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Molecular and Cellular Endocrinology 521 (2021) 111097

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

# Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19

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ARTICLE INFO

*Keywords:*
COVID-19
SARS-CoV-2
Thyroid dysfunction
Prognosis

ABSTRACT

*Background:* Coronavirus disease (COVID-19) has resulted in considerable morbidity and mortality worldwide. Thyroid hormones play a key role in modulating metabolism and the immune system. However, the prevalence of thyroid dysfunction (TD) and its association with the prognosis of COVID-19 have not yet been elucidated. In this study, we seek to address this gap and understand the link between TD and COVID-19.

*Methods:* Herein, we enrolled patients who were hospitalized with COVID-19 and had normal or abnormal thyroid function test results at the West Court of Union Hospital in Wuhan, China, between 29 January and February 26, 2020. We carried out follow up examinations until April 26, 2020. Data on clinical features, treatment strategies, and prognosis were collected and analyzed. TD was defined as an abnormal thyroid function test result, including overt thyrotoxicosis, overt hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, and euthyroid sick syndrome.

*Results:* A total of 25 and 46 COVID-19 patients with and without TD, respectively, were included in the study. COVID-19 patients with TD had significantly higher neutrophil counts and higher levels of C-reactive protein, procalcitonin, lactate dehydrogenase, serum creatine kinase, aspartate transaminase, and high-sensitive troponin I and a longer activated partial thromboplastin time but lower lymphocyte, platelet, and eosinophil counts. A longitudinal analysis of serum biomarkers showed that patients with TD presented persistently high levels of biomarkers for inflammatory response and cardiac injury. COVID-19 patients with TD were more likely to develop a critical subtype of the disease. Patients with TD had a significantly higher fatality rate than did those without TD during hospitalization (20% vs 0%, $P = 0.002$). Patients with TD were more likely to stay in the hospital for more than 28 days than were those without TD (80% vs 56.52%, $P = 0.048$).

*Conclusions:* Our preliminary findings suggest that TD is associated with poor outcomes in patients with COVID-19.

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https://doi.org/10.1016/j.mce.2020.111097
Received 31 August 2020; Received in revised form 21 November 2020; Accepted 25 November 2020
Available online 2 December 2020
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## 1. Introduction

Coronavirus disease (COVID-19) has spread rapidly worldwide, resulting in considerable morbidity and mortality rates. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which 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 (Li et al., 2020a), making the thyroid gland a possible target of SARS-CoV-2. However, data on thyroid involvement of coronaviruses are scarce.

Alterations in circulating hormone levels are a common phenomenon during critical illness (Van den Berghe, 2001). These changes have been reported to be correlated with disease severity, detrimental complications, and outcomes of critical patients in the intensive care units (ICUs) (Marx et al., 2003; Schuetz et al., 2009). Thyroid hormones play a key role in promoting body growth during infancy, childhood and adolescence, modulating metabolism, and regulating the immune system. Researchers have reported that thyroid dysfunctions (TD) is associated with increased mortality among the critical patients in ICU (Rothwell and Lawler, 1995; Rothwell et al., 1993). In the current study, TD was defined as an abnormal thyroid function test result, including elevated or decreased thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels. The reference ranges for TSH, FT3, and FT4 in our laboratory were 0.35–4.94 μIU/mL, 2.63–5.7 pmol/L, and 9–19.18 pmol/L, respectively. Specifically, the abnormal thyroid function in the current study could be classified as overt thyrotoxicosis (decreased TSH values and increased serum FT3 and/or FT4 levels), overt hypothyroidism (increased TSH values and decreased serum FT4 and/or FT3 levels), subclinical hypothyroidism (increased TSH values but normal FT4 and FT3 levels), subclinical hyperthyroidism (decreased TSH values but normal FT4 and FT3 levels), and euthyroid sick syndrome (ESS; decreased FT3 but normal TSH levels) (Docter et al., 1993; McIver and Gorman, 1997; De Groot, 1999; Chopra, 1996).

Recently, a number of comorbidities, and complications have been independently associated with mortality from COVID-19. However, no evidence currently substantiates the presence of TD in patients with COVID-19 and its association with prognosis (Huang et al., 2020; Wang et al., 2020).

Therefore, in the current study, we retrospectively analyzed and summarized data from a single centre in Wuhan, China, to examine the association between TD and the prognosis in patients with COVID-19.

## 2. Methods

### 2.1. Study design and participants

This was a retrospective cohort study of hospitalized patients with COVID-19 in several wards at the West Campus of Union Hospital of Huazhong University of Science and Technology between 29 January to February 26, 2020. These patients were followed up until April 26, 2020. This study's protocol was reviewed and approved by the Ethics Commission of Xiangya Hospital of Central South University (No.202003049) and the Ethics Commission of the Union Hospital of Huazhong University of Science and Technology. The requirement for written informed consent from each participant was waived by the ethics board of the designated hospital for emerging infectious diseases.

