Analysis of thyroid function in Japanese patients with coronavirus disease 2019

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Abstract. Thyroid dysfunction that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is becoming increasingly recognized. However, only a few reports in Japan have addressed this issue to date. In this study, we sought to clarify whether infection with SARS-CoV-2 affected thyroid hormone levels and whether these hormones could be better predictors of prognosis in patients with coronavirus disease 2019 (COVID-19). Accordingly, we retrospectively examined 147 cases wherein thyroid hormones were measured at the time of admission among 848 Japanese patients with COVID-19 admitted to the Hyogo Prefectural Kakogawa Medical Center. All patients underwent thyroid function testing upon hospital admission. More than half (59.1%) of the patients were euthyroid. Twenty-four percent of patients had serum thyroid-stimulating hormone (TSH) levels lower than the reference range with normal serum free thyroxine (fT4) levels, and 3.4% of the patients had low TSH with high fT4 levels. Over 70% of the patients with moderate and severe COVID-19 had low serum free triiodothyronine (fT3) levels. Serum TSH and fT3 levels were inversely correlated with disease severity. The mortality rate in patients with low serum fT3 levels was significantly higher than that in those with normal serum fT3 levels.

Key words: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Mortality, Thyrotoxicosis, Non-thyroidal illness
Serum TSH, fT3, and fT4 levels were measured using the Elecsys® TSH assay, Elecsys® fT3 III assay, and Elecsys® fT4 II assay (Roche Diagnostics, Mannheim, Germany), respectively. The reference ranges for TSH, fT3, and fT4 levels were 0.5–5.0 μU/mL, 2.3–4.0 pg/mL, and 0.9–1.7 ng/dL, respectively. Latex agglutination was used to measure D-dimer and Krebs von den Lungen 6 (KL-6). D-dimer and KL-6 were measured using the Nanopia® D-dimer and Nanopia® KL-6 (SEKISUI MEDICAL CO.LTD, Tokyo, Japan), respectively. In addition, the reference ranges for D-dimer and KL-6 were >1.0 μg/mL and <500 U/mL, respectively.

Data on demographics and underlying disease were recorded. COVID-19-related symptoms, including oxygen concentration (SpO2) and supplementary oxygen requirements, were recorded on admission. Chest radiography was performed upon admission. Clinical outcomes, including mortality, were recorded among those who were discharged or had died at the time of manuscript preparation (June 14, 2021).

All the cases were classified into three groups, namely mild, moderate, and severe, according to the Clinical Management of Patients with COVID-19 (version 5.3) issued by the Ministry of Health, Labor, and Welfare of Japan [8]. The clinical classification “mild” included patients with mild clinical symptoms and no pneumonia manifestations; “moderate” included patients with symptoms, such as dyspnea, pneumonia manifestations on imaging, or oxygen saturation ≤93% at rest and respiratory failure requiring oxygen administration; and “severe” included patients with admission to intensive care units (ICUs) or mechanical ventilation requirement.

Data were analyzed using StatMate software (version 4.01, ATMS Co. Ltd., Tokyo, Japan). Data are presented as total number (proportions) for categorical variables and median (interquartile range [IQR]) for continuous variables. The Kruskal–Wallis test was performed for comparisons between the mild, moderate, and severe patient groups, and Dunn’s test was used to identify significant differences between any two of the three groups. The chi-square test was used for categorical variables. Moreover, logistic regression analysis was used for multivariate analyses, and differences were considered statistically significant if the p-value was <0.05.

## Results

This study included a total of 147 patients who were diagnosed with COVID-19, of which 95 (64.6%) were men and 52 (35.4%) were women (Table 1). The mean age was 67.8 ± 13.7 years. There were no patients with subacute thyroiditis since none of them experienced neck pain.

