. Sick euthyroid syndrome on presentation of patients with COVID-19: a potential marker for disease severity. *Endocr Pract* 2021; 27: 101–109
- [23] Horby P, Lim WS, Emberson JR et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384: 693–704
- [24] Samuels MH, McDaniel PA. Thyrotropin levels during hydrocortisone infusions that mimic fasting-induced cortisol elevations: a clinical research center study. *J Clin Endocrinol Metab* 1997; 82: 3700–3704
- [25] Mendel CM, Frost PH, Kunitake ST et al. Mechanism of the heparin-induced increase in the concentration of free thyroxine in plasma. *J Clin Endocrinol Metab* 1987; 65: 1259–1264
- [26] Lui DTW, Lee CH, Chow WS et al. Insights from a prospective follow-up of thyroid function and autoimmunity among COVID-19 survivors. *Endocrinol Metab (Seoul)* 2021; 36: 582–589
- [27] MoHFW | Home [Internet]. [cited 2021 Sep 28]. Available from: <https://www.mohfw.gov.in/>
- [28] Khoo B, Tan T, Clarke SA et al. Thyroid function before, during, and after COVID-19. *J Clin Endocrinol Metab* 2021; 106: e803–e811
- [29] Giovannella L, Ruggeri RM, Ovčariček PP et al. Prevalence of thyroid dysfunction in patients with COVID-19: a systematic review. *Clin Transl Imaging* 2021; 9: 233–240
- [30] Nakamura S, Kido N, Watanabe M et al. Analysis of thyroid function in Japanese patients with coronavirus disease 2019. *Endocr J* 2022; 69: 643–648
- [31] Sen K, Sinha A, Sen S, Chakraborty S et al. Thyroid function test in COVID-19 patients: a cross-sectional study in a tertiary care hospital. *Indian J Endocrinol Metab* 2020; 24: 532–536
- [32] Kumar B, Gopalakrishnan M, Garg MK et al. Endocrine dysfunction among patients with COVID-19: A single-center experience from a tertiary hospital in India. *Indian J Endocrinol Metab* 2021; 25: 14–19
- [33] Gong J, Wang D, Dong H et al. Prognostic significance of low TSH concentration in patients with COVID-19 presenting with non-thyroidal illness syndrome. *BMC Endocr Disord* 2021; 21: 111
- [34] Baldelli R, Nicastrì E, Petrosillo N et al. Thyroid dysfunction in COVID-19 patients. *J Endocrinol Invest* 2021; 44: 2735–2739
- [35] Scappaticcio L, Pitoia F, Esposito K et al. Impact of COVID-19 on the thyroid gland: an update. *Rev Endocr Metab Disord* 2020; 22: 803–815
- [36] Chen W, Tian Y, Li Z et al. Potential interaction between SARS-CoV-2 and thyroid: a review. *Endocrinology* 2021; 162: bqab004

- [37] Dabas A, Singh H, Goswami B et al. Thyroid dysfunction in COVID-19. *Indian J Endocrinol Metab* 2021; 25: 198–201
- [38] Grondman I, de Nooijer AH, Antonakos N et al. The association of TSH and thyroid hormones with lymphopenia in bacterial sepsis and COVID-19. *J Clin Endocrinol Metab* 2021; 106: 1994–2009
- [39] Lui DTW, Lee CH, Chow WS et al. The independent association of TSH and free triiodothyronine levels with lymphocyte counts among COVID-19 patients. *Front Endocrinol (Lausanne)* 2022; 12: 774346
- [40] Das L, Dutta P, Walia R et al. Spectrum of endocrine dysfunction and association with disease severity in patients with COVID-19: insights from a cross-sectional, observational study. *Front Endocrinol (Lausanne)* 2021; 12: 645787
- [41] Ahn J, Lee MK, Lee JH et al. Thyroid hormone profile and its prognostic impact on the coronavirus disease 2019 in Korean patients. *Endocrinol Metab (Seoul)* 2021; 36: 769–777
- [42] Gao W, Guo W, Guo Y et al. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. *J Endocrinol Invest* 2021; 44: 1031–1040
- [43] Hashemipour S, Shahsavari P, Kiani S et al. Wide spectrum of thyroid function tests in COVID-19: from nonthyroidal illness to isolated hyperthyroxinemia. *Int J Endocrinol Metab* 2022; 20: e120709
- [44] Daraei M, Hasibi M, Abdollahi H et al. Possible role of hypothyroidism in the prognosis of COVID-19. *Intern Med J* 2020; 50: 1410–1412
- [45] Campi I, Bulgarelli I, Dubini A et al. The spectrum of thyroid function tests during hospitalization for SARS COV-2 infection. *Eur J Endocrinol* 2021; 184: 699–709
- [46] Chen Y, Li X, Dai Y et al. The association between COVID-19 and thyroxine levels: a meta-analysis. *Front Endocrinol (Lausanne)* 2022; 12: 779692
- [47] Güven M, Gültekin H. The prognostic impact of thyroid disorders on the clinical severity of COVID-19: Results of single-centre pandemic hospital. *Int J Clin Pract* 2021; 75: e14129
- [48] Llamas M, Garo ML, Giovanella L. Low free-T3 serum levels and prognosis of COVID-19: systematic review and meta-analysis. *Clin Chem Lab Med* 2021; 59: 1906–1913
- [49] Zhang Y, Lin F, Tu W et al. Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19. *Mol Cell Endocrinol* 2021; 521: 111097
- [50] Okoye C, Niccolai F, Rogani S et al. Is non-thyroidal illness syndrome (NTIS) a clinical predictor of COVID-19 mortality in critically ill oldest old patients? *J Endocrinol Invest* 2022; 45: 1689–1692