### 2.2. Inclusion and exclusion criteria

Enrolled patients were defined on the basis of the following inclusion criteria: (1) laboratory-confirmed COVID-19 status with positive detection of SARS-CoV-2 (World Health Organization, 2020); (2) age ≥18 year old, without sex limitation; (3) available data of thyroid function tests results, including FT4, FT3, and TSH, within three days of admission. Exclusion criteria included: (1) a medical history of an endocrine disorder or thyroid surgery; (2) concurrent treatment with drugs that could affect hypothalamic-pituitary activity within the past year; (3) pregnancy within the past six months, and (4) patients with incomplete data for key parameters.

### 2.3. Measurements

Demographic (age and sex) and clinical (symptoms, comorbidities, laboratory and radiological findings, disease severity, detrimental complications, treatment strategies, and prognosis) data of the included patients were collected from the electronic medical records. All patients with COVID-19 were diagnosed according to the positive detection of viral nucleic acids of SARS-CoV-2 from respiratory tract specimens using real-time polymerase chain reaction assay, as previously described (Liu et al., 2020). Commercial assays were used to measure the following endocrine parameters: TSH, FT4, and FT3 levels, using electrochemiluminescence. Data on other laboratory indicators, including leucocyte, neutrophil, platelet, lymphocyte, and eosinophil counts, percentages of lymphocytes, concentrations of albumin, alanine transaminase (ALT), aspartate transaminase (AST), serum creatine kinase (CREA), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), myohemoglobin (MYO), pro-brain natriuretic peptide (pro-BNP), creatine kinase isoenzyme MB (CK-MB), potassium, sodium, C-reactive protein (CRP), procalcitonin (PCT), high sensitive troponin I (hsTNI), D-dimer, prothrombin time (PT), and thrombin time (TT), activated partial thromboplastin time (APTT), international normalized ratio (INR), were obtained from each patient.

All data including demographic features, symptoms, pre-existing chronic comorbidities, and laboratory and radiologic results, were analyzed and summarized as well. Data on treatment strategies, such as oxygen support, antiviral and antibiotic therapy, and corticosteroid use, and patient outcomes were also collected during hospitalization.

### 2.4. Definition of conditions

The severity of COVID-19 was identified according to the latest version of the diagnosis and treatment guidelines for COVID-19 (version 7) released by the National Health Committee of China. Patients with COVID-19 were classified as severe if they met one of the following criteria: (1) respiratory rate (RR) ≥ 30 breaths/min; (2) arterial blood oxygen saturation ≤ 93% at rest on room air; (3) Oxygenation index (PaO2/FiO2) ≤ 300 mmHg; and (4) Chest computed tomography showing pulmonary acute exudative lesions with a progression of >50% within a short period. Patients were identified as critical if they met the criteria above and also met one of the following criteria: (1) needs mechanical ventilation due to respiratory failure, (2) shock, (3) multiple organ failure requiring transfer to ICU (Zhang et al., 2020a).

Thyroid function parameters, including FT3 (normal range: 2.63–5.7 pmol/L), FT4 (normal range: 9–19.18 pmol/L), and TSH (normal range: 0.35–4.94 uIU/mL) levels, were measured within three days of admission, with or without re-examination during the hospitalization. In the current study, TD was defined as abnormal thyroid function test results with any one of the following conditions (Batool et al., 2017): (1) overt thyrotoxicosis (decreased TSH values and increased serum FT3 and/or FT4 levels); (2) overt hypothyroidism (increased TSH values and decreased serum FT4 and/or FT3); (3) subclinical hypothyroidism (increased TSH values but normal FT4 and FT3 levels); (4) subclinical hyperthyroidism (decreased TSH values but normal FT4 and FT3 levels); (5) ESS (decreased FT3 but with normal TSH levels). In the current study, TD could be divided into ESS, subclinical hypothyroidism, subclinical hypothyroidism, and hypothyroidism on the basis of the thyroid hormone test results. Acute respiratory distress syndrome (ARDS) was diagnosed on the basis of the Berlin Definition (Force et al., 2012). Cardiac injury was diagnosed when the serum levels of cardiac biomarkers, including hsTNI and CK-MB, were above the upper limit of the normal range or new abnormalities were

observed in echocardiography and electrocardiography (Gao et al., 2020). Acute kidney injury (AKI) was identified by the highest serum level of creatinine or urine output according to the KDIGO clinical practice guidelines for AKI (Kidney disease: improving, 2012).