| Table 1 | Risk factors assessed among patients with different clinical classifications of COVID-19 |
|-----------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                      | All (n = 147) | Mild (n = 22) | Moderate (n = 41) | Severe (n = 84) |
| Age, median (IQR), years | 70.0 (59.5–77.5) | 61.5 (47.3–78.5) | 73.0 (60.0–79.0) | 70.5 (62.0–76.3) |
| Sex Male, no. (%) | 95 (64.6) | 10 (45.5) | 24 (58.5) | 61 (72.6) |
| Female, no. (%) | 52 (35.4) | 12 (54.5) | 17 (41.5) | 23 (27.4) |
| Body mass index, median (IQR) | 24.7 (22.9–27.5) | 23.1 (20.7–25.5) | 24.7 (22.8–27.6) | 25.2 (23.2–28.0) |
| Smoking, no. (%) | 57 (38.8) | 10 (45.5) | 14 (34.1) | 33 (39.3) |
| Hypertension, no. (%) | 80 (54.8) | 7 (31.8) | 19 (46.3) | 54 (64.3) |
| Diabetes mellitus, no. (%) | 45 (30.6) | 2 (9.1) | 9 (22.0) | 34 (40.5) |
| Dyslipidemia, no. (%) | 32 (21.8) | 2 (9.1) | 9 (22.0) | 21 (25.0) |
| Heart failure, no. (%) | 10 (6.8) | 2 (9.1) | 2 (4.9) | 6 (7.1) |
| Chronic kidney disease, no. (%) | 11 (7.5) | 0 | 3 (7.3) | 8 (9.5) |
| Malignant tumor, no. (%) | 18 (12.2) | 5 (22.7) | 6 (14.6) | 7 (8.3) |
| fT3, median (IQR), pg/mL | 1.82 (1.49–2.16) | 2.34 (1.93–2.74)* | 1.89 (1.66–2.23) | 1.64 (1.40–2.02) |
| fT4, median (IQR), ng/dL | 1.18 (1.05–1.39) | 1.18 (1.07–1.35) | 1.18 (1.02–1.32) | 1.18 (1.07–1.48) |
| TSH, median (IQR), μIU/mL | 0.88 (0.44–1.57) | 1.57 (0.96–2.43)* | 1.09 (0.68–1.96)* | 0.55 (0.30–1.10) |
| TSH (mU/mL) × fT3 (pg/mL) median (IQR) | 1.53 (0.65–3.04) | 3.53 (1.89–6.20)* | 2.07 (1.26–4.25)* | 0.86 (0.44–2.07) |
| D-dimer, median (IQR), μg/mL | 1.50 (1.00–2.35) | 0.80 (0.63–1.18) | 1.30 (0.99–2.10) | 1.70 (1.30–3.38) |
| KL-6, median (IQR), IU/mL | 311 (216–500) | 230 (168–333) | 270 (208–373) | 346 (246–622) |

*p < 0.01, when compared with the severe group.

TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; HR, Hazard ratio; CI, confidence interval; KL-6, Krebs von den Lungen 6; COVID-19, coronavirus 2019
Examination of thyroid function indicated that 59.1% (87/147) of the patients had a euthyroid state. However, 24.4% (36/147) of patients had low serum TSH and normal serum fT4 levels, and 3.4% (5/147) of patients had low serum TSH and high fT4 levels (Table 2). Of these five patients, two had serum fT3 levels within the reference range, and three had serum fT3 levels below the reference value. Of these five patients with low TSH and high fT4 levels, only one was retested for thyroid hormone after one month. fT4 normalized spontaneously while TSH was previously low but trended upward.

Among 147 confirmed COVID-19 cases, 22 were categorized into the mild group, 41 into the moderate group, and 84 into the severe group. Most patients in the mild and moderate groups were euthyroid, whereas suppressed serum levels of TSH were frequently observed in the severe group (Table 2). The median serum TSH level in the severe group (0.55 μU/L, IQR 0.30–1.10) was significantly lower than those in the mild (1.57 μU/L, IQR 0.96–2.43) and moderate groups (1.09 μU/L, IQR 0.68–1.96) (p < 0.001) (Table 1). Most patients in the severe and moderate groups had low serum fT3 levels (Table 3). The median serum fT3 levels in the mild, moderate, and severe groups were 2.34 pg/mL (IQR 1.93–2.74), 1.89 pg/mL (IQR 1.66–2.23), and 1.64 pg/mL (IQR 1.40–2.02), respectively (p < 0.001). The median serum TSH × fT3 levels in the mild, moderate, and severe groups were 3.53 pg/mL (IQR 1.89–6.20), 2.07 pg/mL (IQR 1.26–4.25), and 0.86 pg/mL (IQR 0.44–2.07), respectively (p < 0.001). In contrast, the median serum fT4 levels did not differ among groups (Table 1). In most cases, serum fT3/fT4 ratio was <2.0 pg/mL/ng/dL (Fig. 1). In case of high fT3 (Table 3), the patient was admitted to the ICU and placed on a ventilator, but was extubated in six days and could start rehabilitation.