### 2.5. Statistical analysis

Continuous variables following a normal distribution were expressed as the mean and standard deviation and analyzed using a Student's t-test. In contrast, those with a skewed distribution were presented as medians and interquartile ranges and analyzed using the Mann–Whitney *U* test. Categorical variables were summarized as counts and proportions and evaluated using the Chi-square test. A logistic regression analysis was conducted to determine the correlations between TD and disease severity, detrimental complications, treatments strategies, and short-term outcomes among patients with COVID-19. Crude odds ratios and adjusted odds ratios with 95% confidence intervals were calculated and used as the effect size. All statistical analyses and graphs were generated using SPSS version 25.0 (IBM, United States), GraphPad Prism version 7.0 software (GraphPad Software Inc., United States), or R-3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria). A P-value of <0.05 was considered to be statistically significant.

## 3. Results

### 3.1. Baseline characteristics of the patients with COVID-19

A total of 520 patients with confirmed COVID-19 between 29 January and February 26, 2020 were recruited, and 82 patients met the inclusion criteria. Eleven patients were further excluded based on the exclusion criteria. To be specific, seven patients were excluded because they had a medical history of an endocrine disorder or thyroid surgery, one was excluded for concurrent treatment with drugs that could affect hypothalamic-pituitary activity within the past year, one was excluded with pregnancy within the past six months, two were excluded due to incomplete data. Finally, seventy-one patients were included and analyzed in the study. The demographic and clinical features of the included patients with TD (n = 25) or without TD (n = 46) are summarized and presented in Table 1. Of the patients with TD, 12, 7, 4, and 2 were classified as having ESS, subclinical hypothyroidism, subclinical hyperthyroidism, and hypothyroidism, respectively. The mean age was 62.7 ± 1.6 years, and 43.7% were female. The most common symptoms at the time of onset of illness were fever (58 [81.7%]), cough (47 [66%]), fatigue (36 [50.7%]) and shortness of breath (25 [35.2%]). Thirty-six patients (50.7%) had at least one pre-existing chronic comorbidity, including hypertension (28.2%), diabetes (18.3%), coronary heart disease (12.7), cerebrovascular disease (8.5%), chronic renal disease (7.0%), and cancer (7.0%). Compared to patients without TD, patients with TD were older (70.3 ± 2.7 vs. 58.6 ± 1.7, P < 0.0001) and were more likely to have hypertension (52.0% vs. 15.2%, P = 0.001).

**Table 1**
Characteristics of the patients with COVID-19.

| Characteristics | Total (N = 71) | With TD (n = 25) | Without TD (n = 46) | *P* |
|---|---|---|---|---|
| Age (year) | 62.7 ± 1.6 | 70.3 ± 2.7 | 58.6 ± 1.7 | <0.0001 |
| Female, n (%) | 31 (43.7) | 14 (56.0) | 17 (37.0) | 0.122 |
| Diagnosis of TD, n (%) | | | | |
| Euthyroid sick syndrome | | 12 (48.0) | – | |
| Subclinical hypothyroidism | | 7 (28.0) | – | |
| Subclinical hyperthyroidism | | 4 (16.0) | – | |
| Hypothyroidism | | 2 (8) | – | |
| Symptoms, n (%) | | | | |
| Fever | 58 (81.7) | 22 (88.0) | 36 (78.3) | 0.311 |
| Cough | 47 (66.2) | 17 (68.0) | 30 (65.2) | 0.813 |
| Fatigue | 36 (50.7) | 11 (44.0) | 19 (41.3) | 0.405 |
| Shortness of breath | 25 (35.2) | 8 (32.0) | 17 (37.0) | 0.676 |
| Diarrhea | 12 (16.9) | 4 (16.0) | 8 (17.4) | 0.881 |
| Myalgia | 21 (29.6) | 8 (32.0) | 13 (28.3) | 0.742 |
| Nausea | 7 (9.9) | 3 (12.0) | 4 (8.7) | 0.656 |
| Headache | 5 (7.0) | 0 (0.0) | 5 (10.9) | 0.087 |
| Vomiting | 5 (7.0) | 1 (4.0) | 4 (8.7) | 0.460 |
| Chest pain | 2 (2.8) | 0 (0.0) | 2 (4.4) | 0.290 |
| Pharyngalgia | 3 (4.2) | 2 (8.0) | 1 (2.2) | 0.244 |
| Preexisting condition, n (%) | | | | |
| Hypertension | 20 (28.2) | 13 (52.0) | 7 (15.2) | 0.001 |
| Diabetes | 13 (18.3) | 7 (28.0) | 6 (13.0) | 0.120 |
| Cerebrovascular disease | 6 (8.5) | 4 (16.0) | 2 (4.4) | 0.092 |
| Cardiovascular disease | 9 (12.7) | 5 (20.0) | 4 (8.7) | 0.171 |
| Chronic renal failure | 5 (7.0) | 1 (4.0) | 4 (8.7) | 0.460 |
| Cancer | 5 (7.0) | 2 (8.0) | 3 (6.5) | 0.816 |

TD, thyroid dysfunction; Data were presented as mean ± SD or IQR, interquartile range or n (%). A P value < 0.05 was considered statistically significant.