The mortality rate was 3.6% (1/28) in patients with normal serum fT3 levels. However, it was 26.3% (31/118) in patients with low serum fT3 levels, which was statistically significant (p = 0.001) (Table 3). The mortality rate of patients with normal TSH (20.0%, 20/100) and low TSH (26.0%, 12/45) levels was not significantly different (p = 0.48).

In the multivariate analyses, low fT3 and TSH levels were independent risk factors for the severity of COVID-19 (Table 4), and a low fT3 level was an independent risk factor for mortality of COVID-19 (Table 5).

Table 2 Distribution of serum fT4 and TSH among patients with different clinical classifications of COVID-19

| fT4   | TSH   | All (n = 147) | Mild (n = 22) | Moderate (n = 41) | Severe (n = 84) |
|-------|-------|--------------|--------------|------------------|-----------------|
| Normal| Normal| 87           | 17           | 35               | 39              |
| High  | Low   | 5            | 0            | 0                | 5               |
| Low   | High  | 0            | 0            | 0                | 0               |
| Normal| Low   | 36           | 3            | 4                | 29              |
| Normal| High  | 2            | 1            | 1                | 0               |
| High  | Normal| 3            | 0            | 1                | 2               |
| Low   | Normal| 10           | 1            | 0                | 5               |
| Low   | Low   | 4            | 0            | 0                | 4               |

The reference ranges of serum fT4 and TSH levels were 0.9–1.7 ng/dL and 0.5–5.0 mU/mL, respectively.

TSH, thyroid-stimulating hormone; fT4, free thyroxine; COVID-19, coronavirus 2019

Table 3 Distribution of serum fT3 levels among patients with different clinical classifications of COVID-19

| fT3    | All (n = 147) | Mild (n = 22) | Moderate (n = 41) | Severe (n = 84) | Non-survivor (n = 32) | Survivor (n = 105) |
|--------|---------------|--------------|------------------|-----------------|----------------------|--------------------|
| Low    | 118           | 12           | 33               | 76              | 31                   | 87                 |
| Normal | 28            | 10           | 8                | 7               | 1                    | 27                 |
| High   | 1             | 0            | 0                | 1               | 0                    | 1                  |

The reference range of serum fT3 levels was 2.3–4.0 ng/dL.

fT3, free triiodothyronine; COVID-19, coronavirus 2019
Discussion

In this study, we demonstrated the characteristics of thyroid function in patients with COVID-19 in Japan for the first time. We assessed serum TSH, fT3, and fT4 levels in relation to disease severity and found that serum TSH and fT3 levels upon hospital admission might be a predictor of prognosis in patients with COVID-19.

SARS-CoV-2 had a lower impact on thyroid function in patients with mild or moderate COVID-19. Most patients with less severe conditions had a euthyroid state, as shown in Table 2. This observation is in agreement with a previous report from the United Kingdom [7]. In contrast, in the severe group, 34.5% of patients had serum TSH levels below the reference range and normal serum fT4 levels (Table 2). In a previous study by Beltrão et al. [9], 77% of patients with severe and critical COVID-19 had changes in thyroid hormone levels, 27.7% of whom had low TSH and/or high fT4 levels. Only five patients in the severe group (5.8%) and none in the mild or moderate group had low serum TSH and fT4 levels (Table 2). In this study, the five patients with low to normal serum fT3 levels could have had both thyrotoxicosis and non-thyroidal disease (NTI). Lania et al. [5] demonstrated that thyrotoxicosis is closely related to high circulating levels of interleukin-6 (IL-6). Their results, which were consistent with ours, indicated that thyrotoxicosis might be induced by SARS-CoV-2 in relation to the severity of the disease. Additionally, Chen et al. [4] reported decreased serum levels of TSH and normal levels of serum total T4 in Chinese patients with COVID-19. Another report referred to these conditions as SARS-COV-2-related atypical thyroiditis [6].