### 3.2. Laboratory and radiological findings on admission

The laboratory and radiological results of the included COVID-19 patients with or without TD on admission are presented in Table 2. The results showed that those with TD had lower lymphocyte, platelet, and eosinophil counts but higher neutrophil counts and inflammatory markers levels, including CRP, PCT, LDH, and higher biomarkers expression for cardiac injury, including hsTNI and pro-BNP. Other parameters, including CREA, AST, APTT, and plasma fibrinogen, differed between COVID-19 patients with TD and those without TD. Radiological imaging showed that most patients (97.2%) had abnormal findings with bilateral lesions. Additionally, analysis of the longitudinal changes in serum biomarkers expression showed that COVID-19 patients with TD had higher dynamic biomarker expression, including inflammatory markers (CRP, PCT, and LDH); higher D-dimer levels; and higher acute cardiac injury marker (hsTNI) expression than did patients without TD during the period of hospitalization (Fig. 1). This indicates that TD might be associated with stronger inflammatory response, coagulation function, and cardiac injury, resulting in poorer outcomes from COVID-19.

### 3.3. Analysis of disease severity, treatment strategies and prognosis

Next, the disease severity, treatment strategies, and prognosis of the COVID-19 patients with or without TD are compared in Table 3. Compared to subjects without TD, patients with TD were more commonly categorised as critically ill and were more likely to receive antibiotic treatment, corticosteroids, high-flow oxygen, non-invasive ventilation, and invasive mechanical ventilation. Logistic regression analysis showed that TD was independently associated with the critical subtype of COVID-19, ARDS, antibiotic treatment, corticosteroid treatment, high-flow oxygen, non-invasive ventilation, and invasive ventilation after adjusting for age, sex, and hypertension (Table 3). No patients without TD received invasive mechanical ventilation or died; therefore, the odd ratios could not be calculated.

### 3.4. TD is associated with a higher risk of fatality in patients with COVID-19

As of April 26, 2020, 93% of the patients were discharged from the hospital, and five had died. Notably, all deceased patients had manifestations of TD. Patients with TD had a significantly higher fatality rate than those without TD during hospitalization (20% vs. 0%, P =0.002). The Kaplan-Meier survival curves are shown in Fig. 2. Additionally, patients with TD were more likely to stay in hospital for more than 28 days than those without TD (80% vs. 56.52%, P = 0.048) (Table 3).

**Table 2**
Laboratory and radiological findings of COVID-19 patients at admission.

| Variable | Total (N = 71) | With TD (n = 25) | Without TD (n = 46) | *P* |
|---|---|---|---|---|
| Leucocytes ( $\times 10^9$/L), median (IQR) | 6.1 (4.3, 7.7) | 6.3 (4.2, 11.5) | 5.8 (4.3, 7.3) | 0.271 |
| Neutrophil ( $\times 10^9$/L), median (IQR) | 4.2 (2.7, 5.8) | 4.9 (3.0, 9.4) | 4.0 (2.6, 5.2) | 0.003 |
| Lymphocyte ( $\times 10^9$/L), median ± SD | 1.1 ± 0.1 | 0.9 ± 0.1 | 1.2 ± 0.1 | 0.003 |
| Lymphocyte percentage (%), median (IQR) | 18.6 (12.3, 28.2) | 14.5 (5.7, 22.7) | 22.2 (14.5, 29.7) | 0.007 |
| Platelets ( $\times 10^9$/L), median (IQR) | 223 (164.5, 284.8) | 177 (122.5, 231.0) | 239 (200.5, 327.0) | 0.003 |
| Eosinophil ( $\times 10^9$/L), median (IQR) | 0.03 (0.01, 0.1) | 0.01 (0, 0.02) | 0.06 (0.02, 0.06) | 0.002 |
| Albumin (g/dL), median±SD | 32.25 ± 0.71 | 30.50 ± 1.22 | 33.25 ± 0.84 | 0.063 |
| CRP (mg/L), median (IQR) | 14.2 (3.0, 50.1) | 61.2 (25.3, 121.3) | 4.1 (1.6, 15.4) | <0.001 |
| PCT (ng/ml), median (IQR) | 0.06 (0.05, 0.20) | 0.22 (0.07, 0.39) | 0.05 (0.03, 0.07) | <0.001 |
| pro-BNP (pg/mL), median (IQR) | 36.2 (12.8, 92.6) | 90.6 (32.2, 203.25) | 18 (9.24, 41.65) | 0.002 |
| LDH (U/L), median (IQR) | 251 (186.8, 325.3) | 319 (263, 465) | 212 (175.5, 284.5) | <0.001 |
| CREA (μmol/L), median (IQR) | 66.2 (53.2, 88.8) | 76.6 (66.2, 129.2) | 57.9 (50.2, 74) | 0.001 |
| BUN (mmol/L), median (IQR) | 4.36 (3.67, 6.26) | 5.42 (3.91, 10.08) | 4.16 (3.26, 5.05) | 0.004 |
| MYO (ng/mL), median (IQR) | 37.7 (24.8,64.4) | 70.4 (48.68, 118.4) | 29.6 (22.7,39.2) | <0.001 |
| hsTNI (pg/mL), median (IQR) | 4.95 (2.18, 18.5) | 12.6 (5.55, 48.7) | 2.8 (1.5, 7.65) | <0.001 |
| CK-MB (U/L), median (IQR) | 12 (10, 14) | 12 (10, 22) | 11 (8, 14) | 0.239 |
| ALT (U/L), median (IQR) | 33 (20, 45.5) | 33 (19, 46) | 34 (20, 47) | 0.708 |
| AST (U/L), median (IQR) | 29 (21, 41) | 38 (25, 48) | 27 (20, 36) | 0.003 |
| Potassium (mmol/L), median (IQR) | 3.85 (3.40, 4.16) | 3.97 (3.42, 4.58) | 3.76 (3.38, 4.03) | 0.129 |
| Sodium (mmol/L), median (IQR) | 140.6 (137.7, 143.7) | 140.2 (134.9, 145.8) | 140.8 (138.8, 142.6) | 0.970 |
| D-Dimer (μg/mL), median (IQR) | 0.52 (0.31, 1.46) | 0.92 (0.34, 2.38) | 0.42 (0.26, 1.42) | 0.091 |
| FIB(g/L), median±SD | 4.17 ± 0.13 | 4.6 ± 0.22 | 3.94 ± 0.15 | 0.015 |
| PT (sec), median (IQR) | 13.2 (12.5, 13.9) | 13.5 (12.7, 14) | 12.9 (12.3, 13.9) | 0.079 |
| APTT (sec), median (IQR) | 35.8 (32.6, 39.2) | 37.3 (33.6, 46.5) | 34.1 (31.5, 37.9) | 0.006 |
| TT (sec), median (IQR) | 15.4 (14.9, 16.4) | 15.7 (14.9, 16.4) | 15.4 (15, 16.4) | 0.953 |
| INR, median (IQR) | 1.02 (0.95, 1.09) | 1.05 (0.97, 1.1) | 0.99 (0.93, 1.09) | 0.145 |
| Abnormal Chest CT images, n (%) | 69 (98.6) | 24 (96.0) | 46 (100) | 0.172 |
| Bilateral lung involved | 68 (97.2) | 24 (96.0) | 44 (95.7) | 0.945 |
| Unilateral lung involved | 3 (4.3) | 1 (4.0) | 2 (4.4) | |

TD, thyroid dysfunction; IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; BNP, N-terminal pro-B-type natriuretic peptide; LDH, lactate dehydrogenase; FBG, fasting blood glucose; CREA, serum creatine; BUN, blood Urea nitrogen; MYO, myohemoglobin; hsTNI, High-sensitivity troponin; CK-MB, creatine kinase isoenzyme MB; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FIB, Plasma fibrinogen; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; INR, international normalized ratio.
Data were presented as mean ± SD or IQR, interquartile range or n (%). A P value $< 0.05$ was considered statistically significant.

## 4. Discussion

The present study is the first to demonstrate a correlation between TD and the prognosis of COVID-19. TD was associated with an unexpectedly higher risk of fatality and poorer clinical outcomes during the hospitalization.