![Graph showing distribution of serum TSH levels and fT3/fT4 in COVID-19 patients with mild, moderate, and severe conditions.](image)

TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine

Table 4  Multivariate analysis with risk factors of the severity of COVID-19

| Risk Factor                        | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | HR      | 95% CI     | p-value | HR      | 95% CI     | p-value |
| Age, years                        | 1.01    | 0.99–1.04  | 0.33    | 1.71    | 0.80–3.68  | 0.17    |
| Male, no. (%)                     | 2.26    | 1.13–4.51  | 0.02    | 1.71    | 0.80–3.68  | 0.17    |
| Body mass index                   | 1.07    | 0.97–1.17  | 0.17    | 1.98    | 0.85–4.59  | 0.11    |
| Smoking, no. (%)                  | 1.03    | 0.49–2.17  | 0.94    | 1.98    | 0.85–4.59  | 0.11    |
| Hypertension, no. (%)             | 1.87    | 0.91–3.84  | 0.09    | 1.98    | 0.85–4.59  | 0.11    |
| Diabetes mellitus, no. (%)        | 3.01    | 1.39–6.51  | 0.005   | 1.98    | 0.85–4.59  | 0.11    |
| Dyslipidemia, no. (%)             | 1.58    | 0.70–3.58  | 0.27    | 1.98    | 0.85–4.59  | 0.11    |
| Heart failure, no. (%)            | 1.15    | 0.31–4.25  | 0.84    | 1.98    | 0.85–4.59  | 0.11    |
| Chronic kidney disease, no. (%)   | 2.01    | 0.52–7.79  | 0.31    | 1.98    | 0.85–4.59  | 0.11    |
| Malignant tumor, no. (%)          | 0.43    | 0.16–1.19  | 0.1     | 1.98    | 0.85–4.59  | 0.11    |
| fT3, pg/mL                        | 0.37    | 0.18–0.74  | 0.004   | 0.48    | 0.23–0.98  | 0.04    |
| fT4, ng/dL                        | 1.87    | 0.58–6.04  | 0.3     | 1.98    | 0.85–4.59  | 0.11    |
| TSH, μU/mL                        | 0.57    | 0.41–0.80  | 0.001   | 0.66    | 0.46–0.93  | 0.02    |
| D-dimer, μg/mL                    | 1.02    | 0.99–1.04  | 0.19    | 1.00    | 1.00–1.00  | 0.36    |
| KL-6, IU/mL                       | 1.00    | 1.00–1.00  | 0.05    | 1.00    | 1.00–1.00  | 0.36    |

TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; HR, Hazard ratio; CI, confidence interval; KL-6, Krebs von den Lungen 6; COVID-19, coronavirus 2019
thyroid gland expresses angiotensin-converting enzyme 2 (ACE2), which is bound by SARS-CoV-2 during viral entry into host cells [10]. Thus, thyrotoxicosis might be caused by the direct action of SARS-CoV-2 on the thyroid gland. However, this condition is different from that of classical subacute thyroiditis, which is caused by other viral infections, since none of the patients experienced neck pain, and the increased level of serum fT4 was subtle in our study.

The marked elevation in endogenous cortisol secretion caused by general stress may affect the suppression of serum TSH levels. Hypercortisolism suppresses TSH secretion [11]. In vitro studies have shown that dexamethasone administration alters serum thyrotropin-releasing hormone (TRH) levels, hypothalamic TRH concentration, and/or pro-TRH mRNA levels [12]. A study showed that patients with COVID-19 experience a marked acute cortisol secretion, higher than that in patients without COVID-19 [13]. Another possible explanation for the decreased serum TSH levels is the direct cytopathic damage by SARS-CoV-2 on thyrotropes in the pituitary gland, where ACE2 is also present [10, 14, 15].

Furthermore, our study revealed a high prevalence of low serum fT3 levels and low serum fT3/fT4 ratio, which indicate decreased thyroxine deiodination, not only in the severe group but also in the mild and moderate groups (Table 3, Fig. 1). Similarly, NTI may be one of the factors that suppresses serum levels of TSH and fT3. Further, a previous report demonstrated that serum levels of total triiodothyronine (tT3) were significantly lower in patients with COVID-19 than in those with non-COVID-19 pneumonia [4]. In the study by Torpy et al., [16] serum T3 of healthy controls was decreased by a single bolus infusion of IL-6. There are reports of an inverse correlation between IL-6 and serum T3 concentrations in patients with COVID-19 [4, 17].

Finally, we demonstrated that the mortality rate of patients with low serum fT3 levels on admission was significantly higher than that in those with normal fT3 levels (Table 3). As shown in Table 1, serum TSH and fT3 levels were significantly lower in the severe group than in the mild or moderate group, whereas serum fT4 levels were not different among groups. Patients with low serum TSH and tT3 levels were more likely to have severe COVID-19 according to a previous report; low TSH and tT3 levels were related to the severity of the COVID-19 [4]. Additionally, patients with COVID-19 who died due to illness had lower serum TSH and fT3 levels than survivors [18, 19].

Our study has some limitations. First, we did not include a control group of healthy individuals or patients without COVID-19 with severe general conditions. Second, we did not measure serum IL-6 and cortisol

Table 5 Multivariate analysis with risk factors of the mortality of COVID-19

|                         | Univariate analysis | Multivariable analysis |
|-------------------------|---------------------|------------------------|
|                         | HR                  | 95% CI                 | p-value | HR                  | 95% CI                 | p-value |
| Age, years              | 1.04                | 1.00–1.08              | 0.02    | 1.85                | 0.72–4.77              | 0.2     |
| Male, no. (%)           | 2.12                | 0.87–5.2               | 0.1     |                     |                       |         |
| Body mass index         | 0.97                | 0.86–1.08              | 0.54    |                     |                       |         |
| Smoking, no. (%)        | 1.69                | 0.67–4.27              | 0.27    |                     |                       |         |
| Hypertension, no. (%)   | 0.90                | 0.41–1.98              | 0.79    |                     |                       |         |
| Diabetes mellitus, no. (%) | 3.16           | 1.42–7.03              | 0.005   | 1.72                | 0.70–4.2              | 0.23    |
| Dyslipidemia, no. (%)   | 1.59                | 0.65–3.88              | 0.31    |                     |                       |         |
| Heart failure, no. (%)  | 3.11                | 0.84–11.6              | 0.09    |                     |                       |         |
| Chronic kidney disease, no. (%) | 7.86 | 2.11–29.2              | 0.002   | 3.73                | 0.93–15.0              | 0.06    |
| Malignant tumor, no. (%) | 0.34              | 0.07–1.68              | 0.18    |                     |                       |         |
| fT3, pg/mL              | 0.28                | 0.12–0.69              | 0.006   | 0.34                | 0.13–0.90              | 0.03    |
| fT4, ng/dL              | 0.75                | 0.36–1.55              | 0.75    |                     |                       |         |
| TSH, μIU/mL             | 0.96                | 0.68–1.37              | 0.83    |                     |                       |         |
| D-dimer, μg/mL          | 1.02                | 1.00–1.04              | 0.03    | 1.00                | 0.98–1.03              | 0.76    |
| KL-6, IU/mL             | 1.00                | 1.00–1.00              | 0.005   | 1.00                | 1.00–1.00              | 0.29    |

TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; HR, Hazard ratio; CI, confidence interval; KL-6, Krebs von den Lungen 6; COVID-19, coronavirus 2019
levels and thyroid autoantibodies. Third, since our hospital is a foundation hospital in the area, few patients with mild conditions were admitted to our institution compared to other hospitals. Fourth, of the 848 patients admitted with COVID-19, 636 were excluded because their fT3 measurements were unavailable. Hence, further studies are required to clarify the unique impact of SARS-CoV-2 on thyroid function.

In conclusion, we demonstrated the characteristics of thyroid function in Japanese patients with COVID-19. The majority of patients had a euthyroid state, and low TSH and fT3 levels suggest aggravation of the disease. Patients with low serum fT3 levels had a higher mortality rate than those with normal fT3 levels. Therefore, a thyroid function test on admission, particularly for serum TSH and fT3 levels, may be an indicator for the prognosis of COVID-19.

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