As of July 7, 2020, there have been more than 11 million laboratory-confirmed cases of COVID-19, resulting in more than 500,000 deaths globally. Severe respiratory distress is usually considered the main cause of death in patients with COVID-19 (Wu et al., 2020). Several studies have reported the possible risks and predictors of poor prognosis in patients with COVID-19, including older age (Feng et al., 2020; Zhou et al., 2020), pre-existing medical conditions such as diabetes (Yan et al., 2020; Zhang et al., 2020b), complications (Wu et al., 2020), cardiac injury (Shi et al., 2020), inflammatory response (Li et al., 2020b), and coagulation disorders (Arachchillage and Laffan, 2020). However, the presence of TD and its association with the prognosis of COVID-19 has not yet been reported, even though TD has been commonly observed among patients with severe COVID-19. Our study is the first to suggest that TD is associated with a higher fatality rate and longer hospitalization in patients with COVID-19. Compared to those without TD, patients with TD presented with a severe subtype of critical illness and more complications such as ARDS, acute cardiac injury, and AKI, and as a result, received more antibiotic treatment, corticosteroids, and mechanical ventilations.

Changes in circulating hormone levels are common during critical illness (Li et al., 2020a), and thyroid hormones play a key role in modulating metabolism and the immune system. Therefore, thyroid hormones are associated with the prognosis of critically ill patients (Rothwell and Lawler, 1995; Rothwell et al., 1993). In the current study, 25 (28%) of the 71 patients with COVID-19 presented with TD. Of the patients with TD, ESS (48%) and subclinical hypothyroidism (28%) were the most common and second-most common types of TD, respectively. Previous studies have reported that TD is commonly seen in patients infected with viruses, including human immunodeficiency virus (HIV) (Brown, 2011; Ji et al., 2016), hepatitis C virus (HCV) (Zhang et al., 2015), and hepatitis B virus (HBV) (Deutsch et al., 1997). Treatment with interferon (IFN) and ribavirin has been reported to be closely associated with TD in patient with chronic hepatitis B or C (Chang et al., 2019). In patients with HIV, the virus can directly infiltrate the thyroid with opportunistic agents but lead to non-thyroid illness. However, treatment with highly active antiretroviral therapy could result in subclinical hypothyroidism and low FT4 levels (Brown, 2011). The two groups did not receive different antivirus treatment with IFN and/or ribavirin in the current study. Therefore, we could not determine the effect of antiviral agents on TD. Few studies have reported the prevalence of TD in coronavirus diseases, including severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19. The thyroid gland tissue has high ACE2 expression, making it a targeted organ for SARS-CoV-2 (Li et al., 2020a). An autopsy study in five patients with SARS showed marked destruction of the thyroid's follicular and parafollicular cells (Wei et al., 2007). However, a biopsy study of three patients with COVID-19 did not reveal pathologic thyroid illness (Yao et al., 2020). Further studies are required to examine whether SARS-CoV-2 can directly impair the thyroid.

Several studies have reported that thyroid hormones serve as potential prognostic predictors in sepsis. However, the findings of studies have not been consistent (Foks et al., 2019; Hosny et al., 2015). Sepsis can reduce adenosine triphosphate (ATP) production in cells due to hypoxia, which is influenced by thyroid hormones. Thyroid hormones are closely related to the immune system, regulated by the function and activity of neutrophils and other immune cells (Maxime et al., 2007). Additionally, we found that COVID-19 patients with TD presented with persistently higher inflammatory biomarkers (CRP and PCT). This further indicates that TD might be closely associated with a more severe inflammatory response. Additionally, acute cardiac injury

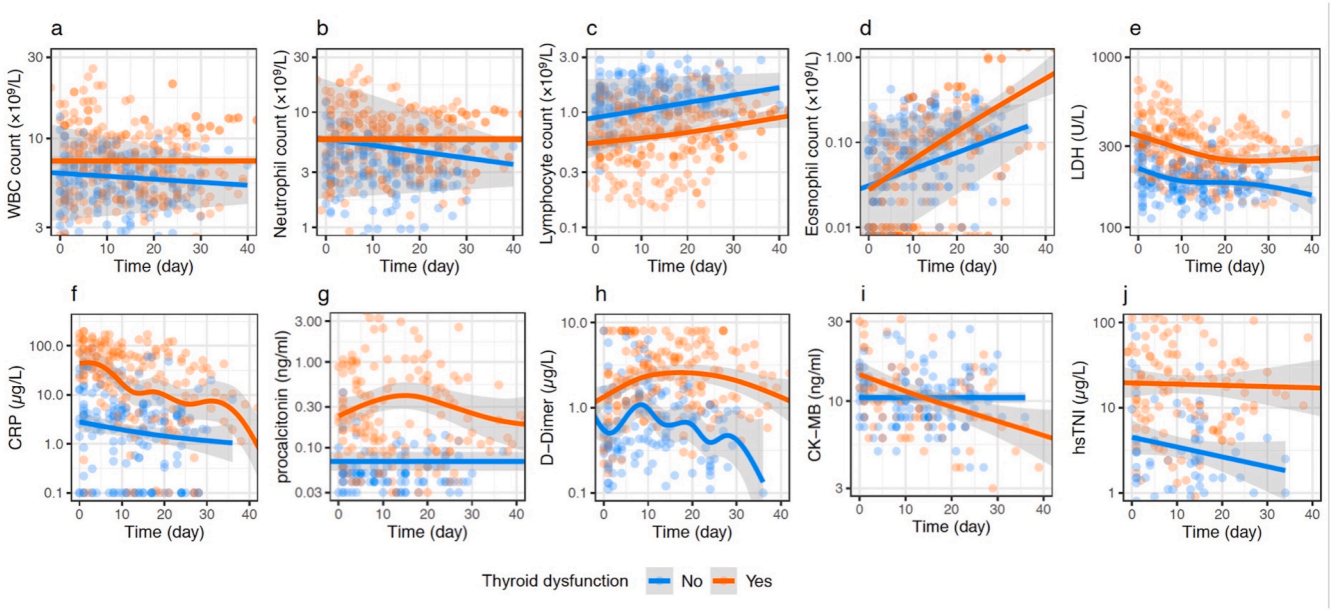


**Fig. 1.** Longitudinal leucocytes, neutrophils, lymphocytes, eosinophil, C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH), D-dimer, creatine kinase isoenzyme (CK-MB), and high-sensitivity troponin (hsTNI) changes in COVID-19 patients with or without thyroid dysfunction (TD) during hospitalization.

**Table 3**
Disease severity, treatment, and prognosis of COVID-19 patients.

| Variable | Total (N = 71) | With TD (n = 25) | Without TD (n = 46) | *P* | COR (95%CI) | AOR (95%CI) |
|---|---|---|---|---|---|---|
| Severity, n (%) | | | | | | |
| Mild to moderate | 4 (5.6) | 1 (4.0) | 3 (6.5) | <0.001 | 0.597 (0.059, 6.063) | 0.947 (0.064, 14.013) |
| Severe | 50 (70.4) | 10 (40.0) | 40 (87.0) | | 0.100 (0.031, 0.323) | 0.142 (0.040, 0.507) |
| Critical | 17 (23.9) | 14 (56.0) | 3 (6.5) | | 18.242 (4.445, 74.862) | 11.063 (2.478, 49.398) |
| Complications, n (%) | | | | | | |
| Acute respiratory distress | 14 (19.7) | 11 (44.0) | 3 (6.5) | <0.001 | 11.262 (2.744, 46.216) | 8.494 (1.817, 39.717) |
| Acute cardiac injury | 13 (18.3) | 8 (32.0) | 5 (10.9) | 0.028 | 3.859 (1.103, 13.499) | 1.707 (0.373, 7.804) |
| Acute kidney injury | 7 (9.9) | 5 (20.0) | 2 (4.4) | 0.035 | 4.190 (0.710, 24.730) | 1.657 (0.213, 12.899) |
| Medication, n (%) | | | | | | |
| Antiviral agent | 66 (93.0) | 24 (96.0) | 42 (91.3) | 0.460 | 2.286 (0.241, 21.642) | 3.557 (0.251, 50.359) |
| Antibiotic | 55 (77.5) | 23 (92.0) | 32 (69.6) | 0.031 | 5.031 (1.041, 24.317) | 4.459 (0.842, 23.598) |
| Corticosteroid | 25 (35.2) | 14 (56.0) | 11 (23.9) | 0.007 | 4.050 (1.431, 11.463) | 3.270 (1.021, 10.475) |
| Oxygen support, n (%) | | | | | | |
| Nasal cannula | 57 (80.3) | 22 (88.0) | 35 (76.1) | 0.228 | 2.305 (0.578, 9.193) | 3.217 (0.652, 15.866) |
| High-flow oxygen | 12 (16.9) | 10 (40.0) | 2 (4.4) | <0.001 | 14.667 (2.881, 74.659) | 10.449 (1.787, 61.086) |
| Non-invasive ventilation | 10 (14.1) | 8 (32.0) | 2 (4.4) | 0.001 | 10.353 (1.993, 53.772) | 10.639 (1.726, 65.567) |
| Invasive ventilation | 5 (7.0) | 7 (20.0) | 0 (0) | 0.002 | N/A | N/A |
| Prognosis, n (%) | | | | | | |
| Hospital stay≥28 days | 46 (64.79) | 20 (80.0) | 26 (56.52) | 0.048 | 3.077 (0.984, 9.623) | 2.630 (0.713, 9.700) |
| Death | 5 (7.0) | 5 (20.0) | 0 (0) | 0.002 | N/A | N/A |
| Discharged | 66 (93.0) | 20 (80.0) | 46 (100) | | N/A | N/A |

TD, thyroid dysfunction. Data were presented as n (%).COR, crude odd ratios; AOR, Adjusted for age, sex and hypertension; CI, confidence interval. A P value < 0.05 was considered statistically significant.

has been observed in patients with COVID-19 and has been found to be correlated with the fatality (Shi et al., 2020). Appropriate thyroid hormone levels are essential for the maintenance of the normal electrical activity of the heart muscle (Cheng et al., 2010). Therefore, TD may favor cardiac injury and influence the prognosis of COVID-19. This was consistent with our finding that COVID-19 patients with TD presented with a higher level of hsTNI during hospitalization and more detrimental complications of acute cardiac injury than did those without TD. Thyroid hormones are also associated with respiratory system. Increased serum T3 levels could enhance the synthesis of pulmonary surfactant, thereby reducing alveolar surface tension, increasing lung compliance, and improving lung function (Dulchavsky et al., 1991, 1993). As the main pathophysiology of death in patients with COVID-19 involves multiple organ dysfunction, these close associations between TD and multiple organ disorders support the possibility that TD is a novel prognostic factor among patients with COVID-19.

### 4.1. Limitations

This study had several limitations. Firstly, the current study was a retrospective study with a relatively small sample size, and a large cohort study is needed to confirm our findings. Second, thyroid hormones also presented dynamic changes, which were not captured by our study. Third, thyroid autoantibodies were not detected in most patients in the study. Thus, there is a lack of evidence on the dysregulated immune status of the thyroid gland caused by COVID-19. Lastly, none of the patients included in the current study received supplementary treatment for dysregulated thyroid hormones, and the potential role of thyroid hormones in COVID-19 needs to be investigated further.

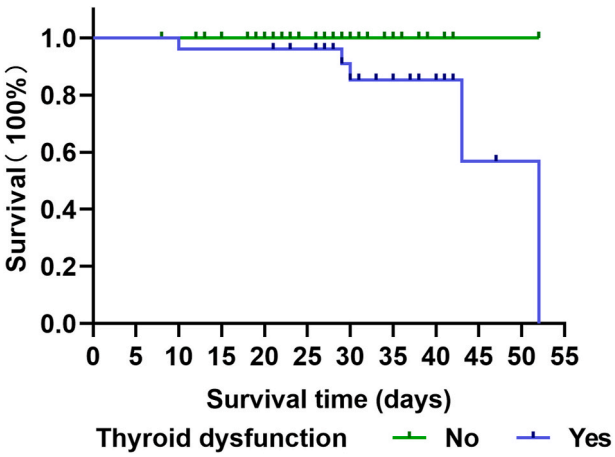


**Fig. 2.** Kaplan-Meier Curve for mortality in COVID-19 patients with thyroid dysfunction (TD) or those without TD.

## 5. Conclusions

In this study, we showed that TD is closely associated with greater disease severity and poorer prognosis, including longer hospitalization and a higher mortality rate. More intensive surveillance and treatment should be considered for COVID-19 patients with complications of TD. However, our results are preliminary, and the mechanism for TD in COVID-19 should be investigated in the future with larger, more robust studies.

## Funding

This study was supported by the Emergency Project of Prevention and Control for COVID-19 of Central South University (No. 160260004 and 502701002); Special Program on COVID-19 of Changsha Department of Science and Technology (No. kq2001049); Health and Family Planning Commission of Hunan Province (B20180778); Science and Technology Innovation Project of Hunan Province (No. S2018SFYLJS0108); National Key R&D Program of China (No. 2016YFC1304204).

## CRediT authorship contribution statement

**Yan Zhang:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Methodology. **Fengyu Lin:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing. **Wei Tu:** Investigation, Resources. **Jianchu Zhang:** Investigation, Resources. **Abira Afzal Choudhry:** Writing - review & editing. **Omair Ahmed:** Writing - review & editing. **Jun Cheng:** Investigation, Data curation. **Yanhui Cui:** Investigation, Data curation. **Ben Liu:** Investigation, Supervision. **Minhui Dai:** Investigation, Data curation. **Lingli Chen:** Investigation, Data curation. **Duoduo Han:** Investigation, Data curation. **Yifei Fan:** Investigation, Data curation. **Yanjun Zeng:** Validation, Data curation. **Wen Li:** Validation, Data curation. **Sha Li:** Supervision, Data curation. **Xiang Chen:** Resources, Data curation. **Minxue Shen:** Project administration, Methodology, Software, Visualization. **Pinhua Pan:** Funding acquisition, Investigation, Project administration, Resources, Supervision.

## Declaration of competing interest

The authors declare no conflicts of interest.

## Acknowledgements

We would like to thank all patients involved in this study. We would also like to thank all medical staff who are fighting the spread of COVID-19.

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